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NEW STRATEGIES IN THE MANAGEMENT OF CANINE DIABETES MELLITUS
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Diabetes mellitus is a heterogeneous condition in the dog rather than a single disease entity. The incidence of diabetes mellitus is similar for the dog, with the reported frequency varying from 1 in 100 to 1 in 500. Diabetes mellitus is characterised by a relative or absolute deficiency of insulin secretion by the beta cells of the islets of Langerhans in the pancreas. Carbohydrate metabolism and in particular blood glucose concentration is controlled by the balance between the action of catabolic hormones, for example glucagon, cortisol, catecholamines and growth hormone on the one hand, and the principal anabolic hormone, insulin, on the other. A relative or absolute deficiency of insulin results in decreased utilisation of glucose, amino acids and fatty acids by peripheral tissues, particularly liver, muscle and adipose tissue. Failure of glucose uptake by these cells leads to hyperglycaemia. Once the renal threshold for glucose reabsorption is exceeded, an osmotic diuresis ensues with loss of glucose, electrolytes and water in the urine. Compensatory polydipsia prevents the animal becoming dehydrated. The loss of glucose leads to catabolism of the body's reserves especially of fat. Excessive fat catabolism leads to the production and accumulation of ketone bodies (acetoacetic acid, β-hydroxybutyric acid and acetone) and the onset of diabetic ketoacidosis. In diabetic ketoacidosis, the dog is unable to maintain an adequate fluid intake and becomes rapidly dehydrated due to the uncontrolled osmotic diuresis. The dehydration and acidosis requires emergency care if the animal is to survive.

In man, diabetes is classified as type I, insulin-dependant diabetes mellitus (IDDM), type 2, non-insulin-dependant diabetes mellitus (NIDDM) type 3 due to other causes. Type 1 diabetes is characterised by a combination of genetic susceptibility and immunological destruction of beta cells, with progressive and eventually complete insulin insufficiency. The presence of circulating autoantibodies against insulin, the beta cell, and/or glutamic acid decarboxylase (GAD) usually precedes the development of hyperglycaemia or clinical signs. Type 2 diabetes mellitus is characterised by insulin resistance and "dysfunctional" beta cells; defects believed to be genetic in origin are evident for a decade or longer before hyperglycaemia and clinical signs of diabetes develop, and the deleterious effects can be accentuated by environmental factors such as obesity. This classification has not proved very useful in veterinary medicine since nearly all dogs with diabetes mellitus require insulin therapy regardless of the underlying aetiology require treatment with insulin.

Clinical signs
Diabetes mellitus is a disease of middle-aged dogs with a peak incidence around 8 years of age. Genetic predisposition to diabetes has been found in Keeshunds and Samoyeds. Cairn terriers, poodles and dachshunds may also be over-represented, although a recent survey showed over half the diabetic dogs were Labrador retrievers, collies and Yorkshire terriers. Entire females are more frequently affected than males and this is due mainly to the induction of growth hormone secretion by progesterone and other progestogens. Polyuria, polydipsia, increased appetite and weight loss develop over a few weeks in uncomplicated cases. In entire bitches, this usually occurs during the metoestrus phase of the oestrus cycle. Hepatomegaly, muscle wasting and infections of the urinary or respiratory tracts may be noted on clinical examination. Ulcerative skin lesions and cutaneous xanthomata have occasionally been reported. If the diabetes remains uncontrolled, an accumulation of ketone bodies may occur which causes metabolic acidosis and leads to depression, anorexia, vomiting, rapid dehydration. Coma and death may result from severe hypovolaemia and circulatory collapse.

Diagnosis
Urine analysis reveals persistent glycosuria and often ketonuria. Despite the high solute load in the urine, which would tend to increase the specific gravity of the urine, many older dogs may have impaired renal concentrating power and thus the specific gravity of the urine is variable, typically ranging between 1.015 and 1.045. Bacterial cystitis is common and occasionally may involve gas-producing organisms which can cause emphysematous cystitis. Plasma biochemistry reveals a fasting hyperglycaemia (> 10 mmol/l) and hyperlipidaemia. In some patients the blood will be lactescent due to lipaemia. Liver enzymes are usually raised and liver function tests such as bile acid concentrations may be abnormal. In cases where diabetes is associated with pancreatitis, amylase and lipase concentrations may be elevated.

In diabetic ketoacidosis, there are serious derangements in fluid, electrolyte and acid-base status. The most frequent abnormalities are pre-renal azotaemia, hyponatraemia and metabolic acidosis. The cat appears to be less prone to developing diabetic ketoacidosis.

**Routine stabilisation of diabetes mellitus in the dog**

The primary goal of diabetes therapy is to maintain normoglycaemia and thereby control the signs that occur secondary to hyperglycaemia and glycosuria which result in the development of complications. Complications of diabetes mellitus include: hypoglycaemia, ketoacidosis, cataract formation, hepatic lipidosis, pancreatitis, infections, retinopathy, diabetic nephropathy, diabetic neuropathy and skin disease. The essentials of good stabilisation of diabetes mellitus requires understanding by the owner, and adherence to a regular daily routine that involves diet, insulin administration and regular, controlled exercise.

Stabilisation can be carried out satisfactorily at home, but particularly if the patient is ketotic, it may be preferable to hospitalise the animal during stabilisation since it is easier to monitor blood glucose more closely.

Most diabetic dogs are presented with complete islet cell degeneration and atrophy. Therefore diabetes mellitus in dogs is insulin-dependent. Rarely, bitches may be presented during the metoestrus phase of the oestrous cycle before islet cell exhaustion has occurred. If ovariohysterectomy is performed in these patients immediately the signs of diabetes become apparent, there can be complete resolution of the disease. However, in the majority of bitches this opportunity is missed or goes unnoticed and permanent damage to the islet cells occurs.

**Dietary therapy.** Appropriate dietary therapy is an essential part of the management of diabetes. The diet must be well-balanced and constant in both composition and amount fed at each meal. It is therefore most convenient to use a commercial diet. Canned or dry foods which contain digestible complex carbohydrates should be fed as slow digestion minimises the fluctuations in post-prandial blood glucose concentrations. Semi-moist foods which contain a predominance of easily assimilated carbohydrates in the form of disaccharides and propylene glycol should be avoided because of marked post-prandial hyperglycaemia. There is evidence that diets with high fibre content improve glycaemic control by delaying starch hydrolysis and glucose absorption thereby reducing post-prandial fluctuations in blood glucose. High fibre diets are also beneficial in correcting obesity. However, there may be disadvantages in using high fibre diets such as reduced palatability and the fact the low caloric density may cause the patient to lose excessive weight or fail to gain weight in those patients already below ideal body weight. The author tends to reserve high fibre diets for those patients that are difficult to stabilise and/or are obese.

Finally, the feeding schedule should be designed to enhance the action of insulin and minimise post-prandial hyperglycaemia. The daily caloric intake should occur when insulin is present in the circulation and capable of handling glucose absorbed from the intestine. Several small meals are preferable to one large feed as these will help minimise post-prandial hyperglycaemia and thus help to control fluctuations in blood glucose. The author routinely recommends two equal meals fed at times to coincide with insulin activity. In cases that prove difficult to stabilise 3–4 smaller meals are fed during the day. Titbits and scavenging must be avoided as they tend to destabilise diabetic patients.
**Insulin therapy.** For routine stabilisation in the dog insulin zinc suspension (lente) which contains a mixture of 30% insulin zinc suspension (amorphous) and 70% insulin zinc suspension (crystalline) is the preparation of choice in the UK. When given by subcutaneous injection, it is an intermediate acting insulin with an onset of activity at 1–2 hours, peak activity around 6–12 hours and a duration of action of between 18 and 26 hours in the dog. The times for peak activity and duration of action vary with the individual, but in most dogs once daily administration is adequate. Lente insulin is usually given as a single morning injection at the same time or just before the first meal with the second meal given 6–8 hours later to coincide with peak insulin activity. An initial dose of between 0.5–1.0 unit/kg is used. Insulin is probably best dosed on body surface area rather than a simple weight basis. Thus small dogs (<15 kg) tend to require 1.0 unit/kg and larger dogs (>25 kg) receive 0.5 unit/kg. Although the subcutaneous route is ideal for long term use, the intramuscular route may be used initially, especially in mildly dehydrated or ketotic animals, because absorption from subcutaneous depots in these patients may be slow and erratic. Insulin should be administered using specific 0.5 ml or 1.0 ml syringes calibrated in units (100 or 40 units/ml depending on the preparation). Insulin preparations should be stored in a refrigerator at 2–8° C because they are adversely affected by heat or freezing. Preparations should be rolled gently to re-suspend the particles before use.

A diabetic patient will usually take 2–4 days to respond fully to a dose of insulin or a change in preparation. It is important to avoid increasing the dose too quickly before equilibration has occurred as this can lead to a sudden and precipitous fall in blood glucose due to overdosage with insulin. In most cases, adjustments in the insulin dose should be made in small changes of one to four units per injection.

The type of preparation and frequency of administration may require alteration in those patients that prove difficult to stabilise with this standard routine. However, it is good for the clinician to become familiar with one type of insulin preparation and only change from that preparation if the insulin is the cause of the instability.

**Monitoring therapy**

Ideally monitoring should consist of serial blood glucose concentrations as tighter diabetic control can be gained than with urine glucose estimations. Initially at least two blood glucose estimations should be made, one before insulin is administered and the second just before the second feed. Once the dog appears fairly stable more frequent blood samples should be taken throughout the day to assess the degree of stabilisation. An assessment of daily water intake can also provide useful information about the degree of diabetic control.

Blood glucose concentrations should ideally be maintained between 5 and 9 mmol/l. The blood glucose concentration will usually be highest in the morning before insulin is administered and lowest just before the second feed. A trace of glucose in the morning urine sample may be acceptable but the urine should be negative at other times in the day. However, it is important to remember that urine glucose may not reflect the blood glucose concentration at the same point in time and if the urine glucose is negative, the blood glucose concentration could be hypoglycaemic (< 3.0 mmol/l), normoglycaemic or hyperglycaemic (> 5.5 mmol/l).

Although the author’s clients monitor urine for glucose and ketones regularly, he does not advocate adjusting daily insulin dosages on the basis of morning urine glucose measurements. Instead, he prefers to continue with a fixed insulin dosage unless the patient remains unstable for more than several days.

Measurement of glycated proteins such as fructosamine and glycosylated haemoglobin is used increasingly in the dog to monitor the response to treatment. The irreversible, non-enzymatic glycation process occurs throughout the life span of the protein, mainly albumin in the case of fructosamine, and is proportional to the glucose concentration over that time. These measurements reflect the average blood glucose concentration over the preceding one to two weeks in the case of serum fructosamine and two to three months in the case of glycosylated haemoglobin. Fructosamine concentrations less than 400 mmol/l indicate good glycaemic control whereas concentrations above 500 mmol/l are found in newly diagnosed or poorly controlled diabetics. Glycosylated haemoglobin is less routinely available as an assay. Well controlled
diabetic dogs have between 4 and 6 per cent glycosylated haemoglobin, whereas poorly controlled diabetics have concentrations greater than 7 per cent. A diabetic record should be kept by the owner for each patient as alterations to stability can be assessed more easily over a period of time. Insulin requirements will be increased by infection, oestrus particularly the metoestrus phase to the cycle, pregnancy and ketoacidosis. It is recommended that entire bitches should undergo ovariohysterectomy to avoid insulin resistance at subsequent seasons.