

Guide to feline diabetes

Diagnosis and treatment guidelines of the
RVC Diabetic Remission Clinic

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Diabetes mellitus (DM) is a common endocrinopathy in cats, with an increasing prevalence, likely reflecting the changes in nutrition and housing of domestic cats, while the genetic basis of our cats still supports a hunting lifestyle (Forcada et al, 2014). Management of the disease requires active involvement of the diabetic cat owner and optimal communication with and within the veterinary care team. The aim of this guide is to highlight the most important steps in the management of diabetes in cats, based on current recommendations by the team running the Royal Veterinary College Diabetic Remission Clinic.

Classification and diagnosis

To provide the best possible treatment options and an accurate prognosis, classification of the type of diabetes should be offered at time of diagnosis. This is especially relevant since the discovery that 1 in 3 to 1 in 5 diabetic cats has underlying acromegaly or hypersomatotropism (Niessen et al, 2015). Additionally, a high percentage of diabetic cats have elevated feline pancreatic lipase immunoreactivity (fPLI); pancreatitis could be present as direct consequence of the diabetes, a coincidental co-morbidity, or even the root cause of the diabetes (Forcada et al, 2008). At time of diagnosis the Clinic discusses with owners the benefits of performing the following tests to confirm and classify the diabetes mellitus in cats:

- Record solid evidence of pathological hyperglycaemia, while bearing in mind stress hyperglycaemia as a complicating phenomenon, by:
 - Documenting clinical signs compatible with diabetes mellitus including scoring of clinical signs using the validated Diabetic Clinical Score (DCS) (Venzon et al, 2016; *Table 1*)
 - Documenting hyperglycaemia and concurrent glucosuria on at least one and preferably more occasions, and preferably when fasted
 - Documenting an increased fructosamine.
- Offer screening for presence of acromegaly/hypersomatotropism (prevalence 1 in 4 diabetic cats; phenotype usually initially unremarkable)
 - Test serum insulin-like growth factor-1 (IGF-1) at time of diagnosis

- If the cat's diabetes proves difficult to control, IGF-1 measurement is repeated 6 weeks after the start of exogenous insulin
- Offer screening for presence of pancreatitis (prevalence unknown, yet likely significant)
 - Test fPLI; if fPLI is increased or if animal has unreliable appetite, offer abdominal ultrasound
- Offer screening for a urinary tract infection (prevalence >1 in 10 diabetic cats)
 - Offer cystocentesis for full urinalysis, sediment examination and culture.

Apart from the most common type of feline diabetes mellitus (the feline equivalent of type 2 diabetes in humans) and hypersomatotropism induced diabetes mellitus, other less common types include a form of diabetes associated with hyperadrenocorticism (due to a pituitary or adrenal tumour). The clinician should pay attention to the presence of skin lesions, including fragile or easily-injured skin and coat colour changes. Pituitary-adrenal-axis testing should be considered in such cases, as well as abdominal ultrasound to assess adrenal size, possibly followed by pituitary imaging.

Administration of diabetogenic drugs (e.g. steroids, progestagens) could be involved in the cause of diabetes mellitus; this type of diabetes is often still considered under the umbrella-term of type 2 diabetes mellitus. Gestational and type 1 diabetes mellitus are not currently considered of relevance in cats.

The Diabetic Clinical Score

Every glycaemic parameter used in the diagnostic and monitoring process can prove inaccurate due to various reasons, therefore paying particular attention to the clinical signs associated with diabetes mellitus is key to making a successful diagnosis, as well as achieving treatment success. Diabetic cats typically present for investigation of polyuria, polydipsia, polyphagia and weight loss, although the ratio in which these individual signs occur may vary between patients. Reduced activity, attitude, ability to jump, plantigrade (and even palmigrade) posture and unkempt hair coat might also be present. Since the clinical signs are key to diagnosis and follow-up and since most diabetic cats are seen by multiple clinicians, the Clinic recommends use of the DCS (*Table 1*).

Assessment for co-morbidities

Since most diabetic cats are elderly, many will have one or more co-morbidities that may have relevance to the future care of the diabetic cat and either directly or indirectly interfere with treatment success. Depending on the owner's commitment, finances and the physical examination and history findings, clinicians could offer additional diagnostic tests if a significant co-morbidity is suspected.

Overall treatment goals

The main treatment goals in cats with DM are to resolve clinical signs and improve the quality of life (QoL) of the cat and the owner. These can be achieved by obtaining good glycaemic control (keeping glucose levels under the renal threshold of about 15 mmol/l) while preventing hypoglycaemia and other complications (e.g. diabetic ketoacidosis). Some diabetic cats can enter a state of diabetic remission, with exogenous insulin no longer needed. However, this will only be achieved in some cats; current estimates within populations relevant to first opinion practice indicate remission should be feasible in 30–40% of cats. Previously reported higher remission rates likely came from suboptimal study design (Gostelow et al, 2014). Therefore, remission is best not stated as the major treatment goal, rather as a welcome bonus.

Treatment principles trump treatment protocols

Many protocols have been proposed to achieve the above goals. The Diabetic Remission Clinic, however, prefers to promote the use of treatment principles, not protocols (except when running clinical trials). Protocols assume that every diabetic cat and every diabetic cat owner is the same and therefore can and wants to comply with the stated protocol. Recent QoL research has emphasised the need for flexibility. Up to 30% of diabetic cats are euthanised within the first year of treatment, many due to significant negative effects on the QoL of the cat owner, as well as the cat (Niessen et al, 2010). Significant improvements are possible when clinician and diabetic cat owner do their best to evaluate what treatment style is preferred for the individual diabetic cat-owner combination, taking into

account e.g. the character of the cat, the flexibility of the owner's lifestyle, the anxiety of cat and owner with regards to treatment and hypoglycaemia, financial and time limitations. Using the scientifically-validated QoL tool DIAQoL-pet (included in the RVC Pet Diabetes App) may help highlight these specific areas. There are three mainstays of diabetic cat treatment:

1) Treat the underlying cause if possible; treat interfering co-morbidities

Diabetes is not a disease; it is the consequence of a disease or set of circumstances. Clinicians should aim to correct or at least modify any known underlying cause or contributing circumstance. Hypersomatotropism-induced diabetes could be treated by hypophysectomy, pasireotide injections or radiotherapy; 85% of acromegaly-induced diabetes cases will achieve complete diabetic remission following surgery. Obesity-associated diabetes mellitus should be treated with a comprehensive, long-term weight loss strategy. Where diabetogenic-drugs are involved, management should incorporate ceasing these or finding alternatives for them. In some patients, pancreatitis-associated diabetes mellitus may be linked to conditions such as inflammatory bowel disease or cholangiohepatitis; treatment of these might result in a decrease of frequency or severity of pancreatitis relapses. Any co-morbidity causing unreliable appetite or gastro-intestinal absorption should be dealt with. Hyperadrenocorticism-induced diabetes mellitus could be treated by hypophysectomy, adrenalectomy, trilostane, pasireotide or radiotherapy.



The RVC Pet Diabetes App.

2) Use a long-acting insulin to reduce the pathological hyperglycaemia

Two insulin preparations are currently licensed for treatment of feline diabetes in the UK: Caninsulin® (MSD Animal Health; porcine lente type insulin) and ProZinc® (Boehringer Ingelheim; protamine zinc recombinant human insulin); these preparations should be considered first before other insulin types are used. While there is no legitimate reason to switch cats that are well-controlled on Caninsulin to ProZinc, current treatment guidelines recommend to initiate treatment of DM in cats using insulin preparations with the longest possible duration of action. In the cat, protamine zinc insulin (ProZinc) is therefore preferred (Sparkes et al, 2015). Most studies found protamine zinc insulin, glargine and detemir to be associated with the longest duration of action, though direct comparison studies are still lacking (Gostelow et al, 2014). Insulin types with a lower concentration (veterinary licensed options: 40 units/ml, versus human insulin types: 100 units/ml) enable more accurate administration of typical cat dosages. Each patient will show an individual response to an individual insulin type, introducing a significant

element of unpredictability. The bottom line remains: use the insulin type that achieves the principle goal of sufficiently lowering the blood glucose to enable a good quality of life without hypoglycaemia or diabetic ketoacidosis.

The starting dose of any insulin type is a dose that is safe and is unlikely to cause hypoglycaemia. This is often achieved with one (average sized cat) or two (big cat) units per cat per injection. After starting the cat on insulin, it is sent home and the dose remains unaltered until re-evaluation (at home or in-clinic) 7–14 days later. The dose is only altered earlier than 7 days should hypoglycaemia be suspected or documented (unlikely given the modest starting dose).

3) Reduce and standardise the glycaemic impact of meals

Feeding a suitable diet is an essential part of treatment (Gostelow et al, 2014). In overweight/obese cats, weight loss should be attempted; this increases the insulin sensitivity, aids improvement of glycaemic control and can even induce diabetic remission.

When choosing the diet, the following guidelines should be considered:

Table 1. The Diabetic Clinical Score can be used to improve and standardise the communication of key clinical signs

Clinical sign	Severity (compared to prior to diabetes-onset)	Score
Unintended weight loss over the past 2 months (assessed using body weight measurement)	None, or weight gain	0
	Mild (<5% loss)	1
	Moderate (5–10% loss)	2
	Severe (>10% loss)	3
Increased drinking and/or urination (assessed by questioning owner)	None	0
	Mild – some increase noted	1
	Moderate – increased filling of water bowl	2
	Severe – constantly seen to drink	3
Increased appetite (assessed by questioning owner)	Normal appetite	0
	Mild – finishes food eagerly	1
	Moderate – finishes food eagerly and begs for more	2
	Severe – obsessed with food	3
Decreased activity/ attitude (assessed by questioning owner)	Normal or increased activity	0
	Mild – slightly less active	1
	Moderate – certainly less active	2
	Severe – mainly lying around	3
	Total score	/12

- The diet has to be palatable to ensure consistency in day-to-day caloric intake
- Carbohydrate content should be as low as the cat will eat. Current recommendations are $\leq 12\text{--}15\%$ of metabolisable energy (ME) carbohydrate, with protein content $\geq 40\text{--}45\%$ ME (low carbohydrate, high protein diet), though others quote $< 7\%$ of ME (Zoran and Rand, 2013; Sparkes et al, 2015)
- Wet food is preferred to kibbles as the carbohydrate content is usually lower
- If another medical condition requiring dietary therapy is present (e.g. food allergy/intolerance, chronic kidney disease), this often should take priority over the diabetic diet
- The number of calories needed should be calculated based on estimated optimal BW, e.g. : caloric need (in kcal) = $30 \times \text{BW (kg)} + 70$. This is only a guide and might need to be adjusted based on regular weight checks (initially once a week)
- If weight loss is attempted, this should ideally be $0.5\text{--}1\%$ of BW/week. This often requires strategies to increase overall physical activity
- The optimal frequency of feeding has not been established. The Clinic recommends leaving intrinsically grazing cats to graze, as long as they do not gain weight beyond the optimal body weight. Cats that do not normally graze can be given their food before or at time of insulin injection.

Oral hypoglycaemic agents

Oral hypoglycaemic agents rarely provide sufficient glycaemic control as sole therapies and are not recommended as first line treatment (Gostelow et al, 2014). They could be considered if an owner absolutely declines insulin treatment or is unable to inject insulin. Note no veterinary licenced products are available.

Monitoring to assist individualised treatment

Several monitoring protocols have been described and recommended in veterinary and lay literature. One protocol will not be the right answer for all pet-owner combinations. It is more appropriate to adhere to monitoring principles, underpinned by knowledge of the advantages and disadvantages of each monitoring

tool. The right monitoring strategy will be different for each cat and owner, and can also change over time for the same cat and/or owner. Some cats and owners will benefit from more intense or more complete monitoring using many of the tools available when seeking to avoid hypoglycaemia at all cost (e.g. with anxious owners or when cats are normally left unsupervised and therefore hypoglycaemia could prove lethal). Other owners are keen to maximise the chances of diabetic remission, again benefiting from the use of many tools to fine-tune the glucose concentrations more carefully and more frequently. Others will benefit from a more pragmatic approach and less intense management (e.g. when working to a tight budget or working with a very busy or unmotivated owner or 'feisty' cat). The main characteristics of the main monitoring tools available are summarised in *Table 2*. Initially, reassessment of the diabetic cat is recommended using the most appropriate tool(s) for the specific cat-owner combination at hand every 7–14 days. On each occasion insulin can be increased by $0.5\text{--}1$ unit per injection until the treatment goals have been achieved. Reassessment also occurs following any implemented treatment change. Assessment of the clinical picture should ALWAYS precede any evaluation of any glycaemic parameter and the Clinic recommends the DCS be determined on each occasion (*Table 1*). This provides a tool to improve communication between owner and clinician, focusing the conversation on the most relevant clinical signs and urging the owner to quantify the degree of improvement or deterioration, and improves the communication of progress when different clinicians are involved in a cat's care.

Get to know the owner and get them involved

The owner's active participation in the treatment of diabetic cats is essential. In a survey evaluating the QoL of diabetic cats and their owners, boarding difficulties, owner wanting more control over their cat's diabetes, difficulties leaving cat with friends or family, general worry about diabetes, worry about hypoglycaemia, need for adjusting social and/or working life and the costs of the treatment have been identified as issues most negatively impacting QoL (Niessen et

Table 2. Main glycaemic monitoring tools

Tool	Details	Advantages	Disadvantages
History, Diabetic Clinical Score (DCS) and physical examination including body weight and body condition score	Key prior to assessing any glycaemic parameter. The DCS is a validated tool to quantify the main clinical signs	Clinical picture never lies Cheap Scoring system available	Quality is owner and clinician dependent
Serial blood glucose measurements (blood glucose curve)	Usually taken 2–3 hourly from injection till next injection, more often when glucose <10 mmol/l	Only tool with potential to show nadir, percentage of time in target zone and duration of insulin action Can be done at home	Susceptible to stress Financial and time costs Impossible in some cats Biological day-to-day variation in values
Fructosamine	Serum sample reflecting the average glycaemic control over the last 1–3 weeks	Single blood sample Not affected by stress hyperglycaemia Often smaller investment in time and money than glucose curve	Does not provide detailed information about nadir and thus hypoglycaemia risk Can also be higher with hypoglycaemia-induced hyperglycaemia Assay and sample issues
Spot blood glucose test	Single blood glucose determination	If low, overdosing or remission possible; insulin should be reduced Could be used pre-insulin: assess for insulin overdosing	Not useful for assessing whether insulin dose needs to be increased, since time of nadir cannot be predicted (day-to-day variability of nadir) Affected by stress
Urine glucose	Urine glucose concentration determined by dipstick; the concentration depends on glucose spill-over and volume of urine produced	Easy and cheap Can be done at home Absence of urine glucose implies overdosing and/or remission	Exact concentration rarely useful: can be high e.g. if urine volume low Can be affected by stress Presence of glucose even with well controlled cats
Urine ketones	Urine ketone concentration determined by dipstick	Easy and cheap Can be done at home	Ketones sometimes present in well-controlled diabetic cats

al, 2010). These issues should be discussed with the owners on an individual basis and adjustments in the treatment plan made as appropriate (e.g. consider adjusting the 12-hourly injection times to 8 am and 10 pm if this significantly improves the owner's lifestyle). Access to veterinary support and guidance is crucial for treatment success, and QoL research highlights that most diabetic cat owners would like

to feel more empowered and have more control over their cat's diabetes management than they currently are experiencing; it is the veterinary care team's duty to ensure this is the case, since this will improve achieving long-term compliance and success. The free RVC Pet Diabetes App for iPhones, Android and tablets enables easy communication of all aspects of having a pet with diabetes. It features a diabetes diary

function, as well as the QoL tool that helps highlight particular issues that warrant individualising the management regimen. It also features a medication reminder, the ability to perform the DCS, a body condition score function and a calculator for caloric requirement. It is designed to get the owner actively involved, communicating clinical findings at the touch of a button with the veterinary care team and feeling generally more in control.

What to do if clinical signs suggest poor glycaemic control

- Check if the poor glycaemic control is the reason for the persistence/deterioration of the clinical signs (e.g. blood glucose curve, fructosamine)
- Check owner's routine including insulin storage, handling and injection technique
- Review the history of previous insulin dose adjustments and monitoring (e.g. dose was increased too quickly or without previous monitoring)
- Test for the presence of a co-morbidity or occult underlying disease (e.g. acromegaly, pancreatitis).

Remission in diabetic cats

No single test can predict the occurrence of remission in an individual cat. Treatment with longer acting insulin preparations and low carbohydrate, high protein diet seem to be related to higher success rates. Achieving good glycaemic control early in the course of the disease is likely to increase the chance of remission. How low a blood glucose is needed to maximise success is currently unknown. Protocols that dose insulin to achieve complete euglycaemia (rather than lowering glucose below the renal threshold) have so far not been proven to be superior (Gostelow et al, 2014).

Cats that achieve remission have persistently impaired β -cell function and should be continued on low carbohydrate, high protein diet lifelong. About 30% of these cats will relapse and need insulin treatment to be reinstated (Gottlieb et al, 2015). Therefore, monitoring for re-occurrence of clinical signs and re-assessment if these re-occur is strongly advised.

More information can be found on: www.facebook.com/RVC.Diabetic.Remission.Clinic

Key Points

- The main treatment goals are to eliminate the clinical signs and ensure good quality of life of both the cat and the owner.
- The owner's active participation in the treatment is essential: consider using modern technology such as Apps.
- Insulin (preferably a longer-acting preparation) and a low carbohydrate, high protein diet are the mainstays of treatment.
- Achievement of good glycaemic control early in the course of the disease will increase the chance for remission.
- Clinicians should individualise treatment and monitoring protocols to suit the needs of each cat-owner combination.

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