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Safety and effectiveness of the sodium-glucose cotransporter inhibitor bexagliflozin in cats newly diagnosed with diabetes mellitus

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Active (concentrative) reuptake of glucose by the kidney is principally performed by sodium-glucose cotransporter 2 (SGLT2), an integral membrane protein responsible for the recovery of >90% of glucose from the glomerular filtrate of healthy animals.

Pharmacological inhibitors of SGLT2 have been found to improve glycemic control in humans with type 2 diabetes mellitus (T2DM), a disease characterized by insulin resistance.4

Administration of SGLT2inhibitors to healthy humans results in a loss to urine of approximately half of the glomerular flux of glucose, with the remainder reabsorbed by the increased compensatory action of sodium-glucose cotransporter 1.

Additional benefits of SGLT2 inhibitor treatment reported in studies of humans include weight loss, a decrease in systolic blood pressure, decreased susceptibility to major adverse cardiovascular events, and a decrease in the rate of progression of chronic kidney disease

Inhibition of SGLT2 in healthy and diabetic humans does not result in hypoglycaemia although episodes of hypoglycaemia have been observed with coadministration of other antidiabetic agents, particularly insulin, and sulfonyl ureas

Diabetes mellitus (DM) in cats shares some attributes with T2DM in humans:

- obesity
- respond to changes in diet.
- More prominently in the cat, pancreatic amyloidosis is observed
    - The amyloid deposits result from the aggregation and precipitation of amylin, aβ-cell peptide hormone co-secreted with insulin.
    - In cats, DM is associated with amyloidosis of the exocrine pancreas as well as a destruction of β-cells that is more typical of advanced disease in humans.

A pilot study has reported the utility of bexagliflozin as an adjunct to insulin for the management of DM in cats poorly controlled by insulin alone.

Bexagliflozin was found to decrease the insulin dose requirement and decrease mean blood glucose concentration measured by a serial inpatient sampling every 2 hours for 10 hours.

AIM

Principal hypothesis was that bexagliflozin veterinary tablets,15 mg, would be safe and effective for the management of DM in cats when administered once daily as monotherapy

METHOD

Client owned cats
Newly dx with DM
Eligible cats required to exhibit

i) 2 separate fasting (>6 hours) BG conc >250mg/dl
ii) Glucosuria
iii) Serum fructosamine conc >358 umol/L
iv) Documented history of ≥1 of the following csx PU, PD, polyphagia or wt loss

Exclusion

- pregnant, lactating, in estrus
- heart failure,
- advanced chronic kidney disease (InternationalRenal Interest Society stage 3 or 4),
- hyperthyroidism,
- hypertension,
- neoplasia,
- history of feline idiopathic cystitis,
- major infectious pro-cesses (other than treatable acute urinary tract infections), or
- any other conditions that would, in the opinion of the clinician, interfere with obtaining or monitoring blood samples, treatment administration or assessment of effectiveness of the investigational veterinary product (IVP)
- Cats exhibiting inappetence in the previous week, or with serum withβ-hydroxybutyrate (β-OHB) concentration≥37.0 mg/dL were not eligible.
- Cats withβ-OHB concentration >25.0 mg/dL but<37.0 mg/dL could be enrolled if they were not inappetent and had no history of either renal disease or acidosis.
- Cats with insulin-like growth factor 1 (IGF-1) higher than the upper limit of the laboratory reference interval (92 nmol/L) could be enrolled but were excluded from the endpoint analysis.
- Cats with a history of urinary tract surgery or with planned elective surgeries requiring general anaesthesia during the study period were ineligible, with the exception of dental surgery after day 56.

- Cats that had a history of ongoing pharmacologic management of DM were excluded.
- Previously treated diabetic cats that were determined to be in remission, had not received insulin for at least 3 months, and met the enrolment criteria could be enrolled, but none of the cats in the study met these criteria.
- Cats with baseline alkaline phosphatase or alanine aminotransferase activity 3 times the upper limit of normal or with a feline pancreatic lipase (FPL) immuno-assay concentration >5.3µg/L also were excluded from the study.
- If an enrolled cat was determined to have an increased IGF-1 concentration at screening or had received corticosteroids or progestogens between day 0 and 56, the cat was evaluated for safety but not effectiveness.
- Enrolment continued until at least 80 cases evaluable for the effectiveness endpoint had been enrolled in the study

Prospective , open labelled , historically controlled, multisite pivotal clinical field study

Initial visit – 8 hour BGC with 5 glucometer measurements at 2 hour intervals

After visit owner was provided with IVP and dosing instructions

Visits 14, 28,56,84, 112, 140 and 180 days after treatment initiation for blood and urine collection and owner and investigator assessment of effectiveness , tolerance and safety

All visits included an 8 hour BGC (alphtrak)

Tx started at day 0 – 15 PO SID bexagliflozin

Recommended for the cat to have low CHO diet but not required

HX, PEx at all visits and upon withdrawal from study if possible – BP , PU/PD or polyphagia body wt and BCS were recorded,

Hair coat quality, muscle mass and neurological status – rating 0 to excellent 1 good 2 fair and 3 poor

Blood samples for CBC, serum chemistry analysis, fructosamine, specific pancreatic lipase, symmetric dimethylarginine (SDMA), andβ-OHB concentration were collected at screening and every scheduled visit after initiation of treatment. Urine samples also were collected at each visit for routine urinalysis, including urine ketones and bacterial culture

TT4 and IGF-1 were only recorded at initial visit

Owner questionnaire on day 56 and before the visit – asked about PU/PD , polyphagia

- Each clinical sign was scored as significantly improved , somewhat improved , unchanged or worsened compared to day 0

Day 0 and 56 QOL questionnaire – used previously validated instrument developed to evaluate life quality for owners of cats with DM

- Lower scores reflect greater adverse impact of the disease on owner quality of life.22
- Importance was scored as “very important”(4),“important”(3),“moderately important”(2),“low importance”(1), or “not at all important”(0),
- whereas frequency was scored as “all the time”(3),“often”(2),“occasionally”(1), or “rarely”(0)

Effectiveness was determined at the day 56 visit and was based on the change from baseline in serum fructosamine concentration, mean BGC results over 8 hours, change in body weight, and owner assessments of clinical signs

Each cat was classified as a treatment success or failure on day 56.

- Success was defined as
    - attainment of glycemic control (mean of 8 hour in-clinic BGC < 250 mg/dL or serum fructosamine concentration <358µmol/L) and
    - improvement from baseline of at least 1 clinical sign (polyuria, polydipsia, polyphagia, or weight loss).
    - Body weight was deemed to have improved if the weight on day 56was≥the weight at baseline
- Failures
    - Animals withdrawn from the study for any reason, including owner dissatisfaction of any sort,
    - All cats in the effectiveness population that were not defined as a treatment success were considered treatment failures

RESULTS

Effectiveness

- 84 cats enrolled and received at least 1 dose of IVP
- 81 were effectiveness evaluable (2 had increased IGF-1 at baseline and 1 was the sole cat enrolled at study site)
- 43 male /41 female
- Mean age 10.8 yr (3-18.5yr)
- Median wt 5.4kg (3.3-11.3kg)
- 68/81 treatment success -> 84%
- 13/81 failures –
    - 6 removed from study before day 56 after adverse events , 5 were serious adverse events (SAE)
    - 4 cats did not meet the glycaemic control criteria but meet the criteria for improvement of clinical signs
    - 3 cats met glycaemic control criteria but did not meet the criteria for improved csx
    - No cat failed by both glycaemic control and clinical sign criteria
- 75 effectiveness evaluable cats in the study at the 56 day end point –
    - 9 cats did not meet the serum fructosamine target but did meet the mean blood glucose conc target and were classified as glycaemic control successes

    - 4 cats did not meet the fructosamine target or the mean BG conc -> failures

Blood glucose curves

- mean blood glucose concentration measured during the BCGs decreased rapidly during the 8 hours after initiation of treatment
- At subsequent visits, the decrease in mean blood glucose concentration was maintained.
- The mean of the 5 blood glucose concentration determinations:
    - Day 0 - 281.5 mg/dL (95% CI, 264.6-298.5)
    - Day 56- 143.7 mg/dL (95% CI 129.2-158.3)
    - Day 180 - 133.7 mg/dL(95% CI 122.7-144.7)

Blood glucose concentration

- Mean BG conc was
    - Day 0 – 439.8 mg/dL (95% CI, 424.2-455.4)
    - Day 56 – 161.4mg/dL (95% CI 132.1-161.5)
    - Day 180 – 144.4 mg/dL(95% CI 126.1-162.6)
    - On day 56, the blood glucose con-centration was within the laboratory normal reference interval(65-155 mg/dL) for 43 of 75 cats (57.3%).

Serum fructosamine concentration

- The mean serum fructosamine concentration decreased from 542.5µmol/L (95% CI, 523.0-562.0) on day 0 to 301.3µmol/L(95% CI, 280.4-322.2) on day 56 and 305.6µmol/L (95% CI,269.1-342.0) on day 180.
- The fructosamine concentration was within the laboratory normal reference interval (154-275µmol/L) for 34 of 75 cats (45.3%) on day 56.

Serumβ-OHB concentration

- The β-OHB concentration dropped rapidly from a base line of 13.7 mg/dL (95% CI, 11.3-16.1) to 2.91 mg/dL (95% CI, 1.8-4.1) on day 56 and 3.21 mg/dL (95% CI, 1.3-7.5) on day 180.
- On day 56, 51 of 75 cats (68.0%) were within the laboratory normal reference interval (≤1.9 mg/dL)

Body weight

- Of the 75 cats completing the day 56 visit, 43 (57.3%) either maintained or gained weight from day 0 to day 56.
- A significant increase(uncorrected for multiplicity) was observed in mean body weight from day 0 to day 84 and at all subsequent visits

Clinical Signs

- Of the 75 effectiveness-evaluable cats, 68 (90.7%) were found to have improved by at least 1 clinical sign of hyperglycemia

- Compared to baseline, the owner-assessed overall quality of life of the cat indicated:
    - improvement in 65 cats (86.7%),
    - no change in 9 (12.0%),
    - and worsening in 1 (1.3%) -consequence of missing information that resulted in the assignment of the least favorable score to all owner assessments according to the prespecified analysis

Investigator evaluations

- Initial scores were favorable for neurological signs and less improvement accordingly was seen.
- Musculature and hair coat quality showed more improvement with time in study

Owner quality of life

- The mean score increased from day 0 to day 56

Evaluation of fructosamine half-life

- The rapid and sustained action of bexagliflozin allowed the half-life of serum fructosamine to be estimated as 6.8 days in diabetic cats

Safety

- 84 cats included in the safety analysis population.
- Over the 6-month study duration, 75 of the 84 cats (89.3%) in the safety analysis population accounted for 559 investigator-reported adverse events, of which 524 were considered nonserious and 35, affecting 8 cats, were considered SAE
- 93/559 – considered unrelated to exposure to bexagliflozin
- 263/559 to have an unknown relationship to exposure
- 187/559 to have a possible relationship to exposure,
- 16/559 to have a probable relationship to exposure.
- Twelve of the 84 enrolled cats (14.3%) were withdrawn before completing the 6-month study
- 70 cats were evaluated within the 3-day window for the final 180 day visit, with 2 cats evaluated outside the prescribed window for evaluation
- Adverse events reported for≥5% of the enrolled cats over the study duration
- The most common adverse events were vomiting, diarrhea, anorexia, lethargy and dehydration (most sporadic but some occurred with concurrent illness)
- 8 cats had SAEs
    - 3 died or were euthanized
        - 3 deaths were attributed to weight loss with anemia, an unknown cause, and hepatic lipidosis
        - One cat with diagnosed DKA experienced a progressive increase in trans-aminase activity, hypokalemia, and anemia despite supportive care and was euthanized. The cause of death was determined to be hepatic lipidosis

- Four of the 8 cats with SAEs experienced anorexia and lethargy
  - 3 of the 4 cats with anorexia and lethargy were diagnosed with diabetic ketoacidosis (DKA), which occurred in the absence of acute hyperglycemia
- remaining 4 cats were observed in 1 cat each and included:
  - poor glycemic control, constipation, and pancreatitis;
  - dehydration and weight loss;
  - weight loss and anemia; and
  - dehydration with presumed DKA and pyelonephritis.
- All but 1 of the 8 cats were withdrawn from the study as a result of the SAEs.
- A clustering of events close to initiation of treatment was observed,
  - with 4 of the 8 cats receiving a total of 2, 3, 3, and 5 doses before cessation of treatment.
  - Anorexia and lethargy were present in 3 of the 4 cats, and 2 had underlying infections (urinary tract infection and presumed pyelonephritis).
  - Because DKA can emerge in the setting of diabetes with concurrent disease, a specific aetiology cannot be ascribed, but at minimum the possibility of the co-occurrence of DKA with other diseases should be considered in the setting of bexagliflozin treatment, and anorexia or lethargy appearing shortly after initiation of treatment should be promptly investigated.
- In our study, DKA was diagnosed or presumed present on days 2, 3, 4, and 31.
  - One of the cats died and the remainder were transitioned to insulin treatment.
- No episodes of symptomatic hypoglycaemia were observed

DISCUSSION

- In our study, bexagliflozin veterinary tablets, 15 mg, decreased blood glucose and serum fructosamine concentrations, and decreased clinical signs of DM in newly diagnosed diabetic cats when administered PO once daily
- Treatment was successful for 84% of enrolled cats measures of owner quality of life improved.
- Bexagliflozin was well-tolerated by most cats with SAEs reported for 8 cats
- bexagliflozin incurred minimal risk of hypoglycaemia, with no symptomatic episodes of hypoglycaemia observed.
- The action of bexagliflozin was apparent after administration of the first dose, as detected by a prompt and reproducible decrease in blood glucose concentration measured over the course of an 8-hour,5-sample evaluation.
- Durable effects on mean blood glucose concentration and mean fructosamine concentration were observed over the 6-month span of the study. Serumβ-OHB concentration decreased for the study population as a whole.
- The number of cats that were classified as achieving treatment success was higher for polydipsia and polyuria than for polyphagia and weight gain.
- Improvement in the clinical signs of hyperglycaemia was expected to be confounded by their overlap with the mechanistic consequences of SGLT2 inhibition. Upon administration to healthy animals, bexagliflozin produces

severe glucosuria with compensatory increases in food and water consumption, creating the clinical impression of an animal with severe DM. Although an initial increase in clinical signs would be expected in diabetic cats, for the animals in our study the decrease in blood glucose concentration induced by SGLT2 inhibition apparently resulted in a lower glucose efflux overall, with attendant improvement in the clinical signs

- Polyphagia was the clinical sign least likely to show improvement, consistent with previous studies in other species indicating that the caloric wasting induced by SGLT2 inhibition frequently gives rise to compensatory hyperphagia
- Because SGLT2 inhibitors have an insulin-independent mechanism of action, they may be useful for the treatment of acromegaly-associated DM, and a small study in humans has supported this view
- Because of the distinct character of the DM attributable to acromegaly, cats with high IGF-1 were not included in the effectiveness evaluation. However, both cats with high baseline IGF-1 met the glycemic and clinical sign criteria for success and both cats remained enrolled for the 6-month duration of the study
- The SAE most plausibly attributed to bexagliflozin treatment in our study was DKA, a rare complication of SGLT2 inhibitor treatment in humans
- Inpatients treated with SGLT2 inhibitors, recognition of ketoacidosis may be delayed because the characteristic high blood glucose concentration associated with ketoacidosis is masked by inhibitor action.22Inour study, ketoacidosis was diagnosed in 3 cats and presumed present in another cat and in all cases was observed in the context of good glycaemic control. In humans, the corresponding clinical condition often is described as euglycemic DKA.
- Clinical signs in our study included anorexia and dehydration and some of the cats had concurrent illness
- Physiological form, ketosis is a nonpathological response associated with fat catabolism in response to depletion of glycogen reserves, the principal stores of which are found in liver and muscle.
- Adaptive ketosis can be induced by restriction of carbohydrate intake in humans, but the most effective dietary manipulation in rodents is restriction of both carbohydrate and protein, presumably because restriction of dietary protein decreases the conversion of amino acids into glucose via gluconeogenesis.
- Fat catabolism in both rodents and humans is antagonized by insulin, which suppresses lipolysis in adipocytes and effectively terminates the acidotic state.
- In healthy rats, the SGLT2 inhibitor dapagliflozin has been reported to produce ketosis by a mechanism that requires dehydration. Administration of dapagliflozin resulted in a decrease in blood glucose concentration of approximately 25 mg/dL and a corresponding decrease in plasma insulin concentration of approximately 50%.
- In rats that had water withheld, plasmaβ-OHB concentration increased 8-fold and bicarbonate concentration decreased by 30%.
- The role of dehydration in the induction of ketoacidosis appeared to be indirect, and mediated by increases in corticosterone and catechol-amines. Infusion of glucose overcame the dapagliflozin-mediated hypoglycaemia and

resulted in an increase in insulin production and suppression of adipocyte lipolysis

- Osmotic diuresis associated with glucosuria produces mild volume contraction and may increase the risk of dehydration-dependent ketonemia. Although a dehydration-dependent increase in glucocorticoids and catecholamines represents 1 mechanism for initiation, other precipitating factors might account for susceptibility to ketoacidosis.
- Experiments with healthy mice have shown that ketonemia associated with fasting or occurring in the context of administration of SGLT2 inhibitors has little dependence on glucagon. Whether these conclusions apply to diabetic cats treated with SGLT2 inhibitors is uncertain.
- Appropriate reduction of risk of ketoacidosis in bexagliflozin treatment is an important objective. The dapagliflozin rat model identifies access to water as an important factor, and diet may be another. Provision of a diet with a consistently high proportion of metabolizable energy in the form of carbohydrates should be considered, because restriction of carbohydrate intake is a well-documented method to induce adaptive ketosis in humans. In healthy rats,β-adrenergic blockade nearly completely suppresses dehydration-dependent ketonemia, and this approach may have utility for the management of cats with ketosis secondary to bexagliflozin administration
- Bexagliflozin exposure produces minimal risk of hypoglycemia, but may be associated with increased risk of DKA (see comparability discussion below). Insulin can quell the latter but poses a substantial risk of hypoglycaemia
- Overdose and serious drug reactions rare

LIMITATIONS

- Unblinded and no comparator arm
- Relied on owner evaluations
- End post measuring clinical remission was not included

In studies reporting the effects of traditionally manufactured protamine zinc insulin and recombinant human protamine zinc insulin, mean serum fructosamine concentration decreased from 598 to419µmol/L and from 505 to 375µmol/L, respectively, over 45 days, whereas in our study, a decrease from 543 to 301µmol/L was observed over 56 days

Thus, 21 of 176 cats died or were euthanized over 181 days compared to 3 out of 84 over 180 days in our study. In the insulin study, 4 cats were diagnosed with DKA during the initial 45-day effectiveness evaluation period. If there were no additional DKA events in the study, the proportion of cats experiencing DKA would be approximately half that seen in our study (in which 4 cats with known or presumed DKA were found out of 84 over180 days)

Some studies have evaluated insulin glargine management of DM in cats with generally favourable results but with smaller numbers of enrolled animals, either 13,24, or 13 cats. Serum fructosamine concentrations decreased from 556 to 458, 568 to 543, and 604 to366µmol/L, respectively, and tabulations of adverse events were not reported. Insulin glargine appears to have several advantages over insulins approved for veterinary use but a definitive study has yet to be reported

Bexagliflozin represents a new option for the management of DM in cats newly diagnosed with the disease. It favourably affects owner quality of life, provides excellent glycaemic control, and facilitates owner compliance by providing an easily administered, once-daily PO tablet formulation. The principal risk attributable to bexagliflozin treatment may be DKA. Other common adverse effects such as vomiting, diarrhea, anorexia, and lethargy are typically mild and self-limiting.

Limitation only measured IGF 1 at start of treatment. IGF-1 require insulin thus should have retested at another time point to assess IGF-1 levels.

Pathophysiology of Prediabetes, Diabetes, and Diabetic Remission in Cats

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IGT – impaired glucose tolerance
OGTT – oral glucose tolerance test
IR – insulin resistance

Feline diabetic remission is most often defined as maintenance of normoglycemia for at least 4 weeks without the need for antihyperglycemic medications. A carbohydrate-reduced diet is not typically considered an antihyperglycemic medication for this definition.

The final stage in the development of prediabetes and DM is failure of pancreatic β -cells to secrete adequate insulin to maintain normoglycemia. This β -cell failure might result from β -cell destruction, abnormal β -cell function, or failure of β -cell production to compensate for peripheral IR.

The deciding role of β-cell function accounts for why not all cats with risk factors for DM, such as obesity or glucocorticoid treatment, develop DM because patients with sufficient Beta cell function can differ between patients, beta cell function is the common final step in the development of DM

Most cats DM type 2
There is little evidence for type 1 DM, associated with immune-mediated islet inflammation, in cats. Only a couple of suspected cases, with lymphocytic insulitis, have been reported.
Gestational DM has not been reported in cats

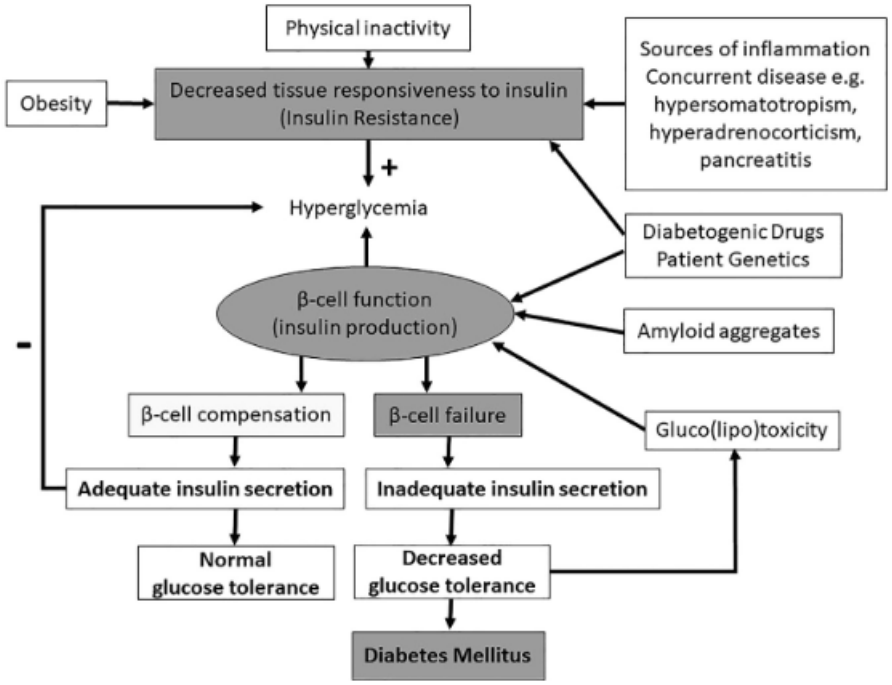

Fig. 2. Major contributing factors that might lead to the development of DM in cats. Although underlying cause can differ between patients, β-cell failure is the common final step in the development of DM.

Factors contributing to diabetes Mellitus in cats

<u>Obesity</u>

- Insulin sensitivity is reduced in obese cats compared with those that are lean
  - One study using euglycemic hyper insulinemic clamps estimated 30% loss in insulin sensitivity for each kilogram increase in body weight.
  - However, when obese cats lost weight and became lean, insulin sensitivity returned and was no different from lean cats without a history of obesity

- Obesity could therefore represent a reversible cause of IR in cats if weight loss can be achieved.
  - However, it is also possible that the IR documented in obese cats might occur because of factors associated with an overweight state.
  - For example, IR might develop as a result of feeding certain diets, leading to intestinal inflammation and increased intestinal permeability, which has been shown in mouse models fed high-fat diets.
  - Consequently, microbiome modulation or inhibition of intestinal inflammation might have the potential to improve glucose tolerance.
  - It has yet to be shown whether these factors are applicable in cats.
  - Furthermore, it has been discussed that, in people, hyperinsulinemia might be the primary abnormality, leading to weight gain and obesity, which is in contrast with the classical concept of obesity leading to IR and hyperinsulinemia

- Not all cats develop glucose intolerance following the development of obesity.

- One study suggested that cats who became glucose intolerant after becoming obese typically had several intravenous (IV) glucose tolerance (IVGTT) findings suggestive of abnormal glucose homeostasis even when in a lean state. However, this did not reach statistical significance.

- Obese cats have both subcut fat and visceral fat mass increase to similar extent and correlate with decreased insulin sensitivity (contrast people where visceral fat more important with development of IR than subcut fat)

- The molecular mechanisms by which obesity might be linked to IR in cats have not been fully elucidated, and it is also possible, as discussed above, that obesity is a consequence of IR rather than being its cause.

- The glucose transporter GLUT4 is responsible for insulin-mediated glucose uptake in the muscle and adipose tissue, and reduced expression of GLUT4 was demonstrated in people with type 2 DM and severe IR.

    - In cats, the expression of GLUT4 in both muscle and adipose tissue decreased as cats became overweight and was shown to correlate with a decrease in glucose tolerance judged by IVGTT.

- Obesity in cats and people is also associated with altered production of adipose tissue–derived hormones (adipokines),particularly a decrease in the insulin-sensitizing adipokine, adiponectin and increased concentrations of leptin (hyperleptinemia).

    - Decreased serum total adiponectin concentrations are associated with increased likelihood of DM in people,
    - overweight cats have been shown to have both decreased concentrations of total adiponectin and a relative decrease in high-molecular-weight adiponectin, which is thought to be the most biologically active form.
    - This decrease in the proportion of high-molecular-weight adiponectin also correlated with decreased insulin sensitivity.
    - Increasing adiposity is associated with the development of hyperleptinemia in both cats and people.
    - Leptin also acts on the central nervous system to decrease food intake and promote energy utilization.
    - Obese people show a decreased response to these properties, which is described as leptin-resistance.
    - In overweight cats, weight loss is associated with an increase in total adiponectin concentration and a reduction in leptin concentration to levels similar to those of lean cats

- Adipose tissue inflammation might not contribute to IR in over-weight cats.
    - increased TNF-alpha concentrations have been documented in the adipose tissue of obese cats but there is little evidence for systemic inflammation.

- Blood concentration of IL-1, IL-6, and TNF-alpha do not alter when lean cats become obese, and blood concentrations of the acute phase proteins, serum amyloid A and haptoglobin, do not change in overweight cats that undergo weight loss.
- This lack of systemic inflammation is a proposed reason overweight cats do not develop the cardiovascular complications of metabolic syndrome in people

Glucotoxicity

- β -cell destruction and dysfunction, which is proposed to result from chronic exposure to supraphysiologic glucose concentrations.
- By affecting both β -cell function and survival, glucotoxicity is proposed to have both reversible and irreversible components.
- Iatrogenic hyperglycaemia causes a rapid decline in serum insulin concentrations, and β -cell apoptosis, in healthy cats, suggesting that glucotoxicity might play a role in the development of feline DM
- Proposed mechanisms of glucotoxicity, based on in vitro studies, include:
  - depletion of intracellular insulin stores, which can be replenished by β -cell rest,
  - endoplasmic reticulum stress, which might lead to β -cell apoptosis and impaired insulin signaling

- Lipotoxicity refers to the potential deleterious effects on β -cell function and mass that might result from excessive fatty acid exposure.
  - This synergistic, deleterious effect is attributed to hyperglycaemia directing cellular metabolism away from fatty acid oxidation, leading to a cytosolic accumulation of fatty acid derivatives, which can contribute to β -cell dysfunction.
  - In cats, infusion of fatty acids failed to cause glucose intolerance based on the results of IVGTT performed after 10 days of lipid infusion.
  - However,cats receiving lipid infusion had higher glucose concentrations when compared with saline-infused cats, whereas insulin concentrations did not differ in these 2 groups, suggesting that some impairment of β -cell function might have been present.
  - Never-the less, the insulin-positive area on pancreatic islet immunostaining did not differ between lipid- and saline-infused cats, and β -cell apoptosis was not documented after 10 days of lipid infusion, indicating that hyperlipidaemia alone might not play a major role in the development of DM.
  - However, as this was a short-term exposure(10 days) in previously healthy research cats, it is unknown whether glucolipotoxicityis a pathogenic mechanism in the development of feline DM if present over longer time periods

Islet Amyloidosis

- extracellular amyloid deposition within the islets of Langerhans, which is a common histologic change in diabetic cats.

- Islet amyloid is formed from insoluble, polymerized fibrils of the b-cell secretory product, amylin, which is co-secreted with insulin.
- However, the role that amyloid deposits play in the development of feline DM is controversial because the pancreata of nondiabetic cats can show a similar degree of amyloidosis.
- In vitro research suggests that amyloid-related b-cell death during the development of DM might be caused by toxic amylinoligomers, which form secondary to ER stress and abnormal protein folding, rather than by mature amyloid deposits.
- Islet amyloid deposition is therefore not considered to be a primary cause of DM in cats, but could contribute to islet damage

<u>Diabetogenic Drug Treatment</u>
- Glucocorticoids

<u>Other Endocrinopathies</u>
- Hypersomatotropism
- Hyperadrenocorticism

<u>Pancreatitis</u>
- Cause or consequence ??
- Experimental hhyperglycaemia is shown to increase pancreatic neutrophil count – so it is possible that chronic hyperglycaemia in cats with DM contributes to pancreatic inflammation rather than pancreatitis being a major cause of DM in cats

<u>Genetics</u>
- Burmese UK, Europe and Australia but not in Burmese in America
- Other breeds Tonkinese, Norwegian Forest , Russian Blue and Abyssinian
- A single candidate gene study in diabetic cats has been published, which identified a nonsynonymous single nucleotide polymorphism (SNP)in the coding sequence of feline melanocortin-4 receptor gene (MC4R:c.92C>T) to be associated with type 2–like DM in overweight domestic shorthair (DSH) cats.
    - Variants of this gene are also associated with obesity and type 2 DM in people.
- Three GWAS of DM in cats have been published to date, including 1 in DSH cats and 2 studying DM in Burmese cats

<u>Epidemiologic Risk Factors</u>
- Decreased physical activity/indoor confinement
    - Exercise increases insulin sensitivity, and sedentary lifestyle is also a risk factor for obesity in people, explaining the link between DM and reduced physical activity
- Increasing age – associated with obesity, HS and HA
- Male (but not increased if Burmese)
    - This might be due to male cats' tendency to have lower insulin sensitivity when lean, and a greater increase in body weight when fed ad libitum, compared with female cats
- One study found feeding dry food was a risk factor for DM,

- whereas another did not find such an association.
- The former study identified dry food as a risk factor for DM in normal weight cats only, whereas overweight cats were predisposed irrespective of diet type.

PREDIABETES IN CATS

- Abnormal glucose homeostasis
- The European Society of Veterinary Endocrinology ALIVE Project working group recently commented that there is currently insufficient evidence on prediabetes in cats (and dogs) to draw conclusions on its clinical relevance.
- However, their guidelines recognize the possibility of subclinical DM.
- Because of inability to accurately apply a diagnosis of prediabetes in cats, much of this section refers to subclinical DM in cats
- Identifying cats with subclinical DM is challenging for several reasons.
  - mild elevations are challenging to interpret and often attributed to stress hyperglycaemia.
  - In most cases, the diagnosis of DM is only made when a cat is presented to a veterinarian for clinical signs referable to DM.
  - Recognizing cats with subclinical DM, in which these signs might be absent, is therefore difficult.
  - The presence of predisposing factors for DM, such as obesity, cannot be used as an indicator of prediabetes (i.e., increased future risk of DM in cats), as many individuals with diabetogenic risk factors will maintain normal glucose tolerance as long as β -cell compensation remains sufficient
  - In people, the criteria for diagnosing prediabetes vary between major health care organizations and are based on several indicators of glycaemic control, including FPG, HbA1c, and OGTT results.
  - However, the use of similar measures of glucose tolerance as accurate markers of prediabetes in cats presents challenges.
  - Reference intervals for capillary glucose concentration both at the time of hospital admission and following an 18-to 24-hour fast have been suggested for healthy senior cats that were 8 yearsold.
    - This revealed a reference interval of 67 to 189 mg/dL (3.7–10.5 mmol/L) for admission BG, and an upper limit of 116 mg/dL (6.4 mmol/L) for fasting BG,
    - authors suggested that cats with an admission BG of greater than 189 mg/dL(10.5 mmol/L) should undergo fasting glucose measurement to assess for persisting hyperglycemia.
    - The same group also proposed a methodology and cut points for using fasting BG after an 18- to 24-hour fast, and BG 2 hours after administration of 0.5 g/kg glucose IV, to assess for prediabetes in cats.
    - This study suggested a similar upper limit for fasting glucose of 117 mg/dL (6.5 mmol/L), and an upper cut point for 2-hour glucose of 176.4 mg/dL (9.8 mmol/L).
    - Seven of the 51 (13.7%) overweight/obese cats in this study had a 2-hour BG above the proposed upper cut point, but only one of these had increased fasting glucose.

        - However, it is unknown whether any of these cats developed DM in the future, and the findings of this study cannot be used as diagnostic criteria for prediabetes in cats.
        - To the authors' knowledge, no studies have prospectively examined the ability of any markers of glycaemic control to predict the development of DM in cats, making it currently impossible to apply a diagnosis of prediabetes in cats as is done in people
- The appropriateness of both OGTT and IVGTT to assess glucose homeostasis in cats has been questioned because carbohydrate digestion in cats bears several differences to other species as a result of cats' evolution as carnivores.
    - In people, OGTTs are used to assess glucose tolerance as they assess the incretin effect, which accounts for a substantial component of post meal insulin secretion.
    - The incretin effect refers
        - augmentation of insulin secretion, which is seen following an oral glucose load compared with IV glucose administration.
        - This effect occurs because of secretion of the gastrointestinal hormones glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) following feeding.
    - Differences in incretin secretion between cats and people following an oral glucose load might contribute to the difficulties in interpreting OGTTs in cats.
    - The incretin effect is estimated to account for at least 50% of total insulin secretion following glucose ingestion in healthy people, but only 30% in healthy cats.
    - This difference might be caused by lack of GIP secretion following glucose ingestion in cats, whereas in people, GIP is responsible for most of the incretin response to oral glucose.
    - The lack of GIP response to glucose in cats might be explained by their inability to sense glucose as a result of pseudogenization of the Tas1r2gene, the gene encoding for the sweet taste receptor.
    - One study reported substantial overlap between OGTT results in obese and lean, age-matched cats, although it was unknown how this related to these cats' insulin sensitivity.
    - OGTT is also impractical in cats, as it requires feeding tube placement

Diabetic Remission

- If beta cell failure is the final step in the development of prediabetes/DM , it seems reasonable that diabetic remission occurs when beta cell compensation returns to a level that can sustain glucose tolerance once again
- This return of beta cell compensation might be due to improvements in beta cell function , improvement in insulin sensitivity , decreased glucose load or a combination of these 3 factors
- 2 aspects that have been considered to have an important influence on the development of feline diabetic remission include reversal of glucotoxicity and whether the cause of the cats DM allows for improvements or reversal in any of the 3 factors stated above

- Reversal of glucotoxicity and diabetic remission in cats is shown to be accompanied by a return of insulin secretion during IVGTT
- Greater likelihood of diabetic remission in cats that have
    - shorter duration of DM
    - less severe hyperglycaemia at dx
    - achieve good DM control more promptly -> likely due to lower degree of glucotoxicity and therefore have greater potential for beta cell recovery

- Diabetic neuropathy has been associated with a decreased likelihood of remission, possibly because affected cats typically have poor long term DM control and therefore a greater risk of prolonged glucocotoxicity

- Insulin type
    - little evidence to strongly recommend the use of 1 insulin type over another.
    - Proposals that glargine and detemir are associated with particularly high remission rates is largely based on studies that examined a select group of cats who also received intensive home BG monitoring and ultra-low-carbohydrate diet, making it challenging to extrapolate these results to other populations.
    - PZI, the evidence for achieving high remission rates can only be derived indirectly from a study looking at the effect of different dietary carbohydrate contents on remission rates.
        - In this study, 85% of cats were treated with PZI, alongside moderate- or low-carbohydrate diet,
        - high remission rates achieved in both groups,
        - although somewhat higher with the low-carbohydrate diet.
        - However, this study was not designed to assess the effect of insulin.
    - It is assumed that the longer duration of action of glargine, detemir, and PZI when compared with lente insulin in cats might provide better glycaemic control and limit glucotoxicity
    - It is therefore currently unproven whether any single insulin type offers better control, and greater likelihood of remission, than others.
- There is also reasonable evidence that feeding a carbohydrate-restricted diet promotes better glycaemic control, and a greater chance of remission, in diabetic cats
    - Dietary carbohydrate restriction decreases postprandial hyperglycaemia and mean BG in healthy cats.
    - Similarly, beneficial effects in cats with DM could aid in reducing glucotoxicity, besides other effects, including reduced glucose load leading to decreased insulin requirements
    - These effects might account for why studies reporting the highest rates of feline diabetic remission have typically fed diets containing a maximum of 12% metabolizable energy as carbohydrate

<u>DM Cause</u>

- Remission is likely to be encouraged by improvement, or resolution, of pathogenic factors that contribute to a cat's DM by causing IR, impaired β -cell function, or increased glucose load.
    - Examples of diabetogenic factors, which have been linked toa greater likelihood of remission if adequately treated, include obesity in cats with type 2–like DM, and several causes of "other specific types of DM," including recent glucocorticoid therapy, and the presence of HS or naturally occurring HA.

- There is initial evidence to support that planned weight loss encourages remission in diabetic cats who are overweight.
    - This could be due to improvements in obesity-related IR, or resolution of other factors associated with an overweight state (see earlier section on "Obesity").
    - One study found a greater likelihood of remission among cats who achieved at least 2% weight loss in the first month of treatment with either every 12-hours PZI or glargine.
    - Cats with a higher percentage body fat, measured by dual-energy X-ray absorptiometry, have also been demonstrated to have a greater chance of remission, which was usually associated with an eventual reduction in their percentage body fat.
    - Controlled weight loss should therefore form part of the treatment plan for overweight or obese diabetic cats once DM-associated weight loss has stabilized.

- Cats with DM secondary to HS or naturally occurring HA typically show a poor response to standard DM management, but can achieve DM remission if their underlying HS or HA is adequately controlled.
    - This includes DM remission rates of 60% to 90% reported in cats with HS-associated DM treated using transsphenoidal hypophysectomy (see separate article in this issue).
- Several studies have found that diabetic cats that have previously received glucocorticoids have a greater likelihood of remission compared with cats without a history of glucocorticoid treatment, which could be due toa return of normal glucose tolerance once the diabetogenic effects of their glucocorticoid therapy wane

GLUCOSE TOLERANCE IN DIABETIC REMISSION

- It is likely that many cats in diabetic remission have ongoing glucose intolerance despite being able to maintain euglycemia without the need for antihyperglycemic therapy.
- A previous study found that approximately 20% of diabetic cats in remission were hyperglycemic (defined as BG > 6.5 mmol/L [117 mg/dL]) after a 24-hour fast, and approximately 74% had abnormal glucose clearance based on IVGTTs.
- Diabetic cats in remission also had significantly greater serum fructosamine concentrations than healthy control cats.
- Ongoing glucose intolerance likely contributes to the high rate of DM relapse (26%–30%) among cats in diabetic remission.

- Identifying which cats in diabetic remission might have ongoing glucose intolerance is associated with the same challenges discussed under “Prediabetes in Cats.”
- To limit the chance of DM relapse, it is advisable that potential causes of IR, increased glucose load and β ell dysfunction, are avoided, as much as possible, in the management of cats in diabetic remission
- Cats in remission should also be carefully monitored for DM relapse.

The Future of Diabetes Therapies

New Insulins and Insulin Delivery Systems, Glucagon-Like Peptide 1 Analogs, Sodium-Glucose Cotransporter Type 2 Inhibitors, and Beta Cell Replacement Therapy

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Ultra-Long-Acting Insulin

- Duration of action greater than 24 hr
- Less intra and inter-dose variability -> allows tighter glycaemic regulation and decrease the risk of hypoglycaemia
- Used in people as basal-bolus protocols (ultra long acting dosed and then short acting at meal times)
- Insulin glargine U300(Toujeo, Sanofi) and insulin degludec (Tresiba , novo Nordisk)
- Insulin glargine U300
    - contains the same insulin analogue as insulin glargine U100 (eg, Lantus, Semglee), but in a threefold more concentrated solution, forming a denser subcutaneous depot, which slows insulin release.
- Insulin degludec
    - human insulin analogue with a fatty acid moiety, which facilitates the formation of subcutaneous depots and increases protein binding.
    - These features delay absorption, provide a flatter time-action profile, and reduce day-to-day variability in glucose con-centrations.
- Information about veterinary use of insulin glargine U300 and insulin degludec can be found in “Insulin Therapy 1: General Principles”, “Insulin Therapy2: Dogs”, and “Insulin Therapy 3: Cats” in this issue
- Insulin icodec
    - once-weekly, ultra-long-acting, basal insulin currently in phase 3 trials in human patients.
    - It’s extremely long half-life(196 h in people) and duration of action are attributable to strong, reversible albumin binding, reduced enzymatic degradation, and slow receptor-mediated clearance.

    - In preclinical trials, insulin icodec had an average half-life of 60 h in dogs so, although weekly administration seems unlikely, alternate or every third-day administration might be a possibility.
    - Insulin icodec has not been evaluated in cats so, given the large species differences in pharmacokinetic properties (rat t1/2526 h), it is impossible to predict how this insulin will behave in feline patients
- Another approach is the development of synthetic polypeptides in which insulin is expressed as a fusion protein with the Fc portion of immunoglobulin.
    - The Fc region binds to the neonatal Fc receptor allowing intracellular trafficking and recycling of the molecule , which significantly extends the insulins half life
    - An insulin-feline Fc fusion protein was recently evaluated in five diabetic cats, administered subcutaneously once weekly for 7 weeks.
    - In this pilot study, cats showed adequate glycaemic control without significant clinical signs of DM, clinical hypoglycaemia, or adverse effects- not commercially available

Glucagon-like peptide 1-based therapies

- Glucagon-like peptide 1 (GLP-1) is an incretin hormone secreted by L cells in the intestines in response to luminal nutrients, bacterial products, and secondary bile acids.
- Following a meal, GLP-1 acts as an “early warning system,” preparing the rest of the body for the nutrient load, particularly glucose, about to arrive via the portal circulation.
- In the pancreas, GLP-1 increases insulin secretion by sensitizing beta cells to glucose stimulation and decreases glucagon release by alpha cells.
- It also increases satiety by delaying gastric emptying and suppressing appetite.
- These features make GLP-1 an attractive strategy for diabetic therapies

- Glucotoxicity and beta cell dysfunction are key features of feline DM.

- GLP-1 both inhibits beta cell apoptosis and promotes beta cell differentiation and proliferation. Effect on feline patients unknown

- One possible reason these drugs are so effective in people is that treatment of T2DM is generally initiated early in the course of the disease, when significant beta cell mass still exists.

- In cats, DM is usually detected with the onset of clinical signs, after widespread beta cell loss has occurred.

- Although GLP-1 analogues help maximize the function of the remaining tissue, optimal use might only be achieved when paired with early detection strategies, which have yet to be implemented in cats.

- Another important consequence of this difference in management is that, in human patients,GLP-1 analogues can be used as a single agent or in combination with other non-insulin glucose-lowering drugs.

- However, based on current experience, these drugs need to be combined with insulin to achieve appropriate glycaemic control in cats.

- Exenatide (Byetta, Astra-Zeneca) is a synthetic version of a peptide originally isolated from Gila monster venom with a high affinity for the GLP-1 receptor and intrinsic resistance to proteolysis byDPP-4.

    - Subcutaneous exenatide lowers blood glucose and increases insulin secretion in healthy cats in a dose-dependent manner.
    - An extended-release, depot formulation (exenatide ER; Bydureon, AstraZeneca) is available that allows for once weekly administration, which results in fewer gastrointestinal side effects in both people and cats compared with the twice daily immediate-release formulation.
    - Three small randomized, controlled, clinical trials have evaluated exenatide or exenatide ER in diabetic cats in combination with insulin and dietary therapy
    - From these the major effect on exenatide appears to be on body weight rather than glycaemic control (either lost weight or maintained wt compared with placebo but no stat signif difference in glycaemic control or diabetic remission rates)
    - When treated with immediate-release exenatide, cats did have a lower median daily insulin requirement and exenatide ER lowered glycaemic variability, which could reduce the risk for hypoglycemia.
    - Thus, despite its lack of impact on primary diabetic outcomes, exenatide may still have certain benefits for feline patients.
    - Recently, two novel exenatide delivery systems have been developed for cats:
        - a once-monthly, microsphere-based, subcutaneous injection and a subcutaneous implantable device that could last up to 6 months.
        - These systems could have the potential to enhance diabetic regulation while minimally impacting owner treatment burden, but they require further study.
- Two other GLP-1 analogues have also been evaluated in small animals, both administered once daily.
    - Liraglutide (Victoza, Novo Nordisk)
        - GLP-1 analogue with a fatty acid residue that increases plasma protein binding and extends duration of action.
        - In healthy cats, liraglutide increases insulin secretion and decreases body weight, but its effects have not been evaluated in diseased animals.
        - A single dose of liraglutide also showed glucose-lowering effects in a small cohort of diabetic dogs but multidose studies are needed.
    - Lixisenatide (Adlyxin, Sandofi),
        - which is structurally related to exenatide, decreased glucose concentrations in a single-dose study in healthy dogs.

SODIUM-GLUCOSE COTRANSPORTER TYPE 2 INHIBITORS

- SGLT-2 exert their glucose-lowering effect by preventing glucose resorption in the proximal renal tubule, causing significant glucose elimination in the urine.
- As such, this is the only family of antidiabetic drugs that exerts its glucose-lowering effect in an insulin-independent manner.
- Can be used for type 1 diabetes when mono therapy with insulin alone results in poor glycaemic control
- In addition to their effects on glycaemic control, SGLT-2 inhibitors have significant health benefits for patients with cardiac and renal disease.
    - They facilitate both weight and blood pressure reduction in human patients.
    - SLGT-2 inhibitors slow the progression of diabetic nephropathy by increasing distal tubule sodium delivery, normalizing glomerulotubular balance, and decreasing glomerular hyperfiltration.
    - They also have a positive impact on cardiovascular outcomes. A variety of mechanisms likely contribute to this effect including increased diuresis and natriuresis, weight and blood pressure reduction, improved cardiac energy metabolism, and altered autonomic nervous outflow.
    - These benefits are supported by several, large, randomized controlled clinical trials, which have led to the recommendation that SGLT-2 inhibitors be used as first-line agents in T2DM human patients with heart failure or chronic kidney disease.
- two studies have investigated SGLT-2 inhibitors in diabetic cats
    - A single-arm trial evaluated bexaglifloxin, which was recently approved for cats by the FDA, as an add-on therapy in 5 cats with poorly controlled DM.
        - Mean blood glucose and insulin dose significantly decreased over 4 weeks of treatment and clinical signs were improved or resolved in all 5 cats.
    - A recent randomized, clinical trial compared once-daily oral velagliflozin to twice-daily insulin injection in diabetic cats (n513 per group).
        - Cats in both groups showed similar improvement in clinical and biochemical outcomes.
    - Larger trials are needed, but these preliminary results are quite promising.
- The renal effects of SGLT-2 inhibitors in cats are also under investigation.
    - Whether or not diabetic nephropathy occurs in small animals is unclear but, regardless, chronic kidney disease is very common in elderly animals.
    - If SGLT-2 inhibitors have renoprotective effects in feline DM, as they do in human DM, this could be an additional benefit for cats with comorbid chronic kidney disease
- An important consideration for the potential use of SGLT-2 inhibitors in cats and dogs is the adverse effect profile.
    - Although multiple adverse effects have been attributed to these drugs, the ones supported by large clinical trials and meta-analyses in people are fungal genital infections and increased risk for diabetic ketoacidosis, the latter more commonly occurring in insulin-dependent patients.

- SGLT-2 inhibitors also induce diuresis, which can lead to clinical polyuria.
    - This is often transient, but some patients do require drug discontinuation.38If SGLT-2 inhibitors induce significant polyuria and polydipsia in diabetic animals, it may limit their therapeutic potential, particularly because resolution of clinical signs is a major indicator of diabetic regulation.
    - Investigators disagree on whether SGLT-2 inhibitors induce polyuria and polydipsia in healthy cats.
    - The discordance may be explained by study differences in drug, drug dose, population characteristics, or other methodological disparities.
    - Water consumption and urine output were not explicitly reported in the clinical diabetic cat studies, but polyuria and polydipsia were not reported as overt adverse effects.
- In the second clinical trial, 8/13 cats treated with velagliflozin developed soft stools, half of which resolved without intervention.
    - Thus, gastrointestinal signs may be an important adverse effect of SGLT-2 inhibitors in this species, potentially due to off-target inhibition of the SGLT-1 isoform expressed in the intestines.

NON-INJECTABLE INSULINS

- frequent injections significantly and negatively impacts the quality of life for both people with DM and owners of diabetic pets
- Currently, the only FDA-approved, non-injectable insulin product is Afrezza (MannKind Corp.).
    - Afrezza is an inhalable, ultra-rapid-acting, recombinant human regular insulin.
    - Following administration with an inhaler, Afrezza passes through the thin alveolar lining and is rapidly absorbed through pulmonary circulation.
    - By this mechanism, it quickly reaches peak effect, comparable to injectable ultra-rapid-acting insulin analogues.
    - Afrezza is a prandial insulin and, in people, must be paired with a long- or ultra-long-acting insulin to achieve glycaemic control throughout the day, similar to a basal-bolus protocol.
    - Such a protocol might be feasible for some veterinary patients and insulin is absorbed by the inhaled route, at least in cats.
    - However, the Afrezza inhaler device does not contain an actuator and functions solely on passive inhalation, so cannot be used with spacers that allow traditional inhalers to be adapted for veterinary patients
- Oral insulin would be ideal but two major barriers exist to insulin administration via the oral route.
    - First, insulin is a polypeptide susceptible to degradation by gastric acid and digestive enzymes.
    - Second, insulin is much larger than typical non-peptide drugs and so is relatively impermeant through mucosal surfaces.
    - Strategies to overcome these barriers include co-formulation with enzyme inhibitors and/or absorption enhancers, which target the tight junctions of the intestinal epithelium to facilitate paracellular drug uptake.

- Microsphere and nano-capsule technologies have also been used to protect insulin molecules from degradation in the gastrointestinal tract.60An important consideration is that, despite these approaches, oral insulin bioavailability is currently very low compared with parenteral insulin, which increases dose requirements and cost

CONTINUOUS INSULIN INFUSION

- These devices contain a reservoir of rapid- or ultra-rapid-acting insulin that is administered at an adjustable rate and through a subcutaneous cannula, either connected by an infusion line or with the pump attached directly to the body.
- A basal infusion rate is set to deliver insulin throughout the day and intermittent boluses can be administered through the same infusion set at mealtimes.
- When used correctly ,these devices eliminate the need for multiple daily insulin injections.
- In addition, the basal rate can be adjusted as needed, allowing improved glycaemic control and decreasing the risk for hypoglycaemia
- pump and infusion set are too cumbersome for a dog or cat to wear without risking disconnection.
- Infusion sets require frequent changing and rotation of sites on the body to prevent the development of fibrotic tissue, which could block insulin absorption at the insertion site.
- Species differences in skin thickness and composition might further complicate the adaptation of insulin pumps for dogs and cats.
- However, because infusions sets come with varying insertion cannula lengths and angles, and made of either steel or soft Teflon, it is possible that an infusion set could be found that would work well for a given veterinary patient
- insulin patches and pods (eg, OmniPod, Insulet Corp.).
    - These devices are similar to insulin pumps but have a smaller profile and the reservoir attaches directly to the skin with an adhesive, eliminating the need for an infusion line.
    - They can also deliver insulin at very low rates, which might be beneficial for very small patients that could not otherwise benefit from insulin infusions.
    - Given these features, insulin patches and pods seem a viable strategy for small animals;
    - however, tampering with the device (eg, chewing, rubbing)could cause inadvertent insulin boluses and hypoglycaemia, so safety should be carefully evaluated before adaptation for veterinary use

SMART INSULIN

- refers to therapies in which a technology regulates insulin release or effect.
- Currently available smart technologies include smart insulin pens, smart pen caps, and open- and closed-loop systems.
- Smart insulin pens are pens with an electronic component built-in, whereas pen caps are electronically-enabled devices that can be added onto a standard insulin pen.
- Features include tracking dose amount and dose timing as well as measuring remaining insulin in the pen. These devices help reduce missed doses and could be readily applied in veterinary medicine to improve owner compliance.

- Some insulin pens also integrate with continuous glucose monitors (CGMs) to suggest dose adjustments. These systems would require a close evaluation and probable modification for canine and feline diabetics because the algorithms that derive the dose recommendations are specific to human physiology
- The integrated smart pen is an example of an open-loop system in which a CGM tracks glucose concentrations and calculates a new insulin dose, which the patient then administers.
- Continuous insulin infusion pumps are also commonly integrated into open-loop systems, in which the operator manually adjusts the infusion rate based on CGM recommendations.
- The next advancement in smart insulin technologies is the closed-loop system in which a CGM communicates directly with the insulin pump to adjust the infusion rate.
- The basal rate is adjusted automatically based on measurements from the CGM, and prandial insulin doses are calculated by the pump based on user input of carbohydrate amounts consumed in a given meal.
- Fully automated, closed-loop systems (ie, the artificial pancreas) that do not require direct user input are in development.
- However, accurately delivering prandial insulin is more complicated than basal insulin because it requires predicting blood glucose based on interstitial glucose concentrations and accounting for the time to onset of subcutaneously administered insulin.
- A fascinating innovation in this technology is the bi-hormonal system, which delivers both insulin and glucagon in response to CGM measurements. In experimental trials, these devices reduce the incidence of hypoglycaemia, particularly during exercise or sleep.
- Closed-loop systems compound the translational concerns of dosing algorithms and infusion pumps for use in cats and dogs. However, if these hurdles are overcome, such systems may become a treatment option, especially for clients interested in intensive diabetic management. A highly innovative strategy in smart insulin technology is the development of glucose-responsive insulin formulations, which intrinsically sense glucose concentrations and alter the release or action of insulin.
- In the matrix-based approach, insulin molecules are embedded in a resin or polymer, usually administered as a subcutaneous depot or transdermal patch.
- The matrix has glucose-responsive chemicals or enzymes that release insulin proportionately to the glucose concentration in surrounding milieu. In the molecular approach, the insulin molecule itself contains a glucose-responsive element. Some compounds change their pharmacokinetics based on blood glucose concentrations, particularly by altering plasma protein binding or by changing drug clearance.
- Others smart analogues undergo a conformational change to expose the insulin receptor binding site in the presence of hyperglycaemia. These technologies are still in their infancy and their commercial viability is untested. However, if they do eventually come to market, they could be an attractive “smart” option for dogs and cats because they eliminate the need for external devices

BETA CELL REPLACEMENT THERAPY

- Standard therapy for T1DM assumes that, once beta cell mass is gone, it cannot be replaced, and exogenous insulin must be supplemented life-long. In contrast, beta cell replacement therapy attempts to restore endogenous insulin secretion. Trans-planted beta cells can sense glucose and respond appropriately, sometimes in concert with other secretory islet cells, leading to tighter and more natural glycaemic regulation. Practical considerations and complications have thus far limited wide-spread beta cell replacement therapy in human diabetic patients, let alone veterinary species.
- Traditional beta cell replacement involves transplantation of either whole pancreas or isolated pancreatic islets from an organ donor.
- In human patients, insulin-independence rates are as high as 60% to 80% at 10 years post-transplantation.
- Serious complications can occur including technical failures and acute rejection.
- Immunosuppression is generally required to prevent transplant rejection, which increases the risk for opportunistic infections, although novel techniques are in development that may reduce or eliminate this requirement.
- Donor sourcing would also be a particular problem for small animal patients because, although cadaveric isolation techniques have been developed for dogs, the large infrastructure for human transplantation does not exist in veterinary medicine.
- Future beta cell replacement therapies likely revolve around cellular techniques.
- Both mesenchymal and induced pluripotent stem cells can be differentiated into beta-cell-like cells in culture.
- Once again, dogs feature prominently in preclinical development for potential therapies. If these new approaches are clinically successful in human medicine, they have the possibility to be translated to small animal diabetic patients in the future

Evaluation of bexagliflozin in cats with poorly regulated diabetes mellitus

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Introduction

- Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a newer class of orally administered antidiabetic agents that inhibit glucose absorption from the kidney.
- SGLT2 is located within the early proximal tubule and is responsible for 90% of renal glucose reabsorption
- Inhibition of renal glucose reabsorption has the highly desirable effect of lowering blood glucose with minimal risk of inducing hypoglycaemia
- The SGLT2 inhibitors dapagliflozin and velagliflozin have been evaluated in healthy cats and found to be well-tolerated and result in significant urinary glucose excretion without inducing hypoglycaemia
- Bexagliflozin is a potent and highly selective SGLT2 inhibitor that has completed phase-3 clinical trials in adults with type-2 diabetes mellitus and is waiting for approval from the Food and Drug Administration (FDA).

- Pharmacokinetic and pharmacodynamic studies conducted in healthy research cats showed that bexagliflozin yielded similar results to prior studies of SGLT2 inhibitor use in cats

Aim

- investigate the effect of bexagliflozin on glycaemic control in poorly regulated diabetic cats and to evaluate for adverse events associated with this medication.
- Hypothesis was that bexagliflozin would lower both blood glucose and serum fructosamine concentrations and would be well-tolerated in cat

Materials and Methods

- 5 client owned cats with poorly regulated DM
- Considered poorly regulate if PU/PD, polyphagia and wt loss in addition to a nadir blood glucose conc of >250 mg/dl despite insulin dose adjustment over a minimum period of 8 week before enrolment
- Exclusion
    - <2 yr or >15 yr
    - Wt <3.0kg
    - CKD Iris stage ≥2
    - Elevated serum TBIL
    - Elevated ALT ≥ 2.5 x RI
    - Active urinary infection
    - Use of corticosteroids with past 8 weeks
    - CHF
    - Uncontrolled hyperT
    - Hx of DKA with in the proceeding 2 mth

- included if had hx of LUTI if the infection responded to a course of antibiotics and the urine culture was negative at the time of enrolment following the discontinuation of ab

- 4 week study period with designated time points measurement on Days 0, 14 and 28

- Day 0 – Hx, (diet), PEx, Bwt, BCS , MCS, CBC, MBA, UA , U aerobic culture(cystocentesis) , TT4 , BGC(BG q 2hr for 19hr using alpha trak) and serum fructosamine

- Mean BG conc was calculated as the average of 5 blood glucose measurements that were obtained during the 10 hour BGC

- At discharge on Day 0 all owners were shown how to measure blood glucose conc at the home using the alpha trak and asked to measure BG BID and at times of suspected hypoglycaemic events

- All cats remained on their typical diet and type/brand of insulin

- To minimise the risk of hypoglycaemia the insulin dose was reduced by 50% on Day 0 and further reductions were based on BG conc obtained from at home and in hosp assessments

- Hypoglycemia was defined as the presence of supportive clinical signs and/or BG ≤60mg/dL

- Owners were advised to check BG prior to insulin and reduce dose by at least 25% if BG was persistently 100-200mg/dL and t withhold insulin if BG <100 mg/dL

- Owners were required to record at home BG readings at each scheduled hospital visit on Days 0,14 and 28 and complete a questionnaire about the insulin dose and times and dates of bexagliflozin admin

- Changes to thirst, urination , attitude ,appetite and any additional abnormalities

- Bexagliflozin was dispensed to the owners, with instructions that it be started on Day 1

- The first cat received a dose of 10 mg, PO, q24h.

- Subsequent cats received 15 mg, PO, q24h based on further research by the manufacturer that demonstrated maximal renal glucose excretion at the higher dose

- Follow-up evaluations on Days 14 and 28 included a history, physical examination, body weight, BCS, MCS, BGC, serum biochemical profile, and serum fructosamine, in addition to a CBC on Day 28.

- Serum was collected on Days 0, 14, and 28 for measuring beta-hydroxybutyrate (b-OHB)

Results

- 9 month study period
- Breeds DSH =2, DLH =2 , Siamese =1
- range 5-10 years , median 8 yr
- 4 MN and 1 FS
- Median body wt 6.7kg (3.2-7.8kg)
- Median BCS 7 (3-8)
- Comorbidities – dental disease , HCM , IBD and asthma
- 1 cat with HCM on clopidogrel and lisinopril and also had IBD controlled with diet and probiotic therapy , as well as asthma that is managed with environmental modification
- Median insulin treatment duration was 86 days prior to enrolment
- 4 cats were on prescription diets for DM
- 1 cat on feline maint diet dry and canned

- All cats on glargine SQ q12hr at day 0 median insulin dose was 0.67 U/kg Bwt (0.53-1.56 U/kg BW q12hr)

Base line dx

- Day 0 CBC wnl for all cats
- MBA – all hyperglycaemic and glucosuria , no ketonuria , 1 cat had mild increase LAT 1.07x RI but was stable for 2 months at that level
- Median beta OHB 0.14 mmol/L (0.00-0.18 mmol/L) and median fructoasmine conc was 507 umol/L (410-594 umol/L)
- Median BG conc during hospital BGC was 380 mg/dL (312-479 mg/dL)

Response to tx with bexaglifozin

- MBG conc from in hosp BCGs decrease significantly during the 4 week study period
- Median decrease in MBG was 193 mg/dL (range 81-313 mg/dL)
- Serum fructosamine conc decreased in 4 of the 5 cats with a median decrease of 152 umol/L (range 103-241 umol/L) although this did not reach statistical significance
- Insulin dose was decreased significantly in all cats during the study period , median insulin dose decreased 0.55 U/kg (0.52-0.99 U/kg)
- Insulin was discontinued in 2 of the 5 cats on day 14
- Median beta OHB conc increased 0.33 mmol/L (0-1.31 mmol/L) which was not stat significantly
- Median serum BG conc decreased significantly during the study period , total can conc increased but still within ref range , ALKP decreased signif during the study period , anion gap increased signif
- No cat had any documented episodes of hypoglycaemia at home or in hosp or reported CSx
- Owners of the 3 cats reported that Csx were resolved at the end of the 28 day study period
- Clinical signs reported in the remaining 2 cats included PU/PD and polyphagia although reportedly improved based on subjective client assessment
- Wt loss stopped in 3 cats during the study period whereas the remaining 2 cats lost 0.09kg and 0.25kg which was a % wt loss 2.3 and 3.8% - not stat significantly
- There was no change in BCS during the 28 day study period

Adverse effects

- No significant adverse effects
- One cat with hx of pancreatitis developed hyporexia on the last day of the study .
    - This cat also experienced a marked progressive increase in TG conc at day 14, day 28 compared to day 0 as well as increases in beta OHB conc from Day 0 0.15mmolL to day 28 1.46mmol/L

Long term follow up

- Insulin was discontinued in 2 cats during the study
- One of these cats continued to receive bexagliflozin for over 2 yr and receiving this medication as sole therapy when this article was submitted

- The other cat received bexaglifozin for an additional 5 wk until it was stopped and insulin was restarted due to the development of small bowel diarrhoea that the owner reported as moderately severe
    - The diarrhoea resolved after bexagliflozin was discontinued
    - this cat had a hx of IBD and prior episodes of D
- The cat receiving 10mg of bexagliflozin once daily continued to require insulin therapy for the duration of the 4 week study period .
    - On completion of the study the dosage was increased to 15mg and insulin discontinued , with successful management of DM for further 17 mths until an episode of pancreatitis resulted in the need to supplement with 1IU of insulin glargine BID to control hyperglycaemia
- The 4th cat continued on 1IU insulin bid in addition to bexagliflozin until hyporexia developed at day 28.
    - Immediately after the trial discontinued bex and insulin 2 IU given and hyporexia ceases .
    - 1 month post study bloods revealed marked increase in TG and this cat was gradually increased to 4 IU of glargine BID which resulted in ongoing control of CSx of DM
- 5th cat was continued on 2IU of glargine BID in addition to bex after completion of the study due to ongoing clinical improvement of DM .
    - Bex was discontinued due to concerns about diarrhoea , but the diarrohea did not improve , insulin was increased to 4IU BID after bex discontinued

Discussion

- Showed that the oral administration of the SLGT2 inhibitor, bexagliflozin, significantly lowered blood glucose and insulin dose in poorly regulated diabetic cats over a 28-day period. Insulin was discontinued in 2 out of 5 cats.
- Although serum fructosamine concentration decreased in 4/5 cats during the study period, this decrease did not reach statistical significance.
    - This could be due to the small number of cats in this study and lack of power to reach statistical significance.
    - Additionally, fructosamine concentrations can vary among individual cats and may be influenced by non-diabetic factors, including body weight, sex, serum protein concentration, and hydration status.
- Three cats in the study did experience asymptomatic ketosis as evidenced by elevations in β -OHB during the study.
    - This is not unexpected as mild elevations of β -OHB would likely result from decreased exogenous insulin until β- cell recovery and improvement in endogenous insulin secretion occurs
    - Given the mechanism of action of SGLT2 inhibitors, the body must be able to produce some endogenous insulin to allow complete withdrawal of exogenous insulin or else ketosis will ensue.
    - Advise monitoring ketones in cats receiving SGLT2 inhibitors esp if signs of illness
    - Although the elevations in b-OHB in this group of cats were not high enough to be considered clinically significant, we cannot rule out the possibility that ketonemia may have contributed to the hyporexia observed in 1 cat at the end of the study.

        - This cat also experienced marked hypertriglyceridemia at Day 28, however, which may have contributed to clinical signs of hyporexia.
        - Hypertriglyceridemia in this cat may have been due to lack of adequate insulin production.
        - Although we cannot rule out the possibility that hypertriglyceridemia is an adverse effect related to the use of SGLT2 inhibitor in cats, SGLT2 inhibitors have been shown to reduce serum triglyceride levels in humans and mice
- In clinical trials of SGLT2 inhibitors in humans with type-2 diabetes mellitus, the risk of hypoglycaemia is rare due to the selectivity of these drugs.
    - SGLT1 function is preserved as are counter-regulatory mechanisms that prevent hypoglycaemia, including decreased insulin secretion and increased glucagon levels.
    - However, the risk of hypoglycaemia increases with co-administration of sulfonylureas or insulin
    - Since the cats in this study were receiving insulin in addition to bexagliflozin, the risk of hypoglycaemia was deemed to be higher.
    - The insulin dose was therefore reduced by 50% at the onset of enrolment before Day 0.
    - The dosage of insulin was subsequently titrated further based on at-home blood glucose monitoring and in -hospital BGC
- As osmotic diuresis accompanies glycosuria, urine output often increases during treatment with SGLT2 inhibition in human patients
    - This side effect has also been reported in healthy cats.
    - Unexpectedly, 3/5 cats in this study had client-reported resolution of polyuria and polydipsia and no cat had worsening of these signs.
    - Two of the 3 cats with resolution of polyuria and polydipsia were taken off insulin and improvement in hyperglycaemia may have helped control these signs.
- Because of the presence of SGLT1 in the small intestine, diarrhea occurs with nonselective SGLT2 inhibitors but is not expected to occur with highly selective SGLT2 inhibitors such as bexagliflozin

<u>Limitations</u>

- Small sample size
- 1st cat enrolled received lower dose 10mg vs 15mg – but this cat still had stat signif decrease in median BG conc and insulin dose
- Lack of control grp
- Drug only used in cats with poorly regulated DM
- Short duration of study