

Diabetes mellitus

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Diagnosis:

The animal should have a consistent history ie pu/pd, pp and weight loss. Dogs are usually straightforward. Cats are a little trickier. Stress hyperglycaemia can go well above 20 mmol/l AND can spill over into the urine if you annoy the cat for long enough. Usually if the blood sample collection is the only stressor, there won't be enough glucose in the urine to confuse you. Occasionally dogs can do this too. The renal threshold for glucose in cats is 12 - 15 mmol/L and in dogs is about 10- 12 mmol/L. Remember that alpha 2 agonists (xylazine, medetomidine) cause a glucosuria

If your cat has ketones AND glucose in the urine, you can probably believe the high serum glucose is due to diabetes and start insulin

If in doubt, run a fructosamine

Treatment

Before you start treating, determine if the patient has any complications of diabetes. Some of these can cause insulin resistance and make stabilization a lot more difficult.

- **Ketoacidosis** - if also inappetent and vomiting, a ketoacidotic patient should be hospitalized, placed on IV fluids and treated with regular insulin to begin with. You also need to search for the trigger for the ketoacidosis (often a concurrent infection / inflammatory process)
- **hypertension** - control with amlodipine and / or an Angiotensin converting enzyme inhibitor (ACEi)
- **proteinuria** - if you've excluded a urinary tract infection and an ejaculate in the urine, your patient will benefit from ACEi therapy. Diabetic nephropathies are common in humans and there is a huge body of evidence supporting the benefits of ACEi for affected people.
- **cataracts** - 80% of dogs with DM will develop these, often acutely. Diabetic cats will also eventually develop lens opacities but they don't usually affect sight noticeably.
- **uveitis** - usually lens (cataract) induced. Initially treat with Maxidex, Maxitrol or similar. Remember that there will be some systemic absorption of the corticosteroid which will affect your patient's insulin requirements. Ideally remove lens once patient is stable.
- **peripheral neuropathy** - most commonly observed in cats who develop a plantigrade stance.

Screen for common concurrent diseases/conditions:

- pancreatitis
- infections (abscesses in cats)
- urinary tract infection and bladder stones
- hyperthyroidism (cats)
- dioestrus - progesterone causes insulin resistance. Intact female dogs will be easier to stabilize if they are sterilized.
- chronic renal failure
 - NOTE - glucose is dissolved in the urine - and the SG measures dissolved solute. The SG of a diabetic cat with concurrent CRF may not be below 1.035 if there is a strong glucosuria. As a general rule of thumb a 2% or 4+ glucosuria

will increase the urine SG by 0.008 to 0.010 when SG is measured using a the refractometer.

- If your animal has another reason to be pu/pd (eg CRF, hyperthyroidism, Cushing’s etc) you cannot use this sign to determine the efficacy of the insulin.

Initial stabilization

Cats:

- Glargine: start on 0.25 IU/kg bid
- PZI (long acting insulin) : 0.2-0.5 IU/kg bid, maximum total dose of 1 IU per cat per injection
- Caninsulin: start at 0.25-0.5 IU/kg bid with a maximum dose of 2 IU / cat per injection

Dogs:

- Caninsulin: go with instructions in box
- Lente insulin eg Protophane: start on 0.25 IU / kg bid

Important points !

- Start with a lower dose low and work up
- Use insulin *bid* if at all possible
- Don’t change dose more frequently than every 5 days (7d for glargine)
- NEVER base a decision to change treatment on one observation/result on its own

Aim: abolish lethargy, maintain weight, resolve polydipsia (< 60 ml/kg/d if dry food), no ketonuria. May still be slightly glucosuric at times

Get the owner to keep some sort of diary (example below) so that you both can pick up trends in the patient’s progress. What exactly is recorded can be altered to suit each individual.

	date	date	date	date
Insulin am - time and amount				
Insulin pm - time and amount				
Food - amount				
Appetite				
Water intake in ml				
Body weight, condition score				
Habitus				
Urine (accidents indoors, how often waking owner at night)				
exercise				
Hypos / other observations				

Feeding:

Dogs should be fed the same amount of the same food at the same time every day

- **exactly the same amount** of food for each insulin injection to “work on”. While you’re stabilizing him he will probably need to eat more than the weight guide of the food suggests. That’s OK. You don’t want a skeleton, so feed more. But agree on the

amount with the client and keep it the same every day till you both decide to change that amount)

- **exactly the same food** (I don't insist on a prescription diet for dogs unless they have concurrent problems or are proving difficult to stabilize) but do avoid tinned foods with simple carbohydrates.
- **at the same time** every day. Feed twice a day in dogs, at same times as insulin injections - as close to 12 hrs apart as practical / possible for the owners
- **NO TREATS** while stabilizing. You know your client. If this is impossible, the treats need to be incorporated into the daily allowance and kept **the same every day**.

Cats won't eat at prescribed times, usually. I agree on a daily amount of food in grams with the client and ask them to stick to that. It's important that the cat eats approximately the same amount of food after each insulin injection. If your patient eats 100g of food after the morning insulin injection and only 30g after the evening one, you cannot expect to stabilize the cat unless you also vary your insulin dose. This is tedious (because there's a good chance someone is going to need to check blood glucoses in the middle of the night) and it takes a lot longer to stabilise the cat. Feeding a prescription high protein low carbohydrate diet shows significant benefits in diabetic cats.

Glucose toxicity in cats: Chronic hyperglycaemia is toxic to beta cells and decreases insulin release. The pathogenesis is not clear. Once it resolves and endogenous insulin secretion increases, exogenous insulin requirements may fall drastically or even disappear. Insulin resistance may also improve dramatically as the cat loses weight (studies have shown that a 1kg weight gain decreases insulin sensitivity by 30% in cats!). This means you **MUST** monitor diabetic cats closely. Your clients may find this tedious but:

- * if you get your treatment right, you may be able to wean the cat off insulin completely
- * if you don't continue monitoring and the glucose toxicity resolves, the cat will have episodes of hypoglycaemia. If you're lucky, signs will be mild (a bit of a wobble), but if you're not, you could have severe neurological symptoms developing : seizures, brain oedema and resultant blindness (thankfully often temporary).

Possible responses to insulin overdose:

- Somogyi overswing - the high insulin dose causes the glucose to drop below 3.3 mmol/l. This stimulates the release of counter regulatory hormones including glucagon, adrenalin, cortisol - which cause a rapid increase in blood glucose. This yoyo effect happens quickly and is one reason why glucose readings should be taken at least every 2 hrs during a curve. If I have a patient in hospital whose glucose readings are approaching 3 mmol/l I will often take more frequent readings for 2 reasons: so as not to miss a hypoglycaemic episode that needs treatment and also not to miss a Somogyi overswing. Animals that have had a Somogyi overswing may have persistently and uncharacteristically high glucose levels for 2-3 DAYS after the glucose dip. If you happen to do your glucose curve during this time, the patient will often appear insulin resistant. This illustrates why it is important to take a good history and why you should never make a decision about changing a patient's insulin dose based on one test alone - not even if that test is a glucose curve.
- The patient adapts to low glucose (rather like an insulinoma dog). This becomes more likely the more frequently the patient is hypoglycaemic. These patients only show clinical signs when the blood glucose goes really low.
- Clinical signs of a hypoglycaemic episode (hypo) : Tachycardia, nervousness, tremor, strange behaviour, hungry, seizing, coma

Assessing response to treatment:

There are various methods than can be used.

Clinical signs: As per the monitoring table. Urine glucose is included amongst these but should NEVER be used on its own to make treatment decisions.

Example: A patient that is experiencing Somogyi overswing may be persistently glucosuric. If the glucosuria is used as the only measure to determine insulin dose this patient would receive an even higher dose, whereas in fact it needs a dose reduction . Persistent glucosuria is an indication that the patient is not as stable as one would like but further information/testing is needed before you can decide whether a dose increase or decrease would be most appropriate.

It is possible to stabilize a straight forward diabetic using just the clinical signs in the table above.

Fructosamine: This serum protein reflects blood glucose over last 1-2 weeks and requires a single blood sample. It is not affected by stress hyperglycaemia. Fructosamine is however variable in veterinary patients serial measurements are of more use to monitor improvement or control in the individual patient. Fructosamine will not show that there are very low blood glucose nadirs (hypoglycaemia) and will also be falsely elevated by haemolysis and dehydration and falsely decreased by hypoproteinaemia, hypoalbuminaemia, hyperthyroidism, hyperlipidaemia, azotaemia and prolonged sample storage at room temperature

Normal range	225-365 µmol/l
Excellent control	350-400 µmol/l
Fair control	400-450 µmol/l
Poor control	> 500 µmol/l

Glucose curves

How:

- Ideally done at home: spend the time to **train the owner**. This first 2-3 curves are training for owner and patient
- Measure blood glucose every 2 hours -
 - for 12 hours if *bid* insulin
- for 24 hours if *sid* insulin or appears to be doing strange things - (can cut a corner and stop once glucose **starts increasing again** after the last insulin dose)sampling:
 - use an insulin needle to collect sample if taking from a vein. Put a dressing on the vein - you'll be wanting to sample from here many 10s of times, try and keep it healthy!
 - Sample from the edge of the ear to limit ear "squeezing", or if the dog has a tail - clip the hair on the tail tip and use that. This saves the poor ear from being squeezed to death.
 - You can get false low results if the blood drop is obtained with difficulty and mainly tissue fluid or serum is being sampled!
 - Avoid using catheters for sampling if at all possible. Samples are easily diluted by the flush needed to keep the catheters patent resulting in false low readings. This issue means that you need to draw much larger volumes of blood for each sample which can become a problem when your patient is small.

Interpretation of a glucose curve

- Does glucose decrease at all? Is the insulin effective?
- How low does the blood glucose go - is it safe? What is the nadir?
- What is the duration of the insulin's effect?
- How high does it start out at?

Aim : dog - between 3.3 - 10 mmol/l

Aim cat : 3.3 - 15 mmol/l

1. If nadir < 3 mmol/l - decrease dose by 50%
2. If nadir 3-5 mmol/l or is pre-insulin blood glucose < 10 mmol/l - decrease dose by 20%
3. If pre-insulin glucose < 5 mmol/l, leave out next dose of insulin and then decrease dose by 20%
4. If pre-insulin glucose < 3 mmol/l, leave out next dose of insulin and then decrease dose by 50%
5. If nadir > 8 mmol/l and pre-insulin glucose > 10 mmol/l - increase insulin dose by 20%... but if there are no clinical signs of DM, increase by 1 unit only

Glucose curves have limitations

- Curves on sequential days are rarely the same. There are lots of variables - the food, exercise, hormone levels.
- Time to nadir can vary from day to day in THE SAME ANIMAL
 - NB Don't try to save money and cherry pick what times you want to sample. A lot can happen in a 3-4 hr gap and you could be missing a very low nadir. Several studies have shown that glucose curves and the timing of the nadir will vary from day to day in the same dog / cat, even when they are stable. So you cannot assume that a dog that had its nadir at 11 am on a previous curve will do the same again tomorrow even with a very good owner who sticks to EXACTLY the same feeding and exercise regime.
 - The only thing a random blood glucose is useful for is to confirm that a hypoglycaemic event is currently happening.

Stress plays havoc with curves - so try and have the clients do them at home

- Only start a curve after the animal has been stable and nothing has changed in the management for 5-7 days
- NB only change the dose if your glucose curve agrees with the clinical signs and history. If not, try another curve

Problem cases

These are usually animals whose clinical signs persist despite high insulin doses (> 2 IU/kg/dose), animals who have repeated unexplained hypoglycaemic episodes or animals whose insulin requirements appear to fluctuate. To solve these, consider

Visit 1: (a long consultation!)

Status quo: client should have a diary and should be recording. Look at diary (see table above) and determine trends

Food: take a careful history to determine how closely client is sticking to the prescribed schedule. Ask about treats, rewards, what happens during braai's and parties, how are they coping with small kids dropping food, how are they pilling dog. The carbohydrate load may be important esp in cats: amount of carbohydrate in diet as well as the glycaemic index of the source.

Insulin storage and administration

Storage: in fridge, not next to the freezer compartment, in the dark

Ideally replace every 2 months - if in doubt, use a new bottle and see whether problem resolves

Administration: Insulin should be rolled not shaken to re-suspend it otherwise you break the crystalline structure of the protein.

- Check that the client is drawing up exactly the correct amount - without bubbles.
- Check that the syringes are appropriate to the amount of insulin. Get 0.3 ml or 0.5ml syringes if giving small doses.
- Check insulin is injected s/c not into the skin.
- Check that client is rotating the site and is aspirating. Palpate the injection areas for s/c thickening or injection site reactions
- Use the proper insulin syringes with swaged on needles initially to get the client used to injecting: the needles are shorter, the bubbles are easier to see and fewer bubbles form - so the whole process is less stressful. Once the client is comfortable you could progress to 1ml syringes and 25 G needles. Elderly client's patients often have poor near vision and have difficulty seeing the numbers on an insulin syringe. If you're injecting whole units of insulin, an insulin pen that allows the client to dial in the correct number may be a better be

Insulin absorption: absorption of insulin injected s/c can be variable depending on site, scarring, local blood supply and hydration status. Exclude absorption problems causing apparent lack of response by administering a dose of the normal insulin i/m or a dose of soluble insulin i/v and monitoring glucose every 2 hours

Look for complications of diabetes that may have developed since induction of therapy. Apart from uveitis, these don't usually cause significant insulin resistance, but you'd want to manage these problems

- a. ketoacidosis
- b. hypertension
- c. proteinuria
- d. infections
- e. cataracts, (diabetic retinopathy), uveitis, dry eye

Resolve these issues and then (after nothing has changed for 5-7 days).

DO A GLUCOSE CURVE, ideally at home. Consider the following:

- is the insulin having any effect at all. If no, see 1 - 5
- is there a Somogyi overswing. If yes, decrease dose by 50%
- is the effect lasting long enough. If no, change from *sid* to *bid* treatment or change to a longer acting insulin does the insulin drop the glucose levels but just not low enough. If yes, exclude 6 - 8 and increase the dose

Concurrent conditions which may cause insulin resistance:

- Insulin resistance is defined as an insulin requirement of $= > 2 \text{ IU /kg/ injection}$
- Medications: eg prednisolone , progestagens, propranolol
- season/ pregnancy/dioestrus- spay bitch
Common concurrent diseases: pancreatitis, urinary tract infection, dental disease, Cardiac disease, exocrine pancreatic insufficiency and in cats also hyperthyroidism and chronic renal failure, Cushings, acromegaly - more common than you think in cats, any other concurrent infection / illness

- Somogyi overswing: which is defined as a blood glucose < 3.6 mmol/l and > 17 mmol/l in the same 24 hr period. An overswing may be difficult to actually document because the counter-regulatory hormones released after a hypoglycaemic episode may make the animal appear insulin resistant for several DAYS after the hypoglycaemic event. Thus a Somogyi overswing should be suspected if the patient has shown convincing clinical signs of a hypo historically BUT is persistently glucosuric / hyperglycaemic. It is most often documented in animals that given insulin once daily and who have their insulin doses adjusted according to urine glucose.
- (Rapid metabolism of insulin or anti-insulin antibodies)
- glucagonoma, phaeochromocytoma, hypothyroidism - (all very rare in cats)

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