**Feline Diabetes Mellitus – The 2014 Approach**
Dr David Miller BVSc Hons MMedVet [Med]
Johannesburg Specialist Veterinary Centre
dave.miller@jsvc.co.za

**Abstract:**
1. The 1st rule of controlling the diabetic cat is to start insulin immediately and do regular curves to get the tightest control possible.
2. The key to managing a diabetic cat is to feed a low carbohydrate, tinned, non fattening, consistent diet.
3. Obesity in cats contributes to insulin resistance, but not all obese cats will become diabetic.
4. Although low carbohydrate diets are essential to try and achieve diabetic remission it is not shown that normal to high carbohydrate diets cause diabetes, rather it is shown to be linked to indoor lifestyle, obesity and inactivity.
5. Cats that shows stress hyperglycaemia, are probably type II diabetics and should be managed with a high-protein low carbohydrate tinned diet, with regular check ups to determine if they also require insulin.
6. One can obtain Diabetic remission or cure within days to weeks in up to 50 - 70% of newly diagnosed diabetic cats. Remission may relapse within weeks to months, so regular monitoring of these cases is essential as cats out of remission cats can regain remission if tight control is achieved.
7. 2x/day insulin must be done in all cats [Glargine / Detemir]
8. Home or in hospital monitoring should be done for the first three days after initiating therapy to prove the cats is not going hypoglycaemic.
9. Pre-insulin values appear to be more helpful than assessing the nadir for adjusting dosage at weekly AT HOME glucose curves.
10. Good glucose-lowering is achieved within 3-5 days but no dose increments should be done within 7 days of initiating therapy.
11. The future? - Incretins are hormones produced in the intestines as a response to diet and cause Beta cell regeneration as well as Beta cells to produce insulin and the liver to stop glycogen breakdown before the food is digested/absorbed.

**Introduction:**
The primary goal of management of a newly diagnosed diabetic is to try and control clinical signs and control body weight and in appropriate cases to attempt to achieve diabetic remission. Diabetes is diagnosed by demonstrating persistent high blood glucose levels. In cats, Diabetes [DM] is the 2nd most common endocrinopathy and is diagnosed relatively late in the disease, usually once BG levels exceeds the renal threshold [12-14 mmol/l] and signs of polyuria, polydypsia and weight loss are already apparent. In all cats that do not have renal disease, all cats with raised BG, above 8 mmol/l [so still below the renal threshold] should be started on a tinned, low carbohydrate high protein diet to help protect the pancreatic Beta cells.
In diabetic cats that achieve remission and are on the correct diet, it has been shown that 25-30% have no evidence of glucose intolerance on a glucose tolerance test, meaning that they are cured.
The remaining 70% have various levels of impaired glucose intolerance, and hence should be classified as pre-diabetic. With appropriate therapy, remission is achievable in over 50% of newly diagnosed diabetic cats and they are able to maintain euglycemia without insulin therapy. Remission rates are substantially lower in cats with longstanding diabetes or any signs or neuropathy or where hyperglycemia has been inadequately controlled because of inappropriate insulin type or dose, or were underlying disease such as acromegaly or cushings disease precludes achieving excellent glycemic control. Whatever the underlying cause of diabetes in an individual cat, chronic hyperglycemia causes toxic damage to beta cells which initially is reversible but later probably irreversible as cats with peripheral insulin resistance produce amyloid together with insulin which is insoluble and its presence in the pancreas causes Beta cell
die off as well as beta cell dysfunction. For those cats not achieving remission, the goals are to resolve clinical signs and avoid hypoglycemia.

Is the Cat Diabetic?
If one is unsure if a hyperglycaemic cat is overtly diabetic:
- Check urine – if there are ketones, it is diabetic
- Check Fructosamine [nb – sample handling] but is often normal in diabetic cats
- Give ½ to 1 IU glargine or detemir insulin daily and monitor response:
  - if diabetic – no or little change to BG for 3-5 days
  - if stress hyperglycaemia – BG will drop considerably
[These cats are probably “type II”, non overt diabetics and should be managed with weight loss, exercise and correct, low carbohydrate nutrition]

Pathogenesis of Hyperglycaemia and Diabetes:
Feline diabetes is "similar but different" to human type II diabetes with too low insulin secretion from the pancreas together with peripheral insulin resistance. There is a strong genetic influence and in Australia and parts of Europe Burmese cats are over represented but the American Burmese do not seem to have the same genes. Diabetic cats are approx. 6 times less sensitive to insulin than normal cats.
1. Insulin resistance:
Most likely due to genotype, obesity and physical inactivity as well as high glucose levels in the blood. To date DM has only been linked to indoor cats that are overweight with low activity levels. High carbohydrate diets have not been proven as causal factor. Acromegaly has an insidious onset, causing severe insulin resistance and thus clinical diabetes is usually the earliest clinical manifestations of acromegaly. Insulin resistance can be quite severe requiring more than 10-20 U of insulin twice daily.
Top tip - Acromegalic cats are often overtly diabetic but often show no weight loss.
2. Impaired Insulin secretion:
Loss of B-cells appears to be secondary to hyper-function.
- Obesity is a major contributor to hyper-function, insulin resistance and amyloid deposition in the pancreas.
- Pancreatitis is seen concurrently in about 30% - 50% of diabetic cats and we do see patients becoming diabetic as a result of chronic pancreatitis. These cats have so much longstanding disease that the beta cells are damaged by the presence of severe chronic inflammatory change and eventual fibrosis.
- Thyroid hormone alters glucose metabolism. While hyperthyroidism is a common condition of older cats, less than 1% of hyperthyroid cats are also diabetic. But, when diabetics becomes hyperthyroid, control of the thyroid disease generally leads to better regulation of the diabetes.
- When cats are forced to put out more insulin they secrete a molecule of amylin in the pancreas.
- Cats with chronic stomatitis/gingivitis can become quite insulin resistant. We used to stabilise cats completely and then clean their teeth, now we get them stable enough to handle a GA and we clean the teeth ASAP.
- Cats with pancreatitis often get waxing and waning insulin requirements because of the flare-ups of their pancreatitis and when the disease is active, they get insulin resistance, they may become overtly diabetic. As the pancreas calms down and the inflammation is subsiding, then we get a reversal of their diabetes mellitus.
- If you want to grow your own diabetic, give an indoor, sedentary, obese, middle-aged male cat repeated shots of Depo-Medrol, so steroids or Ovarid/megestrol acetate as
they are potent potentiaters of insulin resistance.

**Pre-Clinical Diabetes:**
It is believed that a fair number of our feline diabetics spend substantial amounts of time, weeks to months, in a condition of a preclinical diabetes. These are patients with mild hyperglycemia that are not able to make enough insulin to maintain euglycemia. There is a slowly progressive hyperglycemia and then they develop glucose toxicity. In the past one tended to associate glucose Toxicity with very high BG levels but the reality is that BG only needs to be slightly raised. In many cats, blood sugar concentrations that are below the renal threshold, 10 to 14 mmol/l. They are a preclinical diabetic, but that glucose is having negative effects on many cells. The presence of sustained, even modest, hyperglycemia severely affects the islet cells causing shut-down of the beta cells. Some die, some shut down, and thus the cat progresses to a cat that is overtly diabetic. Neuropathies often start to form in this stage and even before these cats are overtly diabetic they are unable to jump properly if not yet plantigrade.

**Client Discussion and Goal setting:**
Once you have the diagnosis you need a very honest conversation with the client. For many of our owners, a diagnosis of diabetes in their cats is overwhelming. They may have very negative associations with the disease with knowledge of diabetes that was poorly managed. They need to be updated re the disease but this must be presented realistically but positively. To do this, you need to know their relationship with the cat, who takes care of the cat, how many people take care of the cat, how easy is it going to be for them to administer 2x/day medication to the cat? When you ask the client for their input, it’s not unusual for clients to ask “Will he lose his leg, will his kidneys fail, will he go blind?” So one needs to handle these fears as well. Next one needs to handle goals. What is their expectation, because one finds there is a tendency for us to define success from a very different perspective to our owners. We have an academic perspective to success and can quote numbers and data points that are very important to us managing a feline diabetic, but ultimately what determines success is the perception of the owner.

**Treatment/Management:**
Goal – resolve clinical signs AND avoid hypoglycaemia AND achieve diabetic remission where possible and unless I am dieting them, I want my feline patients to have a stable body weight.

**General:**
Diabetics that are not keto-acidotic or sick and present with typical clinical signs of polydipsia and polyuria are considered uncomplicated diabetics and are treated with low carb. food and insulin. Remember - some diabetic cats, with mild hyperglycaemia, on correct nutrition, dosed only 1-2 IU glargine BID can become hypoglycaemic within 3 days, so home monitor or hospitalise these cats for the 1st 3 days and perform pre insulin BG levels and then 4, 6 & 8 hour checks. The cat is then sent home and owners perform weekly glucose curves or they are done in hospital.

**Diet:**
Avoid obesity, it induces insulin resistance and independent of obesity, what is eaten directly impacts the health of their pancreatic beta cells due to hormones called incretins. The incretins have recently been highlighted by the recognition that human patients undergoing gastric bypass often go into diabetic remission not solely due to weight loss but due to regrowth of their beta cells! The incretins are hormones and they are released by specialized enterocytes. These enterocytes, sample the nutrients entering the intestine and release endocrine messenger hormones - incretins. Incretins directly impact the function of the liver and the pancreas. They signal the liver and pancreas that food is coming and in response the liver stops releasing glucose by inhibiting gluconeogenesis, and the beta cells release insulin. All this before those nutrients have entered the bloodstream. They also have a powerful trophic effect on the beta cells and Beta cell division and regeneration are enhanced. In human patients with type 2 diabetes mellitus, there are synthetic incretins now licensed for managing their disease and potentially might have some impact on how we manage our feline patients in the next decade as
cats have basically identical incretin molecules to people. The food triggers vary and in people and dogs, incretins are triggered by carbohydrates, fats principally and proteins have a modest effect. In cats, the incretins are triggered by proteins, a little by fats and minimally by carbohydrates, so when we switch a cat to a high protein, high fat, low carb diet, we are enhancing their appropriate endocrine response to food. Ideal carbohydrates levels is a diet that has less than 15% carbohydrates. If the cat is overweight, we aim for gradual weight loss of about 1-2% per week. Pick an ideal body weight, feed the appropriate amount of the appropriate food, to get a slow and gradual weight loss. By reducing obesity, we improve insulin sensitivity and by switching them to a so-called diabetic diet, we actually can enhance beta cell health and, hopefully resume normal function.

There is a 4x higher likelihood to achieve remission in cats on low rather than high carbohydrate diets but when required, dietary management of renal disease using a restricted-protein diet should take precedence over dietary management of diabetes. In these cases, the literature advises that Acarbose can be used to reduce glucose absorption from the gastrointestinal tract but only works well in cats that consume their food within a short time after it is offered and is much less effective in cats which eat multiple small meals during the day. Most feline weight loss diets are low-fat, high-carbohydrate diets and are not recommended for newly diagnosed diabetic cats. Given the frequency of renal disease in diabetic cats (17% in one study in 5-10 year old cats), attention should be paid to the phosphate content of the diet. Many grocery-line low-carbohydrate-high-protein feline maintenance diets are high in phosphate. Cats in stage 1 or 2 renal failure which do not require protein or phosphate restriction should be placed on a low-carbohydrate diet formulated for feline diabetics that is low in phosphate.

**Insulin:**
The long-acting insulin’s, glargine [Lantus] and detemir [Levemir], maximize the probability of remission. Cats presented with diabetic ketoacidosis can be treated with subcutaneous glargine during stabilisation. Glargine is started at 0.25 to 0.5 IU/kg q12h and blood glucose levels 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 to assist in dose changes. It often takes 3-5 days for a good glucose-lowering effect to be seen. Many cats will need to have their initial dose reduced within 2 weeks and many will achieve remission within 4-6 weeks. Detemir is a newer synthetic insulin with long duration due to prolonged absorption from subcutaneous tissue at the injection site and results in similar remission rates and time to remission as glargine. The same dosing protocol as for glargine is used. Although, the median maximum dose was approximately 30% less than with glargine for diabetic cats, this is unlike the situation in dogs, where the dose of detemir is approximately ¼ of that for glargine [starting dose 0.1 IU/kg bd]. Monitoring and adjusting insulin dose when using glargine or detemir should be based on pre-insulin and nadir glucose concentration, water intake, urine glucose concentration and clinical assessment. Owners should be encouraged to do home glucose monitoring to facilitate tight glycaemic control. Home monitored cats still need to return frequently for veterinary visits, ideally once a week, until remission is achieved. Glargine has a shelf-life of 4 weeks once opened and kept at room temperature but up to 6 months when refrigerated.

**Starting a cat on glargine/detemir insulin [see table 1]:**
If BG > 20mmol/L begin at 0.5U/kg ideal body weight BID with maximum dose of 3IU bd while if BG < 20mmol/L begin at 0.25U/kg ideal body weight BID and check for hypoglycaemia for first 3 days [pre insulin and then 4,5 and 8 h post insulin]. After 1 week, perform a 12hr glucose curve [preferably at home] with samples 2 hourly if BG over 6 and hourly if under 6. DO NOT increase dose for the first week. Most cats BG will hardly drop in the first 3-5 days but by day 5-7, good glycaemic control is usually achieved. Decrease dose if biochemical or clinical hypoglycaemia occurs. Recheck glucose curve weekly till cat is controlled and then 3-4 x/year or if signs of hyperglycaemia recur.

**Monitoring cats receiving glargine/detemir insulin:**
When performing a glucose curve, owners to feed cat at home and give insulin and then bring cat in immediately or owners to test pre insulin glucose and then perform curve at home. Cats that usually graze all day should be allowed to do so, while cats with set meals must follow same routine. With the long duration of action of these insulins, in well controlled cats, there should be minimal periods when blood glucose is >14mmol/L. Somygi over swing is rare with Glargine/detemir and cats can have profound hypoglycaemia and not over swing.

**Table 1: Starting Glargine or Detemir insulin.**

<table>
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<tr>
<th>Adjusting dose:</th>
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<td>Once a cat has been partly stabilized on long acting insulin, after minimum 1 week of therapy, the dose may need to be increased or decreased.</td>
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1. **Indications for increasing the dose of insulin**
   a. If pre-insulin glucose conc. is >12mmol/L, then increase dose by 0.25-1.0 U/injection &/OR
   b. If nadir glucose conc. is >10mmol/L then increase dose by 0.5-1.0 U/injection
   c. For well controlled cats after several weeks of therapy, if nadir is over 8 mmol/L, suggests that the dose should be increased 0.25-1.0 U/injection.

2. **Indications for maintaining the same dose of insulin**
   a. If pre-insulin glucose conc. >8 & <12mmol/L AND/OR
   b. If nadir glucose conc. is 5-9mmol/L
   c. For well controlled cats after several weeks of therapy, aim for a nadir of 4-8 mmol/L

3. **Indications for decreasing the dose of insulin**
   a. If pre-insulin glucose conc. <8 mmol/l decrease 0.5-1.0 U
   b. If nadir glucose conc. <3 mmol/l decrease 1 U
   c. If clinical signs of hypoglycaemia develops, then reduce dose by 50%

Altered from table – Dr J Rand, Kirk’s Current Veterinary Therapy, Chapter 44, 2009

**General observations on Detemir/Glargine insulin.**

*Controlling doses may be high* - Some cats initially require a dose of 5 to 8 IU/cat BID to establish glycaemic control. This dose can usually be reduced as insulin sensitivity returns. Cats on these high doses need to be carefully monitored for hypoglycaemia.

Some cats require only small doses of insulin- (<1 U/cat BID) and only go into remission if the dose is reduced very slowly giving the few remaining beta cells a chance to recover.

*Nadirs can be variable* - For many cats, the time at which the nadir (lowest) glucose concentration occurs is often not consistent from day to day, or between cats. Sometimes it occurs somewhere between the two doses, but sometimes the nadir occurs around the time of the next dose. Some cats consistently have their nadir glucose concentration in the evening just before the next insulin injection, and less commonly, it occurs around the time of their morning injection.

*To increase the chance of remission* - we suggest aiming for perfect control or possibly slightly overdosing as soon as possible and then during the first 2 months, provided the veterinarian and owner can carefully monitor the cat. There is the potential risk of hypoglycaemia, but we believe this is outweighed by the benefit of diabetic remission.

Cats requiring intermittent or chronic corticosteroid administration that are either in remission or at risk of developing diabetes can usually safely be placed on 1U SID or BID. It is a very common observation by owners that when long-term stable diabetic cats are changed over to Glargine/Detemir, usually they do better clinically, even if blood glucose results do not support the clinical improvement.

*NB* - For some reason stress hyperglycaemia appears commonly in cats stabilised on Glargine so if you get hyperglycaemia on a curve in hospital first redo the curve in the home environment before calling it treatment failure.
**What is “Diabetic Remission?”**
In a patient that has got hyperglycaemia and pancreatic amyloid deposition, some of the beta cells immediately undergo apoptosis. They have died and they are not coming back. But a proportion of the beta cells are a little bit hardier and they are simply suppressed. Essentially, they are doing nothing but are not dead. If we can maintain euglycaemia by administering appropriate amounts of insulin and by improving insulin responsiveness and correct the diet composition to increase Incretin production, then some of these beta cells are going to be able to recover. When they are restored to function, we get a cat in a diabetic remission.

**Who does, or does not go into Remission?**
The cat that will typically go into remission is a cat that has obvious reasons to be insulin resistant that we can reverse
- An obese, sedentary cat, particularly a cat that is on a high carbohydrate diet, that has had recent been exposed to a glucocorticoid but that is not steroid dependent.
- An episode of DKA does not rule out remission or even change the chances of remission

But Cats with chronic pancreatitis will tend to jump in and out of remission and most of our cats with chronic pancreatitis do not achieve more than a transient remission, they go into remission for two to three months and then the diabetes often re-emerges.

In patients that require steroids to manage some other disease, remission is extremely unlikely but a patient that is given glucocorticoids for a transient skin condition or asthma that is actually manageable through non-injectable/non-oral steroids, are still ideal candidates for remission.

A patient that is really unlikely to go into remission is a cat that is steroid dependent because of concurrent disease like severe intestinal disease or asthma that is not manageable by inhaled glucocorticoids. Also, cats that have got substantial ongoing chronic disease are very unlikely to go into sustained remission like CKD, cats with heart failure, other chronic inflammatory conditions.

The other big reason that makes a cat unlikely to achieve remission would be if it could not transitioned onto a so-called “diabetic diet”.

Any cat with a peripheral neuropathy, is also extremely unlikely to go into remission

BUT
- Never say a cat cannot go into remission because sometimes they will surprise you.

**Determining if the cat is in remission:**
Can occur within 1-4 weeks, on relatively low doses of insulin, or can take months and very high doses of insulin [up to 6 -10 IU bd]. To rapid insulin withdrawal can cause the remission to be reversed and have to be re acquired. Once in remission, cats can tolerate 0.5-1IU total dose OID or bd without clinical signs of hypoglycaemia. Due to this, it is not recommended that insulin therapy is stopped within 2 weeks of initiating therapy and insulin dose should be reduced gradually at approx 1-2 week intervals as described below.

1. **Insulin dose should be gradually reduced by 0.25-1 U/cat/injection/1-2weeks if nadir blood glucose is in the normal range of 4-7 mmol/L or pre-insulin glucose concentration is < 10mmol/L.**
   - Withdraw insulin **SLOWLY** until dose is 0.25 - 1 U once daily (SID).

2. **After a minimum of 2 weeks of insulin therapy or long term tapering of insulin dose, insulin should be withheld and a 12hr glucose curve performed.** If at the next due dosing time the blood glucose is >12mmol/L, then insulin can be re-administered at 1U BID and then gradually reduced again. If blood glucose is <10mmol/L then continue to withhold insulin and discharge with a follow-up visit in 1 week. Water intake and urine glucose should be closely monitored and insulin re-instituted if glycosuria returns or water intake increases.

3. Some cats may have a pre-insulin glucose concentration <10mmol/L within 2 weeks, but insulin therapy should be maintained for a **MINIMUM** of 2 weeks to give beta cells a better chance to recover. Use 0.5-1U BID or once daily until insulin is withdrawn.

4. Maintaining ideal body weight, correct food and avoiding drugs such as corticosteroids and progestins are important in maintaining remission.

5. Monitoring with Fructosamine – special serum handling needed, insensitive, used for fractious cats.
Poorly Controlled Diabetics: Acromegaly in Cats

If we have a large cat, particularly a cat that has not lost any weight associated with his diabetes mellitus, then we should be looking for acromegaly. Chronic hypersecretion of growth hormone [GH] results in acromegaly, causing overgrowth of connective tissue, bone, and viscera. The predominant cause of acromegaly in cats is a GH-secreting tumor of the pituitary gland. Acromegaly occurs in older male cats (90% are male), and they show an increase in body size, prognathia inferior, and weight gain despite poorly regulated diabetes. Acromegaly has an insidious onset and is often not noticed by owners. Due to this, severe insulin resistance and clinical diabetes are usually the earliest manifestations of acromegaly. Insulin resistance can be quite severe, many times requiring more than 10-20 U of insulin twice daily. Diagnosis requires high serum concentrations of GH or insulin-like growth factor (IGF-1). One must wait until the cat has been on insulin for about four to six weeks before you run these tests as the test is unreliable when diabetic cats are poorly controlled. Diagnosis is often based on identification of conformational changes in a cat with insulin-resistant diabetes, persistent increase in body weight despite diabetes, and evidence of a pituitary mass on CT or MR imaging. The short-term prognosis for cats with acromegaly appears to be relatively good. Severe insulin-resistant diabetes mellitus can generally be satisfactorily controlled using large doses of insulin in divided daily doses. On physical exam, things that might guide us to acromegaly would be: changes in the face esp. mandibular enlargement so the shape of their face will actually change. Sometimes it is helpful if clients are able to bring in photographs of the cat from a few years ago. Sometimes you will find that the incisors are separated because the jaw bone is bigger [Like tombstones] and another thing that we see is big feet. Steriotactic radiation therapy or Hypophysectomy is the only current therapy.

Hyperthyroidism in Cats

Insulin resistance has been noted to occur with feline hyperthyroidism. The exact mechanism is unknown. Thyroid hormone administration in normal cats has been reported to result in decreased glucose clearance and endogenous insulin resistance, and similar alterations have been reported in cats with naturally occurring hyperthyroidism. Cats have been shown to still have a decrease in glucose clearance 6 months after treatment with radioiodine. The clinical effect of treating hyperthyroidism on insulin dose is not always consistent. However, resolution of diabetes can occur after treatment in few cats, especially if diabetes is of recent onset. Even if diabetes persists, daily insulin requirements decrease in most diabetic cats after resolution of their hyperthyroidism.

Hyperadrenocorticism in Cats

Clinical signs of hyperadrenocorticism in the cat are much more subtle than the signs that we see in the dog. Signs that are often seen are poor musculature and obvious abdominal adiposity. [cats with little round, fat tummies]. They sometimes have thin skin and sometimes you see blood vessels through the skin on the ventrum and in some cushingoid cats, if you part the hair along the back, you see more skin than you would expect.

Last little GEM's

Frederick Banting, the man who discovered insulin, did this in the 1920s and he was the youngest person to win the Nobel Prize for medicine. Surprisingly, it is to me anyway, his primary job was ...... he was an orthopadaedic surgeon!

AAHA guidelines on management of the feline and canine diabetics - [diabetes management guidelines]

REFERENCES


Website