There are a number of endocrine based disease states that can result in a patient presenting in a crisis, including some cats with hyperthyroidism, or even dogs in a myxoedema coma with hypothyroidism, this presentation will concentrate on three particular disease states – Diabetic Ketoacidosis, Hypoadrenocorticism and Hypoglycaemia.

**Diabetic Ketoacidosis**
Diabetic Ketoacidosis (DKA) is a serious complication of diabetes mellitus seen in both dogs and cats. In some situations patients will not recover despite therapy, and the therapy itself can be quite challenging in some patients.

**Pathophysiology**
Ketone bodies are produced as a result of the oxidation of free fatty acids in the liver, and can be used as an energy source by many tissues in times of relative glucose deficiency. Free fatty acids in the liver can be incorporated into triglycerides, may be metabolised in the TCA cycle to carbon dioxide and water, or can be converted into ketone bodies. There are three main ketones bodies are acetoacetate, $\beta$-hydroxybutyrate and acetone. The acetoacetate is produced directly by oxidation of free fatty acids, and can be reduced to $\beta$-hydroxybutyrate. Acetone is produced by the spontaneous decarboxylation of acetoacetate. Ketones are metabolised with other substrates in peripheral tissues and the liver as an energy substrate, but if their production is excessive they can accumulate in the circulation. In the absence of insulin, or in a situation of relative insulin deficiency there can be increased lipolysis and mobilisation of free fatty acids from adipose tissue and a shift from fat synthesis to fat oxidation and production of ketone bodies in the liver.

Levels of counter-regulatory hormones such as catecholamines, cortisol, growth hormone and glucagon can increase in a number of different disease states. These hormones can all have beneficial effects in states of illness and stress. However they can all cause insulin resistance, stimulate lipolysis and increase ketogenesis, which becomes an issue in a patient that is diabetic. The result can be a progressive decline in an affected animal’s metabolic status.

In diabetes mellitus there is a physiological state of tissue starvation. Initially the development of ketones is not detrimental as ketones can provide an energy source for many tissues. However as the glucose and ketone levels rise the threshold for renal tubular resorption is exceeded, resulting in an osmotic diuresis. The ketones are negatively charged so positively charged ions, such as sodium, potassium, calcium and magnesium are drawn with them to maintain electrical neutrality. The result is a loss of electrolytes and water, with resultant hypovolaemia and reduced tissue perfusion. Insulin deficiency in itself can result in increased renal loss of water and electrolytes, and also results in protein catabolism, reduced
protein synthesis and a negative nitrogen balance. There are often significant losses of potassium and phosphorus as well, which must be considered for therapy.

When ketones are produced in the liver, equivalent numbers of hydrogen ions are also produced. The buffering system eventually becomes overwhelmed with increased hydrogen ion and reduced bicarbonate concentrations, and a resultant metabolic acidosis. This stimulates the chemoreceptor trigger zone with resultant vomiting, causing further loss of volume and electrolytes. The patient will typically have reduced food and water intake, exacerbating the hypovolaemia. The metabolic acidosis worsens, and the hypovolaemia results in reduced renal perfusion, glomerular filtration rate (GFR) and azotaemia can ensue. The reduced GFR further reduces renal excretion of glucose, ketones and hydrogen ions. Plasma osmolality can increase, and this results in cellular dehydration, which can result in neurological signs. Ultimately if left untreated diabetic ketoacidosis can be fatal.

**Signalment**

Given that ketoacidosis is a complication of diabetes mellitus, the signalment of affected animals is going to reflect that seen for diabetes. Whilst animals of any age can be affected, it is more common in middle aged to older animals, and any breed can develop DKA. There is a suggestion that DKA is more common in female dogs and male cats. A non spayed female dog is more at risk of DKA because of the hormonal changes that occur in dioestrus.

**History**

The history of affected animals can vary significantly. Some patients may have been previously diagnosed with diabetes mellitus, whereas some will not. In animals that have already been treated they may become acutely unwell with signs of inappetance and vomiting. These could be patients that were somewhat brittle with their diabetic control, or patients that had been well controlled. Animals that had not been previously diagnosed with diabetes may have preceding signs of diabetes such as polyuria, polydipsia, polyphagia and weight loss, that may be short term or even long term in nature, but others will present with owners having been unaware of such signs. Some patients may present still systemically well, whereas others will present with signs of severe illness. In some patients there may be historical signs that relate to the underlying disease that is causing insulin resistance. These could include clinical signs of a urinary tract infection, pyometra, acromegaly in cats (such as conformational changes), and other metabolic diseases such as renal failure or hyperthyroidism.

**Physical Examination**

A thorough physical examination is always indicated on a patient with DKA. Clinical signs of ketoacidosis could include sweet smelling breath, but this may not be detected in all patients or by all examiners. The hydration status should be evaluated. Vital signs are important – a fever may reflect underlying disease, and marked bradycardia could suggest that hyperkalaemia may be a risk. There may be non specific signs of illness such as obtundation, weakness etc. Slow, deep respiration may be a reflection of metabolic acidosis. There may be signs detected of underlying disease such as vaginal discharge, abdominal pain or distension, enlarged lymph nodes, systolic heart murmurs, signs of alopecia, this skin or hyperpigmentation or abnormal lung sounds.

**Diagnostics**
There are different levels of diagnostics indicated in patients with diabetic ketoacidosis. The initial step is to confirm the presence of diabetes and an indication of accumulation of ketones. This can simply be achieved by checking a blood glucose on a glucometer or in house analyser, and a basic evaluation of a urine sample with a specific gravity and dipstick. Hyperglycaemia and glucosuria are consistent with diabetes mellitus, and the presence of ketonuria indicates a diagnosis of diabetic ketosis at a minimum or potentially diabetic ketoacidosis (especially if they are unwell). The urine test strips detect acetone and acetoacetic acid, but not β-hydroxybutyrate. If there is severe hypovolaemia, tissue hypoxia or lactic acidosis there can be relatively more β-hydroxybutyrate, so the urine test strips may have reduced sensitivity.

The degree of diagnostic evaluation can vary with the severity of the clinical disease. A ‘well’ ketonuric diabetic potentially does not require as much investigation as an unwell patient. In the unwell patient it is important to determine the underlying disease that is almost certainly present so that it can be corrected. There are some important values that would ideally be evaluated in any patient that is diabetic and ketonuric. This includes a blood glucose, serum electrolytes, an evaluation of the acid base status, and a urinalysis.

A complete blood count will not necessarily have characteristic results. There may be elevations in the haematocrit if there is haemoconcentration, or may be reduced as a result of chronic disease. There may be alterations in the leucogram – potentially a stress leucogram, or an inflammatory leucogram depending on the underlying disease. The platelets may be normal, potentially elevated if there is inflammation, or they may be reduced if there is a severe underlying disease and disseminated intravascular coagulopathy.

The biochemical profile may have some changes as a result of the diabetic ketoacidosis. There can be alterations in the sodium level, most commonly a hyponatraemia. The hyponatraemia can be the result of natriuresis as a result of osmotic diuresis and insulin deficiency (as insulin promotes distal renal tubular sodium resorption), a dilutional effect of hyperglycaemia, along with gastrointestinal losses. There is typical a whole body deficiency of potassium as a result of urinary losses due to diuresis, but the serum potassium concentration may be elevated in some cases as a result of a transcellular shift as a result of metabolic acidosis and also impaired potassium entry into cells as a result of insulin deficiency. There will typically be a metabolic acidosis as evidenced by a reduced bicarbonate concentration. An elevated anion gap (measured or calculated using the formula AG= (Na + K) – (Cl + HC03)) is typically detected and reflects a metabolic acidosis. The serum osmolality can be measured directly, or can be calculated using the formula 2(Na + K) + Glucose. The serum osmolality may be elevated in some patients with DKA, and is important to consider when treating affected patients. The urea and creatinine may be increased as a result of a pre-renal azotaemia, but in some cases there may be concurrent renal azotaemia. The liver enzymes may be elevated because of a primary hepatopathy, the diabetes itself, or secondary to hyperadrenocorticism. The serum calcium level is typically normal, but can be reduced or increased if there is concurrent renal failure, or may be reduced if there is pancreatitis. The serum phosphorus is variable, but is important to consider in terms of therapy. Cholesterol and triglyceride levels are commonly elevated in DKA patients as a result of insulin deficiency. Amylase and lipase have limitations in the diagnosis of pancreatitis. If a patient undergoing therapy for DKA has resistant
hypokalaemia despite supplementation a magnesium level can be assessed, as correction of hypomagnesaemia can aid in correction of hypokalaemia.

A urinalysis and urine culture is indicated on all patients with DKA. Diabetes mellitus can sometimes mark the signs of a urinary tract infection, so even in the absence of pyuria a culture is indicated.

Further diagnostic testing is often directed at searching for an underlying disease that could be the source of insulin resistance typically present in a DKA patient, or to evaluate the overall condition of the patient. An ECG can be used to assess if cardiac arrhythmias are present as a result of alterations in serum potassium. Thoracic radiographs and abdominal ultrasonography are useful to search for underlying disease. Blood gas analysis can provide a more precise assessment of the acid base status to help guide therapy. Pancreas specific lipase levels can help determine in pancreatitis is present or not. Adrenal function testing is rarely indicated in the acute setting of a DKA patient as significant non-adrenal illness can result in false positive results.

**Therapy**

The therapy will differ between a healthy diabetic with ketosis but not acidosis and a patient with DKA. In a healthy patient there is the option of regular insulin therapy, given subcutaneously every 8 hours at a dose rate of 0.1 – 0.2 U/kg. The regular insulin is continued until the ketonuria has resolved, and then a more standard insulin therapy would be replace the regular insulin. The other alternative is a more standard insulin initially, with close monitoring of the patient for any signs of deterioration, and monitoring of the urine ketones to ensure they are clearing.

There are a number of aspects of therapy of an ill ketoacidotic diabetic patient. One important aspect that will not be directly addressed here is that the underlying disease that is the source of the insulin resistance should be treated. For example a bacterial infection should be treated with appropriate antimicrobial therapy, or in the case of a female dog with a pyometra an ovariohysterectomy should be performed as soon as the patient is stable enough for surgery.

Fluid therapy should be the first step in therapy. The fluids will correct dehydration, improve blood pressure and tissue perfusion, improve urine production and can help lower blood glucose concentrations, but they will not lower the blood concentration of ketone bodies. The electrolyte levels will dictate the fluid type, but 0.9% saline is often a suitable choice based on the expected total body sodium deficits. If 0.9% saline is not available a balanced electrolytes solution will be suitable. The fluid rate should be based upon calculation of the fluid deficit, ongoing losses from vomiting and maintenance requirements. Replacement of fluid deficits over 24 hours is often sufficient, unless there are signs of hypovolaemic shock. Care should be taken in a patient that appears to have significant hyperosmolality, as there is a risk of cerebral oedema if the serum osmolality is dropped too rapidly. There should be close monitoring to ensure the patient is producing urine, along with heart rate, respiratory rate, mucous membrane colour, capillary refill time and body weight. Blood pressure should be monitored if possible. An indwelling urinary catheter is an option to allow precise measurement of urine production.
The majority of patients with DKA will have a significant deficit in total body potassium, no matter whether the serum potassium is low, normal or elevated. Potassium should be supplemented aggressively initially unless there is a measured hyperkalaemia, as the serum potassium will tend to drop rapidly with fluid and insulin therapy as the levels will fall as potassium moves intracellularly with correction of the metabolic acidosis and the insulin therapy. Typically at least 30 mmol/L of potassium will be added to the 0.9% saline, and potentially up to 60 mmol/L if there is severe hypokalaemia. Care should be taken to ensure the rate of potassium supplementation does not exceed 0.5 mmol/kg/hour. In patients with severe hypokalaemia a separate potassium infusion can be administered. The serum electrolytes should ideally be monitored every 8 hours, and if possible a blood gas analysis is preferable to help assess the acid base status. Magnesium supplementation may be indicated in hypomagnesaemic patients with refractory hypokalaemia.

Phosphate supplementation may be indicated in patients that develop hypophosphataemia. Rapid development of hypophosphataemia can result in weakness, ataxia, or more significantly haemolysis. There is debate about the value of phosphate supplementation as a prophylactic measure in patients that are not hypophosphataemic. If required potassium phosphate is added to calcium free intravenous fluids and is administered at a rate of 0.01 – 0.03 mmol/kg/hour. The phosphate should ideally be assessed at least every twelve hours, and the supplementation can be discontinued once the serum phosphate normalises.

Bicarbonate supplementation is a controversial topic in the treatment of patients with DKA. Some advocate its supplementation in patients with severe metabolic acidosis, and a pH of < 7.1. If supplementing the amount required can be calculated using the formula

Bicarbonate Supplementation = 0.3 x Base Deficit x Body Weight

However the majority of patients will spontaneously correct any acid base abnormalities with correction of fluid deficits and appropriate supplementation of insulin.

Insulin therapy will always be required to correct diabetic ketoacidosis, as insulin inhibits lipolysis, suppresses hepatic gluconeogenesis and promotes glucose and ketone metabolism in tissues. The insulin therapy can be delayed a few hours to allow initial fluid therapy and potassium supplementation. Regular insulin is the insulin of choice as it has a rapid onset and short duration of action. It can be administered via a number of routes, including intravenously, intramuscularly or subcutaneously.

In critical patients an intravenous infusion of regular insulin is preferable. There are a number of techniques described with variable insulin concentrations and rates utilised. A simple technique is the addition of 25 units of regular insulin to a 500 ml bag of 0.9% saline, making a 50 mU/ml solution. Ideally 50 – 100 ml of the solution should be run through the administration set and discarded. The infusion is then administered using an infusion pump at a rate of 25 mu/kg/hour (0.5 ml/kg/hour). This is a conservative rate and will slowly drop the blood glucose level. The blood glucose level will normalise before the ketones, and so ketonuria may persist for two to four days. When the blood glucose level falls to approximately 12 mmol/L, the intravenous fluids should be supplemented with glucose at a rate of 2.5%.
There are alternative techniques of regular insulin administration described. There is an intramuscular technique of an initial dosage of 0.2 u/kg, then 0.1 u/kg hourly until the blood glucose is 12 mmol/L, and then the insulin is administered subcutaneously every 6 hours. If there is less ability for close monitoring of patients the regular insulin can be administered at a dose rate of 0.25 – 0.5 U/kg subcutaneously every 6 – 12 hours as needed.

Ongoing monitoring of the patient is important. The blood glucose should be measured every 2-4 hours initially. The placement of a central venous catheter can ease blood collection. As discussed previously there should be close clinical monitoring of vital signs, hydration status, urine output, urine glucose and ketones, PCV/TP, serum electrolytes, phosphorus and acid base balance. Other parameters may be monitored depending on the underlying disease such as biochemical profiles, haematology, or imaging studies. Once the patient has normal hydration, an acceptable appetite, negative urine ketones, and controlled blood glucose levels the patient could have intravenous fluids discontinued, and be commenced on a more standard insulin regime.

Complications of therapy can include hypoglycaemia, cerebral oedema, severe hypokalaemia, severe hypophosphataemia and haemolytic anaemia, and occasionally severe hypernatraemia and hyperchloraemia. These complications can be minimised by conservative therapy and appropriate monitoring. If cerebral oedema occurs mannitol therapy may be indicated. If hypophosphataemia occurs with haemolysis intravenous phosphorus supplementation is required, and packed cell transfusion as necessary.

**Prognosis**
The outcome of DKA will vary with the severity of disease and sometimes the nature of the underlying disease. There are some patients that have severe underlying disease that will not survive, or occasionally there can be death as a result of therapeutic complications (haemolytic anaemia, cerebral oedema). One study described a 70% survival rate for DKA patients, with lower survivals in patients with ionised hypocalcaemia, anaemia, and hyperadrenocorticism.

**Hypoadrenocorticism**

**Adrenal Glands and Basic Physiology**
There are two adrenal glands – one on either side of the body, and they sit just next to the kidneys. The adrenal glands produce a number of different types of hormone. There are glucocorticoids which play a significant role in many tissues (in fact nearly all as they have some roles in cellular function) in the body. There are also mineralocorticoids that act in the kidney to control the balance of sodium and potassium in the body. Changes in the sodium level affect fluid balance in the body. The adrenal glands can also produce some sex hormones.

The hypothalamic-pituitary-adrenal axis is a feedback system that in a normal animal keeps the cortisol level well controlled. The hypothalamus in the brain produces a hormone called CRH (corticotrophin releasing hormone). The CRH can act on the pituitary gland at the base of the brain produces which ACTH (adrenocorticotropic hormone), and CRH stimulates its production. The ACTH acts on the adrenal glands to stimulate the production of cortisol.
The hypothalamus and pituitary gland can detect the amount of cortisol in the blood. When it is high, the production of CRH and ACTH both fall, so there is less stimulus for cortisol production. When the level of cortisol is low, CRH and ACTH production increase, which stimulates the adrenal glands to produce more cortisol.

**Pathophysiology**

In hypoadrenocorticism there will typically be a deficiency of glucocorticoids and mineralocorticoids, but in occasional cases there will only be a deficiency of glucocorticoid. Glucocorticoids have very wide ranging effects on many body systems. Cortisol plays supportive roles in vascular tone (by potentiating the action of catecholamines), vascular endothelial integrity, vascular permeability and also distribution of body water. Cortisol also plays a role in carbohydrate and protein metabolism, has a permissive effect on erythropoietin, and has a role in the body's response to stress.

Mineralocorticoid (Aldosterone) release primarily controlled by the renin-angiotensin system, but its release can also be stimulated by hyperkalaemia, and to some degree by ACTH. Aldosterone stimulates sodium retention and potassium excretion in the distal renal tubules. In the situation of aldosterone deficiency there can be a reduction in total body sodium stores, and thereby a loss of volume. There is impaired urine concentrating ability because of loss of the medullary concentrating gradient in the kidney. Hyperkalaemia develops, and can have adverse effects on cardiac function.

**Aetiology**

Hypoadrenocorticism means that both adrenal glands are dysfunctional. It can be primary in nature, or occasionally is secondary to dysfunction of the hypothalamic-pituitary-adrenal axis. Hypoadrenocorticism can also be iatrogenic with the sudden removal of glucocorticoid therapy. In the majority of cases the cause is not detected. Some of the potential mechanisms of primary hypoadrenocorticism include

- Immune mediated disease
- Surgical removal of both adrenal glands (this is occasionally done to treat hyperadrenocorticism)
- Ischaemia – if blood clots affect both adrenal glands
- Trauma
- Metastasis of neoplasia to the adrenals
- Mitotane or Trilostane Therapy

**Signalment**

Affected dogs tend to be young to middle aged, and it is more common in female dogs than males. Some of the more commonly affected breeds include standard poodles, some terriers (Westies and Wheaten terriers), Great Danes, and Portugese Water Dogs.

**History/Clinical Signs**

This disease is sometimes referred to as ‘the great pretender’. The clinical signs are often very vague, and can look like many other illnesses.
Some dogs will present in a ‘crisis’ with the disease. They may be collapsed, dehydrated, with low heart rates, weak pulses, vomiting, diarrhoea, weak pulses etc. The problem is other diseases can present with similar signs, such as serious gastrointestinal disease or acute renal failure.

Other dogs present with a more waxing and waning history. There may be episodes of being dull, inappetant, gastrointestinal signs (vomiting/diarrhoea), weight loss, weakness, tremors, or even polydipsia and polyuria. Unless you keep hypoadrenocorticism in mind for these patients, the diagnosis will be missed.

Because of the very vague clinical signs, sometimes the first time a veterinarian may be suspicious of hypoadrenocorticism is when they get the results of the routine laboratory tests.

**Diagnostics**

Haematology should be part of the diagnostic evaluation. In unwell patients a stress leucogram would often be expected. In hypoadrenocorticism as there is no cortisol, so a stress leucogram will often NOT be seen. Therefore in a very sick dog where a stress leucogram would be expected, its absence is suspicious. Some dogs with hypoadrenocorticism have a mild, non regenerative anaemia. Sometimes a more severe anaemia may be associated with significant gastrointestinal haemorrhage.

A biochemical profile is where many veterinarians become suspicious of hypoadrenocorticism. Many dogs with the disease have a marked hyperkalaemia and hyponatraemia and possibly hypochloraemia. In some patients though the aldosterone is not low, but the glucocorticoids are low – so they have hypoadrenocorticism, but the sodium and potassium are normal. In many patients there may be a mild to moderate or occasionally severe azotaemia. The azotaemia is typically pre-renal, and the increase in urea can be exacerbated by gastrointestinal haemorrhage. Some other laboratory changes that will be seen are hypoglycaemia because cortisol stimulates glucose production, so in its absence it gets low. There may also be a hypocholesterolaemia, and hypercalcaemia. There may be hypoproteinaemia if there is gastrointestinal haemorrhage.

A urinalysis should be performed. Sodium is very important in concentrating urine, so in hypoadrenocorticism because of the lack of sodium the urine may be very dilute. If the kidneys are getting damaged there may be cells and debris in the urine sediment.

Whilst many of these changes can suggest hypoadrenocorticism, acute renal failure, a ruptured bladder or a blocked urethra, or bad gut disease (such as with whipworms) can cause some of the changes discussed above. Therefore it is vital to perform tests to confirm the diagnosis of hypoadrenocorticism. The treatment for the disease is lifelong, so it is important to be sure of the diagnosis.

Other testing may sometimes be performed. In animals with an abnormal cardiac rhythm an electrocardiogram may reveal signs of hyperkalaemia including bradycardia, t wave changes, widened QRS complexes, reduced amplitude and increased duration of p waves, prolonged p-r intervals, loss of p waves, and s-t segment changes. Thoracic radiographs may reveal microcardia suggestive of hypovolaemia.
An ACTH Stimulation Test is the ideal test to confirm the diagnosis. A low basal cortisol and inadequate response to ACTH with a post stimulation cortisol < 50 nmol/L confirms the diagnosis. A basal cortisol is NOT the test of choice to confirm the diagnosis. However if you have a patient that you are suspicious of the disease, and do not have any ACTH on hand, checking a basal cortisol is better than nothing – if a normal patient is very unwell, they will be stressed and normal adrenal glands will produce more cortisol, so the level should be elevated. In hypoadrenocorticism the cortisol level will be low.

Hypoadrenocorticism can be a true medical emergency, so in house testing has a lot of value.

**Treatment**
Acute hypoadrenocorticism is a true medical emergency. Patients will require intravenous fluid therapy and close monitoring. Typically 0.9% saline is the fluid of choice, and the rate of fluid administration will depend on the condition of the patient, but in some cases may be approaching shock rates. If there is marked hyperkalaemia glucose infusions may be used to help reduce the potassium level, or a bicarbonate infusion can drive potassium intracellularly. Calcium therapy can be used if there is a severe cardiac arrhythmia – it does not alter the potassium level, but can afford the myocardium some temporary protection from the effects of hyperkalaemia.

Specific therapy may commence before a final diagnosis is reached if the suspicion of disease is high. The ideal therapy in this situation is a hydrocortisone infusion which provides both glucocorticoid and mineralocorticoid supplementation. A 1 mg/ml solution of hydrocortisone can be formulated, and infused at a rate of 0.5 mg/kg/hour. This can be continued until a patient is able to eat and keep food down, at which time oral therapy can be commenced.

Maintenance therapy will typically involve glucocorticoid therapy. Suitable choices include cortate or prednisolone. Dosage adjustments will be based upon clinical signs. There are two choices for mineralocorticoid supplements if required – an oral medication (fludrocortisone), or an injectable medication (desoxycorticosterone pivalate). The DOCP is administered subcutaneously or intramuscularly every 25 – 28 days. The adequacy of mineralocorticoid supplementation can be easily determined based on measurement of serum electrolytes. The adequacy of glucocorticoid supplementation is determined based upon clinical signs.

**Hypoglycaemia**

**Pathophysiology**
Cells in the body require an energy source for normal function. Ingestion of energy sources in the form of fat, protein and carbohydrate, with adequate energy provided for up to 8 hours after eating. After this time there must be the provision of energy from endogenous sources, with hepatic production of glucose the primary source. This is initially accomplished using hepatic glycogen stores, but these stores may be exhausted within 2-3 days. In this situation there can be gluconeogenesis, where there is delivery of glucose precursors such as amino acids (from muscle, primarily alanine and glutamine), lactate (an end product of anaerobic metabolism peripherally) and glycerol (supplied by the breakdown of triglycerides
in adipose tissue) from peripheral tissues. Lipolysis also releases ketone bodies that can be used by the central nervous system as energy sources during times of starvation. In addition to an adequate supply of substrates for gluconeogenesis from peripheral tissues, adequate hepatic function (and blood supply) is necessary to allow conversion of these substrates to glucose. The renal cortex has some potential for gluconeogenesis, but its contribution is typically small, but its relative contribution may increase if there is hepatic dysfunction.

The endocrine system is also necessary to maintain euglycaemia. Insulin is the primary hormone to lower blood glucose. There are a number of hormones however that increase blood glucose – the ‘Counterregulatory’ hormones. These include glucagon, catecholamines, cortisol and growth hormone and they can stimulate hepatic gluconeogenesis and inhibit peripheral tissue utilisation of glucose. Catecholamines are the primary stimulus for renal gluconeogenesis.

The CNS is solely dependant on plasma glucose, so if hypoglycaemia develops there is a well defined neurogenic and hormonal response to maintain an adequate glucose supply. As discussed hepatic glycogenolysis and gluconeogenesis occur. Some tissues such as skeletal and cardiac muscle, renal cortex and liver can utilise mobilised triglycerides as an energy source to spare glucose for the CNS, erythrocytes and renal medulla that require glucose as their energy source.

The blood glucose concentration is the primary determinant in the secretion of hormones that contribute to glucose regulation. Hypoglycaemia suppresses insulin secretion, which enables glycogenolysis and lipolysis, promotes hepatic glucocoenogenesis and ketogenesis, and reduces peripheral glucose utilisation. Hypoglycaemia also affects the counterregulatory hormones. Initially there is release of catecholamines and glucagon, and subsequently increases in cortisol and growth hormone secretion. The glucagon produced by alpha cells in the pancreas accesses the liver directly via the portal circulation to stimulate hepatic gluconeogenesis and glycogenolysis. The catecholamines stimulate hepatic glycogenolysis and hepatic and renal gluconeogenesis. The catecholamines also stimulate the release of muscle glycogen and lipolysis as fuel sources, and mobilise the release of gluconeogenic precursors. Cortisol facilitates lipolysis and protein catabolism, stimulates gluconeogenesis and reduces peripheral glucose utilisation. Growth hormone promotes lipolysis and reduces peripheral glucose utilisation. Stimulation of the adrenergic nervous system also plays a role in the response to hypoglycaemia. Alpha adrenergic stimulation inhibits insulin secretion and increases cerebral blood flow via peripheral vasoconstriction. Beta adrenergic stimulation stimulates glycogenolysis and lipolysis, increases glucagon secretion, and can increase cardiac output increasing cerebral blood flow.

Hypoglycaemia can result in neurological dysfunction as the neural cells are reliant on a continuous supply of glucose that originates outside of the CNS. The more active areas of the CAN are most dependant on the glucose supply, so in times of hypoglycaemia the cerebral cortex will be the first to show signs. The entry of glucose into the neurines is mainly via diffusion, and is not an insulin dependant phenomenon. Therefore even in the case of an insulinoma causing hypoglycaemia, the neurones are deprived of glucose. As a result of hypoglycaemia there is reduced ATP levels in the neurones resulting in cellular changes that mimic those of hypoxia, along with increased vascular permeability, vasodilation and oedema. The changes are most severe in the cerebral cortex, basal ganglia,
hippocampus and vasomotor centres. Occasionally peripheral nerve changes will also be noted. There can be permanent damage in the CNS as a result of hypoglycaemia, but the counterregulatory response minimises this risk.

The clinical signs of hypoglycaemia are a combination of the effects of neuroglycopaenia, such as weakness, lethargy, ataxia, altered behaviour, seizures and coma, and also stimulation of the adrenergic nervous system such as tremors, nervousness, hunger and restlessness.

**Aetiology**

There are a number of potential causes for hypoglycaemia in dogs. In many patients the primary differential diagnosis is an insulinoma, a functional tumour of the beta cells in the pancreas. These tumours do not respond normally with a suppression of insulin production in response to hypoglycaemia, but they may still increase insulin secretion in response to glucose. These tumours tend to behave in a more malignant fashion based on metastatic potential. The most common sites of metastasis include the liver and regional lymph nodes. Patients are considered to have Stage I disease if there is no apparent metastasis, Stage II if regional nodes are involved, or Stage III if there is distant metastasis. In animals with insulinoma the secretion of insulin continues despite hypoglycaemia, so there is continued peripheral utilisation of glucose, combined with suppression of glycogenolysis and gluconeogenesis.

Hepatic dysfunction can also cause hypoglycaemia, either from hepatocellular failure, or more commonly a portovascular abnormality. Despite appropriately suppressed insulin concentrations, there are insufficient hepatic glycogen stores and reduced potential for hepatic gluconeogenesis. Glycogen storage diseases are an uncommon congenital hepatic disease where there is an inability to convert glycogen to glucose because of deficiency of specific enzymes in a metabolic pathway.

Hypoadrenocorticism can be associated with hypoglycaemia, as a result of glucocorticoid deficiency. There will be reduced insulin concentrations in response to the hypoglycaemia, but the relative cortisol deficiency reduces hepatic gluconeogenesis. Theoretically a glucagon deficiency could also result in hypoglycaemia. Hypopituitarism and reduced ACTH and growth hormone secretion can also predispose to a fasting hypoglycaemia.

Non beta cell neoplasia has also been occasionally associated with hypoglycaemia. The mechanism of the hypoglycaemia is unclear, but may be a result of glucose consumption by the tumour, or potentially impaired glyogenolysis or gluconeogenesis. Increased insulin like growth factor II levels have been reported in some patients. Reported tumours in dogs associated with hypoglycaemia include some hepatic neoplasia (hepatoma or hepatocellular carcinoma), some other carcinomas (metastatic mammary, salivary or pulmonary), leiomyoma and leiomyosarcoma, haemangiosarcoma, plasmacytoma, lymphocytic leukaemia and metastatic melanoma.

Hypoglycaemia may occur in juvenile dogs, especially in toy and miniature breeds less than six months of age. Affected animals may be under stress, or may have gastrointestinal disease. The disease normally resolves as they grow. Sepsis or endotoxaemia are uncommon causes of hypoglycaemia, with increased peripheral glucose utilisation and reduced hepatic glucose production suggested mechanisms. Severe erythrocytosis can also be associated with
hypoglycaemia, likely as a result of glucose consumption by the erythrocytes. Iatrogenic hypoglycaemia can be the result of excess insulin administration. It is also important to note that hypoglycaemia may be an artefact if there is significant delay in the processing of a blood sample.

**Signalment**
Insulinomas tend to occur in middle aged to older dogs, with no sex predilection. Larger breeds are more commonly affected. Hypoadrenocorticism is addressed elsewhere in this presentation. Animals with portosystemic shunts tend to be younger, but acquired hepatic disease may occur at any age. Sepsis is not age specific.

**History**
As previously discussed, the clinical signs of hypoglycaemia can be those of neuroglycopenia and include lethargy, weakness, collapse, seizures or coma, or may be the result of sympathetic stimulation, such as tremors, agitation, restlessness etc. These signs may have been noted for days to months in patients with insulinomas. The signs tend to be episodic as the counterregulatory response attempts to maintain adequate glucose levels. The severity of signs is variable – some animals that have been chronically hypoglycaemic can be asymptomatic at quite low blood glucose levels. Signs may be exacerbated by exercise, excitement or fasting.

With other causes of hypoglycaemia there may be concurrent signs of another disease process. Animals with portosystemic shunts or hepatic failure may have poor body condition, signs of encephalopathy, gastrointestinal signs, or urinary tract signs. Hypoadrenocorticoid dogs can have variable and intermittent signs, including potentially gastrointestinal signs or polydipsia and polyuria. Animals that are septic may have signs that help localise the underlying disease process. Animals with a congenital hypopituitarism may be of small stature.

**Physical Examination**
The physical examination may be unremarkable in hypoglycaemic patients. Some may manifest the clinical signs as described previously. Some animals with insulinomas may have signs of a peripheral neuropathy, for which the pathogenesis is unknown. In animals with an underlying disease process there may be indications on examination, such as neurological signs if encephalopathy, palpable abdominal masses with some hepatic tumours, or lesions associated with sepsis such as haemorrhagic diarrhoea, signs of pyometra, prostatomegaly, signs of pleural effusion (tachypnoea, dyspnoea) if pyothorax, or an abdominal effusion if peritonitis. Animals with erythrocytosis may have very pink mucous membranes, and potentially altered retinal vessels or signs of retinal haemorrhage.

**Diagnostic Evaluation**
In many cases the initial diagnostic evaluation may include clinicopathological testing. If there is a strong suspicion of hypoglycaemia patient side evaluation of a blood glucose using a glucometer will be indicated.

Haematology may or may not provide significant diagnostic information. In an insulinoma patient it would be expected to be normal. In cases of erythrocytosis there will be an increased haematocrit. If there is sepsis there may be an increase in the white cell count with
a possible left shift of neutrophils, but in other cases there may be leucopaenia as a result of consumption. Whilst a lymphoid leukaemia is an unusual cause of hypoglycaemia, a blood count and smear review may be diagnostic.

A biochemical profile should confirm the presence of hypoglycaemia. In an insulinoma patient there may be no other abnormality, but other changes sometimes reported include hypokalaemia, hypophosphataemia and elevated liver enzymes, but these are non specific. In other causes of hypoglycaemia the biochemical profile may show some other changes. In cases of hepatic failure there may be concurrent hypoalbuminaemia, hypcholesterolaemia and a reduced blood urea. Hypoadrenocorticoid patients may have hyponatraemia, hypochloraemia, hyperkalaemia, azotaemia and hypercalcaemia. If there is hepatic neoplasia there may be alterations in hepatic enzymes.

A urinalysis will typically be unremarkable in patients with insulinomas. In patients with hepatic failure there may be ammonium biurate crystals noted. Patients with sepsis may have pyuria or bacteriuria. Animals with hypoadrenocorticism will have reduced concentrating ability.

In patients with a marginal blood glucose that hypoglycaemia is suspected, they can be fasted and have regular blood glucose measurements. Most patients will become hypoglycaemic within 8 hours, but patients should be closely monitored during fasting to avoid severe episodes of hypoglycaemia. A low serum fructosamine level can be supportive of persistent hypoglycaemia.

Evaluation beyond this point in time will vary with the patient. In a patient with a suspicion of an insulinoma a serum insulin level would be the next step. The sample should be collected when the patient is hypoglycaemic (<2.5 mmol/L). Historically there was assessment of insulin:glucose ratios, glucose:insulin ratios and an amended insulin:glucose ratio. These were found to be of little diagnostic value. Rather the insulin level should be assessed in light of the blood glucose concentration. If the serum insulin is elevated the diagnosis is clear. Even an insulin concentration in the mid reference range is inappropriate and consistent with an insulinoma. If the diagnosis is confirmed, pre-surgical evaluation would typically include thoracic radiographs (even though metastasis is rare to the lungs), and abdominal ultrasonography. The pancreas should be evaluated, but lesions will not always be detected. The liver and regional lymph nodes should also be evaluated for indications of metastatic disease. Advanced imaging such as CT scans or MRI scans are theoretically an option. Somatostatin receptor scintigraphy has been described to confirm the presence of an insulin secreting tumour.

Further diagnostics in patients without insulinomas will vary on the patients signs. In young, toy breed dogs faecal parasitology would be indicated. If a portosystemic shunt or hepatic failure is suspected hepatic function testing and abdominal imaging would be indicated. Abdominal imaging would also be indicated if intra-abdominal neoplasia is suspected, or if there is sepsis, and thoracic imaging may also be indicated for the latter. Collection of samples for cytology or histopathology may be indicated for mass lesions, or for cytology and microbiology in septic patients. An ACTH stimulation test can be used to determine if hypoadrenocorticism is present or not.
**Therapy**

Therapy can be divided up into a number of categories, including therapy for patients with an acute hypoglycaemic crisis, therapy for insulinoma patients, and therapy for patients with hypoglycaemia not related to an insulinoma.

Therapy for a patient in an acute hypoglycaemic crisis will vary with the location of the patient. If providing telephone advice to a patient at home that is collapsed or seizuring, some emergency therapy would be indicated before transport. Carefully applying Karo syrup or a sugar rich solution to the gums (do not place fingers into the oral cavity) will often alleviate the immediate signs. Once conscious a high protein or complex carbohydrate meal should be given to the dog. Once stable it should be kept quiet and transported to the clinic. If the patient is in hospital and is seizuring or a has a reduced state of consciousness, intravenous 50% glucose should be administered. This should be administered slowly and to effect. Rapid intravenous glucose can stimulate the neoplastic beta cells and can further increase insulin secretion, creating a situation with ongoing hypoglycaemia. Once the animal is conscious it should be fed a high protein meal. If a patient has persistent neurological signs after seizures, or the seizures persist further therapy may be required, such as a glucose constant rate infusion, the use of anticonvulsants, or potentially mannitol and glucocorticoids if cerebral oedema is suspected. A constant rate glucagon infusion has been reported for use in acute hypoglycaemia to increase the blood glucose, but glucagon can also increase insulin secretion, so this technique can have challenges.

In patients with an aetiology that is not related to an insulinoma, therapy should be directed towards treating the underlying disease if possible. In a hypoadrenocorticoid patient the administration of glucocorticoids should stabilise the glucose level. In an animal with juvenile hypoglycaemia frequent feeding may help avoid clinical signs. In a septic patient appropriate therapy (such as drainage of septic effusions, or removal of affected tissue if appropriate) including antimicrobials is indicated. Patients with hepatic failure may be treated medically or potentially surgically if a shunt.

Some insulinomas can be treated surgically, which is beyond the scope of this presentation. Potential advantages of surgery include mass removal or debulking, which can potentially improve survival. Challenges of surgery can include the presence of metastatic disease, persistent signs of disease despite surgery, or challenges in determining the location of the tumour. The masses are located with similar frequency in either limb of the pancreas, or less commonly in the body of the pancreas. Techniques involving the infusion of methylene blue to identify the insulinoma at surgery have been described. Other challenges of surgery can include diabetes mellitus, pancreatitis, haemorrhage, or occasionally cardiac arrhythmias. If animals are persistently hyperglycaemic and glucosuric post-operatively insulin therapy may be indicated, but the patient will need to be closely monitored as the diabetes is usually transient. Owners can measure urine glucoses at home and if persistently negative the insulin dosage can be reduced or the insulin withdrawn. In other cases hypoglycaemia will persist after surgery, which is suggestive of metastatic disease. If this occurs medical therapy should be instituted for hypoglycaemia.

Long term medical therapy will be necessary in patients that are not surgical candidates or have persistent hypoglycaemia post surgery. The aim of therapy is not necessarily to normalise the blood glucose, but rather to maintain it at a level that alleviates or minimises
clinical signs. Dietary management should be implemented. Feeding a diet high in complex carbohydrates, protein and fat slows gastric emptying, and if provided in small amounts frequently (four to six meals a day) provides a steady source of nutrient, but avoids spikes in blood glucose levels that can stimulate insulin secretion. Dry and canned dog foods are often suitable, but semi moist foods are contraindicated as they contain larger amounts of simple sugars.

Drug therapy is indicated if diet alone does not control the clinical signs of disease. Prednisolone is often the first alternative. It will increase gluconeogenesis and reduce peripheral glucose uptake, and can stimulate glucagon excretion. An initial dosage of 0.5 mg/kg/day is reasonable, but can be gradually increased as necessary up to even 4 mg/kg/day. Diazoxide is a benzothiadiazide diuretic that inhibits insulin secretion via an effect on ATP dependant potassium channels in the beta cells. It also increases glycogenolysis and gluconeogenesis, and reduces peripheral glucose uptake. The starting dose is 5 mg/kg every twelve hours, but this can be increased. Diazoxide is very difficult to source however, and it can cause anorexia and vomiting, hypersalivation, and potentially pancreatitis and bone marrow suppression. Octreotide is a somatostatin analogue, and it has the ability to inhibit insulin secretion as a result of binding to somatostatin receptors. People have five subtypes of receptors, and dogs only one. Despite this the effects have been inconsistent in dogs, likely because somatostatin can also suppress glucagon and growth hormone secretion, potentially blunting the counterregulatory response.

Streptozotocin is a nitrosourea antibiotic that selectively destroys pancreatic beta cells in the pancreas or in metastases. The drug has the potential for nephrotoxicity, so diuresis around the time of administration is important. Vomiting is also a common side effect. Protocols are described using the drug every three weeks. In one study there appeared to be no statistically significant difference between dogs treated with streptozotocin and those treated with surgery or medically.

**Prognosis**

The long term prognosis with patients with insulinoma is guarded as a result of the metastatic potential of the tumour. The prognosis with surgery is better in dogs with Stage I disease than those with Stage II or III disease (50% of Stage I dogs normoglycaemic at 14 months post op compared to 20% of Stage II or III dogs). The prognosis is better in patients that are normoglycaemic or hyperglycaemic post operatively than those that are hypoglycaemic. Median survival times are reported at 12-14 months. A more recent study reported longer survival times in patients undergoing surgery with subsequent medical therapy when signs recurred with median survivals of 1316 days.

**Recommended Reading**


