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**The secrets about diabetic ketoacidosis and hyperglycemic hyperosmolar state**

**Claudia E. Reusch**

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are severe complications of diabetes mellitus. Although both represent acute hyperglycemic situations, DKA is more characterized by ketonemia and anion-gap acidosis and HHS by hyperosmolality and dehydration. It is important to note, however, that DKA and HHS are not distinct disorders. They should be best considered as part of a spectrum of findings in patients with insulin deficiency (Rose and Post 2001).

## Diabetic ketoacidosis (DKA)

### *Pathogenesis and pathophysiology*

DKA is a relatively common, life-threatening complication of diabetes mellitus. It results from absolute or relative insulin deficiency and increased concentrations of the counterregulatory hormones glucagon, catecholamines, cortisol and growth hormone. Two major steps are required for ketogenesis to occur: 1) Lipolysis must be increased to enhance the delivery of free fatty acids to the liver. In insulin deficiency fat mobilization is accelerated due to the abolition of the inhibitory effect of insulin on the hormone sensitive lipase and due to the activity of epinephrine, norepinephrine, cortisol and growth hormone. 2) Alteration of hepatic metabolism, so that formation of ketones occurs. In the liver fatty acids can either be used in the cytosol for triglyceride synthesis or they undergo beta oxidation within the mitochondria which converts them into acetyl-CoA. The rate limiting step in hepatic ketogenesis is the entry of fatty acids into the mitochondria. In poorly regulated diabetes glucagon excess plays a major role in ketogenesis, as it leads to increased entry of fatty acids into the mitochondria by increasing the activity of the enzyme carnitine palmitoyl transferase (carnitine shuttle). Normally acetyl-CoA mainly enters the citric acid cycle to form carbon dioxide and water. In case of poorly regulated diabetes, however, oxaloacetate deficiency will shift the metabolism of acetyl-CoA towards ketone body formation (Rose and Post 2001, Stojanovic and Ihle 2011, Maletkovic and Drexler 2013). Acetoacetate (AcAc) is the initial ketone body, which is converted to β-hydroxybutyrate (BHB) and acetone. AcAc and BHB are strong acids and their accumulation will lead to acidosis. Acetone is responsible for the distinctive smell on the breath of patients with DKA. While AcAc and BHB are normally present in approximately equal concentration, the ratio is shifted towards BHB in DKA. In humans it is known that the ratio may rise to 10:1 (Laffel 1999). In dogs and cats the predominant ketone body is also believed to be BHB. A recent study, however, suggested, that in dogs with high serum ketone concentration AcAc may be the predominant ketone body (Durocher et al 2008). Insulin deficiency causes decreased glucose utilization and increased glycogenolysis leading to hyperglycemia, osmotic diuresis (aggravated by ketonuria), loss of water and electrolytes and dehydration. A recent study suggested, that dysregulation of cytokines may play a role in the pathogenesis of DKA in dogs (O'Neill et al 2012).

### *Precipitating factors and clinical signs*

DKA often occurs in animals with previously untreated diabetes. It may also develop in case of indadequate therapy, often in conjunction with one or several concurrent diseases. Any disease can cause an increase in counterregulatory hormones, thereby triggering the development of DKA. The most commonly identified diseases are pancreatitis, chronic kidney disease, urinary tract infection, neoplasia, hepatic lipidosis, cholangiohepatitis, cardiac disease and hypercortisolism (Bruskiewicz et al 1997, Hume et al 2006, Sieber-Ruckstuhl et al 2008, Cooper et al 2015).

Initial clinical signs are pu/pd, polyphagia and weight loss; with progressive ketone body production and acidosis lethargy, anorexia, vomiting and dehydration develop. The severity of clinical signs is directly related to the severity of metabolic acidosis. The time interval from the onset of initial signs of diabetes to development of signs of DKA is unpredictable and

ranges from days to months. Once ketoacidosis begins to develop, severe illness becomes apparent within a week (Nelson 2015).

***Laboratory findings/diagnostic criteria***

The diagnosis is based on clinical signs, hyperglycemia and the documentation of increased ketone bodies and metabolic acidosis. Presence of metabolic acidosis differentiates diabetic ketosis from diabetic ketoacidosis. According to the ADA DKA is defined as pH < 7.3 and serum bicarbonate < 18 mmol/l (Kitabchi et al 2009). The commonly used nitro-prusside test strips for testing the presence of ketones in the urine may be misleading as it only measures AcAc and acetone. Urine ketone testing may therefore be negative or may underestimate the degree of metabolic derangement and should not be used to exclude DKA. Interestingly, using the test strip in plasma revealed a higher sensitivity than in urine and it was assumed that there is a AcAc threshold (Zeugswetter and Pagitz 2009). Measurement of BHB in blood is the preferred method and can easily be done using a portable ketone meter (Precicion Xceed, Abbot GmbH), previously validated for use in dogs and cats (Di Tommaso et al 2009, Henderson and Schlesinger 2010, Weingart et al 2012, Zeugswetter and Rebuzzi 2012, Bresiani et al 2014). There is good agreement between capillary and venous blood BHB and good overall correlation of the portable meter with the reference method. At high concentrations measurement with the meter was lower than the reference method in 3 studies (Weingart et al 2012, Zeugswetter and Rebuzzi 2012, Bresciani et al 2014) and higher in another study (Henderson and Schlesinger 2010). Studies in dogs proposed a cut-off of 2.3 mmol/l with a sensitivity of 100% and a specificity of 70% for the diagnosis of DK (Di Tommaso et al 2009), and a cut-off of 3.8 mmol/l with a sensitivity and specificity of 70% and 92% (Bresciani et al 2014). In cats a cut-off of 2.55 mmol/l had a sensitivity and specificity of 94% and 68% (Zeugswetter and Rebuzzi 2012). Of note, BHB may also be increased in dogs and cats without diabetes mellitus but various other diseases, in particular in cats with hepatic lipidosis (Aroch et al 2012, Gorman et al 2016, Hurrell et al 2016).

***Therapy***

The cornerstones of treatment are: fluid therapy, electrolyte supplementation, insulin administration and treatment of concurrent diseases.

Fluid therapy

IV fluid therapy should be initiated immediately. 0.9% NaCl is considered the initial fluid of choice because most patients are hyponatremic on presentation. The amount of fluid is calculated based on the degree of dehydration + maintenance + ongoing losses. Ongoing losses may be huge due to increase in GFR and osmotic diuresis, vomiting and diarrhoea. The total amount is given over 12-24 hrs. Calculation of fluid deficits are estimates and requirements may be higher. 0.9% saline is a non-buffered solution, which may contribute to metabolic acidosis. We therefore switch to a buffered crystalloid solution (such as Plasma-Lyte) as soon as phosphate supplementation is no longer needed (see later).

Potassium supplementation

The potassium deficit can be severe, although serum potassium concentration may be normal or even elevated. The initial dose depends on the pretreatment potassium concentration and is given according to the well known guidelines (DiBartola and De Morais 2012). Intravenous potassium administration should not exceed 0.5 mmol/kg/h to avoid cardiac arrhythmias.

Phosphate supplementation

Similar to potassium, the organism is phosphate deficient, regardless of the serum phosphorus concentration. We usually add half of the calculated dose of potassium as potassium phosphate and the other half as potassium chloride. Potassium phosphate should not be mixed with calcium containing fluids, such as Ringers solution and Plasma-Lyte.

Bicarbonate supplementation

The metabolic acidosis typically resolves with fluid therapy and insulin administration. The use of sodium bicarbonate is controversial in human and veterinary medicine. We only administer bicarbonate if pH is < 6.9, similar to the recommendations of Kitabchi et al (2009).

Insulin therapy

Insulin therapy is essential in the treatment of DKA, because without insulin ketonemia does not resolve and ketogenesis continues. However, an additional effect of insulin is a shift of potassium into cells, which may lead to life-threatening hypokalemia in potassium depleted individuals. Therefore, insulin therapy should be postponed until potassium (and phosphorus) have been supplemented and serum levels are stable. We routinely wait for 4 hours until insulin therapy is started; initiating insulin > 6 hours was shown to lead to delayed resolution of DKA (DiFazio and Fletcher 2016). Regular insulin as well as short-acting insulins (lispro, aspart) can be used (Sears et al 2012, Walsh et al 2016).

*Intermittent, intramuscular protocol*

Short acting insulin is given at a dose of 0.05 – 0.1 U/kg IM every hour and blood glucose concentration is measured prior to each application. The desired decrease of glucose is 3-4 mmol/l/h until a glucose concentration between 12-15 mmol/l is reached. If the blood glucose concentration decreases to less than 12 mmol/l, glucose is added to make a 5% glucose solution (e.g. 100 ml 50% glucose to 1000 ml 0.9% NaCl). Short acting insulin is then given every 4-6 hrs at a dose of 0.1-0.3U/kg SC.

*Continuous rate infusion protocol*

This protocol involves administration of short-acting insulin diluted in 0.9% NaCl using an infusion pump in a separate line. In Zurich an insulin solution is made by adding 1 U/kg (dogs) or 0.5 U/kg (cats) insulin aspart (NovoRapid) in 50ml 0.9% NaCl, which is then infused in a separate line according to a sliding scale. When blood glucose has decreased to 12-15 mmol/l glucose is added to the Plasma-Lyte solution to create a 5% glucose solution. It has been our impression that resolution of DKA is faster with the continuous rate infusion than with the IM protocol.

### *Prognosis*

Prognosis is largely dependent on the intensity of treatment and monitoring and on the severity of concurrent diseases. Reported mortality ranges between 5% and 39% (Bruskiewicz et al 1997, Hume et al 2006, Cooper et al 2015, Nelson 2015).

## Hyperglycemic hyperosmolar state (HHS)

### *Definition, pathogenesis and pathophysiology*

In human medicine HHS was previously named hyperglycemic hyperosmolar nonketotic coma, but it was found that it often times presents without coma. It was also named hyperglycemia hyperosmolar nonketotic state, but in some patients some degree of ketonuria is found. The term HHS has been recommended by the American Diabetes Association (ADA) and it is now also used in veterinary medicine (Nugent 2005, Maletkovic and Drexler 2013, Nelson 2015).

HHS is characterized by extreme hyperglycemia, hyperosmolality and dehydration. As is the case in DKA, HHS results from reduced or absent insulin levels and increased levels of counter-regulatory hormones. The factors responsible for the absence of ketoacidosis in HHS are not completely understood. One proposed factor is the different sensitivity of fat and glucose metabolism to the effects of insulin. Studies in humans showed that the insulin concentration necessary to suppress lipolysis is only one-tenth that required to promote glucose utilization. In HHS insulin levels seem to be somewhat higher than in DKA, this amount of insulin is sufficient to block lipolysis, but not enough to enhance glucose utilization. The result will be hyperglycemia without ketoacidosis, because even high levels of the counter-regulatory hormone glucagon will not produce ketoacidosis if delivery of free fatty acids (as precursor of ketone bodies) is not increased (Rose and Post 2001, Kitabchi et al 2009). As long as GFR is normal, glucosuria will prevent severe hyperglycemia. However, with ongoing osmotic diuresis, hypovolemia will develop, leading to progressive decline in GFR and worsening hyperglycemia (Pasquel and Umpierrez 2014). The hyperglycemia of HHS tends to be more severe than the hyperglycemia in DKA. One reason for this difference

is certainly, that the low to undetectable concentrations of ketones remove an important and early contributor of clinical signs. Consequently, the hyperglycemia of HHS progresses for a longer period of time until veterinary care is sought (Nelson 2015). With increasing plasma osmolality water moves out of the cells, which is most relevant in the brain, leading to neurological impairment, profound lethargy and coma.

***Precipitating factors and clinical signs***

Any underlying disease can provoke the release of counterregulatory hormones, lack of food and water intake contributes to increase in counterregulatory hormones and exacerbates dehydration.

In cats with HHS serious concurrent diseases were diagnosed in 88% of cases. The most common were renal failure, respiratory compromise, infection, congestive heart failure, neoplasia and gastrointestinal tract diseases. Compared to cats with DKA, significantly more cats with HHS had chronic renal failure (58.8% vs. 12.5%) and congestive heart failure (29.4% vs. 3%) (Koenig et al 2004). Similarly, dogs with hyperosmolar non-ketonuric diabetes had significantly higher BUN and creatinine than dogs with hyperosmolar ketonuric diabetes (Trotman et al 2013).

Median duration of diabetes prior to presentation was 18 months (0-108) in cats with HHS compared to 1 month (0-84) in cats with DKA (Koenig et al 2004). Similarly, dogs with hyperosmolar non-ketonuric diabetes had significantly longer duration of diabetes than dogs with hyperosmolar ketonuric diabetes (Trotman et al 2013). Clinical signs include pu/pd, anorexia, vomiting, (severe) dehydration, lethargy, progressive weakness and possibly coma. Cats with HHS were less likely than cats with DKA to have anorexia and weight loss (Koenig et al 2004).

***Laboratory findings/Diagnostic criteria***

HHS is characterized by extreme increase in blood glucose (> 34 mmol/l), calculated total serum osmolality $\geq$ 350 mOsm/kg or calculated effective serum osmolality $\geq$ 330 mOsm/kg. Effective osmolality is calculated as 2x $Na^+$ + glucose. The pH is > 7.3 and bicarbonate > 18 mmol/l (Kitabchi et al 2009). Prerenal or renal azotemia is common. Despite depleted body potassium stores serum potassium can be high, normal or low. Similarly, variable changes of serum sodium can occur with hyperglycemia. Generally, mild hyponatremia or normal serum sodium suggest moderate volume deficits. Hypernatremia despite hyperglycemia points to substantial water loss and severe volume deficit (Nelson 2015). Urine is either negative for ketones or shows trace ketonuria. Most of the criteria used in veterinary medicine have been adapted from humans and their validity for dogs and cats has not been thoroughly investigated.

***Therapy***

Therapy of HHS is similar to therapy of DKA and consists of fluid administration, restoration of potassium and phosphate deficits, insulin administration and treatment of any precipitating factors. The ADA guidelines list one relevant difference between DKA and HHS with regard to maintaining serum glucose levels in humans. They should be kept between 11-17 mmol/l in HHS patients until they are mentally alert and between 8 and 11 mmol/l in DKA patients until resolution of DKA (Kitabchi et al 2009). The reason is that rapid changes in plasma and brain osmolality due to fluid administration could result in brain edema; in HHS this risks may be higher due to the more pronounced hyperosmolality.

***Prognosis***

The prognosis is guarded to poor. Sixty-five percent of HHS cats did not survive the initial hospitalization, most cats died or were euthanized within 10 hours of presentation. The long-term survival was 12% (Koenig et al 2004).

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