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REVIEW ARTICLE

SGLT2 inhibitor use in the management of feline diabetes mellitus

Audrey K. Cook[1] | **Ellen Behrend**[2]

[1]Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, Texas, USA

[2]Veterinary Information Network, Davis, California, USA

Correspondence
Audrey K. Cook, Texas A&M University, Mailstop 4474, College Station, Texas 77843-4474, USA.
Email: akcook@cvm.tamu.edu

Abstract

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are routinely used in the management of human type 2 diabetes and have been shown to effectively mitigate hyperglycemia and reduce the risks of cardiovascular and renal compromise. Two SGLT2 inhibitors, namely bexagliflozin and velagliflozin, were recently FDA approved for the treatment of uncomplicated feline diabetes mellitus. These oral hypoglycemic agents are a suitable option for many newly diagnosed cats, with rapid improvements in glycemic control and clinical signs. Suitable candidates must have some residual β-cell function, as some endogenous insulin production is required to prevent ketosis. Appropriate patient selection and monitoring are necessary, and practitioners should be aware of serious complications such as euglycemic diabetic ketoacidosis.

KEYWORDS
bexagliflozin, cat, diabetes, velagliflozin

1 | INTRODUCTION

In health, glucose is freely filtered across the glomerulus and almost all is reabsorbed and returned to the systemic circulation. Approximately 90% of glucose uptake occurs in the early proximal tubule, mediated by sodium-glucose cotransporter (SGLT)2, a low-affinity, high-capacity glucose transporter; SGLT1 removes the remaining glucose in the later parts of the proximal tubule (Vallon, 2015). The pharmacological agents, SGLT2 inhibitors, competitively inhibit SGLT2. These drugs, therefore, decrease renal glucose reabsorption; this increases glucose excretion and, in patients with diabetes mellitus (DM), may normalize blood glucose concentration (BGC). The higher the BGC, the higher the renal filtered load, and the more glucose that is excreted (Vallon, 2015).

1.1 | DM: The human perspective

Type 2 DM (T2DM) is a common human endocrinopathy, estimated to affect more than 35 million Americans. The prevalence in those over age 65 is >25%, and T2DM is consistently listed as one of the top 10 causes of death in the United States. The consequences of T2DM are substantial, with hundreds of billions of dollars annually in direct medical costs and reduced productivity in the US alone (American Diabetes Association, n.d.).

The underlying cause of T2DM is sustained insulin resistance coupled with pancreatic β-cell dysfunction (Chatterjee et al., 2017). Impaired tissue sensitivity to insulin increases the workload on β cells, as more insulin is required to move glucose into the intracellular compartment. Concurrent hypersecretion of pancreatic amylin (aka islet amyloid polypeptide) impairs islet function and β-cell

viability. Over time, β-cell function is inadequate to maintain euglycemia, and BGC begins to rise. A BGC over 11 mmol/L (200 mg/dL) is damaging to various cells, a process referred to as "glucose toxicity" (Campos, 2012; Giaccari et al., 2009). The actual mechanisms behind this effect are incompletely understood, but likely involve reactive oxygen species. Unfortunately, β cells are highly vulnerable to the damaging effects of hyperglycemia, with subsequent suppression of insulin secretion and eventual apoptosis (Campos, 2012). Ironically, hyperglycemia also promulgates peripheral insulin resistance, with decreased insulin receptor expression and impaired responses to insulin by both adipose tissue and skeletal muscle (Giaccari et al., 2009). T2DM is, therefore, characterized by a relative, rather than absolute, insulin deficiency.

There are numerous causes of insulin resistance, but obesity and a sedentary lifestyle are the most common drivers in people (Chatterjee et al., 2017). Efforts to improve insulin sensitivity with weight loss, dietary modification, and exercise can enhance insulin responsiveness and mitigate hyperglycemia. However, most people with T2DM rely on medical therapy to control BGC, primarily oral hypoglycemic agents, such as biguanides (e.g. metformin), sulfonylureas (e.g. glipizide), dipetidyl peptidase-4 inhibitors (e.g. sitagliptin), and SGLT2 inhibitors (Marín-Peñalver et al., 2016). Most oral hypoglycemic agents improve glycemic status by enhancing peripheral insulin sensitivity and/or increasing insulin secretion. In contrast, SGLT2 inhibitors directly lower BGC through increased urinary glucose excretion. This strategy reduces the workload on the pancreas and, in patients with residual β-cell function, is proposed as a mechanism to reverse glucose toxicity. Endogenous insulin production again becomes sufficient to maintain euglycemia. Additional advantages for SGLT2 inhibitors include favorable alterations in blood pressure, body weight, and fat distribution, along with a low propensity for clinical hypoglycemia (Horii et al., 2020). The minimal risk for hypoglycemia is thought to reflect increases in renal glucose reclamation by SGLT1, along with the appropriate release of counterregulatory hormones such as glucagon (Vallon & Thomson, 2017).

The first SGLT2 inhibitor licensed for the management of human T2DM was dapagliflozin. This was approved in Europe in 2012 and was soon followed by canagliflozin in the USA in 2013. Numerous SGLT2 inhibitors are now approved for use in the USA, Europe, or Asia, with minor differences in bioavailability and protein binding, and more impactful differences in selectivity for SGLT2 over SGLT1 (250 fold to 2900 fold) (Wright, 2021). Current guidelines from the American Diabetes Association and the American Association of Clinical Endocrinology list SGLT2 inhibitors as first-line treatment options in T2DM patients with cardiovascular or renal complications, or in combination with metformin in individuals with inadequate glycemic control (ElSayed et al., 2022; Samson et al., 2023). Interestingly, a combined SGLT1/SGLT2 inhibitor (sotagliflozin) was recently FDA approved for use in patients with T2DM and is licensed by the European Medicines Agency as adjunctive therapy for type 1 (insulin dependent) DM. Concurrent inhibition of gastrointestinal uptake of glucose appears to increase glucagon-like peptide 1 secretion and decrease post-prandial BGC (Avgerinos et al., 2022; Sands et al., 2015).

1.2 | Feline DM

Our current understanding of feline DM is that most cats have underlying insulin resistance and subsequent β-cell dysfunction; this condition, therefore, has strong similarities to human T2DM (Gostelow & Hazuchova, 2023; Gottlieb & Rand, 2018; Rand, 2013; Sparkes et al., 2015). The presence of viable β cells and a relative insulin-deficient state is supported by evidence that the majority of cats are not ketotic at the time of diagnosis, and the finding that many insulin-treated diabetic cats undergo remission (defined by Project ALIVE as the ability to maintain a euglycemic state for 4 weeks without insulin) (Bjornvad & Jessen, 2015; Gottlieb et al., 2015; Niessen et al., 2022; Zini et al., 2010). The incidence and duration of remission vary, but effective control of BGC, mitigation of disorders causing insulin resistance, and reversal of glucose toxicity appear to play a role (Gostelow et al., 2014; Gostelow & Hazuchova, 2023).

In people, glucose toxicity is associated with BGC >11 mmol/L (200 mg/dL), and peripheral insulin sensitivity is not fully restored until it falls below this threshold (Giaccari et al., 2009; Robertson et al., 2003). Similar data are not available for feline diabetics, but experimental studies have clearly demonstrated the impact of hyperglycemia on β-cell function and insulin secretion in healthy cats. In one placebo-controlled study, BGC was clamped between 25 and 30 mmol/L (450–540 mg/dL) for 10 days (Zini et al., 2009). Plasma insulin concentrations initially increased, but dramatically declined after 2 days and were close to the detection limit of the assay from days 5–10. Interestingly, no treated cats became ketonuric over the 10-day study period, and plasma β-hydroxybutyrate (BHB) concentrations at the end of the study were similar for glucose-infused and control cats. This suggests that minimal insulin secretion was sufficient to prevent excessive lipolysis. Pancreata were harvested after 10 days; the glucose-infused cats had a 50% decrease in β-cell numbers, and immunohistochemical staining for insulin was 80% lower.

Another study in healthy cats investigated the impact of 42 days of severe (target: 30 mmol/L [540 mg/dL]) or moderate (target: 17 mmol/L [306 mg/dL]) hyperglycemia on insulin secretion and β-cell function (Link et al., 2013). In the severe hyperglycemia group, insulin secretion increased fourfold from the baseline within 24 h but returned to baseline by day 4. From day 11 to 25, mean insulin concentrations were lower than baseline. By day 25, 6/8 cats required exogenous insulin to prevent ketosis/ketoacidosis; insulin was necessary for about 2 weeks beyond the end of the 42-day study period. A similar initial rise and decline in insulin secretion was noted in the moderate hyperglycemia group. However, mean insulin concentrations in this cohort were modestly higher than baseline from days 5–25. No cats in the moderate hyperglycemia group developed ketonuria, and all could maintain a euglycemic state within 7 h of discontinuation of glucose infusion on day 42.

Veterinarians have traditionally relied upon exogenous insulin to treat feline DM (Behrend et al., 2018; Sparkes et al., 2015). This approach addresses hyperglycemia and prevents ketosis; in cats with viable β cells, mitigation of glucose toxicity allows β-cell recovery and diabetic remission (Behrend et al., 2018; Callegari et al., 2013; Marshall et al., 2009; Zini et al., 2010). However, responses to exogenous insulin are variable, and cats may remain significantly hyperglycemic (Gostelow & Hazuchova, 2023). An alternative approach in which BGC is quickly lowered independent of insulin (exogenous or endogenous) allows for rapid creation of a euglycemic state and potentiates β-cell recovery; the SGTL2 inhibitors provide this opportunity (Behrend et al., 2023; Hadd et al., 2023; Niessen, Roth, et al., 2022). Although endogenous insulin production is not adequate to maintain euglycemia without the support of the SGLT2 inhibitor, it is inferred that insulin secretion is usually sufficient to prevent ketosis and maintain patient well-being.

2 | SGLT2 INHIBITORS AS SOLE THERAPY FOR FELINE DIABETES

Two selective SGLT2 inhibitors are currently FDA-approved as stand-alone treatments for feline diabetes, namely bexagliflozin (Bexacat®, Elanco) and velagliflozin (Senvelgo®, Boehringer Ingelheim) (BEXACAT, n.d.; SENVELGO, n.d.). The feline formulation of bexagliflozin is a 15-mg tablet. In a US field study, the drug (15 mg/cat once daily PO) was administered to 84 newly diagnosed diabetic cats for 56 days with a 124-day extension to evaluate safety and duration of efficacy (Hadd et al., 2023). Cats weighing <3 kg, a recent history of inappetence or serum BHB >3.6 mmol/L were ineligible. A low carbohydrate diet was recommended but not required.

Serial measurements of BGC were performed over an 8-h period at day 0 and repeated at specific intervals throughout the study. Within 8 h of administration of the first dose of bexagliflozin, mean BCG decreased from >25 mmol/L (450 mg/dL) to <11 mmol/L (200 mg/dL). Treatment success was determined on day 56 and was defined as attainment of glycemic control (mean of 8-hr in-clinic blood glucose curve <13.9 mmol/L [250 mg/dL] or serum fructosamine concentration < 358 μmol/L) and improvement from baseline of at least 1 clinical sign attributable to DM (i.e., polyuria, polydipsia, polyphagia, or weight loss).

On day 56, efficacy was evaluable in 81 of 84 cats; 68/81 (84.0%) were deemed treatment successes. Mean BGC was 8.0 mmol/L (144.4 mg/dL) (95% CI 7.0–9.0 mmol/L [126.1–162.6 mg/dL]) and was within the reference interval (3.6–8.6 mmol/L [65–155 mg/dL]) in 43/75 (57.3%). Mean fructosamine was 305.6 μmol/L (95% CI, 269.1–342.0; reference interval: 154–275 μmol/L) and was within the reference interval in 34/75 (45.3%). Mitigation of at least one clinical sign was reported in 68/75 cats (90.7%); polyphagia, polydipsia, and polyuria had improved in 47 (62.7%), 61 (81.3%), and 54 (74.7%), respectively. Over half the cats (57.3%) maintained or gained weight over this 8-week time period.

A total of 70 cats continued to receive bexagliflozin from day 56 to day 180, with monthly in-clinic evaluations. Vomiting was the most common potential adverse effect noted, occurring in 42 cats (50%). Diarrhea was also common (32/84, 38%), followed by anorexia (31/84, 37%) and lethargy (17/84, 20%). As vomiting and anorexia were present in cats with other disorders such as diabetic ketoacidosis (DKA), these signs may not always be a direct consequence of bexagliflozin administration. Four cats (4.8%) were diagnosed with DKA (confirmed in 3; presumptive in 1), three of which had euglycemic DKA, defined as DKA with BG <13.9 mmol/L (250 mg/dL). No episode of clinical hypoglycemia occurred.

In another study, a small group of insulin-treated cats ($n = 10$) were switched to bexagliflozin (FOI, 2024a). One cat could not be medicated and was withdrawn almost immediately. Five of the ongoing cats experienced an increase in serum BHB and three developed DKA. Four cats met the criteria for treatment success after 28 days of bexagliflozin, with mean BGC 3.9–10 mmol/L (70–180 mg/dL) or fructosamine ≤330 umol/L.

Velagliflozin is supplied as a 15 mg/mL oral solution. For the US licensing study, 252 non-ketonuric cats received ≥2 doses (1 mg/kg PO once daily) for up to 180 days (Behrend et al., 2023). Thirty-eight of these cats were previously receiving insulin but were poorly controlled; 214 cats were naïve to treatment or had been treated with insulin for ≤4 days. After one month of treatment, 88.4% of the 198 cats still enrolled had improvement in at least one clinical sign associated with DM (polydipsia, polyuria, polyphagia, unintended weight loss, or neuropathy) and in one glycemic variable (i.e., mean BGC ≤16.7 mmol/L (300 mg/dL) over a 9-h time period or serum fructosamine ≤450 μmol/L and lower than baseline) (FOI, 2024b). Median spot BGC and fructosamine at this time point were 8.5 mmol/L (153 mg/dL) and 310 μmol/L, respectively (Behrend et al., 2023). On day 180, 81% of cats still enrolled had BGC and/or fructosamine with reference intervals (Behrend et al., 2023). Median BGC was 6.9 mmol/L (125 mg/dL) and median fructosamine was 263 umol/L. Polyuria and polydipsia were improved in 88.6%, and 87.7% of affected cats, respectively.

Clinical hypoglycemia was not noted in any cat over the 180-day study period (Behrend et al., 2023). The most common adverse event was a change in stool consistency, which was noted in just over half (52%) of cats (FOI, 2024b). Eighteen cats (7.1%) were diagnosed with DKA, with the majority (13; 72.2%) becoming unwell within the first 7 days of treatment with velagliflozin (Behrend et al., 2023). Just over 5% of naïve diabetics developed DKA (11/214; 5.1%), whereas almost 20% of previously insulin treated cats (7/38; 18.4%) developed this complication. Fourteen of the cats with DKA (77.8%) were euglycemic.

In a European clinical trial, diabetic cats (both naïve and insulin-treated) were assigned to receive velagliflozin (1 mg/kg orally, once daily) or porcine lente insulin (SQ every 12 h; dose adjusted as appropriate) (European Health, 2024). Treatment efficacy was assessed at day 45, with success defined by both an improvement in one clinical sign associated with DM and one glycemic parameter (i.e., mean BCG ≤13.9 mmol/L [250 mg/dL] or BGC nadir ≤8.9 mmol/L [160 mg/

dL] during a standard curve or fructosamine ≤450 μmol/L). Glycemic parameters were consistently superior for the cats receiving velagliflozin throughout the study, with 53.7% of cats on this protocol meeting the criteria for success at day 45 compared to 41.9% of those on twice daily insulin.

The response to velagliflozin (1.0 mg/kg orally, once daily) was compared to titrated lente insulin (given subcutaneously, twice daily) in a prospective, randomized, open-label, 60-day field study (Niessen, Roth, et al., 2022). Twenty-six cats (both naïve and poorly controlled on insulin) were included, with 13 in each treatment group. Mean BGC was significantly lower in the velagliflozin-treated cats compared to those receiving insulin on days 7, 14, and 30. Overall, control of glycemic parameters and clinical signs were similar. DKA occurred in one cat receiving velagliflozin.

2.1 | Patient selection and screening

Current label recommendations for SGLT2 inhibitor use in cats emphasize appropriate patient selection (BEXACAT, n.d.; SENVELGO, n.d.). The ideal candidate is an otherwise healthy, newly diagnosed diabetic, with a good appetite, and without significant comorbidities. Key considerations include the presence of ketosis, renal function, exocrine pancreatic status, and concurrent endocrinopathies (see Table 1).

Ketosis reflects the exuberant generation of ketone bodies, namely BHB, acetoacetate, and acetone. In health, insulin limits both lipolysis and hepatic fatty acid metabolism; sustained insulin deficiency results in hyperglucagonemia and subsequent production of ketone bodies, primarily BHB. In healthy non-diabetic cats, plasma BHB concentrations are usually <0.1 mmol/L (<10 mg/dL) (Weingart et al., 2012); values up to 1 mmol/L are routinely reported in well managed, insulin-treated diabetics. A value over 2.4 mmol/L indicates substantial ketosis and was shown to be 100% sensitive and 87% specific for DKA in one study; a cut-off of >2.55 mmol/L was 94% sensitive and 68% specific in another study evaluating a handheld ketometer (Zeugswetter & Rebuzzi, 2012). Urine dipsticks identify acetoacetate, with a "trace" color change approximating a concentration of 0.5 mmol/L in the fluid tested; BHB is not detected. In one study, a 1+ color change (≥1.5 mmol/L acetoacetate) using urine samples was reported in just 2/11 cats with plasma BHB >2.5 mmol/L (Zeugswetter & Pagitz, 2009). Interestingly, evaluation of plasma using the urine ketone dipstick was found to be more sensitive, with a 1+ result noted in all 11 cats with BHB >2.5 mmol/L. In light of superior sensitivity for detection of significant ketosis, the authors strongly advocate the measurement of blood BHB concentrations in every cat prior to initiation of an SGLT2 inhibitor. In our opinion, BHB >2.4 mmol/L indicates the need for exogenous insulin, even if the cat appears hydrated and clinically stable.

Chronic kidney disease (CKD) is a relative contraindication to SGTL2 inhibitor use in people (Thomas & Cherney, 2018). Velagliflozin has not been evaluated in cats with serum creatinine >177 μmol/L (2 mg/dL), and the package insert for bexagliflozin states that this drug should not be used in cats with reduced renal function, although cats with IRIS Stage 1 and 2 CKD were included in the open-label clinical trial for this drug (BEXACAT, n.d.; Hadd et al., 2023). If an SGLT2 inhibitor is used in a cat with CKD, the authors recommend careful monitoring of renal function and clinical

TABLE 1 Recommended database to establish suitability for SGLT2 inhibitor therapy for cats with DM. See text for further details.

Test	Indication(s)	Comments
Complete blood count	• Establish baseline • Screen for inflammatory disorders	
Serum biochemistry panel with electrolytes	• Establish baseline • Screen for other metabolic disease(s)	Insulin treatment recommended if: • Creatinine >250 μmol/L (2.8 mg/dL) • Bilirubin >8.6 μmol/L (0.5 mg/dL) • Liver enzymes >×3 upper end of reference interval • Hypercalcemia
Urinalysis	Screen for ketosis	Treat with insulin if ketonuria noted
Total thyroxine (T4)	Screen for hyperthyroidism	If hyperthyroid, start SGLT2 inhibitor (if otherwise appropriate) and initiate therapy for hyperthyroidism
Blood beta-hydroxybutyrate (BHB)	• Screen for ketosis • Establish baseline	Treat with insulin if >2.4 mmol/L (25.0 mg/dL)
Plasma acetoacetate measurement using urine dipstick	• Screen for ketosis	Less specific than blood BHB but superior to urine testing; Treat with insulin if ≥1+

status, as these cats may be more vulnerable to dehydration. In addition, it seems probable that substantial renal compromise may impact drug efficacy, as affected cats may not have the capacity to excrete enough glucose to significantly lower BGC and reverse glucose toxicity.

The package inserts for both bexagliflozin and velagliflozin direct against initiating the drug in cats with clinical or imaging findings suggestive of pancreatitis (BEXACAT, n.d.; SENVELGO, n.d.). Pancreas-specific lipase activity (Spec fPL™; Idexx Laboratories/Texas A&M GI Laboratory) >5.3 μg/L is listed as a contraindication for bexagliflozin; the lack of a similar caveat for velagliflozin should not be regarded as evidence that either product is more or less likely to cause pancreatic injury. Most cats with pancreatitis manifest a chronic, waxing and waning clinical course; pancreatic histopathology is characterized by lymphocytic infiltration, fibrosis and acinar atrophy (Bazelle & Watson, 2014, 2020; Forman et al., 2021). A single fPL within the reference interval does not, therefore, exclude the possibility of on-going, low-grade inflammation. Although the FDA has flagged a potential link between acute pancreatitis and gliflozin use in people, it is unclear if human patients with a history of pancreatitis receiving an SGLT2 inhibitor are at increased risk for an acute episode (Couto & Estrin, 2022; Dziadkowiec et al., 2021). It is prudent to institute insulin therapy in cats with clinical signs of clinically pancreatitis, as vomiting, decreased food intake, and a suboptimal body weight are well-established risk factors for DKA in people taking SGLT2 inhibitors (Long et al., 2021; Rosenstock & Ferrannini, 2015).

Concurrent endocrinopathies associated with insulin resistance, namely hyperthyroidism, hypercortisolism /Cushing's syndrome (both spontaneous and iatrogenic), and hypersomatotropism (aka acromegaly), are routinely identified in cats with DM and can substantially complicate insulin therapy (Cook & Evans, 2021; Niessen et al., 2015; Schaefer et al., 2017). Situations in which insulin sensitivity may change, such as the reversal of a hyperthyroid or hypercortisolemic state, put patients receiving insulin at risk of hypoglycemia. Diabetic cats with hyperthyroidism and hypercortisolism may be excellent candidates for an SGLT2 inhibitor, assuming that the cat has no contraindications to treatment with a gliflozin and is routinely monitored for ketosis.

Cats with DM and hypersomatotropism present unique challenges and are often highly refractory to insulin therapy, with little response to extremely large doses (Niessen, 2010; Scott-Moncrieff, 2010). Anecdotal evidence suggests a low propensity to ketosis and DKA in this patient population, and it is noteworthy that the majority undergo remission following hypophysectomy (Fenn et al., 2021; van Bokhorst et al., 2021). These findings suggest viable β cells are routinely present in cats with hypersomatotropism and support the use of an SGLT2 inhibitor. Polyphagia is unlikely to resolve with achievement of euglycemia as it is directly driven by growth hormone excess, but polydipsia and polyuria may diminish as BGC decreases. The authors recommend measurement of insulin-like growth factor 1 (IGF-1) in all newly diagnosed diabetic cats with an acromegalic phenotype (see Table 2). It is also important to bear in mind that insulin is needed for hepatic expression of IGF-1, and that IGF-1 concentrations may be less sensitive for the diagnosis of hypersomatotropism prior to initiation of insulin treatment (Niessen, 2010).

An SGTL2 inhibitor should be started promptly in suitable patients. Blood BHB should be rechecked before starting treatment if therapy is delayed for any reason after initial screening. Both bexagliflozin and velagliflozin are given once daily at a consistent time, either with a small amount of food to ensure ingestion or on an empty stomach. They can also be given directly into the mouth. Due to the remarkable safety profile of both drugs, accidental administration of an extra dose is not expected to be problematic. Similarly, the occasional missed or delayed dose is not a concern.

2.2 | Dietary considerations

Current nutritional recommendations for cats with DM support the use of high protein, low carbohydrate (<14% ME) diets; this approach improves glycemic control in insulin-treated cats and may increase the likelihood of diabetic remission (Gostelow et al., 2014; Sparkes et al., 2015). It is noteworthy that people taking SGLT2 inhibitors are not encouraged to limit carbohydrate intake, and carbohydrate restriction is known to increase the likelihood of ketosis (Goldenberg et al., 2016; Musso et al., 2020). However, people and cats respond differently to major food groups, and cats are clearly adapted for a carnivorous diet and hepatic gluconeogenesis (Gilor et al., 2011; Verbrugghe et al., 2012; Zoran, 2002). The authors currently routinely recommended high protein, low carbohydrate diets for diabetic cats, unless precluded by comorbid conditions. It is prudent, however, to delay a dietary transition for the first 1–2 weeks, so that changes in appetite or stool consistency related to SGLT2 inhibitor therapy can be reliably identified and addressed. Moving forward, controlled studies are needed to define optimal feeding strategies for cats receiving SGLT2 inhibitors.

2.3 | Monitoring

Routine monitoring is a key component of diabetic care. For cats receiving insulin, recheck visits are needed to assess the patient's well-being, body weight, polyuria/polydipsia/polyphagia, and glycemic control. The same considerations apply to cats receiving SGLT2 inhibitors, although there are some logistical differences and regular surveillance for ketosis is required (see Table 3).

The cat should be weighed at every visit, along with assessments of body and muscle condition scores. Rapid or unexplained weight loss may indicate dehydration, the onset of ketosis, or inadequate glycemic control. Clinical signs associated with DM are expected to improve. Polyphagia may persist but should not be extreme. A profound or aggressive hunger in a euglycemic diabetic cat is suggestive of hypersomatotropism; measurement of IGF-1 should be considered.

TABLE 2 Optional/conditional tests to establish suitability for SGLT2 inhibitor therapy for cats with DM.

Test	Indication(s)	Comments
Pancreas-specific lipase activity (Spec fPL™)	History, physical exam or imaging suggest pancreatitis	Spec fPL™ ≥ 8.8 μg/L is consistent with active pancreatic inflammation
Insulin-like growth factor (IGF-1)	Physical examination suggests hypersomatotropism	Measurement may have limited sensitivity in an untreated diabetic patient
Quantified urine culture	Bacteriuria or pyuria AND clinical signs referrable to the lower urinary tract	Current guidelines do not support the use of antibiotics in bacteriuric cats in the absence of clinical signs referrable to the lower urinary tract or evidence of pyelonephritis
Fructosamine	• Establish baseline • Confirm the diagnosis of DM	

TABLE 3 Recommended monitoring schedule for cats receiving an SGLT2 inhibitor for DM.

Day	Test	Comment
2–3	Review history	Investigate poor appetite, vomiting, lethargy: *Switch to insulin*
	Physical examination	Monitor attitude, bodyweight, hydration
	Evaluate for ketosis	Blood BHB >2.4 mmol/L (25 mg/dL): *Switch to insulin* 1.0–2.4 mmol/L (10.4–25 mg/dL): Recheck in 2–3 days, sooner if ill
		Plasma acetoacetate (using plasma on urine dipstick) ≥1+: *Switch to insulin*
		Urine dipstick ≥Trace: *Switch to insulin*
7	Review history and PE	See above; review presence of clinical signs of DM
	Evaluate for ketosis	See above
	Check BGC	Spot check is sufficient
14	Review history and PE	See above
	Evaluate for ketosis	See above
	Check BGC	Expect to see BGC < 13.9 mmol/L (250 mg/dL) OK to continue SGTL2 inhibitor if cat otherwise doing well despite hyperglycemia
30	Review history and PE	See above Excessive weight loss (>8% from baseline): *Switch to insulin*
	Evaluate for ketosis	See above
	Check BGC	Expect to see BGC <13.9 mmol/L (250 mg/dL) BGC >13.9 mmol/L (250 mg/dL) with on-going signs of DM: *Switch to insulin*
	Fructosamine	Expect normalization or significant improvement from baseline Not improved by >50 μmol/L from baseline and on-going signs of DM: *Switch to insulin*
Q3 mos	As for Day 30	

In cats on an SGLT2 inhibitor, glycemic regulation may be evaluated by direct measurements of BGC, or a surrogate marker such as serum fructosamine or hemoglobin A1c (HbA1c). As clinical hypoglycemia is unlikely, there is little need to perform a glucose curve or place an interstitial monitoring device. Glycemic status can often be determined by simply checking a single BGC, as this varies minimally throughout the day. If the spot check BGC is high, it is prudent to measure serum fructosamine or HbA1c, as these parameters are not impacted by stress hyperglycemia and reflect average BGC for the previous 7–10 or 50–60 days, respectively (Link & Rand, 2008; Mori et al., 2009). In many cats, BGC is within the reference interval within 14 days after starting therapy with an SGLT2 inhibitor, and serum fructosamine concentrations are substantially improved (i.e., have decreased by >50 μmol/L) or normalized by day 30 (Behrend et al., 2023; Hadd et al., 2023). A substantially elevated or unimproved fructosamine after 1 month of therapy should prompt a transition to insulin.

In addition, it is essential to routinely check for ketosis, particularly during the first 2 weeks of treatment, and any time the cat is vomiting, hyporexic or dehydrated. Cats receiving an SGLT2 inhibitor can be euglycemic despite substantial ketone generation; checking for ketosis is therefore more important than measuring BGC. As discussed earlier, direct measurement of blood BHB concentrations is preferable to reliance on urine dipstick testing, as the former can be reliably trended and is more sensitive for ketosis. As a general rule, BHB >2.4 mmol/L should prompt a switch to insulin; if BHB is 1–2.4 mmol/L, the cat should be rechecked in 2–3 days.

Both BGC and BHB can be measured at home using hand-held devices (Chong & Reineke, 2016; Zeugswetter & Rebuzzi, 2012). The

authors recommend the AlphaTRAK 3 (for BGC; made by Zoetis) and the Precision Xtra (for BHB; made by Abbott). Many owners can collect a capillary sample from the edge of a cat's ear using a lancet or hypodermic needle and are therefore able to identify problems promptly. Alternatively, owners can be provided with ketone dipsticks and encouraged to test urine. This approach has some limitations, but recognition of even trace ketones (indicating acetoacetate ≈0.5 mmol/L) alerts the owner to potential problems and need for immediate assessment.

2.4 | Diabetic ketoacidosis and euglycemic DKA

Diabetic ketoacidosis is a life-threatening complication associated with DM in all species. It may be evident at the time of diagnosis or occur despite treatment with insulin. In the latter instance, significant ketosis is usually triggered by a change in insulin sensitivity secondary to pancreatitis or infection, etc (Cooper et al., 2015). Substantially inadequate insulin secretion allows pancreatic α cells to secrete excessive amounts of glucagon, which triggers lipolysis with subsequent generation of ketone bodies from free fatty acids. In the absence of insulin, ketone generation exceeds use, resulting in ketonemia and metabolic acidosis. It is important to remember that it takes much less insulin to prevent ketosis than to maintain euglycemia (Link et al., 2013; Zini et al., 2009), which is why many poorly regulated insulin-treated cats do not become ketotic despite sustained hyperglycemia.

Cats treated with an SGLT2 inhibitor are similarly vulnerable to excessive lipolysis due to unchecked glucagon secretion. A small number of newly diagnosed diabetics were diagnosed with DKA during the safety trials for bexagliflozin (4.8% of 81 cats) and velagliflozin (5.1% of 214 cats; 6.6% of 61 cats) (Behrend et al., 2023; FOI, 2024b; Hadd et al., 2023). It is unclear if the likelihood of DKA is different for newly diagnosed cats started on insulin, as limited data are available. A potentially useful comparison is provided by a 45-day study looking at the efficacy of protamine zinc insulin (Nelson et al., 2009). One hundred seventy-five cats were enrolled, of which 133 (120 newly diagnosed and 13 previously treated) completed the study. Just one cat (<0.6%) developed DKA during the study period. In a more recent report of 185 diabetic cats managed for an average of 4 years at a first opinion practice, 7 (3.8%) developed DKA whilst on insulin therapy (Restine et al., 2019). In contrast, another retrospective study reported that 93/775 (12%) diabetic cats seen over a 10-year period were diagnosed with DKA; however, this report included untreated diabetic cats, and reflected a population evaluated at a tertiary referral center (Cooper et al., 2015).

In the bexagliflozin and velagliflozin trials, DKA was usually identified within 2 weeks of starting an SGLT2 inhibitor (Behrend et al., 2023; FOI, 2024b; Hadd et al., 2023). Although sustained use of an SGLT2 inhibitor may ultimately improve insulin secretion by mitigation of glucose toxicity, there is evidence in other species to support the hypothesis that a sudden and substantial decrease in BGC following initiation of SGLT2 inhibitor therapy may acutely decrease insulin production by ailing β cells with compromised sensitivity to glucose (Rosenstock & Ferrannini, 2015). It has also been suggested that SGLT2 inhibitors may decrease the insulin: glucagon ratio through a direct effect on α cells (Rosenstock & Ferrannini, 2015). Irrespective of the mechanism, the authors emphasize the need for frequent assessment of blood BHB concentrations during the first 14 days of SLGT2 inhibitor use.

The incidence of DKA in people receiving an SGLT2 inhibitor for treatment of T2DM is much lower than for cats, with estimated rates of <0.15% (Rosenstock & Ferrannini, 2015; Yang et al., 2017). In addition, a recent metanalysis considered 36 studies involving over 50,000 patients and concluded that SGLT2 inhibitor use did not appear to increase the risk of DKA when compared to other oral hypoglycemic drugs or placebo (Yang et al., 2023). Putative triggers for DKA in people with T2DM receiving a gliflozin include concurrent systemic illness, surgery, hyporexia, carbohydrate restriction, and alcohol abuse. The apparent discordance between the likelihood of DKA in people versus cats is unexpected and may reflect our inability to reliably identify an insulin-dependent feline diabetic. In contrast, people with type 1 DM are readily differentiated from those with T2DM and are therefore appropriately provided with exogenous insulin (Leslie et al., 2016). The authors also hypothesize that cats may be more vulnerable to DKA because of substantial delay between the onset of hyperglycemia and an eventual diagnosis of DM. This may set the scene for extensive β-cell loss and/or an increased vulnerability to acute insulin deficiency following the introduction of an SGLT2 inhibitor.

Untreated diabetic cats or those on insulin who develop DKA are predictably markedly hyperglycemic. In contrast, a cat on an SGLT2 inhibitor may have a normal BGC despite substantial ketonemia. This condition is referred to as euglycemic DKA and is characterized in people by a BGC <13.9 mmol/L (250 mg/dL) accompanied by ketosis and metabolic acidosis (Long et al., 2021). It is important to recognize the possibility of euglycemic DKA, because delayed diagnosis results in progressive patient compromise (Nasa et al., 2021). Treatment protocols for euglycemic DKA are similar to those for hyperglycemic DKA, with the notable exception of immediately administering glucose (dextrose) along with insulin (Long et al., 2021).

More data are needed to clarify optimal treatment protocols for cats with euglycemic DKA. However, the authors recommend administering an initial bolus of 50% dextrose (0.25 mL/kg IV; dilute to 12.5% if given into a peripheral vein) immediately prior to starting regular insulin (0.1 U/kg/h) given as a continuous rate infusion (preferred) or by intramuscular injection, along with a dextrose infusion. Each 0.1 U of insulin should be matched by at least 0.2 gm of dextrose in a euglycemic patient. As the glycosuric effect of the SGLT2 inhibitor may continue for several days after discontinuation, additional allowance should be made for ongoing renal glucose loss (≈0.05 gm/kg/hr in people (Thomas & Cherney, 2018)). We therefore recommend starting the dextrose infusion at 0.25–0.3 gm/kg/h. BGC should be checked every 2 h and dextrose therapy adjusted as appropriate. Serum electrolytes should be monitored, and

deficiencies addressed as necessary. It is important to remember that insulin may cause rapid translocation of potassium and phosphorus from the extracellular compartment, with subsequent decreases in serum concentrations (Rudloff, 2017). Regular insulin and dextrose (as appropriate) should be continued until ketones have cleared and the cat can be transitioned to a longer acting product.

2.5 | Other adverse events

Increases in stool frequency and fecal water content are routinely reported in cats receiving an SGLT2 inhibitor (Behrend et al., 2023; Benedict et al., 2022; Hadd et al., 2023) and likely reflect cross-over inhibition of SGLT1 within the small intestine (Wright, 2021). SGLT1 inhibition results in incomplete glucose absorption from the bowel lumen and secondary osmotic diarrhea. Based on human studies, carbohydrate restriction may ameliorate this effect (He et al., 2020), but further work is needed to determine the best approach in feline diabetics. In most cats, this side effect is not substantially problematic and is often self-limiting. Probiotics, psyllium, canned pumpkin, or intestinal adsorbents may be considered; the authors advise against empirical antibiotic administration.

Glycosuria is a well-established risk factor for urinary tract infection in many species, and positive cultures are routinely reported in cats with DM (Bailiff et al., 2006; Dorsch et al., 2019; Weese et al., 2019). Metanalyses in human patients taking SGLT2 inhibitors suggest a trivial increase in the risk of urinary tract infection compared to people prescribed other oral hypoglycemic drugs (Lega et al., 2019; Scheen, 2019; Wilding, 2019). The authors recommend culture-directed antibiotic therapy only in cats with dysuria or clinical findings suggestive of pyelonephritis. Although SGLT2 inhibitor use in people is associated with a significant increase in the incidence of genital mycotic infections, this condition has not been described in a feline patient receiving a gliflozin (Lega et al., 2019).

2.6 | Diabetic remission

None of the reports describing SGLT2 inhibitors in diabetic cats assessed the incidence of remission. The understanding of feline diabetic remission is incomplete, as there are limited data regarding contributory factors, and—until recently—"remission" was inconsistently defined (Gostelow et al., 2014; Gostelow & Hazuchova, 2023; Niessen et al., 2022). Dietary carbohydrate reduction may be beneficial (Gostelow et al., 2014; Gostelow & Hazuchova, 2023), as well as tight control of BGC (Nack & DeClue, 2014; Roomp & Rand, 2009). Given the high percentage of cats receiving an SGLT2 inhibitor who achieve euglycemia and/or normalization of serum fructosamine concentrations, it seems likely that remission may occur in cats treated with this drug class (Behrend et al., 2023; Hadd et al., 2023).

In diabetic cats receiving insulin, remission is suspected when a low dose of insulin (e.g., 1 U/cat once or twice daily) is sufficient to maintain excellent diabetic control or -more significantly- causes hypoglycemia. Since the dose of an SGLT2 inhibitor is independent of BGC and administration does not cause hypoglycemia, the only way to determine if a cat receiving an SGLT2 inhibitor is still diabetic is to suspend drug administration for several days. Appropriate timing for stopping SGLT2 inhibitor administration cannot be predicted. Longer periods of time in a euglycemic or near euglycemic state should allow for normalization of peripheral glucose sensitivity and greater β-cell recovery. Thus, waiting at least 60 days before assessing for remission seems prudent. If the BGC rises and clinical signs of DM return, the SGLT2 inhibitor should be restarted immediately. Serum ketones should be closely monitored for the first 2 weeks after resumption of treatment, as re-establishing euglycemia does not preclude the development of significant ketosis. Remission in insulin-treated cats is most likely to occur within 6 months (Gostelow et al., 2014; Gostelow & Hazuchova, 2023; Zini et al., 2010); it seems reasonable to assume the same would hold true for cats on SGLT2 inhibitors and that failing to achieve remission within this time period suggests a life-long requirement for medical therapy.

DM routinely recurs in cats undergoing remission, as 'recovered' cats have persistently abnormal glucose homeostasis and β-cell function (Gottlieb et al., 2015, 2020). Glycemic control can be lost at any time due to recurrence of insulin resistance, or further β-cell compromise for any reason (Gostelow & Hazuchova, 2023; Gottlieb et al., 2015; Zini et al., 2010). Thus, given the very low chance of hypoglycemia in a cat receiving an SGLT2 inhibitor, an argument could be made for lifelong administration in order to prevent recurrence of DM and its attendant problems. Experimental evidence demonstrates that even short-lived periods of hyperglycemia result in glucose toxicity and β-cell death (Link et al., 2013; Zini et al., 2009); withdrawal of an SGLT2 inhibitor in a well-controlled cat therefore carries the risk of additional β-cell loss and could result in irreversible insulin dependency.

3 | ADDITIONAL CONSIDERATIONS

SGLT2 inhibitors are routinely used in combination with insulin in people with both type 1 and 2 DM (Min et al., 2017; Yang et al., 2017). This approach improves glycemic control but may increase the incidence of hypoglycemia (Horii et al., 2020; Sands et al., 2015). Bexagliflozin was used in combination with insulin in a 4-week study of 5 cats with poorly regulated DM (Benedict et al., 2022). Enrolled cats had received insulin for a median of 86 days (range 76–318) and had signs of uncontrolled diabetes. Cats remained on their previous diet; insulin dose was reduced by 50% when bexagliflozin treatment was initiated. Bexagliflozin dose was 10 mg PO once daily for the first cat and 15 mg/cat for the others. BGCs were measured in the hospital (10-h curve) at baseline and on days 14 and 28, and a minimum of twice daily at home using a handheld glucometer. Mean BGC during 10-h glucose curves improved

for all cats, with a median decrease of 10.7 mmol/L (193 mg/dL); range 4.5–17.4 mmol/L (range 81–313 mg/dL). Insulin dose also decreased significantly by a median 0.55 U/kg (range 0.52–0.99). According to the owners, clinical signs resolved in three cats and improved in two during the study. Insulin administration was discontinued on day 14 in two cats.

Clinical hypoglycemia was not reported in any cat; all values throughout the study period were >3.3 mmol/L (60 mg/dL). Detection of hypoglycemia may have been limited by the small number of cats, short study duration, and relatively few measurements of BGC.

On the last day of the study, mild hyporexia and a substantial increase in serum triglyceride concentration were noted in one cat receiving both insulin and bexagliflozin. Bexagliflozin was discontinued, and the insulin dose increased. Another cat remained on dual therapy for some time, although bexagliflozin was eventually stopped because of diarrhea, which did not improve, suggesting that bexagliflozin was not the cause. A third cat was on both insulin and bexagliflozin (10 mg/day) at the end of the study; bexagliflozin was increased to 15 mg/day, and insulin was discontinued for over a year. Of the two cats on bexagliflozin alone on day 28, one remained on this as sole therapy for at least 2 years. The other cat developed diarrhea and was switched back to insulin 5 weeks after the end of the study. Diarrhea had been reported in the cat previously but did subsequently resolve.

4 | SUMMARY

The SGLT2 inhibitors are an exciting new addition to current treatment options for uncomplicated feline DM. For many owners, a once-daily oral medication is highly preferable to twice daily insulin injections, and this simplified approach is likely to improve outcomes for a substantial number of cats. In addition, the essentially negligible risk of clinical hypoglycemia provides a substantial advantage over traditional insulin therapy and will mitigate a concern routinely expressed by caretakers of diabetic pets (Albuquerque et al., 2020; Niessen et al., 2010; Rothlin-Zachrisson et al., 2023). However, this drug class is not a suitable choice for all feline diabetics, as some residual β-cell function is necessary to prevent significant ketosis. Practitioners should familiarize themselves with current recommendations regarding initial screening and monitoring and be aware of adverse events associated with SGLT2 inhibitor use in cats with DM. It is likely that further studies will guide 'best practices' with respect to optimizing patient selection, nutritional interventions, and the management of complications such as euglycemic DKA.

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No animal research was performed.

ORCID

Audrey K. Cook https://orcid.org/0000-0002-2840-6497
Ellen Behrend https://orcid.org/0000-0002-5010-2983

REFERENCES

Albuquerque, C. S., Bauman, B. L., Rzeznitzeck, J., Caney, S. M., & Gunn-Moore, D. A. (2020). Priorities on treatment and monitoring of diabetic cats from the owners' points of view. *Journal of Feline Medicine and Surgery*, *22*(6), 506–513.

American Diabetes Association American Diabetes Association: Diabetes and Statistics. https://diabetes.org/about-diabetes/statistics

Avgerinos, I., Karagiannis, T., Kakotrichi, P., Michailidis, T., Liakos, A., Matthews, D. R., Tsapas, A., & Bekiari, E. (2022). Sotagliflozin for patients with type 2 diabetes: A systematic review and meta-analysis. *Diabetes, Obesity & Metabolism*, *24*(1), 106–114.

Bailiff, N. L., Nelson, R. W., Feldman, E. C., Westropp, J. L., Ling, G. V., Jang, S. S., & Kass, P. H. (2006). Frequency and risk factors for urinary tract infection in cats with diabetes mellitus. *Journal of Veterinary Internal Medicine*, *20*(4), 850–855.

Bazelle, J., & Watson, P. (2014). Pancreatitis in cats: Is it acute, is it chronic, is it significant? *Journal of Feline Medicine and Surgery*, *16*(5), 395–406.

Bazelle, J., & Watson, P. (2020). Is it being overdiagnosed? Feline pancreatitis. *Vet Clin Small Anim Pract.*, *50*(5), 1107–1121.

Behrend, E., Holford, A., Lathan, P., Rucinsky, R., & Schulman, R. (2018). 2018 AAHA diabetes management guidelines for dogs and cats. *Journal of the American Animal Hospital Association*, *54*(1), 1–21.

Behrend, E., et al. (2023). Velagliflozin, an SGLT2 inhibitor, as once-daily, oral solution, stand-alone therapy for feline diabetes mellitus. ACVIM forum 2023 (abstract). *Journal of Veterinary Internal Medicine*, *37*(6), 2654.

Benedict, S. L., Mahony, O. M., McKee, T. S., & Bergman, P. J. (2022). Evaluation of bexagliflozin in cats with poorly regulated diabetes mellitus. *Canadian Journal of Veterinary Research*, *86*(1), 52–58.

BEXACAT Bexagliflozin Product Information. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=f918583d-0337-40da-8da1-1e1320b8d027&type=display

Bjornvad, C. R., & Jessen, L. R. (2015). Reviewing the evidence: Feline diabetic remission. *Veterinary Journal*, *203*(3), 268–269.

Callegari, C., Mercuriali, E., Hafner, M., Coppola, L. M., Guazzetti, S., Lutz, T. A., Reusch, C. E., & Zini, E. (2013). Survival time and prognostic factors in cats with newly diagnosed diabetes mellitus: 114 cases (2000–2009). *Journal of the American Veterinary Medical Association*, *243*(1), 91–95.

Campos, C. (2012). Chronic hyperglycemia and glucose toxicity: Pathology and clinical sequelae. *Postgraduate Medicine*, *124*(6), 90–97.

Chatterjee, S., Khunti, K., & Davies, M. J. (2017). Type 2 diabetes. *Lancet*, *389*, 2239–2251.

Chong, S. K., & Reineke, E. L. (2016). Point-of-care glucose and ketone monitoring. *Topics in Companion Animal Medicine*, *31*(1), 18–26.

Cook, A. K., & Evans, J. B. (2021). Feline comorbidities: Recognition, diagnosis and management of the cushingoid diabetic. *Journal of Feline Medicine and Surgery*, *23*(1), 4–16.

Cooper, R. L., Drobatz, K. J., Lennon, E. M., & Hess, R. S. (2015). Retrospective evaluation of risk factors and outcome predictors in cats with diabetic ketoacidosis (1997–2007): 93 cases. *Journal of Veterinary Emergency and Critical Care*, *25*(2), 263–272.

Couto, M. S., & Estrin, M. A. (2022). Is there a relationship between gliflozins and acute pancreatitis? Evidence-based analysis. *Data Metadata*, *1*, 39.

Dorsch, R., Teichmann-Knorrn, S., & Sjetne, L. H. (2019). Urinary tract infection and subclinical bacteriuria in cats: A clinical update. *Journal of Feline Medicine and Surgery*, *21*(11), 1023–1038.

Dziadkowiec, K. N., Stawinski, P. M., & Proenza, J. (2021). Empagliflozin-associated pancreatitis: A consideration for SGLT2 inhibitors. *ACG Case Rep J.*, *8*(1), e00530.

ElSayed, N. A., Aleppo, G., Aroda, V. R., et al. (2022). 9. Pharmacologic approaches to glycemic treatment: Standards of care in diabetes—2023. *Diabetes Care*, *46*(Suppl 1), S140–S157.

European Health. (2024). European health documents registry; velagliflozin summary of product characteristics. https://ec.europa.eu/health/documents/community-register/2023/20231120160841/anx_160841_en.pdf

Fenn, J., Kenny, P. J., Scudder, C. J., Hazuchova, K., Gostelow, R., Fowkes, R. C., Forcada, Y., Church, D. B., & Niessen, S. J. (2021). Efficacy of hypophysectomy for the treatment of hypersomatotropism-induced diabetes mellitus in 68 cats. *Journal of Veterinary Internal Medicine*, *35*(2), 823–833.

FOI. (2024a). Freedom of information summary for bexagliflozin tablets. https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/13222

FOI. (2024b). Freedom of information summary for velagliflozin oral solution. https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/14320

Forman, M. A., Steiner, J. M., Armstrong, P. J., Camus, M. S., Gaschen, L., Hill, S. L., Mansfield, C. S., & Steiger, K. (2021). ACVIM consensus statement on pancreatitis in cats. *Journal of Veterinary Internal Medicine*, *35*(2), 703–723.

Giaccari, A., Sorice, G., & Muscogiuri, G. (2009). Glucose toxicity: The leading actor in the pathogenesis and clinical history of type 2 diabetes – Mechanisms and potentials for treatment. *Nutrition, Metabolism, and Cardiovascular Diseases*, *19*(5), 365–377.

Gilor, C., Graves, T. K., Gilor, S., Ridge, T. K., Weng, H. Y., & Dossin, O. (2011). The incretin effect in cats: Comparison between oral glucose, lipids, and amino acids. *Domestic Animal Endocrinology*, *40*(4), 205–212.

Goldenberg, R. M., Berard, L. D., Cheng, A. Y. Y., Gilbert, J. D., Verma, S., Woo, V. C., & Yale, J. F. (2016). SGLT2 inhibitor–associated diabetic ketoacidosis: Clinical review and recommendations for prevention and diagnosis. *Clinical Therapeutics*, *38*(12), 2654–2664. e1.

Gostelow, R., Forcada, Y., Graves, T., Church, D., & Niessen, S. (2014). Systematic review of feline diabetic remission: Separating fact from opinion. *Veterinary Journal*, *202*(2), 208–221.

Gostelow, R., & Hazuchova, K. (2023). Pathophysiology of prediabetes, diabetes, and diabetic remission in cats. *Veterinary Clinics of North America: Small Animal Practice*, *53*(3), 511–529.

Gottlieb, S., & Rand, J. (2018). Managing feline diabetes: Current perspectives. *Veterinary Medicine: Research and Reports*, *9*, 33–42.

Gottlieb, S., Rand, J., Anderson, S. T., Morton, J. M., Dias, D. A., Boughton, B. A., Roessner, U., & Ramadan, Z. (2020). Metabolic profiling of diabetic cats in remission. *Frontiers in Veterinary Science*, *7*, 218.

Gottlieb, S., Rand, J. S., Marshall, R., & Morton, J. (2015). Glycemic status and predictors of relapse for diabetic cats in remission. *Journal of Veterinary Internal Medicine*, *29*(1), 184–192.

Hadd, M. J., Bienhoff, S. E., Little, S. E., Geller, S., Ogne-Stevenson, J., Dupree, T. J., & Scott-Moncrieff, J. C. (2023). Safety and effectiveness of the sodium-glucose cotransporter inhibitor bexagliflozin in cats newly diagnosed with diabetes mellitus. *Journal of Veterinary Internal Medicine*, *37*(3), 915–924.

He, Y., Schofield, J., Mahling, P., Mendonza, A. E., & Hinder, M. (2020). Investigation and management of stool frequency and consistency associated with SGLT1 inhibition by reducing dietary carbohydrate: A randomized trial. *Clinical Pharmacology and Therapeutics*, *108*(5), 995–1002.

Horii, T., Oikawa, Y., Kunisada, N., Shimada, A., & Atsuda, K. (2020). Real-world risk of hypoglycemia-related hospitalization in Japanese patients with type 2 diabetes using SGLT2 inhibitors: A nationwide cohort study. *BMJ Open Diabetes Research & Care*, *8*(2), e001856.

Lega, I. C., Bronskill, S. E., Campitelli, M. A., Guan, J., Stall, N. M., Lam, K., McCarthy, L. M., Gruneir, A., & Rochon, P. A. (2019). Sodium glucose cotransporter 2 inhibitors and risk of genital mycotic and urinary tract infection: A population-based study of older women and men with diabetes. *Diabetes, Obesity & Metabolism*, *21*(11), 2394–2404.

Leslie, R. D., Palmer, J., Schloot, N. C., & Lernmark, A. (2016). Diabetes at the crossroads: Relevance of disease classification to pathophysiology and treatment. *Diabetologia*, *59*(1), 13–20.

Link, K. R., & Rand, J. S. (2008). Changes in blood glucose concentration are associated with relatively rapid changes in circulating fructosamine concentrations in cat. *Journal of Feline Medicine and Surgery*, *10*(6), 583–592.

Link, K. R. J., Allio, I., Rand, J. S., & Eppler, E. (2013). The effect of experimentally induced chronic hyperglycaemia on serum and pancreatic insulin, pancreatic islet IGF-I and plasma and urinary ketones in the domestic cat (*Felis felis*). *General and Comparative Endocrinology*, *188*, 269–281.

Long, B., Lentz, S., Koyfman, A., & Gottlieb, M. (2021). Euglycemic diabetic ketoacidosis: Etiologies, evaluation, and management. *The American Journal of Emergency Medicine*, *44*, 157–160.

Marín-Peñalver, J. J., Martín-Timón, I., Sevillano-Collantes, C., & del Cañizo-Gómez, F. J. (2016). Update on the treatment of type 2 diabetes mellitus. *World Journal of Diabetes*, *7*(17), 354–395.

Marshall, R. D., Rand, J. S., & Morton, J. M. (2009). Treatment of newly diagnosed diabetic cats with glargine insulin improves glycaemic control and results in higher probability of remission than protamine zinc and lente insulins. *Journal of Feline Medicine and Surgery*, *11*(8), 683–691.

Min, S. H., Yoon, J. H., Hahn, S., & Cho, Y. M. (2017). Comparison between SGLT2 inhibitors and DPP4 inhibitors added to insulin therapy in type 2 diabetes: A systematic review with indirect comparison meta-analysis. *Diabetes/Metabolism Research and Reviews*, *33*(1), e2818.

Mori, A., Lee, P., Mizutani, H., Takahashi, T., Azakami, D., Mizukoshi, M., Fukuta, H., Sakusabe, N., Sakusabe, A., Kiyosawa, Y., & Arai, T. (2009). Serum glycated albumin as a glycemic control marker in diabetic cats. *Journal of Veterinary Diagnostic Investigation*, *21*(1), 112–116.

Musso, G., Saba, F., Cassader, M., & Gambino, R. (2020). Diabetic ketoacidosis with SGLT2 inhibitors. *BMJ*, *371*, m4147. https://doi.org/10.1136/bmj.m4147

Nack, R., & DeClue, A. E. (2014). In cats with newly diagnosed diabetes mellitus, use of a near-euglycemic management paradigm improves remission rate over a traditional paradigm. *The Veterinary Quarterly*, *34*(3), 132–136.

Nasa, P., Chaudhary, S., Shrivastava, P. K., & Singh, A. (2021). Euglycemic diabetic ketoacidosis: A missed diagnosis. *World Journal of Diabetes*, *12*(5), 514–523.

Nelson, R. W., Henley, K., Cole, C., & PZIR Clinical Study Group. (2009). Field safety and efficacy of protamine zinc recombinant human insulin for treatment of diabetes mellitus in cats. *Journal of Veterinary Internal Medicine*, *23*(4), 787–793.

Niessen, S. J., Forcada, Y., Mantis, P., Lamb, C. R., Harrington, N., Fowkes, R., Korbonits, M., Smith, K., Church, D. B., et al. (2015). Studying cat (Felis catus) diabetes: Beware of the acromegalic imposter. *PLoS One*, *10*(5), e0127794.

Niessen, S. J. M. (2010). Feline acromegaly: An essential differential diagnosis for the difficult diabetic. *Journal of Feline Medicine and Surgery*, *12*(1), 15–23.

Niessen, S. J. M., Bjornvad, C., Church, D. B., Davison, L., Esteban-Saltiveri, D., Fleeman, L. M., Forcada, Y., Fracassi, F., Gilor, C., Hanson, J., Herrtage, M., Lathan, P., Leal, R. O., Loste, A., Reusch, C., Schermerhorn, T., Stengel, C., Thoresen, S., Thuroczy, J., & ESVE/SCE membership. (2022). Agreeing language in veterinary endocrinology (ALIVE): Diabetes mellitus – a modified Delphi-method-based system to create consensus disease definitions. *Veterinary Journal*, *289*, 105910.

Niessen, S. J. M., Powney, S., Guitian, J., Niessen, A. P. M., Pion, P. D., Shaw, J. A. M., & Church, D. B. (2010). Evaluation of a quality-of-life tool for cats with diabetes mellitus. *Journal of Veterinary Internal Medicine*, *24*(5), 1098–1105.

Niessen, S. J. M., Roth, V., Kroh, C., & Hennings, L. (2022). Once daily oral therapy for feline diabetes mellitus: SGLT-2-inhibitor velagliflozin as stand-alone therapy compared to insulin injection therapy in diabetic cats. ECVIM congress 2022 (abstract). *Journal of Veterinary Internal Medicine*, *36*(6), 2512–2513.

Rand, J. S. (2013). Pathogenesis of feline diabetes. *Veterinary Clinics of North America: Small Animal Practice*, *43*(2), 221–231.

Restine, L. M., Norsworthy, G. D., & Kass, P. H. (2019). Loose-control of diabetes mellitus with protamine zinc insulin in cats: 185 cases (2005–2015). *The Canadian Veterinary Journal*, *60*(4), 399–404.

Robertson, R. P., Harmon, J., Tran, P. O., Tanaka, Y., & Takahashi, H. (2003). Glucose toxicity in β-cells: Type 2 diabetes, good radicals gone bad, and the glutathione connection. *Diabetes*, *52*(3), 581–587.

Roomp, K., & Rand, J. (2009). Intensive blood glucose control is safe and effective in diabetic cats using home monitoring and treatment with glargine. *Journal of Feline Medicine and Surgery*, *11*(8), 668–682.

Rosenstock, J., & Ferrannini, E. (2015). Euglycemic diabetic ketoacidosis: A predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care*, *38*(9), 1638–1642.

Rothlin-Zachrisson, N., Öhlund, M., Röcklinsberg, H., & Ström, H. B. (2023). Survival, remission, and quality of life in diabetic cats. *Journal of Veterinary Internal Medicine*, *37*(1), 58–69.

Rudloff, E. (2017). Diabetic ketoacidosis in the cat: Recognition and essential treatment. *Journal of Feline Medicine and Surgery*, *19*(11), 1167–1174.

Samson, S. L., Vellanki, P., Blonde, L., Christofides, E. A., Galindo, R. J., Hirsh, I. B., Isaacs, S. D., Izuora, K. E., Low Wand, C. C., Twining, C. L., Umpierrez, G. E., & Marcos, V. W. (2023). American Association of Clinical Endocrinology Consensus Statement: Comprehensive type diabetes management algorithm – 2023 update. *Endocrine Practice*, *29*, 305–340.

Sands, A. T., Zambrowicz, B. P., Rosenstock, J., Lapuerta, P., Bode, B. W., Garg, S. K., Buse, J. B., Banks, P., Heptulla, R., Rendell, M., Cefalu, W. T., & Strumph, P. (2015). Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. *Diabetes Care*, *38*(7), 1181–1188.

Schaefer, S., Kooistra, H. S., Riond, B., Suchodolski, J. S., Steiner, J. M., Prins, M., Zini, E., & Reusch, C. E. (2017). Evaluation of insulin-like growth factor-1, total thyroxine, feline pancreas-specific lipase and urinary corticoid-to-creatinine ratio in cats with diabetes mellitus in Switzerland and The Netherlands. *Journal of Feline Medicine and Surgery*, *19*(8), 888–896.

Scheen, A. J. (2019). An update on the safety of SGLT2 inhibitors. *Expert Opinion on Drug Safety*, *18*(4), 295–311.

Scott-Moncrieff, J. C. (2010). Insulin resistance in cats. *The Veterinary Clinics of North America. Small Animal Practice*, *40*(2), 241–257.

SENVELGO Velaglfiflozin Product Information. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=3ec5ca1f-bded-459e-a813-24d931d50b9a&type=display

Sparkes, A. H., Cannon, M., Church, D., Fleeman, L., Harvey, A., Hoenig, M., Peterson, M. E., Reusch, C. E., Taylor, S., Rosenberg, D., & ISFM. (2015). ISFM consensus guidelines on the practical management of diabetes mellitus in cats. *Journal of Feline Medicine and Surgery*, *17*(3), 235–250.

Thomas, M. C., & Cherney, D. Z. I. (2018). The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. *Diabetologia*, *61*(10), 2098–2107.

Vallon, V. (2015). The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. *Annual Review of Medicine*, *66*(1), 255–270.

Vallon, V., & Thomson, S. C. (2017). Targeting renal glucose reabsorption to treat hyperglycaemia: The pleiotropic effects of SGLT2 inhibition. *Diabetologia*, *60*(2), 215–225.

van Bokhorst, K. L., Galac, S., Kooistra, H. S., Valtolina, C., Fracassi, F., Rosenberg, D., & Meij, B. P. (2021). Evaluation of hypophysectomy for treatment of hypersomatotropism in 25 cats. *Journal of Veterinary Internal Medicine*, *35*(2), 834–842.

Verbrugghe, A., Hesta, M., Daminet, S., & Janssens, G. P. J. (2012). Nutritional modulation of insulin resistance in the true carnivorous cat: A review. *Critical Reviews in Food Science and Nutrition*, *52*(2), 172–182.

Weese, J. S., Blondeau, J., Boothe, D., Guardabassi, L. G., Gumley, N., Papich, M., Jessen, L. R., Lappin, M., Rankin, S., Westropp, J. L., & Sykes, J. (2019). International Society for Companion Animal Infectious Diseases (ISCAID) guidelines for the diagnosis and management of bacterial urinary tract infections in dogs and cats. *Veterinary Journal*, *247*, 8–25.

Weingart, C., Lotz, F., & Kohn, B. (2012). Measurement of β-hydroxybutyrate in cats with nonketotic diabetes mellitus, diabetic ketosis, and diabetic ketoacidosis. *Journal of Veterinary Diagnostic Investigation*, *24*(2), 295–300.

Wilding, J. (2019). SGLT2 inhibitors and urinary tract infections. *Nature Reviews. Endocrinology*, *15*(12), 687–688. https://doi.org/10.1038/s41574-019-0275-6

Wright, E. M. (2021). SGLT2 inhibitors: Physiology and pharmacology. *Kidney360*, *2*(12), 2027–2037.

Yang, S., Liu, Y., Zhang, S., Wu, F., Liu, D., Wu, Q., Zheng, H., Fan, P., & Su, N. (2023). Risk of diabetic ketoacidosis of SGLT2 inhibitors in patients with type 2 diabetes: A systematic review and network meta-analysis of randomized controlled trials. *Frontiers in Pharmacology*, *14*, 1145587.

Yang, Y., Chen, S., Pan, H., Zou, Y., Wang, B., Wang, G., Zhu, H., et al. (2017). Safety and efficiency of SGLT2 inhibitor combining with insulin in subjects with diabetes. *Medicine (Baltimore)*, *96*(21), e6944.

Zeugswetter, F., & Pagitz, M. (2009). Ketone measurements using dipstick methodology in cats with diabetes mellitus. *The Journal of Small Animal Practice*, *50*(1), 4–8.

Zeugswetter, F. K., & Rebuzzi, L. (2012). Point-of-care β-hydroxybutyrate measurement for the diagnosis of feline diabetic ketoacidaemia. *The Journal of Small Animal Practice*, *53*(6), 328–331.

Zini, E., Hafner, M., Osto, M., Franchini, M., Ackermann, M., Lutz, T. A., & Reusch, C. E. (2010). Predictors of clinical remission in cats with diabetes mellitus. *Journal of Veterinary Internal Medicine*, *24*(6), 1314–1321.

Zini, E., Osto, M., Franchini, M., Guscetti, F., Donath, M. Y., Perren, A., Heller, R. S., Linscheid, P., Bouwman, M., Ackermann, M., Lutz, T. A., & Reusch, C. E. (2009). Hyperglycaemia but not hyperlipidaemia causes beta cell dysfunction and beta cell loss in the domestic cat. *Diabetologia*, *52*(2), 336–346.

Zoran, D. (2002). The carnivore connection to nutrition in cats. *Journal of the American Veterinary Medical Association*, *221*(11), 1559–1567.

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