DIAGNOSIS AND MANAGEMENT OF FELINE DIABETES – WHAT'S NEW?

Diabetes mellitus is not a single disease but a manifestation of various pathophysiological processes. David B Church BVSc PhD MACVSc MRCVS vice principal, The Royal Veterinary College, outlines these processes and looks at what has changed in their management over the last decade

Diabetes mellitus is perhaps best defined as clinically significant glucose intolerance caused by an absolute or relative lack of insulin. In any individual patient, the degree of insulin deficiency can fluctuate over time. These changes may be influenced by many factors. For example, any animal with pancreatitis may develop clinically significant impaired insulin secretion. This is generally reversible and resolves as the inflammation subsides. Perhaps more obscurely, any condition resulting in chronic insulin resistance results in hyperinsulinism that may lead to so called "islet exhaustion" in susceptible individuals. This may be variably reversible depending on the length of time the islets have been exposed to this increased secretory demand and the presence of inherent individual susceptibility to the damaging effects of chronic insulin 'hypersecretion'.

Research carried out at the Royal Veterinary College indicates in the general practice population approximately 33% of all diabetic animals diagnosed have been euthanased within 12 months of diagnosis. Approximately half of these occur at the time of diagnosis and the other half over the ensuing 12 months. The most common reasons are concerns about quality of life for the owners and, to a lesser extent, quality of life for their diabetic pet. Interestingly giving regular injections is not one of the areas cited as being important in making their decision. This evidence suggests it is very important that in managing a diabetic patient we firstly do all we can to optimise the level of diabetic control but that this is done within the framework of what is suitable for the owners and indeed as convenient as possible.

Many veterinarians are keen to obtain a 'protocol' or series of protocols to help with managing diabetic patients. However, the one inevitable consequence of a diabetic management protocol is a somewhat inflexible sequence of events that need to be followed by the owners and to some extent the diabetic patient. In other words, protocols tend to create inflexibility and ignore the variable needs that inevitably occur from patient to patient and owner to owner. Hence, the following discussions are all based around principles rather than protocols.

CLINICAL SIGNS

Most diabetic animals will present with various combinations of polydipsia, polyuria, polyphagia and weight loss. This is particularly true in dogs and less so in cats. Physical examination may reveal varying degree of muscle wasting (although some animals can be obese at the time of presentation), hepatomegaly and cataracts (almost exclusively dogs). Additionally, if they are becoming ketoacidotic they may present with signs of dehydration, depression, inappetence, vomiting and diarrhoea. They will also have a ketotic breath although only a proportion of humans can detect the ketotic odour. It is vitally important to remember that, in the absence of marked ketoacidosis, diabetes mellitus is unlikely to be the explanation for an animal presenting with inappetence or varying degrees of gastrointestinal dysfunction or depression and lethargy.

The presence of this sort of clinical picture in the absence of moderate to marked ketoacidosis suggests the concurrent presence of subnormal islet reserves and some other disease process causing the observed clinical signs. Consequently, if an explanation is not apparent further targeted investigation to uncover an underlying cause is almost always warranted.

DIAGNOSIS

Generally, in the dog a diagnosis of diabetes mellitus is confirmed by the presence of fasting hyperglycaemia of greater than around 14mmol/L. In the cat, elevations in blood glucose of this magnitude, or higher, can be a result of stress due to any illness and further corroborating evidence should be obtained. In both dogs and cats with glucosuria, hyperglycaemia should be confirmed before treatment is considered.

Blood glucose estimations provide an estimate of the blood glucose concentration at the time of sampling. An elevated fasting blood glucose is likely to be an indication of persisting hyperglycaemia (especially if there are concurrent consistent clinical signs) however in cats that are unwell or 'stressed' fasting hyperglycaemia may be a transient phenomenon.

If the clinician is in any doubt as to the significance of the hyperglycaemia it is possibly worth determining the glycosylated haemoglobin or plasma fructosamine level. Both parameters estimate the proportion of haemoglobin and albumin respectively that has glucose bound to it in a non-enzymatic irreversible way. As the process is both non-enzymatic and irreversible the proportion of the relatively constant protein that is 'glycated' is an estimate of the 'average' blood glucose concentration over a preceding period that appears to be somewhat variable depending upon whether we are dealing with cats or dogs.

In the dog the fructosamine concentration probably reflects the blood glucose levels over the last two to four weeks. In the cat the accuracy of the fructosamine as a reflection of previous blood glucose levels appears to be more variable and more a reflection of the blood glucose levels over the previous five to 10 days.

Regardless of these differences, clearly plasma fructosamine levels can be helpful in differentiating short-term hyperglycaemia from persistent hyperglycaemia. However, it should be remembered that in the cat many disorders can cause an elevated blood glucose thus an increase in fructosamine should not be considered diagnostic for diabetes mellitus. It is simply an indication of a sub-acute or chronic moderate to marked blood glucose elevation.

Where glycosylated haemoglobin and fructosamine estimations are most valuable is in evaluating effective management of the diabetic patient. In many patients the need for repeated blood glucose estimations (glucose curves) can be avoided by a single blood sample for a glycosylated haemoglobin or fructosamine estimation. Of course, a glucose curve can still be valuable in those animals proving difficult to manage.

Treatment of uncomplicated diabetes mellitus

Clearly whenever underlying explanations for insulin resistance can be identified it is important to correct these whenever practicable as this may well result in resolution of clinical signs and indeed result in the patient no longer requiring insulin. Additionally, some obese diabetic cats may initially require insulin injections, but requirement may diminish or cease when their body weight normalises. However, especially in dogs, in many cases the clinically significant glucose intolerance will not resolve with the reduction in insulin resistance-inducing factors and the clinician will have to consider implementing insulin therapy.

WHICH INSULIN IS BEST?

Insulins such as lente insulin, isophane (also known as NPH) insulin and protamine zinc insulin (PZI) have been the mainstay of insulin therapy for diabetes mellitus in cats and dogs for some time. Over the last few years the synthetic insulin analogues, insulin glargine and insulin determir, have been recommended for use as a twice daily exogenous insulin in cats. The perceived advantages of these two insulins is a relatively 'peakless' profile and longer duration of action than is seen with insulin lente or possibly even PZI. It has been suggested these products' alleged relatively 'peakless activity profile' may make them a more suitable insulin for those cats that are keen to "graze". In the author's opinion a preferable approach to manage these 'grazing cats' is to, whenever possible, increase the frequency of insulin dosing without changing the total daily insulin dose.

It is important to remember when studies are 'corrected' for diet, currently there is no robust clinical data that suggests cats receiving twice daily glargine or determir are any better controlled or any more likely to go into remission than cats receiving twice daily protamine-zinc insulins.

Additionally, while recent work at the Royal Veterinary College suggested diabetic cats changing from lente insulin to protamine zinc showed some clinical improvement, there was no significant difference in diabetic control between diabetic cats receiving glargine insulin verses matched diabetic cats receiving protamine-zinc insulin. Numerous indicators of diabetic control were utilised including average blood glucose, fructosamine, diabetic clinical score and insulin dose.

Remember the overall aim of insulin therapy is to administer the insulin so that its time of peak activity corresponds to the peak demand i.e. when the blood glucose is rising after feeding. The aim is to lower blood glucose concentration over the 24-hour period and to minimise fluctuations.

Regardless of the insulin used, successful insulin therapy is based around reducing the average blood glucose levels to levels where clinical signs are effectively controlled. The phrase 'effectively controlled' can be difficult to define and will mean different things to different owners and indeed different veterinarians. Regardless 'effectively controlled' invariably requires:

- Insulin being administered at least twice daily with;
- The meal being offered an hour to an hour and a half after the insulin;

- Some form of monitoring of the insulin and meal's effects on serial blood glucose levels. The mechanism for assessing how effectively the management is controlling the blood glucose varies and the optimum means of doing this can be different for different patients and owners. Ideally a stable well controlled patient can be monitored with regular serum fructosamine estimations and/or serial blood glucose 'curves.' More specific and detailed information about practical guidelines for managing diabetic cats and dogs is given below; and
- Regardless of the methods used to quantify blood glucose levels the owners and members of the veterinary team should be encouraged to use the diabetic clinical score (DCS) to 'semi-quantify' the degree of diabetic control being achieved. The DCS is a score out of 12 made up by giving a rating of between zero and three to four clinical parameters associated with poor diabetic control. The four components are: weight loss over the past two months; degree of polydipsia and polyuria; degree of increased appetite; and degree of decreased activity and attitude.

To facilitate the regular use of the DCS, the Royal Veterinary College has developed the Pet Diabetes App which is freely available from all usual App stores for iPhone and android smartphone platforms.

MONITORING DIABETIC CONTROL

As stated above first and foremost our considerations need to be contextualized around the patient's DCS. The mechanism for assessing how effectively these activities are controlling blood glucose varies and the optimum means of doing this can be different for different patients and owners. Ideally a stable well controlled patient can be monitored with regular serum fructosamine estimations and/or serial blood glucose 'curves.' Serum fructosamine estimations are an estimate of the average blood glucose over the last two weeks. They always need to be interpreted with care as there are various reasons for fructosamine values to change that are unrelated to the patient's diabetic control.

Serial 'blood glucose estimations' can be performed either in hospital or at home, either by repeated estimations of the blood glucose using various home glucose monitoring devices or by continuous glucose monitoring (CGM) devices. The former should use very small amounts of blood (<25ul) and ideally will be used to obtain four to six blood glucose values over a 12hour cycle. This repeated sampling can be carried out once or twice weekly, or less frequently if the patient has a satisfactory and stable DCS.

The CGM devices estimate blood glucose by continuously measuring subcutaneous glucose concentrations through a sensor generally placed dorsally just caudal to the cat or dog's withers. Sensors generally last around two weeks and transmit their data to a programmed reader allowing as many estimates of the 'blood glucose' as the operator wants to record. While there is some debate around the precision of the absolute values they produce, there is consensus that the methodology is consistent, and they are thus able to provide accurate estimates of changes over time for individual patients.

FEEDING AND EXERCISING THE DIABETIC PATIENT

The diet must be consistent – the animal should consume the same caloric intake morning and night and from day to day. The food should be controlled and consistent: commercial canned preparations with variable amounts of dry food are a convenient food type for diabetics as their caloric content is relatively predictable and consistent. However, they may not be attractive to all patients, particularly if they have not been a traditional part of the animal's diet.

When using relatively short duration insulins it is vital that all the offered food is consumed within a short space of time. In other words, caloric content and palatability are equally important. As a result, some diabetic dogs and cats need to be stabilised on standardised portions of their usual diets.

In those cats that like to graze rather than eat all of the meal offered in one sitting it is worth considering the possibility of increasing the frequency of insulin dosing. Whatever the form of the calories fed to the diabetic patient, the timing and the caloric content must remain consistent. Any changes in the animal's diet can only be made if the overall caloric content remains unchanged.

No snacks should be provided except when they are used to facilitate the insulin injection process. As a general guide feed 50-70 kcals/kg body weight. There is no evidence that adding fibre to a diabetic's diet is likely to significantly improve poor diabetic control.

LOW CARBOHYDRATE, HIGH PROTEIN DIET – GOOD OR BAD?

Lowering the overall carbohydrate intake by feeding a diet low in carbohydrate and high in protein may, theoretically, lower insulin requirements and/or improve diabetic control. Over the last few years numerous clinical trials have demonstrated improved diabetic control and reduced insulin requirements in diabetic cats fed a low carbohydrate-high protein diet. In a number of these studies the 'control' group were fed a high fibre (and, hence, high carbohydrate) diet of differing starch sources (which may have an impact on the glycaemic index). However, notwithstanding these limitations the collective results strongly suggest feeding cats diets with constituent composition more closely resembling the composition of their natural carnivorous diet will increase diabetic remission rates, especially in those cats with marked insulin resistance through obesity. Further, to the author's knowledge, there is no evidence to support differences the way the high-protein diet is achieved be it commercially available products or so-called natural diets.

The proportion of cats with uncomplicated diabetes mellitus likely to achieve a state where they no longer require exogenous insulin after receiving a combination of exogenous insulin and being switched to a high protein, restricted

carbohydrate diet is still a point of conjecture. However, it is generally accepted up to 40% of early diabetics may ultimately be able to be managed without exogenous insulin. This invariably requires an initial period of exogenous insulin administration combined with ongoing high–protein diet and weight-loss to a normal body condition score.

While feeding a high protein diets is likely to have benefits for improving diabetic control in the cat, there is no evidence that this type of diet or indeed the more traditionally recommended high-fibre diet, has any role or impact on improving control of diabetes mellitus in the dog.

EXERCISE

Exercise has the capacity to lower insulin requirements hence exercise should be consistent and encouraged. As diabetics are usually older animals that have been obese due to overfeeding and lack of exercise, over-exercise is not usually a problem.

PRACTICAL PRINCIPLES AND GUIDELINE FOR INSULIN THERAPY IN CATS

It is imperative to ensure that the cat truly requires insulin. Many cats have hyperglycaemia due to insulin resistance produced by concurrent disease and/or obesity in the presence of subnormal insulin secreting capacity. Correction of the reasons for the insulin resistance, together with the feeding of low glycaemic index foods (ie. low in carbohydrate and relatively high in protein) may result in a significant proportion of these cats no longer requiring exogenous insulin therapy.

STARTING DOSE

If the cat is a true diabetic, start on an insulin dose of one to two units of PZI or glargine per cat twice daily. As all diabetics prior to receiving insulin are relatively insulin resistant and this resistance diminishes as they start to receive regular insulin injections, there isn't a great deal of benefit in trying to establish the precise insulin dose needed straight away.

As it usually takes at least a few days for an affected animal's sensitivity to stabilise, it is preferable to get the cat back in four to five days after starting insulin to check blood glucose levels. Also remember the fructosamine is going to reflect the average blood glucose over the last 14-20 days thus there is little point in determining fructosamine levels within the first three weeks of the diagnosis.

In cats, because of the potential for their diabetes to resolve and their potential for a visit to the veterinarian to produce variably severe anxiety-induced hyperglycaemia, many veterinarians recommend home-glucose monitoring using one of the many devices currently available on the market and specifically designed for this purpose.

Checking morning urine for glucose can be helpful – there should always be some glucose in the first urine sample of the day and if there is not this is an indication that the cat is at risk of hypoglycaemia. It is worth remembering that there is some evidence to suggest with identical 12-hour dosing, glucose levels tend to be lower overnight. It is also noteworthy that rebound hyperglycaemia, although very uncommon, does occur meaning that just because there is glucose in the urine it does not rule out potential excessive dosing.

MAIN REASON FOR PROBLEMS IN CATS

Many diabetic cats are usually easily controlled if they really require insulin. The two problem areas that occur are:

- Treating cats that have 'reversible' (at least in the short-term) diabetes where the continued administration of insulin results in clinically significant hypoglycaemia; and
- A subset of cats that have clinically significant insulin resistance. While the explanations for this insulin resistance can be numerous, there is now substantial evidence that hypersomatotrophism (or acromegaly) is potentially a far more common explanation for this disorder than has been previously reported. Consequently, it is well worth checking any diabetic cat with insulin resistance or variable insulin requirements for the presence of hypersomatotrophism.