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Treatment of Feline Diabetes mellitus: New Concepts and Current Thoughts

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Overview:

The treatment of Diabetes mellitus in cats involves dietary therapy and insulin therapy initially. The first question that should be answered is: what is the goal of therapy? There are 2 possible goals:

1. Attain diabetic remission, where the patient remains asymptomatic and euglycemic, without the need for insulin therapy
2. Maintain diabetic control, with diet and insulin, to maintain the patient with a stable body weight, good appetite, no PU/PD, and avoid hypoglycemia.

Regardless of the goal, diet change and insulin therapy should be started as soon as possible after diagnosis. In a recent study, 81-84% of cats went into diabetic remission when treated with glargine insulin and low carbohydrate diet when treatment was initiated within 6 months of diagnosis. If treatment was not initiated within 6 months of diagnosis, remission rates dropped to 34%.

Dietary therapy:

Diets that are low in carbohydrate and high in protein have been shown to reduce post-prandial hyperglycemia and insulin concentrations in healthy cats. Feeding a low carbohydrate diet has been shown to reduce blood glucose and fructosamine values in diabetic cats, reduce insulin requirements, and lead to increased rates of diabetic remission. Current diet recommendations include Hill's MD, Purina DM, or Royal Canin Diabetic DS.

Obesity in cats leads to reduced insulin sensitivity, and it is recommended that an obese diabetic cat have their food intake restricted, so that weight loss occurs at a rate of 1-2% of body weight per week. Most commercial weight loss diets for cats are low fat, high carbohydrate diets, and these should be avoided in a diabetic cat. Obese diabetic cats should be fed a low carbohydrate diet, with calorie restriction to ensure weight loss.

Insulin therapy:

Recent research has shown that glargine (Lantus) and detemir (Levemir) insulin lead to a higher diabetic remission rate than other insulin types, and are currently the insulin of choice for newly diagnosed diabetic cats. Glargine is a synthetic insulin (in 100U/ml vials) produced by

recombinant DNA technology using E.coli. The insulin has a pH of 4, and when the acidic solution interacts with the relatively neutral pH of the subcutaneous tissues, it forms microprecipitates. These microprecipitates have a long and relatively constant systemic absorption. Glargine should not be mixed or diluted.

The pharmacokinetics and pharmacodynamics of once daily administration of glargine compared with two of the most commonly used insulin preparations, porcine lente and protamine zinc insulin (PZI) has been reported in healthy cats. Once daily administration of glargine was found to have a similar mean daily glucose concentration and area under the 24hr glucose curve to PZI, and both were significantly lower than lente insulin. Glargine produced a glucose nadir later than PZI or lente, and had longer duration of action than lente. The duration of action for glargine was 22hrs, and 5 of the 9 cats had significantly decreased blood glucose concentration at 24hrs.

The administration of glargine once daily versus twice daily has been compared in healthy cats. A longer effect was achieved by administering glargine BID compared to once daily. Once daily administration of glargine has been shown to produce similar remission rates to twice daily dosing of lente insulin. Because excellent glycemic control facilitates remission and superior glycemic control is achieved if glargine is injected twice daily, twice daily dosing should be used for at least the first 4 months of treatment after diagnosis.

The usefulness of glargine for treating newly diagnosed diabetic cats has been evaluated. Twenty-four newly diagnosed diabetic cats (17m,7f) were treated with either glargine, PZI or lente (n=8 for each group) and fed a very low carbohydrate-high protein diet (Purina DM canned). Insulin was initially given at 0.5U/kg BID SQ if blood glucose was >360mg/dl, and 0.25U/kg BID SQ if blood glucose was <360mg/dl. Insulin dose was then adjusted based on serial blood glucose curves and water intake. Cats were defined as achieving diabetic remission if normoglycemia was maintained without insulin therapy for more than 2 weeks. At diagnosis, there was no statistical difference between treatment groups for age, body weight, body condition score, or concentrations of fructosamine, blood glucose, B-hydroxybutyrate or bicarbonate.

There was a non-significant trend for glargine treated cats to have lower 12hr glucose concentrations after 10 and 17 days, than those treated with PZI or lente. Mean 12hr blood glucose at 4 weeks was significantly lower for glargine than PZI and lente treated cats. Fructosamine concentration after 4 weeks of treatment was significantly lower than at diagnosis for glargine treated cats but not for PZI or lente.

All 8 cats treated with glargine went into diabetic remission within 4 months of beginning treatment, while 3 cats treated with PZI and 2 cats treated with lente achieved diabetic remission.

Only 1 cat treated with glargine required an increase in insulin dose above 0.5U/kg BID, and 7 of 8 cats had their insulin dose reduced in the first 3 days of treatment. This is an important factor when initiating treatment with glargine, as there is usually a carry-over effect from the previous dose that may take several days to become apparent.

A significant finding in this trial was that no cat treated with glargine showed clinical hypoglycemia despite having biochemical hypoglycemia, while 2 cats treated with lente and 1 cat treated with PZI insulin exhibited signs of clinical hypoglycemia.

Glargine can be safely instituted at 0.5U/kg bid and serial blood glucose curves should be obtained daily for 3 days either in hospital or at home. When evaluating the blood glucose curve using glargine, it is often more useful to assess pre-insulin glucose concentration rather than the nadir glucose. It may take 3-5 days for a good glucose-lowering effect to be seen in the glucose curves, possibly because of the long duration of action and carry-over effect of glargine. Almost all cats will need to have their initial dose reduced within 2 weeks and many will achieve remission within 4 weeks.

Detemir is a newer synthetic insulin analogue with long duration of action that is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*). The insulin molecule is modified by the addition of an acylated fatty acid chain that enables reversible binding to plasma proteins, especially albumin, from where it is released slowly into plasma. This modification leads not only to a prolonged absorption from the subcutaneous tissue, but slow release from plasma proteins. Detemir results in similar remission rates and time to remission as glargine, but the median maximum dose used (1.75 IU/cat BID) is about 30% less than with glargine (2.5 IU/cat BID)

Monitoring and adjusting insulin dose when using glargine or detemir should be based on a number of parameters including; pre-insulin and nadir glucose concentration, water intake, urine glucose concentration and clinical assessment.

PZI has been used in cats for many years, with good success, at a starting dose of 0.5U/kg BID. Treatment with PZI insulin has been shown to significantly improve control of glycemia in newly diagnosed diabetic cats and poorly controlled diabetic cats previously treated with other insulin preparations. PZI-VET has been used with excellent results in diabetic cats, but as an animal-derived product it may be problematic. It can be expensive and difficult to obtain. Recently, recombinant human insulin was formulated as a protamine zinc product (PZIR). Studies have shown that PZIR is safe and effective in the management of feline diabetes. PZI insulin is a good insulin choice for management of diabetes mellitus in cats.

NPH and lente (Vetsulin) insulins have a nadir that is typically much shorter than for glargine, detemir or PZI insulin. In general, these insulin types are not recommended as first line treatments for diabetes in cats.

Adjusting Insulin Doses:

Parameters for changing insulin dosage when using insulin glargine or detemir together with home monitoring of blood glucose concentrations have been developed and tested in more than 70 diabetic cats. In cats which had been previously treated for a median of 4 months with intermediate-acting insulin and had failed to achieve remission, 81-84% achieved remission with

detemir or glargine and home monitoring using the intensive protocol, provided the changes were instituted within 6 months of diagnosis. Higher remission rates are achieved if the protocol is instituted immediately after diagnosis. Blood glucose was measured at least 3 times daily with a glucometer. Until blood glucose concentration is well controlled, frequent monitoring of blood glucose concentration should be encouraged. It is recommended that as a minimum, owners measure blood glucose just before the morning and evening insulin injection and again before they go to bed, 6 days out of 7 and on one day in the week, measure blood glucose every 3-4 hrs throughout the day until they go to bed. If they are able to measure blood glucose more frequently than 3 times a day on more than one day a week, that is preferable, but it requires a committed owner with the time available.

In cats, dose adjustments for intermediate-acting (lente or NPH) insulin rely on measurement of nadir glucose concentration which occurs typically 3-6 hours after insulin administration. Pre-insulin blood glucose concentration is only used as an indicator to decrease the dose in cats on intermediate-acting insulin. For cats on intermediate-acting insulin, blood glucose concentration should be measured every 2 hours until a nadir (usually 3-6 hrs after insulin) is evident. Use of intermediate acting insulin in cats significantly reduces remission rates and is not recommended in newly diagnosed diabetic cats. For long-acting insulin, dose is adjusted based on pre-insulin blood glucose concentration and nadir glucose concentration.

Single measurements of blood glucose concentration have limited value and can lead to inappropriate dose adjustments unless they are pre-insulin measurements or taken when an animal has signs consistent with hypoglycemia. The time of nadir glucose concentration typically varies considerably between days and is usually missed if a single measurement of blood glucose is being made, although in cats treated twice daily with intermediate-acting insulin, the nadir is usually between 3 and 6 hours, with 4 hours typical. For long-acting insulin in cats, nadir glucose concentration may occur just prior to the next insulin dose.

Because normoglycemia is being aimed for, choice of glucometer is important. To avoid clinical hypoglycemia or unnecessarily high blood glucose concentrations, it is important to recognize and understand whether the meter is calibrated for human or cat blood. In a recent study, six portable blood glucose meters were evaluated in dogs, and there were substantial differences in accuracy. Meters calibrated for human diabetic patients that report glucose concentrations for whole blood (not plasma-equivalent) read cats' blood glucose on average 25-35 mg/dL lower than actual blood glucose concentration. The protocol for intensive blood glucose control utilizing home monitoring recommends dose increases to initially achieve a nadir (lowest glucose concentration) close to the normal range and then later to increase dose so the majority of maximum concentrations are also in this range. For meters calibrated for feline blood, aim for a range of 80-130 mg/dL and for meters which give readings in whole blood and calibrated for human patients, use a target range of 50-100 mg/dL.

Parameters used for dosage adjustment when using glargine or detemir:

- Begin with 0.5 U/kg if blood glucose \geq 360 mg/dL or 0.25/kg of **ideal weight** if blood glucose is lower.
- Do not increase in first week unless minimum response to insulin occurs, but decrease if necessary.
- Monitor response to therapy for first 3 days. If no monitoring is occurring in the first week, begin with 1U/cat BID.
- If pre-insulin blood glucose concentration $>$ 220mg/dL, provided nadir is not in hypoglycemic range **or** if nadir blood glucose concentration $>$ 180mg/dL, increase by 0.25-1U.
- If pre-insulin blood glucose concentration 180-220mg/dL **or** nadir blood glucose concentration is 90-179mg/dL, keep the same dose.
- If pre-insulin blood glucose concentration is 120-180mg/dL **or** if nadir glucose concentration is 55-89 mg/dL, use water drunk, urine glucose and next pre-insulin glucose concentration to determine if insulin dose is decreased or maintained.
- If pre-insulin blood glucose concentration $<$ 120mg/dL **or** if nadir blood glucose concentration $<$ 55mg/dL, reduce by 0.5-1U. If total dose is 0.5-1U SID, stop insulin and check for diabetic remission
- If clinical signs of hypoglycemia are observed, reduce dose by 50%.

If blood glucose measurements are not available:

- If water intake is \leq 20mls/kg/day on wet food or \leq 60mls/kg/day on dry food, keep same dose.
- If water intake is $>$ 20mls/kg/day on wet food or $>$ 60mls/kg/day on dry food, increase dose by 0.5-1U.
- If urine glucose is $>$ 3+ (scale 0-4+), increase dose by 0.5-1U.
- If urine glucose is negative, decrease dose until 0.5-1 U SID and then check for diabetic remission.

Pre-insulin glucose concentrations measured at home can be used to safely modify daily doses of glargine or detemir. Cats treated with glargine should have a negative, 1+ or 2+ urine glucose (scale 0-4+) and a value of 3+ or 4+ likely indicates that a dose increase is required.

The good glycemic control achieved when using glargine or detemir likely reverses glucose toxicity of the B-cells, which facilitates endogenous insulin production and a reduced requirement for exogenous administration. Insulin dose may be reduced sequentially as indicated by blood glucose concentration, urine glucose and water intake until the dose is $\frac{1}{2}$ -1U/cat SID. Even if normoglycemic, it is recommended that insulin is not withdrawn within 2 weeks of commencement of therapy. Sequential reduction of insulin dose to $\frac{1}{2}$ -1 U/cat SID is recommended before insulin is withdrawn, and the cat should be carefully monitored afterwards to ensure remission has continued. It is also imperative that cats remain on a low-carbohydrate diet with calorie control to prolong the remission period. Newly diagnosed diabetic cats that have good glycemic control within the first few weeks of therapy are very likely to go into diabetic remission. Cats that have been long-term diabetics are less likely to go into remission, probably because of progressive B-cell loss associated with glucose toxicity.

Oral hypoglycemic agents:

Acarbose is an α -glucosidase inhibitor that reduces intestinal glucose absorption. Acarbose may be beneficial as an additional therapy in cats which require a high carbohydrate diet, provided the acarbose is added to the food and they are meal fed. In diabetic cats with advanced renal disease, dietary management for the renal disease, with a restricted protein diet, should take precedence over dietary management of diabetes. Older cats with renal insufficiency or renal failure would need a low protein, high carbohydrate diet, and could have acarbose added to their food to help with glycemic control. It is generally not effective in the treatment of feline diabetes mellitus alone, but can be used in conjunction with insulin to gain better control of blood glucose.

Sulfonylureas, such as glipizide or glyburide, directly stimulate the pancreas to secrete insulin. These drugs can be used if there are functional *B* cells in the pancreas, and the cat is by definition non-insulin dependent. The recommended dose of glipizide is 2.5mg PO BID. A small percentage of cats will be candidates to respond well to this type of medication.

Difficult to regulate diabetic cats:

When cats treated with insulin fail to stabilize, a number of underlying causes and approaches to treatment should be considered. It is important to remember that some cats take up to 4 months to stabilize. Lente and NPH insulins provide inferior control of blood glucose and are more difficult to adjust to get good glycemic control, and are more likely to be associated with problem cats. These insulins are more often associated with marked changes in blood glucose concentration and clinical hypoglycemia than longer acting insulin such as glargine, detemir and PZI.

The most common problems resulting in poor control are excessive dose, miscalculation of dose, too short duration of insulin action, or poor absorption of insulin. When using lente, NPH or Ultralente, some cats are mistakenly labeled problem cats when the clinical signs are well controlled, but blood glucose measurements are less than ideal. This usually occurs when there are unrealistic goals for glycemic control using these insulins and lack of understanding that for 4 hours twice daily, cats treated with these insulins have negligible blood glucose lowering effect from the insulin. If the glucose nadir is below 180mg/dL after each insulin injection, peak action occurs >3 hours after administration, and hypoglycemia is not occurring, glycemic control is usually adequate. These cats usually have good clinical control (stable body weight, good coat condition, active, alert, water drunk <100ml/kg/24h). Switching to a longer acting insulin such as glargine or detemir will usually improve glycemic control and improve the probability of remission.

Problem cats have persistent clinical signs including polydipsia (water drunk > 100 mL/kg/24h), low body condition score, polyphagia, lethargy, and a poor hair coat; an insulin dose higher than normal (1.5-2 or more U/kg/injection); and either a nadir glucose > 180 mg/dL or hypoglycemia. For problem-solving in problem cats, it is important to first rule-out administration problems. Expired insulin, heat affected insulin (e.g., left in a car in the summer), poor mixing of suspensions (e.g., lente insulin), failure of administration (e.g., injecting through the skin pinch onto the hair-coat), and the presence of air bubbles in the syringe causing a lower administered

dose, all occur regularly in practice. Insulin syringes can be difficult to manage for elderly owners with arthritic hands and poor vision. These owners are often better able to cope with insulin pens. Misunderstandings between the owner and veterinarian regarding the number of units to be administered can occur when using 40U/mL insulin in a 100U/mL syringe, because the cat is only getting 40% of the dose indicated by the markings on the syringe.

In dealing with a difficult to regulate cat, the first step is to watch the owner administer the insulin. If it is an old bottle of insulin, change to a new one. If the cat has been treated for at least 8 to 12 weeks and insulin is being correctly administered, but poor control is still evident, measure water intake over consecutive days at home (measure fructosamine concentration if water intake cannot be measured), and obtain a blood glucose curve.

Poor control may result from an excessive dose of intermediate acting insulin, which may cause apparent insulin resistance (dose >1.5-2 U/injection with persistent hyperglycemia), or short duration of insulin action. In many cats treated with the intermediate-acting insulins such as lente and NPH, these potent insulins rapidly lower blood glucose. This stimulates counter-regulatory responses, even when blood glucose concentration is not in the hypoglycemic range. The resulting counter-regulatory response, through secretion of glucagon, epinephrine, cortisol and growth hormone, increases blood glucose concentration, and causes an apparent short duration of insulin action. Because the glucose lowering effect of Lente and NPH in cats is less than 8 hours, most diabetic cats have blood glucose concentrations of 360 to 430 mg/dl at the time of the next insulin dose, predisposing them to premature counter-regulation. The result is that in some cats, lente and NPH insulin may only lower blood glucose for 2 to 3 hours. This inherent short duration of action of lente, NPH and ultralente insulins, coupled with the response of the hypothalamic neurons, can be very frustrating for practitioners. It also is dangerous for diabetic cats, because their insulin dosage often is wrongly increased. The end result is that the effect of lente, NPH and ultralente is often too short to achieve good glycemic control, and insulin resistance and signs of hyperglycemia and hypoglycemia ensue.

For cats on potent insulin such as lente or NPH, if the cat is polydipsic and insulin seems to have little effect, especially when previously it caused substantial lowering of glucose, or the duration of action seems to be short, there are two options. The preferred option is to switch to glargine or detemir. Alternatively, you could try lowering the dose of insulin to 0.3 to 0.5 U/kg for 10-14 days to see if blood glucose or water intake improves towards the end of the period. If clinical control is not improved with a lower dose, check the glucose response to a standard dose of 0.5 U/kg of insulin, to determine the duration of effect. If the glucose nadir occurs 2-3 hours after injection, switch to a longer acting insulin (glargine or detemir), or increase the frequency of administration to TID. With PZI or ultralente, if there is little response to insulin, try switching to glargine or detemir and slowly increasing the dose until glycemic control is achieved, which may require a dose of 5-10U/cat twice daily in some problem cats.

If there is still polydipsia (water drunk >100ml/kg/24 h) and little glycemic response after 1-2 months at a dose of 5-6U/cat twice daily, check the cat for hyperthyroidism, hyperadrenocorticism, acromegaly or other systemic disease such as renal failure. Some cats

with periodontal disease may have improved glycemic control following dental surgery in combination with short-term antibiotics. In the meantime, increase the dose by 1U every 1-2 weeks until some glycemic response is achieved. Control is achieved in most difficult cats, with the exception of cats with acromegaly, once the glargine dose is 5-10 U/cat twice daily (4-5 U/cat with detemir). Warn the owner that a severe hypoglycemic episode can occur with this protocol, and to be particularly vigilant regarding the early signs of hypoglycemia (lethargy, mental dullness, wobbliness, trembling and dilated pupils). In some cats which appear insulin resistant, but no cause can be found, admitting them to the hospital for carefully observed intensive insulin therapy to normalize blood glucose for several days, may substantially reduce the subsequent insulin doses that achieve control. Most cats are eventually controlled on 1-3 U/cat BID of glargine or 1-2 U/cat BID of detemir, even if they required a dose as high as 5-6 U/cat BID in the first 1-3 months to control blood glucose.

Avoiding and Dealing with Relapse in Remission Cats:

Once remission is achieved, it is likely that the pancreas retains decreased function because of the underlying disease process and damage caused by hyperglycemia. Therefore, situations which reduce insulin sensitivity and require the pancreas to increase insulin secretion to maintain normoglycemia can lead to diabetic relapse, and should be avoided. Medications that produce insulin resistance and hyperglycemia (in particular corticosteroids and megestrol acetate) should be avoided and the cats should continue receiving a strict low carbohydrate diet. Continued once monthly home testing is recommended, to ensure that owners have an up-to-date set of equipment and remain practiced in home testing if a relapse occurs. It is also important to detect early increases in blood glucose concentration before ensuing damage to the pancreatic beta cells occurs. Veterinary exams every 6 months are recommended, including comprehensive blood panels and, when necessary, dental prophylaxis.

Approximately one quarter of cats in remission will relapse and require insulin again. Cats which relapse should be investigated to determine the cause of the relapse. One possible reason for relapse is the development of hyperthyroidism, which is common in older cats. Euthyroid older cats' T4 will gradually drop with age and therefore older cats with rising T4 concentrations or T4 concentrations at the upper end of the normal range should be carefully evaluated for hyperthyroidism.

References:

1. Mazzaferro EM, Greco DS, Turner AS, Fettman MJ (2003) Treatment of feline diabetes mellitus using an α -glucosidase inhibitor and a low-carbohydrate diet, *Journal of Feline Medicine and Surgery* 2003;5(3), 183-189.
2. Nelson RW (2005) Diabetes mellitus. In Ettinger SJ, Feldman EC (Eds.), *Textbook of veterinary internal medicine* (Vol. 2, pp. 1563): Elsevier Saunders .

3. Marshall RD, Rand JS. Comparison of the pharmacokinetics and pharmacodynamics of glargine, protamine zinc and porcine lente insulins in normal cats, *Journal of Veterinary Internal Medicine* 2002, 16(3):358.
4. Marshall RD, Rand JS. Comparison of the pharmacokinetics and pharmacodynamics of once versus twice daily administration of insulin glargine in normal cats, *Journal of Veterinary Internal Medicine* 2002, 16(3):373.
5. Marshall RD, Rand JS. Treatment with glargine results in higher remission rates than lente or protamine zinc insulins in newly diagnosed diabetic cats. *Proceedings 24th ACVIM Forum 2005*.
6. Michiels L, Reusch CE, et.al. Treatment of 46 cats with porcine lente insulin – a prospective, multicentre study, *Journal of Feline Medicine and Surgery* 2008;10, 439-451.
7. Rand JS, Marshall RD Diabetes mellitus in cats. *Vet Clin North Am Small Anim Pract* 35[1]:211-24 2005.
8. Roomp, Rand. Intensive blood glucose control is safe and effective in diabetic cats using home monitoring and treatment with glargine. *Journal of Feline Medicine and Surgery* 2009;11:668-682.
9. Nelson RW, Lynn RC, Wagner-Mann CC, et.al. Efficacy of protamine zinc insulin for treatment of diabetes mellitus in cats. *J Am Vet Med Assoc* 2001;218:38-42.
10. Nelson RW et.al. Field Safety and Efficacy of Protamine Zinc Recombinant Human Insulin for Treatment of Diabetes Mellitus in Cats. *J Vet Intern Med* 2009;23:787-793.
11. Hall TD, Mahony O, et.al. Effects of diet on glucose control in cats with diabetes mellitus treated with twice daily insulin glargine. *Journal of Feline Medicine and Surgery* 2009;11, 125-12. Cohen TA, Nelson RW, et.al. Evaluation of six portable blood glucose meters for measuring blood glucose concentrations in dogs. *J Am Vet Med Assoc* 2009;235:276-280.
13. University of Queensland website, Dr. Rand: <http://www.uq.edu.au/ccah>