INTRODUCTION
Management of a patient with Diabetes Mellitus can be quite rewarding, but at times also quite challenging. While a majority of patients regulate easily with standard protocols, a subset can prove problematic with persistence of clinical signs, persistent hyperglycemia, & lab work changes consistent with unregulated endocrine disease despite appropriate care. Relapse of a previously regulated patient can also occur, despite previously effective therapy. When a diabetic patient is treated with exogenous insulin and the clinical signs of disease fail to improve despite appropriate dosing and/or the dose approaches 1 unit/kg of body weight twice a day (ranges up to 2 units/kg published), an investigation for diseases which causes insulin resistance should be pursued.

PHYSIOLOGY
Insulin is a hormone that is adjusted constantly in basal and postprandial phases to maintain euglycemia in the dog and cat. Insulin attaches to an insulin receptor on cell membranes. This facilitates the opening of glucose channels and promotes glucose uptake into the cell. Insulin also is involved in signaling pathways associated with lipid and protein metabolism. When considering insulin resistance, we think of possibilities that may prevent the insulin from reaching the receptor, affect its attachment to the cell membrane, and/or affect its intracellular mechanisms.

Pre-receptor causes can include insulin degradation, inappropriate insulin handling, insulin antibodies, and lack of appropriate subcutaneous absorption. Receptor and post-receptor causes include all those which effect insulin binding & its intracellular pathways. Many causes can be implicated, but the most common in our patients include: drug use (prednisone), infection (urine, dental), inflammation (pancreatitis), neoplasia, obesity, and other concurrent endocrinopathies (hypothyroidism, acromegaly, Cushing’s disease, hyperthyroidism, hypertriglyceridemia). Lack of insulin responsiveness with concurrent disease leads to further beta cell exhaustion and perpetuation of hyperglycemia and clinical signs.

PATIENT HISTORY & CLINICAL SIGNS
Dog and cat patients typically present for continued weight loss, persistence of polyuria, polydypsia, & polyphagia, and/or possibly ketonuria. A thorough diagnostic work-up is necessary to determine if an insulin overdose OR insulin resistance is present, as clinical signs can be similar.

DIAGNOSIS
A minimum database for any unregulated patient should include a CBC, serum chemistry, urinalysis, and urine culture. Keep in mind that renal insufficiency, liver disease, and cardiac disease are all associated with insulin resistance in addition to those mentioned above. A 12-24 hour blood glucose curve should be performed, to determine if a Somoygi effect is noted or if there is chronic persistent hyperglycemia. This study will also allow the clinician to assess the
nadir of the current insulin preparation and thus the duration of action of the current insulin preparation. A spot blood glucose should never be used to guide therapy unless it shows evidence of hypoglycemia.

An elevated serum fructosamine level can be used to confirm dysregulation, but is often not necessary with concurrent routine urine glucose monitoring or blood glucose curves. After its first use as a tool to confirm the disease process in virgin diabetic patients, an elevated fructosamine value CANNOT predict if more or less insulin is needed. It can simply identify that the patient is not well regulated.

Imaging can be pursued to evaluate for concurrent neoplastic disease (thoracic +/- abdominal x-rays, abdominal ultrasound) amongst other causes of resistance such as pneumonia, pancreatitis, intestinal disease, and adrenomegaly. In addition, the following disease processes (and associated tests) should be considered in the appropriate patients.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DOG</th>
<th>CAT</th>
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<tbody>
<tr>
<td>Hypothyroidism</td>
<td>T4/FreeT4 +/- Panel</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Uncommon</td>
<td>T4 +/- FreeT4</td>
</tr>
<tr>
<td>Cushing’s Disease</td>
<td>ACTH Stimulation and/or LDDS</td>
<td>LDDS</td>
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<tr>
<td>Exocrine Pancreatic Insufficiency</td>
<td>Fasted TLI</td>
<td>Fasted TLI</td>
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<tr>
<td>Acromegaly</td>
<td>Uncommon</td>
<td>IGF blood level +/- CT or MRI</td>
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<tr>
<td>Hypertriglyceridemia</td>
<td>Fasted TG level</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>cPL (Quantitative PLI)</td>
<td>fPL (Quantitative PLI)</td>
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An endogenous insulin level may be helpful in determining the presence of insulin resistance but is often not necessary with the rest of the database. Intact females should be spayed as hormones associated with diestrous can cause significant insulin resistance.

**TREATMENT**

If a short duration of action, or lack of a response to an appropriate dose of insulin is noted, a change in insulin preparation should be considered. It is vital to review insulin storage, administration technique, and handling with all the clients involved in the patient’s care. This includes visually inspecting the insulin syringe to ensure the proper concentration (U-40 vs. U-100) is being used.

If a concurrent illness is found and treated, resolution of the insulin resistance is expected. Owner monitoring at home (urine or blood) is vital, as with disease regulation hypoglycemia may become apparent as insulin resistance resolves. This is also true for diet management and weight loss.

Urine glucose monitoring (Keto Diastix) and blood monitoring (AlphaTrak 2) are helpful for reviewing patient progress and guiding your client therapy. Self adjustments based on individual numbers (as is seen in human diabetics) does not typically work well in the canine and feline patient.
PROGNOSIS
The prognosis for insulin resistance is typically good as long as the underlying cause is identified and treated. In the presence of multiple co-morbidities, the regulation can be much trickier and the prognosis for complete resolution of clinical signs can be fair to guarded. General goals of therapy should include a resolution of the clinical symptoms that affect the patient welfare, as well as a goal of blood glucoses in the 150-300 mg/dL range over the course of the insulin’s action.

With some insulin resistant processes which cannot be cured (or finances limit cure), such as advanced renal disease, heart disease, acromegaly, and neoplasia, recurrence of ketoacidosis and hyperosmolar-like syndrome can move the prognosis to guarded to poor.

SELECTED REFERENCES