Endocrine Emergencies

Canine Diabetes - Past, Present and Future.

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Diabetes Mellitus

Diabetes Mellitus (DM) is a complex condition that is not a single disease, but a combination of multiple pathophysiological problems that combine to cause the clinical condition. The common feature to all cases is fasting hyperglycaemia in combination with a relative or absolute insulin deficiency. As with hyperadrenocorticism, as thorough understanding of the normal physiology of blood glucose control is vital to the understanding and management of our clinical cases. This importance is highlighted in diabetic cases due to the significant differences we encounter between dogs and cats with respect to their pathophysiology and subsequently potentially different treatment requirements.

Normal Physiology
In normal animals, insulin is secreted from the pancreatic b-islets in response to increased circulating concentration of glucose or amino acids and facilitates the cellular uptake of sodium, potassium and glucose. It consists of two peptide chains linked by a disulphide bond and is stored as a larger pro-hormone and therefore is synthesised by cleavage of this pre-cursor molecule. The cleaved peptide, termed “C-peptide” is also secreted in equimolar concentrations along with insulin. Glucagon is the counter-regulatory hormone to insulin and is secreted from the pancreatic a-islets in response to hypoglycaemia and increased circulating amino acids (in order to prevent hypoglycaemia following protein-stimulated postprandial insulin secretion). There is therefore a constant balance being achieved in normal animals between insulin and glucagon levels (along with other anabolic and catabolic hormones) to maintain blood glucose within the normal reference range.

Pathophysiology of Diabetes Mellitus
If there is either an absolute deficiency of insulin production, or a failure of the insulin to work properly, decreased utilisation of glucose, amino acids and fatty acids by peripheral tissues (especially the liver, muscle and adipose tissue) results. Because insulin is required to facilitate glucose uptake into cells, failure of glucose uptake in the absence of insulin leads to hyperglycaemia and once the renal threshold for glucose is exceeded (approximately 10mmol/l), glucosuria develops. This causes an osmotic diuresis, with the resultant loss of glucose, electrolytes and water in the urine. To prevent the animal from becoming dehydrated a compensatory polydipsia develops, hence the classical clinical signs of PUPD and glucosuria. However, if untreated, the loss of glucose and the failure of glucose utilisation causes catabolism of the animal's energy stores, particularly of the adipose tissue. This excessive catabolism leads to the production and accumulation of ketone bodies (acetocacetic acid, b-hydroxybutyrate and acetone) resulting in ketoacidosis (DKA). The main problem in DKA is that the animal is unable to drink a sufficient volume of fluids to meet its demands, so it rapidly becomes dehydrated, which only serves to worsen the acidosis.
Clinical signs
In dogs, DM is most common in middle-aged dogs, with a higher incidence seen in entire females. A genetic predisposition has been noted in Keeshonds and Samoyeds, with some studies also showing that poodles, Cairn terriers and dachshunds may also be over-represented. In cats, secondary DM due to obesity can occur at any age but primary DM is more common in middle aged – older male cats. The classic history for any patient is PUPD with polyphagia and weight loss (with the exception of acromegalic patients who tend to gain weight). Metoestrus bitches obviously tend to present in the first few weeks following their season.

Clinical examination will also reveal some or all of the following abnormalities:
- Hepatomegaly
- Muscle wasting
- Cataracts
- Evidence of URT or respiratory tract infections
- Ulcerative skin lesions (not common)
- Depression, anorexia vomiting and dehydration may be apparent if the patient is in DKA

Treatment - DKA
DKA is a serious condition in which there are usually marked alterations in fluid, serum electrolyte and acid-base balances, the most common problems being:

- Pre-renal azotaemia
- Hyponatraemia
- Metabolic acidosis

DKA is less common in the cat but is can still occur and treatment must be rapid and careful in order to prevent further deterioration. Once stable the animal can be treated as a normal diabetic. Treatment of DKA can be viewed as a 7-point plan, as shown below:

1. **IVFT**
   a. 0.9% NaCl is usually best, thereby allowing accurate quantification of any potassium added to the fluids. Urine output really should be assessed and quantified and if possible, measurement of central venous pressure should be considered.

2. **Insulin therapy**
   a. Low-dose insulin infusions can be set-up by adding 5iu to a 500ml bag of saline and giving it through a second catheter at a dose of 0.1 iu/kg/hour. Blood glucose should be assessed every 90 – 120 minutes.
   b. Soluble insulin injection (crystalline insulin) can also be used. A dose of 1iu/kg is prepared and ¼ of the dose given intravenously and ¾ given intramuscularly every 4 hours. Blood glucose should again be monitored every 60 – 120 minutes.

3. **Potassium**
a. In acidosis, potassium is exchanged for $\text{H}^+$ across cell membranes in an attempt to reduce the acidosis, causing an increase in $\text{K}^+$ excretion and a gradual depletion in total body $\text{K}^+$. Insulin causes $\text{K}^+$ to return to the intracellular compartment, thereby further reducing extracellular $\text{K}^+$ concentration to potentially fatal levels. Serum potassium concentrations therefore must be assessed every 60 – 120 minutes during the first 24 hours of treatment and supplemented as required.

4. Phosphate
   a. Phosphate moves in the same manner as $\text{K}^+$ in DKA patients, but marked hypophosphataemia is only usually seen in severely ill DKA patients. It does need to be monitored along with glucose and $\text{K}^+$ to prevent it causing complications. If supplementation is required, a dose of 0.01 – 0.03 mmol/kg/hour of potassium phosphate in a calcium-free fluid can be administered.

5. Correction of acidosis
   a. Generally, bicarbonate therapy is not required as long as renal function is preserved and the fluid therapy is correct.

6. Antibiotics
   a. The combination of hyperglycaemia, glucosuria, stress, shock and acidosis all combine to cause marked immune suppression in DKA patients and there is an increased risk of bacterial translocation through the gut wall. Good quality, broad spectrum antibiosis (eg: ampicillin and metronidazole given intravenously) is indicated in all DKA patients, even if there are not pyrexic.

7. Continuing IVFT
   a. Once the dehydration is corrected and the blood glucose is back below 10 mmol/l, fluid therapy should still be continued but with a maintenance solution (eg: 0.18% NaCl with 4% glucose) rather than a replacement solution

Treatment once the DKA has been corrected
The aim of treatment now is to normalise blood glucose concentrations as much as possible and treat the patient as a standard primary diabetic (assuming no other causal pathology has been identified during your diagnostic evaluation), thereby preventing all the secondary complications that can arise, such as cataracts, hepatic lipidosis, pancreatitis, retinopathies, nephropathies, infections and cutaneous disease. The vast majority of patients can be well controlled at home, but it is absolutely essential that the owner is fully informed regarding the aims of treatment and that they understand exactly what we are trying to achieve. Maintaining good relations and communications with the clients is vital for success with these patients.

The type of insulin used is usually decided upon by a combination of personal preference and the ease of administration for the owner. Current thoughts on the “Gold Standard” for both cats and dogs is to use an intermediate-acting preparation
such as insulin lente twice daily, with 2-4 feeds being given through the day for dogs (see later for feeding cats). Once daily administration of lente is adequate in most canine patients but superior control is usually achieved using BID dosing. However in cats, if twice daily dosing is not possible then lente usually does not have a sufficiently long half-life to be effective when given once daily, so a longer-acting preparation such as PZI insulin is required. PZI can be used in dogs, but it has a duration of action of up to 36 hours in many canine patients making regular administration and control difficult to achieve, so its routine use cannot be recommended as an initial insulin preparation in dogs.

If once daily dosing is used, then a regular pattern of dosing, feeding half the daily measured ration 30 minutes later and then giving the second feed 6-8 hours later (ie: at the nadir point) should be established. If twice daily dosing is used, each dose should be 75-80% of the dose that would have been used in a once daily dosing schedule. The total calorific requirement each day does not change. Most animals respond best with once daily dosing starting at 0.5iu/kg; twice daily dosing therefore uses 0.4iu/kg each dose at the beginning of therapy.

Regular feeding schedules and the correct diet are also fundamental to success in stabilising diabetic patients, especially canine diabetics. The reason for species difference this relates to the differences in carbohydrate metabolism between cats and dogs. Dogs derive their glucose from dietary carbohydrates along with fat and glycogen stores when necessary, but cats derive most of their glucose via gluconeogenesis and protein catabolism, hence in part why cats are obligate carnivores. Cats therefore, unlike dogs, do not have a post-prandial hyperglycaemic peak to any great extent and they can be allowed to feed ad lib during the day, whereas dogs need to have their feeds and insulin co-ordinated to prevent significant post-prandial hyperglycaemia. This is not to say that cats can have unlimited quantities of food. For both cats and dogs, every diabetic patient MUST have their daily calorie intake requirement calculated, which can be done using the following simple equations:

Dog:  Basal energy requirement in kcal = 70 + (30 x BW)
Cat:  Basal energy requirement in kcal = 50 x BW

The calorific content of foods is available from the manufacturer or is often printed on the tin of prescription food. Exactly what type of food to feed is also important. There are several studies showing quite clearly that dogs fed on a high fibre diet have significantly lower mean 24-hour and post-prandial glucose concentrations, lower fructosamine and glycosylated haemoglobin levels and show significant improvements in their activity and demeanour. The fibre content of the food appears to be more important than the fat content. The situation is cats is not so well established, as one study has showed that glycemic control could be improved by feeding a diet containing 12% insoluable fibre (dry matter basis). However an earlier study suggested that allowing ad libitum feeding of normal commercial cat foods did not adversely affect glycemic control in cats with primary DM. The best advice for cases of primary DM is that dogs should be fed a high fibre food such RCW Glucomodulation diet, but that cats can probably be fed on a commercial cat
food initially and then swapped to a high fibre food if not appearing to be well controlled.

Problem diabetics

There is a small but significant number of diabetics that will seem normal and simple primary DM cases to start with and then seem to become resistant to insulin, which is defined as having any case that is receiving in excess of 2.2iu/kg/dose insulin. In these cases, it is imperative to firstly show that the animal is failing to respond at all to the insulin by performing a glucose curve and then secondly to obtain a diagnosis and establish exactly what is causing the treatment failure. Causes of failure to respond and apparent insulin resistance can be divided quite easily under five main headings:

1. Owner problems
   The first thing to establish is whether or not the owner is carrying out your instructions properly, especially with regard to injection of the insulin, handling and storage of the insulin, feeding regimes (especially the necessity for the patient not to get tit-bits!). Make sure the insulin has not passed its expiry date and review the day to day routine. A glucose curve in these situations is so important, as Somogyi overswing will appear like insulin resistance, as there will always be glucosuria and the fructosamine levels will be high. Ruling out somogyi overswing has to be second in the order of process after you have ensured there are no specific problems with the owner keeping to the protocol. If you are happy that this is all OK, then proceed to look for an underlying medical cause.

2. Endocrine disease
   Endocrine disease is a very common cause of insulin resistance. The commonest one to consider are hyperadrenocorticism, hyperthyroidism, hypothyroidism and acromegaly (caused by a pituitary tumour producing growth hormone). Diagnosis therefore must proceed with careful clinical examination to look for any evidence of these problems. An ACTH stimulation test is the best way to diagnose HAC in the presence of a non-adrenal illness. The exogenous administration of steroids must also obviously be avoided in all diabetic patients. Diagnosis of hyperthyroidism is usually quite straightforward but diagnosing hypothyroidism can be difficult at the best of times – see previous lectures! Acromegaly is diagnosed by the classical clinical appearance of excessive soft tissue and widened inter-dental spacing combined with measuring Insulin-like Growth Factor 1. Growth hormone is too labile to be used as a diagnostic test, so it is better to measure the molecule that growth hormone stimulates the production of, ie: IGF-1. The University of Cambridge published a series of 9 cats all with acromegaly causing insulin-resistant DM that we have treated with radiotherapy. Five of the six are now completely stable, two of them now off insulin all together and three controlled on normal doses. One has been lost to follow-up and one developed renal failure before radiotherapy could start. It would appear therefore that radiotherapy (10 fractions on a Monday-Wednesday-Friday schedule to a total dose of 40Gy is highly effective at treating feline acromegaly. No major side effects at all have been recorded with this treatment.
3. Infection
If there is no evidence of an endocrine disease, then careful evaluation for a systemic infection should be undertaken. Pyelonephritis is an example of an infection that in some patients can be extremely hard to locate, so full culture and sensitivity studies should be performed. It is sometime justifiable to run a course of broad spectrum antibiotics if you are uncertain, but a definite diagnosis should always be your aim if possible.

4. Neoplasia
Once endocrine and infectious causes have been ruled out, the search for a neoplasm has to be performed as cancer can cause quite marked insulin resistance. A good clinical examination coupled with detailed imaging studies (that might need to repeated over a period of time) should enable a diagnosis to be made with biopsy and histopathological confirmation.

5. Genuine insulin resistance
If all investigations have reached a negative conclusion, the possibility that the animal has genuine antibody-mediated insulin resistance must be considered. However this is a difficult diagnosis to confirm. Dr. Brian Catchpole and his team at the RVC can measure endogenous anti-insulin antibodies. However in such cases, it is usually best to start using an insulin derived from a different species (eg: if the dog is receiving Caninsulin, which is porcine, swap to human recombinant lente insulin or the insulin analogue, Glargine).

Problem diabetics do need a great deal of careful thought and a logical approach to ensure that no problems are missed. However, an underlying cause is usually identifiable in most cases!
References and further reading for Diabetes Mellitus


