Canine diabetes mellitus

Diabetes mellitus is a common endocrinopathy in dogs and can be a frustrating disease to manage, both for the owner and the veterinarian, write Sivert Nerhagen DVM and Carmel T Mooney MVB MPhil PhD, University College Dublin Veterinary Hospital

Diabetes mellitus (DM) is one of the more common endocrine diseases in dogs. In a population of 180,000 insured dogs from Sweden, the incidence was 13 cases per 10,000 dog-years (Fall et al, 2007). In another study of over 120,000 dogs from UK first-opinion practices, the prevalence of DM was 0.34% (Mattin et al, 2014).

The disease is characterised by hyperglycaemia and glucosuria and it is these abnormalities that give rise to the majority of clinical signs. It is not a single disease but rather a heterogeneous group of disorders that arise because of insulin deficiency or reduced insulin sensitivity in target tissues, or both. In most dogs, regardless of underlying cause, DM is associated with hypoinsulinaemia with an absolute requirement for exogenous insulin treatment to avoid ketoacidosis and death. The prognosis is favourable, with the highest mortality occurring during the first six months and a median survival time between two and three years thereafter (Fall et al, 2007).

PATHOGENESIS

In humans, DM is classified into different types depending on the aetiopathogenesis of the condition (Gilor et al, 2016; [see Table 1]). Type 1 disease is associated with immune-mediated beta cell destruction leading to absolute insulin deficiency. Type 2 disease is characterised by impaired insulin secretion together with insulin resistance, does not always require insulin for its management and typically develops in older, inactive and obese patients. Other specific types arising from primary pancreatic diseases and endocrinopathies such as hyperadrenocorticism and hypersomatotropism and gestational DM comprise the remainder.

An attempt has been made to classify DM in dogs according to the human scheme but there has been no widely accepted consensus. Canine DM has been most commonly likened to latent autoimmune diabetes of adults, a variant of type 1 disease that tends to occur in older patients. The insulin deficiency and dependency on insulin treatment in the majority of dogs, and the identification of specific immune system haplotypes in predisposed breeds, support such a theory. However, other evidence is limited and the classification remains controversial. Histopathological evidence for insulitis or demonstration of relevant circulating autoantibodies has been previously demonstrated in between 10% and 53% of diabetic dogs but the studies were small and only included between 13 and 40 dogs (Alejandro et al, 1988; Hoenig and Dawe 1992; Davison et al, 2008a, 2008b, 2011). In a more recent study of 121 diabetic dogs there was no insulitis and no evidence of circulating autoantibodies against islet cells or GAD65 (Ahlgren et al, 2014). On the other hand, there is some evidence that pancreatitis may play a role in some dogs although identifying a clear cause or effect relationship is difficult (Davison, 2015). Insulin resistance induced by other hormones (eg. progestagens, glucocorticoids) plays a role in many dogs with the ensuing hypoinsulinaemia, potentially resulting from the effects of glucose toxicity or eventual ß-cell exhaustion (Alejendro et al, 1988; Hess et al, 2000; Fall et al, 2010). By contrast, type 2 DM appears to be rare in dogs, if it occurs at all. Compensatory hyperinsulinaemia has been identified in obese dogs (Tvarijonaviciute et al, 2012) but consequent overt DM is not yet reported.

It is clear that attempts to classify DM as human patients, are not as meaningful in dogs. Perhaps a more practical system is to perceive all diabetic dogs as insulin dependent at the time of diagnosis irrespective of the underlying causes that may be multifactorial (see Table 2). If possible, any causative or contributing factor(s) should be identified and concurrently treated while managing the hyperglycaemia. Treating such factors is important to maximise the chances of successful diabetic therapy but may also to help in achieving remission in certain specific circumstances (eg. ovariectomy in entire females).

Type 1	**Immune-mediated ß-cell destruction**
Type 2	**Insulin resistance with relative insulin deficiency**
Other specific types (type 3)	**Genetic defects of insulin action** **Genetic defects of ß-cell function** **Diseases of the exocrine pancreas** **Other endocrinopathies (acromegaly, hyperadrenocorticism)** **Drug-induced**
Gestational	**Diabetes mellitus that develops during pregnancy**

Table 1: Aetiological classification of human diabetic patients.

Impaired insulin secretion	Peripheral insulin resistance
Congenital	**Metoestrus**
Autoimmune destruction	**Other endocrine disorders/drugs**
Pancreatitis	**Obesity**
	Physical inactivity

Table 2: Causes of and contributors to diabetes mellitus in dogs.

SIGNALMENT AND CLINICAL SIGNS

DM tends to occur in middle aged to older dogs (five-12 years of age). Female dogs were traditionally thought to be affected twice as frequently as males, but in a 2005 UK survey, only 53% of the dogs were female (Catchpole et al, 2005). This trend is most likely because of the increasing practice of elective neutering. Certain breeds are more likely to develop DM and those known to be predisposed include the Samoyed, Tibetan Terrier, Cairn Terrier, Yorkshire Terrier and Miniature Schnauzer.

Common clinical signs in dogs include polyuria and polydipsia (PU/PD), weight loss, development of bilateral cataracts and lethargy. PU/PD develops when the blood glucose concentration exceeds the renal tubular threshold (>12mmol/L), in turn causing osmotic diuresis. Weight loss, although a significant feature of chronic DM, might not be noticed in dogs that have recently become diabetic.

Cataracts develop frequently as a result of the unique sorbitol pathway by which glucose is metabolised in the lenses, leading to oedema and opacification. Development of cataracts has been reported in 50% of dogs within five to six months of diagnosis, with the number increasing to 80% after 16 months regardless of the appropriateness of diabetic control (Beam et al, 1999). The development of cataracts can be rapid, with owners reporting a sudden onset of blindness.

Urinary tract infections (UTIs) are also commonly seen, with 21% to 37% of dogs with DM being culture-positive at presentation (Hess et al, 2000; Forrester et al, 1999). Potential mechanisms suggested to increase the risk of UTI in dogs with DM include enhanced bacterial growth in urine due to the presence of glucosuria and decreased neutrophilic chemotaxis secondary to the glucosuria (Latimer et al, 1984; Forrester et al, 1999).

Without effective treatment, dogs will develop ketonaemia, ketonuria and eventually ketoacidosis. Such cases present with lethargy, anorexia, vomiting and dehydration. Ketoacidosis is a life-threatening complication of DM that requires immediate intervention. The reader is encouraged to find additional literature on this subject elsewhere.

DIAGNOSIS

Diabetes mellitus is diagnosed by demonstration of persistent fasting hyperglycaemia and glycosuria with consistent clinical signs. The use of glucometers and urine-reagent strips allows a rapid and relatively inexpensive method of diagnosing canine DM. However, a more thorough evaluation of the dog is recommended once the diagnosis is made, as it is important to identify any concurrent disorders that warrant treatment or that might interfere with eventual diabetic stability (see Table 3). The minimum laboratory evaluation in any newly diagnosed diabetic dog should include haematology, serum biochemistry and urinalysis with bacterial culture. The haematology is often unremarkable, but a stress leucogram may be present. On biochemistry, hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia, and increased alanine aminotransferase and alkaline phosphatase activities are common. Glycosuria is consistently found on urinalysis, while the presence of proteinuria, bacteriuria and ketonuria are more variable. Pancreatitis is relatively common in diabetic dogs, indicating that measurement of canine pancreatic lipase immunoreactivity (cPLi) should also be considered. An abdominal ultrasound is indicated to assess for any abnormalities (eg. pancreatitis, adrenomegaly, urinary tract pathology). Additional testing might be warranted based on the results of these tests or any other clinical signs exhibited by the dog.

Clinical assessment
Assess the overall health of the animal (history,physical examination, medications, diet)
Identify any concurrent illness often associated with the disease (eg. cataracts, urinary tract infections, pancreatitis)
Identify conditions that may interfere with response of the diabetic dog to treatment (eg. obesity, hyperadrenocorticism, hypothyroidism, dioestrus)

Table 3: Considerations in the assessment of a diabetic dog (modified from American Animal Hospital Association guidelines).

TREATMENT

The mainstay of treatment for DM is insulin, together with diet modification. The primary goal is to eliminate owner-observed signs (eg. reduction of PU/PD and stable body weight). Limiting marked fluctuations in blood glucose concentration and maintaining it below the renal threshold will minimise clinical signs. It is not as important to maintain blood glucose concentrations within the reference interval 24/7 (Rucinsky et al, 2010). As well as insulin therapy and dietary modification, consideration should be given to regular exercise, prevention and control of inflammatory, infectious, neoplastic and hormonal disorders, and avoidance of drugs with insulin-antagonistic effects. Consideration should be given to surgery for cataracts once the DM has been stabilised.

Insulin therapy should be initiated once a diagnosis has been made. Initially, intermediate acting insulin, such as porcine lente insulin (Caninsulin), is the preferred choice as it is licensed for use in the dog. The duration of action is close to 12 hours in most dogs, and an initial dosage of 0.25-0.5IU/kg (depending on degree of hyperglycaemia) administered twice a day, rounded to the nearest unit, is recommended (Rucinsky et al, 2010). The first injection should preferably be monitored with blood glucose measurements every hour at expected peak insulin activity (four to six hours after administration), so that the nadir can be determined. Dose adjustments are made based on subsequent nadir blood glucose concentrations. If the blood glucose concentration remains >8.0mmol/L, an increased dose is required. Usually, dose adjustments are made in 10% increments. If the nadir blood glucose concentration is <3.5mmol/L, a larger dose decrease (25% to 30%) is indicated (Rucinsky et al, 2010).

Generally, the dose of insulin is fixed once the blood glucose concentration remains between 3.5mmol/L and 8.0mmol/L for three consecutive measurements.

Dogs can be hospitalised with insulin-dose adjustments occurring on a daily basis. This has the advantage of a short duration until a fixed dose is achieved (usually six to 10 days). Alternatively, providing hypoglycaemia has not been demonstrated after starting insulin, the dog can be discharged and blood glucose concentrations repeated after three to seven days. This has the advantage of allowing time for the glucose to equilibrate after each dose adjustment (usually takes three days) but results in a longer time period until the insulin dose is fixed. In most cases, a total insulin dose of less than 1.0IU/kg/injection is needed for good glycaemic control. Once the insulin dose is fixed, the dog should be monitored at regular intervals, but at least every three months. Assessment of diabetic stability is based on owner-observed signs, physical examination findings, and stability of body weight. Measurement of serum fructosamine concentration can add further information to the status of glycaemic control (see Table 4). Because of the variability of blood glucose curves from day to day, they are usually retained for investigation of unstable diabetic cases rather than as a routine monitoring tool (Fleeman and Rand, 2003).

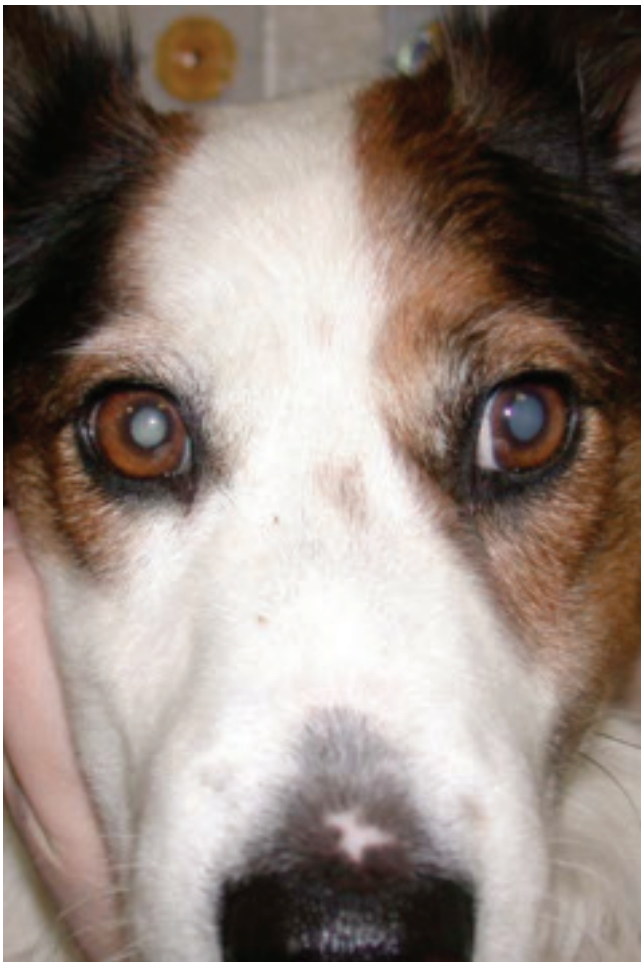
Client education is also of paramount importance, as the treatment regimen can be daunting. Generally, a 30-to-60-minute consultation with a nurse and a pre-written info sheet is recommended to educate clients on insulin injections and storage, as well as common mistakes and clinical signs of hypoglycaemia.

Degree of control	Fructosamine concentration
Excellent control	350-400umol/L
Good control	400-450umol/L
Fair control	450-500umol/L
Poor control	>500umol/L
Prolonged hypoglycemia	<300umol/L

Table 4: Interpretation of fructosamine concentrations.

COMPLICATIONS OF THERAPY

Recurrence or persistence of clinical signs can be frustrating and demanding, both for the veterinarian and the owner (Nelson 2015). Problems with management (see Table 5) can usually be ascertained by careful questioning of the owner and observing their injection technique. Insulin ineffectiveness is usually caused by issues concerning insulin bioactivity, storage, or response to the insulin (see Table 6). Insulin resistance is characterised as a reduced biologic response to a normal amount of insulin and is often caused by concurrent diseases (see Table 7). Insulin resistance should be suspected if control of hyperglycaemia is present in the face of doses greater than 1.5-2.0IU/kg per injection (Hess, 2010). Appropriate investigations should be performed based on additional clinical signs or clinicopathological features. Hypoglycaemia is a common complication of



Gross appearance of bilateral cataracts in a diabetic dog.

insulin therapy, and is usually due to a sudden large increase in the insulin dose, either because of excessive overlap of insulin duration, periods of inappetence or strenuous exercise (Ettinger et al, 2017). Signs of hypoglycaemia include lethargy, weakness, ataxia, seizures and coma. In some cases, there are no overt signs of hypoglycaemia but a Somogyi overswing occurs. This is a physiological response to hypoglycaemia, where the low blood glucose stimulates increased glycogenolysis and secretion of anti-insulin hormones (epinephrine, glucagon, growth hormone and glucocorticoids; [Hess, 2010]). This causes a marked hyperglycaemia within 12 hours, lasting for two to three days with typical clinical signs of hyperglycaemia. The persistence of clinical signs of DM often leads to the conclusion that the dog is not well controlled, and a false assumption that the dog needs an increased insulin dose. Diagnosis of Somogyi response requires documentation of hypoglycaemia (<3.5mmol/L) followed by hyperglycaemia (>16mmol/L). This usually requires hospitalisation and a serial blood glucose curve. If a Somogyi response is seen, a dose reduction is warranted (Hess, 2010). Excessive overlap of insulin duration may occur if insulin lasts longer than 12 hours, and such overlap increases the risk of hypoglycaemia. It is usually observed when the glucose nadir occurs 10 or more hours after injection and treatment options are decreasing the frequency of administration or changing insulin type to one

with a shorter duration of action (Ettinger et al, 2017). Management of a diabetic dog can be challenging and frustrating, and it requires commitment and communication between veterinarian and client about the treatment, costs and home care. With appropriate client education, monitoring, and a firm understanding of the variables that can be controlled, DM can be well-managed in almost all diabetic dogs.

Insulin administration	**Inappropriate syringe type**
	Incorrect filling of syringe
	Injection into fat/fibrous tissue
	Timing
	Responsibility and record keeping
	Magnitude and frequency of dose changes
Diet	**Timing of meals**
	Consistency
	Appropriate nutrients
Exercise	**Amount**
	Frequency
	Consistency

Table 5: Management problems that can lead to diabetic instability.

Inactive insulin
Diluted insulin
Out-of-date insulin
Inadequate dose
Somogyi response
Short/prolonged duration of action
Impaired insulin absorption
Anti-insulin antibody excess

Table 6: Causes of insulin ineffectiveness.

Drugs with anti-insulin effect
Hyperadrenocorticism
Hypothyroidism
Infection
Chronic inflammation
Dioestrus
Renal disease
Liver disease
Cardiac disease
Exocrine pancreatic insufficiency
Neoplasia (eg. glucagonoma, phaeochromocytoma)

Table 7: Causes of insulin resistance.

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