

# An Introduction to the Medical Management of Uncomplicated Feline Diabetes Mellitus and Diabetic Ketoacidosis

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## Classification of Diabetes

Feline diabetes mellitus [DM] has traditionally been classified according to human diabetes classification systems as primary or secondary DM.

### 1. Primary Diabetes

#### a) Type I:

Autoimmune destruction or permanent loss of functional beta cells in the pancreas means these individuals are dependent on insulin for survival [insulin dependent DM or IDDM]. Onset may be sudden or gradual. These cases may present initially in a ketoacidotic crisis. This type of DM is common in dogs but is very rare in cats.

#### b) Type II:

These cases suffer from insulin resistance, variable degrees of beta cell dysfunction and increased hepatic basal glucose synthesis. Insulin production is insufficient to maintain normal blood glucose levels, but sufficient to prevent the development of diabetic ketoacidosis [DKA]. In humans these cases are usually non insulin dependent diabetics [NIDDM] however many cats need insulin to control their symptoms. Type II DM is by far the commonest type of DM in cats.

### 2. Secondary Diabetes:

These cases are caused by drugs or diseases that either impair the secretion of insulin, or its effects at peripheral tissues.

#### a) Drug Induced:

Progestones eg. megestrol acetate [Ovarid] or corticosteroids can both induce diabetes in cats, largely by inducing insulin resistance.

#### b) Disease induced:

Hyperthyroidism, acromegally [a pituitary tumour that produces excess growth hormone], hyperadrenocorticism, pancreatitis and pancreatic neoplasia have all been associated with secondary diabetes in the cat.

Although the above classifications help to describe the underlying cause of diabetes, practically cats fall into two categories.

1. Those that require insulin. A typical example would be the thin ketoacidotic cat.

2. Those that do not initially require insulin. A typical example would be the obese non-ketoacidotic cat.

In Australasia around 70% of cats with DM need insulin, and up to 30% can be controlled without insulin. Around 20% of cats have transient DM, these cats require insulin or oral hypoglycaemics to control their DM at some times and not at others.

## Pathogenesis of Diabetes

### Type I DM:

Auto immune destruction of beta cells leads to a failure of insulin production.

### Type II DM:

Type II DM is the commonest type of diabetes in cats and its pathogenesis is thought to be similar to type II DM in people. In both species the key features are impaired insulin secretion, insulin resistance and increased amyloid deposition in the pancreatic islets. Major risk factors for type II DM in people are increasing age, obesity, physical inactivity and genetic predisposition. These factors also seem to be important in cats.

### Glucose and Lipid Toxicity, What Is It and Why Is It Important?

Prolonged hyperglycaemia and hyperlipidaemia causes impaired secretion of insulin from beta cells. This is called glucose toxicity [GT] and lipid toxicity respectively. GT is an important feature of DM in cats and it leads to impaired insulin secretion within 48 hours of persistent hyperglycaemia. Initially GT is reversible, but with time irreversible structural damage to beta cells occurs. GT explains why measurement of insulin at the time of diagnosis of DM is not helpful in categorising cats as IDDM or NIDDM ie. all diabetic cats are likely to have low levels of endogenous insulin at this time even if they have significant beta cell mass. GT is important as studies in humans have shown that diabetics with the best glycaemic control retain some endogenous insulin production. It is therefore in our best interest to preserve as much beta cell mass as possible in our feline diabetics, by promptly diagnosing and controlling hyperglycaemia. GT also helps explain why more cats with type II diabetes are insulin dependent than people. This is because most cats have prolonged hyperglycaemia

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before DM is diagnosed, so more beta cells are irreversibly damaged. In addition cats have more extensive amyloid deposits in their pancreas than people and amyloid deposition also contributes to beta cell loss.

Recovery from GT takes at least 1-2 weeks of good glycaemic control, but can take up to 2-3 months in some cats.

#### Signalment

Age: middle aged to older [most > 6years]

Sex: males are more commonly affected except for Burmese, where both sexes are equally represented.

Breed: in Australasia Burmese are predisposed [not sex linked, appears to be a polygenic or multifactorial genetic basis]

Body weight: obesity predisposes to DM by inducing insulin resistance.

#### History and Clinical Signs

Classically diabetic cases present with polydipsia [PD], polyuria [PU], polyphagia[PP] and weight loss. However in a recent study of 60 cats with DM the top four presenting signs were PU/PD in 80% of cases, decreased activity in 70%, weight loss in 60% and anorexia in 50%. Only about 15% of diabetic cat owners reported PP. Less common signs were vomiting [30%] and plantigrade stance [10%].

Minor clinical signs detected on physical examination may include hepatomegaly, icterus and poor hair coat.

#### Differential Diagnoses

Important differential diagnoses for cats presenting with weight loss +/- PU/PD include hyperthyroidism, renal failure and infiltrative gut disease [such as inflammatory bowel disease [IBD] and lymphoma]. It is thus important to collect a thorough history, perform a detailed physical examination and run appropriate diagnostic investigations. The latter should include a CBC, serum biochemistry and electrolytes, urinalysis [dipstick, SG, sediment and aerobic culture] and in cats over 6 years old a serum T4. More detailed investigations such as chest radiographs and abdominal ultrasound may also be indicated in some patients.

#### Diagnosis

Specific criteria for deciding exactly when a cat has DM are not clearly defined, however a persistent fasting blood glucose over 12.6mmol/L is likely to lead to complications from hyperglycaemia and warrants therapy. This will also exceed the renal threshold for glucose, which is around 12mmol/L in the healthy cat. **Demonstration of concurrent hyperglycaemia and glycosuria is mandatory for the diagnosis of DM.** Remember that transient stress hyperglycaemia is often not prolonged enough to cause detectable glycosuria. Primary renal glycosuria is rare but it causes glycosuria with a normal blood glucose. I occasionally see renal glycosuria as an acquired complication of chronic renal failure in cats.

Conditions associated with hyperglycaemia in the cat include:

1. Stress [blood glucose of up to 22mmol/L may be caused by stress]
2. Primary DM
3. Secondary DM eg. due to diabetogenic drugs [progestogens and glucocorticoids], hyperadrenocorticism, acromegally, pancreatitis [up to 50% are hyperglycaemic], exocrine pancreatic neoplasia [in one study 18% of cats with DM had pancreatic neoplasia], and renal insufficiency
4. Glucose containing fluids [especially total parenteral nutrition fluids]
5. Lab error

Conditions associated with glycosuria include:

1. DM
2. Renal tubular resorptive defect
3. False positive from Rx eg chlorambucil.

#### How Do I Know If It's Diabetes Or Stress Hyperglycaemia?

Cats are particularly susceptible to stress hyperglycaemia. One author has found that if a cat struggles during blood sample collection, blood glucose will increase by ~ 5mmol/L. However stress can cause blood glucose elevations of up to 22mol/L. Remember also that while some cats show obvious signs of stress, others will internalise stress while appearing calm on the surface. If a cat has concurrent hyperglycaemia and glycosuria but you are uncertain whether it is truly diabetic, the following steps can help clarify the problem.

1. Are there appropriate clinical signs of DM such as weight loss and PU/PD?
2. Repeat the blood glucose. Note that healthy cats do not experience significant post prandial hyperglycaemia, so fasting is not usually required. If blood glucose still exceeds 12.6mmol/L your index of suspicion for DM should increase.
3. Are there ketones in the urine? Ketones are highly specific for DM in the cat.
4. Is there glycosuria at home? Persistent glycosuria at home helps support a diagnosis of DM. Plastic aquarium gravel or commercial non-absorbable kitty litter can be used to collect urine samples at home.
5. Run a serum fructosamine: Fructosamine is a glycated serum protein that reflects the average blood glucose in the preceding 2-3 weeks. The higher the blood glucose the more fructosamine is synthesised. Fructosamine does have limitations however as levels may be normal in very recent onset DM and in hyperthyroidism, and levels may be elevated with dehydration and stress from chronic disease. Although a single fructosamine can be helpful in initial diagnosis of DM, **monitoring trends over time is more valuable** in long term diabetes management. The aim is a steady decrease towards the normal range. In healthy cats fructosamine is usually lower than ~ 360umol/L, well controlled diabetics will have levels below 400umol/L, but adequate control is

often achieved with levels in the 400-500umol/L range.

#### Therapy

Diabetic cats are not always easy to manage, as blood glucose levels can vary from day to day even with the same insulin dose. Cats also seem to be more susceptible than dogs to developing clinical hypoglycaemia if their blood glucose is too tightly controlled.

Clients should be warned that providing an undiagnosed intercurrent disease is not present, it usually still takes 2-3 months to satisfactorily control DM. They should also be advised that 20% or more of cats are transient diabetics whose insulin requirements wax and wane.

#### Exercise:

Although exercise has been shown to improve glycaemic control in people this option is not readily available in cats [but some do love chasing laser lights, or will hunt for their food if it is hidden around the house].

#### Diet:

The evidence to support a high fibre diet in controlling DM is much less compelling in cats than in humans and dogs. In my opinion, dietary control with high fibre diets is really only necessary to reduce weight [and therefore insulin resistance] in obese cats. A recent study looking at the effect of dietary insoluble fibre on control of hyperglycaemia in cats with naturally occurring diabetes mellitus, demonstrated a lower mean preprandial and 12 hour serum glucose compared to cats eating a low fibre diet. However there was no significant difference in glycosylated haemoglobin, mean insulin dose or improved clinical signs between the low and high fibre groups. More recent data suggests that feeding a low carbohydrate high protein diet may be advantageous in diabetic cats. This is supported by a small clinical trial comparing feline Science Diet growth canned food [low carbohydrate, high protein] with w/d [high fibre]. In this study, half of the cats on the growth diet were able to discontinue insulin entirely, but none of the cats in the high fibre group were able to discontinue insulin. Although these findings are preliminary, it begs the question as to whether we should be feeding low carbohydrate diets to our diabetic cats. Be warned that all growth diets are not low in carbohydrates and that dry diets can not be formulated with as low levels of carbohydrate as canned diets.

Healthy cats do not normally experience significant postprandial increases in blood glucose, this means the timing of feeding in relation to the insulin injection is not critical. I encourage owners not to disrupt the cat's normal feeding schedule [if it is a grazer, let it continue grazing]. However if the cat is usually meal fed, I recommend offering the cat a meal, and then giving the insulin injection once you are sure it is eating.

**My goals in controlling cats with DM are:**

- **Control PU/PD [ie, drinking less than 70ml/kg/d at home]**
- **Maintain an ideal and stable bodyweight**
- **Aim for a blood glucose nadir of 7-9 mmol/L. As cats rarely suffer from diabetic cataracts, and as hypoglycaemia is a potentially life threatening event that will cause many owners to abandon therapy, stricter glycaemic control is not usually needed.**

#### A note about in-house glucometers:

Hand held glucometers are a cheap and easy way to monitor blood glucose in the clinic or at home. However they are designed to use human capillary blood and they deliberately underestimate blood glucose levels. The latter provides an early warning of hypoglycaemia to human diabetics. It is thus important that your glucometer is calibrated by your veterinary laboratory. They can let you know if the glucometer is reliable over a range of glucose levels for your canine and feline patients, plus provide you with a factor to multiply your readings by to reflect the true serum glucose [eg based on our lab's calibrations, we multiply our blood glucose by 1.3 to get the actual blood glucose].

#### Oral Hypoglycaemics

Oral hypoglycaemics are most likely to be effective in the early stages of type II DM. Anecdotal evidence suggests they are more effective when combined with a low carbohydrate high protein diet. The most commonly used and studied oral hypoglycaemic agent is the sulfonylurea glipizide.

#### When should I use glipizide?

Glipizide works by several mechanisms including increasing insulin secretion, increasing tissue sensitivity to insulin and reducing hepatic glucose synthesis. In order to work effectively it relies on a functional population of beta cells. As discussed previously many cats with DM are suffering from glucose toxicity and have reduced beta cell mass from amyloid deposition. In spite of this up to 30% of diabetic cats may be successfully controlled with glipizide.

Glipizide [Glipid: Pacific] is given orally at an initial dose of 0.5mg/kg BID. Reported side effects include vomiting, and cholestatic hepatitis [icterus and elevated liver enzymes]. Adverse effects are reported in fewer than 15% of cases and are usually reversible by withdrawal of the drug for ~5 days, and reinstatement at a lower dose [1.25mg/d/7d, then 2.5mg/d/7d, then 2.5mg BID/14d then 5mg BID]. Theoretical concerns that glipizide may exhaust the remaining beta cells or that amyloid deposition may worsen with glipizide use, have to date been unfounded.

Accurately predicting which cats will respond to glipizide and which won't is not easy but it should be considered in the following cases.

- a) Clients who refuse to use insulin. Although glipizide has no advantage over insulin in terms of cost, time required for therapy or frequency of monitoring, it does buy time for the cat. Most owners who refuse to give insulin would euthanase their cat otherwise, but with time many will come around to giving insulin injections if needed, especially when they discover how hard it can be to pill a cat regularly.
- b) b.) Cats who are very sensitive to low doses of insulin [ $<2U$  per dose] and who have repeated problems with hypoglycaemia.
- c) c.) Transient diabetics who fluctuate in and out of DM.
- d) d.) Obese nonketotic cats whose blood glucose is only mildly elevated [14-15mmol/L].

NB. Never use glipizide in an anorexic/ketotic cat or where complications of diabetes, such as acute loss of more than 10% bodyweight or diabetic neuropathy have occurred.

#### Glipizide dosing regime

Day 1: 2.5mg PO BID with food [enhances absorption]. Weigh the cat and ask the client to monitor water intake [less than 70ml/kg/d is ideal] and if possible urine for ketones at home. If the cat is obese start a reduced calorie high fibre diet.

Day 14: Blood glucose curve [ideally measure blood glucose every 2 hours]. **Aim for a blood glucose of less than 12mmol/L** on at least one sample **and resolution of clinical signs**. If clinical signs of DM have not resolved, or if blood glucose does not reduce below 12mmol/L increase to 5mg BID.

Day 28: Continue with 5mg BID if the above treatment goals have not been met, checking a glucose curve monthly for 3 months.

If glycosuria and clinical signs resolve and blood glucose drops below 12mmol/L, glipizide should be tapered or stopped [monitor blood glucose weekly initially as you taper or after you stop].

Stop glipizide and start insulin if the cat develops diabetic neuropathy, if adequate control is not achieved after 12 weeks at 5mg BID or if ketonuria develops.

#### Other oral hypoglycaemics

Glimepiride is a new sulfonylurea with fewer side effects than glipizide. In people once daily dosing is required and preliminary use in cats suggest it may be viable at 1-2mg/cat PO q24hr. Drugs that reduce glucose absorption from the GI tract [acarbose], or increase insulin sensitivity [chromium, vanadium and metformin] are also being investigated in cats. Acarbose may be beneficial at 12.5mg/cat PO q12hr in combination with a low carbohydrate high protein diet. Vanadium may help reduce the dose of insulin required to maintain euglycaemia. Metformin has been associated with unacceptable side effects in cats and is not recommended. Of the above drugs only acarbose and metformin is currently available in NZ.

#### Insulin Therapy

#### Does this cat need insulin?

YES: If there is ketonuria, an acute loss of more than 10% body weight, anorexia or diabetic polyneuropathy. NB, beware that enrofloxacin will give a false positive for ketones in urine.

NO: obese cat with no/minimal weight loss AND no ketonuria [try oral hypoglycaemics, but remember glucose toxicity may reduce the cat's ability to respond to oral hypoglycaemics. Consider using insulin initially in these cats to help overcome glucose toxicity]

#### Special considerations on insulin use in cats:

1. The magnitude and duration of insulin action varies considerably from day to day in cats, especially with the longer acting [ultralente] formulations.
2. Cats have a short duration of insulin action. Even ultralente insulins require twice daily dosing in most cats.
3. Stress hyperglycaemia complicates stabilisation and monitoring
4. Transient DM occurs in ~20% of cats
5. Realistically most cats take 2-3 months to stabilise [providing an undiagnosed cause of insulin antagonistic disease is not present]. Remember to tell the client this!

#### Insulin therapy for the non-ketoacidotic or well ketotic cat:

I prefer to start with lente insulin twice a day. In some cats lente insulins are too short acting and you will need to switch to an ultralente preparation. Other authors recommend starting with ultralente, but around 30% of cats fail to absorb this insulin satisfactorily, and most cats will need twice daily dosing even with ultralente insulin. Feline insulin most closely resembles bovine insulin with just one amino acid difference, however porcine and human insulins are currently the only ones available in NZ. Fortunately, although these latter two insulins differ from feline insulin by two or three amino acids, clinically significant anti-insulin antibodies appear to be very rare in the cat. My preference is to use the porcine insulin Caninsulin, its main advantage being its concentration. At 40U/ml small insulin doses are easier to titrate, particularly when dispensed in the 0.3 or 0.5ml U100 insulin syringes. Using U100 syringes, one unit of Caninsulin equates to 2.5U, thus two actual units of Caninsulin becomes five on the syringe, a much easier amount for the client to accurately measure.

#### Remember the therapeutic goals:

1. Resolve clinical signs at home [water intake  $< 70ml/kg/d$ ]
2. Achieve ideal body weight
3. Avoid hypoglycaemia
4. Nadir of 7-9mmol/L at least once in the day

#### Initial insulin doses:

Fasting morning blood glucose of 12-19mmol/L  
0.25U/kg lente insulin SC q 12hour

Fasting morning glucose > 20mmol/L  
0.5U/kg lente insulin SC q 12hour

Perform a glucose curve on the first day [screens for the occasional cat who is very sensitive to insulin and experiences hypoglycaemia]. Discharge the cat and ask the clients to monitor and record daily water intake, and if possible urine for ketones and glucose at home. The latter can be achieved by using non-absorbable kitty litter and Keto-Diastix [Bayer]. I usually ask the clients to collect urine twice a week, and advise them to contact me if glucose is not detected, or if ketones are detected in the urine. This provides an early warning system that the cat's insulin requirements may be declining, or that diabetic ketoacidosis is developing.

Repeat blood glucose curve every 10-14 days, increasing the insulin dose by one unit per dose until the desired therapeutic goals are met.

### **Blood glucose curves:**

Glucose curves are the gold standard for assessing onset and duration of insulin action and glucose nadir.

#### Protocol:

Be flexible, the cat's injection regime should not be changed on the day of the glucose curve if at all possible ie. ask the client to inject and feed the cat at home if this would normally occur before the clinic opens. This also checks the client's insulin administration technique. A pre-insulin blood glucose can be useful, but is not an essential part of the glucose curve.

Take blood glucose every 2 hours over the day, for a twelve hour period.

Good clinical control

- glucose < 25mmol/l before insulin
- nadir 7-9 mmol/L

If glucose is > 25mmol/L before insulin suspect stress hyperglycaemia/concurrent illness causing insulin resistance/somogyi overswing.

#### Interpreting glucose curves:

##### Nadir

= peak insulin effect, determines **dose** of insulin given

- aim for a nadir of 7-9mmol/L
- do not let nadir get as lower than 5mmol/L
- if nadir is too high AND the cat is still symptomatic, increase insulin dose by ONE unit and reassess in 14 days

##### Duration of insulin action

= time from insulin injection to blood glucose increasing over 14mmol/L

- determines **frequency and type** of insulin administration
- as cats usually require twice daily insulin, this test is most useful for assessing the type of Insulin used. If the duration of action is too short, you will need to change to a longer acting insulin.

- always assess with nadir [eg somogyi typically has a nadir of < 3.6mmol/L, with rebound hyperglycaemia that 'falsely' reduces duration of insulin action]
- best to achieve 'ideal' nadir before altering frequency or type of insulin injections

##### Onset of insulin action

= time for insulin to significantly reduce blood glucose.

- requires adequate nadir to interpret
- helps determine type and dose of insulin
- prolonged onset means prolonged hyperglycaemia and persistence of PU/PD. Change to an insulin with better absorption [eg if using Ultratard, change to a lente insulin such as Monotard or Caninsulin].

##### Glucose curve troubleshooting

Stress hyperglycaemia can confound interpretation of glucose curves just as it can complicate diagnosis of DM. Cats with hospitalisation/transport induced stress hyperglycaemia have a history that doesn't fit with their glucose curve ie. their owners report that they are not PU/PD at home and their weight is stable. Other hints for stress hyperglycaemia include

- first morning blood glucose > 24mmol/L, and persistently above 17mmol/L during the day
- lowest blood glucose at first sample with progressive increase over the day

If you are still unsure, measure serum fructosamine levels. Trends rather than individual doses are more useful, remember that well controlled diabetics have higher fructosamines than healthy cats. Remember also that cats experiencing repeated somogyi overswings have a blood glucose above normal for much of the day. These cats will have elevated fructosamine levels, but need their insulin dose decreased not increased.

Placing an indwelling jugular catheter the day before performing a glucose curve provides a stress free route for blood collection in cats that are susceptible to stress hyperglycaemia.

##### Somogyi overswings:

The somogyi phenomenon occurs if blood glucose drops below 3.6mmol/L OR drops rapidly regardless of the nadir. The physiological response to this drop in glucose is rapid release of counter regulatory hormones [eg epinephrine, glucagon and cortisol]. These hormones increase hepatic gluconeogenesis and glycogenolysis and reduce peripheral glucose use, resulting in pronounced hyperglycaemia of 22-44mmol/L for periods of 36 hours or more. A hint for a somogyi overswing is a morning blood glucose of > 25mmol/L, and a history of PU/PD at home interspersed with days of apparently good control. **In my experience somogyis occur most commonly when the insulin dose has been increased too rapidly.** It takes 10-14 days for the cat to equilibrate to a new insulin dose, and you should not increase the insulin dose more frequently than this.

If you suspect a somogyi overswing and the cat is receiving <5U of insulin, decrease the dose by 25%. If it is on >6U start again [ie blood glucose < 20mmol/l start on 0.25U/kg lente insulin BID, >20mmol/L 0.5U/kg lente insulin BID]

### **Insulin resistance**

You should suspect insulin resistance when a cat is receiving more than 1.5-2U/kg of insulin per dose AND all the blood glucose over the day are over 17mmol/L. If you suspect insulin resistance, it is first important to recheck the cat's medication history. If insulin antagonist drugs such as corticosteroids or progestogens are being used, these should be withdrawn wherever possible.

1. **The commonest cause of apparent insulin resistance is due to improper insulin storage, handling and administration.** Check injection technique by administering the insulin yourself, and check insulin storage by using a fresh bottle of insulin. It is recommended that insulin bottles are replaced 2 monthly regardless of whether they have been completely used to reduce potential problems associated with storage. Insulin should never be diluted with anything other than manufacturer approved diluents, otherwise insulin activity can decline unpredictably. Ensure that insulin injection sites are rotated regularly to avoid tissue fibrosis and reduced insulin absorption. Remember that longer acting insulins are more poorly absorbed than shorter acting formulations. If insulin resistance is a problem, and you are using an ultralente insulin, try switching to a lente formulation. If using a lente insulin, try adding in regular insulin or using a commercial human insulin that combines regular and lente insulin.
2. Next search for intercurrent disease that may be causing insulin resistance. Many illnesses are associated with release of diabetogenic hormones such as glucagon, growth hormone, epinephrine and cortisol. Failure to recognise and treat these conditions can make it difficult or impossible to control DM. Examples of diseases recognised commonly in diabetic cats include hyperthyroidism, renal failure, infections [especially periodontal disease and urinary tract infections], neoplasia, pancreatitis, liver disease and inflammatory bowel disease
3. Consider screening for acromegally and Cushings. Although these are well recognised causes of insulin resistance in cats, they are rare.
4. Insulin antibodies are a very rare cause of insulin resistance in cats. In fact if antibodies do develop, insulin release is slowed and better glycaemic control is usually achieved.

### **Management of Diabetic Ketoacidosis**

Cats with urinary ketones who are bright and eating can be treated with lente insulin as previously described, but those who are anorexic/vomiting need hospitalisation and therapy with regular insulin and

intravenous fluids. Monitoring of sick ketoacidotic patients is intensive. Acid-base, electrolyte and blood glucose levels can change rapidly during therapy and close monitoring of these parameters is mandatory. For example, it is not uncommon for 3-4 changes of fluid type to be required in the first 24 hours of therapy. If in-house monitoring of electrolytes and acid base status is not available an outside laboratory who can supply results within a couple of hours is essential.

The primary goals for therapy of DKA are

1. Correct dehydration and electrolyte deficits
2. Correct acidosis if required
3. Treat with regular insulin to prevent ketogenesis and reduce hyperglycaemia
4. Identify and remove any precipitating factors [eg infection]

#### **1. Correct dehydration and electrolyte deficits:**

Intravenous fluids are essential in management of DKA. Fluids will not only re-hydrate the cat but will lower plasma glucose by improving urine flow and encouraging excretion of glucose. An isotonic fluid such as 0.9% saline is a suitable initial choice in most cases. The typical DKA dog or cat is 6-12% dehydrated, this fluid deficit should be replaced over a 24-48 hour period unless the patient is in shock. In addition maintenance fluids at 1.5-2 times maintenance [3-4mls/kg/hour] should also be provided. All patients receiving fluid therapy must be monitored to ensure hydration is adequate, and that over or under hydration is not occurring. Subjective assessments of hydration include the cat's alertness, capillary refill, heart rate, and respiration [eg. regular auscultation of the chest can detect dependent crackles in over hydrated cats who are developing pulmonary edema]. Other assessments of hydration include weighing the cat twice daily, performing at least once daily PCV /total protein and ensuring urine output is more than 0.5ml/kg/hour [a simple way to measure urine output is to weigh the litter tray before and after urination]. Fluid infusion rates should be adjusted as your clinical findings dictate.

At presentation most patients with DKA are normo to hypokalaemic, however fluid therapy, insulin and correction of metabolic acidosis will drive potassium back into cells and enhance urinary potassium losses.

**Profound hypokalaemia can develop during therapy for DKA** and this warrants aggressive therapy. Ideally replacement of potassium should be based on measurement of serum potassium [see table at end of notes]. If serum potassium is not immediately available, add 40mmol of KCL to each litre of fluids. Subsequent adjustments in K+ supplementation should be based on serum potassium which is ideally measured every 6-8 hours [12 hours minimum] until K+ is stable and in the normal range. Phosphate shifts from the intra and extracellular compartments in parallel with potassium, hence **hypophosphataemia commonly develops** during the first 12-24 hours of therapy for DKA. Hypophosphataemia can cause acute haemolysis and

this may be life threatening. **Development of severe hypophosphataemia can be reduced by routine supplementation of half the potassium deficit with potassium phosphate.** If serum phosphorous levels drop below 0.5mmol/L, phosphorous will need to be supplemented at doses from 0.01-0.06mmol/kg/hr [monitoring serum Pi every 6 hours]. Overzealous phosphate supplementation can lead to hypocalcaemia, and efficacy of therapy should be based on twice daily serum phosphate measurements. NB. Do not add KPO<sub>4</sub> to calcium containing fluids such as lactated ringers as CaPO<sub>4</sub> will precipitate.

## 2. Correction of acidosis:

In most cases correction specific therapy for metabolic acidosis is not required as insulin and fluid therapy facilitates metabolism of ketone bodies and their urinary excretion. Serum bicarbonate is only required if plasma HCO<sub>3</sub> drops below 12mmol/L and these animals are usually profoundly depressed. The bicarbonate deficit is calculated as:

$$\text{mmol HCO}_3 = \text{kg [body weight]} \times 0.4 \times [12 - \text{patient bicarbonate}] \times 0.5.$$

HCO<sub>3</sub> should be administered slowly over 6 hours and acid base status should be rechecked before any more is administered. Overzealous HCO<sub>3</sub> administration should be avoided as it can raise plasma osmolality, impair oxygen delivery to tissues and cause paradoxical CNS acidosis.

## 3. Insulin therapy:

The goals of insulin therapy are to **slowly reduce serum glucose** [no more than 3-5mmol/hour] to 11-14mmol/L **over 6-10 hours using regular insulin.** More rapid reduction of blood glucose levels can cause large shifts in osmolality with potentially serious consequences.

The **low dose intermittent intramuscular regime** usually works well:

A single injection of 0.2U/kg regular insulin IM is followed by hourly injections of 0.1U/kg IM [consider diluting insulin, ideally use special diluents, to titrate the dose more accurately]. Blood glucose should be measured hourly, and once serum glucose drops below 16mmol/L regular insulin injections should be reduced to 0.1-0.4IU/kg every 4-6 hours. The insulin dose needs to be titrated in each individual patient. Once serum glucose falls below 16mmol/L dextrose should be added to the fluids [2.5% dextrose if serum glucose is 8-15mmol/l, 5% dextrose if serum glucose is < 8mmol/L]. A 5% dextrose solution is made by adding 50ml of 50% dextrose to 500ml of fluids. **Administration of dextrose is important as more insulin is required to metabolise ketone bodies than is needed to normalise blood glucose.**

Longer acting insulin [eg. lente q 12hours] can be started once the cat is eating, has stable electrolytes and acid-base status and is off IV fluids. The initial dose of insulin is similar to the last dose of regular insulin given.

An alternative to the low dose IM insulin regime is a **constant rate infusion [CRI] of IV regular insulin.** An accurately calibrated infusion or syringe pump is needed, and the protocol is as follows:

Add 25IU regular insulin to 500ml saline, run out 100ml over 20mins [as insulin binds to plastic], infuse at 1ml/kg/hour monitoring glucose hourly. Again the aim is **slow** reduction of blood glucose by around 3-5mmol/hour. Once the blood glucose drops to ~15mmol/L add dextrose to your fluids and switch to IM insulin every 4-6 hours.

A third alternative is an **intermittent high dose combined IM/SC regime.** Initially regular insulin is given at 0.25-0.5U/kg/IM q4hrs for 1-2 doses. Fluid therapy is started concurrently and once the patient is rehydrated, regular insulin is given at the same dose SC q6-8hrs. Initially blood glucose is monitored hourly, with dextrose being added to the IV fluids once blood glucose drops below 16mmol/L. Although this technique is less labour intensive, blood glucose can decrease rapidly increasing the risk of hypoglycaemia.

## 4. Identifying and treating concurrent illness:

DKA occurs when insulin deficiency occurs concurrently with an insulin antagonist illness. Common concurrent diseases include bacterial infection/sepsis, pancreatitis, renal failure and congestive heart failure. Therapy will need to be directed at the intercurrent disease in these patients, but insulin therapy should never be delayed as it is the only means by which the DKA will be controlled.

A thorough history and physical examination plus haematology, serum biochemistry and urinalysis are mandatory in patients with DKA, as identification of intercurrent disease will impact directly on therapy and prognosis. **A cystocentesis urine sample should be always be cultured, as urinary tract infections are common in DKA.** Ill ketoacidotic patients should routinely be placed on broad spectrum bacteriocidal antibiotics pending urine culture. An example of suitable antibiotic cover would be clavulanate-amoxicillin combined with enrofloxacin. Depending on the cats' clinical presentation, chest radiographs, abdominal ultrasound and culture of other body fluids may also be indicated [eg. blood, joint fluid]. Of the potential intercurrent diseases, pancreatitis is the most challenging to diagnose. Abdominal ultrasound is a fairly specific but insensitive means of diagnosis while serum amylase, lipase and feline trypsinogen like immunoreactivity [TLI] are not reliable. Identification of pancreatitis can be important as severe necrotising pancreatitis is an important cause of death during initial therapy of DKA.

## Complications Of Dka Therapy And Prognosis

DKA is a complex disorder with a high mortality if management is inadequate or if there is severe underlying disease. Complications usually arise from inadequate patient monitoring, or over-aggressive or under-aggressive therapy. Hypoglycaemia, cerebral edema, hypophosphataemia and hypokalaemia are all

potentially life-threatening complications of DKA. The outcome for an individual patient will depend on the severity of intercurrent disease and your ability to manage the metabolic complications of DKA. In one study the median survival in 104 cats with DM [DKA and non-ketotic DM] was 20 months.

#### Looking To The Future

Combinations of insulin and oral hypoglycaemics are likely to be used more commonly. The use of pancreatic islet cell implants is also being investigated. In home monitoring of blood glucose, using 'prick and suction' devices on the pinna may help overcome the problems of stress induced hyperglycaemia encountered in the clinic.

#### Potassium Supplementation For Fluid Therapy

Serum K [mmol/L]	mmol K per L of fluid	Max infusion rate [ml/kg/hr]
<2	80	6
2-2.5	60	8
2.6-3	40	12
3.1-3.5	30	18
3.6-5	20	25

NB Max infusion rate is 0.5mmol/kg/hr of K

Mmol = mEq

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Pru was a recent recipient of the Educating the Educators award sponsored by Hill's Pet Nutrition, IVABS, CAS and the FCE.