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Managing Diabetic Patients Mini Series

Session One: Pathophysiology of Diabetes Mellitus

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Diabetes.

Diabetes mellitus is a complex disease, with stabilisation of blood glucose levels being affected by confounding disease processes, efficacy of the primary disease control treatment, diet and exercise programme and weight control. Thus a full history of the animal, including all these factors must be taken. There are several possible causes of diabetes mellitus, including pancreatitis, obesity, drugs (glucocorticoids, progestins), concurrent illness (hyperadrenocorticism, acromegaly), genetics, immune-mediated insulitis, infections and Islet amyloidosis. Obtaining an ideal body condition score in both cats and dogs is the ideal goal in all of these cases, with obesity increasing the risk of non-insulin dependent diabetes mellitus (NIDDM) in cats by fourfold. Obese diabetic animals may have difficultly losing weight, but stabilisation of the diabetes is the initial aim, followed by a conservative weight loss programme, which does need to be carefully monitored by a veterinary professional.

Underweight animals once stabilised should be fed a modest increase in calories in order to promote repletion. Dietary therapy can only help to improve glycaemic control, but emphasis should be placed on adjustment of the insulin (or oral lypoglycemic – not commonly used due to efficacy) dosage and schedule, and control of concurrent disease.[1]

With IDDM, the beta cells within the pancreas lose their ability to secrete insulin. This can be congenital or as a result of pancreatitis, or prolonged disease to the pancreas. Exogenous insulin administration is required as the treatment. The monitoring of pancreatic specific enzymes should also occur when conducting routine monitoring of these cases, as it can be a primary cause. NIDDM is defined as insulin resistance occurring at the site of the peripheral tissues. Dysfunction of the beta cells can also be a causal factor of NIDDM, (Figure 12A). The quantity of insulin secreted by the beta cells can be increased, decreased, or can remain normal. In some texts Type 2 diabetes, which resolves is sometimes classed as transient Type 2 NIDDM. This is more commonly noted in obese cats when insulin resistance becomes established. Once the cat obtains and then maintains an ideal body condition score, NIDDM can resolve itself. If the beta cells also become exhausted; a period of exogenous insulin administration may be required. The beta cells can start secreting insulin after a period of time, and therefore is not a true NIDDM. Hyperglycaemia is toxic to beta cells and aggravates the situation by further reducing insulin secretion. This mechanism can also explain why the more obese the animal and the longer that this animal has been obese the greater the incidence of the onset of diabetes.

Diagnosis of Diabetes.

Glycated protein levels

Fructosamine and glycosylated haemoglobin

Fructosamine and glycosylated haemoglobin (GHb) are 2 glycated proteins commonly used for monitoring diabetic human patients. These 2 proteins are markers of mean glucose concentration and their amount is proportional to the blood glucose concentration. The concentration of these proteins is not affected by stress, therefore they are often used by veterinary practices to diagnose and monitor diabetic cats.

Although fructosamine and GHb are good tools for determining regulation, they will not identify an underlying problem, nor will they replace glucose curves done for therapy adjustments. Rather, they give an idea of glycaemic control over a long period: fructosamine reflects the glycaemic control for the previous 2 to 4 weeks and GHb for the prior 2 to 4 months.

Fructosamine is preferred over GHb to assess glycaemic control. It is more commonly evaluated than GHb, because simpler, less time-consuming analytical assays are available. Also, successful monitoring and regulation can be achieved with weekly or monthly measurements of serum fructosamine.

It is important to measure fructosamine when the animal is well hydrated and not acidotic. The fructosamine level can change by 100umol/l with no change in the glucose level in a 24hour period.

Advantages of measuring fructosamine

- Distinguishes hyperglycaemic, non–diabetic cats from diabetic cats with chronic hyperglycaemia.
- Not influenced by stress hyperglycaemia in cats.
- Useful in confirming diagnosis in cats.
- Helps evaluate long-term control and owner compliance with insulin treatment.

Limitations of fructosamine measurements

- Unable to detect short-term or transient abnormalities in the blood glucose concentration, eg, transient daily episodes of hypoglycaemia. This would require serial measurement of blood glucose concentrations.
- Hyperthyroid cats with diabetes mellitus may have decreased fructosamine concentrations despite having normal serum protein concentrations. This results from an increase in the protein turnover rate (decreased protein half-life) caused by increased thyroid hormone concentrations.
- Globulin and fructosamine concentrations are correlated in cats. Hypoglobulinemia will result in decreased fructosamine concentration—consult the laboratory performing the analysis as to whether a correction is required and whether this has been done.

Fructosamine is affected by quick metabolism: therefore it is normal to low levels in hyperthyroid cats. Diabetic and hyperthyroid: Fructosamine is not accurate in telling glycaemic control. Diabetic cats with fructosamine below 400umol/l by suspicious of hyperthyroidism.

Glycosylated hemoglobin (GHb)

GHb is produced by the non-enzymatic, irreversible binding of glucose to haemoglobin in erythrocytes. The glycation of haemoglobin is a gradual process and is not affected by acute or transient hyperglycaemia.

Use GHb concentration as a screening test for diabetes mellitus, as well as to monitor glycaemic control in treated diabetic animals.

Advantages of GHb measurements

- Unaffected by stress-related or postprandial hyperglycaemia.
- Useful in long-term monitoring of diabetic animals over the previous 2 to 3 months (2-4months in dogs).

Limitations of GHb measurements

- Test not widely available for cats.
- Not the most effective test due to the relatively long erythrocyte lifespan (~68 days in cats, ~110days in dogs).
- Less effective for short-term monitoring than fructosamine, because hyperglycaemia must be present for at least 3 weeks before increased values are detectable.
- Affected by haemoglobin concentrations—may be increased or decreased due to polycythaemia or anaemia, respectively.

Urinalysis.

Performing good urinalysis is important in both diagnosis of diabetes but also during the stabilisation period. Urine dipsticks should show:

- Bilirubin: Dogs negative to +1, cats negative.
- Blood: Negative; positive results may be caused by trauma induced by collection method.
- Glucose: Negative.
- Ketones: Negative.
- Nitrite: Test pad unreliable in cats and dogs.
- pH: 5.5-8.5
- Protein: Negative; trace to +1 in highly concentrated samples.
- Specific Gravity: Test pads unreliable in dogs and cats.
- Urobilinogen: Negative
- White cells (leukocytes): Test pad unreliable in cats and insensitive in dogs.

Urine glucose is more useful for adjusting insulin dose with glargine or determir than the intermediate-acting insulins (Lente). It isn't useful for detecting remission. This is as once at the correct dose of insulin, the pet should have no glucose in its urine (or just a trace).

Sediment analysis is also important, and it should be checked whether there is an active sediment or not. Normal findings include:

- RBCs/hpf : 0-5 (Feline and Canine)
- Casts/lpf : Occasional hyaline (Feline and Canine), no others should be seen.
- Epithelial Cells/hpf : Occasional
- Fat Droplets /hpf: Uncommon in dogs, common in cats.
- Bacteria /hpf: Negative
- Crystals/hpf: Variable

Bacteriology of a urine sample needs to be performed ideally from a cystocentesis sample. Voided sample will be contaminated, if sent to an external laboratory need to ensure that the lab knows how the sample was collected. All sample will be cultured for bacteria. Sediment analysis can give false negative very easily. Urinary tract infections can make the pet easily unstable.

Performing Serial Blood Glucose Tests.

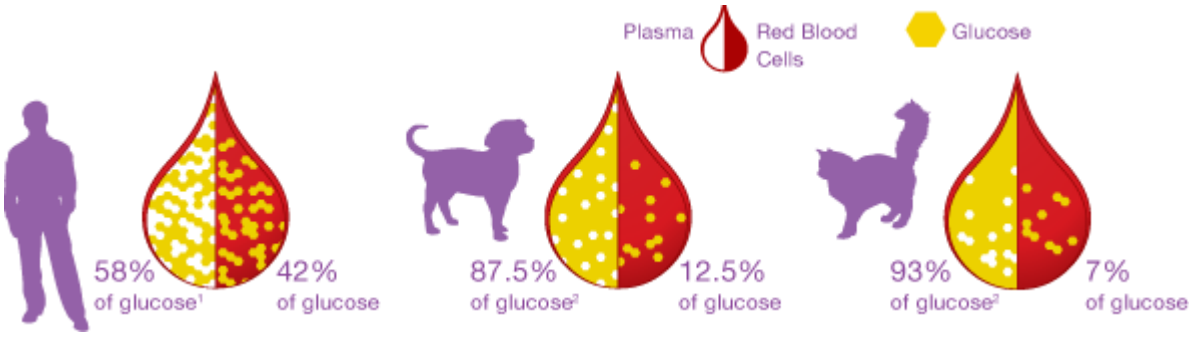
Serial blood glucose testings are useful for the monitoring of insulin therapy in dogs, and initial assessment of the response to insulin in cats. When initiating insulin therapy serial blood glucose levels should be monitored every two hours. The purpose of the monitoring is to establish whether the insulin is effective, length of effectiveness and time of nadir. There is a tendency when performing serial blood glucose tests to plot a graph and join up the dots. This can lead to misinterpretations of graphs, as if tests are two hours apart, glucose levels can be lower or higher than expected and not on the line drawn between two readings. Serial blood glucose testing is difficult in cats, and it has been shown in cats that even on consecutive days serial blood glucose testings would have caused two very different conclusions in what the veterinary surgeon would have interpreted the results and altered the insulin levels. More accurate levels can be achieved through monitor blood glucose levels at home.

Any changes in insulin should be performed slowly, and only by half a unit every 7-10days if required. It takes the body over a week to adapt to insulin level changes and therefore more rapid changes can be detrimental.

Reasons for using serial blood glucose testing:

- Determine need for insulin / Control glucose levels
- Determine the effectiveness of the treatment
    - Length of action of each injection.
    - Identify timing of nadir
    - Identify blood glucose level at nadir
- Avoid / minimise
    - Visible symptoms
    - Consequences of poor control
    - Long-term effects of diabetes (cataracts, renal and liver problems, etc.).

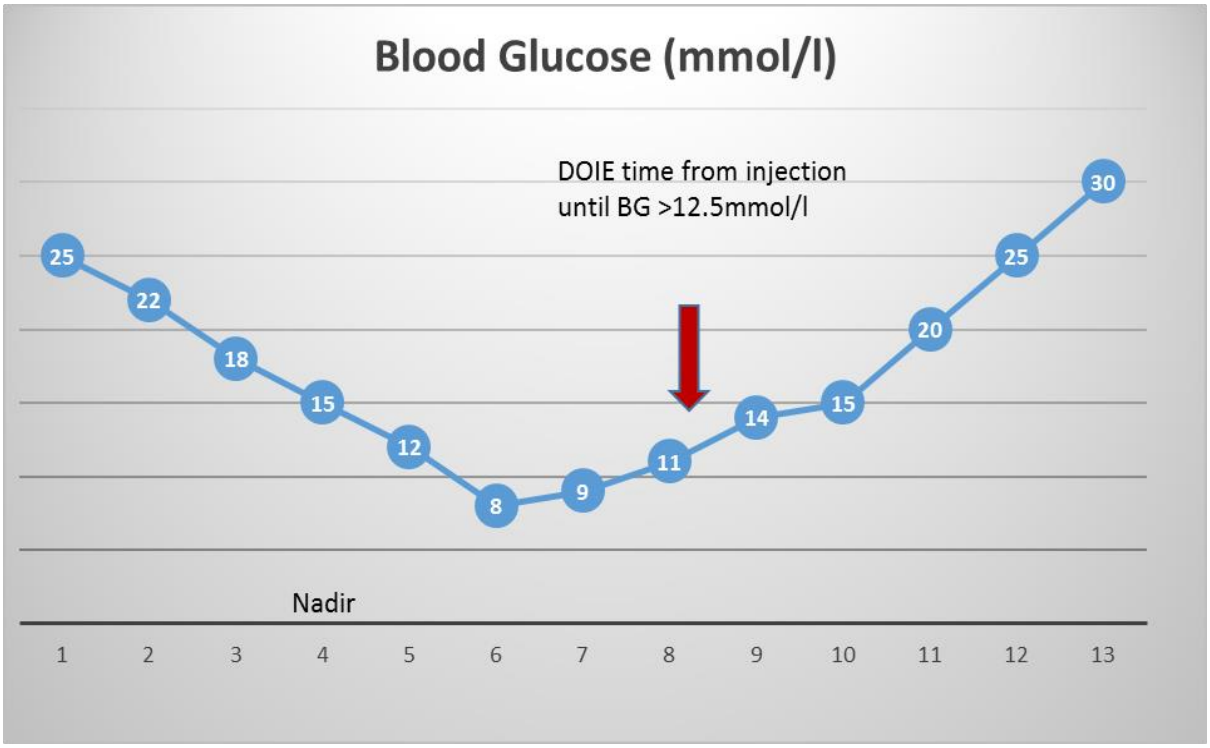
It is important to use a species specific monitor as there are large variations between species, it gives more accurate readings for the pet. Some insurance companies will allow claims for glucose monitors.



There are different types of human glucometers and some owner can't or won't want to buy a species specific glucometer. Human whole blood calibrated monitors are approximately 20-25% lower than species specific (~1-2mmol/l). Human plasma equivalent monitors tend to read 10-15% lower. If owners are using human glucometers, find out type and adjust for the glucose concentration.

Definitions:

- Nadir: Lowest point of the blood glucose.
- DOIE: Duration of Insulin Effect, this is defined as the time from insulin injection until the blood glucose exceeds 12.5mmol/l.
- SBG: Serial blood glucose.
- SBGC: Serial blood glucose curve.
- NPH Insulin: *Neutral Protamine Hagedorn* Insulin.
- PZI: Protamine Zinc Insulin.



Types of Insulin.

Caninsulin manufactured by MSD, is a veterinary porcine lente intermediate-acting insulin, made up of 30% semilente (short-acting) and 70% ultralente (long acting) insulins. ProZinc from Boehringer – Protamine Zinc insulin (long acting insulin). Long acting insulins such as Glargine and Determir are both not licenced for the veterinary market. Likewise Neutral (Soluble) insulin – solely used in cases of diabetic ketoacidosis.

Glargine.

Offers really good clinical control when used SID in cats, remission rates similar to Lente. Though there has been shown to have better remission rates when used BID. Glargine is only available as 100IU/ml, can't be diluted; so can be difficult to get good compliance with administration. Some clinical studies have shown up to 80% remission rates when used in combination with appropriate diets. Glargine has a unique method of slow release – it forms crystals in the sub-cutaneous tissues that allows slow release over time. Anything that increases the circulation to this area will therefore increase the release of the insulin into the bloodstream.

- If blood glucose conc. > 20mmol/L begin glargine at an initial dose of 0.5U/kg ideal body weight twice daily (BID)
- If blood glucose conc < 20mmol/L begin at 0.25U/kg ideal body weight BID.

Perform a 12hr glucose curve with samples taken every 4hrs
DO NOT increase dose for the first week. Decrease dose if biochemical or clinical hypoglycaemia occurs. It is suggested that cats stay in hospital for 3 days to check the initial response to insulin, or home glucose curves are obtained for the first 3 days. If the owners have limited funds; can start Glargine at 1IU/cat and monitor after a week.

Most cats started on 0.25-0.5IU/kg bwt will need a reduction after the first three days. After three days of monitoring – home, with rechecks every seven days. Subsequent curve every 5-7days until remission or after 4months of treatment less frequently.

Unlike Lentes the pre-insulin blood glucose test is used to adjust insulin levels rather than the nadir.

If owners are competent in home monitoring normally recommend testing every 3-6hours. Examples of testing times would be 8am, 12pm, 4pm, 8pm, just before bedtime.

Determir.

Determir is a human recombinant insulin with amino acid distribution, available as 100IU/ml. There are very limited studies performed in cats, but has started to be quite promising. It has been shown that it may have a longer duration than glargine.

Caninsulin.

Caninsulin is structurally identical to canine insulin, and is licensed for both canine and feline use. The licenced starting insulin dose range is:

- 0.25- 0.5IU/kg **twice** daily - larger bodyweight dogs started at the lower end of the range.

Dose can also be dependent on initial blood glucose concentrations. Remember to round the pet's bodyweight down to the nearest whole kilogram and the calculated dose down to the nearest whole unit.

- Dosage Blood glucose concentration

Starting insulin dose

<20mmol/l (360mg/dL) = 0.25IU/kg

>20mmol/l (360mg/dL) = 0.5IU/kg

ProZinc.

ProZinc (PZI insulin) has a long duration of effect, with the glucose nadir normally 9hours post administration. It is a recombinant human insulin in a protamine zinc combination. Only four amino acids differ from feline insulin.

Stabilising the Diabetic Patient.

Our initial aims are to control clinical signs, (PD/PU, polyphagia), and to maintain the blood glucose between 5.5 to 14mmol/l. Performing the serial blood glucose testing will give you guidance. The first thing to look at is does the blood glucose level drop when insulin is administered. If it does then good. If it doesn't and the insulin dose is <1iu/kg bwt then consider insulin under dosage. If insulin dose is >1 to 1.5iu/kg bwt then consider insulin ineffectiveness or insulin resistance. If the fructosamine level is <450µmol/l consider Somoygi over swing, poor injection technique or stress hyperglycaemia.

The ideal blood glucose level is between 5.5 and 7mmol/l, (though there are a lot of different reference ranges). If the nadir was >8.5mmol/l, then the insulin dose can be increased by 10%, and reassessed in 7-10days time. If the nadir was <5.5mmol/l, then the insulin dose can be decreased by 10-20% and reassessed in 7-10days time. Based on using Caninsulin.

If using Glargine or Determir if pre-insulin >10mmol/l, and the nadir >8mmol/l, increase the insulin by 0.5-1IU. If the pre-insulin is >10mmol/l and the nadir 5-8mmol/l.

Keep the insulin at the same levels for several weeks, then aim to reduce the nadir to 4-7mmol/l. If the nadir <4.5mmol/l and the pre-insulin <10mmol/l decrease by 0.5-1iu/injection.

There are three phases of treatment with Glargine therapy.

1.) Increasing the dose every 5-7days by 0.25-1iu depending on current dose of insulin and degree of hyperglycaemia. Aiming to increase the dose until all blood glucose concentrations are within 4-11 throughout the day.

2.) Holding the dose, once within 4-11 throughout the day.

3.) Decrease the dose if pre-insulin <10mmol/l OR nadir <4mmol/l.

If near remission, keep to the trigger points (pre-insulin and nadir levels). Keep decreasing insulin by 0.5iu/cat bid through to 1/2iu/cat SID. If the pre-insulin is 10mmol/l on 0.5-1iu SID (per injection) withhold the insulin and check for remission. Need to overcome the glucose toxicity for the beta cells to recover and go into remission.

Pancreatitis.

Diagnosis can be difficult in these cases, but using Species specific pancreatic Lipase tests alongside clinical signs is important. The statistics are quite high with 50% of diabetic cats, and 13% of diabetic dogs having pancreatitis. The inflammation can be fluctuating and therefore the insulin requirements can also vary. Regular testing should occur for those that have proven to have pancreatitis; and be instigated for those where there are issues with stabilisation.