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PRACTICE GUIDELINES

2025 iCatCare consensus guidelines on the diagnosis and management of diabetes mellitus in cats

Practical relevance: Diabetes mellitus (DM) is a common feline endocrine disease. Developments in therapy mean there are now more options for treatment, including various types of insulin and novel oral medications. Use of continuous glucose monitoring (CGM) devices has increased, providing more detailed information on affected cats. Selecting the appropriate treatment for DM, monitoring the cat's response and treating complications can present challenges, but these patients are nonetheless rewarding cases to manage for clinicians.

Aim: The '2025 iCatCare consensus guidelines on the diagnosis and management of diabetes mellitus in cats' provide practical information on the management of complex as well as more routine cases. The importance of a team approach, involving veterinary professionals and the caregiver, is emphasised as this is likely to optimise patient outcomes.

Clinical challenges: The pathogenesis of DM in cats, including absolute or relative insulin deficiency, can complicate management. Moreover, conditions such as hypersomatotropism, which is a prevalent underlying cause, as well as comorbidities that are common in affected populations of cats, warrant special consideration. Selecting the most appropriate therapy for the individual cat with DM relies on a thorough assessment of the case, including testing for comorbidities, if indicated, and excellent communication with caregivers. Treatment with either insulin or sodium–glucose cotransporter-2 inhibitors may be appropriate and should be combined with a diet and a monitoring regimen that are suitable and manageable for both cat and caregiver. Monitoring, to determine the response to treatment and to detect complications such as diabetic ketoacidosis or hypoglycaemia, may include placement of a CGM device.

Evidence base: These Guidelines have been created by a panel of experts brought together by the International Cat Care (iCatCare) Veterinary Society. Information is based on the available literature, expert opinion and the panel members' experience.

Keywords: Hypersomatotropism; sodium–glucose cotransporter-2 inhibitor; SGLT2i; insulin; glucose; continuous glucose monitoring

Diabetes-specific abbreviations: BG = blood glucose; CGM = continuous glucose monitoring; DCS = Diabetic Clinical Score; DKA = diabetic ketoacidosis; DM = diabetes mellitus; eDKA = euglycaemic diabetic ketoacidosis; HST = hypersomatotropism; IGF-1 = insulin-like growth factor 1; PZI = protamine zinc insulin; SGLT2i = sodium–glucose cotransporter-2 inhibitor

international cat care VETERINARY SOCIETY

Samantha Taylor BVetMed(Hons), CertSAM, DipECVIM-CA, MANZCVS, FHEA, FRCVS*
Panel Chair
International Cat Care, Tisbury, Wiltshire, UK

Martha Cannon BA, VetMB, DSAM(Fel), FRCVS
Oxford Cat Clinic, Oxford, UK

David Church BVSc, PhD, MANZCVS, FHEA, MRCVS
Royal Veterinary College, Potters Bar, Hertfordshire, UK

Linda Fleeman BVSc, PhD, MANZCVS
Animal Diabetes Australia, Melbourne, VIC, Australia

Federico Fracassi DVM, PhD, DipECVIM-CA
Department of Veterinary Medical Sciences, University of Bologna, Italy

Chen Gilor DVM, PhD, DACVIM (SAIM)
University of Florida, Gainesville, FL, USA

Jocelyn Mott DVM, DACVIM (SAIM), FACVIM (feline and canine diabetes)
University of Florida, Gainesville, FL, USA

Stijn Niessen DVM, PhD, DECVIM, PGCertVetEd, FHEA, MRCVS
Royal Veterinary College, Potters Bar, Hertfordshire, UK; and Veterinary Specialist Consultations and VIN Europe, Hilversum, The Netherlands

*Corresponding author: sam.taylor@icatcare.org

Introduction

Diabetes mellitus (DM) is one of the most common endocrinopathies in cats,[1–3] with prevalence thought to be increasing.[3] In this species, DM has a complex pathogenesis, and affected cats may have comorbidities and develop complications requiring adjustments in therapy. Management of cases requires a thorough understanding of the condition, as well as excellent communication skills to work with caregivers on aspects of both monitoring and treatment. This is an area of feline medicine that has seen much research and development over the past 10 years since the previous 'ISFM consensus guidelines on the practical management of diabetes mellitus in cats' were published.[4] An important advancement has been the inception of the 'Agreeing Language in Veterinary Endocrinology' (ALIVE) project, which aims to create a body of agreed terminology and a standardised scoring system for the diagnosis of DM and other endocrinopathies in companion animals. ALIVE terminology is used where possible in these Guidelines, which aim to provide practitioners with information

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RESOURCE FOR CAREGIVERS

iCatCare's resource for caregivers complements the information and advice offered in these Guidelines.

- Managing the diabetic cat: a guide for caregivers

Available as supplementary material and also at: icatcare.org/advice/cat-carer-guides

on the pathogenesis, diagnosis and practical treatment and monitoring of DM, based on the latest available evidence and expert opinion.

Pathogenesis and aetiology

DM is a syndrome characterised by hyperglycaemia that is caused by defects in insulin secretion, insulin sensitivity or both.[5,6] Regardless of the pathogenic cause, a relative or absolute deficiency in insulin action on target tissues leads to myriad abnormalities in carbohydrate, fat and protein metabolism. 'Prediabetes' is a state of abnormal blood glucose (BG) concentrations (either fasting or after a glucose load) that do not yet meet the criteria for DM.

Prediabetes in cats

In human medicine, prediabetes is defined as hyperglycaemia below the cut-off for DM and/or impaired glucose tolerance.[7] This phenomenon likely also occurs in cats (eg, with obesity or hypersomatotropism [HST]). However, to date, a lack of information/evidence on the topic (eg, validated glucose tolerance tests) has precluded identification of this stage of disease in cats.[8]

Type 2 diabetes mellitus

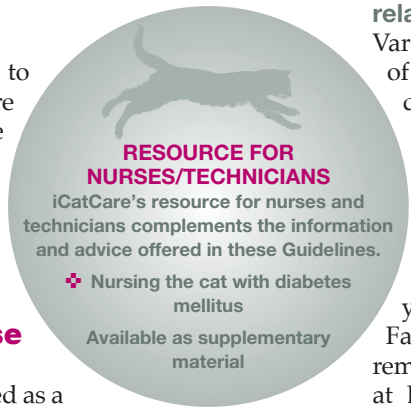
Feline DM is currently assumed to have a similar aetiology to human type 2 DM in 75% to 80% of cases and to occur secondarily to HST in 20–25% of cases (see 'Hypersomatotropism and other causes of insulin resistance').[5]

Type 2 DM is characterised by a combination of partial beta cell dysfunction, beta cell loss and insulin resistance (see later). Dysfunction and loss of beta cells reduce the capacity of the pancreas to release insulin and compromise the organ's ability to compensate for insulin resistance by increasing insulin secretory capacity. Insulin resistance (regardless of cause) leads to a relative insulin deficiency. Over time, the metabolic consequences of insulin deficiency such as glucotoxicity (and potentially other phenomena such as lipotoxicity) cause further

Risk factors for diabetes mellitus

- Increasing age has been reported as being the most important risk factor for feline DM; most cats are diagnosed at over 8 years of age, with incidence reported to peak in cats aged 10–13 years.[1,3,10,11]
- DM is most common in domestic long- and shorthaired cats. Purebred cats are largely underrepresented, an exception being Burmese cats, which are overrepresented in the UK, Australia and New Zealand.[12–14]
- Obesity causes insulin resistance, interferes with glycaemic control and confers a high risk of DM in cats.[1,3,15–18]
- Neutered male cats are at greater risk than neutered females, even when controlled for body weight.[12,13]
- Other risk factors include indoor confinement and low levels of physical activity.[19,20]

beta cell injury and dysfunction, leading to a vicious cycle that promotes yet more dysfunction and loss of beta cells (Figure 1).[9] Eventually this process leads to the classic clinical picture of severe hyperglycaemia, glucosuria, polyuria and polydipsia (PU/PD), increased appetite and weight loss.



RESOURCE FOR NURSES/TECHNICIANS

iCatCare's resource for nurses and technicians complements the information and advice offered in these Guidelines.

- Nursing the cat with diabetes mellitus

Available as supplementary material

Diabetic remission and relapse

Remission in diabetic cats has been defined as a state of zero requirement for exogenous insulin for at least 4 weeks, with no clinical signs of DM.[21] Diabetic remission has been associated with longer survival times and caregiver-reported improved quality of life,[22,23] However, although it might last for years, remission is, by definition, a temporary state and, therefore, efforts to maintain it should be considered, with treatments aimed at the underlying disease. One possible exception to this is diabetic remission in cats treated for HST or other causes of severe insulin resistance. In these cats, addressing the underlying cause of the insulin resistance might lead to cure of DM.

Remission in cats treated with sodium–glucose cotransporter-2 inhibitors (SGLT2is) is not well researched (see 'Management of the cat with diabetes mellitus: sodium–glucose cotransporter-2 inhibitor [SGLT2i] therapy'). Hence, the information in this section applies specifically to insulin-treated cats.

Incidence of remission and subsequent relapse

Variable incidence rates for diabetic remission of 11% to over 60% have been reported in different studies,[24–27] likely reflecting the heterogeneous nature of feline DM. Thus, not all cats will achieve remission, and those that do probably do not have normal glucose tolerance despite the lack of requirement for exogenous insulin.[28] The duration of remission may be weeks to years, with a median of 120–150 days.[27,28] Factors associated with a shorter duration of remission include a higher BG concentration at DM diagnosis[27] and more severe hyperglycaemia as assessed by intravenous (IV) glucose tolerance testing.[28] In contrast, regular reassessment and ongoing support of caregivers to follow nutritional recommendations and prevent obesity appear to be associated with a long duration of remission.[26,29]

Between 13% and 40% of cats are reported to relapse,[26–29] and a second remission seems generally less likely.[27,28,30]

Predictors of remission

For a diabetic cat to enter remission, beta cell capacity to release insulin must exceed or meet insulin requirements. Broadly speaking, this can be achieved by decreasing insulin requirement (reducing insulin resistance, reducing dietary digestible carbohydrates, increasing loss of glucose through the urine) or increasing beta cell capacity (resolving glucotoxicity and using glucagon-like peptide 1 [GLP-1] receptor agonists). More specifically:

- Remission is more likely in cats with a shorter duration of DM and less severe hyperglycaemia at diagnosis, as well as those achieving good glycaemic control rapidly. In these cases there is a greater tendency towards reversal of glucotoxicity and recovery of beta cell function.[24,30,31]
- Obesity is a cause of insulin resistance and leads to an increased insulin requirement. Weight loss (≥2% body weight) in obese cats in the first month of insulin treatment of DM has been identified as a predictor of remission.[8]

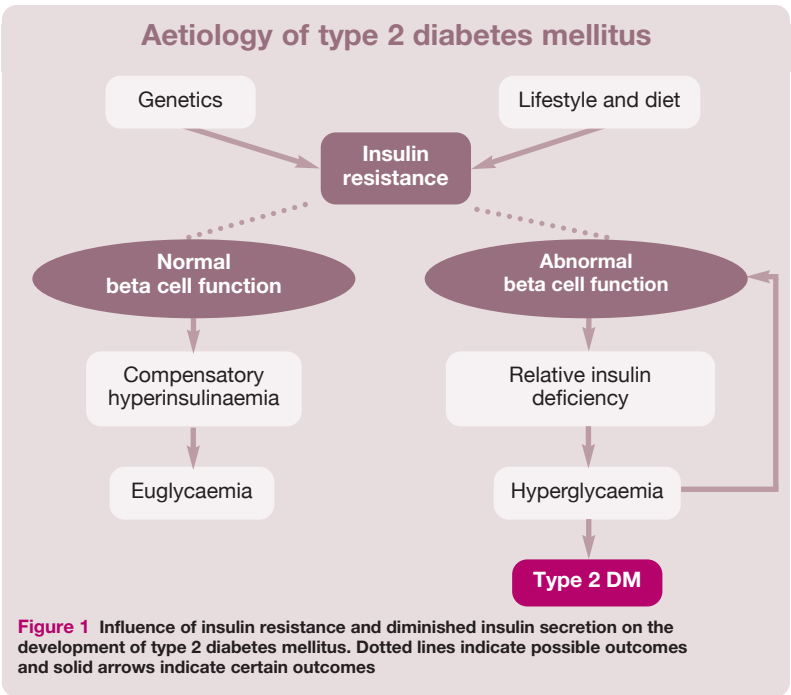


Figure 1 Influence of insulin resistance and diminished insulin secretion on the development of type 2 diabetes mellitus. Dotted lines indicate possible outcomes and solid arrows indicate certain outcomes

Box 1

How to maximise the chance and optimise the duration of diabetic remission

- Promote early diagnosis of DM; for example, with senior health clinics and monitoring of at-risk cats and those in remission with home urine glucose measurement and assessments of body weight/body condition score (BCS).
- Where possible, discontinue diabetogenic drugs if DM is diagnosed and avoid in cats in remission.
- Start treatment for DM promptly after diagnosis with twice-daily use of an intermediate-acting (eg, glargine U100, PZI) or long-acting (glargine U300) insulin. As noted in the text, the effect of SGLT2is on remission is poorly studied.
- Feed a low-carbohydrate diet (ideally a diet containing ⩽12% metabolisable energy as carbohydrate).
- Promote safe weight loss in obese cats with a controlled weight management programme and maintain a BCS of 4–5/9 during remission.
- Where possible, manage underlying causes and/or comorbidities causing insulin resistance (eg, HST, inflammatory disease).
- Monitor the response to treatment and adjust accordingly to achieve good glycaemic control.

- Cats treated with corticosteroids who develop DM are more likely to enter remission when corticosteroids are discontinued.[30,32]
- Cats with evidence of neuropathy are less likely to enter remission, presumably due to more prolonged periods of hyperglycaemia.[30]
- Long-acting insulin formulations are likely optimal for control and, therefore, remission.
- Studies comparing protamine zinc insulin (PZI) with glargine U100 in terms of the likelihood of remission have reported similar remission rates.[33,34]
- Dietary carbohydrate restriction is thought to offer a higher chance of remission (see 'Feeding the cat with diabetes mellitus').[25,35]

Practical recommendations for helping to achieve diabetic remission, as well as optimise its duration, are given in Box 1.

Identification of remission and related actions

Remission is associated with resolution of clinical signs of DM and is indicated by persistent normoglycaemia or episodes of hypoglycaemia (identified on continuous glucose monitoring [CGM] [Figure 2] or home BG curves), normal fructosamine concentrations, clinical hypoglycaemic events or negative glucose in urine on dipstick testing at home. Appropriate responses if remission is suspected are summarised in Box 2.

Remission is a treatment goal for some cases, but this depends on assessment of both the cat and caregiver. An individualised approach to each case is discussed later (see 'Management of the cat with diabetes mellitus: initial assessment').

Box 2

Recommended actions when diabetic remission is suspected

Event	Actions
Clinical hypoglycaemia	Discontinue insulin immediately until relapse of hyperglycaemia, at which point a lower dosage is usually indicated (eg, 50% of previous dosage, or less)
Persistently normal glucose on CGM for 3 days, normal BG concentration over an 8–10 h sampling period, normal fructosamine	Reduce insulin dosage by 10–50% Repeat assessment in 3–7 days
Dosage reduction occurred and cat remains normoglycaemic*	Reduce insulin dosing by 1 U per dose Repeat assessment in 1 week
Insulin dosage of 1 U/cat q12h reached and cat remains normoglycaemic*	Reduce dosing interval of 1 U insulin to q24h Repeat assessment in 3–7 days
Insulin withdrawn and cat remains normoglycaemic*	Follow recommendations for prolonging remission and monitor with home BG assessment, CGM or urine dipsticks, initially q24h and then reducing over following weeks

*BG ⩽9 mmol/l (⩽162 mg/dl)

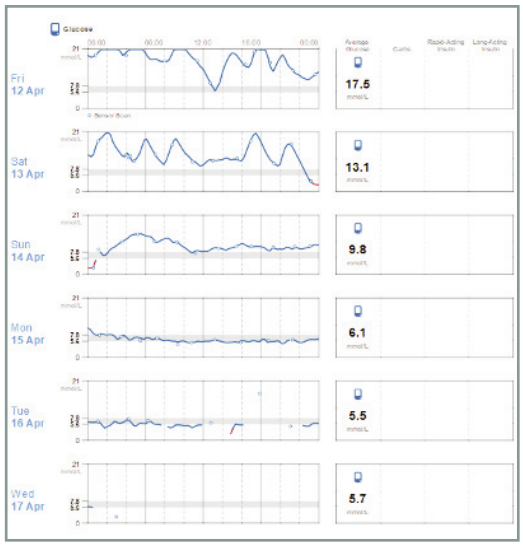


Figure 2 **Continuous glucose monitoring results (FreeStyle Libre; Abbott Laboratories) from a cat entering diabetic remission.** *Image courtesy of Rachel Korman*

Hypersomatotropism and other causes of insulin resistance

There are various causes of insulin resistance leading to poor diabetic control (Box 3), but cat-related factors including HST and other endocrinopathies are detailed here.

Hypersomatotropism

HST is the clinical syndrome resulting from excess growth hormone (GH) and is a preferred term over 'acromegaly' as external acromegalic features are often absent in cats (Box 4).[36] Previously considered rare, HST is thought to occur in between 1 in 3 and 1 in 5 cats with DM, and is the leading cause of clinically relevant insulin-resistant DM in cats.[36–39] HST can variously be seen without DM, with DM that is relatively easy to control, with DM that goes into remission and also with DM connected with severe insulin resistance. The last scenario can often be associated with the requirement for very high insulin doses, although some cats with HST have a lower insulin requirement than others, and may even enter temporary remission early in the disease process.[36,40]

Box 3

Conditions associated with insulin resistance in cats

- Obesity
- Infections: urinary, dental
- Inflammatory conditions: pancreatitis, obesity, chronic enteropathy, gingivostomatitis
- Drugs: corticosteroids, progestogens
- Endocrinopathies: HST, hypercortisolism, hyperthyroidism
- Other diseases: chronic kidney disease (CKD), neoplasia
- Gestation

Adapted from Niessen[36]

Insulin resistance

Traditionally, insulin resistance was defined by the requirement for high dosages of insulin (>1.5 U/kg q12h), but the definition has been updated to reflect the interplay between beta cell function and the dynamic influences of different causes of insulin resistance. The current ALIVE criteria purposely do not define the term by the exogenous insulin dosage required, instead describing insulin resistance as 'the presence of varying degrees of interference of insulin action on target cells'.[21]

Box 4

Key facts about hypersomatotropism

- HST is common among diabetic cats and is likely underdiagnosed in non-diabetic cats.
- HST is the most likely differential diagnosis in the insulin-resistant cat.
- Hyperplasia or adenoma of the pars distalis of the anterior pituitary is usually the cause of HST; carcinoma is uncommon.
- Only rarely does the pituitary mass itself cause neurological signs due to a mass effect.
- Excess GH and insulin-like growth factor 1 (IGF-1) secretion is the root cause of the subsequent pathologies.
- Affected cats may not show detectable physical changes.
- A serum IGF-1 measurement >1000 ng/ml is diagnostic for HST, with a grey zone existing between 700 and 1000 ng/ml.

Clinical presentation

Most cats with HST (75%) have no phenotypic changes that can be identified through a physical examination that distinguish them from regular diabetic cats.[37]

Although testing for HST was traditionally reserved for those cats showing a poor response to insulin therapy, screening for this condition should be discussed with caregivers of all diabetic cats, particularly as non-insulin therapies are now available and identification of insulin resistance may not occur to prompt further testing. Weight gain despite suboptimal diabetic control, extreme polyphagia or a recent onset of respiratory stridor or cardiac changes in a diabetic cat should raise suspicion of HST. However, these clinical signs are not consistently present and thus their absence should not deter practitioners from offering the screening process (Table 1).

Table 1 Characteristics of diabetic cats with and without underlying hypersomatotropism (HST)

Clinical sign(s)	Prevalence in cats with DM secondary to HST	Prevalence in cats with uncomplicated DM
Polyuria	87%	75%
Polydipsia	87%	85%
Polyphagia	75% (of which extreme, 20%)	55% (of which extreme, 0%)
Weight loss	42%	60%
Weight gain	17%	0%
Respiratory stridor or stertor	38%	10%
CNS signs (excluding lethargy)	1.7%	0%
Lethargy	25%	35%
Stiffness/mobility problems	10%	10%
Abdominal organomegaly (renomegaly and/or hepatomegaly)	40%	25%
Prognathia inferior and increased spacing between the incisor teeth (Figure 3)	18%	10%
Clubbed paw appearance	13%	0%
Broad facial features	37%	0%
Heart murmur	18%	20%
Plantigrade stance	3%	10%

Adapted from Niessen et al[37] and Niessen and Scudder[40]
CNS = central nervous system; DM = diabetes mellitus

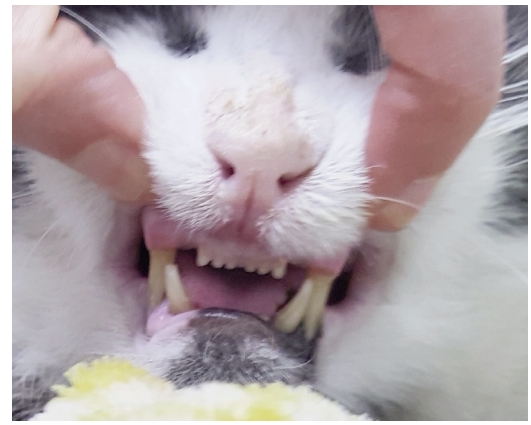


Figure 3 Increased spacing between the incisor teeth in a cat with hypersomatotropism. *Image courtesy of Linda Fleeman*

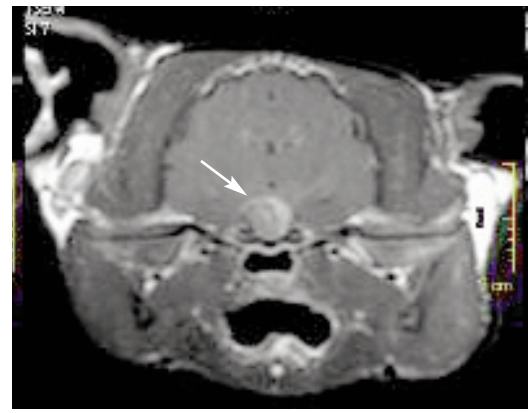


Figure 4 Postcontrast MRI scan of a 14-year-old cat with hypersomatotropism (HST) caused by a pituitary adenoma protruding from the sella turcica (arrow). A diagnosis of HST is not excluded by normal advanced imaging findings, but 95% of affected cats will have an abnormality. *Image courtesy of Samantha Taylor*

Diagnosis

Screening is best conducted by evaluation of serum IGF-1, which has been shown with a validated assay to have a minimum 95% positive predictive value for the presence of HST at a cut-off of 1000 ng/ml and 94% at a cut-off of 900 ng/ml.[37] IGF-1 concentrations of 700–1000 ng/ml could represent a 'grey zone' and prompt reassessment (eg, 2 months later).[41]

As insulin is required for normal hepatic synthesis of IGF-1 in response to GH stimulation, serum IGF-1 concentration is very likely to be lower when there is insulin deficiency. Consequently, measurement after 6–8 weeks of DM treatment (either with insulin or with an SGLT2i) is likely to provide a more reliable result.

Once a diagnosis is made on the basis of serum IGF-1, next steps could involve intracranial imaging (contrast-enhanced CT or MRI, Figure 4), although there are limitations (eg, microadenoma or hyperplasia may not be detected).[42] Visceral organomegaly may be observed on extracranial imaging.[41,43]

Treatment

Once elevated serum IGF-1 concentrations have been documented, treatment options and prognosis can be discussed with caregivers (Table 2). Definitive treatment, and in particular hypophysectomy, has been shown to be associated with the longest survival times and owner satisfaction scores but has limited availability and lifelong medication will be required.[58]

Previously considered rare, hypersomatotropism is thought to occur in between 1 in 3 and 1 in 5 diabetic cats, and is the leading cause of clinically relevant insulin-resistant diabetes mellitus in cats.

Table 2 Treatment options for cats with hypersomatotropism (HST)

Treatment	Advantages	Disadvantages	Studies
Hypophysectomy	✣ High success rates (diabetic remission 71–92%, IGF-1 control 90%, survival time 853–1347 days)	✣ Cost and availability ✣ Mortality rate 4–15% ✣ Requirement for postoperative care ✣ Lifelong medication required	Meij et al[44,45] van Bokhorst et al[46] Fenn et al[47] Neilson et al[48]
Radiotherapy	✣ Reduction in tumour size ✣ Well tolerated ✣ Diabetic remission in 21–34% of cats (17–62% with fractionated radiotherapy) ✣ Improvement in neurological signs in patients with pituitary mass effects	✣ Cost and availability ✣ IGF-1 elevations persist ✣ Recurrence of clinical signs frequent ✣ Requirement for multiple anaesthetics	Wormhoudt et al[49] Littler et al[50] Watson-Skaggs et al[51] Dunning et al[52]
Pasireotide (somatostatin analogue)	✣ Well tolerated ✣ Reduction in insulin requirements in all treated cats	✣ Cost ✣ No effect on tumour size ✣ IGF-1 elevations persist ✣ Self-limiting gastrointestinal side effects	Gostelow et al[53] Scudder et al[54]
Cabergoline (dopamine agonist)	✣ Well tolerated ✣ Modest success in reducing insulin requirements (1 in 4 cases) ✣ Cost effective	✣ No effect on tumour size ✣ IGF-1 elevations persist ✣ Self-limiting gastrointestinal side effects	Scudder et al[55] Miceli et al[56]
Treatment of consequences of HST (escalating insulin dosage, instigation of SGLT2i therapy, management of CHF and OA)	✣ Widely available ✣ Good quality of life in some cats	✣ Uncontrolled clinical signs ✣ Risk of hypoglycaemia with high doses of insulin ✣ No effect on tumour size ✣ IGF-1 elevations persist	Borgeat et al[57]

CHF = congestive heart failure; IGF-1 = insulin-like growth factor 1; OA = osteoarthritis; SGLT2i = sodium–glucose cotransporter-2 inhibitor

Cats receiving high-dosage glucocorticoid therapy should be monitored for the development of diabetes mellitus.

Hypercortisolism

Hypercortisolism (HC), or Cushing's syndrome, is a less common underlying endocrinopathy than HST, leading to overt DM in approximately 80% of affected cats.[59–61] Diagnosis relies on:

- ✣ A suggestive clinical picture; for example, coat changes such as fading of coat colour, alopecia spreading from the inguinal region, fragile skin syndrome, prominent abdominal veins, pendulous abdomen (Figure 5), polyphagia, lethargy/exercise intolerance, muscle wastage, weight gain or weight loss and wound healing problems.
- ✣ Exclusion of other diseases with a possible similar presentation (eg, HST causing insulin resistance, weight gain and polyphagia).
- ✣ Suggestive endocrine testing using a low-dose dexamethasone suppression test (0.1 mg/kg dexamethasone), adrenocorticotrophic hormone stimulation test or oral dexamethasone suppression test with a series of urinary corticoid:creatinine ratio tests.

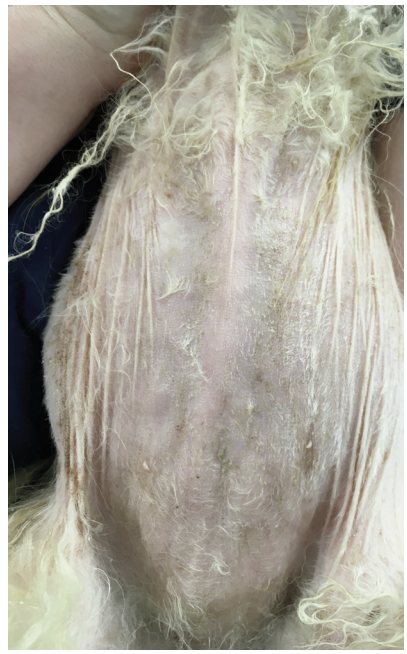


Figure 5 The majority of cats with hypercortisolism will have diabetes mellitus, but also additional clinical signs such as fragile, thin skin, a pendulous abdomen and prominent abdominal veins, as in this 12-year-old affected cat. *Image courtesy of Samantha Taylor*

- ✣ Suggestive imaging findings such as enlarged adrenal(s) and an enlarged pituitary gland.

Feline DM and HC can be treated in various ways including medically (trilostane), surgically (adrenalectomy, hypophysectomy) or with radiotherapy, depending on the type of HC and caregiver preference. For detailed information on the management of cats with DM and HC, readers are referred to 'Feline comorbidities: recognition, diagnosis and management of the cushingoid diabetic' by Cook and Evans.[60]

Drug-induced diabetes mellitus

Glucocorticoid therapy has been suggested as being a predisposing factor for the development of DM in cats.[10,62,63] High-dosage prednisolone therapy (≥1.9 mg/kg q24h for >3 weeks) resulted in the development of DM in 9.7% of cats in one study, mainly within the first 3 months of treatment.[64] Cats receiving high-dosage prednisolone or other glucocorticoid therapy should be monitored for the development of DM using, for example, home urine testing or fructosamine measurement. Progestogens may also result in insulin resistance and predispose cats to DM.[63,65]

Box 5

Strategies for optimising early identification of diabetes mellitus

- Promote senior cat health clinics offering regular examination and weight recording, and diagnostic testing (eg, basic urinalysis) if unexplained weight loss or other signs are identified.
- Encourage caregivers to monitor body weight and BCS at home.
- Enhance caregiver awareness of DM to encourage prompt reporting of clinical signs; for example, using wellness questionnaires, social media and waiting room displays.
- Perform dipstick testing for glucose on free-catch urine samples collected at home or in the clinic at wellness visits.
- Pursue additional examination and screening for cats at increased risk of DM (eg, overweight/obese cats, Burmese cats, cats treated with diabetogenic medications).

Other potential causes of insulin resistance

Other causes of insulin resistance are listed in Box 3. Pancreatitis commonly coexists with DM in cats,[66] but the relationship between the two conditions is not completely clear. There may be a bidirectional association, with pancreatitis both occurring as a result of DM and also being a cause of DM via destruction of islets in the pancreas, hence contributing to insulin resistance.[67] Pancreatitis may increase glycaemic variability (fluctuations in BG concentration over the day) and reduce the chance of remission,[66,68] but other factors are also involved and a diagnosis of pancreatitis does not preclude good control of DM or remission.

Maintaining a normal body condition is recommended for all cats with DM, given that obesity is a risk factor[15] and a reversible cause of insulin resistance. Various pathophysiological processes, including inflammation, are involved, albeit the mechanisms are not fully understood.

A diagnosis of pancreatitis does not preclude good control of diabetes mellitus or remission.

Clinical signs of diabetes mellitus

Clinical signs of DM classically include PU/PD, weight loss despite polyphagia and lethargy. However, comorbidities are common among the age group of cats predominantly affected and these may influence the presenting signs. For example, a cat with concurrent CKD or pancreatitis may not be polyphagic. Cats with acromegaly may, as discussed earlier, have some additional clinical signs due to soft tissue growth. Cats with diabetic ketoacidosis (DKA) may present acutely unwell, with vomiting and inappetence, prior to a diagnosis of DM or during treatment (see 'Complications in the management of diabetes mellitus'). Prolonged hyperglycaemia can lead to a diabetic neuropathy causing a plantigrade stance and gait (Figure 6).[69]

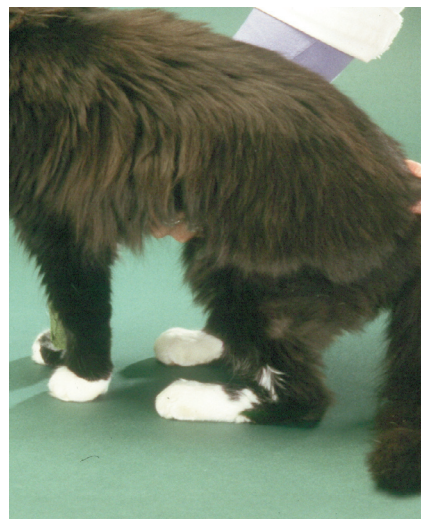


Figure 6 **Plantigrade stance in a cat with diabetes mellitus.** *Image courtesy of Sarah Caney*

Diagnosis and treatment early in the course of the disease can optimise the chance of diabetic remission,[24] as well as improve patient outcomes by avoiding significant weight loss and the development of complications. Strategies to identify affected cats promptly are summarised in Box 5.

Diagnosis of diabetes mellitus

ALIVE criteria

Agreed criteria for the diagnosis of feline DM are defined by the ALIVE project[21] and summarised in Box 6. The criteria highlight the need to avoid an incorrect diagnosis due to stress hyperglycaemia, which can be of any magnitude. There may be cases where DM and stress hyperglycaemia cannot be distinguished, and home BG measurement, CGM and dipstick testing of home-collected urine samples may be useful. If concerns over the presence of true DM persist, periodic re-evaluation is recommended.

Glycated proteins

Serum fructosamine is indicative of the average BG concentration over the preceding 7–10 days or so, and is, therefore, less affected by short-term stressful events. Fructosamine can be normal in early DM and is affected by the half-life of serum proteins. Diseases that decrease the half-life of serum proteins (eg, hyperthyroidism, protein-losing enteropathies) will falsely decrease serum fructosamine values; diseases that increase the half-life of serum proteins (eg, hypothyroidism) will falsely increase serum fructosamine values. Serum fructosamine is also affected by haemolysis, but the direction of change is unpredictable.[70,71]

Haemoglobin A1c represents glycaemic status during the lifespan of the red blood cells (68–77 days in cats) and is used for screening in humans with suspected DM. It has been shown to differentiate cats with DM from normal cats.[72,73] Anaemia falsely increases A1c values but, unlike serum fructosamine, A1c is not affected by haemolysis or abnormalities in serum protein turnover rate.

Box 6

ALIVE criteria for the diagnosis of feline diabetes mellitus

- A random (fasted or unfasted) BG concentration ⩾15 mmol/l (⩾270 mg/dl) with classic clinical signs of hyperglycaemia* (with no other plausible cause) or a hyperglycaemic crisis, *and at least one* of the following criteria:
  - Increased glycated proteins (eg, fructosamine);
  - Glucosuria on more than one occasion on a naturally voided sample acquired in a home environment at least 2 days after any stressful events.
- A random (fasted or unfasted) BG concentration >7 mmol/l (>126 mg/dl) and ⩽15 mmol/l (⩽270 mg/dl) *and at least two* of the following criteria:
  - Classic clinical signs of hyperglycaemia* (with no other plausible cause) or hyperglycaemic crisis;
  - Increased glycated proteins (eg, fructosamine);
  - Glucosuria on more than one occasion on a naturally voided sample acquired in a home environment at least 2 days after any stressful events.

*In some cases clinical signs may not be reported by the caregiver. From Niessen et al[21]

The ALIVE definition implies that a species-validated method is used to measure glucose as well as glycated proteins (eg, fructosamine), and that conditions other than DM that specifically affect the concentration or metabolism of glycated proteins (eg, albumin) are excluded. Moreover, glycated proteins should be measured by a methodology with a relevant, established reference interval and supported by regular quality assurance.[21]

Management of the cat with diabetes mellitus: initial assessment

There is no 'best' approach to the management of DM in cats. Instead, there is a spectrum of appropriate care, and the management approach should be individualised for each case.

Guidance on the initial assessment of a cat newly diagnosed with DM is provided in Figure 7. The first step is to identify whether complicating factors or concurrent diseases are present. Inappetence/anorexia, dull demeanour, severe lethargy, dehydration and/or other signs of serious illness typically indicate that urgent treatment is warranted. It will often be appropriate to use a protocol for the management of DKA in

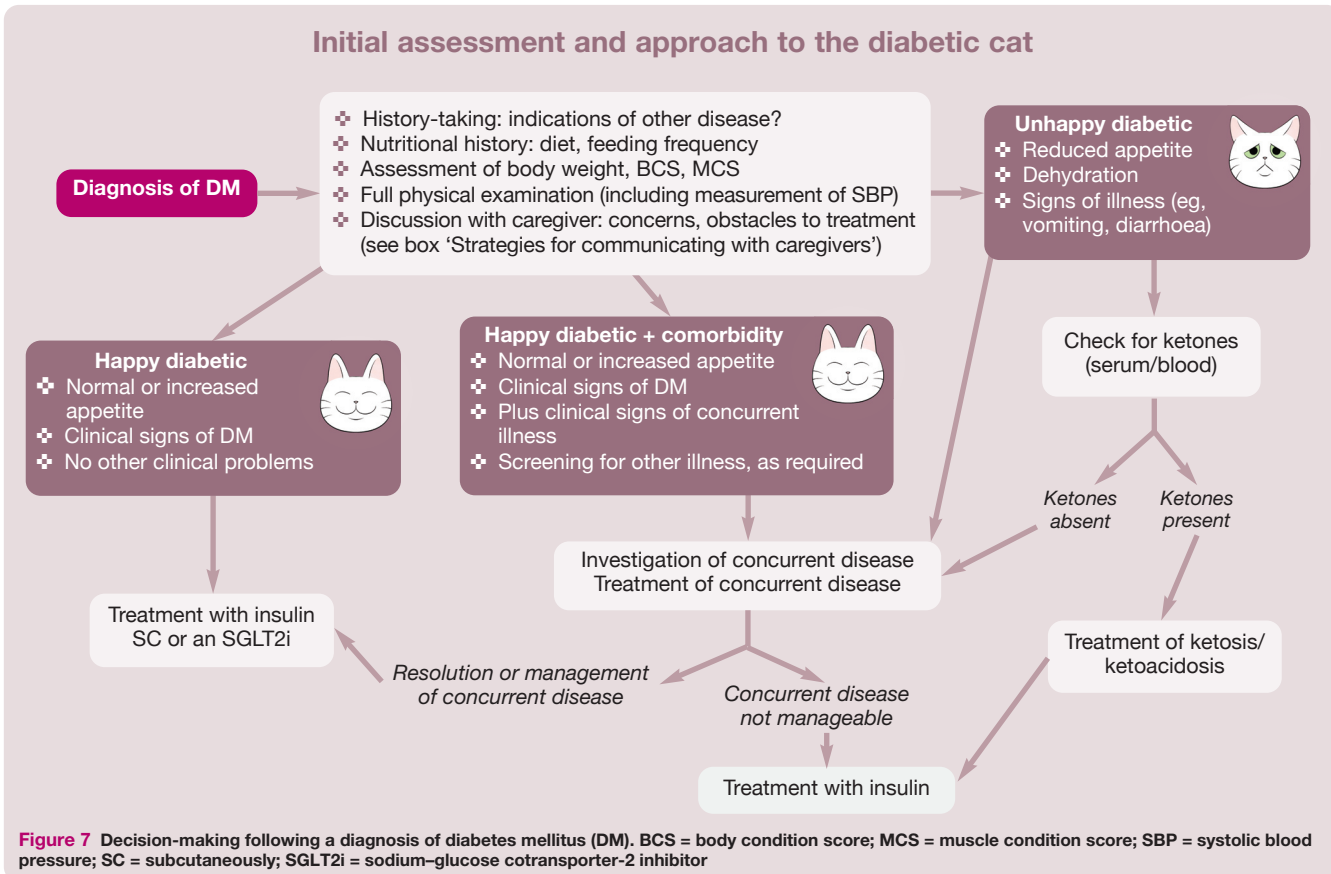


Figure 7 Decision-making following a diagnosis of diabetes mellitus (DM). BCS = body condition score; MCS = muscle condition score; SBP = systolic blood pressure; SC = subcutaneously; SGLT2i = sodium–glucose cotransporter-2 inhibitor

this scenario (see 'Diabetic ketoacidosis and euglycaemic diabetic ketoacidosis').

For newly diagnosed diabetic cats with a normal or increased appetite, the focus of history-taking and physical examination should be to:

- Identify any indication of concurrent disease (ie, clinical signs other than those expected in a diabetic cat such as weight loss, PU/PD, lethargy or diabetic neuropathy);
- Obtain details about current management factors that will be relevant for the diabetic cat, including diet and dietary habits (feeding schedule, treats, meal or ad libitum feeding, multi-cat household, etc);
- Document any medications the cat is receiving;
- Record current body weight, estimated ideal body weight, BCS and muscle condition score.

For more information, readers are referred to the 'WSAVA nutritional assessment guidelines'[74] and accompanying global nutrition toolkit, available at wsava.org/global-guidelines/global-nutrition-guidelines. It is anticipated that recently drafted 'Guidelines for nutritional management of feline diabetes mellitus: a proposed classification system

Box 7

Team approach to the cat with diabetes mellitus

Management of DM can be time-consuming for a veterinary clinic. Veterinary nurses and technicians who have received training in the management of DM can play a key role in communicating with caregivers (in person or via telephone, email or text), demonstrating injection techniques and use of insulin pen devices, explaining SGLT2i dosing, providing follow-up support, and assessing and monitoring cats with DM (home BG, CGM, use of Diabetic Clinical Score [see 'Monitoring clinical signs']). Nurse/technician appointments and 'diabetic cat clinics' can demonstrate the clinic's dedication to affected cats and provide a link between caregivers and veterinarians. Clear documentation/note keeping can assist communication between team members and ensure clear and consistent advice is given to caregivers to avoid confusion. In the experience of the authors of these Guidelines, the entire clinic team can derive satisfaction from working with caregivers to achieve the best outcome for each individual cat with DM.

Strategies for communicating with caregivers

Good communication with caregivers can influence management decisions. Moreover, listening to and addressing concerns about treating a cat with DM is crucial for establishing the all-important team approach to care (Box 7), which will help to ensure the best outcome for the individual cat.[75]

Recognise caregiver concerns

Caring for a cat with DM can have profound emotional, financial and social impacts on caregivers, to the extent that they may choose euthanasia rather than to begin or continue treatment, with 10% of cats being euthanased at the time of diagnosis,[76] 15% within a month of diagnosis[23] and another 10% within the first year of treatment.[76] Risk factors for euthanasia include both cat-related factors, like older age and concurrent disease, and caregiver-related challenges such as treatment costs, concerns regarding quality of life, complications (hypoglycaemia, DKA) or poor glycaemic control, time constraints and impact on lifestyle (work commitments, social life, trouble finding holiday care), difficulties with treatment including injections and, concerningly, poor veterinary support.[23,76,77]

There is a wide range of appropriate treatment and monitoring options for cats with DM, which allows for flexibility in treatment decisions based on discussion and agreement with the caregiver. Once the veterinarian understands the caregiver's capabilities and constraints, they can create an individualised management plan based on the spectrum of care (ie, individual factors that will influence treatment goals; Figure 8). Relevant discussion points include:

- **Lifestyle** What schedule can the caregiver reasonably manage?
- **Treatment goals** Remission? Management of clinical signs?
- **Financial limitations** Where do cost constraints lie on the spectrum from none to significant?
- **Resources and support system** Are multiple caregivers involved or only one? Where relevant, are family members, friends and other caregivers supportive of treating the cat?
- **Risk aversion** What is the caregiver's tolerance for complications like hypoglycaemia or DKA?

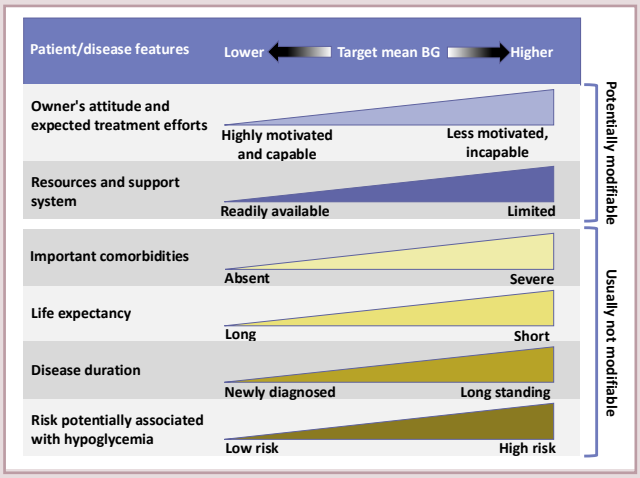


Figure 8 Spectrum of care: the management approach and glycaemic targets should be individualised based on a range of factors and reassessed periodically. **BG = blood glucose.** *Reproduced from Gilor and Fleeman*[78]

Explain long-term positive outcomes of treatment

Caregivers who opt to treat their diabetic cat report some positive effects on their own quality of life such as strengthening of the bond and more interaction with their cat.[77] If remission of DM is achieved, then caregivers report an improved quality of life for their cat.[77] Enhancement and maintenance of the cat–caregiver bond and remission of DM are, therefore, very desirable treatment goals that should be discussed from the outset. It is logical to focus on strategies that will be most practical to implement in each case and to periodically review the management plans.

(Continued on next page)

integrating medical considerations'[35] will provide another useful resource.

This baseline information improves outcomes by allowing individualised management for the diabetic cat. If there are indications of concurrent disease, this should be investigated and treated as appropriate, with the level of diagnostic testing being influenced by the cat's clinical condition. If the concurrent disease can be resolved or controlled, then management of DM may often proceed in the same way as for a cat with uncomplicated DM (see 'Diabetes mellitus and comorbidities'). It may well be necessary to begin treatment of the DM before any additional diagnostic investigations are completed. Some concurrent diseases will preclude treatment with an SGLT2i (see 'Management of the cat with diabetes mellitus: sodium–glucose cotransporter-2 inhibitor [SGLT2i] therapy').

Management of the cat with diabetes mellitus: insulin therapy

Insulin therapy is associated with many inherent challenges that must be overcome for treatment to be safe, effective and sustainable. These relate to the complex nature of glycaemic control, the pharmacological limitations of available insulin formulations and the lifelong caregiver burden.[79] These challenges have significantly diminished in human medicine with the shift from traditional insulin suspensions that are relatively unpredictable and require the use of syringes and needles, to the use of the more predictable recombinant insulin analogues, injection pens, insulin pumps and CGM systems.

There is currently little published evidence that any one insulin formulation is advantageous over any other for the treatment of feline DM.[80]

(Continued from previous page)

Empower caregivers with knowledge to overcome obstacles

It is crucial that the caregiver feels informed and supported, and adequate time should be allocated for initial conversations. With the benefit of a collaborative approach to caregiver education, involving the entire veterinary team, individual hurdles may be managed and responses given to all concerns (see table).[75] Detailed instructions focusing on short-term goals should be provided, including the actions required until the next veterinary assessment, together with expected outcomes.

Overcoming caregiver-related obstacles to the treatment of diabetes mellitus

Treatment obstacle	Considerations and actions
Cost of treatment and monitoring	❖ Compare long-term costs of insulin and SGLT2i products, including monitoring costs ❖ Reduce monitoring to encompass DCS: clinical signs, body weight and water intake ❖ Demonstrate home monitoring to reduce clinic visit costs ❖ Provide clear education on signs of complications to avoid severe illness (eg, DKA) and its associated costs
Excessive demands on lifestyle	❖ Communicate around flexibility of injection timing (eg, flexible q12h dosing with intermediate and long-acting insulins, alternative dosing schedules to strict 12 h intervals, permission to skip occasional insulin injections) ❖ Long-acting insulin may allow for q12–24h dosing with more flexibility around injection schedule ❖ Clarify that feeding is not required at the time of injection ❖ Discuss use of SGLT2i therapy ❖ Create a flexible plan taking into account caregiver commitments
Unreasonable/ unrealistic expectations of treatment	❖ Discuss differences in human and animal healthcare (tighter control desirable in people due to long-term complications such as kidney damage) ❖ Explore how realistic 'tight' control would be for the caregiver ❖ Explain the likelihood of remission and determine if this is a feasible goal
Concerns about complications	❖ Ensure open communication to discuss specific concerns ❖ Provide education on signs of complications (eg, DKA, hypoglycaemia) ❖ Explain that even a low dose of insulin is usually sufficient to prevent DKA, and that hypoglycaemia is often self-limiting and rarely life-threatening ❖ Communicate scheduled contact times with the clinic (in person or online/telephone) ❖ Ensure caregiver awareness of point of contact at the clinic in case of concerns (including out-of-hours providers) ❖ Modify therapeutic protocol if caregiver has specific areas of concern (eg, hypoglycaemia)
Insulin-injection issues: – fear of needles – dexterity/vision problems	❖ Discuss use of SGLT2is instead of insulin, if appropriate ❖ Consider use of an insulin-dosing pen, ensuring clear labelling of syringe (eg, with tape to dose line) and aided by demonstration (including videos) and support from the veterinary team ❖ Provide 'district' or home-visit care option to enable injections to be given or observed

DCS = Diabetic Clinical Score; DKA = diabetic ketoacidosis; SGLT2i = sodium–glucose cotransporter-2 inhibitor

Caring for a cat with diabetes mellitus can have profound emotional, financial, and social impacts on caregivers.

General principles of insulin therapy

Insulin formulations differ in their average time–action profile, cost and methods of administration (Table 3). Currently, there are two veterinary insulin formulations approved for use in cats, compared with more than 10 human formulations, some of which are routinely used in cats. The choice of formulation depends on many factors that relate not only to the individual cat but potentially also to different time points for the same cat. Factors include disease pathophysiology (including concurrent diseases), insulin-related factors (including pharmacology, cost, regional prescribing regulations), cat and caregiver compliance, diet (composition and feeding frequency), monitoring strategy and the goals of therapy for the cat, concerns regarding hypoglycaemic risk and the likelihood of remission (Figure 9).

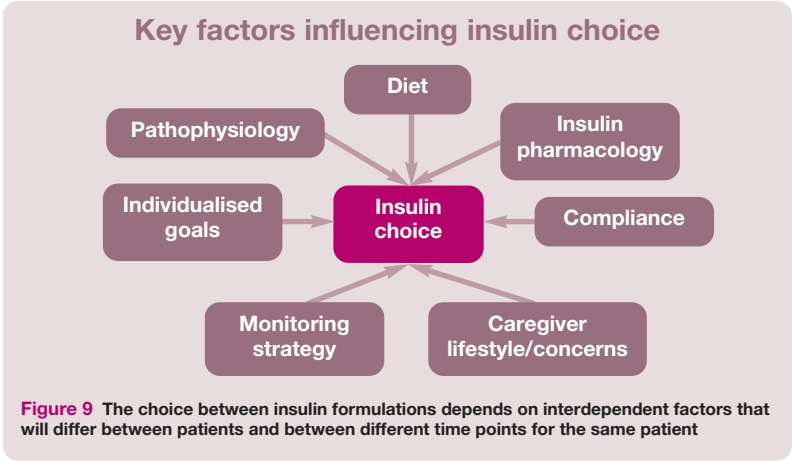


Figure 9 The choice between insulin formulations depends on interdependent factors that will differ between patients and between different time points for the same patient

The usual goal with the use of twice-daily intermediate-acting insulin protocols is alleviation of DM-associated clinical signs. Considering intraday BG fluctuations associated with these formulations, the goal of treatment should be BG that ranges from normal (4.5–5.5 mmol, 80–100 mg/dl) at its lowest to 14–19 mmol/l (250–350 mg/dl) at the peak. Although uncommonly realised,[81,82] the 'ideal' BG curve typically aims to be at the high end of this range just prior to insulin administration.[83,84] Fructosamine concentration in an insulin-treated cat is expected to be above the reference interval of a non-diabetic cat provided by the laboratory. A within-reference interval value should prompt assessment for remission and/or overdosing. If using the long-acting insulin formulation glargine U300, the aim is to achieve a 'flat' curve with euglycaemia for most of the day; the nadir may be at the time of the next injection.

Nonetheless, evidence that any particular glycaemic target is associated with any particular outcome is lacking. Thus, micromanagement should be avoided and all management steps should serve the ultimate treatment outcome of a good quality of life for cat and caregiver alike.[21]

Key facts and practical recommendations in relation to insulin therapy are presented in Box 8.

Table 3 Guidance on the frequency of administration of specific insulin formulations in cats, based on duration of action and time to peak action

Formulation	Brand name(s)	Concentration (U/ml)	Duration of action	Frequency of administration	Comments
Human recombinant solutions: lispro, aspart, glulisine	Humalog (Eli Lilly) NovoLog/NovoRapid (Novo Nordisk) Apidra (Sanofi) Humalin R (Eli Lilly) Novolin R (Novo Nordisk)	100	Short-acting	As CRI or IM injection q1–2 h	Rapid-acting 'neutral/regular/soluble' insulins with a short duration of action Used for treatment of DKA as a CRI or IM injection
Human recombinant NPH suspension	Humulin N (Eli Lilly) Novolin N (Novo Nordisk)	100	Short-acting	q8h	Duration of action likely too short to be useful in most cats with DM
Porcine lente suspension	Vetsulin (Merck) Caninsulin (MSD Animal Health)	40	Intermediate-acting	q8–12h	Available as an insulin-dosing pen as well as in a vial Should be vigorously shaken to resuspend
Protamine zinc suspension	ProZinc (Boehringer Ingelheim)	40	Intermediate-acting	q12h (occasionally q24h)	Should be gently rolled to resuspend
Human recombinant glargine solution	Lantus (Sanofi) Optisulin (Sanofi) Basalglar (Eli Lilly) Semglee (Biocon Biologics) Abasaglar (Eli Lilly)	100	Intermediate-acting	q12h (occasionally q24h)	Available as an insulin-dosing pen as well as in a vial
Human recombinant degludec solution	Tresiba (Novo Nordisk)	100/200	Intermediate-acting	q12h	Available as an insulin-dosing pen
Human recombinant glargine solution	Toujeo (Sanofi)	300	Long-acting	q12–24h	Available as an insulin-dosing pen Flatter time–action profile compared with glargine U100

CRI = constant rate infusion; DKA = diabetic ketoacidosis; DM = diabetes mellitus; IM = intramuscular; NPH = neutral protamine Hagedorn

Box 8

Insulin therapy: key facts and practical recommendations

- No insulin formulation should be considered 'best' by default. Rather, the choice of insulin should be tailored to the specific clinical situation and caregiver considerations.
- There is no need to administer insulin with, or immediately after, a meal.
- Insulin-dosing pens can help some caregivers to administer insulin, thereby improving compliance.
- Porcine lente and neutral protamine Hagedorn (NPH) insulins tend to have a shorter duration of action compared with degludec, PZI, glargine U100 and glargine U300.
- Glargine U300 seems currently to be the only formulation that comes close to meeting the criteria for a 'basal' insulin formulation in some cats because it has a flat time–action profile and minimal day-to-day variability.
- Once-daily doses of glargine U300, PZI or glargine U100 can achieve acceptable levels of clinical control in some cases, especially in cats with residual beta cell function, but high doses increase the risk of hypoglycaemia.

Choice of insulin and chance of remission

Insulin glargine U100 has been claimed to be advantageous in inducing remission in cats with DM, but this assertion is based on uncontrolled and non-randomised studies and, as such, there is little compelling evidence to support it.[32] In a small clinical study, once-daily insulin glargine U100 was compared with twice-daily porcine lente insulin in cats. Both treatment groups experienced improved glycaemia and 4/13 cats achieved remission of DM, but only one of these cats was in the glargine U100 group.[85] Other studies comparing glargine U100 with either PZI or detemir found no difference in remission rates.[30,34,86]

There is currently little published evidence that any one insulin formulation is advantageous over any other for the treatment of feline diabetes mellitus.

Timing of insulin in relation to feeding

In health, the rate of secretion of insulin is relatively constant between meals ('basal' secretion) and is increased during meals ('bolus' secretion) proportional to the amount of absorbed carbohydrates. In cats fed a single dry food meal after a 12 h fast, bolus insulin secretion lasts from 6 h to >12 h, with a relatively low peak in plasma insulin (1.5–3 times baseline) at 1–8 h, depending on the diet fed. However, when the daily caloric intake is divided into four meals, the increase in plasma insulin is minimal and sustained for the 24 h period.[87]

It is not necessary to administer insulin after a meal, especially for cats fed diets that are low in digestible carbohydrates, cats who 'graze' on food or cats who are treated with a basal insulin (ie, an insulin that does not have a substantial peak after injection, such as insulin glargine U300). Even for cats treated with an insulin that has a substantial peak and fed regular meals of a carbohydrate-rich diet, it is still unnecessary to give the insulin after the meal. This is because the unpredictable rate of carbohydrate absorption, combined with the unpredictable absorption of insulin from the subcutaneous depot (for most formulations), makes it unlikely that hypoglycaemia is prevented by feeding.

There is therefore no rationale to recommend withholding an insulin injection when a diabetic cat does not eat at the time, as long as the cat is otherwise well and inappetence is not ongoing. However, caregivers often elect to feed their cat around the time of insulin administration to encourage engaging emotions associated with injection. This also allows monitoring of appetite, which is important, as reliable and predictable food intake indicates health and is required for weight management.[35]

Insulin choices: formulations

Different insulin formulations are available, including suspensions (porcine lente, NPH, PZI) and solutions (degludec, glargine U100, glargine U300). Insulins can also be categorised according to their duration of action, although the majority used in feline practice are intermediate-acting.[84]

Insulin suspensions

Suspensions contain various additives (zinc for porcine lente, protamine for NPH and both for PZI), causing precipitation at the injection site,[88] slowing absorption and thus leading to a slower onset and longer duration of action. One disadvantage of these formulations is the need for even resuspension before each use; this requires either gentle rolling and then inverting of the vial or, in the case of porcine lente insulin, vigorous shaking of the vial until completely mixed. If resuspension is inconsistent, it will lead to inaccurate dosing.[89] Moreover, highly variable and unpredictable breakdown of the precipitate can alter insulin absorption patterns.[90–92] A third potential disadvantage of these formulations can be their slow onset of action and overly long duration of action, which fails to mimic bolus and basal secretion.[88,92] However, this may not be important given the specific characteristics of feline insulin secretion physiology, as described earlier.

Insulin solutions

Insulin solutions do not require mixing prior to administration; hence, dosing can be more accurate, and they could potentially be associated with reduced glycaemic variability and a lower risk of hypoglycaemia. Solutions used in veterinary medicine include glargine (U100, U300) and degludec.

Insulin choices: duration of action

Intermediate-acting insulin formulations

Porcine lente, NPH, PZI, glargine U100 and degludec are considered intermediate-acting insulins, requiring at least twice-daily administration for best results. In cats, porcine lente and NPH insulins tend to have a shorter duration of action compared with PZI, glargine U100 and degludec.[33,93,94] When using these insulins, there is often a difference between insulin requirement and delivered dose that causes fluctuations in BG concentration. This may be less obvious in cats with residual beta cell function, because their endogenous insulin could 'close the gap' between required and delivered insulin. In contrast, cats with no residual beta cell function are more prone to substantial glycaemic variability.

Insulin degludec was originally formulated to be used every other day in people with diabetes. In cats, its duration of action is about 12 h and it has a substantial peak in activity. Hence, in this species, it is considered an intermediate-acting insulin and, as such, is generally not recommended as a once-daily insulin.

If a once-daily basal insulin is desired, insulin glargine U300 seems most promising, although insulin glargine U100 and PZI might also suffice in some cats.

Long-acting insulin formulations

Basal insulins have time–action profiles that are evenly distributed from soon after injection until metabolised and are effective for 16–24 h, without a distinct peak in activity.[80] For a basal insulin to be effective and safe as a once-daily injection, it should provide relatively constant action throughout a 24 h period. Insulin glargine U300 is currently the closest to meeting this standard in cats.[95]

Insulin glargine U300 is biochemically identical to insulin glargine U100 but three times more concentrated and not bioequivalent.[96] Compared with insulin glargine U100, the same dose of concentrated glargine U300 is delivered in a smaller droplet with a smaller surface area; absorption is slower, the duration of action is longer, the time–action profile is flatter, and there is decreased day-to-day glycaemic variability.[96–99] Emerging evidence from several small studies and clinical experience in cats suggest that insulin glargine U300 provides better control of DM than insulin glargine U100, although its duration of action is often insufficient for once-daily administration (Table 3).[95,100] Because of its high concentration, insulin glargine U300 can only be delivered using a dosing pen (Box 9) and not a syringe.

Long-acting insulin analogues were developed for use in people as once-daily basal formulations; however, they do not meet this

Box 9

Practical use and advantages of insulin-dosing pens

Multiple studies in people have identified advantages such as improved treatment compliance, a reduction in hypoglycaemic events, more accurate dosing and cost savings when insulin-dosing pens rather than syringes and needles are used.[101,102] Currently, one veterinary insulin-dosing pen is produced for cats (Vetsulin/Caninsulin – VetPen [MSD Animal Health]). Initial pilot studies have shown the device to be easy to use, well tolerated under real life conditions, more accurate than traditional vial/syringe systems (especially for small doses) and preferred over syringe use by many caregivers.[103,104] Other insulin-dosing pens, designed for use in humans, are also used to treat diabetic cats (eg, with glargine [Figure 10]). Many are limited to delivering 1 U increments, with no 0.5 U option, which can be a disadvantage but in practice is rarely an issue.

'Priming' the insulin-dosing pen (ie, performing an 'air shot') with 1–3 U of insulin is recommended by manufacturers prior to every injection, potentially making pens less economical for use in cats, although vial/syringe techniques also involve wastage.[105] Certainly, a new pen should be primed to verify that it works. Although most of the panel recommend following the manufacturer's instructions, one US-based author (CG) advises that these may be modified as follows to make dosing more cost-effective. Having primed a new pen to verify that it works, it may be acceptable not to perform further priming routinely. However, it is important to consider that, without regular priming, air bubbles in the pen might interfere with accurate dosing or it may not be noticed if a pen is becoming faulty. Accordingly, the pen must be checked if a cat does not respond to insulin as expected.

Figure 10 Glargine-dosing pen designed for human use but successfully used to manage feline diabetic patients. *Image courtesy of Linda Fleeman*

It is advisable to regularly check the insulin reservoir visually and eject any air bubbles. The problem of air bubbles can additionally be avoided by tilting the pen during injection so that the plunger is higher than the needle tip, drawing any air bubbles away from the needle.

In people, it is recommended to keep the needle of the pen under the skin for at least 3 s after injection to allow the dose to be completely delivered. This does not seem to be necessary in diabetic cats, given the small doses required.

For a more comprehensive review of the use of insulin-dosing pens, readers are referred to Thompson et al.[106]

standard in cats. It is generally recommended to use them twice daily. If a once-daily basal insulin is desired, insulin glargine U300 seems most promising, although insulin glargine U100 and PZI might also suffice in some cats.

Insulin dose adjustments

Although the cat's clinical picture and quality of life should always lead the monitoring process, interstitial glucose or BG concentrations in the range of 5–20 mmol/l (90–360 mg/dl) are typically associated with good clinical control of DM. Stepwise (eg, 1 U) increases in the total daily insulin dose may be required to achieve this, especially in cats with insulin resistance. Interstitial glucose or BG concentrations that are consistently <10 mmol/l (<180 mg/dl) for several days, or persistent absence of glucosuria, indicate excellent control with minimal glycaemic variability, but could increase the risk of periods of hypoglycaemia.

Hence, once it is established that excellent control is being maintained, stepwise decreases in insulin dose are typically recommended to facilitate recognition of diabetic remission (see Box 2) and to minimise the risk of hypoglycaemia.

Management of the cat with diabetes mellitus: sodium–glucose cotransporter-2 inhibitor (SGLT2i) therapy

Mechanism of action of SGLT2is

In the kidney, glucose is freely filtered at the glomerulus, and sodium–glucose cotransporter (SGLT) membrane proteins expressed in proximal renal tubules (SGLT2 and, to a lesser extent, SGLT1) actively reabsorb all filtered urinary glucose. SGLT2 is located in the early proximal renal tubules and reabsorbs 97% of filtered urinary glucose (Figure 11).[107,108] SGLT1 mostly mediates glucose absorption from the gastrointestinal tract; however, it reabsorbs the remaining urinary glucose (3%) in the distal proximal renal tubules.[108]

By administering an SGLT2i, SGLT2 cannot reabsorb filtered glucose, resulting in increased urinary glucose excretion and lowering of BG concentrations in cats with DM. This loss of urinary glucose results in improved glycaemia – often euglycaemia in cats with DM.[109,110] SGLT1 can increase its reabsorption of filtered urinary glucose to about 40–50% during SGLT2i administration in humans,[108] preventing hypoglycaemia. This likely explains why clinical hypoglycaemia has not been reported in cats with DM treated with SGLT2is, although other factors may also play a role in this species.[109,111–113]

The mechanism of action of SGLT2is is unique compared with other antidiabetic drugs in that SGLT2is work independently of insulin secretion, beta cell function and tissue insulin sensitivity. SGLT2is effectively and rapidly decrease BG concentrations (Figure 12),[114] thereby reducing the workload of pancreatic beta cells and, in some cases, reversing beta cell dysfunction. As a result, these cats could plausibly increase their endogenous insulin secretion to prevent the development of DKA, maintain euglycaemia and achieve long-term independence from exogenous insulin.

Key facts and practical recommendations in relation to SGLT2i therapy are presented in Box 10.

Sodium–glucose cotransporter-2 inhibitors are unique compared with other antidiabetic drugs in that they work independently of insulin secretion, beta cell function and tissue insulin sensitivity.

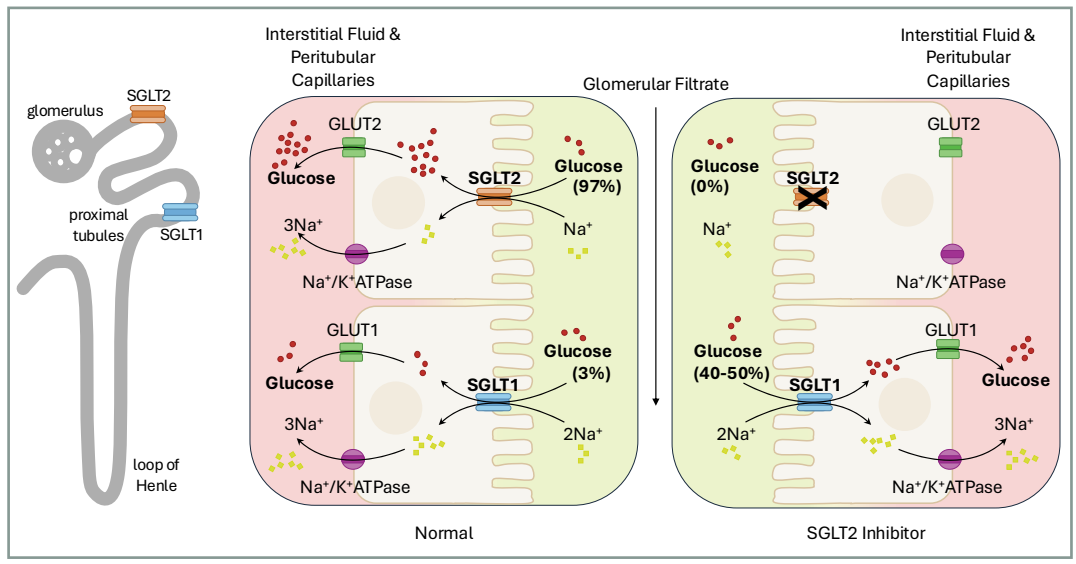


Figure 11 Mechanism of action of sodium–glucose cotransporter-2 inhibitors (SGLT2is). Glucose is freely filtered at the glomerulus and is primarily (~97%) reabsorbed in the proximal renal tubules by SGLT2 in segments S1/S2, with SGLT1 handling the remaining ~3% in segments S2/S3. Administration of an SGLT2i blocks SGLT2-mediated glucose reabsorption, leading to increased urinary glucose excretion and lower blood glucose concentrations, despite partial compensation by SGLT1 (up to 40–50%). (GLUT1/GLUT2 are other glucose transporters found in the kidney)

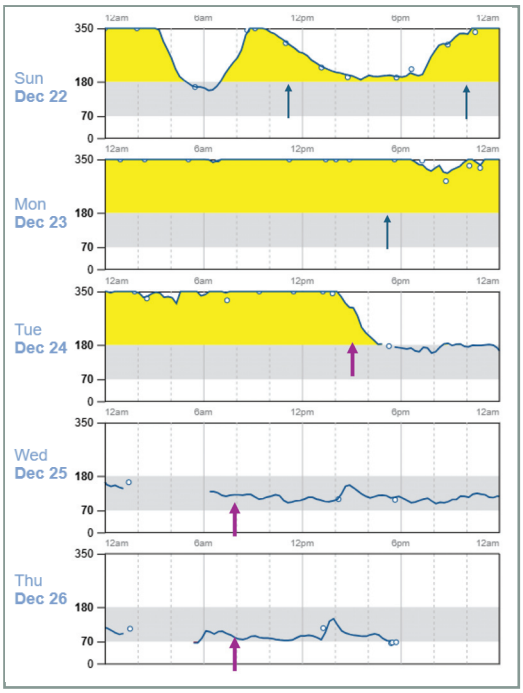


Figure 12 **Comparison of the glycaemic response, as determined by CGM, of a 12-year-old male neutered cat with newly diagnosed diabetes mellitus to therapy with insulin and then a sodium–glucose cotransporter-2 inhibitor (SGLT2i). The caregiver was unable to medicate the cat more than once a day and hence the decision was made to switch from insulin glargine U100 (administered on 22 and 23 December) to bexagliflozin (Bexacat; Elanco). A single tablet was administered at 15.00 on 24 December, and the dramatic and rapid effect of the SGLT2i resulted in euglycaemia that remained consistent over the next 1.5 days before the sensor detached. Blue arrows represent glargine U100 1 U/cat SC. Purple arrows represent bexagliflozin 15 mg PO.** *Image courtesy of Jocelyn Mott*

Box 10

SGLT2i therapy: key facts and practical recommendations

- SGLT2is work by increasing urinary glucose excretion, resulting in reduced BG concentrations and control of the clinical signs of DM.
- Screening for suitability for SGLT2i therapy should be performed before prescribing these drugs.
- SGLT2is should ideally be used in newly diagnosed diabetic cats, but may be considered for those previously treated with insulin.
- In cats with DM, two types of SGLT2i have been studied and licensed for the management of DM: velagliflozin and bexagliflozin.
- SGLT2is are given orally once a day, with or without food.
- A standard dosage is given to all cats (1 mg/kg q24h PO velagliflozin; 15 mg/cat q24h PO bexagliflozin) with no requirement to titrate the dosage up or down.
- Clinical hypoglycaemia has not been reported in cats on SGLT2i therapy.
- Monitoring for complications (DKA and diarrhoea) is most important in the first 2 weeks of treatment.
  - The most serious, but uncommon, adverse effect of SGLT2i therapy is euglycaemic DKA (eDKA).
  - Caregivers should be actively informed to promptly contact the veterinary clinic if lethargy, inappetence or vomiting/diarrhoea are noted.

Efficacy of SGLT2is

Field studies have demonstrated that velagliflozin and bexagliflozin are effective in treating feline DM in around 80–90% of cases, based on an improvement in mean BG or fructosamine concentrations as well as an improvement in at least one clinical sign (PU/PD, polyphagia or weight loss).[109,112] Furthermore, in a study comparing velagliflozin with porcine lente insulin in both naive and previously insulin-treated cats, the SGLT2i was associated with a good quality of life and glycaemia without clinical hypoglycaemia, and was concluded to be non-inferior to porcine lente insulin.[110]

Screening prior to SGLT2i treatment

SGLT2is are suitable for the treatment of DM in clinically well (happy) diabetic cats with no significant underlying conditions that could predispose to adverse events such as eDKA (eg, dehydration, poor body condition, gastrointestinal signs, clinical pancreatitis, ketosis) (see Figure 7). The level of screening to decide if the cat is a happy diabetic prior to SGLT2i therapy varies according to drug licensing requirements (which may be country-specific, even for the same drug) and between individual cases. In most cases, a careful history should be taken and physical examination performed (recording body weight and BCS), along with routine haematology and biochemistry panels (some authors also prefer to include serum beta-hydroxybutyrate [BHB]), and urinalysis for ketonuria prior to prescribing SGLT2is.[114]

Any further assessment would be case-specific and should consider caregiver and cat factors (see 'Management of the cat with diabetes mellitus: initial assessment'). Such pre-SGLT2i therapy screening should always be based on the individual cat's history and physical examination findings. For example, elevated pancreatic-specific lipase results and/or abnormal ultrasound findings in a cat with a normal clinical picture have a low predictive value for clinically relevant pancreatitis. In fact, changes in the ultrasound appearance of the pancreas or elevations in pancreatic lipase immunoreactivity are common in all diabetic cats.[68]

Use of SGLT2is in diabetic cats with concurrent endocrinopathies such as hyperthyroidism, HC and HST is understudied and should only be considered if there are no other contraindications, and with caregiver consent and close monitoring, until more data become available. Initial work suggests that cats with HST treated with velagliflozin, either as monotherapy or with insulin, may show improved diabetic control.[115]

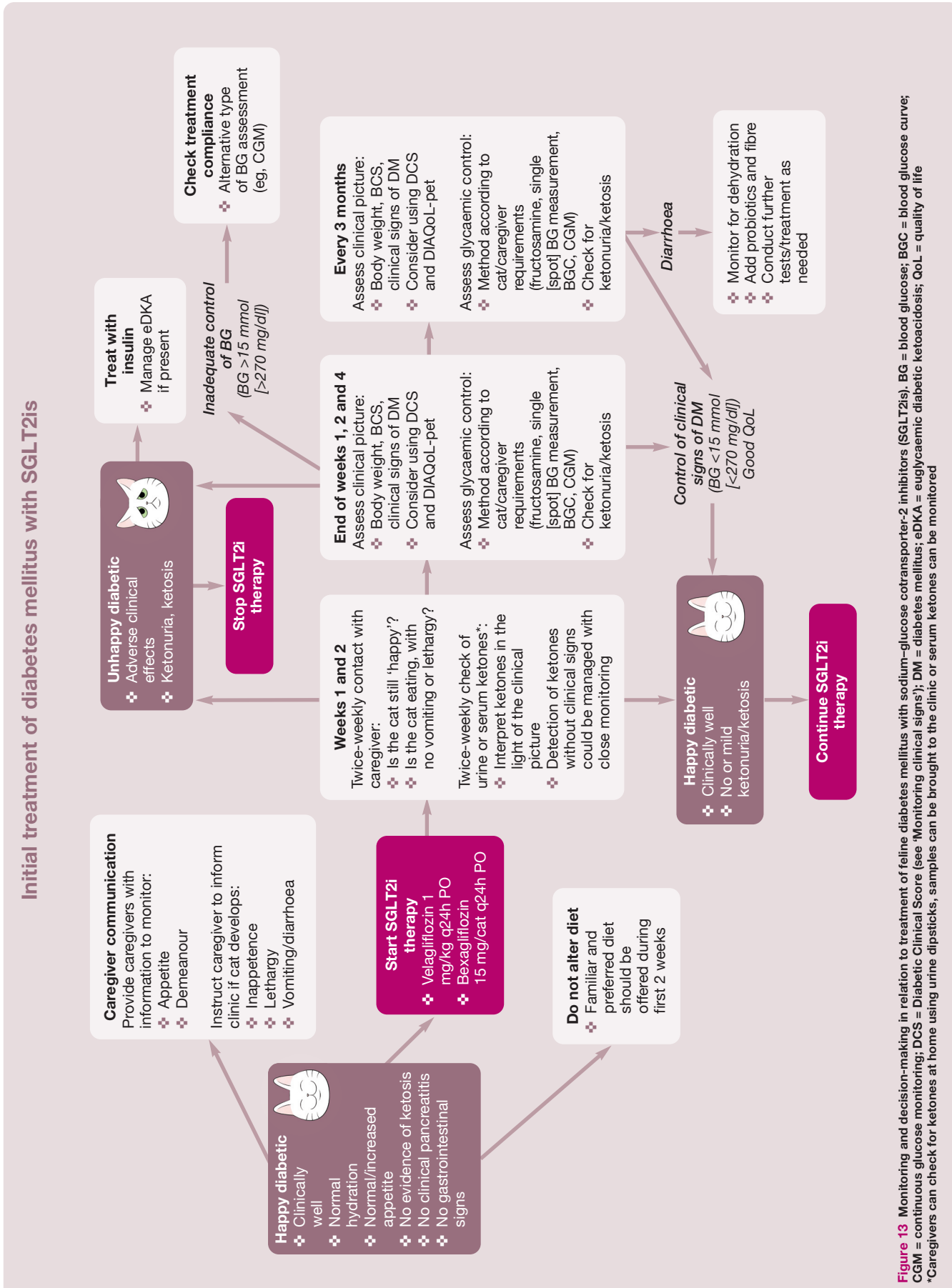


Figure 13 Monitoring and decision-making in relation to treatment of feline diabetes mellitus with sodium–glucose cotransporter-2 inhibitors (SGLT2is). BG = blood glucose; BGC = blood glucose curve; CGM = continuous glucose monitoring; DCS = Diabetic Clinical Score (see 'Monitoring clinical signs'); DM = diabetes mellitus; eDKA = euglycaemic diabetic ketoacidosis; QoL = quality of life
*Caregivers can check for ketones at home using urine dipsticks, samples can be brought to the clinic or serum ketones can be monitored

Monitoring cats treated with SGLT2is during the initial treatment period

In addition to screening to identify a happy diabetic cat suitable for SGLT2i therapy, appropriate monitoring by the caregiver and veterinary team is important, particularly in the first 2 weeks when adverse events and most cases of eDKA are likely to occur (Figure 13). Monitoring should include:

- **Clinical monitoring** (eg, weight, BCS, hydration, demeanour, appetite, occurrence of vomiting and/or diarrhoea).
  - At all times, when a cat does become unwell, determination of urine ketones or blood ketones is mandatory, and the ALIVE criteria for an eDKA/DKA diagnosis can be applied,[116] taking into account that affected cats may be euglycaemic.
  - Cats should be examined in the clinic at the end of weeks 1, 2 and 4 for clinical assessment and measurement of BG ± serum fructosamine concentrations.
- **Monitoring of urine ketones or blood ketones.**
  - It should be noted that the development of ketonuria or ketosis has not been shown to be predictive of impending or subsequent DKA/eDKA and a significant population of diabetic cats exist who remain clinically well despite mild ketosis (eg, trace ketones on a dipstick); in these cases, SGLT2i therapy can be continued with close monitoring of appetite and demeanour, and caregiver consent.
  - The presence of eDKA is associated with a decrease in blood pH as well as ketosis/ketonuria and cats will invariably be lethargic and inappetent, with or without vomiting (ie, 'unhappy'). SGLT2is should be stopped.

Table 4 Adverse events associated with SGLT2i treatment and recommended actions

Adverse event	Frequency	Recommended action(s)
Diarrhoea	Common	Usually self-limiting. If intervention is necessary, the cat may respond to diet change, probiotics or fibre supplementation. If diarrhoea is prolonged and/or severe, discontinue SGLT2i and pursue further diagnostic tests and treatment. Encourage water intake to maintain hydration
Vomiting	Common	Usually minimal. Manage symptomatically. If prolonged and/or severe, discontinue SGLT2i and pursue further diagnostics and therapy, and monitor for dehydration
Hypoglycaemia	Non-clinical hypoglycaemia – uncommon. Clinical hypoglycaemia – not reported	No need to stop SGLT2i treatment. Ongoing BG monitoring (eg, with CGM or home BG assessment) is recommended, with caregiver made aware of signs of clinical hypoglycaemia. SGLT2i dosage could be reduced if non-clinical hypoglycaemia is persistent
UTI/positive urine culture	Uncommon. Not significantly different to insulin-treated cats	If lower urinary tract signs are present, treat based on culture results. SGLT2i treatment can be continued if no other contraindications exist. In the absence of clinical signs, treatment of subclinical bacteriuria is not required
eDKA	Uncommon	Stop SGLT2i treatment. Manage with fluids, electrolyte supplementation, insulin and dextrose CRI (see 'Complications in the management of diabetes mellitus')

Based on Niessen et al[110]
BG = blood glucose; CGM = continuous glucose monitoring; CRI = continuous rate infusion; DKA = diabetic ketoacidosis; eDKA = euglycaemic diabetic ketoacidosis; SGLT2i = sodium–glucose cotransporter-2 inhibitor; UTI = urinary tract infection

Monitoring cats treated with SGLT2is following the initial treatment period

The glycaemic effect of SGLT2i therapy is likely to be seen within 1–2 weeks in the majority of cats in which this drug category proves effective. If by week 2 there is no significant lowering of glycaemic indices, correct administration of medication should be checked and additional glycaemic parameters measured in order to rule out a false-negative effect (eg, through stress hyperglycaemia).

Following the initial treatment period of 14 days, effective glycaemic impact can be assessed around 10–14 days later and then on a 3-monthly basis, as follows (tailored to the needs of the individual cat and caregiver):

- Monitoring improvement in clinical signs (PU/PD, polyphagia);
- Single (spot) glucose monitoring (note this is more useful than for insulin-treated cats, due to flatline BG concentrations associated with SGLT2i treatment);
- Assessment of serum fructosamine concentrations;
- Assessment of stability of body weight (some cats will lose weight in the first week, followed by stabilisation the following week);
- Evaluation of glycaemic response via a CGM system (Figure 12);
- Quality-of-life assessment (eg, using a tool such as the Diabetic Clinical Score[77] or DIAQoL-pet,[77] or simplified versions thereof).

Remember, urine glucose is not useful for monitoring due to the mode of action of SGLT2i drugs.

Adverse events associated with SGLT2is

Adverse events associated with SGLT2i therapy are discussed below, with proposed courses of action outlined in Table 4.

- **Gastrointestinal signs** The most commonly reported adverse events associated with SGLT2i administration are diarrhoea/loose stools (velagliflozin 38–50%;[109,110] bexagliflozin 38%[112,113]) and vomiting (velagliflozin 34%;[109] bexagliflozin 50%[112]). Partial inhibition of SGLT1 in the small intestine of cats treated with SGLT2is can result in diarrhoea or loose stools, but this is usually self-limiting (typically <7 days).[110] Treatment with probiotics, psyllium, canned pumpkin or kaolin products has been recommended.[114] Vomiting is usually intermittent and often does not

require intervention. However, SGLT2i treatment should be discontinued in cats who experience severe or prolonged diarrhoea and/or vomiting, and these cats should be thoroughly investigated for concurrent gastrointestinal or metabolic diseases.

❖ **Hypoglycaemia** With SGLT2 inhibition, SGLT1 in the distal proximal renal tubule may increase glucose reabsorption, as documented in other species, potentially contributing to a low risk of clinical hypoglycaemia; however, this mechanism has not been confirmed in cats with or without DM. Neither the velagliflozin nor bexagliflozin field studies reported any cases of clinical hypoglycaemia;[109,112] non-clinical hypoglycaemia was also uncommon. CGM of cats on SGLT2i therapy will show intermittent episodes of low interstitial glucose, as is observed in healthy cats, cats in remission and cats who are well controlled on insulin; if brief and without clinical signs, no intervention is required. Clinical hypoglycaemia should be managed as described for insulin (see 'Complications in the management of diabetes mellitus'). A lower dose or decreased frequency of administration of the SGLT2i may be attempted, if deemed appropriate by the veterinarian.

❖ **Urinary tract infection/positive urine culture** UTIs or positive urine cultures have been reported in SGLT2i-treated cats with DM,[109,112] with a similar incidence to those treated with insulin,[110] despite concerns that the mechanism of action of SGLT2is could predispose treated cats. Subclinical bacteriuria is common in non-azotaemic, older cats and treatment is not generally recommended.[117,118] Thus, urine cultures should not routinely be performed for cats with DM and no evidence of urinary tract clinical signs.[119] Nonetheless, if a cat on SGLT2i treatment develops a UTI (identified based on clinical signs and positive urine culture results), then antimicrobial susceptibility-based therapy should be initiated. The SGLT2i need not be discontinued.

❖ **Dehydration/volume depletion** Dehydration and volume depletion are recognised in SGLT2i-treated people, rats and cats with diabetes.[112,120,121] In the above-mentioned bexagliflozin field study, cats did not require intervention solely for dehydration, unless it was complicated by vomiting, diarrhoea, eDKA or development of a concurrent illness.[112]

❖ **Anorexia/hyporexia and lethargy** In the bexagliflozin field study,[112] anorexia/hyporexia and lethargy were commonly reported adverse events. Most cats had mild signs that resolved without intervention. However, lethargy, anorexia/hyporexia and dehydration were often associated with DKA/eDKA. Cats exhibiting these signs should, therefore, be assessed for eDKA and treated appropriately, if present.

Use of SGLT2is with insulin

In people, the concurrent use of insulin or an insulin secretagogue with an SGLT2i is a risk factor for clinical hypoglycaemia.[122] In cats, the combination of an SGLT2i with insulin, a sulfonylurea or a GLP-1 receptor agonist may also increase the risk of clinical hypoglycaemia. However, one study in cats treated concurrently with insulin and bexagliflozin did not document any clinical hypoglycaemic episodes.[113]

❖ **Euglycaemic diabetic ketoacidosis** The most serious adverse event experienced by cats with DM treated with SGLT2is is eDKA.[109,110,112] eDKA is not common in these patients, affecting only 1 in 15 newly diagnosed diabetic cats started on SGLT2i therapy or 1 in 10 diabetic cats previously treated with insulin.[109,112] If not quickly recognised and treated appropriately (see 'Complications in the management of diabetes mellitus' for a detailed discussion), eDKA can be fatal.

Remission and SGLT2is

Given the possible recovery of beta cells with resolution of glucose toxicity, cats treated with SGLT2is may restore adequate endogenous insulin production to maintain normoglycaemia. However, as treated cats will have normal BG and serum fructosamine concentrations, the only way to identify such cats is to stop treatment with SGLT2is and monitor BG. Further study is needed and many clinicians might prefer to continue treating with SGLT2is lifelong, given that restarting SGLT2i therapy requires the same period of monitoring for ketones as initial treatment, and cats in diabetic remission may relapse.[114]

In humans, SGLT2is are given in prediabetes to avoid overt DM. It could be argued that once a cat achieves remission, they have entered a post-diabetes state similar to human prediabetes and, as such, SGLT2i treatment could remain beneficial.

Management of the cat with diabetes mellitus: other therapies

GLP-1 receptor agonists have revolutionised the treatment of DM and obesity in people; however, only limited information is available on their use in cats. In healthy cats, GLP-1 agonists potentiate glucose-dependent insulin secretion and glucagon inhibition, slow gastric emptying and promote weight loss.[123–128] In diabetic cats, only a few studies are available but, overall, the trends are similar to what is reported in people, though clinical efficacy is marginal. Treatment with the GLP-1 agonist exenatide is associated with improved metabolic control, decreased exogenous insulin requirements, decreased glycaemic variability and less weight gain when compared with insulin treatment.[129–131]

Table 5 Dosages of glucagon-like peptide 1 receptor agonists in cats

Drug	Potential indication(s)	Dosage
Exenatide extended release	Insulin-dependent and non-insulin-dependent DM	0.13 mg/kg SC q30 days to 0.2 mg/kg SC q7 days
Liraglutide	Weight loss	0.2–0.6 mg/cat SC q24–72h

DM = diabetes mellitus; SC = subcutaneously

In the light of current evidence, GLP-1 agonists are not routinely recommended but might be considered in individual cases of feline DM, especially cats who have the potential to go into remission and those who need to lose weight. Dosages for specific formulations are detailed in Table 5.

Feeding the cat with diabetes mellitus

Integrating dietary management into the treatment of a cat with DM can improve the chances of a good treatment outcome. Some practical guidance for feeding cats with DM is given in Box 11.

Generally, to increase the chance of glycaemic control, transitioning to a diet with a low-carbohydrate content (<25% dry matter, <15% metabolisable energy, <5 g/100 kcal) is recommended. This can be achieved with specific diets designed for diabetic cats or commercial complete wet/canned diets. However, while low-carbohydrate diets with medium to high amounts of protein and fat have been associated with an increased likelihood of remission and glycaemic control,[25,132] each cat with DM is an individual, with their own food preferences and dietary history. Pursuing a particular diet at the cost of food intake or financial pressure on caregivers should be avoided. Remission can still be achieved in cats eating higher carbohydrate diets.[25]

Weight loss in overweight or obese cats with DM is essential to improve outcomes and the dietary regimen should be designed to achieve this. In fact, effective early weight loss is associated with a 15-fold increase in remission odds.[8] Importantly, weight loss in overweight and obese cats should be carefully managed. Aiming for a BCS of 5/9 and a maximum weight loss of around 0.5–1% per week is generally suggested.

Underweight cats also require nutritional attention, with adequate intake being the priority before any change in diet. Cats with DM are typically not hyporexic, so reduced appetite should prompt investigation for a comorbidity. If appetite is suboptimal, appetite stimulants can be helpful in improving food intake but it should be noted that capromorelin can cause hyperglycaemia and a decline in insulin secretion, so alternatives may be more suitable in cats with DM.[133]

Box 11

Practical tips for feeding cats with diabetes mellitus

- Recognise that while feeding does not have to coincide with insulin or SGLT2i administration, this may facilitate assessment of appetite and calorie intake and encourage engaging emotions.
- Perform a nutritional assessment for the cat, incorporating weight measurement, and body and muscle condition scoring.
- Obtain a thorough dietary history, including the cat's preferences (dry vs wet food, specific flavours and favourite treats).
- Avoid making dietary changes when first introducing insulin or an SGLT2i. Feed a familiar preferred diet and transition later.
- Instigate any dietary adjustments only when the cat is eating well at home and pathological weight loss has been addressed; ensure a slow transition while monitoring intake.
- Be aware that changing diet to one branded for diabetic cats is not a suitable strategy for all patients.
- Consider wet/canned diets for all diabetic cats. These are generally lower in carbohydrate and calories than dry foods/kibbles.
- Prioritise comorbidities, such as CKD, when planning a diet change. These usually take precedence in terms of dietary management.
- Where appropriate, use appetite stimulants (eg, mirtazapine) to facilitate acceptance of more suitable diets by cats who are being fed an unbalanced or unsuitable diet.

Feeding cats on SGLT2i treatment

Although controlled studies are needed, general recommendations to feed a low-carbohydrate diet apply to cats on SGLT2i treatment as well as cats on insulin. However, dietary transitions should be delayed at least 2 weeks after beginning treatment so that any changes in appetite and fecal consistency related to SGLT2is can be identified.[114] Supplementation with dietary fibre might help to ameliorate the side effect of diarrhoea.

It is anticipated that the recently drafted 'Guidelines for nutritional management of feline diabetes mellitus: a proposed classification system integrating medical considerations'[35] referred to earlier, which include detailed information on nutritional management of DM, will provide a useful resource.

Monitoring the cat with diabetes mellitus

General recommendations

Various methods for monitoring glycaemic control in cats have been recommended, with each having pros and cons. The choice of monitoring method(s) depends on the choice of treatment (insulin or SGLT2i) and factors such as caregiver preference, cost and convenience, and goals of treatment (eg, remission). Different monitoring methods or combinations of methods may be used as treatment goals change over time. A key factor for cats treated with insulin is to identify clinical improvements as well as progressive changes in glycaemic control so that, firstly, resolution of chronic hyperglycaemia is recognised and, secondly, timely tapering and withdrawal of insulin is facilitated.

Specific details on short- and long-term monitoring of SGLT2i-treated cats are included in the section 'Management of the cat with diabetes mellitus: sodium–glucose cotransporter-2 inhibitor (SGLT2i) therapy'.

Table 6 ALIVE Diabetic Clinical Score system

Factor	Score
Unintended weight loss 0 = None, or gained since last examined 1 = Mild (<5% loss) 2 = Moderate (5–10% loss) 3 = Severe (>10% loss)	
Polyuria and polydipsia 0 = Normal 1 = Mild (some increase noted by owner) 2 = Moderate (increased filling of water bowl) 3 = Severe (constantly at bowl)	
Appetite 0 = Normal or decreased appetite (if decreased appetite, exclude DKA or concurrent disease) 1 = Mild polyphagia (finishes eagerly) 2 = Moderate polyphagia (finishes eagerly and begs for more) 3 = Severe polyphagia (obsessed with food)	
Attitude/activity 0 = Normal 1 = Mild decrease (a bit less running and jumping) 2 = Moderate decrease (a lot less running and jumping) 3 = Severe decrease (lying about all the time) (consider DKA in the ill patient with DM)	
Total score*	

*The range of total score for an individual diabetic cat is 0–12
Available from: esve.org/alive/search.aspx. A modified version for caregivers and the veterinary team is available in the supplementary material
DKA = diabetic ketoacidosis; DM = diabetes mellitus

Monitoring clinical signs

Assessment of clinical signs must be prioritised in any monitoring strategy for insulin- or SGLT2i-treated cats. A practical method is to use the ALIVE Diabetic Clinical Score (DCS) system (Table 6) at each veterinary assessment. This looks at four key clinical factors to provide a score out of 12. Lower scores indicate better diabetic control, with treatment aiming for the lowest score possible without an unacceptably high risk of hypoglycaemia. A modified version for caregivers/veterinary team members to complete prior to/at reassessment is available in the supplementary material.

Changes in diabetic control can be reliably estimated by comparing scores over time. Caregivers should also be encouraged to keep a diary, or use a computer/smartphone app or spreadsheet, to record key monitoring parameters, including the cat's overall demeanour, body weight, water intake and/or urine output.

Adjusting insulin treatment using clinical signs

In many insulin-treated cats, it is possible to achieve reasonably good control of DM with monitoring of clinical signs alone. While subclinical hypoglycaemia cannot be ruled out in these cases, careful and strategic dose alterations based on clinical signs can minimise the risk of hypoglycaemia and obviate the need to measure glucose concentrations.

After ruling out other causes, weight loss in a diabetic cat is a sign of overall insulin deficiency. Unwanted weight gain usually indicates that meal portions need to be reduced, and excessive weight gain might be a sign of overdosing (or undiagnosed HST).

Accurate monitoring of daily water consumption is helpful because 24 h water intake has a degree of correlation with average BG concentrations in insulin-treated cats.[134] If the water bowl is shared between pets, useful trends can also often be obtained if the total daily volume drunk by all pets is measured; alternatively, overnight water consumption by the diabetic cat, if confined alone, can be recorded. Quantification of the cat's water intake in relation to treatment changes is ideal, but not always feasible. When enquiring about clinical signs it is, therefore, important to ask caregivers about changes since the last time therapy was altered, and not just about absolutes. Some caregivers report no change as 'normal' because they have become accustomed to a degree of polydipsia. Use of 'smart' feeders/water fountains/litter trays can be helpful for accurate monitoring.

Importantly, changes in glycaemia will not be reflected by changes in water intake or urine output when BG concentrations fluctuate below the renal threshold. This means that over-regulation cannot be distinguished from good glycaemic control. One approach for differentiating between the two is described in the box 'Over-regulation vs good glycaemic control'.

This approach can be modified with the addition of fructosamine measurements and/or regular urine glucose testing to aid in monitoring and to detect remission. Urine dipsticks may be directly applied to urine or to the liquid obtained by adding water to urine-soaked cat litter.[135] The insulin dose should be increased gradually (every 2–4 weeks) but with the goal of normalising clinical signs and reducing serum fructosamine values. Serum fructosamine concentrations within

Over-regulation vs good glycaemic control

One way to differentiate over-regulation from good glycaemic control when BG concentrations fluctuate below the renal threshold is to begin insulin therapy at a low dose and increase doses gradually (every 2–4 weeks) while carefully monitoring clinical signs. When an increase in insulin dose appears to produce no further improvement in polydipsia, it can be assumed that no better control can be achieved without significantly risking hypoglycaemia. At that point, it is recommended that the dose of insulin is decreased by about 20–25%, with further gradual reductions (every 2–4 weeks) until polydipsia worsens.

If no clinical difference is observed between two doses, it is always safer to choose the lower dose. If hypoglycaemia is suspected, the insulin dose should be immediately reduced by at least 20–25%. This effectively ensures a return to a dose that was previously considered safe and, potentially, even too low. If the clinical signs of suspected hypoglycaemia resolve, even if polydipsia worsens, the insulin dose should not be increased again. Whether or not the patient requires further glycaemic monitoring and/or a trial of a different insulin formulation at that point, or stays on the lower dose of insulin, depends on how intolerable the clinical signs are for the caregiver and the impact on the cat's quality of life.

Procedure for applying a continuous glucose monitoring system

Figure 14 **Images (a) to (l) show a diabetic cat being fitted with a FreeStyle Libre 3 (Abbott Laboratories) continuous glucose monitoring (CGM) system. (a) The dorsal aspect of the neck is clipped; (b) the skin is cleaned with chlorhexidine and alcohol wipes and allowed to dry; (c) the cap is unscrewed from the sensor applicator and the cap is set aside; (d) the sensor applicator is ready (left Libre 3, right Libre 2); (e) a drop of tissue glue is added to the surface of the sensor that will make contact with the skin; (f) the sensor applicator is placed over the site, and pushed down firmly to apply the sensor; (g) if necessary, forceps can be used temporarily to avoid detachment of the sensor before (h) the sensor is secured in place with a patch; (i) by pressing 'get started' on the home screen of the system's mobile app, and touching the sensor with the back of the phone, the sensor is scanned and (j) is ready to measure the interstitial glucose concentration after 60 mins; (k) the sensor is further secured with a layer of cotton bandage covered with elastic bandage; (l) the cat is ready to go home. Images (m) and (n) show alternative locations for placement of the CGM system sensor (in these images a FreeStyle Libre 2 device is being used): (m) the lateral thorax and (n) the lumbar musculature. Note that the cat in (m) also has an oesophagostomy tube in place.** *Images courtesy of Federico Fracassi (a–l) and Samantha Taylor (m,n)*

the reference interval and/or a persistent absence of glucosuria should prompt a gradual reduction in insulin dose (about every 1–2 weeks) as long as clinical signs (Table 1) do not recur and serum fructosamine concentrations and/or urine glucose results remain normal.

Continuous glucose monitoring

In recent years, glucose monitoring has been revolutionised by the development of CGM systems, which are wearable minimally invasive devices that measure interstitial glucose concentrations almost continuously for several consecutive days or even weeks, removing the need for repeated venepuncture and significantly increasing the level of information regarding glucose fluctuations and trends.

Currently, the FreeStyle Libre (Abbott Laboratories) flash glucose monitoring system

Continuous glucose monitoring systems remove the need for repeated venepuncture and significantly increase the level of information regarding glucose fluctuations and trends.

is the most commonly used CGM device in cats. It provides comprehensive glucose data without the need for calibration, and it can be worn for up to 14 days. This CGM system is available in most countries, but there is anecdotal information that similar devices have equivalent functionality in regions where the FreeStyle Libre is not currently available. The latest version, the FreeStyle Libre 3, has a very small sensor, measuring 22 mm in diameter and 2.9 mm in thickness. Figure 14 illustrates the procedure, necessary materials and equipment for FreeStyle Libre 3 application. The

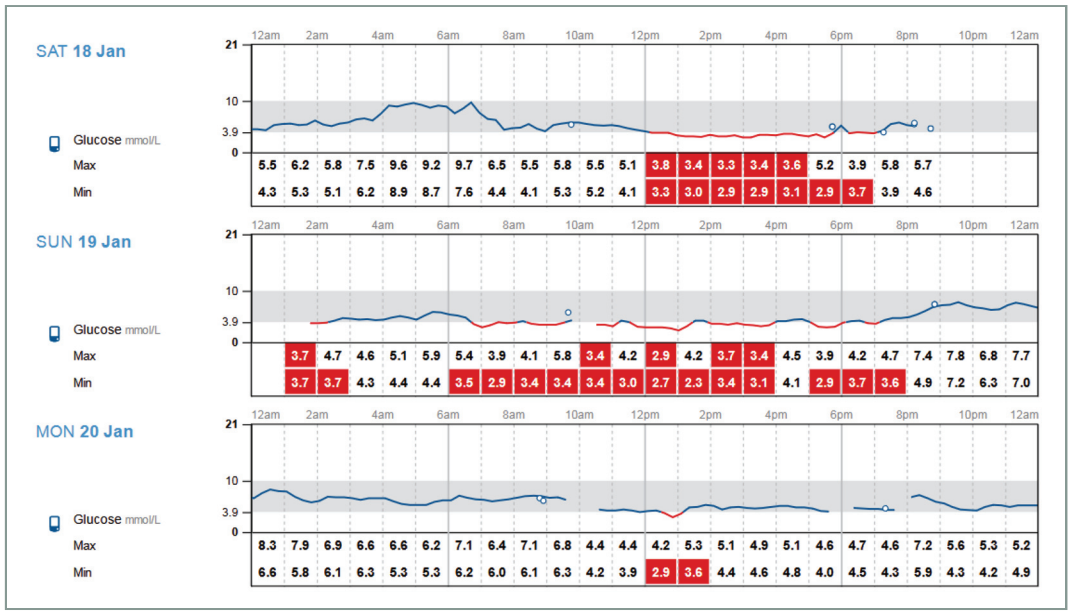


Figure 15 **The daily log from the LibreView platform for a diabetic cat currently in the tapering and withdrawal phase of insulin treatment. The ALIVE Diabetic Clinical Score was 0/12 and there were no clinical signs of hypoglycaemia. Interstitial glucose concentrations <3.6 mmol/l (<65 mg/dl) are common in cats when there is excellent glycaemic control (as in this case), and do not necessarily indicate hypoglycaemia.** *Image courtesy of Linda Fleeman*

Clinicians should access continuous glucose monitoring reports for a period of days to assess glycaemic control.

sensor begins recording data 1 h after application and automatically measures interstitial glucose concentrations every minute.

The data on interstitial glucose concentrations are transferred from the system's sensor to a smartphone with the appropriate mobile app installed. From there, data are automatically uploaded to a cloud-based diabetes management platform (LibreView), which generates summary glucose reports from the uploaded sensor data, including a daily log (Figure 15), and provides a secure repository for data for 3 months.

The accuracy of the FreeStyle Libre has been studied in diabetic cats and is considered acceptable.[136–139] In the hypoglycaemic range, accuracy seems to be lower. A recent study evaluating the performance of the FreeStyle Libre 2 in cats with hypoglycaemia observed that interstitial glucose concentrations underestimated BG concentrations throughout most of the hypo- and euglycaemic ranges, but generally overestimated BG concentrations in cats with marked hypoglycaemia (<3.3 mmol/l [60 mg/dl]).[140] Similar findings were reported with the FreeStyle Libre 3 device.[141] It is, therefore, imperative to evaluate FreeStyle Libre results in this critical range with caution.[140] Moreover, the most common complication encountered with use of the system in cats was reduced sensor lifespan (5.5–10 days).[136–139] This limitation should be discussed with caregivers before considering use of this device in cats.

To efficiently achieve glycaemic control, it is recommended that the FreeStyle Libre is applied continuously to facilitate titration of the insulin dose from the time DM is diagnosed until stabilisation or remission is reached. Once there is stable glycaemic control, the device may variously be applied continuously, once every 2–3 months or whenever the cat shows any signs attributable to hyperglycaemia or hypoglycaemia. Alternatively, the device can be used only when doses are changed or remission/glycaemic variability is suspected. The authors of these Guidelines recommend routine use of the LibreView platform to access detailed patient glucose information over a period of days to assess current glycaemic control. Tracking results daily while the device is in place also allows the impact of changes in protocol to be analysed and hence optimises use of the sensor.

Single blood glucose measurements

A single (spot) measurement is usually insufficient to assess glycaemic control in a diabetic cat receiving insulin therapy. The only exception is when hypoglycaemia is detected. For caregivers familiar with BG testing at home, spot BG measurements are recommended whenever it is suspected that the cat is unwell. Detection of hypoglycaemia, especially in the presence of clinical signs, necessitates a reduction in insulin dose.

Note that spot BG measurements are more useful for monitoring cats on SGLT2is (see 'Management of the cat with diabetes mellitus: sodium–glucose cotransporter-2 inhibitor [SGLT2i] therapy').

Table 7 Comparison of continuous glucose monitoring (CGM) vs home blood glucose (BG) monitoring in diabetic cats

Continuous glucose monitoring	Home blood glucose monitoring
Higher cost of equipment	Lower cost of equipment (after initial meter purchase)
Better tolerated by some caregivers/cats than home BG monitoring	Better tolerated by some caregivers/cats than CGM
Minimal intervention yet pattern of BG is recorded over several days	Increased intervention: need either to measure every 2 h over 12 h* or obtain at least seven to 10 results at different times of the day over 2–3 days
Does not reliably differentiate between low and normal BG ranges	More accurate measurement in the low and normal BG ranges (veterinary-specific meter only)
Will detect all hypoglycaemic events during period of recording	Will potentially miss hypoglycaemic events
Better detection of minimum and maximum BG range	Will typically underestimate the minimum and maximum BG range
Provides detailed data on trends and patterns of glycaemic variability	Provides little data on trends and patterns of glycaemic variability

*This is the standard time frame. In some cases it might need to be extended to 14 h or 16 h (see text)

Home blood glucose monitoring

Home BG monitoring can be a useful tool in the management of the cat with DM. Caregivers are instructed to generate BG curves by taking readings during the day, as well as recording clinical signs. During the initial phase of therapy, BG curves are typically recommended once a week. Once stabilisation is achieved, the frequency is gradually reduced to approximately every 3–4 weeks. BG concentrations are measured before the morning insulin injection and then every 2 h until the evening dose is administered. If a nadir is not observed, caregivers may be advised to extend the monitoring period (eg, perform a 14 h or 16 h BG curve instead of the standard 12 h BG curve). An alternative approach that suits some caregivers is to obtain a total of at least seven to 10 results at different times of the day over 2–3 days.

When advising on home BG monitoring, it is crucial to consider the differences between veterinary-specific and human glucose meters, as the latter typically yield lower readings in cats due to species-specific variations in blood composition.

Individual preferences for monitoring tool

A recent study found that owners reported the FreeStyle Libre to be well tolerated in only 40% of cases,[142] yet approximately 50% of cat owners expressed confidence in performing routine BG measurements at home.[77] Taken together, these findings emphasise the importance of discussing both options and tailoring recommendations to individual preferences. Various pros and cons of CGM vs home BG monitoring are summarised in Table 7.

Limitations of in-clinic blood glucose curves

It is not recommended to admit an otherwise well diabetic cat into the clinic to perform a BG curve because this is expected to result in a stress response in most cats and results are often not representative of glycaemic control in the cat's home environment.

Monitoring based on changes in glycated proteins

The main advantage of measuring protein glycation is that acute fluctuations in glucose (eg, due to stress) do not affect the results. Therefore, protein glycation is a convenient way of assessing long-term trends in response to treatment, provided that no abnormality exists in the protein concentration or half-life. Measuring protein glycation is especially useful when clinical signs are not apparent or when caregivers are unable to accurately report clinical signs.

However, the main advantage of measuring protein glycation is also its principal disadvantage: short-term hypoglycaemic episodes are not captured by these tests. Thus, high concentrations of glycated proteins cannot be used to rule out the possibility of episodic hypoglycaemia.

Serum fructosamine concentrations

Serum fructosamine concentrations reflect glycaemia over around the preceding 7–10 days, depending on the magnitude of glucose changes and rate of protein metabolism (see 'Diagnosis of diabetes mellitus'). Values used by reference laboratories to determine glycaemic control are not well established for cats and do not necessarily reflect the full range of biological variability. Therefore, results often do not match clinical observations. Comparison of serum fructosamine concentrations at different time points is more useful, and it is recommended to obtain a baseline result to compare with a second result 2–3 weeks after a treatment change, and to focus on trends rather than absolute numbers.

Note that serum fructosamine concentrations that are within the reference interval in an insulin-treated cat may indicate remission and/or risk of hypoglycaemia, and should prompt assessment of the current insulin dosage.

Haemoglobin A1c

Glycosylated haemoglobin has been studied in diabetic cats and a point-of-care analyser has recently become commercially available (A1Care; Baycom Diagnostics).[143] In cats, haemoglobin A1c reflects average BG concentrations for the previous 68–77 days and, therefore, it will not be useful for monitoring when relatively frequent changes in therapy are made.

Complications in the management of diabetes mellitus

Diabetic ketoacidosis and euglycaemic diabetic ketoacidosis

DKA consists of the biochemical triad of hyperglycaemia, ketonaemia or ketonuria and metabolic acidosis.[21] The most serious adverse event reported with both velagliflozin and bexagliflozin treatment is eDKA – the triad of high anion gap metabolic acidosis, ketonaemia ± ketonuria and a BG concentration <13.9 mmol/l (<250 mg/dl) (Table 8).

DKA has been reported in 34–41% of newly diagnosed diabetic cats,[22,144] and in 3.8% of 185 cats treated with PZI in one study.[145] The incidence of eDKA in SGLT2i-treated cats is approximately 5–7% (not previously insulin treated 1 in 15, previously insulin treated 1 in 10).[109,112]

Table 8 Diagnostic criteria for diabetic ketoacidosis (DKA) and euglycaemic diabetic ketoacidosis (eDKA)

	Laboratory values	
Parameter	**DKA**	**eDKA**
Blood glucose (mmol/l; mg/dl)	>14; >250	<14; <250
Serum beta-hydroxybutyrate (mmol/l)	>2.4	>2.4
Urine ketones (mg/dl)	>15	>15
Venous/arterial pH	<7.35	<7.35
Bicarbonate (HCO_3) (mmol/l)	<15	<15

Currently, no diagnostic test is available to reliably identify cats with sufficient endogenous insulin secretion to prevent the (uncommon) development of euglycaemic diabetic ketoacidosis.

Pathogenesis

DKA/eDKA results from a decrease in the action of circulating insulin, due to an absolute or relative insulin deficiency complicated by increases in circulating concentrations of hyperglycaemic hormones (eg, glucagon, catecholamines). This triggers a cascade of metabolic processes:

- **Lipolysis and ketogenesis** Free fatty acids released from adipose tissue undergo beta-oxidation in the liver, producing ketone bodies (acetoacetate, BHB and acetone).
- **Metabolic acidosis** Excess ketones lower blood pH, resulting in high anion gap metabolic acidosis.
- **Osmotic diuresis** Hyperglycaemia surpasses renal reabsorption thresholds, leading to glucosuria, polyuria and dehydration.
- **Electrolyte imbalances** Potassium, magnesium and phosphate are depleted due to osmotic losses and cellular shifts.

Concurrent conditions such as pancreatitis, infections or renal disease often exacerbate the metabolic derangements and insulin resistance, compounding the pathophysiological complexity (Box 12).[146]

With SGLT2i administration, proposed mechanisms that alter the insulin:glucagon ratio include loss of paracrine inhibition by insulin during euglycaemia, resulting in increased endogenous glucose production, increased glucagon secretion, reduced tissue glucose disposal, insulinopenia and elevations in plasma cortisol and catecholamines (Figure 16).[121,147–150] Currently, no diagnostic test is available to reliably identify cats with sufficient endogenous insulin secretion to prevent the uncommon development of eDKA.

Clinical signs

Signs of DKA/eDKA can range from subtle to severe. Diabetic cats generally have an excellent appetite. Therefore, DKA/eDKA should be suspected in any diabetic cat with inappetence, especially if this progresses to anorexia. History can range from classic PU/PD to the worrisome systemic signs of severe lethargy, anorexia and vomiting. Clinical examination usually identifies dehydration and lethargy, which without treatment may progress to extreme depression, obtundation, coma and death. Cats with DKA/eDKA may have

Box 12

Risk factors for diabetic ketoacidosis and euglycaemic diabetic ketoacidosis in cats with diabetes mellitus

- Inappetence and dehydration
- Concurrent illness (pancreatitis, UTI, hepatic lipidosis, CKD)
- Inadequate insulin therapy (inappropriate regimen, sequential missed doses)
- Medications (eg, glucocorticoids)
- Weight loss
- Development of concurrent disease (pancreatitis and/or hepatic lipidosis)
- Poor response or poor glycaemic control

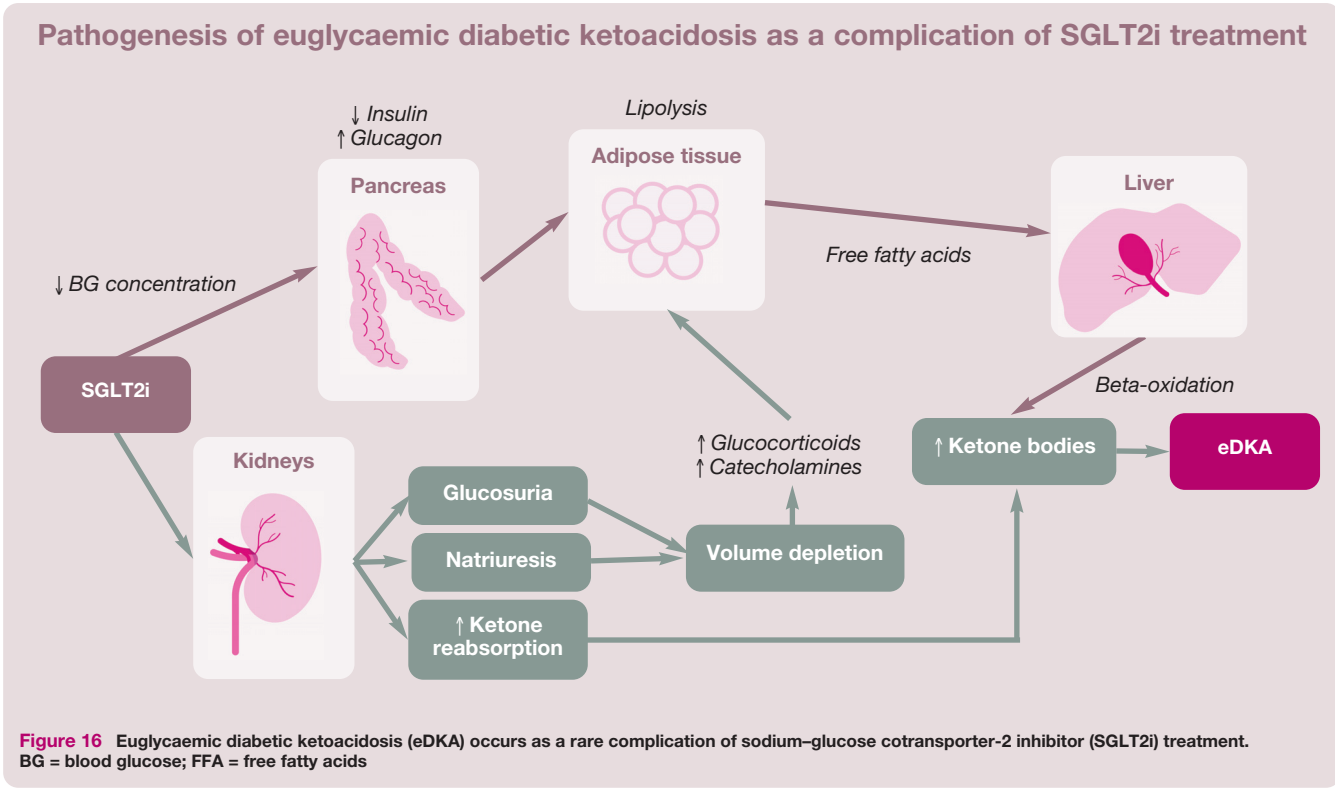


Figure 16 Euglycaemic diabetic ketoacidosis (eDKA) occurs as a rare complication of sodium–glucose cotransporter-2 inhibitor (SGLT2i) treatment. BG = blood glucose; FFA = free fatty acids

additional clinical signs if concurrent diseases are present. Pancreatitis and/or hepatic lipidosis were associated with DKA/eDKA in some cats on SGLT2i therapy in one study.[109]

Diagnosis

DKA is diagnosed in a diabetic cat showing clinical signs, as described above, accompanied by evidence of ketones in the urine or excess ketones in the blood. Identification of metabolic acidosis, when testing is available, provides confirmation of the diagnosis.

More specifically, ALIVE criteria for diagnosing DKA are:[21]

- A diagnosis of DM (according to ALIVE criteria – see Box 6);
- Demonstration of ketonaemia, defined as an increased BHB concentration, and/or ketonuria or ketonaemia, defined as detectable ketones using nitroprusside test strips;
- Demonstration of metabolic acidosis, defined as a venous/arterial blood pH <7.35 and decreased bicarbonate (Table 8). When blood gas analysis is unavailable, a patient who is unwell and meeting the other criteria mentioned above should be suspected of suffering from DKA.

Recently, ALIVE criteria for the diagnosis of eDKA have been defined.[116] These are the same as for DKA other than a relatively normal glycaemia (<14 mmol/l, <250 mg/dl).

BHB is the main ketone body produced in DKA and elevations in BHB will be detected in the serum before urine ketones are present. This is partly explained by the fact that urine dipsticks measure only acetoacetic acid (which BHB is converted to). Measurement of blood BHB is thus more sensitive for early detection of ketosis than measurement of acetoacetic acid in urine using a dipstick.

A validated method of BHB measurement should be used, but the inherent variability of ketone meters means that a hard cut-off cannot be applied. Cats with a BHB concentration of 1–2.4 mmol/l (10.4–24.9 mg/dl) should be monitored more closely and frequently for progression to DKA/eDKA.[114] Progressive elevations in BHB concentrations in a cat who appears clinically well (happy) may not indicate DKA. However, in a clinically unwell (unhappy) cat, even a mild to moderate BHB elevation warrants careful evaluation for DKA.[114]

The presence of urine ketones is also sufficient for a diagnosis of DKA in a clinically unwell cat. Cats treated with SGLT2is can be successfully monitored using urine ketones,[109,110] but if urine ketones are negative and a cat treated with SGLT2is is unwell, serum BHB can be measured to exclude early DKA/eDKA.

Treatment

A suggested therapeutic approach to DKA is described in Figure 17. For cases where finances are limited or infusion pumps are not available, the intramuscular or subcutaneous

Management of the cat with diabetic ketoacidosis

Diagnosis of DKA

Initiate fluid therapy as soon as possible after presentation:
- 0.9% NaCl or buffered isotonic solution (eg, lactated Ringer's) are appropriate
- Monitor and supplement K^+ if needed (which is usually the case)
- Add maintenance fluids (about 2 ml/kg/h) and replacement fluid for losses due to vomiting/osmotic diuresis
- Estimate percentage dehydration and chronicity; aim to correct 60–80% dehydration in the first 10–12 h and the remaining 20–40% in the following 12–14 h
- It is generally better to slightly overestimate than underestimate fluid needs
- Be very cautious with fluid therapy if there is evidence of CKD, congestive heart failure or chronic hyperosmolarity

Provide antiemetics and nutritional support, if indicated:
- Antiemetics:
  - Maropitant
  - Ondansetron
- Nutritional support:
  - Enteral nutrition using a feeding tube (nasoesophageal or oesophagostomy tube)
  - Four to six small meals per day
  - High-protein/moderate-fat diets are preferred

Begin insulin therapy (immediately or after correction of hypovolaemia*):
- IV protocol (recommended by the authors):
  - Use a dedicated IV catheter and a separate line from the fluids for the infusion of insulin
  - Add 1.1 U/kg of soluble/regular or lispro insulin to 48 ml of 0.9% NaCl solution
  - Saturate the binding of insulin to the IV tubing by standing insulin in the line for 30 mins, and then running it through the IV line (this step is skipped by some authors, accepting that the initial CRI could contain less insulin)
  - Re-prepare the solution and start the CRI (see table below)
  - Base the initial starting dose for the CRI on the cat's BG concentration (see table below)
  - Adjust the CRI every 1–2 h based on the cat's BG concentration
- IM protocol:
  - Soluble/regular insulin at 0.1–0.2 U/kg IM q1–2h
  - When blood glucose is <13.9 mmol/l (<250 mg/dl), add 2.5–5% dextrose
- Protocol with insulin glargine U100:
  - 2 U/cat glargine SC q12h followed by up to three doses of 0.5–1 U/cat glargine IM at a minimum of 4-h intervals

* Author recommendations vary on when insulin treatment should be started (immediately or after correction of fluid deficits). Further research is needed and the decision should be dependent on individual case assessment.

Monitor closely and frequently during treatment:
- Blood pH (every 8 h), blood glucose (hourly for the first 24 h, then every 2–3 h) and ketones (ideally blood BHB every 4 h)
- Electrolytes (K, Na, Mg, P) every 8–12 h, supplementing when necessary
- Urine output
- Neurological status
- Respiratory rate (be aware of fluid overload)
- Body weight q12h (be aware of fluid overload)

Resolution of DKA:
- No vomiting, moderate/good appetite
- BHB ⩽1.0 mmol/l (⩽10.4 mg/dl) for two consecutive measurements 1 h apart or absence of ketonuria
- Blood pH ⩾7.3 and/or bicarbonate ⩾15 mmol/l (⩾91.5 mg/dl)

- Start with intermediate- or long-acting insulin (eg, PZI, glargine U100, U300) administration 1–1.5 U/cat SC q12h
- Reduce and then stop fluid therapy

Intravenous constant rate infusion administration of fluid and insulin based on blood glucose concentration

BG concentration (mmol/l [mg/dl])	Fluids	Rate of administration of insulin solution (ml/h)
>13.9 (>250)	0.9% NaCl or lactated Ringer's solution	2
11.1–13.9 (200–250)	2.5% dextrose*	1.5
8.4–11.0 (150–199)	2.5% dextrose*	1.5
5.6–8.3 (100–149)	5% dextrose†	1
<5.5 (<100)	5% dextrose†	Stop insulin infusion

*2.5% dextrose composed of 25 ml of dextrose 50% added to 475 ml of 0.9% NaCl or lactated Ringer's solution
†5% dextrose composed of 50 ml of dextrose 50% added to 450 ml of 0.9% NaCl or lactated Ringer's solution

Cat friendly hospitalisation
Reducing stress can help in the management of cats with DKA:
- Provide a comfortable bed and somewhere to hide.
- Combine procedures (eg, IV catheter management, medicating, sampling) to minimise handling.
- Use anxiolytic medications (if appropriate) to improve tolerance of interventions.
- Consider early placement of an oesophagostomy tube to improve nutrition and allow oral medications to be given without stress; and placement of a central venous catheter to facilitate blood sampling.

Figure 17 Recommended protocol for management of feline diabetic ketoacidosis (DKA). Modified from Xenoulis and Fracassi.[68] BG = blood glucose; BHB = beta-hydroxybutyrate; CKD = chronic kidney disease; CRI = constant rate infusion; IM = intramuscular; IV = intravenous; PZI = protamine zinc insulin; SC = subcutaneous

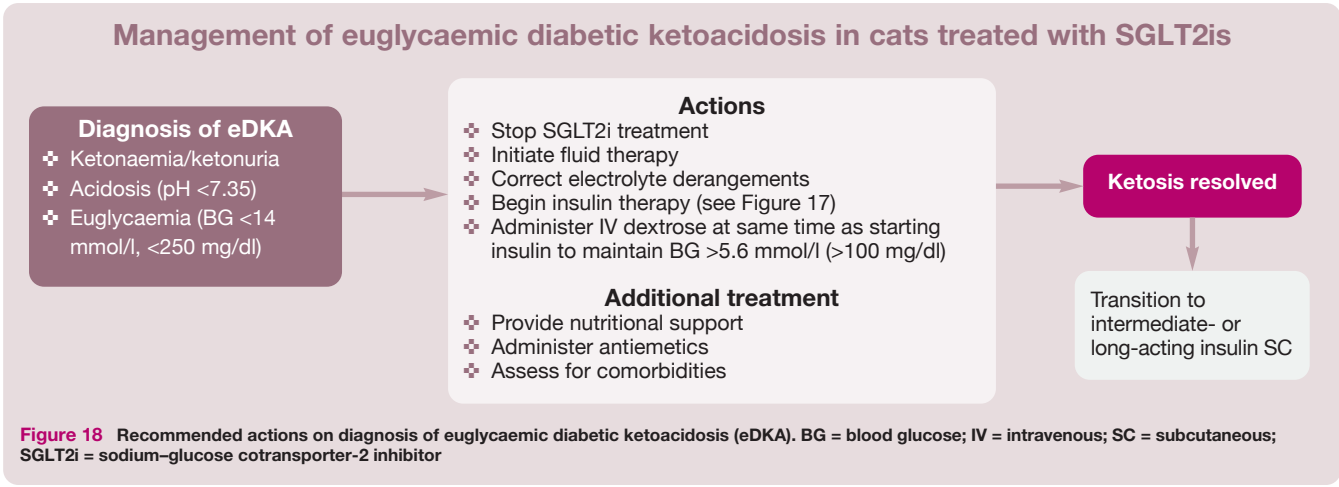


Figure 18 Recommended actions on diagnosis of euglycaemic diabetic ketoacidosis (eDKA). BG = blood glucose; IV = intravenous; SC = subcutaneous; SGLT2i = sodium–glucose cotransporter-2 inhibitor

insulin glargine U100 protocols described may be an alternative. A prospective study found that bolus administration of glargine was effective and safe, with cats with DKA showing similar survival rates to those treated with a constant rate infusion of soluble/regular insulin.[151]

Therapy for eDKA is very similar to that for cats on insulin who develop DKA, with a few caveats (Figure 18):

- SGLT2is should be discontinued immediately.
- Insulin therapy is mandatory. Since these cats are euglycaemic, this may seem counterintuitive; however, without insulin therapy, the ketoacidosis will not resolve.
- To prevent iatrogenic hypoglycaemia with insulin administration, IV dextrose (often at 5% or higher) is required. Close and frequent glucose monitoring (eg, CGM) is needed.
- Reduced renal or liver function may prolong metabolism and clearance of SGLT2is, resulting in euglycaemia for more than 24 h after discontinuation and an ongoing requirement for IV dextrose for this period or longer.
- Cats who develop DKA/eDKA on SGLT2i therapy should transition to insulin and are not generally candidates for further treatment with SGLT2is. (Further data are needed to determine if SGLT2is could be used to treat cats with a history of DKA/eDKA who enter remission and subsequently relapse, or cats with resolution of causes thought to contribute to the DKA/eDKA [eg, corticosteroid treatment, insulin compliance issues, resolution of comorbidities].)
- Nutritional support is also vital to prevent further complications such as hepatic lipidosis. Feeding tubes should be placed sooner rather than later. Further information is available in the '2022 ISFM consensus guidelines on management of the inappetent hospitalised cat'.[152]

Prevention of DKA

Preventing DKA in cats receiving insulin or SGLT2i therapy involves a combination of careful management, regular monitoring, including a focus on clinical signs, and early intervention when needed. Equally as important is choosing good candidates for SGLT2i administration through appropriate screening, and ensuring prompt initiation of therapy (within a few days of screening). Caregiver communication and education on what to look for in their cat that could indicate DKA, and when to contact the veterinary clinic, can expedite identification and management of this complication.

Prognosis

Reported mortality and recurrence rates for cats with DKA range from 26% to 41% and 18% to 42%, respectively.[153–155] One study observed that a poor outcome was associated with increased initial creatinine, urea and total bilirubin concentrations.[154] The prognosis for cats with DKA/eDKA likely improves with early recognition (ie, close monitoring of body weight, clinical signs, serum BHB or urine ketones) and intervention. Establishment of glycaemic control is paramount in preventing severe DKA. A diagnosis of DKA is not associated with decreased chance of diabetic remission.[26]

Glycaemic variability

An important factor for successful diabetic control, including minimising clinical hypoglycaemia, in insulin-treated cats is assessment of whether or not glycaemic variability reduces at the same time that average BG decreases. It is not clear if low glycaemic variability is a cause or a consequence of beta cell recovery, but there is emerging evidence that low glycaemic variability should be a preferential goal when aiming for remission of DM in cats.[130]

Excessive glycaemic variability is a common problem in insulin-treated cats who do not achieve diabetic remission. This is most readily identified using CGM (Figure 19). Patients with increased glycaemic variability may

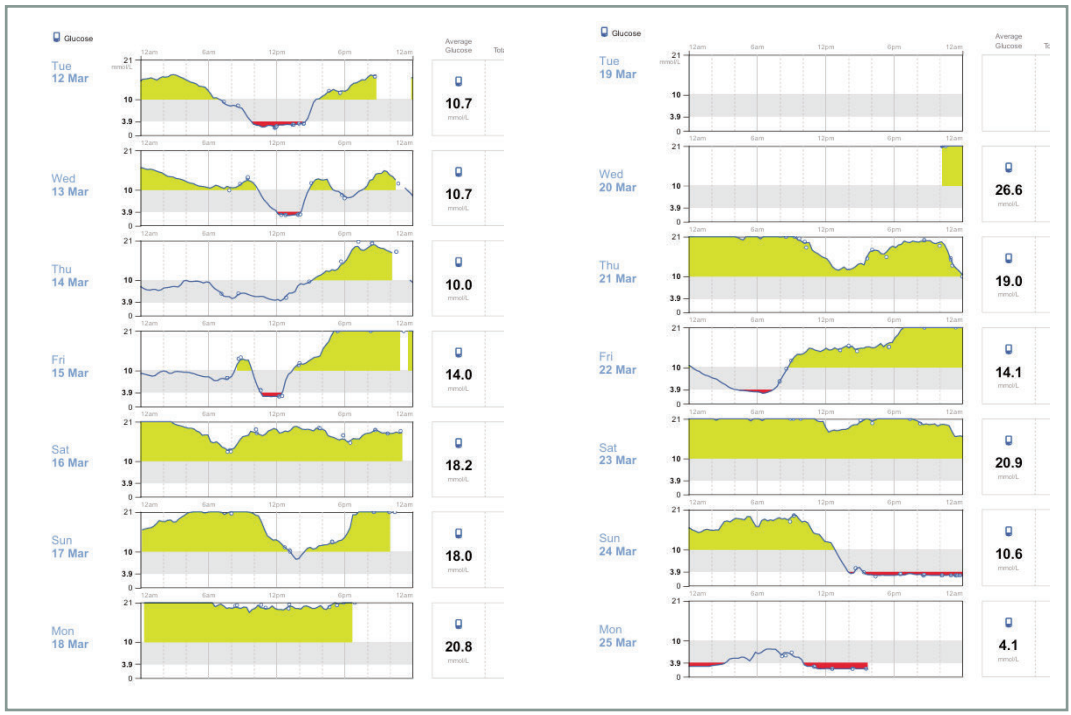


Figure 19 **The weekly summary report from the LibreView platform for a diabetic cat with excessive glycaemic variability despite a strictly consistent regimen that involved feeding a low-carbohydrate wet food and dosing with insulin glargine U300. The ALIVE Diabetic Clinical Score varied from 0–3/12 day to day. There were no clinical signs of hypoglycaemia during the 2 weeks displayed in this figure, but previous mild clinical episodes of hypoglycaemia were reported. The cat was later diagnosed with pituitary-dependent hypercortisolism.** *Image courtesy of Linda Fleeman*

present with poor diabetic control due to the occurrence of frequent hyperglycaemia, whereas most of the hypoglycaemic events are associated with no clinical signs and are often undetected.

In people, high glycaemic variability is a risk factor for hypoglycaemia and other complications of DM. This is probably because it captures both hypo- and hyperglycaemic excursions that separately lead to autonomic dysfunction and impaired counter-regulation.[156] In cats, increased glycaemic variability is associated with a decrease in glycaemic control, but it is unknown whether it is an independent risk factor for hypoglycaemia or other complications.[157]

The mechanisms for glycaemic variability are not well understood in cats. There is likely inadequate endogenous insulin action to 'fill the gaps' between insulin requirements and exogenous insulin action. Compared with dogs, cats with no residual beta cell function might be prone to greater glycaemic variability because the renal threshold for glucose tends to be lower in dogs (10–11 mmol/l, 180–200 mg/dl)[158] vs cats (15 mmol/l, 270 mg/dl);[159,160] this allows dogs, but not cats, to reduce hyperglycaemia in the 10–15 mmol/l (180–270 mg/dl) range by excreting glucose in urine. The mechanism(s) for the periods of hyperglycaemia are poorly understood and probably relate to the multiple causes of hyperglycaemia and insulin resistance in DM.

Excessive glycaemic variability is more likely to persist in cats with concurrent diseases such as CKD and inflammatory conditions.[161]

The mechanisms for glycaemic variability are not well understood in cats. There is likely inadequate endogenous insulin action to 'fill the gaps' between insulin requirements and exogenous insulin action.

It is also observed more commonly in cats fed dry food formulations vs wet foods, especially if there is free access to dry food. Periods of hypoglycaemia are likely caused by excess exogenous insulin, particularly when more potent formulations and/or those associated with substantial day-to-day variability are used. There is no evidence for the 'Somogyi effect' (rebound hyperglycaemia caused by secretion of excessive counter-regulatory hormones following hypoglycaemia) in cats.[162,163] Instead, it is thought that frequent hypoglycaemia can induce physiological unawareness of hypoglycaemia and impaired glucose counter-regulation, which in turn predisposes to an increased risk of neuroglycopenia.[164] However, glycaemic variability that is caused by rapid and excessive increases in insulin dose can improve when the dose is reduced.

Hypoglycaemia

Worry about the potential for hypoglycaemia can often have a greater negative impact on a caregiver's quality of life than any occurrences of clinical hypoglycaemia.[76,77] Therefore, strategies to manage the risk of hypoglycaemia, such as awareness of clinical signs, which are most commonly neurological

(ataxia, trembling, lethargy, vomiting, seizures),[165] and timely reporting of home-monitored BG or CGM results, should be clearly discussed with the caregiver. Caregivers may be reassured by keeping a supply of glucose syrup or honey to apply to the gums in an emergency. A recent study reported that glucagon powder given transmucosally (nasal application) increased BG in healthy cats,[166] and this could be an effective alternative. It is also helpful to emphasise that hypoglycaemia is often self-limiting and, unless severe, is almost never life-threatening; although the goal is to avoid it, any clinical hypoglycaemic event will probably simply be a signal that it is time to decrease the insulin dose. Diabetic remission is associated with an increased risk of hypoglycaemia during the insulin-withdrawal phase.[167]

Although usually subclinical, repeated episodes of mild hypoglycaemia in people lead to impaired counter-regulatory responses to hypoglycaemia, hypoglycaemia (or 'hypo') unawareness (ie, absence of systemic clinical signs of hypoglycaemia before neuroglycopenia ensues) and an increased risk of future, more severe hypoglycaemia. Although these long-term consequences have not been documented to date in cats, they have been well documented in humans and other species.[168]

Emergency treatment of hypoglycaemia

Emergency treatment of severe or clinical hypoglycaemia will include an IV bolus of dextrose at 0.5 mg/kg (eg, 25% dextrose solution at 2 ml/kg over 5–10 mins) followed by a constant rate infusion of 2.5% dextrose adjusted to achieve normoglycaemia. Cats developing hypoglycaemia following overdosing with insulin may also benefit from glucagon therapy.

Diabetes mellitus and comorbidities

Cats with DM are usually mature to senior individuals and hence may have unconnected comorbid conditions requiring sometimes conflicting treatment plans. Concurrent conditions may also cause insulin resistance and result in glycaemic variability.[36] Advice from a veterinary nutritionist can be sought for patients with incompatible nutritional requirements.[169] Management of pain, nausea and malnutrition, as well as stress reduction, is likely to benefit all comorbid conditions.

Box 13 summarises key considerations in the management of DM and common comorbidities. Note that the diets of cats with DM should not be altered during periods of reduced appetite.

Box 13

Considerations for management of comorbidities alongside diabetes mellitus

Pancreatitis

Pancreatitis causes inappetence and fluid deficits, which will complicate the management of a cat with DM and could increase the risk of DKA. Management of the cat with acute pancreatitis and DKA is challenging. For detailed information, readers are referred to 'Feline comorbidities: clinical perspective on diabetes mellitus and pancreatitis' by Xenoulis and Fracassi.[68] A diet that is high in protein, moderate in fat and low in carbohydrate will likely suit both conditions and consistent food intake can be encouraged with antiemetics, analgesics and, where necessary, appetite stimulants or feeding tubes. Fluid deficits should be managed optimally, along with electrolyte abnormalities.

Chronic kidney disease

Studies in cats have not shown a causal relationship between DM and CKD,[170,171] but the two conditions can present as comorbidities. Given the evidence for the survival benefit of feeding a renal diet to cats with CKD,[172] a phosphate-restricted diet may take priority over a diabetic diet, depending on the stage of disease. However, macronutrient content will vary between diets, and choosing a wet, lower carbohydrate renal diet may be a good compromise.[169] Complications of CKD such as hypertension, anaemia, nausea and proteinuria should be managed and nutritional intake optimised.

Hyperthyroidism

Uncontrolled hyperthyroidism may lower glycated protein levels,[68] complicating the diagnosis and monitoring of DM. Conversely, DM could lower thyroxine as part of the euthyroid sick syndrome, complicating the diagnosis and monitoring of hyperthyroidism.[173] Both conditions can result in malnutrition and should be optimally managed. Some antithyroid medications contain sugar and state in the product characteristics that they are not suitable for cats with DM; however, this is not likely to have a significant effect on glycaemic control.

Chronic enteropathy

For cases of food-responsive enteropathy, a limited-antigen diet may reduce the requirement for corticosteroids, which will benefit a cat with DM.[174] Moreover, macronutrient adjustment, such as reducing carbohydrate, may benefit cats with malabsorption and DM.[175] Hence, a balance between conditions can be reached. Many hydrolysed diets will exceed the recommended carbohydrate content for diabetic cats, but wet/canned products may be suitable. For cats with chronic enteropathies that require immunosuppression, chlorambucil or ciclosporin may be corticosteroid-sparing options.

Immune-mediated/corticosteroid-responsive diseases

Treatment with corticosteroids can cause a degree of insulin resistance, so alternative immunosuppressants could be chosen, such as chlorambucil or ciclosporin, if they are sufficiently effective.[176] Glucocorticoids such as budesonide exhibit, in theory, high first-pass hepatic clearance so may cause less insulin resistance but are understudied in cats. When glucocorticoids are required, the insulin dose may need to be increased to overcome the partial insulin resistance. Short-acting drugs like prednisolone should be chosen over depot products, which have less predictable absorption and duration of action, making it more difficult to establish a stable dose of insulin.

Anaesthesia and sedation for the diabetic cat

Cats with DM may need sedation or general anaesthesia for various procedures (eg, to treat painful dental or other disease) or for treatment of diseases that might also contribute to insulin resistance. Ideally, diabetic patients are stabilised prior to anaesthesia/sedation,[177] as uncontrolled hyperglycaemia could result in osmotic diuresis, acid–base and electrolyte abnormalities and hypovolaemia. Other considerations will depend on the individual case (health status, comorbidities, procedure). For example, under anaesthesia, cats with reduced body condition may become hypothermic and obese patients may hypoventilate. While there are no absolute drug contraindications for diabetic cats, potential adverse effects should be considered. Alpha-2 adrenoceptor agonists can exacerbate hyperglycaemia by inhibiting the release of insulin,[178,179] although this is unlikely to be clinically significant. Ketamine has been shown to cause hyperglycaemia in diabetic rats.[180] Frequent monitoring of BG will allow for these changes to be detected if these drugs are administered.

Preanaesthetic fasting and insulin protocols are poorly studied in cats, but a study in dogs has shown no difference in complication rates and perioperative BG concentrations between those fasted for 12 h and given a half dose of insulin and those fasted for 6 h with a full insulin dose.[181] While a consensus on fasting and insulin protocols for cats with DM is absent, and each case should be assessed individually, prolonged fasting should be avoided, with general advice being to fast for 2–4 h after feeding a small meal of wet food.[182,183] A half dose of insulin can be given approximately 1–2 h before the procedure,[184] and assessment of BG on admission allows for correction of hypoglycaemia or hyperglycaemia during the procedure. BG should be monitored every 30–60 mins during the procedure, at extubation and into the recovery period. Placement of a CGM device for the day may facilitate monitoring with reduced stress to the patient.

Sedation and anaesthesia for cats treated with SGLT2is has not been studied but temporary discontinuation of these antidiabetic drugs on the day of the procedure, appropriate use of perioperative fluid therapy to maintain euvolaemia and resumption of dosing once normal appetite has returned (encouraged by stress reduction, analgesia and control of nausea) is recommended by the authors of these Guidelines.

Additional key considerations

- Reduce stress pre- and postprocedure using cat friendly interactions[185] and a quiet environment away from other species.[186]
- Perform procedures in the morning to minimise fasting and allow time for patient monitoring, resumption of normal appetite and return to usual insulin protocol.
- Avoid prolonged fasting periods and encourage prompt food intake postprocedure by using antiemetics (eg, maropitant) and appetite stimulants, if needed, and offering food once awake.
- Optimise multimodal analgesia and balanced anaesthesia to reduce anaesthetic requirements, adverse effects, and postprocedural pain and stress (eg, by incorporating local anaesthetic techniques).[187]
- If dextrose solution is being administered, take blood samples for BG measurement from a dedicated IV catheter to avoid inaccurate results.
- If patients become hypoglycaemic under anaesthesia, treat with IV dextrose (eg, 2.5% solution), as clinical signs will be masked.
- Manage hyperglycaemia with administration of another half dose of the patient's normal insulin[183] or short-acting insulin as a bolus or CRI.
- Administer fluid therapy, as required, to maintain hydration and euvolaemia.
- Correct electrolyte deficits, such as hypokalaemia.

Conclusions

Cats with DM can be complex but rewarding cases to manage. Identifying underlying or concurrent disease processes, especially HST, can prove crucial to the eventual outcome. Each diabetic cat and their caregiver will have individual management requirements and caring for these patients entails offering a range of treatment and monitoring styles, aided by excellent communication, teamwork and flexibility in approach. The advent of SGLT2i therapy provides clinicians with a desirable and effective additional option, obviating the need for injections of insulin. Case selection is critical and SGLT2is should be reserved for clinically healthy (happy) diabetic cats. Promoting early detection of DM, and complications thereof, should be a priority to optimise outcomes regardless of the chosen treatment option.

The future for diabetic cats and caregivers is hopeful as ongoing research adds to the collective understanding of the condition, and experience of treating affected cats grows.

Supplementary material

The following supplementary material files are available at go.jfms.com/diabetesGLs2025_supplementarymaterial:

- Video demonstrating how to check an ear tip blood glucose measurement in a cat. *Courtesy of Rachel Korman, Cat Specialist Services.*
- Diabetic Clinical Score chart for caregivers and the veterinary team.
- Managing the diabetic cat: a guide for caregivers.
- Nursing the cat with diabetes mellitus.

SUMMARY POINTS

- DM is a frequently diagnosed endocrinopathy in cats resulting from a relative or absolute insulin deficiency and is comparable to human type 2 DM.
- Insulin resistance may result from underlying diseases such as hypersomatotropism or obesity.
- Treatment and monitoring protocols can be flexible. They should be selected with due consideration for the individual factors affecting the caregiver and cat, and modified as necessary to sustain compliance.
- Open communication with caregivers can identify specific concerns and reduce the caregiver burden of caring for a cat with DM.
- With appropriate screening, SGLT2is provide an alternative to insulin injections for suitable cats.
- Nutritional management with low-carbohydrate diets can optimise glycaemic control and remission.
- Complications such as DKA/eDKA, glycaemic variability and hypoglycaemia may be encountered and can be successfully managed, with strategies available to mitigate their risks.

Conflict of interest

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Informed consent

This work did not involve the use of animals (including cadavers) and therefore informed consent was not required. For any animals or people individually identifiable within this publication, informed consent (verbal or written) for their use in the publication was obtained from the people involved.

ORCID iD

Samantha Taylor https://orcid.org/0000-0002-8668-0777

Martha Cannon https://orcid.org/0000-0001-7006-6150

Linda Fleeman https://orcid.org/0000-0001-5732-7889

Federico Fracassi https://orcid.org/0000-0003-3121-2199

Chen Gilor https://orcid.org/0000-0003-0393-4135

Jocelyn Mott https://orcid.org/0000-0002-2176-9287

Stijn Niessen https://orcid.org/0009-0000-9667-6678

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