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DIABETES MELLITUS: CLINICAL CASES AND GENERAL TIPS

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ABSTRACT

Diabetes mellitus is the second most common endocrinopathy, after hyperthyroidism and it is believed that the prevalence of this disease is increasing. Risk factors include genetic factors, obesity, gender and neuter status, lifestyle and medication history. Diagnosis can be made more challenging by the stress hyperglycaemia phenomenon that cats are vulnerable to and presence of concurrent diseases which may make interpretation of laboratory parameters more difficult. Management strategies focussing on diet and insulin are often very successful and many patients live for two years or longer with this condition.

KEY WORDS

Diabetes mellitus, cat, insulin, diet, carbohydrate

Diabetes mellitus is estimated to affect around 1 in 200 cats and is the second most common endocrinopathy, after hyperthyroidism. It is believed that the prevalence of this disease is increasing. Risk factors include genetic factors, obesity, gender and neuter status, lifestyle and medication history. A recent UK study reported an increased risk of diabetes in certain breeds including Burmese, Norwegian Forest and Tonkinese (O'Neill et al 2016).

Most diabetic cats are non-ketotic, and their diabetes is analogous to human type 2 diabetes mellitus, characterized by insulin resistance, obesity and pancreatic amyloid deposition. Clinical signs typically include marked polyuria with a compensatory polydipsia and weight loss in spite of an increased appetite. Ketoacidotic diabetic cats are clinically usually very sick and need to be treated urgently, with attention being paid to electrolyte imbalances, fluid therapy and reversing the hyperglycemia and ketoacidosis.

Treatment of diabetes mellitus has the following key aims:

1. If possible, achievement of diabetic remission.
2. Resolution of clinical signs associated with diabetes mellitus.
3. Maintaining blood glucose levels below the renal threshold (12-14 mmol/l) for the majority of the time. This should be associated with prevention/minimisation of ketoacidosis and the development of other long-term complications of diabetes such as peripheral neuropathies.
4. Avoid hypoglycemia by maintaining blood glucose levels above 5 mmol/l.

Early diagnosis and prompt treatment, typically centred on dietary management and insulin therapy, increases the chances of diabetic remission. Where possible, any diabetogenic drugs the cat may be receiving eg glucocorticoids should be withdrawn or replaced with less diabetogenic alternatives (e.g. using inhaled corticosteroids for asthma, Fig 1).

Figure 1. Where possible, diabetogenic medication should be withdrawn. In this patient, asthma control was achieved using inhaled therapy reducing the risk of future diabetes mellitus.

Studies have shown benefits to glycaemic control by feeding diabetic cats a low carbohydrate diet; simple carbohydrates should be avoided in diabetic cats as these are rapidly digested and absorbed. Diabetic remission rates between 33 and 100% have been reported when using a combination of low carbohydrate diet and insulin therapy (Roomp *et al* 2009, Marshall *et al* 2009, Roomp and Rand 2012). There are now a number of specially formulated veterinary therapeutic diets available for this purpose. Wet diets are generally recommended over dry because these often contain lower carbohydrate levels. The lower energy density and greater water content is also useful for managing obesity. Use of low carbohydrate diets may reduce or eliminate the need for insulin therapy in the long term. In those cats where the diet is changed following diagnosis of diabetes, it is important to do this slowly and to monitor the patient carefully since insulin requirements can change very quickly. Low carbohydrate diets are suitable for use in diabetic cats of all weights – whether needing weight loss or gain. Since cats have a very prolonged post-prandial glycaemia, timing of meals is not critical for management of most feline diabetic patients.

If a higher carbohydrate diet is selected for a cat with diabetes mellitus then this should contain complex carbohydrates which are less rapidly broken down into sugars (lower glycaemic index). High fibre diets can help with obesity management in some cats.

Typically, up to half of diabetic cats treated with insulin achieve diabetic remission, and are able to maintain normoglycemia without insulin therapy or use of other glucose-lowering medications (Michiels *et al* 2008, Gostelow *et al* 2014, Hazuchova *et al* 2018). There is evidence that early intensive management with long-acting insulin (glargine or detemir) and dietary management can increase this figure to > 80% in some situations (Roomp *et al* 2009, Marshall *et al* 2009, Roomp *et al* 2012, Gostelow *et al* 2014). Diabetic remission is also possible for patients presenting in diabetic ketoacidosis. Remission typically occurs within 1 to 3 months of initiation of treatment, although relapse occurs transiently or permanently in around a quarter of these. Remission from relapse is generally much harder to achieve. Most patients in diabetic remission have reduced pancreatic function as a result of ß-cell loss and damage resulting from glucose toxicity, as well as any underlying pancreatic pathology which contributed to diabetes development in the first place. Other clinical problems are often present in these cases and also may account for the patient's predisposition to diabetic relapse through increasing insulin requirements. Pancreatitis is a common co-morbidity which can also have an impact on diabetic stability (Zini *et al* 2015, Shaefer *et al* 2017). Other common concurrent illnesses include gingivitis, obesity, hyperthyroidism, concurrent diabetogenic drugs and renal disease. Acromegaly may be more prevalent than once thought – a recent study indicated that the prevalence of this may be as high as 25% of UK diabetic cats (Niessen *et al* 2015).

PRO PLAN® Veterinary Diets Feline DM St/Ox Diabetes Management™ has been shown to reduce insulin requirements by more than 50% on average, with up to 30% of cats going into diabetic remission. (Frank et al, 2001.)

Insulin therapy is required to stabilize most diabetic cats. In general twice daily insulin therapy is associated with better results than once daily, regardless of the insulin preparation chosen although there is considerable inter-cat variation in duration of action and response to insulin. Longer acting insulins, such as protamine zinc, are recommended for treatment of diabetic cats where possible (Sparkes *et al* 2015, Behrend *et al* 2018).

The two veterinary licensed insulins in the UK are:

- Longer acting protamine zinc insulin (Prozinc, Boehringer Ingelheim): a recombinant human insulin in a 40 iu/ml formulation and typical duration of 13-24 hours. Some studies have indicated improved glycaemic control when using twice daily protamine zinc insulin compared to twice daily lente insulin (Gostelow et al 2018) and this should be prioritised for cats with a short duration of action on lente.
- Medium acting lente insulin (Caninsulin, MSD Animal Health): this is a porcine insulin zinc suspension with an insulin concentration of 40 iu/ml and typical duration of 8-10 hours. Caninsulin provides good clinical control of diabetes in many patients.

When using 40 iu/ml preparations it is essential to also use 40 iu/ml syringes. Use of a magnifying glass or 'reading spectacles' can be helpful for care providers with poor eyesight, especially when low doses are prescribed. Caninsulin is available in a pen doser which accurately dispenses insulin in 0.5 iu increments (VetPen, MSD Animal Health). Pens facilitate more accurate dosing, especially when a low dose is required, helping to reduce the risk of hypoglycaemia (Thompson *et al* 2015). Use of pens is associated with fewer 'needle stick' injuries although carers do not always find them easier to use (Albuquerque *et al* 2019).

Most cats require only small doses of insulin. Non-ketotic diabetic cats should be started on insulin at a dose of around 0.25-0.5 units per kg bodyweight per injection (maximum starting dose 2 iu per cat). The dose of insulin should not be increased more often than every 5 days as it takes several days for the effects of a new dose to 'settle out'. Detailed guidelines for diabetic stabilisation and monitoring are available elsewhere in open access consensus guidelines from ISFM and the AAHA (Sparkes *et al* 2015, Behrend *et al* 2018).

Home monitoring, as highlighted in Toots' case, (below) can be a valuable component of veterinary care. Some carers are happy to monitor blood and urine at home and where this is the case it is typically associated with a better clinical outcome (Fig 2). More recently, in-dwelling 'flash glucose monitoring' devices such as the Freestyle Libre (Abbot) have been used with some success in cats. A small device is placed and secured such that a small sensor is within the subcutaneous interstitial space. The sensor collects measurements on interstitial fluid glucose which can then be downloaded via a linked smart phone. Data collection can continue for up to 14 days. Such devices are helpful in cats that are difficult to stabilise, cats with concurrent diseases complicating their stabilisation and especially those vulnerable to stress hyperglycaemia which can make standard glucose curves problematic. Placement of the device is reviewed elsewhere (Fennell 2020).

Figure 2: Home monitoring of glycosuria can be useful in patients suspected of approaching diabetic remission. A 'free catch' urine sample can be collected for dipstick analysis (i) or a crude indication of glycosuria can be obtained by either pressing a dipstick into damp litter or adding some water to litter containing urine and performing a dipstick on this (ii).

Diabetes mellitus is an area of much active research in cats with several current strands of investigation. Future therapies currently being assessed include incretin analogues. Incretins are hormones released by enterocytes in response to small intestine nutrient content; use of incretin analogues such as exenatide may improve diabetic remission rates and reduce/avoid the need for insulin therapy (Gilor *et al* 2016, Behrend *et al* 2018).

CONCLUSIONS

Many cases of diabetes are straightforward to stabilize although it may take several weeks or months to identify an optimal insulin regime. Dietary management ideally involving feeding a therapeutic diet improves patient outcome. Early diagnosis and treatment increases the chances of diabetic remission. A recent study including 185 cats managed with protamine zinc insulin reported a median survival time of 1488 days (Restine et al 2019). A low-carbohydrate diet, occurrence of diabetic remission, lack of diabetic ketoacidosis at diagnosis, lower mean blood glucose value during treatment, and lower blood glucose value at diagnosis were significantly associated with increased survival time.

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The following case studies illustrate key management points and tips for success.

CASE STUDY: BUGSY

Bugsy presented as a 12 year old MN domestic short haired cat who had been obese for some time. Recently Bugsy had started to lose weight rapidly, was markedly polydipsic and weighed 7.8 kg at assessment having weighed 8.5 kg just one month earlier. Blood and urine testing confirmed diabetes mellitus. Bugsy received treatment with protamine zinc insulin twice daily and was transitioned onto a low carbohydrate, therapeutic 'diabetic' diet. Over the following 2 months, Bugsy's diabetes went into clinical remission and he no longer required insulin therapy. Bugsy remained on a low carbohydrate 'diabetic' diet and was clinically stable after 12 months follow up.

Discussion points:

- Bugsy was likely diagnosed relatively early and aggressive treatment was successful in resolving his diabetes. Resolution of glucose toxicity greatly increases the chance of achieving diabetic remission. Glucose toxicity describes the situation whereby prolonged hyperglycemia suppresses insulin secretion by the ß-cells of the pancreas. As glucose toxicity resolves, the ß-cells may recover some ability to produce and secrete insulin leading to improved glycemic control and diabetic remission in some patients. Unless weight is managed, Bugsy is likely to remain vulnerable to a diabetic relapse.
- Monitoring patients for diabetic remission: owner monitoring of water intake is a useful indicator of diabetic control as discussed for Toots, below. Serum fructosamine assessment can also be helpful since this gives an indication of glycaemic control over the preceding 1-2 weeks. Where diabetic remission is suspected, home monitoring of urine for presence of glycosuria and home blood glucose monitoring can also help.

- Obesity management is also essential for a successful outcome. Obesity causes insulin resistance and is an important risk factor for development of feline diabetes. A weight loss regime resulting in around 1-2% loss of bodyweight per week is recommended. A low carbohydrate diet fed at an appropriate caloric intake for weight loss, based on ideal bodyweight, is an ideal choice for an overweight diabetic cat. Access to scales at home can be helpful for owners monitoring weight loss in their cat (Fig 3).

Figure 3: Scales are inexpensive to purchase and can be helpful for health monitoring at home.

- Increasing physical activity increases insulin effectiveness and is especially beneficial in aiding weight loss in an obese inactive cat.
- Diet choice: Bugsy's therapeutic 'diabetic' diet was an important part of his management and in maintaining diabetic remission in the longer term. Should Bugsy gain weight in the future and/or switch to a more standard cat food, he will be at increased risk of diabetic relapse.

CASE STUDY: TOOTS

Toots presented as a 13 year old FN domestic short haired cat with a history of weight loss in spite of a normal appetite. Her coat condition was poor and she was reported to be drinking about half of litre of water each day. Blood and urine testing confirmed diabetes mellitus and concurrent chronic kidney disease (creatinine 240 umol/l, IRIS Stage 2-3). Toots received out-patient treatment with protamine zinc insulin twice daily and was transitioned onto a wet therapeutic renal diet. Toots' diabetes stabilised nicely over the following six weeks and her daily water intake reduced to 120-150 ml per day. Even when diabetically stable, Toots' water consumption was elevated due to presence of concurrent chronic kidney disease contributing to the polydipsia. Two months later, Toots was re-presented due to a deterioration in her diabetic control and relapse of clinical signs; her daily water consumption was now 400-500 ml per day. Investigations identified a bacterial urinary tract infection; treatment with antibiotics was successful in eliminating the infection and restoring diabetic control. A further six months later, Toots started to lose weight and her thirst increased again. Investigations revealed poor diabetic control and presence of hyperthyroidism. Medical management of hyperthyroidism was instituted and this resulted in clinical stabilisation of all co-morbidities and a good quality of life.

Discussion points:

- Monitoring thirst, where possible, is very helpful in monitoring diabetic stabilisation and relapse. In multi-pet households, monitoring total household water consumption is of some value since any changes in water consumption are likely due to the diabetic cat. In Toots' case, rigorous daily monitoring of water consumption (Fig 4) allowed rapid detection of diabetic de-stabilisation and appropriate management.

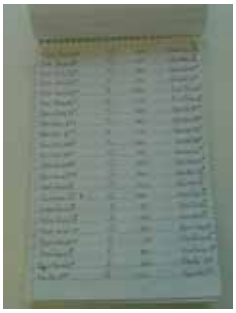

Figure 4: Home monitoring of water consumption is useful in monitoring diabetic stability. Toots' owner recorded 12 hourly water consumption and each line of their notepad corresponded to one 12 hour period. The results here show a period of diabetic instability: water consumption increased from around 120 ml per day to greater than 300 ml per day due to a bacterial urinary tract infection.

Identifying and addressing other underlying conditions is essential at the time of diagnosis and whenever diabetic patients 'relapse'. All inflammatory, infectious and neoplastic conditions have the potential to increase insulin resistance and de-stabilize diabetic control. Successful resolution of these may be enough to result in diabetic remission. For example, dental disease should be addressed early in the course of treatment for diabetes. In Toots' case, pre-existing renal disease was documented and accounted for the persistence of the polydipsia in spite of good diabetic control. Subsequent development of both urinary tract infection and then hyperthyroidism resulted in de-stabilisation of the diabetes which resolved once treated. Urinary tract infections are a potential complication of diabetes and will increase insulin requirements and complicate stabilization. Reported prevalence of bacterial UTIs in cats with diabetes mellitus has varied from 7% to 14.3% (Bailiff et al 2006, Michiels et al 2008, Mayer-Roenne et al 2007, Bailiff et al 2008). Urine culture is recommended as a priority in all newly diagnosed diabetic cats and those whose diabetic control has recently deteriorated.

- Fructosamine assessment is of limited utility in cats with uncontrolled hyperthyroidism. The increased metabolic rate and higher protein turnover experienced by hyperthyroid cats leaves less opportunity for the non-enzymatic reaction between glucose and amino groups of plasma proteins and therefore less opportunity for fructosamine to form.
- In spite of multiple co-morbidities, Toots did well and was stable at the last follow-up, 12 months following initial presentation with diabetes.

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