Approach to the Patient with Diabetes Ketoacidosis

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Introduction

Diabetes ketoacidosis (DKA) is a common endocrine emergency seen in practice. DKA is part of the diabetes mellitus disease complex. Diabetes mellitus (DM) can be categorised into three groups based on presenting signs (1) uncomplicated DM (2) diabetes ketoacidosis, and (3) diabetic coma. For a patient to have DKA they must have ketonuria, glycosuria, ketonemia, hyperglycaemia and a metabolic acidosis.

Diabetes mellitus results from disturbances to carbohydrate, lipid and protein metabolism resulting in hyperglycaemia as a result of a relative or absolute insulin deficiency combined with an absolute or relative excess of glucagon. Therefore, it is a disease of the endocrine pancreas.

Causes of Diabetes Mellitus

The following factors are involved in the etiopathogenesis of diabetes mellitus:

Dogs	Cats
Failure of insulin production Anti-islet autoimmunity Islet cell hypoplasia Drug/chemical toxicities Pancreatitis Pancreatic neoplasia	**Failure of insulin production** Immune mediated destruction of islets Cellular exhaustion Glucose toxicity Lipotoxicity Amylin/amyloid deposition
Failure of insulin transport Insulin antibodies after exogenous insulin therapy	
Failure of tissue sensitivity Obesity Hormonal antagonism *Glucagon:* Infection, uraemia, glucagonoma *Glucocorticoids:* Stress, hyperadrenocorticism, exogenous *Catecholamines:* Stress, phaeochromocytoma *Growth hormone:* Acromegaly, progestogens *Progestogens:* Endogenous, exogenous	**Failure of tissue sensitivity** Obesity Hormonal antagonism *Glucagon:* Infection, uraemia, glucagonoma *Glucocorticoids:* Stress, hyperadrenocorticism, exogenous *Catecholamines:* Stress, phaeochromocytoma *Growth hormone:* Acromegaly, progestogens *Progestogens:* Endogenous, exogenous *Thyroid hormone:* Hyperthyroidism

Hormones of the Pancreatic Islets

The pancreas has exocrine and endocrine functions. DM is a disease of the endocrine pancreas. Pancreatic islets consist of 4 cell types; (1) β-cells that synthesise insulin, (2) α-cells, the source of glucagon, (3) δ-cells producing somatostatin, and (4) PP-cells synthesising pancreatic polypeptide. β-cells make up the majority of the pancreatic islets.

Insulin and glucagon are the important hormones that regulate metabolism. Together they co-ordinate the flow of and the metabolic fate of endogenous glucose, free fatty acids, amino acids and other substrates, ensuring energy needs are met both n the basal state and during exercise. In addition they co-ordinate the efficient deposition of the nutrients from meals. Insulin and glucagon act in a reciprocal fashion.

Function and control of insulin in healthy animals

- **Insulin promotes fuel storage.**
- It is a glucoregulatory, antipolytic, antiketogenic hormone.
- It acts on the liver to increase the rate of glucose uptake from the portal circulation.
- Inhibits lipolysis, proteolysis, ketogenesis, hepatic glucogenolysis, gluconeogenesis, and glucose release.
- Insulin stimulates muscle glucose uptake and glycogen storage, stimulates protein synthesis.
- Insulin promotes the cellular uptake of amino acids, phosphate, magnesium, and potassium.
- Promotes glucose and lipoprotein uptake by fat cells, and stimulates lipogenesis.
- Insulin release from β-cells is stimulated by glucose and food uptake, gastrointestinal peptides, cholinergic and β-adrenergic activity.
- Fasting and exercise inhibit its release.

Function and control of glucagon in healthy animals

- **Glucagon promotes the mobilisation of glucose.**
- Glucagon is released in response to hypoglycaemia promoting glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis.
- Glucose, free fatty acids, and insulin suppress secretion.
- Secretion is increased during fasting and exercise.
- In the liver glucagon secretion stimulates glycogenolysis, gluconeogenesis, fatty acid oxidation, and ketogenesis.
- Glucagon ensures there is an adequate level of circulating glucose for optimal central neurological function as most cells in the CNS do not have insulin-mediated transport of glucose into the cells.

Overview of the Pathophysiology of Diabetes Mellitus

In diabetes mellitus, a relative or absolute deficiency in insulin results in a decreased utilisation of glucose, amino acids, and fatty acids by the liver, muscles and fat cells. This is in part due to a gradual depletion of functional β-cells. Obesity and old age exhaust the remaining functional β-cells resulting in insulin resistance. Hyperglycaemia results from dietary glucose and hepatic gluconeogenesis. Glucose toxicity and lipotoxicity are rapid and potent suppressors of insulin secretion in hyperglycaemic cats. This leads to weight loss, polyphagia, and polydipsia and polyuria.

Once the blood glucose exceeds the renal threshold, glycosuria and an osmotic diuresis occurs resulting in polydipsia and polyphagia clinically.

The satiety centre in the hypothalamus determines the feeling of hunger. This relies on glucose entering these cells under the influence of insulin. Failure of glucose to enter these cells results in polyphagia.

If diabetes mellitus is not diagnosed and treated at this stage the animal may progress to DKA.

Pathophysiology of diabetes ketoacidosis

DKA is a progression of diabetes mellitus. In DKA there is a further increase in gluconeogenesis and ketoneogenesis due to (1) insulin deficiency, (2) diabetogenic hormone excess, (3) fasting, and (4) dehydration.

1. Insulin deficiency and resistance

The majority of cats and dogs with DKA have a relative or absolute insulin deficiency. Insulin deficiency results from a low insulin concentration for hyperglycaemia observed. This may be from a diabetic patient receiving inappropriate low insulin doses. Impaired insulin activity is commonly due to a reduced number and activity of β-cells in the pancreas.

Insulin resistance prevents insulin's actions in normal glucose uptake and utilisation. This may be due to obesity, and hormones affecting post receptor events in glucose metabolism, especially in skeletal muscle. Insulin resistance predisposes the diabetic patient to DKA.

2. Diabetogenic hormone excess

Glucagon, catecholamines, cortisol and growth hormone contribute to the metabolic alterations as they antagonise the actions of insulin. The net effect of these hormonal disturbances is to accentuate the insulin deficiency.

The increased ratio of glucagon to insulin in the portal blood favours hepatic ketogenesis over triglyceride formation.

Catecholamines are released in response to stress and stimulate glycogenolysis, gluconeogenesis and lipolysis contributing to the hyperglycaemia and ketaonemia. Cortisol depresses peripheral glucose utilisation and increases hepatic gluconeogenesis.

Concurrent pancreatitis, infection and gastro-enteritis have the potential to increase diabetogenic hormone secretion.

3. Fasting

Fasting contributes to the increase in diabetogenic hormone concentrations. Fasting may cause a decline in alanine, pyruvate, and lactate which inhibit ketogenesis, but there is a decreased peripheral utilisation of ketones.

4. Dehydration

Dehydration increases the concentrations of circulating glucose and ketones resulting in an osmotic diuresis. The increased osmotic load in conjunction with an acidosis results in the loss of Na and K in urine and vomit, exacerbating the hypovolaemia and dehydration. Fasting, nausea, and confusion also contribute to the dehydration.

The hyperglycaemia together with a reduced glomerular filtration rate secondary to dehydration result in a reduced ability to excrete circulating glucose, ketones and hydrogen ions, perpetuating the DKA.

The insulin deficiency and insulin resistance, together with increased circulating concentrations of diabetic hormone results in lipolysis leading to the production of ketone bodies (acetoacetate, β-hydroxybutyrate) in an attempt to provide energy substrates for the patient. The rate of ketogenesis is linked to the rate of gluconeogenesis and lipolysis. Ketone utilisation is impaired in the peripheral tissues. As ketones accumulate in the blood, the bodies buffering system becomes overwhelmed resulting in a metabolic acidosis. When the renal threshold for ketones is exceeded the ketonuria contributes to the osmotic diuresis enhancing the urinary loss of sodium, potassium and magnesium.

The excessive loss of electrolytes and water leads to further volume contraction and tissue hypoperfusion, ultimately causing a pre-renal azotemia.

The hyperglycaemia and osmotic diuresis result in an increased plasma osmolality, resulting in cellular dehydration.

The final result of these complex metabolic changes is metabolic acidosis, hyperglycaemia, hyperosmolality, polyuria, electrolyte disturbances and hypovolaemia.
These abnormalities may become life threatening.

Clinical Findings of DKA

Signalment

- Common in females dogs, 7-9 years of age and male cats.
- Keeshonds, Cairn Terriers, Miniature pinchers and Burmese cats are predisposed to diabetes mellitus and hence DKA.

History

- History may be suggestive of DM with the patients exhibiting polyphagia, weight loss and polyuria/polydipsia.
- They may have been previously treated for DM. Ensure that previous treatments for DM are recorded.

Clinical signs and findings

- Lethargy – especially cats.
- Weakness.
- Anorexia.
- Polyuria/polydipsia.
- Vomiting and diarrhoea.
- Dehydration.
- Hepatomegaly.
- Concurrent infections (urinary tract infections common), pyrexia and pancreatitis may be present.
- Gait abnormalities.
- Acetone smelling breath.
- Hyperglycaemia and hyperketonemia.
- Glycosuria and ketonuria.
- Renal insufficiency.

Laboratory Database

The initial database should consist of a CBC, biochemistry, electrolytes, blood gas analysis and urinalysis.

Electrolytes and blood gas analysis

- Often DKA patients are hypokalemic, hyponatremic, and hypophosphatemic. Hypochloraemia can occur.
- A metabolic acidosis is present. Insulin will not work if pH is below 7.1.

Biochemistry

- Hyperglycaemia.
- May have elevated liver enzymes and cholesterol.
- Azotemia is common.
- Amylase and lipase may be elevated.
- Lipaemia.

Haemogram

- The haemogram reflects dehydration.
- May be evidence of infection or inflammation – neutrophilic lymphocytosis.

Urinalysis

- Collect by cystocentesis aseptically.
- Urinalysis is important, as glycosuria and ketonuria are the hallmarks of both DM and DKA.
- Urinary tract infections are common.
- Examine urine for ketones, glucose, protein (infection or glomerular damage), USG, and culture and sensitivity performed. Note that urine dipsticks may miss some early ketonuric animals as they only detect acetoacetate but not β-hydroxybutyrate.

Management of DKA

The medical management of DKA involves correction of hypovolaemia present, correction of hyperglycaemia, restoration of normal acid base status, correction and prevention of electrolyte abnormalities, and treatment of any infections present. Precipitating factors should also be identified (pancreatitis) that caused the current illness.

1. Fluid therapy

Most animals are severely dehydrated (7-12%) on presentation, and are acidotic and hyperosmotic. The aim of fluid therapy is restore the intravascular volume deficits over 24-36 hours.

Fluid therapy is beneficial before insulin therapy is commenced because it will dilute the blood glucose in the extracellular space, improve renal perfusion resulting in an increased urinary excretion of glucose, and improve the peripheral circulation, allowing insulin to act where it is needed. It may also dilute counter-regulatory hormones. Fluid therapy alone however will not correct the metabolic acidosis present.

Fluid Therapy Guidelines

1. If the patient is in hypovolaemic shock use colloids and LRS to replace intravascular deficits over 1 hour.
2. Hypertonic saline or 0.9% NaCl is contraindicated as the patient will develop hyperchloremia when ketoacids are excreted in the kidney in exchange for chloride.
3. Once intravascular volume deficits are restored, replace hydration deficits over 2-4 hours in conscious and 6-24 hours in moribund or unconscious patients.
4. Determine best fluid type to be administered for rehydration therapy. As they are hyperosmolar they require "free water" replacement.

   Calculate the "free water deficit" using the following formula:

   $$\text{corrected [Na]} = \text{measured [Na]} + (\text{glucose} - 6)/3.5$$

   If corrected [Na] below 140 mEq/l use 0.9% NaCl (for rehydration only)
   If corrected [Na] is 140-160 mEq/l use lactated ringers solution
   If corrected [Na] over 160 mEq/l use 0.45% NaCl + 2.5% dextrose
5. Measure potassium at the commencement of fluid therapy and 2 hours after commencing rehydration therapy. Hypokalemia is common, supplement as indicated.

The patient should be rehydrated slowly as "idiogenic osmoles" produced in the brain during chronic hyperosmolality maintain cerebral intracellular volume and these cannot change rapidly, resulting in cerebral swelling or oedema, due to an osmotic gradient favouring water movement into these cells. This does not appear to happen very often in dogs and cats.

2. Insulin therapy

This is necessary to resolve the ketosis and hyperglycaemia. Any dose of insulin that will decrease blood glucose will inhibit lipolysis and ketogenesis and stimulate ketone uptake. The effectiveness of insulin in DKA therapy is dependent on the restoration of circulatory volume and tissue perfusion by fluid therapy. Insulin therapy is therefore commenced once the patient has been rehydrated.

Low dose insulin therapy is as effective as high dose insulin therapy to resolve the metabolic complications, and there are fewer complications (hypoglycaemia and hypokalemia). Initially there is some degree of insulin resistance present associated with the concurrent metabolic acidosis and the hypersecretion of counter-regulatory hormones.

Regular insulin (Actrapid™) is used initially in treatment of DKA. You can use as a low-dose IM protocol or constant rate infusion (CRI). Hyperglycaemia generally resolves within in 12 hours if used with fluid therapy. Avoid too rapid a fall in blood glucose as rapid shifts in plasma osmolality can result in loss of intravascular volume or cerebral oedema. It may also contribute to the accompanying insulin resistance. Ketosis takes 2-3 days to resolve so continue using regular insulin beyond the resolution of the hyperglycaemia.

Insulin Constant Rate Infusion Protocol

1. Drawbacks include access to IV pumps, the requirement constant glucose monitoring and 24 hour care.
2. Prepare insulin infusion as follows:

   Add 2.2U regular insulin/kg (Dog) or 1.1 U/kg (Cat) to 250 ml 0.9% NaCl and commence CRI at 11-19 ml/kg/hr.

   OR

   Alternatively 25 U regular insulin can be added to 500 of 0.9% NaCl (or 50 U to 1 l) and commence CRI at 1 ml/kg/hr.
3. Use a separate IV pump and discard first 50-100 ml through the lines as insulin binds to plastic and will be ineffective. Then piggy-back this to the maintenance fluids.
4. Monitor the blood glucose q 1-2 hr initially. Adjust the infusion to maintain glucose between 4.0 and 16 mmol/l.
5. When the blood glucose drops below 13 mmol/l, add 2.5-5% dextrose CRI to the fluid therapy protocol and maintain blood glucose between 5.5-11 mmol/l by adjusting the insulin CRI.
6. Continue the CRI until ketosis resolves in 2-3 days.

Low-Dose Intramuscular Insulin Protocol

1. This may be more useful in practice as the risk of hypoglycaemia is less and the patient does not necessarily require 24-hour care.
2. Initially, **give 0.25 U/kg regular insulin IM. Start with 2U if under 10 kg bodyweight.**
3. Again monitor the blood glucose q 1-2 hour.
4. **Repeat regular insulin doses @0.1-0.2 U/kg IM q 1-2 hours** to decrease the blood glucose. A fall of 2.7-5.4 mmol/l per hour is optimal.
5. When blood glucose falls below 13 mmol/l change insulin therapy to **0.5 U/kg SQ q 6-8 hours** and start 2.5-5% dextrose IV.
6. Continue until ketosis resolved.

Switching to maintenance insulin therapy

Continue regular insulin until the ketosis is resolved and concurrent metabolic disorders are corrected or resolved. When the patient is eating and drinking, switch to longer acting insulin administered twice daily, generally this is **commenced @ 0.3-0.5 U/kg**. Titrate optimal insulin dose based on serial glucose curves.

When stable the patient can be disconnected from IV fluids.

3. Electrolytes

Electrolyte alterations are common complications when treating DKA. Key electrolyte alterations are hypokalemia and hypophosphataemia.

Potassium

Total body potassium stores are depleted due to kaliuresis as a consequence of the osmotic diuresis and reduced dietary intake. Potassium can be normal or high on presentation, as there is an extracellular shift of K^+ in exchange for hydrogen ions as a result of the metabolic acidosis. Hyperglycaemia, insulin deficiency, and poor renal perfusion also contribute to extracellular K^+ concentrations.

Extracellular potassium concentrations decrease when DKA is treated due to (1) an insulin mediated shift of K^+ into the intracellular space; (2) resolution of the acidosis; (3) dilution of K^+ in the extracellular space; and (4) increased kaliuresis due to improved renal function with fluid therapy.

Potassium supplementation will be necessary during the treatment of DKA.

Anticipate hypokalemia and treat early, I tend to start potassium supplementation when the insulin therapy is commenced, based on electrolyte assessment because intravascular deficits have been corrected.

If you do not have access to electrolyte analysis potassium supplementation @ 20 mEq/l or 2g/L of fluids will not cause hyperkalemia provided the animal is hydrated and on insulin therapy.

If the animal is oliguric, restore renal perfusion and urine output before potassium supplementation.

Potassium Supplementation Guidelines

Serum Potassium concentration (mEq/l)	mEq KCl to add to 1 litre of fluid	Maximal fluid infusion rate (ml/kg/hr)
< 2.0	80	6
2.1-2.5	60	8
2.6-3.0	40	12
3.1-3.5	30	18
3.6-5.0	20	25

Phosphorus

Phosphorus is lost due to the osmotic diuresis, impaired phosphate reabsorption in the proximal tubule due to the insulin deficiency, and acidosis-induced inhibition of renal tubular phosphate reabsorption. Concurrent renal disease can also contribute to hypohosphatemia.

Phosphate levels can be normal on presentation due to an extracellular phosphate shift associated with the insulin deficiency and the hyperosmolality.

You may get a severe hypophosphataemia following treatment (12-24 hours post treatment) of DKA, which can result in haemolytic anaemia, and a decreased 2, 3-diphosphoglyceride concentration seen clinically as muscle weakness, rhabdomyolysis, seizure and stupor.

Phosphorus Supplementation Guidelines

1. If phosphorus is below 0.32-0.48 mmol/l supplement with **phosphate at 0.01-0.03 mmol/kg/hr in Ca free IV fluids** (LRS!) over 6 hours.
2. **Potassium phosphate will provide 3.0 mmol PO_4^{3-} and 4.4 mEq K^+.**
3. Re-evaluate every 6-8 hours during supplementation.
4. Complications of phosphate over supplementation include hyperphosphatemia, hypocalcaemia, soft tissue mineralisation, hypotension and renal failure.
5. Supplementation is contraindicated if the patient is oliguric or hypercalcaemic.

4. Correction of Acidosis

In the majority of DKA patient's fluid therapy will correct metabolic acidosis. Insulin supplementation will resolve the ketonaemia and further resolve the acidosis.

Bicarbonate administration may be considered if the **blood pH < 7.2 or HCO_3^- < 10 mEq/l**

AVOID USING BICARBONATE

Bicarbonate therapy is controversial! Studies have shown no change in blood pH following bicarbonate therapy.

Potential harmful affects of bicarbonate therapy include; (1) A negative feedback system helps maintain acid-base homeostasis. (2) Acidemia inhibits ketogenesis and fatty acid availability. HCO_3^- administration may result in ketone production. (3) HCO_3^- has the potential to exacerbate electrolyte disturbances. It may cause or exacerbate a hypokalemia. (4) Acidemia causes a shift of the oxyhaemoglobin curve to the right, and rapid correction of this acidosis may impair tissue oxygen delivery. (5) HCO_3^- therapy has the ability to cause a paradoxical CNS acidosis. HCO_3^- decreases blood pH, decreasing ventilatory drive, causing a rise in $PaCO_2$, resulting in a higher CO_2 in the brain and CNS acidosis.

If you wish to give bicarbonate use standard formulas. In my opinion there are very few cases where I would use bicarbonate.

5. Treat Concurrent Illness

Treatment of DKA often involves the management of concurrent serious illness such as a bacterial infection or pancreatitis. These illnesses may require antibiotic use, analgesics and if they are to have "nil per os" continue the glucose CRI as well as the insulin CRI until the patient is eating. At no stage should insulin therapy be delayed because the metabolic derangement's present will be fatal if left untreated.

Hypersomolar Non-Ketotic Syndrome (HNKS)

This is a rare complication of diabetes mellitus, resulting from the persistent hyperglycaemia and osmotic diuresis. The syndrome is characterised by a severe hyperglycaemia (>33 mmol/l), hyperosmolality (>350 mOsm/kg), severe clinical dehydration, a lack of urine or serum ketones, a lack of or a moderate metabolic acidosis, and CNS depression. HNKS is believed to be continuum of DKA.

There is the establishment of an osmotic gradient between the extracellular and intracellular compartments of the brain resulting in neuronal cellular dehydration and dysfunction. The brain reacts by forming "idiogenic osmoles" to oppose this solute gradient. Extracellular hyperosmolality results in cell dehydration causing the neurologic abnormalities.

Clinical Findings of HNKS

Polyuria/polydipsia, weakness, vomiting, dehydration, hypotension, and depression. Neurological signs include seizures, hemiparesis, hyper-reflexia, muscle fasciculation's, and nystagmus. The patient will have an elevated blood glucose and elevated serum osmolality. Serum Na and K levels are variable.

Calculation of Serum Osmolality

$mOsm/kg = 1.86 (Na^+ + K^+) + (Glucose/18) + (BUN/2.8) + 9$

Normal osmolality is 280-310 mOsm/kg

Significant if over 350 mOsm/kg in HNKS

Treatment

The goals are to restore circulatory volume, resolve the hyperglycaemia and correct electrolyte abnormalities. Care must be exercised, as we need to maintain adequate blood pressure and avoid cerebral oedema, due to a rapid fall in serum osmolality.

Treat as for diabetes ketoacidosis with IV fluids and insulin therapy.

Prognosis for Treatment of DKA Patients

DKA is one of the most difficult metabolic therapeutic challenges in veterinary medicine. Despite sound medical management approximately 30% of cats and dogs with severe DKA die or are euthanased during hospitalisation. Death may be due to the underlying illness, metabolic acidosis or complications that occur during therapy.

However, with good medical management and the recognition of potential complications the patient is likely to have a favourable outcome.

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