Management of Diabetic Cats with Long-acting Insulin

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KEYWORDS

• Diabetes • Insulin • Cats • Glargine • Detemir

KEY POINTS

- Glargine and detemir are associated with the highest remission rates reported in cats and the lowest occurrences of clinical hypoglycemic events.
- Overall, glycemic control using glargine/detemir is superior to protamine zinc insulin because of the long duration of action of these insulin analogues, which reduces periods of hyperglycemia.
- However, it should be noted that no insulin type has been effective in controlling hyperglycemia in all cats, even with twice-daily administration.
- There is a narrow window of opportunity of treatment for diabetic cats; initiating effective treatment within days of diagnosis leads to remission rates greater than 90% using non-intensive blood glucose control protocols with glargine/detemir.

AIMS OF THERAPY

The use of long-acting insulin and high-protein, low-carbohydrate diets have made the goal of achieving remission in most diabetic cats a realistic one, preventing a lifetime of insulin injections, potential health complications, and high costs for owners. Long-acting insulin, in conjunction with low-carbohydrate diets, facilitates achieving excellent glycemic control. Controlling hyperglycemia assists in the resolution of glucose toxicity, which, over time, is responsible for reducing beta cell mass. Eventually, chronic glucose toxicity makes remission impossible because insufficient insulin-secreting tissue remains in the pancreas. It is important to initiate effective therapy as quickly as possible, not only to prevent possible complications, such as nephropathy or ketoacidosis, but to also achieve optimal glycemic control and increase the probability of remission.

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THERAPY WITH LONG-ACTING INSULINS

Types of Long-acting Insulin

Currently, 3 types of long-acting insulin have been used in diabetic cats (**Table 1**).

Glargine (Lantus) is a long-acting human insulin analogue, which gained approval for humans by the Food and Drug Administration (FDA) in the United States in 2000. In this insulin, several amino acid changes have been made (asparagine at position A21 has been replaced by glycine, and 2 arginines have been added to the B chain at positions 31 and 32), which cause it to remain soluble in acidic solution but form precipitates in neutral subcutaneous tissue.[1] Several studies have demonstrated that glargine is effective at controlling blood sugar levels in diabetic cats and achieving high remission rates.[2–4]

Detemir (Levemir) is another long-acting human insulin analogue, which was approved by the FDA for human use for the US market in 2005.[5] In it, the B30 amino acid threonine has been removed and 14-carbon, myristoyl fatty acid is covalently bound to lysine at position B29. Detemir reversibly binds to albumin via its fatty chain, which increases the duration of action of the insulin.[1] Detemir has been shown to work as effectively as glargine in diabetic cats, both in terms of blood glucose control and remission rates.[6]

The development of protamine zinc insulin (PZI) dates back to the 1930s. It has both protamine (strongly basic protein) and zinc (metal ion) added to prolong its duration of action. PZI was removed from the human market in the 1990s.[7] PZI has been used extensively in feline diabetes. For cats, animal origin preparations of PZI were discontinued in 2008 and have been replaced by human recombinant PZI, which has been shown to be equally effective in cats.[8,9] PZI is also available from some compounding pharmacies in the United States, although the use of insulin from such a source is not recommended because of the possibility of variability in consistency and supply and the increased expense for the owner.

Dosage Adjustment Protocols

Dosing protocol on glargine/detemir and glucose monitoring every 1 to 2 weeks

When adjusting the dose based on serial blood glucose measurements every 3 to 4 hours over 12 hours every week (or less optimally every 2 weeks), the dosing algorithm in **Table 2** has been used successfully. Glargine and detemir are always dosed twice daily. Weekly serial glucose curves are continued for the first 4 months of therapy, which is when remission is most likely to occur.

When glucose meters calibrated for feline blood are unavailable, it is recommended that glucometers calibrated for human blood be used. The type of meter used, feline or

Table 1
Long-acting insulin types and their attributes

Insulin	Brand Name	Manufacturer	Unit per Milliliter	Type	Size	Solution/ Suspension
Glargine	Lantus	Sanofi-Aventis	U-100	rDNA origin, human insulin analogue	3-mL Cartridge, 10-mL Vial	Aqueous solution
Detemir	Levemir	Novo Nordisk	U-100	rDNA origin, human insulin analogue	3-mL Cartridge, 10-mL Vial	Aqueous solution
PZIR	ProZinc	Boehringer Ingelheim	U-40	rDNA origin, human insulin	10-mL Vial	Aqueous suspension

Table 2
Dosing protocol on glargine or detemir and glucose monitoring every 1 to 2 weeks using whole-blood human glucometers

Parameter Used for Dosage Adjustment	Change in Dose
Begin with 0.5 IU/kg if the blood glucose is >360 mg/dL (>20 mmol/L) or 0.25/kg of ideal weight if blood glucose is lower. Do not increase in the first week unless minimum response to insulin occurs, but decrease if necessary. Monitor response to therapy for first 3 d. If no monitoring occurs in the first week, begin with 1 IU per cat BID.	
If preinsulin blood glucose concentration is >216 mg/dL (>12 mmol/L) provided nadir is not in hypoglycemic range Or If nadir blood glucose concentration is >180 mg/dL (>10 mmol/L)	Increase by 0.25–1.0 IU depending on degree of hyperglycemia and total insulin dose
If preinsulin blood glucose concentration is ≥180–≤216 mg/dL (≥10–≤12 mmol/L) Or Nadir blood glucose concentration is 90–160 mg/dL (5–9 mmol/L)	Same dose
If preinsulin blood glucose concentration is 198–252 mg/dL (11–14 mmol/L). Or If nadir glucose concentration is 54–72 mg/dL (3–4 mmol/L).	Use nadir glucose, water drunk, urine glucose, and next preinsulin glucose concentration to determine if insulin dose is decreased or maintained
If preinsulin blood glucose concentration is <180 mg/dL (<10 mmol/L) Or If nadir blood glucose concentration is <54 mg/dL (<3 mmol/L)	Reduce by 0.5–1.0 IU depending on blood glucose concentration and total dose; If total dose is 0.5–1.0 IU SID, stop insulin and check for diabetic remission
If clinical signs of hypoglycemia are observed	Reduce by 50%

Abbreviation: SID, once a day.

If a serum chemistry analyzer or plasma-equivalent meter calibrated for cats is used (eg, AlphaTRAK from Abbott Animal Health), increase the target blood glucose concentration by about 1 mmol/L, 18 mg/dL, or adapt the normal range reported for cats as the target nadir glucose concentration (eg, change 3–4 to 4–5 mmol/L, change 54–72 to 72–90 mg/dL).

human and whole blood or plasma, will determine the exact cut points used to adjust insulin dose. If a serum chemistry analyzer or plasma-equivalent meter calibrated for feline blood is used (eg, AlphaTRAK, Abbott Animal Health, Abbott Laboratories, Abott Park, Illinois), the measurements at the low end of the range need to be adjusted and are 30% to 40% higher than for a whole-blood meter calibrated for human blood. The doses, when using such measuring devices, should be changed as follows: the lower limit of the range should be adjusted accordingly by adding approximately 18 mg/dL (1 mmol/L) to the value listed in the protocol in **Table 2**. For example, a target value of more than 54 mg/dL (>3 mmol/L) becomes more than 72 mg/dL (>4 mmol/L) when using a serum chemistry analyzer or a meter calibrated for feline use. Alternatively, use the normal range for feline blood glucose concentrations as a target when using a meter calibrated for feline blood. Most of the major human brands of glucometers now report plasma-equivalent values and these are intermediate between those measured by whole-blood meters calibrated for human blood and plasma-equivalent meters calibrated for feline blood. Be aware that test strips sold by the major human companies now provide plasma-equivalent readings, even when used in older whole-blood meters, although their accuracy and precision are not as good in the whole-blood meters. Typically, the maximum dose of glargine or detemir that at cat will require will be 1.7 to 2.5 IU per cat twice daily. However, some cats will only require a maximum dose of 0.5 IU twice daily and others a maximum dose of 9.0 IU twice daily.

In general, with the availability of accurate and precise glucometers calibrated for feline blood, their use is recommended in preference to meters calibrated for human blood because of the greater accuracy for blood glucose measurements around the normoglycemic range. Using meters calibrated for feline blood facilitates the use of target blood glucose concentrations in the normal range reported for cats and avoids some of the confusion with human meters whether they are reading whole blood or plasma. It is very important that the meter only requires a small volume of blood to obtain a reading; in the author's experience (Rand), meters requiring only 0.3 μL provide a reading significantly more often than those that require a droplet of 0.6 μL or more. Although many lancing devices designed for humans are available, experience by the author (Rand) has found that the Abbott lancet successfully creates a blood bleb of sufficient size to obtain a reading with the Abbott AlphaTRAK meter more often than several other lancing devices that have been trialed.

Dosing protocol on glargine/detemir and intensive blood glucose monitoring

Intensive blood glucose control requires dedicated owners that are willing to monitor their cat's blood glucose concentration a minimum of 3 times per day (on average 5 times per day). The advantage of this approach is that it allows for optimal blood glucose control, maximizing the chances for remission.[3]

The exact protocol is described in **Table 3**. The protocol was tested in cats using human whole-blood glucometers.[3,6] If a serum chemistry analyzer or plasma-equivalent meter calibrated for felines is used, the measurements at the low end of the range need to be adjusted and are 30% to 40% higher.

Dosing protocol for PZI

Detailed dosing algorithms for PZI for home use by owners have not been described in the literature. All published protocols relied on owner perceptions of clinical control together with in-clinic glucose measurements, in contrast to home testing plus veterinary examinations. One such protocol[9] is as follows:

- PZI is dosed twice daily.

- Nine-hour blood glucose curves are performed weekly in the veterinary clinic for at least 4 weeks.
- Blood glucose concentrations should be maintained between 100 and 300 mg/dL, with the nadir between 80 and 150 mg/dL.
- If nadir is less than 80 mg/dL, decrease the dose by 25% to 100% depending on the clinical signs.
- If nadir is more than 80 mg/dL to less than 150 mg/dL, the dose remains unchanged.
- If nadir is more than 150 mg/dL, increase the dose by 25% to 100%, depending on the clinical signs.
- After 4 weeks, if the cat is still not well controlled, dose adjustments should continue to be made appropriately until the blood sugar levels reach satisfactory levels.

Administration of small doses of glargine and detemir: dilution and insulin dosing pens

Administering small doses of detemir and glargine to cats is problematic and limits their use when doses of less than 1 IU are required.

Insulin dosing pens, such as the HumaPen Luxura HD (Eli Lilly, Indianapolis, IN) and the NovoPen Junior (United States)/Demi (other countries) (Novo Nordisk, Copenhagen, Denmark), are specifically designed for use in babies and children and deliver accurate and precise insulin doses in 0.5 IU increments. In some cats, particularly those going into remission and regaining some beta cell function, dose adjustments for glargine and detemir are required in increments less than 0.5 IU.

One method of administering small total doses of less than 2 IU is to hold the syringe vertically with the needle pointing down and with consistent pressure on the plunger, count the number of drops in 2 IU of insulin. Once the owner learns to reproduce the consistent pressure to deliver the same number of drops per unit, 2 IU can be drawn up and the required number of drops can be discarded before administration. For example, for some syringe-needle combinations there are 5 drops per unit of detemir, allowing increments of 0.2 IU if the client can consistently reproduce the slow pressure to deliver this number of drops per unit.

Another method frequently used by diabetic cat owners contributing to the German Diabetes-Katzen Forum is to use an insulin syringe ruler. Paper rulers are available for download at the following Web site: http://www.diabetes-katzen.net/insulinruler.pdf. Cat owners can print out paper rulers from computer files containing templates, cut them to size with scissors, laminate them, and then, holding the ruler up next to the insulin syringe, measure dose adjustments of 0.1 IU (**Figs. 1** and **2**). For ease of handling when drawing up a dose using such a ruler, glargine or detemir insulin cartridges can be attached to a vertical surface with Velcro (Velcro USA Inc, Manchester, NH) stickers (**Fig. 3**). Insulin syringes have been reported to be quite inaccurate at a total dose of one unit (1 IU).[10] Clinically, this inaccuracy can be dangerous. The position relative to the top of the needle at which the scale is printed on the syringe varies between syringes within a given brand, causing some of the difficulties in achieving a consistent dose. When comparing 20 to 30 syringes from one batch, it is generally easy to see that the relative position of the scale is not identical in all syringes. Anecdotal observations by diabetic pet owners are that differences can be 0.25 IU, in some cases almost 0.5 IU. Using the same ruler for each new syringe might help reduce the variation in the dose associated with variations in graduation markings between different syringes. However, clients should use only one brand of syringe for a given ruler; using the same ruler between different brands of syringes or different sized syringes is dangerous because the barrel diameters may be different.

Table 3
Dosing protocol for glargine or detemir and intensive blood glucose monitoring with a minimum of 3 blood glucose measurements per day (average 5) using whole-blood human glucometers

Parameter Used for Dosage Adjustment	Change in Dose
Phase 1: Initial dose and first 3 d on glargine	
Begin with 0.25 IU/kg of ideal weight BID Or If the cat received another insulin previously, increase or reduce the starting dose taking this information into account. Glargine has a lower potency than lente insulin or PZI in most cats.	
Cats with a history of developing ketones that remain >16.6 mmol/L (>300 mg/dL) after 24–48 h	Increase by 0.5 IU
If blood glucose is <2.8 mmol/L (<50 mg/dL)	Reduce dose by 0.25–0.5 IU depending on if cat is on low or high dose of insulin
Phase 2: Increasing the dose	
If nadir blood glucose concentration is >16.6 mmol/L (>300 mg/dL)	Increase every 3 d by 0.5 IU
If nadir blood glucose concentration is 11.1–16.6 mmol/L (200–300 mg/dL)	Increase every 3 d by 0.25–0.5 IU depending on if cat is on low or high dose of insulin
If nadir blood glucose concentration is <11.1 mmol/L (<200 mg/dL) but peak is >11.1 mmol/L (>200 mg/dL)	Increase every 5–7 d by 0.25–0.5 IU depending on if cat is on low or high dose of insulin
If blood glucose is <2.8 mmol/L (<50 mg/dL)	Reduce dose by 0.25–0.5 IU depending on if cat is on low or high dose of insulin

If blood glucose at the time of the next insulin injection is 2.8–5.5 mmol/L (50–100 mg/dL)	Initially test which of the alternate methods is best suited to the individual cat: 1. Feed cat and reduce the dose by 0.25–0.5 IU depending on if cat is on low or high dose of insulin 2. Feed the cat, wait 1–2 h; when the glucose concentration increases to >5.5 mmol/L (>100 mg/dL), give the normal dose. If the glucose concentration does not increase within 1–2 h, reduce the dose by 0.25 IU or 0.5 IU (as above). 3. Split the dose: feed cat and give most of dose immediately and then give the remainder 1–2 h later, when the glucose concentration has increased to >5.5 mmol/L (>100 mg/dL). If all of these methods lead to increased blood glucose concentrations, give the full dose if preinsulin blood glucose concentration is 2.8–5.5 mmol/L (50–100 mg/dL) and observe closely for signs of hypoglycemia. In general for most cats, the best results in phase 2 occur when insulin is dosed as consistent as possible, giving the full normal dose at the regular injection time.
Phase 3: Holding the dose: aim to keep blood glucose concentration within 2.8–11.1 mmol/L (50–200 mg/dL) throughout the day	
If blood glucose is <2.8 mmol/L (<50 mg/dL)	Reduce dose by 0.25–0.5 IU depending on if cat is on low or high dose of insulin
If nadir or peak blood glucose concentration is >11.1 mmol/L (>200 mg/dL)	Increase dose by 0.25–0.5 IU depending on if cat is on low or high dose of insulin and the degree of hyperglycemia
Phase 4: Reducing the dose: phase out insulin slowly by 0.25–0.5 IU depending on dose	
When the cat regularly (every day for at least 1 wk), has its lowest blood glucose concentration in the normal range of a healthy cat and stays less than 5.5 mmol/L (100 mg/dL) overall	Reduce dose by 0.25–0.5 IU depending on if cat is on low or high dose of insulin
If the nadir glucose concentration is 2.2–<2.8 mmol/L (40–<50 mg/dL) at least 3 times on separate days	Reduce dose by 0.25–0.5 IU depending on if cat is on low or high dose of insulin
If the cat decreases <2.2 mmol/L (<40 mg/dL) once	Reduce dose immediately by 0.25–0.5 IU depending on if cat is on low or high dose of insulin
If peak blood glucose concentration is >11.1 mmol/L (>200 mg/dL)	Immediately increase insulin dose to last effective dose
Phase 5: Remission: euglycemia for a minimum of 14 d without insulin	

If a serum chemistry analyzer or plasma-equivalent meter calibrated for cats is used (eg, AlphaTRAK from Abbott Animal Health), increase the target blood glucose concentration by about 1 mmol/L, 18 mg/dL, or adapt the normal range reported for cats as the target nadir glucose concentration (eg, change 2.8 to 3.8 mmol/L; change 50 to 68 mg/dL).

Fig. 1. An insulin syringe filled to 0.8 IU using an insulin syringe ruler. The ruler has been calibrated for BD Micro-Fine+ Demi 0.3-mL U-100 syringes (Becton Dickinson, Franklin Lakes, NJ), containing half unit markings, widely available in Germany, Switzerland, and Austria. The ruler is available for download at the following address: http://www.diabetes-katzen.net/insulinruler.pdf. Note that in Europe, a comma is commonly used instead of a decimal point. The syringes themselves are printed with 0,3 mL, and the packaging for the syringes is also labeled 0,3 mL.

Detemir is a relatively stable insulin and can be mixed with other shorter-acting insulin (eg, lispro or neutral protamine Hagedorn [NPH]). A special diluting medium is also available from Novo Nordisk; but in some countries (United States and Australia), the company will not supply veterinarians. Detemir can also be diluted with sterile water or saline (Shaun O'Mara, 2012 Novo Nordisk, personal communication). However, diluting with saline or water also dilutes the antimicrobial additive (metacresol). Therefore, because of the risk of bacterial contamination, it is recommended that the dilution be done just before the administration of insulin. Having said that, veterinarians in the past have previously diluted other insulin in the bottle and kept it refrigerated and discarded it in about 30 days. Based on experience with other insulin, with time, stability and action seemed to be adversely affected. Therefore, because of the risk of bacterial contamination and unknown changes in time with efficacy, diluting detemir in the bottle is not recommended.

For glargine, neither dilution nor mixing is recommended by the manufacturer and leads to formation of a cloudy precipitate in the syringe. However, human patients

Fig. 2. Measuring ruler strips on a key chain for easy handling. Note that in Europe, a comma is commonly used instead of a decimal point. In this picture, the ruler is labeled with commas (eg, 1,3 IU rather than 1.3 IU).

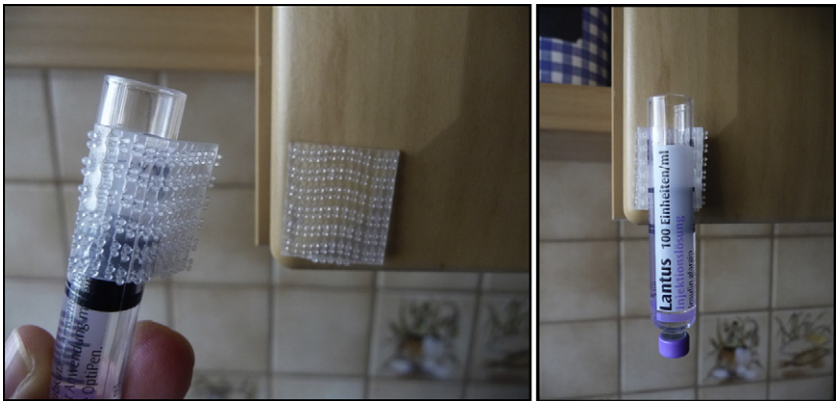

Fig. 3. Velcro sticky-back tape allows insulin cartridges to be temporarily attached to a flat, vertical surface (eg, above counter kitchen cabinet), which leaves both hands free: one for the syringe, one for the measuring ruler.

are mixing glargine with other insulin; a study reported no adverse effect on glycemic control as measured by continuous glucose monitoring.[11] Glargine is a relatively stable insulin; therefore, it would be expected that it could also be diluted with insulin or saline just before injection. Be aware that it will form a cloudy precipitate in the syringe. Mixing in the bottle is not recommended because of problems with accuracy of dosing when the insulin is a precipitate, bacterial contamination and the unknown effect on stability and efficacy.

In general, mixing glargine and detemir with a shorter-acting insulin will change the action profile, mainly of the shorter-acting insulin compared with giving separately. Mixing detemir with a rapid-acting insulin analogue like insulin aspart will reduce and delay the maximum effect of the rapid-acting insulin compared with that observed following separate injections.[12] Mixing glargine with rapid-acting lispro also markedly flattens the early pharmacodynamic peak of lispro.[13]

Storage of glargine and detemir

Glargine is marketed for human use with a 28-day shelf life at room temperature after opening. It is fairly fragile but is chemically stable in solution for 6 months if kept refrigerated.

Detemir is marketed with a 6-week shelf life at room temperature after opening. The US FDA microbiology group has a policy of not recommending longer expiration periods on multiple-use injectable medication vials, even if a preservative is present, because of the risk of bacterial contamination.

Glargine and detemir preparations contain the antimicrobial preservative metacresol, which is thought to be bacteriostatic, not bactericidal. It is most effective at room temperature, hence the recommendation by the manufacturer to keep the vial at room temperature after opening. The FDA thinks the vials have a reasonable probability of becoming contaminated with microbes through multiple daily punctures to withdraw medication past the arbitrary expiration date. However, in veterinary practice, owners of diabetic cats routinely use refrigerated glargine or detemir for up to 6 months or more with no evidence of problems. Owners should be instructed to immediately dispose of any insulin appearing cloudy or discolored because this can represent bacterial contamination or precipitation.

Urine testing

Although suboptimal, the level of glycosuria can be used to guide dosing decisions in cats receiving insulin, such as glargine and detemir. Adjusting the insulin dose based on the level of glycosuria is more successful with glargine or detemir than with lente insulin because lente has an inadequate duration of action, which inevitably results in glycosuria, and this is unassociated with the appropriateness of dose. However, the absence of glycosuria is less meaningful for indicating remission when using glargine or detemir than it is with lente insulin because glargine- or detemir-treated cats with excellent glycemic control typically have no glycosuria, even when they still require insulin. A urine glucose concentration of 3+ or more (scale 0–4+) generally indicates the need for a dose increase (increase dose by 0.5–1.0 IU). A negative urine glucose reading indicates excellent diabetic control or remission (decrease dose by 0.5–1.0 IU).

Urine glucose testing should only be considered if the blood glucose measurement is absolutely not possible.

Fructosamine

Fructosamine reflects blood glucose levels over the period of 2 to 3 weeks and measures the levels of glycated proteins in the serum.[14] Therefore, fructosamine is most useful when the indicators for glycemic control are conflicting, for example, the owner reports signs of good clinical control at home or, alternatively, is unaware of how the cat is progressing clinically at home, and blood glucose concentrations measured in the hospital are high. In these cases, fructosamine is a useful indicator of the mean blood glucose control achieved at home.

Using fructosamine to guide insulin-dosing decisions is not recommended because it is not an accurate guide to recent blood glucose concentrations. Blood glucose monitoring, ideally at home by the owner using a glucometer, is preferred.

Low-Carbohydrate Diet

Cats are obligate carnivores, and it has been demonstrated that glycemic control increases when diabetic cats are fed a low-carbohydrate, high-protein diet (<15% metabolizable energy).[15,16] Wet-food diets more often have a lower carbohydrate content than dry-food diets and are also beneficial in that they have been shown to facilitate weight loss in obese cats.[17–20] The highest remission rates described in diabetic cats have been achieved in studies using glargine or detemir, in which cats were fed a high-protein, low-carbohydrate wet-food diet with 6% or less energy from carbohydrates.[3,4,6] Although the choice of an optimal insulin increases the probability of good glycemic control and remission, the choice of diet also has an important effect.[16] The use of low-carbohydrate food (12% compared with 26% energy from carbohydrate) resulted in statistically higher remission rates (68% compared with 41%) despite similar protein levels.[21] There have been no comparative studies using diets with lower carbohydrate levels, such as those reported to be associated with remission rates of more than 80% in newly diagnosed diabetic cats ($\leq$6% of energy from carbohydrate).

COMPLICATIONS

Hypoglycemia

The only prospective study comparing the frequency of clinical hyperglycemic events in glargine (8 cats) and PZI (8 cats) found that one case occurred in the PZI group and no cases in the glargine group. Blood glucose curves were initially performed weekly in this study and the overall length of the study was 4 months.[4]

A detailed examination of both biochemical and clinical hypoglycemia was made in 2 studies using intensive blood glucose control and glargine (55 cats) or detemir

(18 cats). In these studies, euglycemia was the goal of the dose adjustment algorithm and each cat's blood glucose concentrations were measured an average of 5 times per day (minimum 3 times per day) until stabilization. In the glargine cohort, the median length of time on protocol for insulin-dependent cats was 10 months and 2 months for cats that achieved remission. In the detemir cohort, the median length of time on the protocol for insulin-dependent cats was 10 months and 1.7 months for cats that went into remission. Although biochemical hypoglycemia was frequently observed, only a single episode of mild clinical signs of hypoglycemia was observed in each cohort, which resolved with home treatment by the owner.[3,6]

In a large prospective study of cats receiving PZI (133 diabetic cats [120 newly diagnosed and 13 previously treated]), whereby blood glucose curves were measured on days 7, 14, 30, and 45 (last day of study), the dose was adjusted with the intent to maintain peak blood glucose concentrations between 100 and 300 mg/dL and the blood glucose nadir between 80 and 150 mg/dL. Biochemical hypoglycemia was defined as a blood glucose nadir less than 80 mg/dL and identified in 151 (22%) out of 678 nine-hour serial blood glucose determinations and in 85 (64%) out of 133 diabetic cats. Clinical hypoglycemia was observed in 2 cats, which required veterinary treatment; there were 26 further episodes of owner- or veterinarian-reported clinical signs that were consistent with clinical hypoglycemia. However, these events were not confirmed by blood glucose measurements.[9]

Based on these reports, it suggests that PZI has a higher probability of causing clinical hypoglycemia than glargine or detemir. Also, the frequency of clinical hypoglycemic episodes was not higher using intensive blood glucose control regimens with frequent blood glucose measurements aimed at achieving euglycemia, presumably because low blood glucose concentrations were quickly identified and the insulin dose adjustments made appropriately.

Ketoacidosis

Ketosis and ketoacidosis were not observed in any of the studies described with any of the protocols described previously.[3,4,6,9] However, it should be noted that diabetic ketosis and ketoacidosis are reported in approximately 60% to 80% of diabetic cats at diagnosis based on plasma beta hydroxybutyrate measurements, although ketonuria is present in a smaller percentage of cats. Care should be taken to identify such animals, give a sufficient insulin dose, and stabilize the animal before sending it home.

Both glargine and detemir have a lower potency than insulins, such as NPH and porcine lente insulin. Care should, therefore, also be taken when switching a cat from a more potent (NPH or porcine lente insulin) to a less potent insulin (glargine or detemir) to avoid the development of ketosis. For example, if the cat typically has hyperglycemia and nadir glucose concentrations are 100 mg/dL (5.5 mmol/L) or more, with porcine lente insulin, an equivalent dose of glargine or detemir should be given and increased within 24 to 48 hours if needed.

Handheld point-of-care blood ketone monitors are highly effective tools for identifying ketotic cats.[22–24] They are more sensitive at detecting ketosis because they allow the identification of increased beta hydroxybutyrate concentrations in the blood before increased concentrations can be measured in the urine by dipstick, which measures predominantly acetoacetic acid. The time between increased blood concentrations of beta hydroxybutyrate and a positive urinary dipstick reading is, on average, 5 days; earlier detection of ketosis facilitates earlier treatment.[25] These monitors are also relatively inexpensive and can be used as glucometers with different test strips. Thus, they can be easily used by owners at home to monitor their cat's blood glucose and beta hydroxybutyrate concentrations.

Insulin Resistance

Acromegaly

Acromegaly in diabetic cats is thought to be common. In a study of 184 variably controlled diabetics, 59 showed a marked increase in insulinlike growth factor 1 (IGF-1) (>1000 mg/dL). Of the 18 cats that were available for subsequent imaging studies, 17 had a confirmed diagnosis of acromegaly.[26] Although the actual prevalence among diabetic cats is unknown, acromegaly should be considered in any cat in which the insulin dose with glargine or detemir is more than 1.5 IU/kg. In these cats, it is recommended that IGF-1 be measured and if increased, brain imaging should be considered for a definitive diagnosis. Rarely, some cats with confirmed acromegaly are insulin sensitive and have even achieved remission without specific treatment of acromegaly (Stijn Niessen, 2012).

Cats with acromegaly are typically insulin resistant.[27] In the authors' experience, most cats with acromegaly will require doses of more than 2 IU/kg of glargine or detemir. In fact, cats with such high exogenous insulin requirements invariably also have elevated IGF-1 concentrations when these are measured.

Some animals with acromegaly will require more than 100 IU glargine or detemir per day and may, in some cases, still be hyperglycemic. Cats requiring such high doses of insulin may benefit from combining glargine and detemir with doses of regular insulin to reduce hyperglycemia. Regular insulin is also somewhat less expensive than glargine or detemir, which reduces the financial burden on owners of acromegalic cats. Alternatively, glargine can be administered subcutaneously and intramuscularly simultaneously. When given intramuscularly or intravenously, glargine acts like regular insulin and can also be used this way for the treatment of diabetic ketoacidosis (Detemir does not act like regular insulin via these routes[28]). Cats with acromegaly can achieve remission if the tumor is removed with surgery and less commonly if treated with radiation (refer chapter on Hypersomatotrophism by Niessen SJM, Church DB and Forcada Y elsewhere in this issue).

Hyperthyroidism

Hyperthyroidism is a common endocrine disorder in older cats. Typically, diabetic cats with concurrent hyperthyroidism will not require substantially higher doses of insulin but are resistant to achieving remission or will relapse from diabetic remission. In fact, hyperthyroidism is commonly associated with relapse from diabetic remission (observed in the German Diabetes-Katzen Forum) and a cat's thyroid status should be evaluated should such a relapse occur.

Hyperthyroid diabetic cats (even those receiving medication and, thus, euthyroid) may be more difficult to regulate than nonhyperthyroid diabetic cats.

Insulin-induced rebound hyperglycemia (Somogyi effect)

An evaluation of the prevalence of the Somogyi effect in a cohort of 55 cats undergoing intensive blood glucose control with glargine showed that blood glucose curves that were consistent with insulin-induced rebound hyperglycemia were very rare despite the frequent occurrence of biochemical hyperglycemia.[29]

The fluctuations of blood glucose concentration that were commonly observed in the first weeks, and more rarely months, following the initiation of treatment with glargine, and which might be mistaken for the Somogyi effect, generally resolved with time using consistent dosing.

The dose of glargine or detemir should be reduced if the cat develops asymptomatic or clinical hypoglycemia but not when the blood glucose concentration is high and poorly responsive to insulin.

REMISSION

Remission Rates Comparison

There is only one controlled prospective study in 24 newly diagnosed diabetic cats that compared remission rates between glargine, PZI, and porcine lente insulin. Blood glucose curves were initially performed weekly, and insulin dose adjustments based on an algorithm were also performed weekly. Cats were fed a low-carbohydrate diet (<8%–10% metabolizable energy). The reported remission rate for glargine was 100% (8 out of 8 cats), and this was significantly higher than the remission rate for PZI (38%, 3 out of 8 cats) and porcine lente insulin (25%, 2 out of 8 cats).[30]

The largest study for cats treated with glargine involved 55 previously treated diabetic cats. In this cohort, 91% of the cats had been previously treated with another insulin, predominantly porcine lente insulin, for a median of 15 weeks. Most cats were also fed a very-low-carbohydrate wet-food diet (<6% metabolizable energy) on the first insulin, yet did not go into remission. On switching to glargine, they continued to be fed a very-low-carbohydrate diet. Cats were monitored using home blood glucose measurements at least 3 times daily. The insulin dose was adjusted using an algorithm aimed at achieving euglycemia. Provided the protocol was initiated within 6 months of diagnosis, high remission rates (84%) were achieved. For cats that began on the protocol more than 6 months after diagnosis, a much lower remission rate was achieved (35%). The overall remission rate for all cats, regardless of when the protocol was initiated after diagnosis, was 64%.[3]

For detemir, a cohort of 18 diabetic cats, previously mainly treated with porcine lente insulin, was evaluated using an insulin dosing protocol aimed at achieving euglycemia and fed a very-low-carbohydrate wet-food diet. The remission rates were very similar to those achieved with glargine: the overall remission rate was 67%. Again, there was a difference between cats that initiated the protocol shortly after diagnosis and those that did not; for cats that began the protocol before or after 6 months of diagnosis, remission rates were 81% and 42%, respectively.[6]

No significant differences in terms of remission rate could be identified between glargine and detemir (see **Table 3**).[3,6]

Further recent studies examining the efficacy of PZI in newly diagnosed and previously treated diabetic cats did not explicitly examine remission rates.[8,9]

Relapse

Very few studies have examined the rate of relapse in cats that are in diabetic remission, presumably because of the relatively short time period that many such studies are run. Two studies that have examined the rate of relapse in previously treated diabetic cats treated with glargine or detemir found relapse rates of 26% and 25%, respectively **Table 4**.[3,6]

Frequent causes of relapse are hyperthyroidism and chronic pancreatitis. Very few such cats achieved a second remission because additional glucose toxicity of a further diabetic episode has destroyed too much beta cell mass for a second remission to be possible.

The more quickly effective treatment with insulin begins and the return to euglycemia is achieved, the more likely a second remission will become. It is advisable that cats whose blood glucose concentrations increase and are consistently at more than 120 mg/dL be treated with insulin, beginning with small doses that can be ramped up quickly.

Table 4
Remission rates in diabetic cats comparing different insulins and different time points of initiating treatment

Insulin Type	Newly Diagnosed, Using 1–2 Weekly Blood Glucose Monitoring (%)	Previously Treated with Other Insulin, <6 mo Since Diagnosis, Using Intensive Blood Glucose Control Protocol (%)	Previously Treated with Other Insulin, >6 mo Since Diagnosis, Using Intensive Blood Glucose Control Protocol (%)
Glargine	100	84	35
Detemir	n/a	81	42
PZI	38	n/a	n/a

Abbreviation: n/a = not available.

SUMMARY

- Glargine and detemir are associated with the highest remission rates reported in cats and the lowest occurrences of clinical hypoglycemic events.
- Overall, glycemic control using glargine/detemir is superior to PZI because of the long duration of action these insulin analogues, which reduces periods of hyperglycemia.
- However, it should be noted that no insulin type has been effective in controlling hyperglycemia in all cats, even with twice-daily administration.
- There is a narrow window of opportunity of treatment for diabetic cats; initiating effective treatment within days of diagnosis leads to remission rates more than 90% using nonintensive blood glucose control protocols with glargine/detemir. After this, if intensive blood glucose control is initiated with glargine/detemir within the first 6 months, remission rates are reported to be 81% to 84%. If intensive blood glucose is started more than 6 months after diagnosis, remission rates decrease to 35% to 42%.

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