

DRAT: THAT DIABETIC CAT!

GETTING A BETTER GRIP ON THOSE HYPERGLYCEMIC FELINES

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Diabetes mellitus (DM) is the second most common endocrine disorder in cats. While we tend to think of diabetes as a disease entity, we should remember that it really is a heterogeneous group of disorders in which insulin production is reduced or in which tissue cells are resistant to the effects of insulin, resulting in impaired glucose homeostasis. Regardless of the causes, from a clinical perspective, diabetes mellitus can be challenging to diagnose and treat in the cat because of this species' stress-induced hyperglycemia.

PATHOPHYSIOLOGY REVIEW:

Insulin is secreted after a meal, to facilitate "tissue uptake, utilization and storage of glucose, fat and amino acids in three primary tissues: liver, muscle and fat. With mild insulin deficiency, decreased transfer of ingested nutrients into tissues causes mild to moderate hyperglycemia. Severe insulin deficiency not only hampers tissue uptake of ingested fuels, but also results in marked glucose overproduction and excessive mobilization of the body's protein and fat stores. Marked insulin deficiency, coupled with a relative or absolute glucagon excess, results in an increased delivery of fatty acids to the liver and their subsequent oxidation to ketone bodies (beta-hydroxybutyrate, acetoacetate, and acetone), culminating in the clinical state of ketoacidosis."¹ In short, there is no insulin available to deliver the glucose into the cells, resulting in cell starvation; polyphagia results with concurrent weight loss. Hyperglycemia results in glucose spilling into the urine and drawing water with it. This causes polyuria and compensatory polydipsia.

The polyneuropathy that occurs in some diabetic cats results in functional, structural and biochemical defects in the peripheral motor and sensory nerves of the limbs. The pelvic limbs are generally affected more than the thoracic limbs.²

CLASSIFICATION AND DIFFERENTIATION BETWEEN TYPE 1 AND TYPE 2 DIABETES:

In human diabetes, Type 1 refers to the condition seen in people who are generally lean, young and prone to ketogenesis. Type 2 DM usually occurs in the older human, who is often obese but is less prone to the development of ketoacidosis. Type 1 DM patients require insulin therapy, while Type 2 may be controlled, at least initially, with weight loss, diet and oral hypoglycemic agents.

In cats, the categorization is not as clear. Generally, diabetes is a disorder of the older, often overweight cat, more similar to the Type 2 human patient. However, often by the time the diagnosis of diabetes is made, these cats are insulin dependent although most are not prone to ketogenesis. In addition to these differences, cats may also develop diabetes secondary to primary pancreatic disease, endocrinopathies (acromegaly or hyperadrenocorticism), or drug therapy (glucocorticoids and progestins).

In Type 1 DM, there is beta cell depletion, resulting in absolute insulin deficiency. In Type 2 DM, the problem is one of insulin receptor and post receptor defects, causing impaired insulin uptake by tissues. This insulin resistance and associated hyperglycemia, causes the beta cells to produce more insulin, thus this state is one of a relative insulin deficiency. Obese cats appear to have a defect in insulin secretion along with a lower tissue sensitivity to insulin.^{3,4} Weight loss results in an improvement in tissue sensitivity, thus weight loss, is not only helpful, but also imperative in treatment.

Another important feature about diabetes in cats is that pancreatic islet amyloid deposits are believed to interfere with insulin secretion, and that oral hypoglycemics (such as the sulfonylureas, glucalrol) may actually *increase* islet amyloid polypeptide (IAPP) deposition.⁵ IAPP is co-secreted with insulin. Islet amyloidosis occurs in 90% of humans with Type 2 DM.⁶

Risk factors include body weight > 7 kg, older age (> 10 years), male gender³, neutered. Unlike in humans, DM does not predispose cats to hypertension.⁷

In the stressed patient, epinephrine release cause hyperglycemia and glucosuria. It is essential to differentiate between this stress response and diabetes. This can be done by either verifying that the hyperglycemia and glucosuria are persistent or request a **fructosamine** level be run on the previously collected sample. Fructosamine measures the protein bound glucose levels over the preceding 10 - 20 days. Similarly, **glycated hemoglobin** is synthesized in red blood cells in an irreversible reaction between glucose and amino acids of the hemoglobin. As glycated hemoglobin levels reflect glycemic control over the preceding 60-90 days, fructosamine detects successful management and changes to management earlier than glycated hemoglobin.⁸

THERAPY AND MANAGEMENT OF THE DIABETIC CAT:

Insulin choice: There are many types of insulin available. Insulins are derived from several sources and have several durations of action. In the United States, the FDA has eliminated any animal sourced insulin from the

market. Thus, beef-pork and beef insulins are no longer available in this country for humans. They are produced from human recombinant technology, giving rise to the "humulin" insulins.

The second part of the label that affects the choice and efficacy is the speed of onset and the duration of the insulin. There are four main categories:

Regular (fast) - rapid onset of action (0.5h), max. effect (1-5h), end effect (8h)

NPH (intermediate) - onset of action (1.5h), max. effect (4-12h), end effect (24h)

Lente - onset of action (2.5h), max. effect (7-15h), end effect (24h)

Semilente - onset of action (1.5h), max. effect (5-10h), end effect (16h)

Combination: 70% NPH: 30% regular - onset of action (0.5h), max. effect (4-8h), end effect (24h)

Ultralente (long acting) - onset of action (4h), max. effect (10-30h), end effect (36h)

Insulin glargine (ultra-long acting) once a day in humans

Remember that these values are for comparison only and that **insulin responses vary with the individual** and that the above listed times are in human patients.

Protamine zinc insulin (PZI) is a long-acting, beef-pork insulin that was considered by many to be the insulin of choice for cats because of its molecular similarity to feline insulin. Despite its long action, it still needs to be administered twice daily. It is not the perfect insulin for every cat, however it may be helpful in patients who are difficult to control with the less expensive humulin insulins.

In Canada, Caninsulin™, an intermediate acting porcine insulin has been available for 5-6 years. Its peak activity is ~3h and duration of 8h. In the United States, this product has recently been released as Vetsulin.

Glargine (Lantus™) is a long-acting human rDNA insulin analog that forms microprecipitates at the site of injection from which small amounts of insulin glargine are slowly released. Thus the glucose nadir occurs later than with PZI or lente. There are several general statements that can be made at this time, based on the use of this insulin is a relatively small number of cats.

- Start at 0.25-0.5U/kg ideal body weight twice daily (BID)
- Do not dilute or mix with anything because the prolonged action is dependent on its pH.
- Opened vials stored in the refrigerator can be used for > 6 months although the label recommendation is for one month.
- Dose changes should be made based on pre-insulin glucose concentration, nadir (lowest) glucose concentration, daily water drunk, and urine glucose concentration.
- Better glycemic control is achieved with twice daily dosing rather than once daily
- More accurate dosing may be achieved using 0.3ml U-100 insulin syringes
- Lantus™ must not be diluted or mixed with any other insulin or solution. If mixed or diluted, the solution may become cloudy, and the onset of action/time to peak effect may be altered in an unpredictable manner.

WARNING: These instructions for using glargine are based on a small number of cats, and caution should be exercised with the insulin until it has been used in a larger number of cats. Because glargine is very long-acting, there is the *potential for prolonged hypoglycemia* if overdosed.

It is critical to know the concentration of the insulin you are using and to match the syringes to that strength. For correct dosage, insulin should be administered using syringes specially calibrated for the strength of insulin used. For example, most insulins are 100 Units/ml (U100) and micro-fine or ultra-fine U100 syringes should be used with them, however, Caninsulin™/ Vetsulin™ is a U40 insulin, and U40 syringes must be used to dose appropriately. Because only small amounts of insulin are often needed in cats, it is helpful to use a 3/10cc or 5/10cc syringe that is appropriately calibrated. This allows even the tiniest dose to be measured accurately.

Regular insulin is used in treatment of diabetic ketoacidosis (DKA); in general, NPH and Ultralente types of insulins (Caninsulin™/ Vetsulin™ or glargine (Lantus™) are the insulins of choice for daily use in non-ketotic cats. The treatment of DKA is beyond the scope of this presentation.

While there are guidelines in choosing the starting dose of insulin for a patient, the maximum DOSE FOR THAT PATIENT WILL BE THE DOSE THAT HE/SHE NEEDS TO RESOLVE HIS/HER CLINICAL SIGNS of excessive urination and drinking, lethargy and weakness. The majority of cats require twice daily injections, regardless of the type of insulin selected.

Client counselling:

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

At this appointment, review the pertinent facts about insulin storage (refrigerator, always), handling (gently), re suspension (gentle figure 8's), drawing up into the syringe, administration (upon exhalation of client, walk through the door of the tent, think canvas, practise on a cat using saline), single use only of insulin syringes for sterility and sharpness sake.

Show the client how to keep the 2 week diary (date, time of insulin administration, dose administered, activity level, BM, amount urinated (# and size of clumps of clumping litter), amount eaten, amount drunk (by difference, measure amount left in bowl the next morning). Counsel on diet to be fed, as determined by the veterinarian. Traditionally veterinarians have recommended higher fiber diet, as these are believed to be absorbed more slowly, thus helping to regulate the blood glucose levels. There is debate as to whether higher fiber is beneficial or not. Lower carbohydrate may be as or more effective. Currently there is also interest in higher protein diets to improve regulation of glycemia. My personal belief, based on (mostly) successful management of feline diabetics, is that cats should have free access to a high protein, lower carbohydrate food all the time, rather than feeding twice daily.

Be sure to counsel on the signs of insulin overdose (and having corn syrup on hand) and ketoacidosis; give them an emergency number to contact.

I do not routinely ask clients to monitor urine glucose at home because even in a "well-regulated" patient, there may be some glucosuria. Measurement of glucose in urine is confusing for clients, veterinarians and veterinary staff. The occasions I feel monitoring urine parameters at home are justified are:

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

A really good chapter to use as a client handout may be found in *Vet Clinics of North America: May 1995, pp 753-759*, entitled: Home management of cats and dogs with diabetes mellitus: Common questions asked by veterinarians and clients, by Drs. Arnie Plotnick and Deb Greco. There is also a terrific information and support site on the Internet: www.felinediabetes.com.

FOLLOW-UP CARE AND MONITORING:

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

At the **blood glucose curve** appointment, hospitalize the cat with food and water, after re weighing him/her and ascertaining what time the insulin was administered and what dose the client gave. If possible, watch the clients administer the insulin from their own bottle, so that you can be sure that insulin handling is correct. Don't assume anything! Measure blood glucose immediately, to get a starting level. Using a 25G needle works well, as a mere drop or two of blood are needed for the portable glucometers. Plotting the values on a graph makes interpretation for staff and client easier. Submit a serum fructosamine as well to determine how the average glycemic control has been over the past 10-20 days.

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

Use of the marginal ear vein is an accurate and easy technique for the measurement of blood glucose.⁹ It is a useful technique in the clinic and, if the concept is introduced to clients with confidence and compassion, many are willing to perform curves at home. In general, these curves are more accurate as the cat's stress level is lower. Additionally, it is valuable for clients to be able to measure a spot glucose if their cat "doesn't look right" before deciding to give insulin or not.

The goals of performing a BG curve are to determine

- 1) whether the insulin is being absorbed
- 2) the glucose nadir
- 3) the duration of insulin effect
- 4) the duration of insulin effect
- 5) and to assess the fluctuations of glucose levels in this individual patient!

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

The "**Somogyi effect**" is rebound hypoglycemia-induced hyperglycemia. If the cat's blood glucose drops too low, the body reacts by releasing catecholamines (epinephrine), glucagon, glucocorticoids and growth hormone. This causes a rapid release of glucose into the serum causing this rebound to occur. It is important to *not* be tempted to increase the insulin dose in these individuals, as this would accentuate the

problem and eventually cause a hypoglycemic crisis. "Spot checks" of blood glucose levels should be avoided as they can be misleading and can mask a rebound effect, and be misinterpreted as needing more insulin.

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

INSULIN RESISTANCE:

Insulin resistance is rare in cats. Defined as peripheral antagonism to the effects of insulin, one sees a patient with persistent hyperglycemia, glucosuria, polyuria, polydipsia, polyphagia and weight loss despite insulin therapy with no beneficial effect occurring with increasing insulin doses. The primary causes of apparent insulin resistance are problems with insulin handling and client administration. Meeting with the client to have them demonstrate their handling and administration technique is advisable. Concurrent illnesses, such as infections (e.g., oral, dermatological, pancreatic, urinary tract), inflammatory bowel diseases, acromegaly, hyperadrenocorticism, and hyperthyroidism should be controlled as well as possible to reduce insulin interference. True immunologic insulin resistance, associated with anti insulin antibodies in cats is rare. Small amounts of insulin antibodies developing, may actually aid in the slower and more even release of insulin throughout the day. If necessary, switching the type of insulin (source) may be advisable if antibody induced resistance is believed to be the problem.

ORAL HYPOGLYCEMIC THERAPY^{10,11}

Clients who are reluctant to administer insulin may ask about alternative therapies. They must be able to administer oral medications consistently. Cats who may be considered candidates for oral hypoglycemic therapy are those with normal to increased body weight, lack of ketones, no history of diabetogenic medications and those with probable Type 2 diabetes without underlying diseases such as pancreatitis or pancreatic tumours. The cat *must* have sufficient beta cell function to respond to these agents.

Agents that promote pancreatic insulin secretion

The sulfonylureas increase insulin secretion but may also cause an increase in hepatic glucose output as well as promoting progression of pancreatic amyloidosis. Response to glipizide therapy has been disappointing. It has been administered at 2.5-5.0 mg PO BID. It is recommended to check the patient every 1-2 weeks for 2-3 months. When the glucose is < 200 mg/dl (< 11 mmol/l), maintain dose and recheck every 2-3 months. If after the initial 2-3 months, the glucose is not below this level, begin insulin therapy. Potential side effects include vomiting: this may resolve if the glipizide is administered with food. Rarely cholestatic hepatitis has been reported, as has severe hypoglycemia. Glimiperide is a new sulfonylurea agent and seems to have fewer side effects than glipizide. Another advantage is that it is dosed once daily at 1-2 mg PO.

Agents that decrease hepatic glucose output

Metformin (GlucophageTM) is a biguanide. These agents act by inhibiting hepatic glucose release and increasing peripheral insulin sensitivity. A recent trial in five cats showed side effects of intermittent lethargy, inappetence, vomiting and weight loss. At 50 mg/cat PO q12h it helped to achieve glycemic control in one cat. The investigators concluded that metformin is beneficial only if detectable concentrations of insulin are present.¹² It is not recommended in humans with renal disease or hepatic dysfunction.

Agents that inhibit intestinal glucose absorption

Alpha-glucosidase inhibitors such as acarbose (PrecoseTM) minimize post-prandial hyperglycemia by inhibiting carbohydrate degradation in the intestine. The dosage in cats is 12.5-25.0 mg PO with meals. It may lower serum glucose levels to the 250-300 mg/dl (< 14-16 mmol/l) range and is used in combination with insulin or other oral hypoglycemic agents in people. They are contraindicated in patients of normal or low body weight as they decrease absorption of carbohydrates. Possible side effects include flatulence, loose stool or diarrhea. The use of a low carbohydrate diet along with acarbose was an effective means of decreasing insulin dependence and improving glycemic control in a study of eighteen diabetic cats.¹³

Agents that improve peripheral insulin sensitivity

The thiazolidinedione compounds such as troglitazone (RezulinTM) improve insulin-dependent glucose disposal and reduce hepatic glucose output by reducing gluconeogenesis and glycogenolysis. In people, use of this drug in early Type 2 DM may slow the progression of diabetes. Dr. Deb Greco has used 200 mg troglitazone PO SID in cats without ill effects, but also without benefit.

Transition metals

Transition metals such as vanadium and chromium have been shown to mimic insulin when administered to mice and rats that had experimentally induced insulin dependent and Type 2 DM. These metals activate glucose metabolism in cells but bypass the insulin receptor and therefore are potentially ideal agents for the treatment of Type 2 DM, which results from a lack of sensitivity of receptors to insulin. Vanadium and chromium do not lower blood glucose in normal animals (unlike insulin). In an USDA study of 180 human

patients with Type 2 DM, 1,000 mg of chromium picolinate once daily helped reduce the classic signs of diabetes and normalized blood levels of hemoglobin A1c.

In cats Dr. Greco has used chromium at a dosage of 200 micrograms/cat daily or vanadium (Vanadyl Fuel™), at 1/2 capsule daily with food. In cats that she felt were in early Type 2 DM, low dose vanadium decreased in blood glucose and fructosamine as well as improved clinical signs such as PU/PD, etc. Initially cats were anorectic and vomited but did not show these effects when vanadium was re-started.

Combining oral hypoglycemics with insulin

Stabilizing a patient with insulin may be advisable when starting oral hypoglycemic agents in order to reduce glucose toxicity. Combining these two modes of therapy may be beneficial in the "sensitive" diabetic who responds to tiny changes in insulin dose and are difficult to regulate. Be cautious of the possibility of creating hypoglycemia.

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