INTRODUCTION
Diabetes mellitus (DM) is a common endocrine disorder, these dogs have insulin deficiency, occurs with an incidence of between 1 in 100 to 1 in 500 dogs. This results in a decreased ability of cells to take up and utilize not only glucose, but also amino acids, fatty acids, and electrolytes. The majority of dogs with diabetes mellitus will be successfully stabilised and will remain stable for long periods of time. The most appropriate therapy in dogs is the administration of insulin. We will discuss the roles of the various insulin preparations currently available and develop a logical approach to the initial and long-term management of diabetes. The key to successful management of the diabetic patient lies in close communication with the pet owner and prompt recognition and treatment of concurrent disorders. The most common cause for instability is failure(s) in the daily management of the patient. When investigating instability always start by checking the daily routine before embarking on a search for complex causes of instability.

KEY FACTS
1. Insulin is still the mainstay of therapy in all dogs with diabetes mellitus.
2. Diet is an important part of diabetic management, especially in obese patients.
3. Oral hypoglycemics may be helpful in combination with insulin to improve glycaemic control.
4. Autoimmune disease, pancreatitis, and amyloidosis are the most common causes of diabetes in dogs and cats.

Successful management of the diabetic patient involves many factors. An understanding of dietary therapy, insulin preparations, and management of concurrent illness are all required to optimize glycaemic control.
The goals of therapy are to control clinical signs, prevent or slow the progression of cataracts, avoid hypoglycaemia, and maintain ideal body weight. The challenge is to address these concerns while attempting to help the owners deal with a time-consuming, expensive, and chronic medical condition.

Diabetes mellitus in dogs results from a decrease in insulin secretion from the beta cells of the pancreas and/or a decrease in insulin action. There are three classifications of diabetes:
1. **Type I** diabetes is comparable to insulin-dependent diabetes mellitus (IDDM) in humans. It results in low basal insulin concentrations with impaired insulin secretion following a glucose load. Treatment requires insulin injections. It is the most common form of diabetes in dogs.
2. **Type II** diabetes is similar to noninsulin-dependent diabetes (NIDDM) in humans and is managed with dietary therapy and oral hypoglycemics. It causes normal to increased basal insulin concentrations with decreased secretion following a glucose load. Insulin may or may not be required for animals with Type II diabetes.
3. **Type III** diabetes is seen most commonly in hormonally induced diabetes in dogs and cats and is similar to impaired glucose tolerance (IGT) in humans. Diabetogenic hormones (epinephrine, cortisol, glucagon and growth hormone) or medications that interfere with insulin action and cause glucose intolerance, which can lead to diabetes.

AETIOLOGY AND SIGNALMENT
There are some distinct differences in the aetiologies of canine and feline diabetes. In dogs, it is generally thought to be an immune-mediated disease with gradual destruction of beta
cells. The progression from normal to glucose intolerant to diabetes is generally slow so that most islets (over 90%) are lost before diabetes occurs. Other causes of diabetes in dogs include genetic predisposition, chronic pancreatitis, and medication-induced diabetes (glucocorticoids and megestrol acetate).

*Genetic predisposition* to diabetes is most listed as most common in the literature in the following breeds: German Shepherd dogs, Schnauzers, Beagles, and Poodles while Golden Retrievers and Keeshonds are more prone to juvenile diabetes. In Johannesburg we feel female Rottweiler’s are overrepresented

*Gender* is a factor in dogs, with females being three times more likely to develop diabetes than males. Generally, diabetes occurs in dogs in middle age (6–9 years) but can also present earlier for specific breeds, particularly the Golden Retriever and Keeshond.

**CLINICAL SIGNS**
The clinical signs of diabetes include PU/PD (polyuria and polydipsia) from hyperglycaemia, resulting in glycosuria and a resultant osmotic diuresis. Polyphagia and weight loss is common, although many animals will still be obese upon presentation. Cataract formation is very common in dogs with diabetes, but rare in cats. Icterus is not common in dogs unless they have pancreatitis while cats often present with icterus as a result of concurrent hepatic lipodosis and/or pancreatitis.

* Differential diagnoses include: hyperthyroidism (in cats), gastrointestinal lymphoma, hepatic disease, renal disease, pancreatitis, hyperadrenocorticism, and acromegaly.

**DIAGNOSIS**
Diagnosis involves testing for persistent fasting hyperglycaemia, with fasting blood glucose greater than 10 mmol/l. Clinicians also will need to rule out transient hyperglycaemia that may be due to postprandial hyperglycaemia, diabetogenic hormones (endogenous or exogenous), or stress hyperglycaemia [more cats].

Laboratory abnormalities include:
1. Haemogram
   a. Nonspecific
   b. Signs of dehydration
2. Biochemistry profile
   a. Hyperglycemia
   b. Increase in AlP and AlT
   c. Increase in bilirubin (usually in cats)
3. Urinalysis
   a. Glycosuria
      i. Renal threshold for glucose
         a) Canine 10-12 mmol/l
         b) Feline 14 to 17 mmol/l
   b. Ketonuria
   c. NB - Up to 40% of patients will have positive urine cultures in the absence of active urine sediments.

**TREATMENT**
The number one cause of death in diabetic dogs and cats is not the disease itself; rather, it is the owner’s frustration with the disease. This is an extremely important point to remember when treating diabetic animals. Good communication with the pet owner is perhaps the most important component of managing the disease.

It is recommended that clinicians schedule a minimum 30-minute appointment with the client at the time of discharge before sending the diabetic patient home for the first time. During this appointment, clinicians should thoroughly discuss the care required for the patient.

Include the following instructions in that discussion: how to give the animal injections; how to store insulin; what types of food to feed and how often; how to recognize the signs of hypoglycaemia and how to react to this condition. Also include information on what clinical
signs to look for in terms of monitoring water intake and urine production. The clients should be given written instructions for use as a reference once they are caring for the patient at home.

The goals of treatment include elimination of the clinical signs of diabetes, prevention or slowing of cataract formation and resulting blindness, prevention of hypoglycaemia, and prevention and/or treatment of concurrent illness.

Therapy for diabetes centres on: treatment of concurrent illness (i.e., urinary tract infections, pyodermas, etc); insulin therapy; and dietary management.

Concurrent illness: Monitoring for concurrent illness is very important in effectively managing diabetic dogs. One must recognize and treat the other disorders, because the concurrent illness will impact the diabetic regulation, and many common diseases have similar clinical signs to diabetes mellitus. Even simple problems such as gingivitis, UTIs and pyodermas can result in activation of stress hormones and result in insulin resistance.

**GOAL OF DIABETIC MANAGEMENT**
The main goal is the elimination of owner-observed clinical signs by limiting blood glucose fluctuations and maintaining near-normal blood glucose levels. These are achieved through:

- Dietary therapy
- Exercise
- Correct insulin type, frequency and administration
- Avoidance or management of concurrent inflammatory, infectious, neoplastic or hormonal diseases

**Dietary fibre and complex carbohydrates**: Diets containing increased amounts of soluble fibre (fruits, legumes, oats) delay gastric emptying alter intestinal transit time and potentiate the actions of insulin in tissues. Small amounts of insoluble fibre (cellulose, vegetables, and grains) alter intestinal transit time and slow starch hydrolysis. The net effect of a high-fibre diet is to slow glucose absorption from the intestinal tract, reduce postprandial fluctuations in blood glucose and enhance glycaemic control of the diabetic patient.

Feeding any extruded diet is better than tinned or wet food [opposite to the cat]. Canned diets tend to be lower in carbohydrates than dry diets but since complex carbohydrates require digestion before absorption, they minimize postprandial fluctuations in blood glucose concentration. Soft moist foods contain simple carbohydrates, which are rapidly absorbed. These diets may result in rapid fluctuations in blood glucose 30–45 minutes after eating. Soft moist foods also contain large quantities of propylene glycol, which cause postprandial hyperglycemia.

Thin diabetics should gain weight. Obesity induces a state of insulin resistance

**Feeding schedule**: Feeding must be regular, scheduled and always the same amount. Routine is the key to managing diabetic animals. Traditionally feeding occurs twice daily, 12 hourly, with injections, i.e., food in the gut should be providing glucose to the blood at the same time that the injected insulin has its peak effect.

**Exercise**: Regular scheduled exercise helps glycaemic control through weight management and enhanced insulin sensitivity.

**INSULIN THERAPY**
There is concern that animals receiving human insulin will develop antibodies resulting in decreased insulin activity and/or effectiveness. Dogs receiving any insulin product that is not derived from pork may make antibodies. However, studies have shown that those antibodies do not interfere with the glucose control. In fact, dogs that made antibodies against insulin had a longer duration of insulin action, which actually enhanced the effect of the insulin rather than decreased its efficacy.

The options with human insulin include ultrashort-acting, short-acting, intermediate-acting, and long-acting insulins. The short-acting insulins are primarily used for ketoacidosis. The intermediate-acting insulins are classified as either NPH or lente, a mixture of semilente and ultralente, which results in a bimodal onset of actions. This is helpful in some patients
because it helps block postprandial hyperglycemia. It is recommended that NPH be used in the majority of dogs and cats with diabetes, and it is also understood that most patients will require two injections a day to achieve glycaemic control [Protaphane, Humilin]

Short acting insulin: This is represented by the crystalline insulin Actrapid®. It is used chiefly in the management of DKA. It may be given by any route. It has a rapid onset of action (minutes) and a short duration of effect (hours) and is very potent.

Intermediate acting insulin: These are represented by Humulin N and Protaphane®. They are used mainly in the management of canine DM on a twice daily basis given subcutaneously. They have an intermediate duration of effect in dogs (lasting 6–8 hours usually) and are moderately potent. These are both intermediate-acting, human-origin insulins. Suggested starting doses are 0.5 units/kg BID.

Long acting insulin: This is represented by Ultratard®. It has a long duration of effect (usually between 12 and 18 hours) but it is the least potent of all the insulins.

Veterinary insulin: Caninsulin®. A zinc, porcine, intermediate-acting insulin. Canine and porcine insulins have an identical amino acid sequence, thereby eliminating the theoretical complication of anti-insulin antibodies and their effect on glycaemic control. The suggested initial starting dose is 0.5 units/kg BID. This insulin is only available at a concentration of 40 iu/ml, so please make sure that proper insulin syringes are provided to the owner.

Reassessment of clinical signs and a serial blood glucose curve should be performed 1 week after starting therapy. It is regarded as an intermediate acting insulin in cats (usually needing twice daily administration) and a longer acting insulin in dogs so some dogs can be controlled on daily administration (but most still usually need twice daily usage). For additional information, see: www.vetsulin.com.

Glargine [Lantus]: We start at 0.25 to 0.5 IU/kg bd and perform 1st curve after 1 week

Levemir [Detemir]: We start on 0.1 to 0.2 IU/kg bd and perform 1st curve after 1 week

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Starting dose</th>
<th>Median dose</th>
<th>Dose range</th>
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<tbody>
<tr>
<td>NPH</td>
<td>0.25–0.5 U/kg</td>
<td>0.5 U/kg</td>
<td>0.2–1.0 U/kg</td>
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<tr>
<td>Lente</td>
<td>0.25–0.5 U/kg</td>
<td>0.7 U/kg</td>
<td>0.3–1.4 U/kg</td>
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<td>PZI</td>
<td>0.5 U/kg</td>
<td>1.0 U/kg</td>
<td>0.4–1.5 U/kg</td>
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<td>Glargine</td>
<td>0.5 U/kg</td>
<td>0.6 U/kg</td>
<td>0.1–1.1 U/kg</td>
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<tr>
<td>Detemir</td>
<td>0.1–0.2 U/kg</td>
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<td>0.07–0.23 U/kg</td>
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Initial Insulin Treatment of the Diabetic Dog

Intermediate insulins are the initial insulins of choice (Monotard®, Protaphane®, Caninsulin®). These are given twice daily (12 hrly with feeding at each injection). The starting dose is kept up for a period of around a week and a glucose curve is then performed to assess dose. NB – The history and owner opinion on how dog is doing, together with water and food intake is as important as the curve and the two together are used to assess efficacy.

Initial Adjustment of Insulin Therapy

The goal for the first visit after therapy is initiated is not to establish the ideal insulin dose as this takes 4–8 weeks as it takes time for the body to equilibrate to the insulin. Then, the insulin dose should not be adjusted without a full history and a blood glucose curve. The first dose adjustment is not done for at least a week on treatment. The dose will need adjustment if the curve is still too high, the owner continues to complain of clinical signs or if at examination there is ongoing weight loss (if not on diet).
There are a limited number of ways that you can do to get “good” glucose curves:
1. Do glucose curves
2. Change the insulin dose to affect the nadir
3. Change the frequency of insulin dosage to affect the duration of effect
4. Eliminate causes of insulin antagonism
5. Ensure that the owner is storing, drawing up and injecting the correct volume (this is still one of the most common problems with DM control)

**GENERATING SERIAL BLOOD GLUCOSE CURVES**
Blood glucose should be measured every 2 hours for minimum 12 hours but ideally 24 hrs. It should always include the lowest blood glucose level (Nadir) and the peak blood glucose level and be close to an insulin administration. This is best done at home but in hospital curves are acceptable (hospitalization is stressful and may make readings higher in nervous dogs). If the blood glucose drops under 6 mmol/l, increase readings to hourly to ensure you capture the nadir reading. Remember, most hand held glucometers under-read blood glucose to prevent missing hypoglycaemia in human patients.

*Common errors* - Running 1 to 3 readings per day or monitoring urine dipstick’s will NOT GIVE you enough intel to make an informed change to the insulin dose. The ideal curve does not exist, we aim to keep glucose between 6.5 and 15 mmol/l and not below 5.5 mmol/l but the owner feedback is as important as the info you derive from the curve so interpret all results together and believe the owner and the clinical examination if it does “not agree” with the curve information. Insulin doses should not be changed by more than 10 to 25% at a time and not more frequently than weekly

**QUESTIONS WE ASK OF THE SERIAL BLOOD GLUCOSE CURVE**
*Is the patient insulin sensitive?* i.e., does the insulin dose have any glucose lowering effect?
Insulin resistance should be considered if the dose used is more than 2 IU /kg /dose in the dog.

*What is the lowest point to which the glucose drops (the glucose nadir)?* Not below 6mmol/l and if higher than 9-12 mmol/l the dose should be increased.

*What is the insulin’s duration of effect?* Duration of effect is defined as the time from insulin injection until blood glucose increases to beyond 12–14 -16 mmol/l.

**WHAT ABOUT FRUCTOSAMINE ?**
Proteins left in the presence of high glucose concentrations will glycate with time and becomes a marker of blood glucose concentrations during the circulating life span of the protein. Glycation takes a long time to occur and is permanent once it has happened. The concentration of a glycated protein thus becomes a reflection of the average glucose control over a long time. The assay requires blood to be drawn and frozen and couriered frozen to the lab and is only helpful in cases that are poorly controlled all the time. In cases that swing widely from high BG around 20-25 down to under 8 mmol/l will usually have normal Fructosamine levels.

**COMPLICATIONS OF INSULIN THERAPY**

*Hypoglycaemia:*
Clinical signs include weakness, shivering, tachycardia and ultimately seizures (due to neuroglycopaenia). This occurs in long term diabetics when the correct extruded diet and insulin, together with weight loss, give good control. It also can occur with sudden increases of insulin dose, sudden poor appetite, strenuous exercise or using insulin twice a day when the duration of effect overlaps slightly and the previous injection has additive effects on the later injection. Treatment must be prompt and can be per os or IV.

*Somogyi Over-Swing Phenomenon:*
Due to a physiologic response to hypoglycaemia, when the blood glucose drops to below 3.3 mmol/l in the non-diabetic dog or a higher level in uncontrolled diabetics (the longer you are diabetic the higher the Somygi overswing threshold sets) or falls very quickly (not only level,
but also rate) catecholamines, cortisol, growth hormone and glucagon are realised and they increase BG. This patient will persist with its diabetic signs, because it still has high glucose levels. The clinician’s "knee jerk” response (a response based on clinical signs alone without glucose curve information) is to raise the insulin dose.

**Short Duration of Insulin Effect:**
The objective of any treatment plan is to try and keep blood glucose below renal threshold for as much of the day as possible. Correction involves increasing the frequency of insulin dosage or using an insulin with longer duration of effect. This is where we reach for Levemir and/or Glargine.

**INSULIN RESISTANCE**

*Definition:* Resistance should be suspected if the dose goes above 2 IU/kg/dose. The most common cause of this is poor technique on the part of the owner.

*Obesity:* Reversible insulin resistance occurs because of down regulation of receptors.

*Administration techniques and insulin activity problems:* Ensure that you observe the person who injects the insulin so that it is given properly. Insulin is stored in a sealed container in the fridge drawer to avoid temperature changes. The insulin should be rolled not shaken as it is a sensitive protein.

*Impaired insulin absorption:* Vary the injection site. If only one site is used, there will be skin thickening which will delay absorption.

*Concurrent diseases causing insulin resistance:* In dogs, Cushing’s disease, bacterial infections, organ insufficiency, pancreatitis, di-oestrus and hypothyroidism should be considered important causes of insulin resistance.

**REFERENCES:**