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MANAGEMENT OF THE COMPLICATED DIABETIC

Debra L. Zoran, DVM, PhD, Diplomate ACVIM
Texas A&M University
College Station, TX

INTRODUCTION
Diabetes mellitus is a common endocrinopathy in dogs and cats, and in most animals presents as a problem that is readily recognized and managed with routine diagnostic and therapeutic approaches. However, there are always exceptions to every rule, and this true for diabetes as well. This manuscript will review the recognition and management of insulin resistance, diabetic ketoacidosis, and the very uncommon, but challenging problem of nonketotic, hyperosmolar diabetes.

The Complicated Diabetic –
Insulin Ineffectiveness or Insulin Resistance?
There are a number of factors that must be assessed in a dog or cat with diabetes that does not have adequate glycemic control. The first step is to determine whether the patient is an uncontrolled diabetic because of ineffective insulin or because of insulin resistance. There are many recognized causes of insulin ineffectiveness, and these include:

- inactive insulin
- diluted insulin
- improper administration technique
- inadequate dose
- somogyi effect
- inadequate frequency of insulin administration
- impaired insulin absorption
  (especially long acting insulins)
- anti-insulin antibody

Insulin effectiveness should be assessed first, as it is the simplest group of problems to recognize and treat. Insulin ineffectiveness can be caused by inactive insulin, which is most often due to improper handling (e.g. insulin was damaged by heat or being dropped, shaken, etc). This problem is easily assessed by re-evaluating the patient after administration of insulin from a new bottle. In small animals, insulin is often diluted to make it easier for owners to see and draw up the appropriate amount; however, this is not recommended and only should be done when absolutely necessary, and should be done by a pharmacist. Improper insulin administration can also cause insulin ineffectiveness – especially if the insulin is inadvertently injected into the hair. It is always advisable to re-evaluate the owner’s technique when a diabetic is not responding as expected to the therapy.

In addition to owner-related causes of insulin ineffectiveness, there are several that are under the direct control of the veterinarian in charge: dose, frequency, and somogyi effects. These problems are best evaluated by performing a serial glucose curve, which will determine the nadir of insulin effect, the duration of it’s effect and whether or not a somogyi phenomenon is likely. The nadir of the blood glucose is most important for determining whether a somogyi effect is occurring (e.g. a blood glucose below 60 mg/dL is highly suggestive and below 100 mg/dL is suspicious – whether or not clinically evident hypoglycemia is observed). In addition, the nadir is important in determining whether or not the insulin is having the desired effect (e.g. a reduction in blood glucose) and at what time (e.g. is there the potential for insulin overlap if the nadir occurs close to the time for the next insulin injection – thus increasing the risk of hypoglycemia with the next dose). In addition to dosing and insulin duration problems, impaired insulin absorption should be considered next. The most common culprit for impaired insulin absorption is the use of long acting insulins, such as ultralente or PZI. While some cats do very well on PZI insulin given once daily, it is not unusual for them to require it twice daily due to its variable absorption. In dogs, this is even more likely, and thus, there is no advantage to the use of this insulin at all in dogs. Finally, development of insulin antibodies can be a problem in a small number of dogs and cats. Canine insulin most closely resembles pork insulin, while feline insulin is closest to beef insulin. Thus, where possible use of beef insulin in cats (e.g. PZI is a beef/pork mixture), or pork insulin (Pork Lente) in dogs is desirable. Because animal source insulins are less readily available than human recombinant insulin (e.g. Humulin), many animals are placed on these insulins first. In general, this is a reasonable practice, as it is uncommon for antibodies to form. Nevertheless, it is a problem that should be considered in an animal that suddenly is not responding to insulin therapy as expected.

Once the causes of insulin ineffectiveness are ruled out, the causes of insulin resistance should be considered next. There are a number of major causes of insulin resistance, and they include:

- diabetogenic drugs
- hyperadrenocorticism (dogs)
- diestrus (dogs)
- acromegaly (cats)
- infection (periodontal disease, UTI)
- hypothyroidism (dogs)
- hyperthyroidism (cats)
- renal insufficiency
- liver insufficiency
- cardiac insufficiency
- glucagonoma (dog)
- pheochromocytoma
- chronic inflammation, especially pancreatitis
- exocrine pancreatic insufficiency
- severe obesity
- hyperlipidemia
- neoplasia

The most common causes of insulin resistance in dogs is hyperadrenocorticism or exogenous steroids, bacterial infection, hypothyroidism, and diestrus (in that order). In cats, acromegaly, hyperadrenocorticism, and renal failure are the most common (with similar prevalences of 15-18%), with hyperthyroidism, infection and steroids being next. In cases where insulin resistance is suspected, these disorders should be carefully ruled out before consideration of the less common causes of the problem. It is also important to recognize that there is no insulin dose that clearly defines insulin resistance; however, for most dogs (and cats), good control can be achieved with a dose of insulin near or less than 1 U/kg/dose, and insulin resistance should be suspected if the dog or cat has poor glycemic control and is receiving a dose of insulin greater than 1.5 u/kg/dose. There is no definitive fructosamine level that defines insulin resistance, but levels greater than 700 mg are suggestive. Further, it is
also important to recognize that insulin resistance can be mild, and thus easily overcome by increasing the insulin dosage, or severe, where the animal is not responsive to any type or dosage of insulin. Thus, if an animal has been well controlled previously, but now requires increasing dosages of insulin to maintain glycemic control, mild forms of insulin resistance should be considered.

**DIABETIC KETOACIDOSIS (DKA)**

Ketoacidotic diabetes is confirmed by the presence of the clinical signs of diabetes, hyperglycemia, glucosuria, ketonuria, and metabolic acidosis. In most cases, ketoacidotic diabetics are clinically ill (e.g. vomiting, anorexia, dehydration, weakness, etc), in addition to having the standard signs of diabetes. Severely unregulated diabetics may have ketones in their urine (ketotic diabetes), but in the absence of metabolic acidosis, they are not considered to have DKA, and do not require the same aggressive therapeutic approach to manage their disease. Because many animals with DKA are extremely ill, diagnostic evaluation and initiation of therapy must occur quickly and concurrently.

Clinical evaluation of the DKA patient requires immediate laboratory evaluation to aid in the determination of a treatment protocol. The minimum required tests for assessment of a DKA patient are urinalysis, quantitative urine glucose, hematocrit, total protein, blood glucose, venous TCO2 assessment of a DKA patient are urinalysis, quantitative urine ketones, blood gases, and electrolyte concentrations.

**THERAPEUTIC CONSIDERATIONS**

Therapy of DKA patients requires an aggressive and coordinated effort to restore fluid volume, correct acid base disturbances and electrolyte abnormalities that are life threatening, and then initiate control of hyperglycemia and hypoinsulinemic metabolic problems (hypertriglyceridemia, etc). Fluid therapy goals include volume resuscitation, rehydration, and correction of hyponatremia and hypochloremia. The fluid chosen should be an isotonic, sodium-based crystalloid solution such as 0.9% sodium chloride, lactated ringers, plasmalyte-148, or normosol-R. Each of these fluids will replace sodium adequately, however, the balanced polyionic solutions also provide bicarbonate precursors (e.g. lactate, acetate or gluconate) that may assist with correction of acidoses. The rate of fluid administration should be based on replacement of losses, correction of dehydration, and providing maintenance fluids.

- Maintenance fluids (ml fluid) = BW (kg) x 80 ml/kg/day
- Dehydration (ml fluid) = BW (kg) x % dehydration (0.10 for 10%) x 1000 ml/kg
- Ongoing losses = estimate ml

Total requirement in ml is divided by 24 hours to give amount in ml/hour.

**HYPOKALEMIA**

Potassium replacement can be addressed by one of two methods:

- Potassium replacement scale: use with mild to moderate hypokalemia
  
<table>
<thead>
<tr>
<th>Serum potassium</th>
<th>mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3.5</td>
<td>20</td>
</tr>
<tr>
<td>3.0-3.5</td>
<td>40</td>
</tr>
<tr>
<td>2.5-3.0</td>
<td>60</td>
</tr>
<tr>
<td>&lt;2.5</td>
<td>80</td>
</tr>
</tbody>
</table>

- Potassium replacement by calculation: use with severe hypokalemia
  
  0.3-0.5 mEq/kg/hr = mEq/hr
  
  Add amount of potassium in mEq to fluid to give rate/hour (e.g. if fluid rate is 25 ml/hr, add potassium to bag of fluids (or biuret or syringe pump, etc) at the concentration calculated x ml/hr

  - RECHECK serum potassium every 4 hours when administering potassium at high rates and reduce potassium in fluids as the levels increase
  
  - Do not start insulin therapy until potassium levels are improved to avoid iatrogenic worsening of the hypokalemia

In patients with severe, concurrent hypophosphatemia, use potassium chloride and potassium phosphate in a 50:50 mixture to replace the potassium.

If the phosphorus is not severely decreased, calculate the phosphorus supplementation by 0.01-0.03 mmol/kg/hr and give separately to avoid oversupplementation.

**HYPOPHOSPHATEMIA**

Hypophosphatemia is becoming increasingly recognized as more laboratories measure serum magnesium as part of their routine panels. Mild hypomagnesemia can be corrected with crystalloids containing magnesium (plasmalyte or normosol-R). However, with severe deficits of magnesium (less than 1.2 mg/dl), a magnesium sulfate infusion (in 5% dextrose) can be administered (1 mEq/kg/day in a constant rate infusion). Monitoring the magnesium levels is important, as the infusion needs to be stopped or decreased as soon as the levels are normal to prevent serious hypermagnesemia (which can cause cardiac arrhythmias).

**BICARBONATE THERAPY FOR ACIDOSIS**

Bicarbonate therapy is controversial due to the that there is no evidence in humans that it improves survival, and aggressive bicarbonate therapy can result in paradoxical CSF acidosis (coma, death). Thus, bicarbonate therapy is not recommended unless the pH is < 7.0, the bicarbonate levels are less than 10 mmol/L, and the patient is becoming mentally dull or comatose as a result of severe acidosis. If bicarbonate therapy is used, only administer half of the calculated dose over 4-6 hours, and then re-assess.
Bicarbonate deficit = base deficit x BW (kg) x 0.3

**Insulin Therapy**

There are three protocols for management of DKA described in the veterinary literature (all using regular insulin):

- IV insulin CRI (2.2 U/kg/day in 0.9% NaCl for dogs, 1.1 U/kg/day for cats)
- IM insulin hourly (0.2 U/kg IM first hr, 0.1 U/kg hourly thereafter until BG < 300, then shift to q4h)
- IM insulin administered every 4-6 hours (0.25 u/kg q4h)

All three are effective in reducing blood glucose and controlling ketogenesis, so the protocol chosen should be based on the experience and preference of the clinician.

In animals that are hyperosmolar or there is a concern that too rapid a decrease of glucose may trigger a hyperosmolar crisis, the IM insulin administered q4h is the safest approach. No matter which protocol is chosen, blood glucose levels must be monitored every 2-4 hours, so that when the glucose levels drop to less than 250 mg/dl, 2.5-5% dextrose is added to the IV fluid therapy. Once the patient is stable (and eating) and ketosis is resolved, the insulin can be switched to an intermediate acting insulin for long term therapy.

**HYPEROSMOLAR NONKETOTIC DIABETES MELLITUS**

The form of diabetes is a very uncommon complication of diabetes in the dog and cat. The syndrome is characterized by severe hyperglycemia (> 600 mg/dl blood glucose), hyperosmolality (> 350 mOsm/kg), and dehydration in the absence of significant ketosis. Patients with this condition often present obtunded or in a coma, due to the severe hyperosmolality. This condition appears to occur more commonly in patients with concurrent renal or cardiac failure, and the prognosis is certainly worsened with the presence of either. This syndrome can also be precipitated by concurrent pancreatitis, sepsis or steroid therapy. In general, the hyperglycemia of hyperosmolar DM tends to be much more severe (600-1600 mg/dL) than that of DKA (600-800 mg/dL). This is due to a combination of impaired glucose excretion (in urine), and in the absence of ketosis there are no early clinical signs, so the hyperglycemia is allowed to progress for a longer time until it is noticed.

The therapy of hyperosmolar DM is similar to treatment of DKA: correct dehydration, restore electrolyte losses, and provide insulin to correct metabolic defects, but the big difference is correction of the hyperosmolar state with fluid therapy (0.9% NaCl) and stabilization of the hyperosmolar state before starting insulin therapy. The main reason is that a rapid decrease in blood glucose can cause rapid decreases in extracellular fluid osmolality, which can promote development of cerebral edema. Unfortunately, unlike DKA, the prognosis for recovery in animals with hyperosmolar DM is poor, as most die from renal failure.

**REFERENCES**