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DIABETES MELLITUS IN DOGS AND CATS

Definition:

- Diabetes mellitus (DM) is a heterogeneous group of diseases with multiple etiologies characterized by hyperglycemia resulting from inadequate insulin secretion, inadequate insulin action or both.

Epidemiology:

- It is one of the most common canine and feline endocrinopathies, affecting approximately 1 in 300 dogs and 1 in 200 cats.
- In dogs DM is most commonly diagnosed in middle-aged to older dogs. Most studies suggest females are at greater risk. A genetic predisposition for or against the development of DM exists in dogs (e.g., Boxer dogs have a very low incidence, whereas Australian Terriers, Schnauzers, Samoyeds, Yorkshire Terriers and many other breeds have a higher incidence of DM).
- In cats the mean age of presentation is between 10 and 13 years (95% of cases have an age >5 years) and about 70% of cases are represented by males.

Pathogenesis:

- Insulin deficiency causes decreased tissue utilization of glucose, proteolysis, lipolysis, accelerates hepatic glycogenolysis and gluconeogenesis, and causes accumulation of glucose in the circulation, i.e. hyperglycemia. When blood glucose (BG) concentrations exceed the capacity of the renal proximal tubule cells to reabsorb the glucose present in the glomerular ultrafiltrate, glycosuria occurs. The resulting glucose-induced osmotic diuresis causes polyuria, i.e. water loss, and activation of the thirst mechanism (polydipsia).
- The negative caloric balance resulting from an inability to utilize glucose leads to polyphagia.
- Protein metabolism shifts toward decreased protein synthesis and increased proteolysis, with loss of muscle mass and possible cachexia.
- Insulin deficiency (or actually a low insulin/glucagon ratio) accelerates lipid catabolism with mobilization of triglycerides, leading to increased concentrations of plasma free fatty acids and ketone bodies; the production of excess ketone bodies can subsequently lead to ketosis and ketoacidosis.

Classification:

- There are two predominant forms of DM in people, type 1 and type 2 DM.
- The most common form of DM in dogs resembles the human type 1 condition, characterized by permanent hypoinsulinemia, and an absolute need for exogenous insulin to control glycemia.
- Most affected cats have a disease comparable to type 2 DM in humans, characterized by a relative to an absolute deficiency of insulin combined with insulin resistance.

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Clinical signs:

- The four classic symptoms of DM are **polyuria**, **polydipsia**, **polyphagia** and **weight loss**.
- Frequently, affected animals are also reported to show lethargy and decreased interaction with family members.
- A relatively common clinical sign in dogs with DM is cataract.

In cats with DM, limb weakness noticeable as decreased ability to jump or walk or Plantigrade stance can be observed.

Diagnosis:

DM in dogs is diagnosed:

1. In a patient with a random (fasted or unfasted) BG concentrations >= 200 mg/dL (11 mmol/L) with classic clinical signs of hyperglycemia (with no other plausible cause).
   - In some cases, clinical signs may not have been reported by the owner
   - In cases with uncertainty over presence/absence of clinical signs, diagnosis should be confirmed by repeat BG measurement and/or documentation of alternative glycaemic parameters such as increased glycated proteins and/or glucosuria.
2. In some patients with fasting BG > 139 mg/dL (7 mmol/L) and <= 200 mg/dL (11 mmol/L) with or without clinical signs of hyperglycemia, DM is differentiated from stress hyperglycemia by documentation of persistent fasting hyperglycemia for more than 24 hours or increased glycated proteins.

DM in cats is diagnosed:

1. In a patient with a random (fasted or unfasted) BG>= 270 mg/dL (15 mmol/L) with classic clinical signs of hyperglycemia (with no other plausible cause) AND at least one of the following criteria:
   - Increased glycated proteins
   - Glucosuria on more than one occasion on a naturally voided sample acquired in a home environment at least 2 days after any stressful events.
2. In cats with random (fasted or unfasted) BG >130 mg/dL (7 mmol/L) and <=270 mg/dL (15 mmol/L) and at least two of the following:
   - Classic clinical signs of hyperglycemia (with no other plausible cause) or hyperglycaemic crisis
   - Increased glycated proteins
   - Glucosuria on more than one occasion on a naturally voided sample acquired in a home environment at least 2 days after any stressful events.

Initial diagnostic work-up:

- The minimum laboratory evaluation in a dog or a cat newly diagnosed with DM should include a complete blood count (CBC), a serum biochemistry profile that includes a serum fructosamine concentration, and urinalysis.
- In dogs the circulating progesterone concentration should be assayed in any intact diabetic female to identify progesterone induced DM.
- Abdominal ultrasound (US) may be indicated to evaluate patients for evidence of pancreatitis, adrenal enlargement, masses, pyometra, ovarian cysts, and other concerns. Other tests, including cPLI/fPLI, TT4, blood pressure measurements and thoracic radiographs, may be indicated.

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TREATMENT

- Diabetes Mellitus is a treatable condition that requires excellent owner compliance and effective communication between the owner and the veterinary team.
- Treatment for diabetic dogs and cats includes medical therapy, dietary management, discontinuation of diabetogenic drugs, and prevention or control of any concurrent diseases (**Table 1**).
- Due to the various factors influencing the diabetic state and the variable response to therapy, DM treatment is often complex.
- Successful DM management is characterized by minimal or no clinical signs of DM (i.e., polyuria, polydipsia, polyphagia, and weight loss), avoidance of complications (e.g., hypoglycemia, diabetic ketoacidosis [DKA]), and maintaining a good quality of life for both the pet and the owner. In cats, achieving diabetic remission is a reasonable goal.
- Regular monitoring is crucial for successfully achieving these goals. Monitoring options include clinical signs observed by the owner, blood glucose curves (BGC), glycated proteins (fructosamine and glycated hemoglobin), and continuous glucose monitoring systems (CGMS). None of these monitoring options is perfect, and clinicians should consider the owner's financial situation, level of motivation, and overall expectations regarding their pet.
- Some owners may find it challenging to comprehend the nature of DM and its various treatments and monitoring methods. Therefore, it is important to provide owners with detailed written information about all technical aspects of DM and offer easy access to care if needed. Furthermore, treatment and monitoring should adhere to a precise and comprehensive protocol.

TABLE 1. Common concurrent diseases implicated in insulin resistance in diabetic dogs and cats.

DISEASE	SPECIES
Obesity	Dogs, Cats
Infection (e.g., urinary tract infection)	Dogs, Cats
Hypothyroidism	Dogs
Hyperthyroidism	Cats
Disease of the oral cavity	Dogs, Cats
Chronic inflammation (e.g., chronic enteropathy)	Dogs, Cats
Hyperlipidemia	Dogs
Cushing's syndrome	Dogs > Cats
Chronic kidney disease	Cats > Dogs
Acromegaly (hypersomatotropism)	Cats
Chronic pancreatitis	Cats > Dogs
Diestrus in intact female	Dogs
Neoplasia	Dogs, Cats

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Diagnostic protocol

1. The presence of ketones is most commonly assessed in urine samples using commercially available nitroprusside test reagent strips. These strips measure only acetoacetate and acetone. Heparinized plasma can also be tested using urine reagent strips. The predominant ketone body produced in diabetic dogs and cats is believed to be beta-hydroxybutyrate, which can be measured using a quantitative enzymatic assay or a portable ketone analyzer. In cats treated with sodium-glucose cotransporter 2 (SGLT2) inhibitors, regular monitoring of ketones is very important.

8. Glucose concentrations can be assessed through BGC or CGMS. The latter are minimally invasive wearable devices that continuously measure interstitial glucose concentrations. CGMS allows more accurate identification of glucose nadirs, postprandial hyperglycemia, hypoglycemic episodes, and day-to-day variations in glycemic control compared to serial BGC. This enables the clinician to make more informed decisions regarding insulin dosage. The authors recommend the routine use of the Freestyle Libre® CGMS for glucose monitoring in diabetic dogs and cats.

9. Fructosamine and/or glycated hemoglobin should never be used as the sole indicator of glycemic control and should always be interpreted in conjunction with the owner's perception of clinical signs and glucose concentrations. Not all laboratories generate equivalent results for glycated proteins, and reference to previously published cut-offs for differentiating various degrees of glycemic control is not appropriate. Instead, it is advisable to monitor individual patients based on their previous values.

Diagnosis

2. Diagnosis of DKA includes the presence of hyperglycemia and ketonemia and/or ketonuria and a metabolic acidosis (with an increased anion gap). Clinicians should be aware that cats treated with SGLT-2 inhibitor can develop DKA despite normal or near-normal (<250 mg/dL [<14 mmol/L]) glucose concentration, a condition known as euglycemic DKA (eDKA). Hyperglycemic hyperosmolar syndrome (HHS) is characterized by severe hyperglycemia (>600 mg/dL or >33 mmol/L) and serum osmolality >350 mOsm/kg. DKA and HHS are life-threatening complications of DM and require early recognition and intensive care management.

4. Concurrent inflammatory, infectious, neoplastic, and metabolic conditions are common in diabetic dogs and cats (**Table 1**). These conditions can cause insulin resistance and/or glycemic variability, significantly impacting DM management. If a concurrent disease is identified, the clinician should prioritize resolving and treating that underlying condition to improve glycemic control.

11. Clinical hypoglycemia is defined as a glucose measurement of less than 60 mg/dL (3.3 mmol/L) associated with clinical signs (i.e., lethargy, weakness, tremor, ataxia, collapse or seizures). In patients experiencing clinical hypoglycemia, insulin administration should be discontinued until glucose concentrations are > 180 mg/dL (10 mmol/L). Thereafter, insulin should be restarted with a dose reduced by approximately 50% per injection.

12. Remission of diabetes is defined as a situation in which a patient, previously diagnosed with DM, ceases to receive exogenous insulin therapy and shows no evidence of DM according to ALIVE criteria after 4 weeks. Diabetic remission can be achieved in about 25-50% of newly diagnosed diabetic cats and most often occurs during the first 3 to 4 months of therapy. Diabetic remission is rare in dogs, but may occur in female dogs diagnosed with DM during diestrus or pregnancy.

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Therapy

3. The goals of treatment include restoring intravascular volume and electrolyte losses, resolving dehydration, suppressing lipolysis and ketogenesis, correcting acid-base imbalance, and providing a carbohydrate substrate (i.e., dextrose) to allow continued administration of insulin (to block ketogenesis) without causing hypoglycemia. Moreover, clinicians are encouraged to identify and treat any underlying disease. Cats diagnosed with eDKA require the same standard protocol, including insulin therapy and dextrose supplementation, despite having normal glucose concentrations.

5. Dietary recommendations are dictated by the weight of the animal, concurrent diseases, and both owner and animal preferences. Correcting obesity is the most beneficial step that can be taken to improve glycemic control, especially in cats. Diets designed for weight loss should not be fed to underweight dogs or cats. Restricting dietary carbohydrates, achievable only through feeding a canned/wet diet, can improve glycemic control and increase the likelihood of remission in diabetic cats.

6. Sodium-glucose cotransporter 2 (SGLT2) inhibitors (e.g., velagliflozin, bexagliflozin) have recently been licensed for veterinary use and represent a new therapeutic option in cats with DM. The main advantage of these drugs lies in their once-daily oral administration, which improves owner compliance and adherence to the therapeutic protocol. Recent evidence suggests successful DM management in naïve or insulin-pre-treated diabetic cats treated with SGLT-2 inhibitors. These drugs should be avoided in cats with DKA or severe concurrent disease. Moreover, the owner should be informed about the adverse effects associated with the use of SGLT-2 inhibitors (e.g., diarrhea or loose stool, weight loss, vomiting, polyuria, polydipsia, hypoxia/anorexia) and the potential risk of developing eDKA.

7. Various types of insulin are used to treat DM long-term, and none should be considered the best by default (**Table 2**). A smart insulin choice should take into account disease pathophysiology (including concurrent diseases), insulin-related factors (such as insulin pharmacology, costs, and regional prescribing regulations), pet and owner compliance, diet (composition and frequency), monitoring strategy, and therapeutic goals.

TABLE 2. Guidelines for starting dose and frequency of administration of various insulin formulations in dogs and cats newly diagnosed with diabetes mellitus.

INSULIN	BRAND NAME	CONCENTRATION SYRINGE/PEN	DOGS		CATS	
			Starting dose	Frequency	Starting dose	Frequency
Lente	Vetsulin® Caninsulin®	40 U/mL – Syringe/pen	0.25 U/kg	q12h	1-1.5 U/cat	q8-12h
PZI	ProZinc®	40 U/mL – Syringe	0.5 U/kg	q24h (q12h)	1-1.5 U/cat	q12h
NPH	Humulin N® Novolin N®	100 U/mL – Syringe/pen	0.25 U/kg	q12h	1-1.5 U/cat	q8h
Glargine 100 U/mL	Lantus®	100 U/mL – Syringe/pen	0.3 U/kg	q12h	1-1.5 U/cat	q12h
Glargine 300 U/mL	Toujeo®	300 U/mL – Pen	0.5 U/kg	q24h (q12h)	0.5 U/kg	q12h (q24h)
Detemir	Levemir®	100 U/mL – Syringe/pen	0.1 U/kg	q12	1-1.5 U/cat	q12h
Degludec	Tresiba®	100/200 U/mL – Pen	0.5 U/kg	q24h (q12h)	1-1.5 U/cat	q12h

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10. If glycemic control is considered unsatisfactory, the insulin dose is increased/decreased in steps of 0.5-1 U per injection in cats or 10-25% per injection in dogs. The frequency of insulin dose adjustment is dictated by the type of insulin and monitoring method used. Traditional recommendations suggest that insulin dose should not be adjusted more frequently than every 5–7 days. The authors recommend more frequent dose adjustments (every 2-3 days) in patients treated with insulin analogs (characterized by low day-to-day variability) and monitored via CGMS.

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