

FELINE DIABETES MELLITUS
From Diagnosis to Therapy
Debra L. Zoran, DVM, PhD, Diplomate ACVIM

Overview of Diabetes Mellitus in Cats

Like the disease in humans, diabetes in cats is a multi-factorial process combining genetic factors with environmental ones. However, there are two factors that likely have a crucial role in determining whether or not diabetes develops, and if diabetes does occur, whether or not it is insulin dependent. The first of these determining factors in the majority of cats is the presence of persistent hyperglycemia (either as a result of the phenomenon of glucose toxicity or due to one of many factors causing insulin resistance), which is general believed to be the first step in the development of diabetes in the majority of cats. Second major factor that influences the course of the disease is the duration and severity of disease that ultimately results in beta cell damage or destruction. Once islet destruction has commenced, the disease becomes less likely to have a reversible outcome and the need for chronic insulin therapy to achieve control of blood glucose is assured. Thus, the classification of diabetic cats into Type I (insulin dependent or IDDM), Type II (non-insulin dependent or NIDDM) or transient diabetics can be very difficult, frequently confusing, and often in error, because some cats appear to not require insulin initially, and then progress to insulin dependency later. Other cats flip back and forth between insulin dependency and not, as the severity of the impairment of beta cell function, insulin resistance, and other factors wax and wane. These apparent flip-flops are understandable when one realizes the huge variation that occurs in these three things that are important in determining the diabetic state in cats: 1) islet pathology may be quite variable (mild to severe, static to progressive), 2) the ability of the pancreas to secrete insulin is dependant on the degree of islet pathology (which can change with time), and 3) the peripheral tissue responsiveness to insulin, which varies due to many factors (e.g. obesity, inflammatory, infectious, neoplastic or hormonal disorders). Each of these different variables can affect the need for insulin, the dose of insulin, and the overall ease of patient management.

Pathophysiology

While figures vary, recent studies indicate that greater than 35-40% of cats in the United States are overweight or obese. There are a large number of factors that contribute to this problem, including sex (intact vs. neutered, male vs. female), age, activity (indoor vs. outdoor), and feeding style (meal feeding vs free choice). However, the fact remains that obesity is a significant contributor to morbidity in middle aged to older cats. Further, as we are all aware, “it is much harder to take it off, than it is to put it on”. One factor that is increasingly being considered, both in the development of and treatment of obesity, is the role of carbohydrates (CHO) as excess calories in diet. Because of the preference for cats to utilize protein as an energy source, CHO in the diet that are not immediately used for energy (e.g. via exercise or other utilization for energy) will be stored as fat. Recent studies have also shown that cats consuming diets containing moderate levels of CHO had lower resting energy rates than cats on high protein, low CHO diets – thus creating the situation that even requires an even lower intake to prevent over-nutrition. Furthermore, diets higher in CHO can be a major contributing factor to development of glucose toxicity which can lead to the development of islet malfunction and ultimately, pre-clinical diabetes mellitus. These factors will be further discussed in the sections below.

Feline Obesity

Recent studies indicate that 25-40% of cats in the United States are overweight or obese. There are a large number of factors that contribute to this problem, including sex (intact vs. neutered, male vs. female), age, activity (indoor vs. outdoor), and feeding style (meal feeding vs free choice). In a recent paper studying the effects of neutering on hormones and obesity, two very important findings were uncovered: 1) after neutering a rapid increase in IGF-1 and prolactin occurs that is closely followed by an increase in body weight, and 2) dysregulation of glucose metabolism (in association with increases in leptin levels that are significant enough to cause insulin resistance). Thus, to prevent the deleterious effects of these hormonal changes, prevention of obesity by reducing food intake and careful monitoring of body weight becomes essential. Further, because “it is much harder to take it off, than it is to put it on”

– it is important to control weight and diet from the onset (in kittens). Another factor that is increasingly being considered, both in the development of and treatment of obesity, is the role of CHO in the feline diet. Because of their metabolic requirement to utilize protein as an energy source, CHO in the diet that are not immediately used for energy (e.g. via exercise or other utilization for energy in addition to the protein they utilize for energy) will be stored as fat. Successful weight loss requires loss of adipose tissue as well as maintenance of lean body mass, as lean body mass is the driver of basal energy metabolism (loss of lean body mass is a major contributor to weight regain as appetite is not reduced and satiety not reached). Several recent studies have evaluated use of a high protein, low CHO diet (protein 45% or higher) for weight loss in cats, and in those studies, all cats lost weight, but maintained lean body mass. Importantly, high protein, low carbohydrate diets not only result in sustained weight loss in these cats, but also in normalization of appetite (reduced urge to eat constantly because they are satiated). Because dry foods must be extruded to form the kibble, CHO are required in the cooking process, and thus, the best commercial diets for achieving a high protein, low CHO profile are canned (e.g. may be adult or kitten) foods. However, it must be stated that high protein, low CHO diets are not “magical” – their profile is ideal for cats, but the number of calories consumed is the critical key to appropriate weight reduction and control. High protein/low CHO dry foods are generally very calorically dense (m/d has 485 kcal/cup, DM has 580 kcal/cup, Ennova ENO has 540 kcal/cup, etc), and can be difficult to feed in appropriate amounts to achieve target calories. On the other hand, canned foods have lower calories/unit (m/d canned has 165 kcal/can, DM has 180 kcal/can, etc). An important consideration is that most cats need to eat no more than their resting energy requirement to stay at their ideal body weight. However, in cats for which weight loss is needed, a reduction of 60-80% of RER will likely be necessary to achieve weight loss. What does this mean? The veterinarian must counsel cat owners both on the type of food and the amount of food they feed their cats to not only prevent obesity, but to treat it when it is present.

The Role of Amylin

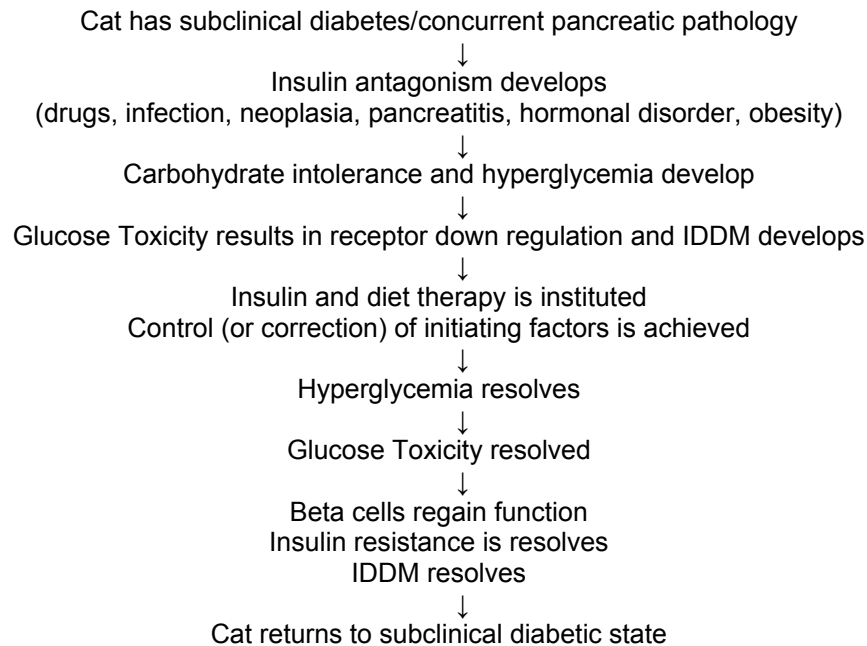
Amylin (or islet-amyloid polypeptide (IAPP) is the principal constituent of amyloid deposited in the pancreas of cats with diabetes. Amylin is co-secreted with insulin by beta cells, thus insulin secretion also results in the secretion of amylin. The role of this neuroendocrine peptide is believed to be as a glucoregulatory hormone counteracting the effects of insulin in the post-prandial state. However, chronic increased secretion of amylin (and insulin), as a result of obesity or other insulin resistance states (e.g. glucocorticoids, acromegaly, infection, etc), results in deposition of amylin in the islet cells as amyloid. Amyloid is toxic to beta cells, resulting in cell death, and thus decreased insulin secretion. If the deposition of amyloid is progressive (e.g. persistent obesity), islet cell destruction progresses and eventually leads to diabetes. It is the severity of this destruction (islet amyloid deposition) that determines (at least in part) whether the cat is insulin dependent or not. Progressive amyloid deposition leads from subclinical or transient diabetes to non-insulin dependent diabetes and finally to insulin dependent diabetes as the islet pathology progresses.

Glucose Toxicity and Transient Diabetes

Approximately 20% (this number may be higher if the condition is recognized earlier) of cats develop “transient diabetes” – whereby within 4-6 weeks of diagnosis and initiation of insulin therapy, the clinical signs resolve, hyperglycemia and glycosuria resolves, and the insulin treatment can be discontinued. If is suspected that these cats have subclinical diabetes (abnormal islets due to amylin deposition –see above), but the condition is uncovered when they undergo stress, receive anti-insulin drugs (e.g. prednisone or megestrol), or develop pancreatitis.

Persistently elevated blood glucose levels also lead to development of a condition called “glucose toxicity” which is a phenomenon affecting the glucose sensing receptors on the pancreatic beta cells – the end result is a down regulation of these receptors – whereby the beta cells simply stop responding to the glucose and stop producing insulin. The end result is development of clinical diabetes; however, if the cause for the persistent hyperglycemia can be reversed (removal of steroids, correction of obesity, treatment of hormonal disorders, etc), and the beta cells are not permanently damaged (e.g. by amyloid deposition), the cat will regain normal insulin secretion and resolution of the diabetic state.

Sequence of events in subclinical/transient diabetes:



Treatment of the Feline Diabetic: A Few Key Points

The goals of management of diabetes in cats:

- Revert a transient diabetic cat to a sub-clinical diabetic if possible
- Elimination of owner observed signs (PU/PD/PP)
- Improved quality of life and normalization of body weight and activity
- Prevention of diabetic complications (hypoglycemia, weakness, chronic infections, neuropathy)

These goals may be accomplished in some cats with diet and drugs alone, others require dietary therapy and short term insulin, other cats require life-long insulin and dietary therapy. There is no “norm” for management of diabetic cats: each is an individual requiring individual attention and adjustments based on their response. However, in management of most diabetic cats, insulin along with dietary therapy is the standard approach. Insulin is important in diabetic therapy of cats, even those with transient diabetes, because it is the most effective tool to control hyperglycemia (which is essential to reversing glucose toxicity and for prevention of further amyloid deposition) – further, since it is impossible (at this point anyway) to determine whether a cat has residual beta cell function (and thus is a transient diabetic) – the most important goal is to reduce hyperglycemia and insulin resistance (reverse obesity, stop steroids). Finally, while periodic blood glucose testing to assess the effectiveness of our therapy is ideal, many cats do not tolerate this (stress hyperglycemia also affects glucose curves!) our methods of monitoring our treatment in cats often has to be modified to balance the needs of the patient.

Insulin Therapy:

Insulin therapy should be tailored to the cat as much as possible within the capabilities of the owner to provide care for their pet. Because of the recent discontinuation of many insulins, there are fewer choices for therapy.

- Humulin® N or Novolin N (Novo Nordisk®) are the only remaining human recombinant intermediate acting insulins available. These are U-100 insulins and when used in cats should be used with a 1/3 cc U-100 syringe for accurate dosing. In cats, these insulins typically have a 8-10 hour duration of action so must be given every 8-12 hours to provide adequate control.

- Lantus® (glargine) is a unique human insulin analogue marketed as a “peakless insulin” – meaning that it serves as a low level or baseline insulin for humans. In cats, this insulin is not peakless, but it is a long acting, slow onset, minimal curve, insulin in cats that is proving to be highly effective for management of newly diagnosed diabetic cats.
- PZI (protamine zinc insulin, a beef or beef/pork mixture) is available from IDEXX/Blue Ridge Pharmaceuticals (products from compounding pharmacies are available). This is a U-40 insulin that has been used with good results in cats due to its longer duration and generally predictable response in cats.
- The newest insulin available to veterinarians is Vetsulin (pork origin insulin labeled for use in dogs). This insulin is likely to have an onset and duration similar to Humulin N and thus may not be ideal for achieving good control when dosed twice daily. Vetsulin is a U-40 insulin.
- **Humulin N, PZI and Lantus are the insulins of choice for cats**
- Most cats, at least initially –even with Lantus – require twice daily dosing of insulin to gain control of the hyperglycemia. Lantus and PZI may be effectively used once daily in some cats.

The human insulin analogue, glargine, has been increasingly used in the treatment of newly diagnosed diabetic cats with impressive results. This insulin is not peak-less in cats, as it is reported to be in humans, for which it was formulated as a “background” insulin to provide a low level, but continuous insulin source throughout the day. Because this insulin has lower pH, it is slowly released from the sub-Q site where it is injected. This different mechanism of action results in considerable variability in the onset, duration, and degree of action, but initial studies suggest that is an effective insulin in cats. Glargine should be given at a low dose (0.5U/kg), once or twice daily for 3-5 days (it takes several days before the effect will be seen). After 3 and 7 days, a blood glucose curve (or spot check) is performed to determine whether the dose needs to be increased in that cat – adjusting the dose downward by 0.5 U if the nadir is < 200. Typically, once the cat has been on this insulin for 7-10 days, the curve will flatten out due to its long duration and slower absorption (overlap occurs with the injections), and in some cats the dose has to be lowered again. At this point, the cat may only need insulin once daily or if transient diabetes is present, may not need insulin at all. In one study, 3 of 5 cats no longer needed insulin after the first 2-3 weeks of therapy. Careful monitoring of the cat in the first 2-4 months is necessary to prevent hypoglycemia due to the potential for clinical remission to occur. Once the cat stabilizes on the insulin, monitoring urine glucose or water intake (reduction of intake to less than 60 ml/kg/day) along with clinical signs as assessment of an appropriate response, rather than a glucose curve, may be possible in many cats.

Key Point: Insulin Dosing in cats should be conservative (0.25-0.5 U/kg SC once or twice daily – (e.g. 1-2 U/10 lb cat) to prevent hypoglycemia during the initial stages of therapy.

Monitoring Insulin Regulation: Cats Often Require Creativity!

Ideally, the goal is to maintain blood glucose levels in cats between 100 – 300 mg/dl throughout the day (this is slightly higher than dogs). However, what is more important is the owner’s perception of the pet’s health, the physical exam findings (including body weight), and absence of common diabetic complications (neuropathies, infections, PU/PD). Blood glucose curves remain the best way of evaluating the insulin effectiveness – but, because of the problem of stress hyperglycemia and the tendency for some cats to lose their “happy demeanor” in the hospital, this method of monitoring the diabetic is sometimes not possible or even counter productive. The key is cautious interpretation of the curve (don’t micromanage!) – or approach monitoring without the use of a “classic” curve at all.

Monitoring Parameters

The best parameters for assessing the cat’s control and quality of life are: 1) owner’s subjective evaluation of improvement in signs (PU/PD, appetite) and log data, 2) weight changes (e.g. weight loss in an obese cat, weight gain in a thin cat), and 3) general appearance (hair coat, muscle mass and neuromuscular function – ability to jump, climb stairs, etc). Measurement of urine glucose and ketones is often possible for many owners at home, and can help identify unregulated diabetics (ketonuria or persistently high urine glucose) or cats that have transient diabetes and are becoming normoglycemic

(persistently negative urine glucose for more than 48 hr). For newly diagnosed diabetic cats that are losing weight, continual adjustments in insulin (less insulin or switching to once daily) may be needed to prevent hypoglycemia. In some settings, owners in single cat households can measure water intake as a determinant of glycemic control. Normal water consumption for 24 hrs in a cat is 40-60 ml/kg/day. Polydipsia is defined as water intake greater than 80-100 ml/kg/day. Well regulated diabetics will consume 60-80 ml/kg/day or less if eating canned food. Finally, for dedicated owners that have uncooperative cats and are willing and able to monitor blood glucose at home, the use of microlancets for blood collection can provide an alternative. See Table 4.

Serial blood glucose curve generated at home

- Alternative for owners with “uncooperative” cats that are able to learn technique
- Use marginal ear prick technique (a lancet can be obtained from human pharmacy – Microlet automatic lancing device from Bayer). Read more about this in chapter on feline diabetes in Feldman and Nelson.
- Drop of blood collected onto glucometer strip
- Typically measure BG every 3 hours over day (4 times)
- No need for restraint (a major cause of stress hyperglycemia)
- Accuracy of results has been shown to be similar to BG results from venipuncture
- Glucometers **routinely** under (or over) estimate BG levels – so caution advised in interpreting results or fine-tuning levels too much!
- Best glucometers at this time: Accucheck® or Glucometer EliteXL
- Biggest problems with this approach: owners become overzealous (monitor BG too often) or attempt to alter insulin levels themselves. Must emphasize need for veterinary advice in altering insulin levels.

It is best to make changes in insulin in small increments (1 U at a time), then allow a period of adjustment before re-measuring blood glucose curves.

In cats for which home monitoring is not feasible, and for which serial blood glucose curves in the hospital are unreliable (due to stress effects), serum fructosamine (SFr) concentrations can still be used to provide a degree of information about the cat’s clinical status. Fructosamines are glycated proteins found in blood of diabetic cats. This glycosylation is an irreversible change, it is non-insulin dependent, and results in glucose being bound to proteins that can be measured in serum. These proteins have a circulating half-life of approximately 1-3 weeks (depending on the protein), and this is why they can be used as a measure of glycemic control.

- In cats that experience stress hyperglycemia or are unmanageable for BG curves, this test offers a method of assessing relative glucose control.
- What this test cannot do is: 1) assess insulin effect (is it working?), 2) assess the glucose nadir (how low does the BG go?), or 3) what is the duration of insulin effect (would another insulin be better?) – only a glucose curve can do those things.
- SFr should be normal in a cat with stress hyperglycemia, so it is a useful test to rule out this phenomenon in diagnosis of feline diabetes.
- Normal SFr = 190-365 umol/L
- Good to Excellent control, SFr = 350-450 umol/L
- Poor control, SFr > 500 umol/L

Adverse effects of insulin therapy in cats

Hypoglycemia is a very important potential problem in diabetic cats because of the potential for their diabetes to be transient and reversible. For this reason, it is vital that cat owners understand hypoglycemia, what it looks like (cats have more subtle signs), and what to do if it occurs. The most overt signs of hypoglycemia are neurologic because of the obligate need for glucose in the CNS: weakness,

lethargy, and stumbling are early signs, later the signs develop into dementia, depression, seizures, collapse or coma. However, because many cats tend to sleep/nap a lot during the day – assessment of lethargy or weakness may be difficult. Further, many cats do not show overt signs of hypoglycemia until the onset of seizure activity – thus, prevention of hypoglycemia is critical.

- Hypoglycemia may be averted in some cats if food is available at all times (this will work well if the cat is a nibbler) or if a mid-day snack is made available (timer food bowls work well for this purpose). A mid-day (and mid-night) meal is especially important in recently diagnosed diabetic cats - if no one is at home most of the day – as the most likely time of reversion to normoglycemia after starting insulin therapy is in the first 2-4 months of therapy. However, if the diabetic is obese, calorie and portion control will still be essential to allow the needed weight loss required to control the cause of the insulin resistance.

Dietary Management of Diabetes in Cats

For all diabetics, the goals of therapy include restoration of normal fasting blood glucose concentrations, normalization of body weight (loss or gain), and reversal or attenuation of chronic complications of diabetes (UTI, neuropathy, etc). In cats, a combination of dietary therapy and insulin supplementation is necessary to control the disease and reverse the clinical progression. For many years, veterinarians applied similar dietary approaches for management of diabetic cats and dogs. However, in recent years, an approach to feeding cats based on their strictly carnivorous nature (and physiologic adaptations), has become the standard of therapy, and has had excellent results. The reason for this is that most cats (including normal cats) fed typical feline diets (e.g. dry, CHO based foods) have mild, but prolonged (18-24 hr) post-prandial hyperglycemia. High protein, low carbohydrate diets provide protein (which the cat needs for energy, insulin stimulation, and maintenance of lean body mass), and have very low levels of CHO (to reduce postprandial hyperglycemia, reduce excess energy from CHO and improve glucose tolerance).

Diets with increased amounts of insoluble fiber that have been traditionally recommended for diabetic cats may reduce the glycemic load (by reducing absorption of glucose in the intestine) just as they do in dogs, but may not be as effective in inducing weight loss (without loss of lean body mass). Further, these high fiber diets are CHO based, and recent studies have shown that better glycemia control is achieved with low CHO diets. In cats with transient or non-insulin dependent diabetes, feeding the high protein/low CHO diet along with addition of an oral hypoglycemic agent may be sufficient for management of the disease. However, most cats require some insulin – even if it is just for a short time – and in this setting, high protein/low CHO diets provide a more appropriate nutrient profile, often result in reduced insulin requirements by 1/2 or more, and will normalize body condition (obese cats tend to lose weight, lean cats tend to normalize their weight). A final note on feeding diabetic cats most feline diabetics respond better to feeding small meals frequently (ad libitum is only acceptable if they are not obese) as it reduces the risk of hypoglycemia and is more likely to result in more consistent blood glucose levels throughout the day. For cats that are obese and diabetic, a high protein, low CHO and low fat (thus, lower calories overall) diet will likely be required to achieve weight loss. The dry diabetic diets are very calorie dense, and thus feeding canned high protein foods (the calories are replaced with water) or low fat, high protein dry foods will be the best alternative.

References

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