



ONLINE VETERINARY CONFERENCE 2024

Clinical Updates on Feline Diabetes Mellitus

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Lecture Notes

Clinical Updates on Feline Diabetes Mellitus “Setting you up for Sweet Success”

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Diabetes mellitus (DM) is defined as **hyperglycaemia** resulting from **inadequate insulin secretion, action or both** (ALIVE criteria).

Before we look at feline DM in more detail we need to remember the main molecules involved:

- **Glucose:** most basic sugar molecule; homeostatic mechanisms function to keep concentration within a narrow set range (reported to be 3.3-6.2 mmol/L in cats, although this is poorly-defined!)
- **Insulin:** anabolic peptide hormone produced by the β -cells of the endocrine pancreas, with hyperglycaemia as the main stimulus. Functions include:
 - o Lowering blood glucose concentrations (e.g. via translocation of GLUT-4 transporters into skeletal muscle cells)
 - o Production of storage molecules (e.g. stimulating hepatic glyco- and lipogenesis)
 - o Inhibiting catabolism of storage molecules (e.g. inhibiting hepatic gluconeogenesis)
- **Glucagon:** main catabolic hormone of the body; antagonises insulin activity by stimulating hepatic gluconeogenesis

PATHOGENESIS

Diabetes mellitus is a common endocrinopathy in cats, with estimates suggesting a prevalence of 1:200. Cats tend to suffer from relative insulin deficiency (analogous to “type 2” or “non-insulin-dependent” DM in people) due to conditions such as obesity and inflammation. The increased demand for insulin and persistent hyperglycaemia results in beta-cell exhaustion. Initially this is reversible, however over time can result in absolute insulin deficiency (analogous to “type 1” or “insulin-dependent” DM in people).

A number of risk factors for feline DM have been well-documented, including:

- **Body condition:** adipocytes release chemicals that antagonise insulin and trigger inflammation. Obese cats are four times as likely to develop DM as lean cats.
- **Age:** the prevalence of DM increases with age,
- **Sex:** male cats have an odds ratio of developing DM of 1.6 compared to female cats. This may be related to an increased propensity for obesity as well as insulin insensitivity
- **Breed:** breeds with a high prevalence of DM include Burmese, Tonkinese and Norwegian Forest Cats. Burmese cats are four times as likely to develop DM as a domestic shorthaired cat.
- **Diet:** cats fed dry food have an odds ratio of 3.8 of developing DM compared to those fed wet food, potentially related to increased calorie intake and increased carbohydrate load. Cats fed ad lib are also at greater risk.
- **Steroids:** glucocorticoids antagonise the effects of insulin. Cats administered immunosuppressive doses of prednisolone have a nearly 10% likelihood of developing DM. Naturally-occurring hyperadrenocorticism is very rare, but carries a high likelihood of concurrent DM (80-90%).
- **Pancreatitis:** the “cause and effect” relationship of pancreatitis and DM is debated, however inflammatory mediators (e.g. TNF- α , IL-6) in acute pancreatitis interrupt the insulin signalling cascade, and chronic pancreatitis can lead to fibrosis and consequently loss of pancreatic islets.
- **Hypersomatotropism (HS):** growth hormone antagonises the effects of insulin. Studies have suggested that HS is an underlying cause of DM in approximately 25% of cats in the UK and 16-20% of Australian cats.

CLINICAL PICTURE

The classic signs of feline DM include:

- Polyuria / polydipsia: due to the osmotic effects of excess glucose in the urine causing diuresis
- Polyphagia: due to lack of available energy at a cellular level and a subsequent reduction in inhibitory signals to appetite centres
- Weight loss: due to lack of available energy and reduced inhibition of protein catabolism
- Neuropathy: due to glucotoxicity affecting neuronal transmission → this occurs in ~10% of cats and most commonly affects the femoral nerve (as one of the longest nerves in the body)

DIAGNOSIS

Clinical signs will always be the first trigger to consider DM as a differential diagnosis. A number of different diagnostic tests are available, each with their benefits and limitations.

- **blood glucose (BG)**: useful for increasing index of suspicion, but can be a false positive due to stress hyperglycaemia)
- **glucosuria**: occurs when BG exceeds the renal threshold of 15 mmol/L. This can also be affected by stress; less commonly by tubular injury and chlorambucil administration
- **fructosamine**: glycated proteins, giving an average BG over the past 2-3 weeks. This is useful to confirm suspicion from spot hyperglycaemia, but can be falsely lowered by concurrent hyperthyroidism or recent onset DM.

The official ALIVE criteria for diagnosing DM in cats is a **BG of > 15 mmol/L** with **classic clinical signs** of hyperglycaemia (with no other plausible cause) and **at least one of**:

- increased fructosamine**
- glucosuria** on more than one occasion (naturally voided sample at home to avoid stress hyperglycaemia)

Once a diagnosis of DM has been reached, additional diagnostics may be warranted to detect any comorbidities causing insulin resistance. A minimum database would be considered a **complete blood cell count, serum biochemistry** and **urinalysis** (the importance of a urine culture in patients without either lower urinary tract signs or new/worsened azotaemia is debated!). Given the high prevalence of HS in diabetic cats, **IGF-1** should ideally be measured in every new diabetic, and especially those that are showing classical signs such as weight gain, morphological changes (broadened facial features, enlarged paws etc) or where stridor / snoring are reported. Additional tests such as thyroid hormone measurement, pancreatic testing and imaging should be performed based on patient presentation (for example, more testing is likely to be warranted in a diabetic cat with a fluctuating appetite or a patient presenting in diabetic ketoacidosis [DKA] than a “well” patient presenting for PUPD).

TREATMENT

The main principles of feline DM management are **improving insulin activity** (by reducing resistance, augmenting endogenous insulin release or providing exogenous insulin) and **reducing carbohydrate load** (by reducing intake and increasing excretion). A multimodal approach is required in nearly all patients.

Diet

Wild cats tend to have a diet where only ~2% of metabolisable energy is in the form of carbohydrate: they therefore have a high level of constitutive gluconeogenesis, meaning that they are primed to produce glucose. Compare this to commercial diets where up to carbohydrates form up to 60% of metabolisable energy. This will result in prolonged and high levels of post-prandial hyperglycaemia. The ideal diet for a diabetic cat is **high in protein** (~40-45% of metabolisable energy), **low in carbohydrate** (<10% of metabolisable energy), uses **complex carbohydrates** (e.g. sorghum rather than rice) and is **wet food** (as dry foods require higher carbohydrate levels to facilitate processing and have a higher energy density).

Weight loss

This is appropriate for any cat with a body condition score above optimal. Studies show that for every 1kg increase in body weight above optimal insulin sensitivity reduces by 30%. Feeding wet diets at carefully restricted calorie intake, using activity feeders and encouraging exercise through creative means can help, with a sustainable aim of 1-2% body weight loss per week.

Oral hypoglycaemics

These are central to managing type 2 DM in people, and a number have been studied in cats, with the GLP-1 analogues (drugs that boost endogenous insulin production for a set BG concentration) exenatide and semaglutide with some evidence of benefit.

The most exciting development in feline DM management (as of 2024!) has been the introduction of sodium-glucose cotransporter-2 (**SGLT-2**) inhibitors: bexagliflozin and velagliflozin. These drugs block glucose reabsorption from the urine in the proximal convoluted tubule of the kidney, resulting in a 30-50% reduction in glucose reabsorption, thereby lowering blood glucose. Velagliflozin is an oral solution administered on food once daily, with a 98% compliance rate.

Studies in Europe and America have shown SGLT-2 inhibitors to be effective in controlling the clinical signs of DM in up to 80-90% of cats, with non-inferiority when directly compared to treatment with porcine lente insulin. When used appropriately in “happy diabetics” (i.e. cats with DM without significant comorbidities) they result in reliable glycaemic control without risk of clinical hypoglycaemia.

Side effects of velagliflozin include diarrhoea (usually mild and self-limiting), vomiting (again mild and tends not to occur if administered with food) and a possible increased risk of bacteriuria (uncertain clinical relevance). The most important side effect to be aware of is **euglycaemic DKA** (euDKA). This occurs because SGLT-2 inhibitors successfully reduce BG concentrations but do not supply the anti-catabolic effects of insulin, allowing ketogenesis to occur. All cats receiving this medication should be frequently monitored for ketonuria / ketonaemia, and any unwell cat receiving SGLT-2 inhibitors should be considered to have euDKA until proven otherwise. Over 85% of euDKA cases occur in the first two weeks of therapy and there is a possible increased risk in cats pre-treated with insulin (as these patients are likely to have had a longer disease duration and so may have less endogenous insulin production).

NB: SGLT-2 inhibitors not licensed and velagliflozin not available in Australia at the time of writing (but watch this space...!)

Insulin

This continues to be the mainstay of treatment for feline DM. Extensive literature is available regarding insulin selection and dosing, with some of the most common insulins listed below:

INSULIN	EXAMPLES	CONCENTRATION	RECOMMENDED STARTING DOSE	NOTES
Porcine lente insulin	“Caninsulin” “Vetsulin”	40iu/ml	1-2 IU per cat SC q12hrs	Short duration in cats (6-12 hours) – <i>not recommended</i> Pen available
Protazmine zinc insulin	“Prozinc”	40iu/ml	0.2-0.4IU/kg SC q12hrs	Longer duration than lente (10-14 hours)
Glargine	“Lantus” “Toujeo”	100iu/ml	0.25-0.5IU/kg SC q12hrs	Increased likelihood of remission over shorter-acting insulins
Glargine	“Toujeo”	300iu/ml	0.5IU/kg SC q12hrs	Smooth action Only available with pen

Hypophysectomy

Cats with hypersomatotropism have a 70-85% chance of entering diabetic remission following hypophysectomy (often within the first week following surgery). Surgical removal of the pituitary gland (via the palate) removes the antagonising effects of growth hormone. Cats undergoing hypophysectomy require life-long supplementation with glucocorticoids (ideally hydrocortisone) and levothyroxine, and for a variable period of time with DDAVP / desmopressin.

MONITORING

Whilst all cats undergoing treatment for DM should be closely monitored, the intensity and frequency of monitoring will depend on the agreed goals of treatment for the individual patient. For example, aiming for remission requires more aggressive therapy and therefore closer monitoring of glucose concentrations than simply ameliorating clinical signs.

- **Diabetic clinical score:** assessment of clinical signs of DM is the cornerstone for monitoring any diabetic patient. A diabetic that is energetic and gaining weight with minimal PUPD clearly has better control of DM than a polyphagic polydipsic cat with marked weight loss, even before any quantitative measurements are performed. The Diabetic Clinical Score proposed by the ALIVE group provides a semi-objective assessment of weight loss, PUPD, appetite and energy levels. This should be performed at every consultation and is useful for standardising clinical assessment amongst practitioners.
- **Urine assessment:** this is of most benefit in monitoring SGLT-2-treated cats for ketonuria, however absence glucosuria in a cat no longer receiving insulin can be a useful indicator of on-going remission.
- **Blood glucose concentrations:** given the impact of stress on BG concentrations obtained in hospital, the benefit of hospitalised glucose curves (and especially spot-BG concentrations) is limited. More information can be derived if clients are able to measure BG at home, however rapid fluctuations or overnight variations may be missed.
- **Fructosamine concentration:** this provides a crude guide to average level of blood glucose but provides insufficient detail to assess whether a high fructosamine concentration is due to persistent hyperglycaemia or insufficient duration of insulin action during the day. The utility of fructosamine measurement is likely to be higher in SGLT-2-treated cats, where BG concentration tends to be static throughout the day.
- **Continuous interstitial glucose monitoring (CIGM):** wearable interstitial glucose (IG) monitors (such as the Freestyle Libre) provide a wealth of information regarding variation in glucose concentration day-to-day and overnight. They are very useful for troubleshooting a diabetic with persistent clinical signs or monitoring response to changes in insulin dosing. Data can be viewed remotely via use of the cloud-based Libreview system. Key to note is that there is a 5-12 minute lag time in equilibration between BG and IG and that CIGM is most useful for providing trends in glucose concentrations rather than exact values. As a word of caution, the vast amount of data can prove a source of anxiety and/or obsession in some clients!

TROUBLE-SHOOTING

Consider the following framework when trying to find a reason for apparently poor or variable diabetic control in a patient:

- **Management issues:**
 - o Feeding regime: diet type, variability, multiple people feeding, hunting
 - o Dosing regime: timing, client technique, multiple people injecting (variation in technique), syringes vs pens
 - o Monitoring: do the numbers reflect the clinical picture?
- **Insulin issues:**
 - o Storage: fluctuations in temperature and light exposure, shelf-life
 - o Handling: PZI = “roll” before drawing up, lente insulin = “shake” before drawing up
 - o Type: lente insulin vs longer-acting “basal” insulins
 - o Injection site: fibrotic tissue, subcutaneous vs intradermal injection
- **Patient issues:**
 - o Comorbidities: cause of resistance vs mimicking clinical signs
 - o Individual response to treatment

REMISSION

Diabetic remission is defined a **normoglycaemia for >4 weeks without medical therapy**. Studies reflect a wide variety in incidence of remission, based on patient population and treatment modality, with a 40-80% incidence being reported.

- **Positive predictive factors** of remission: a more recent diagnosis (< 6 months: these patients likely have greater capacity to produce endogenous insulin); strict glycaemic control (reduces glucotoxicity to β -cells); insulin glargine (provides better glycaemic control than veterinary insulins); prior glucocorticoid usage (removal reduces insulin resistance); older cats (cause uncertain!)
- **Negative predictive factors** of remission: diabetic neuropathy (suggests longer duration of hyperglycaemia); hypercholesterolaemia (lipotoxicity to β -cells)

Cats that manage to enter remission should always be considered as in a “pre-diabetic” state, with up to 75% of cats in remission showing impaired glucose tolerance. There is a 25-30% chance of relapse (with a significant reduction in probability of a second remission), and the most important factor in maintaining remission is to continue to feed a diabetic-appropriate diet.

RESOURCES

- **ALIVE:** Agreeing Language in Veterinary Endocrinology, European Society of Veterinary Endocrinology
- **Overview of feline DM:** Gottlieb S, Rand J. Managing feline diabetes: current perspectives. *Vet Med (Auckl)*. 2018 Jun 19;9:33-42
- **Feline DM epidemiology:** O'Neill, D., Gostelow, R., Orme, C., Church, D., Niessen, S., Verheyen, K. and Brodbelt, D. (2016), Epidemiology of Diabetes Mellitus among 193,435 Cats Attending Primary-Care Veterinary Practices in England. *J Vet Intern Med*, 30: 964-972
- **Dietary assessments:** Balance It Guaranteed Analysis Converter. <https://balance.it/convert>
- **European velagliflozin study:** Niessen, S. J. M. et al. (2023) Efficacy and safety of once daily oral sodium-glucose co-transporter-2-inhibitor velagliflozin compared to twice daily insulin injection therapy in diabetic cats. *JVIM* (2024)
- **Freestyle Libre use in cats:** Knies, M.; Teske, E.; Kooistra, H. 2022 Evaluation of the FreeStyle Libre, a flash glucose monitoring system, in client-owned cats with diabetes mellitus. *J. Feline Med. Surg.* 24, e223–e231
- **The Ralph carer handout on feline DM – *please note the information in this handout is based on drug availability and licensing laws in the UK and does not directly apply in Australia, but can be used as a basis for creating information sheets for clients:***

- Full webinar references:



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