Diagnosis and Management of Diabetic Ketoacidosis

Dr. Elisa Mazzaferro reviews the pathophysiology and treatment of diabetic ketoacidosis.

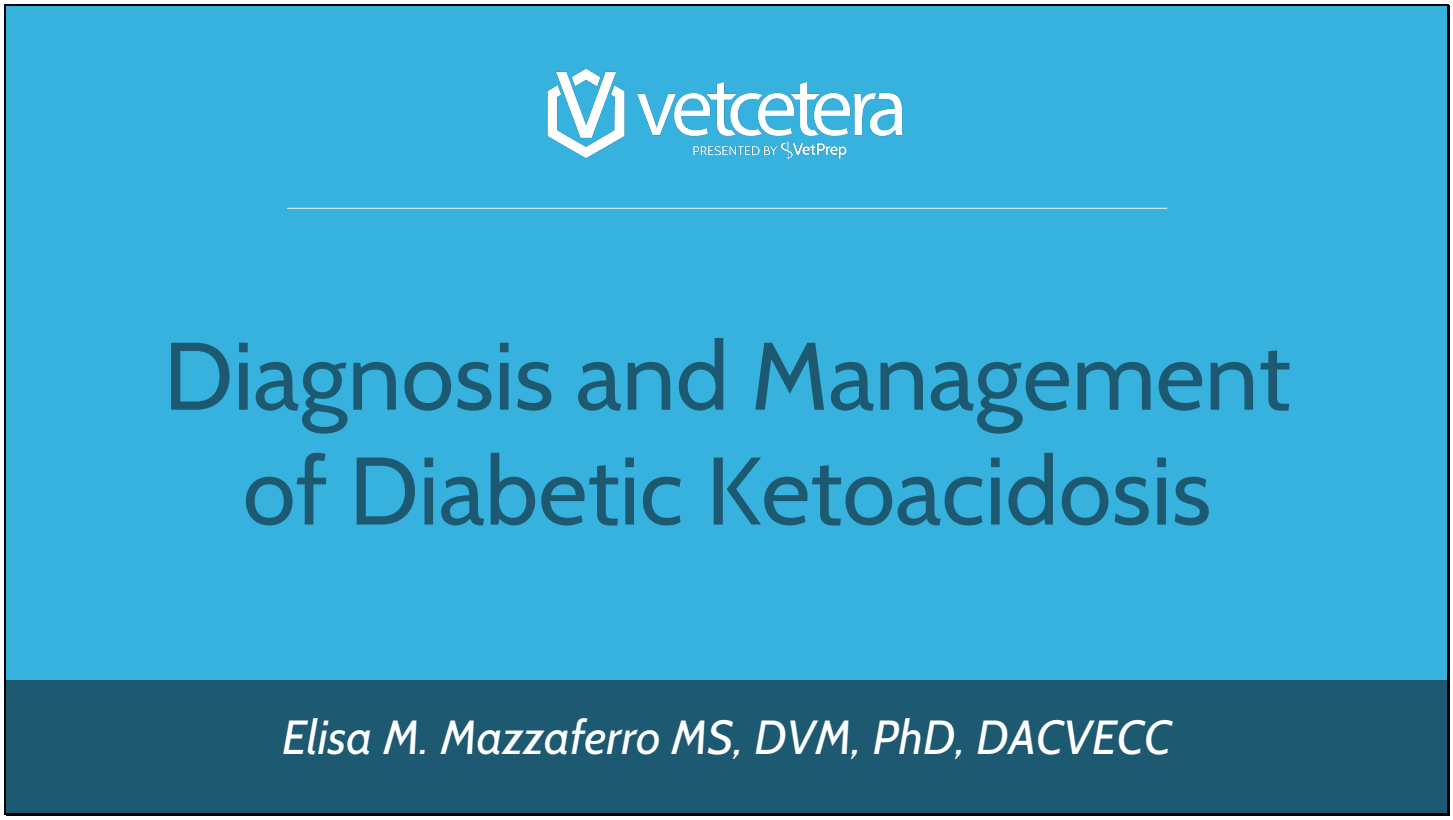
Speaker Bio:

Dr. Elisa Mazzaferro is a Staff Criticalist at Cornell University Veterinary Specialists in Stamford, CT and an Adjunct Associate Clinical Professor of Emergency and Critical Care at Cornell University College of Veterinary Medicine. She is a 1997 graduate of Michigan State University College of Veterinary Medicine. She completed a four-year combined Emergency and Critical Care Residency and PhD in Small Animal Clinical Sciences at Colorado State University and became board-certified by the American College of Veterinary Emergency and Critical Care (ACVECC) in 2002. She is a Past-President of ACVECC and is the current President of the Veterinary Emergency and Critical Care Society. In 2018, she was the recipient of the VECCS Ira Zaslow Distinguished Service Award. Dr. Mazzaferro has given presentations in more than 10 countries and 21 States within the U.S. and has published 4 books, as well as numerous manuscripts and book chapters topics related to Small Animal Emergency and Critical Care. In her spare time, she enjoys gardening and relaxing with her 3 dogs and cat.

Learning Objectives:

1. Know how to diagnose DKA
2. Know how to completely work-up potential causes of insulin resistance that can lead to DKA
3. Know how to manage a patient with DKA, with use of short and long-tern insulin
4. Know how to manage acid-base and electrolyte abnormalities in the patient with DKA
5. Gain insight and confidence in the management of DKA in their practice
6. Share knowledge with their staff of nurses on the nursing management of the patient with DKA

Slide 1



Good evening, everyone. Thank you so much for joining us. Our speaker for tonight is Dr. Elisa Mazzaferro. You guys might remember her, she actually did our very first webinar that we launched with back in October, which was TriageSTAT. And she's back tonight to talk to us about diagnosis and management of diabetic ketoacidosis. She's an emergency critical care veterinarian of staff critical analyst at Cornell, as well as an associate professor. And she has had a ton of experience, she's very experienced with lecturing, and we really enjoyed having her last time. I hope you guys enjoy the lecture tonight. With that, I'll hand it over to her.

All right. Thank you very much, Katie. It's my pleasure tonight to be talking about management of diabetic ketoacidosis. I think, that I would love to see in the chat box, and we can poll later of how many persons love DKA. And how many people diagnose to DKA, and just want to ship them to the nearest emergency critical care facility. Because calculation of all these different CRIs and acid-base and electrolytes are just overwhelming.

All right. Thank you very much, Katie. It's my pleasure tonight to be talking about management of diabetic ketoacidosis. I think, that I would love to see in the chat box, and we can poll later of how many persons love DKA. And how many people diagnose to DKA, and just want to ship them to the nearest emergency critical care facility. Because calculation of all these different CRIs and acid-base and electrolytes are just overwhelming.

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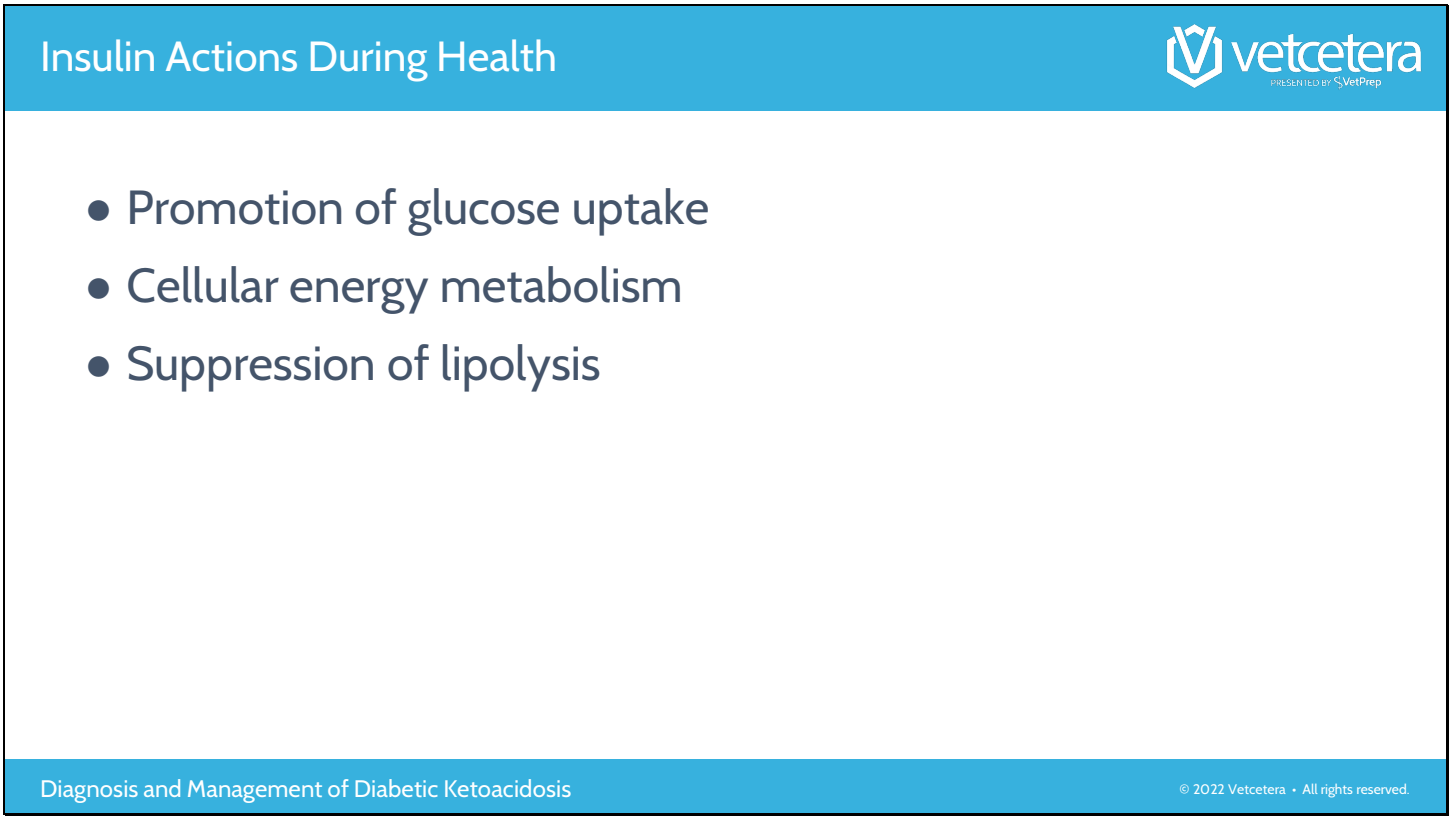


So we're going to talk about the actions of Insulin during states of health. And insulin, as you guys already know, are very important in the promotion of the uptake of glucose. And utilization of carbohydrate sources, as energy. Insulin also helps promote cellular energy metabolism, and suppresses lipolysis or the breakdown of fat for energy. So whether or not, insulin has an actual deficit. Say in animals, that cannot produce enough insulin or if a patient has insulin resistance, and there's some other factor that's blocking or inhibiting the actions of insulin.

We will see animals that are ultimately unable to utilize carbohydrate for energy sources, develop a hypoglycemia. And also-- then as a secondary consequence break down fat for energy and become ketotic.

Slide 3

Classification of Diabetes Mellitus

- Type I
- Type II
- Type III
- Insulin-dependent
- Non-insulin dependent

And so there are different classifications and types of diabetes. And that will depend on whether or not they can produce insulin or whether they have insulin resistance. And we also will discuss Insulin dependent diabetes mellitus, as well as Non-insulin dependent diabetes mellitus.

Slide 4

Type I Diabetes Mellitus

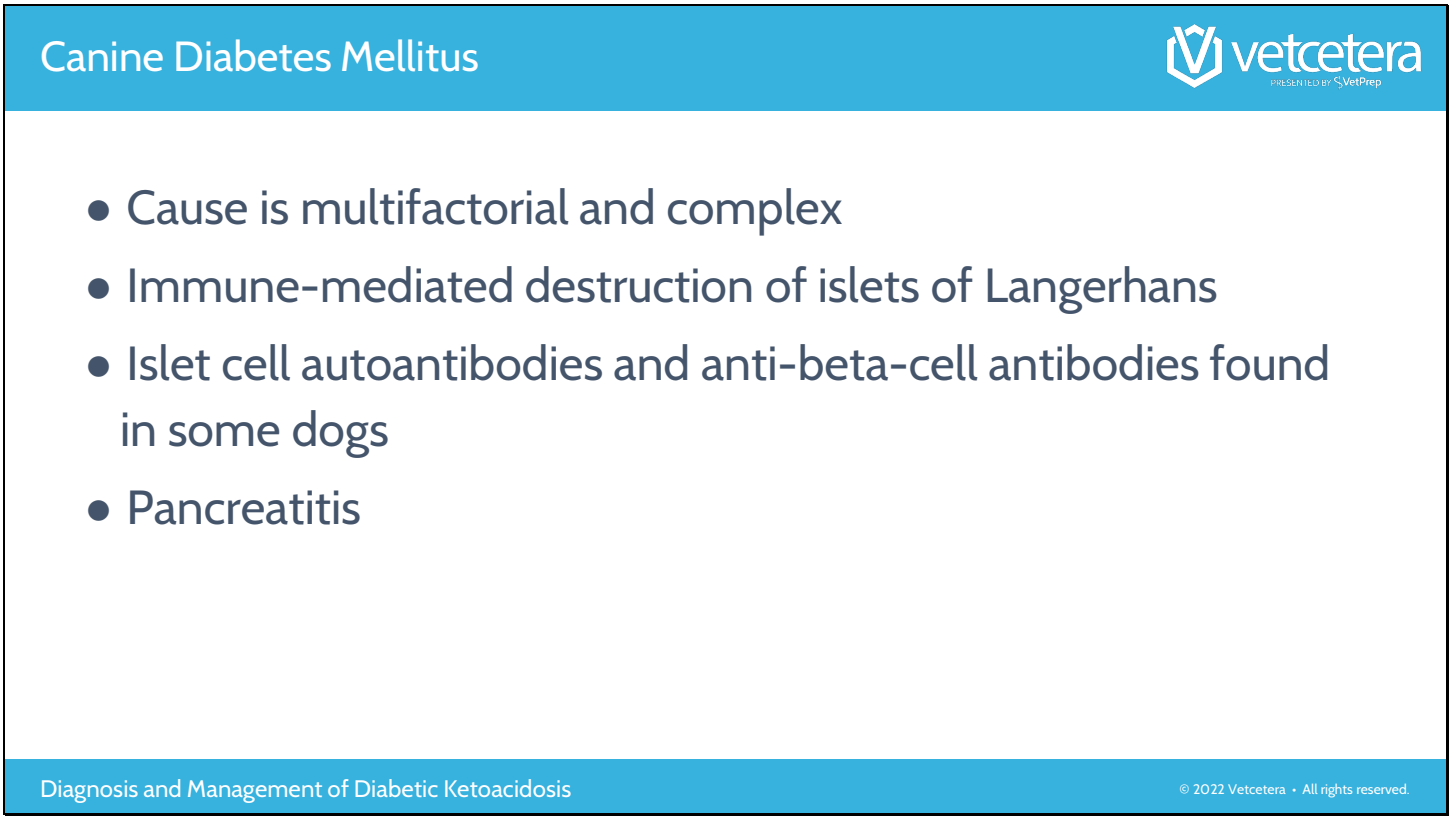
- Immune-mediated destruction of pancreatic beta cells
- Primary cause of DM in dogs and juvenile humans
- Not commonly reported in feline patients
  - Lymphocytic insulinitis in 6 cats (*Nakayama et al, 1990*)

So type 2 diabetes mellitus, is what occurs in dogs and in humans. And it's surprising to me, that I have had friends in their early 20s to mid 20s, actually develop an insulin dependent primary type 1 diabetes mellitus. Where there's immune mediated destruction of the beta cells and islets of Langerhans in the pancreas. And the dog or the person could no longer produce insulin.

And those people and I would say the majority of dogs will become insulin dependent. Means, they will need lifelong therapy to treat their diabetes mellitus. Type 1 diabetes, is very uncommonly reported in feline patients. But Nakayama and others-- Oh, gosh. Now, I don't even want to think of how many years ago that was. I'm dating myself but-- but they did develop a Lymphocytic insulinitis in about six cats.

So I can't say that type 1 diabetes doesn't occur in cats, but it's extremely, extremely rare. Especially when considering, how common type 2 diabetes is in cats.

Slide 5



So the cause of diabetes mellitus in dogs, is multifactorial in complex, which basically is our global statement. Meaning, we don't really understand everything that goes into it. But there is immune mediated destruction of the Islets of Langerhans, and also autoantibodies that are directed against both pancreatic Islet Cells. As well as Anti-B cell antibodies that can be found in some dogs.

We could develop diabetes mellitus or dogs can develop diabetes mellitus, secondary to pancreatitis. Rarely, an animal will develop diabetes, and diabetic ketoacidosis. Secondary to pancreatitis and would have a very small percentage of them could potentially become non-insulin dependent. But I would say that is extremely abnormal and very, very rare.

Slide 6

Canine Diabetes Mellitus

- 4 – 14 years of age
- Peak 7 – 9 years
- Females affected 2x more often than males

In dogs, the peak age is between 7 and 9 years. But it's been reported in dogs spanning many, many years of age from 4 to 14 years with females being having predisposition about twice more commonly than males.

Canine Diabetes Mellitus

- Genetic predisposition in some breeds
  - Cairn Terrier
  - Miniature Schnauzer
  - Keeshond
  - Poodle
  - Dachshund
  - Beagle

There are genetic predispositions in some breeds, including the Cairn Terrier, Miniature Schnauzers, Keeshonds, Poodles, Dachshunds and Beagles.

Slide 8

Type II Diabetes Mellitus

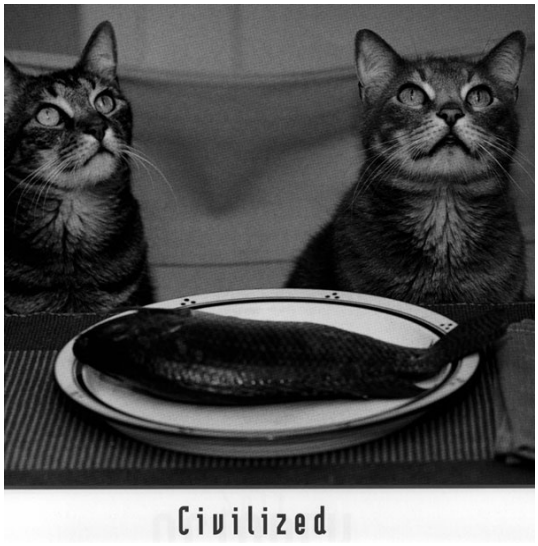
- Hallmarks of Type II DM
  - Peripheral insulin resistance
  - Impaired insulin secretion

And the hallmark-- so that kind of discusses type 1 diabetes. But type 2 diabetes, is what is-- most commonly seen in cats, as well as older aged humans. In the hallmarks of type 2 diabetes mellitus, is impaired insulin secretion, as well as peripheral insulin resistance.

Slide 9

Feline Diabetes Mellitus

- Significance
  - Common disease
  - Frustrating for clients and veterinarians alike
  - Variability
  - fluctuations in insulin requirements



Diagnosis and Management of Diabetic Ketoacidosis

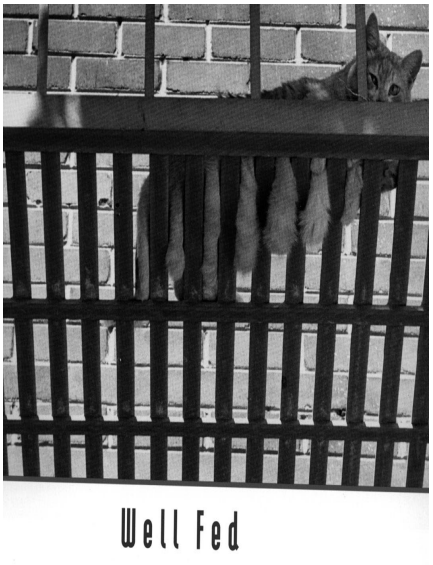
And the significance of type 2 diabetes in cats, is that it's very common. It's very frustrating, because I will diagnose a cat with diabetes. And say, well, for the time being, you're going to need to give your cat insulin, but maybe not always, but sometimes, they may or may not need it. And usually, they'll be doing fine until you come home and find them hypoglycemic.

And then in the future, you might need to give insulin again. But I don't know not always. And the clients are like, what? And so, it's extremely variable, and it's super, super frustrating. There are fluctuations in the insulin requirements that are based not only on the inherent metabolism of the cat, but also whether or not, they develop other things that can cause peripheral insulin resistance.

Slide 10

Epidemiology

- 1:400 incidence (*Panciera et al, 1990)*
- Risk factors
  - Age
  - Gender
  - Obesity
  - Neutering
  - Breed?



Diagnosis and Management of Diabetic Ketoacidosis

In an older study done by Pat Sierra and others. There's about a one to 400 incidents of diabetes in domestic cats. And the risk factors were factors were age, gender, obesity, neutering and possibly breed. And so we don't see diabetes mellitus develop in cats and farm cats, barn cats, that are outside, they're hunting, they're eating a high protein, low carbohydrate, mouse and bird diet. And they have to actually hunt and move to eat where-- how many of you have cats at home? And I love seeing cats. And my cat will lay there on her side and with her paw flick her kibble out of the bowl, and not even lift her head to eat it.

And we have created a lot of these risk factors for our cats, that are inside. They're not moving around very much, they're not very active. We feed them crunches nice dry high carbohydrate crunches, and they become obese. So similar to a person, who's extremely sedentary, either playing video games or watching television, and just mowing down on a bag of potato chips. Or fast food having it delivered by Uber Eats or whatever. And we have created these risk factors.

However, there are genetic predispositions both in humans and in veterinary patients, such as cats.

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Unique Features of Cat Metabolism

- Unrestrained hepatic gluconeogenesis
- Catabolize protein to synthesize glucose
- Low glucokinase activity
- High carbohydrate, low protein meal causes hyperglycemia
- Net result is prolonged hyperglycemia

And so cats are unique in that, they have unrestrained hepatic gluconeogenesis. So irrespective of blood glucose levels, their liver is just going to continue to make sugar, they're going to make glucose. And they'll actually preferentially metabolize protein. They will break down their bodies protein sources. Their body muscle sources to make glucose. They have low glucokinase activity. So they're not going to break down glucose, once it's made.

And then, there's a high carbohydrate, low protein meals, such as those dry crunches will cause them to get hypoglycemic. And the net result is prolonged hypoglycemia

Insulin Resistance

- Downregulation of insulin receptors in muscle and liver
- Impaired insulin receptor binding affinity
- Post-receptor defects in glucoses transport
  - Decreased availability of intracellular glucose to stimulate insulin release

that then causes downregulation of insulin receptors in muscle and liver. And impairs the ability of the insulin receptors and peripheral tissues to bind with insulin. So they get tired. It's kind of like that beeping pump in the background, you hear it so often, that you become immune to it.

Similar to in the sea of plenty of glucose, the insulin receptors, like nah. I don't have to work anymore. I'm not going to bind, because they're still going to be a lot of glucose around. There are Post-receptor defects in the transport of glucose, which eventually leads to a decrease in the availability of glucose that's transported into the cell to stimulate, further insulin release from the pancreas.

Impaired Insulin Secretion

- Glucose toxicity
  - Down regulation of insulin receptors on beta cells
- Amyloid deposition
  - Directly toxic to beta cells
  - Isolates beta cells from glucose and nutrients
    - Impaired glucorecognition
    - Lack of nutrient stimulus, leads to destruction

So this is known as glucose toxicity. Where the insulin receptors on pancreatic beta cells are down regulated. There's also an age-related change, that we see normally in-- even in healthy aged cats. That they will deposit amyloid in their pancreas, and that will surround the Islets and lander-- Langerhans. And impair the glucose recognition.

So it's like, I don't know-- Barrier Reef around an island, that will prevent further things from coming in. So these isolated beta cells cannot absorb glucose, as well as nutrients. And with the lack of nutrients stimulus will lead to the destruction of those pancreatic beta cells.

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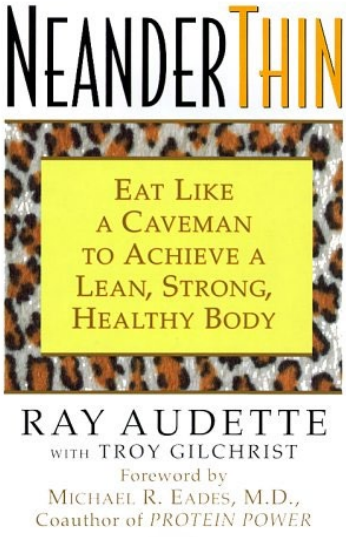
Carnivore Connection Theory



- Natural selection for insulin resistance
- Maintain euglycemia while fasting
- Increased consumption of cereal grains
  - Hyperglycemia
  - Lipogenesis
  - Obesity
  - Pancreatic islet cell atrophy

Diagnosis and Management of Diabetic Ketoacidosis

There's a theory called the Carnivore Connection Theory that discusses a genetic natural selection for insulin resistance.

And so in Hunter-gatherer societies, such as Indigenous persons in the lower 48 states, as well as in Alaska. Where those populations of individuals needed to hunt and gather food for energy. And so insulin resistance was beneficial in those populations to help them maintain U-glycemia will fasting.

And so think about what has happened over the years, as some other civilization has come in, on or near Native American and Indigenous person populations. Those individuals, no longer live on reservations necessarily. But they do also have contact with the outside world. The outside world with fast food chains like Wendy's and McDonald's, and Burger King, et cetera. There's an increased consumption of cereal grains. Things that are made from cereal grains, that are consumed-- also include alcohol. And so we see a higher incidence of hypoglycemia like biogenesis, obesity and pancreatic Islet Cell atrophy, and the development of type 2 diabetes in these populations.

Slide 15

Type III Diabetes Mellitus

- Occurs secondary to some other process
  - Acromegaly (100%)
  - Hyperadrenocorticism (80%)
  - Hyperthyroidism (5%)
  - Pancreatitis (51%)
  - Pancreatitis neoplasia (81%)
  - Exogenous progestins

And so that's similar to what happens with our cats, where we've created, and we've taken those hunter-gatherers. And we've caused them to become more sedentary and we just feed them high carbohydrate, low protein meals, that stimulate them to become obese. And then, they develop insulin resistance from glucose toxicity. And they develop type 2 diabetes mellitus.

In 3 diabetes mellitus, we see less commonly. But can occur secondary to some other usually endocrine problems, such as acromegaly, hyperadrenocorticism, hypothyroidism, rarely pancreatic neoplasia and pancreatic-- pancreatitis. Rarely, secondary to exogenous progesterone compounds. But we don't see those as commonly utilized in our veterinary patients these days.

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Relative Insulin Deficiency

- Low to low normal insulin synthesis
- Clinical signs of diabetes mellitus
- Peripheral insulin resistance
  - Glucocounterregulatory hormones
  - Systemic or local infection
  - Inflammation
  - Neoplasia

And so we can have an absolute deficiency in patients with type I diabetes mellitus. Their body just can't make enough of it or secrete it. But relative insulin deficiency, occurs when animals are kind of smoldering with low to low normal insulin synthesis. And then develop clinical signs of diabetes mellitus, secondary to some other condition that causes a peripheral insulin resistance. Such as stress, like release of glucose or regulatory hormones. Systemic or localized infection, such even something as simple as pneumonia or a urinary tract infection. Pyometra, you're never going to get rid of a DKA or diabetes, unless you actually do surgery to remove the infected uterus.

Prostatitis inflammation, such as pancreatitis or even neoplasia. So for this reason, is why, when we have a newly diagnosed diabetic, whether it be a dog or a cat, we need to do a complete diagnostic workup to make sure that they don't have underlying conditions, that are going to make them resistant to the insulin that we're going to be administering. It could be a game changer for many clients.

And when I make a diagnosis of diabetes, whether it's DKA or a newly diagnosed diabetic, I ask these clients, are they going to be able to be there every 12 hours to give their animal, insulin injections? Will you be able to monitor them? Will be able to go to the veterinarian as needed for glucose curves or will they use at home glucose monitors, whether it's a continuous glucose monitor that's attached to the patient. Or whether it is glucose monitor, and they're actually getting drops of blood from the patient on a day to day basis.

And it's a heart to heart. Because I hate to put an animal through extending this treatment for treatment of diabetes or diabetic ketoacidosis, if the clients aren't going to be able to do the follow up long term.

Lack of Insulin: Consequences

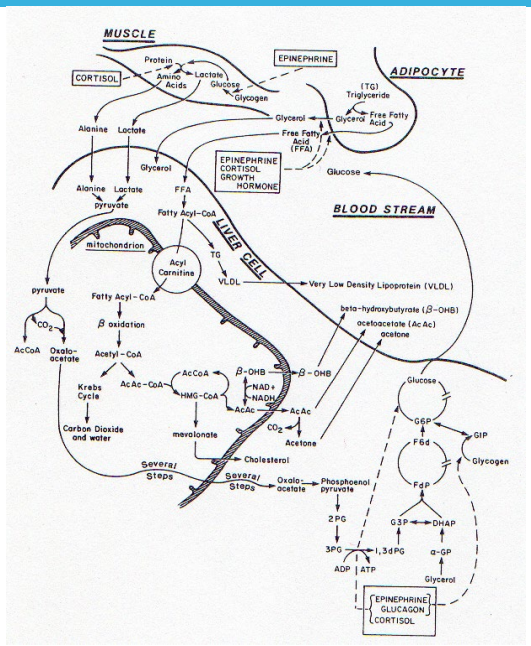
- Increased lipolysis
- Release of nonesterified fatty acids (FFAs)n into circulation
- Shift from fat synthesis to breakdown in the absence of insulin
  - Increased production of ketoacids

The best clients by the way, are the ones that have diabetes themselves or someone in their family. So they kind of know the ropes, and they can take care of the patient's best.

Lack of insulin, overall will result in the increase in the lipolysis or the breakdown of fats for energy purposes. And this release is free fatty acids, that then could shift from fat synthesis to fat breakdown when you don't have enough insulin.

Normal Lipolysis

- FFAs metabolized in liver to intermediates that are fed into the TCA cycle



This results in the production of the Keto acids that are then Fed in to try tricarboxylic acid cycle to make ultimately energy.

Ketone Bodies

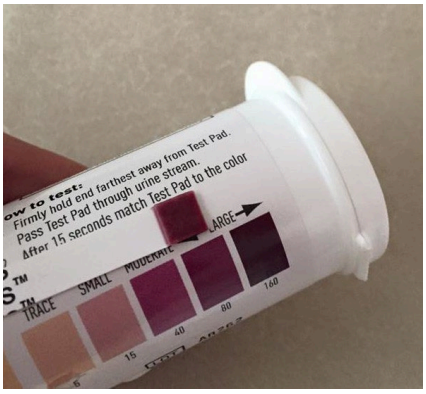
- Small quantities produced during states of health
- Can be utilized by some tissues for energy purposes
- Large quantities produced during unregulated lipolysis in DKA

Small quantities of ketones are produced during states of health. They can be utilized by some tissues for energy, including central nervous system tissues. But large quantities that are produced during states of unregulated light policies will result in an increase in ketoacids. And subsequently diabetic ketoacidosis.

Slide 20

Ketoacids

- Large quantities produced during DKA
- Decreased ability of peripheral tissues to metabolize ketoacids without insulin
- Metabolic acidosis results
  - Acetone
  - Acetoacetic acid
  - Beta-hydroxybutyric acid



Diagnosis and Management of Diabetic Ketoacidosis

And so without the actions of insulin or without insulin present, peripheral tissues will not be able to metabolize these ketones, and they will actually accumulate. And so we'll have a metabolic acidosis from the production of acetone, acetoacetic acid, as well as beta-Hydroxybutyric acid. Beta-hydroxybutyric acid, as the ketone that's produced usually in the highest quantity. But it's the one that's not tested for on the urine who-- ketone strips.

And so we also will use these ketone strips with plasma. I can actually smell ketones, it's genetic thing. It's my veterinary superpower, and probably the only one that I have. But I had COVID back in 2020 and pre-vaccine, and I lost my sense of smell. And one of the first things that started coming back, was my ability to smell ketones. But I couldn't smell puppy breath for about a year, that was sad.

I could smell ketones. And so I don't even bother using a ketone strip. But I know others, the purists will monitor them on a daily basis with that.

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Glucagon

- Increased
- Glucocounterregulatory hormone
- Simultaneous increase in epinephrine, growth hormone, and cortisol
  - Peripheral insulin resistance
  - Muscle catabolism

Will be done is counterregulatory hormone? You can see I'm still at work and there still stats coming in. And it-- it is simultaneously will increase and be released in response to stress and reasons to secrete epinephrine, as well as growth hormone and cortisol.

Glucagon will stimulate peripheral insulin resistance, and the metabolism of muscle.

Glucocounterregulatory Hormones

- Decreased muscle glucose uptake
- Increased glycogenolysis
- Depletion of glycogen stores
- Increased hepatic gluconeogenesis
- Peripheral hyperglycemia

So breakdown of muscle for energy. So when there are the presence of glucose control regulatory hormones, there's decrease in glucose uptake by muscle.

Increased glycogenolysis. So the breakdown of glycogen for energy purposes, and that will ultimately lead to depletion of glycogen stores. It will increase hepatic gluconeogenesis, which is unregulated in cats to begin with. And will lead to a peripheral hypoglycemia.

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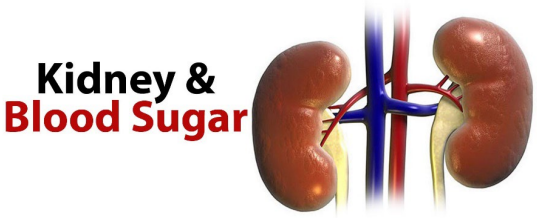
The Renal Threshold

- Serum glucose >180mg/dl
- Osmotic diuresis
- Increased solute excretion and decreased water reabsorption at Henle's Loop
- Dehydration



Diagnosis and Management of Diabetic Ketoacidosis

Once glucose is greater than 180 milligrams per deciliter, that will break the renal threshold, and result in osmotic diuresis.

So there's will be increase in excretion of solutes including glucose into the urine, and decreased water absorption in the loop of Henle. Ultimately leading to dehydration. So in the face of an osmotic diuresis, the animal would become polyuric, but be dehydrated, because they can't absorb water.

And then increase their serum osmolality, and that will stimulate receptors in the hypothalamus to secrete ADH, and then they will actually become thirsty, and they'll become polydipsic, as a result.

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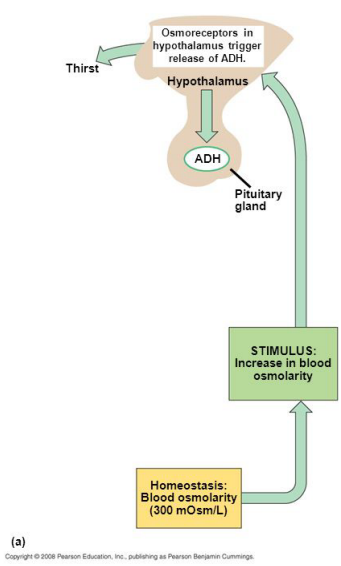
Osmolality

- Increased serum osmolatity
- Osmole receptors in the hypothalamus
- Release of ADH from supraoptic and paraventricular nuclei in hypothalamus



Diagnosis and Management of Diabetic Ketoacidosis

And so again, there's a release of antidiuretic hormone from the supraoptic impaired paraventricular nucleus of the hypothalamus. Ultimately, will lead to increased thirst and cause a patient to drink and urinate more.

And so clients will think that, their animal is urinating or because they're drinking more. But actually, it's sort of vise versa. Ultimately, it's because, these animals are diabetic, and they're spilling glucose into the urine in the absence of insulin.

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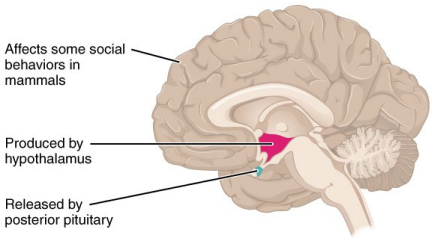
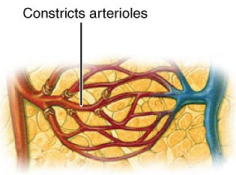
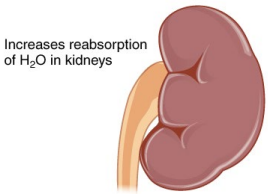
Antidiuretic Hormone

- Acts on distal tubules and collecting duct
- Inserts water pores in luminal membrane
- Promotes passive water reabsorption







Diagnosis and Management of Diabetic Ketoacidosis

Antidiuretic hormone acts on distal tubules and the renal collecting duct, by inserting water pores in the luminal membrane. Will also promote the passive absorption of water.

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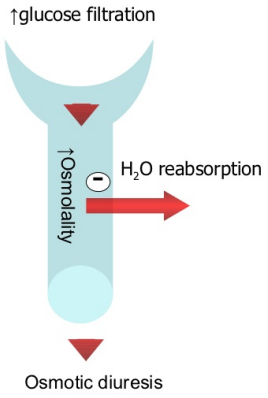
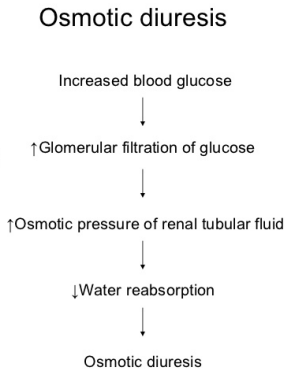
Osmotic Diuresis

- Glucose acts as an osmotic diuretic
- Inhibits water reabsorption
- Promotes dehydration despite increased serum osmolality
- Loss of magnesium, potassium, phosphorus in urine





So glucose will inhibit that water reabsorption. And also will promote the loss of magnesium, potassium, and phosphorus in the urine. And this becomes important, because these ions are depleted in animals with diabetes and diabetic ketoacidosis. And we need to monitor them, and monitor factors, and replenish them when necessary.

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Emetic Actions of Ketones

- Stimulation of the CRTZ in hypothalamus
- Nausea
- Vomiting
  - Contributes to dehydration and prerenal azotemia

Ketones also will stimulate the chemoreceptor trigger zone in the hypothalamus and lead to nausea in appetence and vomiting.

And then, the vomiting can contribute-- then to the dehydration that is present, as well as a prerenal azotemia.

DKA Clinical Signs

- Polyuria
- Polydipsia
- Ravenous appetite then decrease or inappetence
- Muscle wasting
- Weight loss
- Lethargy

And so in addition to polyuria and polydipsia, which may be extremely transient, particularly in animals that develop diabetes secondary to some other inflammation or infectious state.

But animals could slowly develop a ravenous appetite. Then once they become ketogenic, will have a decreased appetite or inhabitants. Oftentimes, despite their polyphasia, an increase in appetite, there will be muscle wasting and weight loss. And then, these animals will also become lethargic when they develop DKA.

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Physical Examination Findings

- Kussmaul respiration
- Fruity ketone odor
- Abdominal pain
  - Pancreatitis
  - Hyperlipidemia
  - Pyelonephritis
- Dehydration
- Lethargy

In physical examination, some of these animals will have a very slow deep breathing. That's consistent with Kussmaul respirations in an attempt to eliminate acid. And these animals will try to blow off CO2. They'll have a fruity ketone odor to their breath. I don't think ketones smell like fruitiness, I think it smells like nail polish remover.

Some of them will have abdominal pain. If they have pancreatitis, pyelonephritis, schnauzers with hyperlipidemia can be uncomfortable. And then, they'll be clinically dehydrated and lethargic. Depending on how severe the diabetic ketoacidosis is, there are very infrequent cases that are still eating and drinking and not vomiting.

So sometimes diabetes mellitus might be found as incidental finding on blood work. And they-- Oh, by the way, they might have 1 plus ketones in their urine. But they're still eating and drinking and not vomiting. Sometimes, I'll actually just start those dogs on long acting insulin. I've done it like twice in my career, it's very, very uncommon. But if they're healthy, I don't see the reason to put them through the rigmarole of intensive monitoring and care.

However, the majority of cases that are presented to me are usually on referral, and they're usually really sick. And we can't get by with doing outpatient care. So we have to rehydrate them, start short acting insulin along with glucose, as an energy substrate to get their condition under control before starting longer acting insulin.

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Differential Diagnosis

- Renal Failure
- Pancreatitis
- Pyelonephritis
- Pyometra
- Prostatitis
- Pneumonia

Differential diagnoses for the clinical signs of polyuria, polydipsia, decreased appetite, weight loss and vomiting. Include renal failure, pancreatitis, pyometra in unspayed dog, stump pyometra.

In some cases, there are people in our area right now, that are actually doing ovary sparing, ovarian hysterectomy. It's thinking it may help animals both with urinary incontinence, as well as decrease the incidence of neoplasia. But where there is an ovary, there could become a stump pyometra at some point in time. Prostatitis in neutered and un-neutered dogs, as well as pneumonia.

Preliminary Diagnostics

- Minimum Data Base (PCV/TS, Glucose, U/A)
- CBC
- Biochemistry profile

And so I start my minimum database, including a PCV total solids glucose and urine analysis. I save a urine sample for culture, as well. And I always-- even if I don't see bacteriuria or pyorrhea, I will always do a urine culture to make sure, that they don't have some type of infection, as a cause for their insulin resistance. Complete blood counts may be normal or it may show an increase of white blood cells neutrophils. Or it might be a decrease depending on the inflammation or infection.

As well as doing a serum biochemistry profile. And sending out in dogs and cats, a Spec FPL or CPO testing, and screening for pancreatitis.

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Diagnosis of Ketonuria

- False negatives on ketosticks
  - Detection of acetate and acetoacetate
  - Beta-hydroxybutyrate present in highest concentration

We've already talked about the false negatives on Keto sticks. In the past it was thought, you could put some hydrogen peroxide in the urine, and break down the beta-hydroxybutyric acid. And then that will cause a-- present on the Keto stick. I don't think, this is very, very useful. And so I don't do it anymore.

But 20 years ago, that's what I was taught. But I don't use hydrogen peroxide anymore to try to detect ketones. Acid-base and electrolyte status, we're going to measure these electrolytes,

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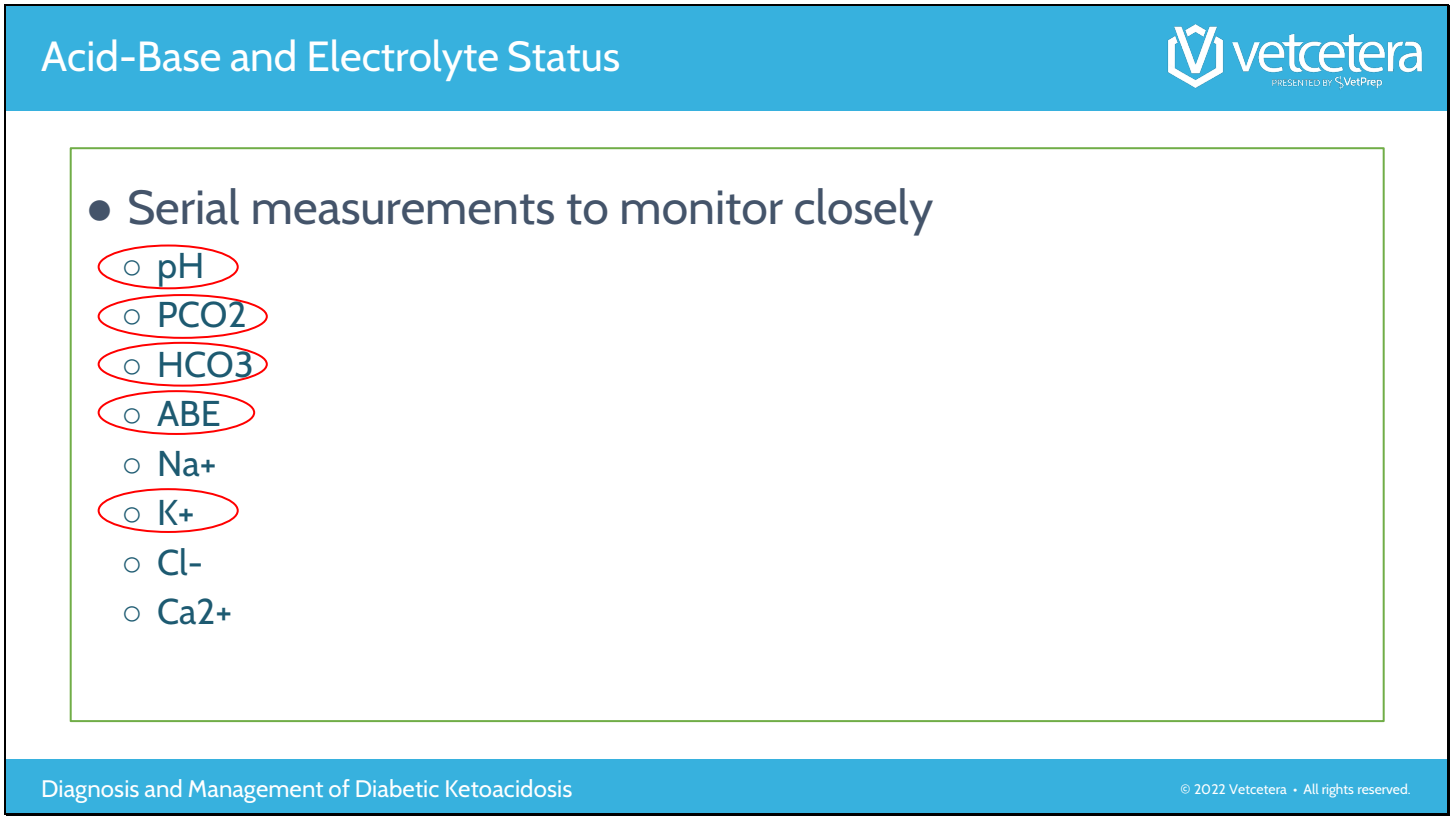

as well as their acid-base status very, very closely. Using caution to not oversample, I have oversampled cats and with DKA and needed to give them a transfusion. But we wanted to monitor their pH and primarily their bicarbonate. Their acid-base excess or deficit in this case.

Sodium and potassium can be very-- that's serious and hypokalemia can be present. And animals with pancreatitis can become hypoglycemic, as they utilize that calcium to saponify peripancreatic fat.

In fact, dogs with pancreatitis and proctitis that become hypoglycemic have worse morbidity and comorbidity, and possibly mortality.

Serum Osmolality

vetcetera
PRESENTED BY VetPrep

Osm (mOsm/kg) =

2 (Na + K) + glucose/18 + BUN/2.8

Normal Range = 290 – 310 mOsm/kg

And so serum osmolality is something to consider. Today, we had two hyperosmolar smaller dogs, canine which is-- I see maybe a couple of year. And the first one that came in had an ischemia with B ran about 200, I think?

The glucose was greater than 684. And so this dog was severely hyperosmolar. And in those animals, we have to rehydrate them before starting insulin therapy. Remember that, also sodium can become low, and actually low on your electrolyte panel. So there is a correction for corrected sodium with respect to hypoglycemia.

Pseudohyponatremia

Nacorrected = Nameasured + [1.6(glucose – 100)/100]

And so corrected sodium with the dog in question, that had the greater than 684 glucose. Their sodium-- I think showed up at like something silly, like 118. But we did correct it, so that we could see where that sodium is. And that helps us gauge what intravenous fluid to administer to help rehydrate them interstitially while we're rehydrating these animals.

So the pseudohyponatremia is a real thing. And I would advocate doing this calculation. So you could correct the sodium and help you determine what fluid to give.

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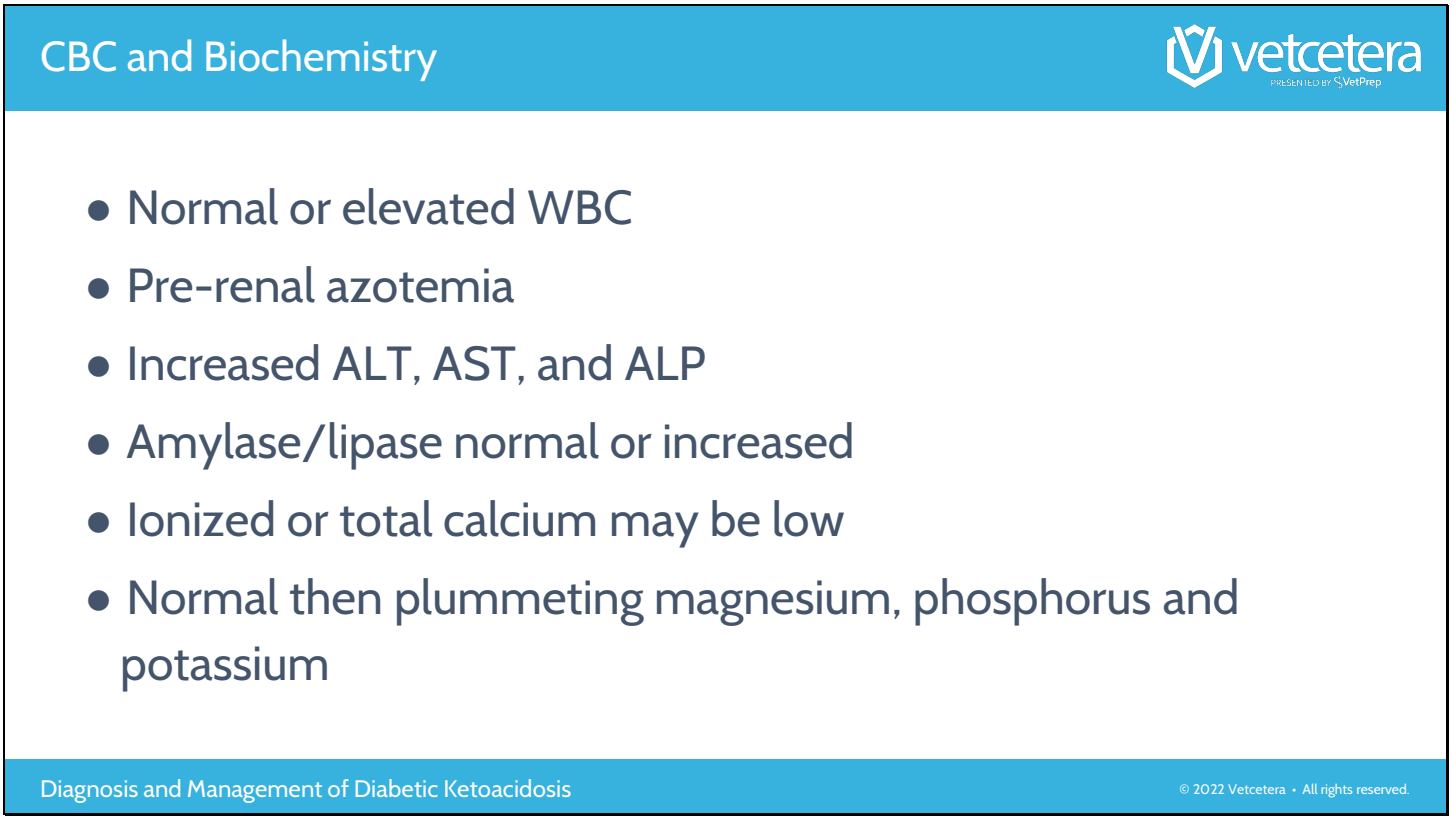

Frequency in biochemistry panel-- again, the White blood cell count could be all over the place depending, if there is an underlying comorbidity. Such as inflammation or infection. You may see a prerenal azotemia, secondary to the dehydration. And the osmotic diuresis, they could have a primary renal azotemia, if there is a pyelonephritis present.

We'll probably see increases in their hepatocellular equally static enzymes, particularly if there is a cholangiohepatitis or pancreatitis present. In a reason like phase, they're kind of useless because they're not specific, necessarily to pancreatitis. So I don't really pay attention, but if they're off the scale in a vomiting patient with abdominal discomfort, I'll say, Oh, Yeah. Their dog probably has pancreatitis. Ionized and total calcium maybe low.

In particularly, if there's pancreatitis present. And then, the electrolytes. This is where it gets really exciting. Because electrolytes do really cool things at the micro-molecular level, and we have to monitor them or at least consider them in our treatment. So that the animals don't develop progressive hyperkalemia, refractory hyperkalemia. Hyphophospatemia to the point of causing red blood cell lysis.

And then what about magnesium? Like magnesium is so important, and that's why it's fun and exciting. And people are like probably throwing things at your computer screen saying, you're crazy a narcissist what-- I don't know, I like DKA. That's why I get excited.

Therapy

- Replenish dehydration
- Correct and maintain acid-base disturbances
- Treat underlying complicating factors
- Administration of insulin

So our therapy is going to first replenish dehydration. Correct acid-base and electrolyte disturbances, treat underlying complicating factors and administer insulin. And not necessarily in this order, I personally-- unless there's a hyperosmolar animal. I'm doing these things all at the same time.

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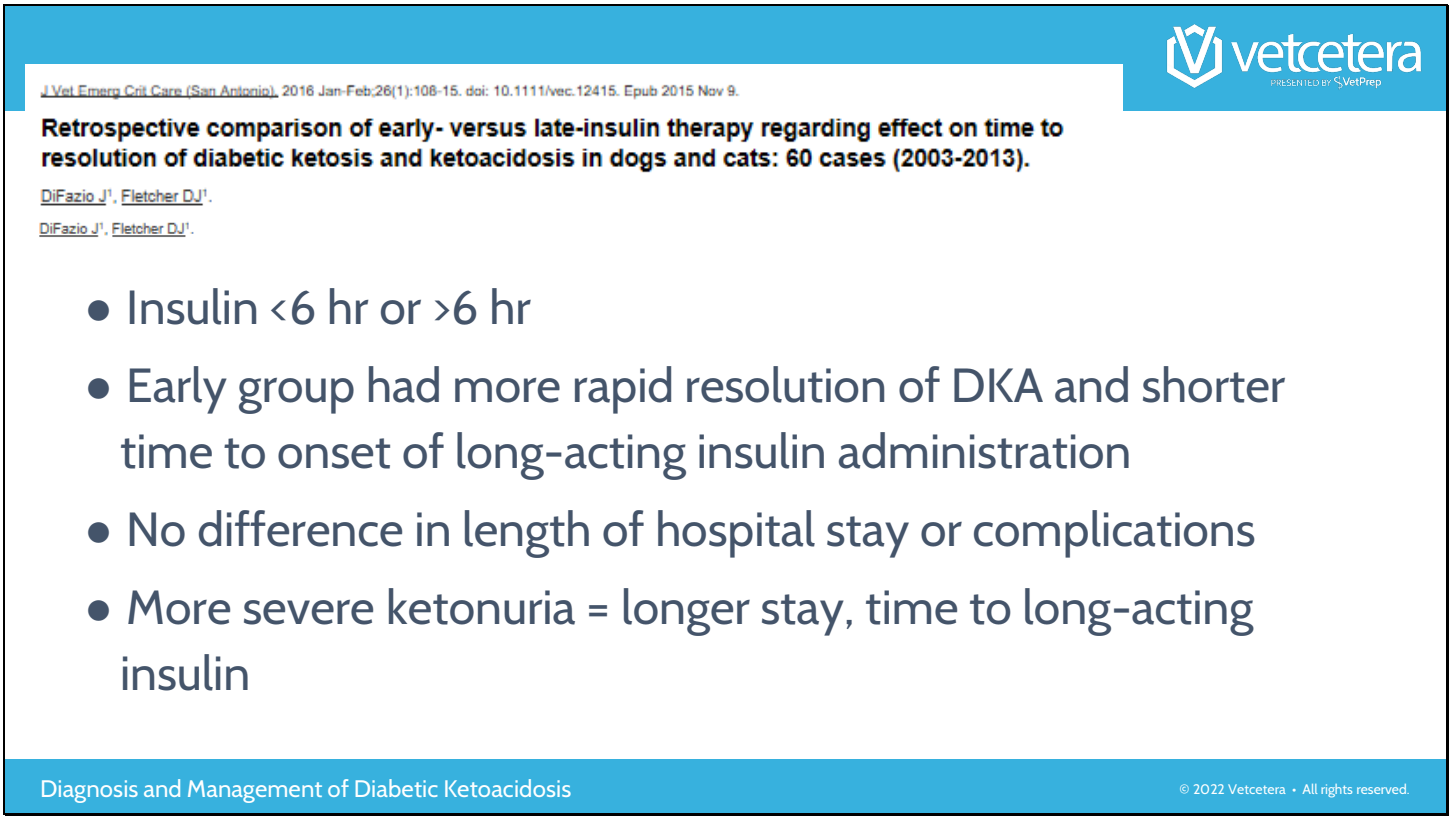


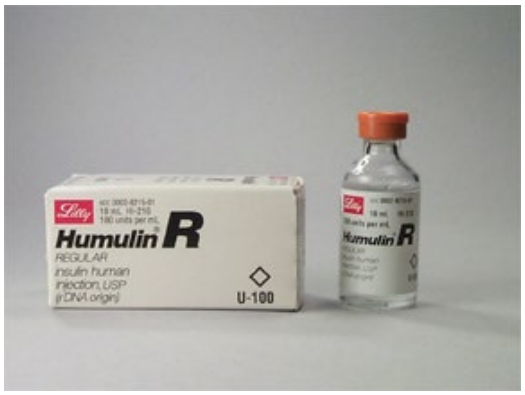
There was a retrospective study by Dr. Jill DeFazio and Dan Fletcher from Cornell University. The mothership. I met their satellite private referral hospital down about 4 and 1/2 hours South of Ithaca.

But Jill and Dan looked retrospectively at dogs with diabetic ketoacidosis. And whether or not insulin was administered early less than six hours, after admission or after six hours after admission, after a period of rehydration. And what they found was, that the early group that had insulin administered earlier. And within six hours of admission, they had an earlier resolution of diabetic ketoacidosis in a shorter time to when long acting insulin can be administered. There was no difference in the length of hospital stay or complications. But the more severe the ketonuria translated to a longer time to stay in the hospital, and longer time to administrate the longer acting insulin.

So in an animal, unless they're hyperosmolar, I will actually start my concentrate infusion of insulin therapy. At the same time, that I start my intravenous fluids.

Types and Routes of Insulin Administration

- Subcutaneous regular insulin
- Intramuscular insulin
- Constant rate infusion
- Combination short and long-acting



So types and routes of insulin administration become very, very important in these dehydrated dogs and cats. Subcutaneous insulin is not going to be absorbed until we rehydrate the interstitial space, and restore perfusion and hypoperfused the animal.

And so insulin by intramuscular injection or as a constant rate infusion are preferred methods. But there has been recent reports of combining both short and longer acting insulin for treatment of animals with DKA. And we'll talk about those studies.

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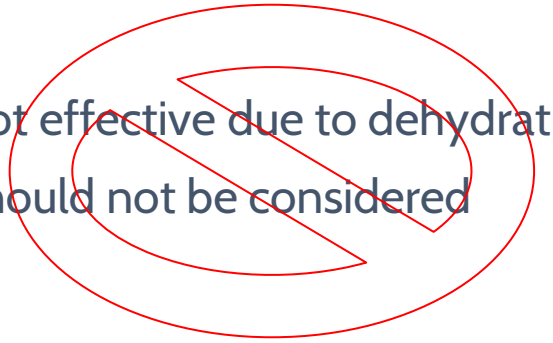
Subcutaneous Insulin



So subcutaneous insulin, I don't use unless I rehydrate the patient. Or potentially, if we're going to combine it with maybe a longer acting insulin and intravenous fluids.

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Intramuscular Insulin

- 0.2 units/kg initially, then 0.1 units/kg hourly until BG <300 mg/dl
- Goal to decrease by no more than 50mg/dL every hour
- Once BG <300 mg/dL, 0.1 units/kg IM every 4 – 6 hours until vomiting and dehydration resolves and patient is eating

Intramuscular insulin, if you guys have ever received an intramuscular injection, it hurts. But some people swear by this method. And if this is where you were trained, then I'm not going to knock it, other than to say that it hurts.

But we'll give two points two units per kilogram initially. And then hourly, we're going to check that dog or cat's blood glucose, and then give 0.1 units per kilogram every hour until the blood glucose is less than 300. And our goal is to decrease by no more than 50 milligrams per deciliter every hour. So once their blood glucose is consistently less than 300, then we could decrease the frequency of monitoring and insulin injections.

And then go to intramuscular injections, every four to six hours. And continue that until vomiting and dehydration resolve, and the patient's eating. And even if the animal still has some ketones, I will-- once they're eating and not vomiting, I will start them on longer acting insulin. That's easy. Easy peasy.

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Insulin by Constant Rate Infusion

- Dedicated insulin line and peripheral catheter
- 2.2 units/kg regular insulin (1.1 units/kg in cats) into 250 ml 0.9% NaCl
- Run 50 ml through IV tubing
- Start rate according to serum glucose

I like-- I prefer to use insulin as a constant rate infusion using a dedicated insulin line and a peripheral catheter.

So insulin is going to go through that catheter. But oftentimes, I will put a sampling line or a central venous catheter in these dogs and cats. Because I'm doing frequent blood sample collection. And I don't want to poke them every time. I have a bunch of bee and venom and wasp allergies, and I have to have four injections every month. My nurses give them to me, but it hurts.

So I try to avoid poking animals, whenever possible. If you're going to use the concentrate infusion, we tend to run about 50 milliliters of the insulin that's deluded into the 0.9% saline. Run that through the insulin in through the IV tubing, because people think that, the insulin will bind with the tubing. I do this, just as a matter of habit. I don't know that this is true or not or, if it's been proven.

But then I start the CRI rate, according to what their serum glucose is doing. Some people will be much, much more aggressive. And I will-- but I use a chart. There was a more recent study that looked at 2.2 units per kilogram in cats. So run it similar to dogs, and their glucose regulated and dropped sooner and faster. So you could use 2.2 units per kilogram for both dogs and cats.

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CRI Insulin

BG in mg/dL	Insulin:Saline Rate in mL	Other fluids
> 250	10	0.9% NaCl
200 - 250	7	0.45% NaCl + 2.5% Dextrose
150 - 200	5	0.45% NaCl + 2.5% Dextrose
100 - 150	5	0.45% NaCl + 2.5% Dextrose
< 100	0	0.45% NaCl + 5% Dextrose

Diagnosis and Management of Diabetic Ketoacidosis

So here's my insulin chart. And it's basically, I dilute the 2.2 units per kilogram of regular short acting insulin in 250 milliliters of 0.9% saline. And then, I run the-- I calculate out the animal's dehydration deficit. And then, I'll run other fluids and change that rate compared to what the blood glucose is. So when an animal's blood glucose is greater than 250 milligrams per deciliter, the insulin solution is run at a rate of 20-- 10 milliliters per hour.

In saying animals, total fluids required based on a calculated dehydration deficit is 35 miles an hour. If they're insulin rate is at 10, their other fluid is at 25. So the textbooks will say to use 0.9% saline. I use Plasma-Lyte A, that is the fluid that I have to isotonic crystalloid that also has buffers.

So sodium chloride fluid--

[COUGHS]

By itself, has no buffers, and is considered an acidifying solution. You will have some degree of metabolism to bicarbonate, as you utilize insulin and dextrose, and metabolize those ketone bodies. But I prefer in an acidemic patient to use. A fluid that contains a buffer. So Plasma-Lyte A, normal salt are lactating Ringer's or all fluids that contain buffers. And I would prefer those overusing sodium chloride for my other fluids.

Once the animal's blood glucose starts to drop, you have to utilize and use some form of dextrose. Because insulin needs dextrose to work. They have to start metabolizing carbohydrates. And so we'll start adding 2 and 1/2, then 5% dextrose.

And again, the 0.45% sodium chloride and 0.9%, that is what the textbooks tell you. I use Plasma-Lyte A.

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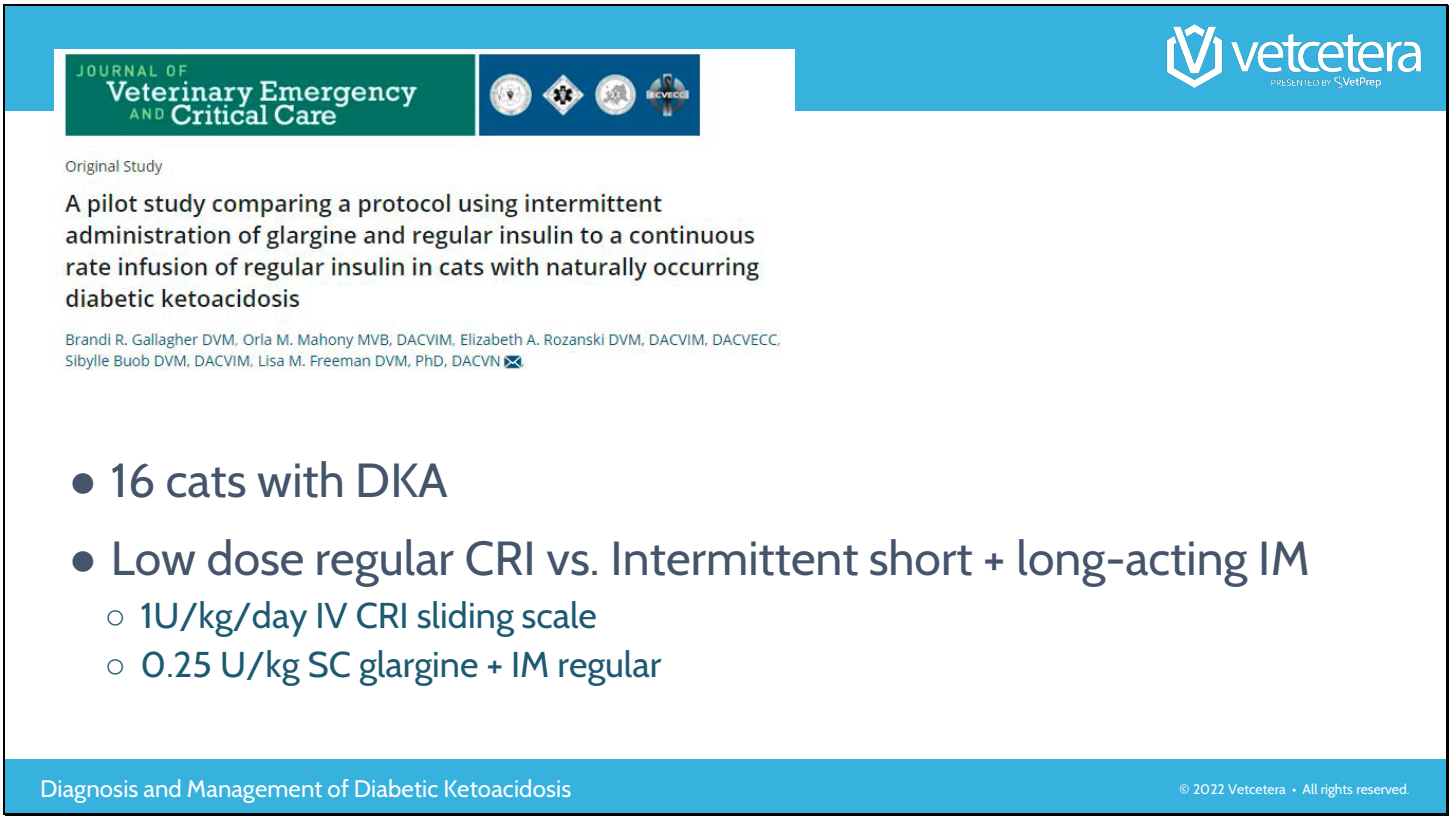

Another study, looked at combining longer acting insulin with short acting insulin. So it was a pilot study that looked at cats with diabetic ketoacidosis and they use glargine. So long acting insulin with about short acting insulin. And they found that they compared the CRI and the sliding scale similar to what I utilize here in hospital.

And in they also used 0.25 units per kilogram of subcutaneous glargine. So the longer acting insulin with intramuscular regular short acting insulin.

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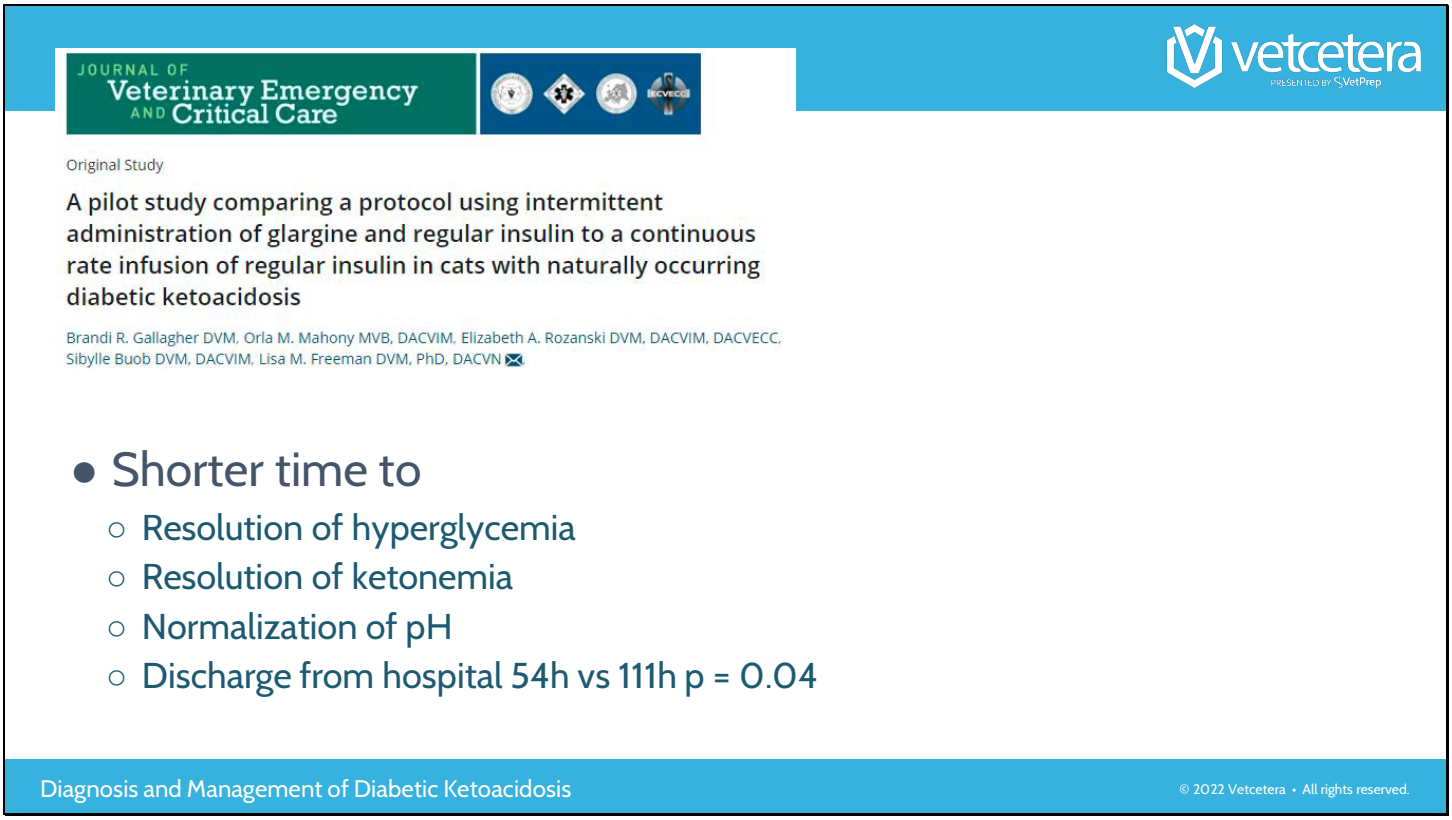

And so what they found was, that there's a shorter time to resolution of hypoglycemia and ketonemia, normalization to pH. And discharged from hospital was almost cut-- it was cut in half. And so that translates to a lot of money saved by the client. And money saving clients usually are happy clients.

So that's something to consider. And in preparing, I've always been a little hesitant. Because I said I'm not going to do it the next time, this next cat I see is going to do this. And I have to be honest with you, I haven't had a chance to do it yet. We see a lot of dogs with diabetic ketoacidosis here, and I haven't met my cat yet.

Oftentimes, the animals will present overnight. And when I receive them in the morning, they're already on some form of therapy. And so I don't do a bait and switch, but I want to try this soon. And I'd love to hear in the chat box, if anyone has utilized this protocol. It's very compelling to me especially just resolving their clinical signs and abnormalities, and getting them out of the hospital sooner.

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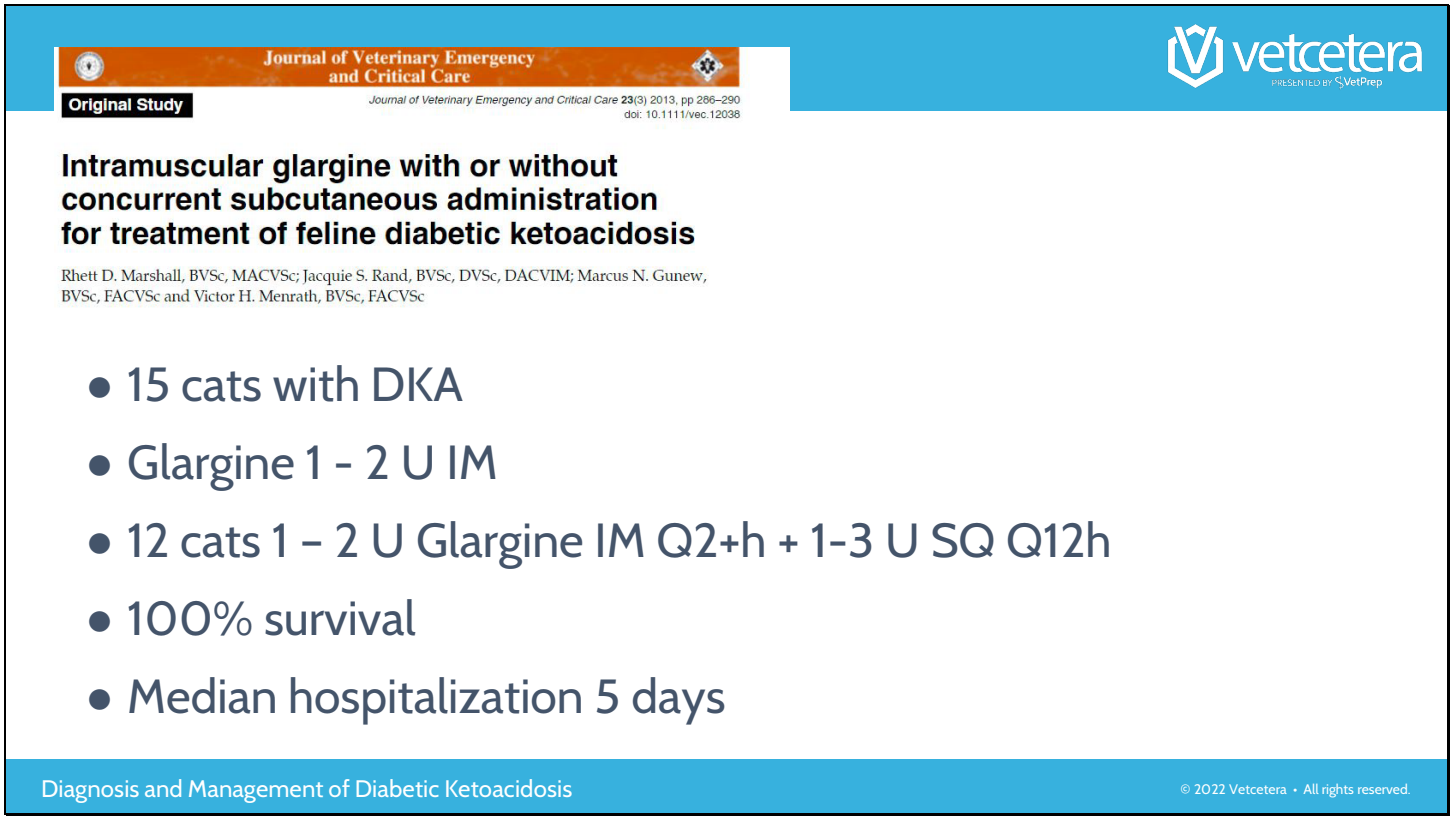

And so similar study was done. Again, in cats, using intramuscular glargine along with subcutaneous, and administration of insulin, all of the cats survived there in the hospital for about five days. But again, they did have success with another protocol using intramuscular glargine, interspersed with a shorter acting protocol.

Bicarbonate?

- Circulating ketones metabolized to bicarbonate
- Serum pH increases with treatment
- Administer exogenous bicarbonate with caution in cases of refractory acidosis

So when do we give bicarbonate? I'm talking about ketoacids, acids, acidemia. When circulating ketones, start being metabolized by the actions of insulin. The end product is bicarbonate. And so just with rehydration and utilization of insulin that you're administering, those ketoacids will eventually drive up the pH.

And so if there's refractory acidosis or if the pH is less than 7, 7.1, I will give a small amount of bicarbonate.

Bicarbonate Deficit

$$\text{mEq } HCO3^- = BW_{kg} \times 0.4 \times (12 - HCO3^-)$$

Consider multiplying by 0.3 to be conservative

But I'm really conservative with the amount that I give. And so I calculate their bicarbonate deficit, by this formula. And then whatever number I get, I multiply it by 0.3, just to be conservative.

And then give it slowly over about an hour. And then, I recheck what their acid-base status is doing. I don't want to cause a refractory alkolosis, it's easier to treat and acidosis than to treat an alkolosis. And so I'm just very conservative and rarely, will I consider giving bicarbonate therapy. I just rehydrate them and start giving them insulin and dextrose.

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Potassium

- Become rapidly depleted with DM and DKA
- May appear normal to increased on initial assessment
- Insulin drives potassium intracellularly
- Rapid depletion and hypokalemia

Diagnosis and Management of Diabetic Ketoacidosis

Potassium. Potassium is one of the most commonly depleted ions in both diabetes mellitus, as well as diabetic ketoacidosis. And so your serum potassium might look normal or even look increased. And it looks increased, because the body tries to buffer, the ketoacids by causing a hydrogen potassium exchange. So it tries to move the hydrogen intracellularly to try to buffer all this acid that's present. And in exchange, it kicks out potassium.

But once you start administering insulin, insulin will drive that potassium intercellularly, you'll metabolize the ketoacids to bicarbonate. So the acid will be start resolving. And potassium to become rapidly depleted, and they could quickly develop a hypokalemia. So I often will start my insulin and without four hours later, I'll start monitoring electrolytes.

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Potassium Supplementation

Serum potassium (mEq/L)	mEq/liter K^+ Supplementation
> 3.6	20
3.0 – 3.5	30
2.6 – 2.9	40
2.1 – 2.5	60
< 2.1	80

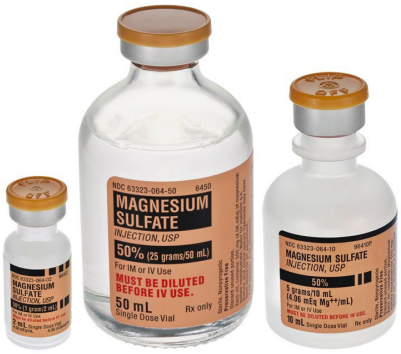
"Not to exceed 0.5 mEq/kg/hour!"

And so electrolytes-- potassium in particular, we've all seen this chart of-- if the serum potassium is equal or less than this number on the left, this is how much potassium to administer per liter of a fluid. And we're not supposed to exceed 0.5 milliequivalents per kilogram, per hour. We will actually use came max, which is giving them 0.5 milliequivalents per kilogram in an hour. And we'll continue that until their serum potassium increases.

I don't do that. If my serum potassium is low and it's refractory, and I'm getting up towards 60 to 80. Milliequivalents per liter of potassium chloride, I think to myself, what is required to regulate and maintain and reabsorb potassium and magnesium? Magnesium is required as a cofactor for the sodium potassium ATPase pump.

Refractory Hypokalemia

- Magnesium supplementation
- Required as a cofactor for Na/K-ATPase pump
- 0.75 – 1.0 mEq/kg/day



And so without magnesium, your potassium is going to be continued to be urinated out, right? So instead of driving K-MAX, K-MAX, K-MAX and worrying about the pump not working, and me giving too much potassium all at once. I just give them empirically, 0.75 to 1 milliequivalents per kilogram per day of magnesium. Usually as magnesium sulfate. And it's amazing, how quickly their potassium will normalize without needing to monitor them as quickly, as closely. And not worrying about driving them up to quickly using K-MAX.

Phosphorus

- Depleted as ATP produced
- <2.0 mg/dL = hemolysis
- 0.3 – 0.5 mmol/kg/hr
- NOTE: Added potassium!
- "Do not exceed >0.5mEq K+/kg/hr"

Diagnosis and Management of Diabetic Ketoacidosis

Phosphorus also is an energy source. It's an ion that becomes depleted, once an animal can start making its own energy. So once we give insulin and they're metabolizing carbohydrates instead of ketoacids into the trickle rock citric acid cycle. While the end products of the TCA Cycle is ATP equals energy. So as those phosphorus and phosphate are metabolized and utilized into these energy substrates. Phosphorus becomes depleted. Red blood cells need phosphorus to maintain integrity of their cell membranes.

And so when the phosphorus starts becoming depleted and drops less than 2 milligrams per deciliter, you can get intravascular hemolysis. So if someone, who's reading a PCB says, Oh, gosh. The PCB is dropped. What's the color of their serum? If they say pink or red, get really, really concerned, that your intravascular hemolysing.

And so potassium phosphate will add some potassium. So just remember that, when you're utilizing this and calculating your total potassium needs. So you don't overzealous the supplement with potassium.

When to Start Long Acting?

- Hydrated
- Eating
- No longer vomiting
- Negative ketones

When do I start longer acting insulin? Well, when they're hydrated, when they're eating, and when they're no longer vomiting. The purists will say, when they're negative for ketones. I usually don't worry about that. If they have strong ketones, they're usually not eating yet. But if they're just small amount of ketones, I don't worry about that.

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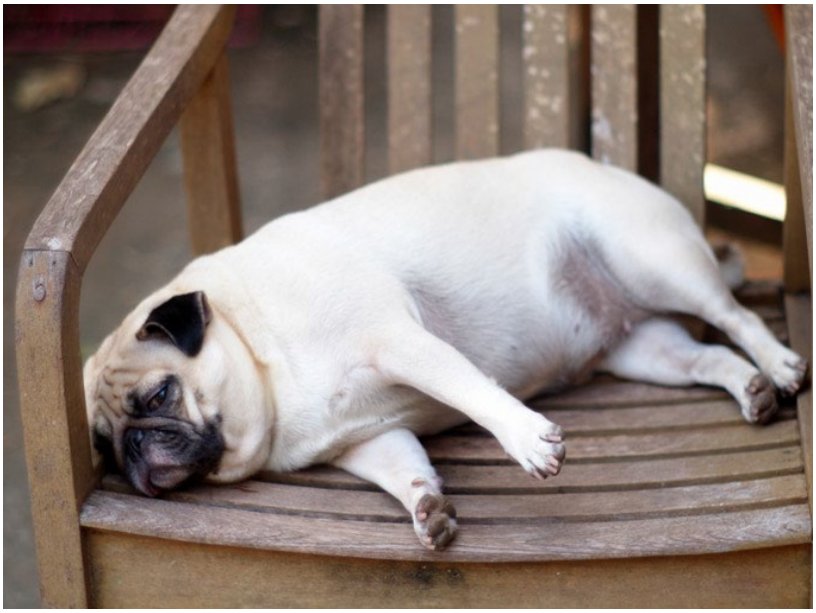

And so long acting insulin and long term management of diabetes, isn't in my repertoire usually in our emergency room, that's where the general practitioners or the internal medicine specialists tend to take over. For those of you, who may have seen some of my lectures before, I always put a pug in the talks. So here's-- not my fat pug, here's a fat pug.

And at this point, I'd like to entertain any questions.

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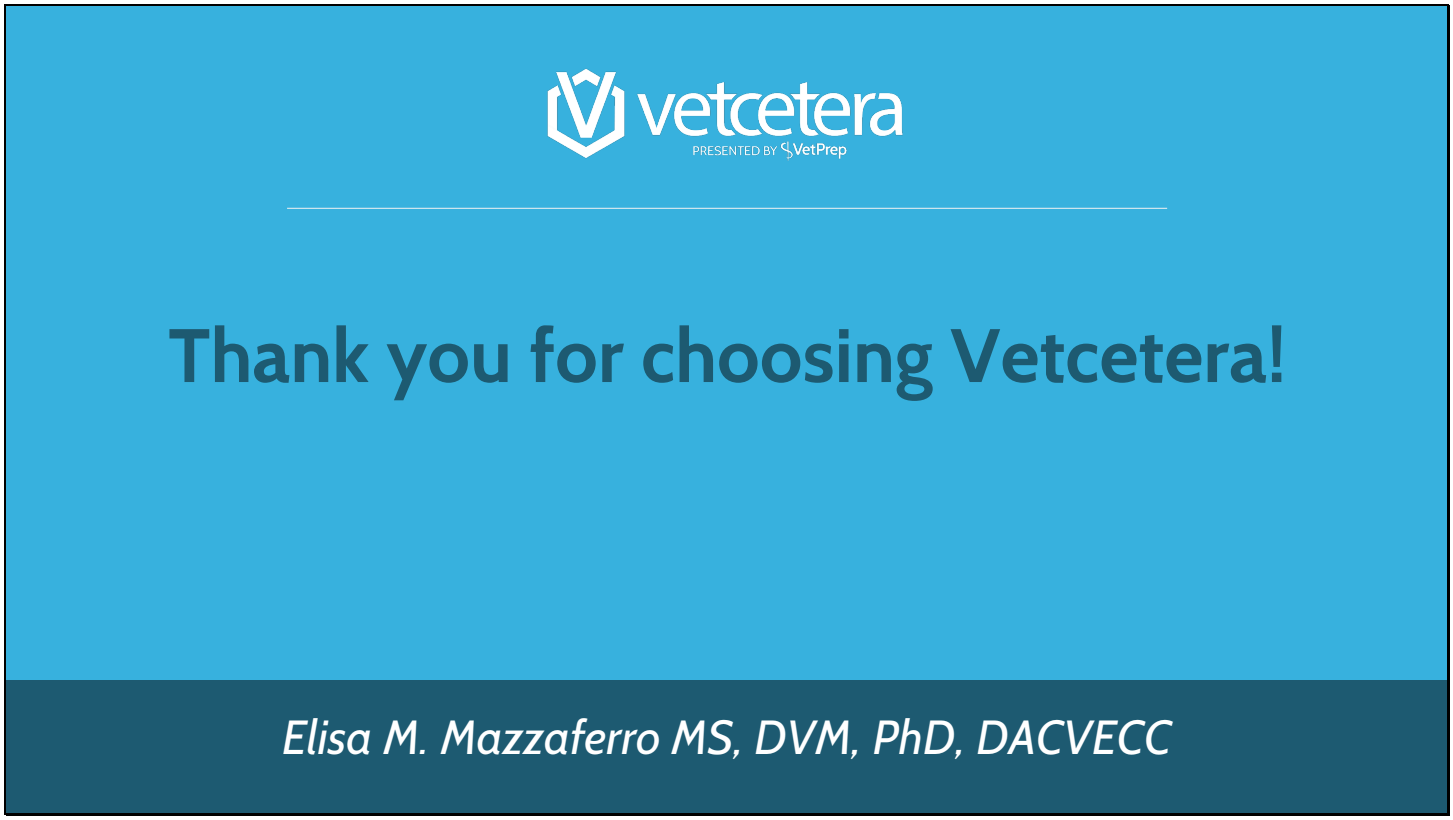

So far it looks like we don't have any questions. We'll get it just a couple of minutes. Thank you so much. That was very informative. I am admittedly one of those people, who does not like to DKAs.

[LAUGHS]

Give me a good Derm case, any day. That's what makes--

Oh! Oh, please! You know what I love about Derm cases, because once in a blue moon, you get a Delusional parasitosis person.

Oh, Yes. I did have a couple of those, that was challenging, for sure. But I always like, they were things usually aren't dying, and it was so satisfying when they came out looking beautiful. So that was my thing.

Looks like we have a question here. How often do you check blood gas when pH initially about 7.1? I'm not sure?

So when-- it depends, if I'm giving bicarbonate or not. And so if I'm going to give bicarbonate, then I'll recheck it probably an hour later. If once I start my insulin therapy, I check my venous gas electrolyte panel every four to six hours

And as it starts normalizing, I decrease the frequency to possibly every 8 to 12 hours. But initially, if there pH is that low, once I start the insulin or if I've given bicarbonate, usually check it an hour later, especially with the bicarbonate. Otherwise, if I don't need to give bicarbonate and the pH is like 7.2 and I haven't given bicarbonate, I'll check it about four hours later.

Great. Thanks. And we have another question. Now, do you always have to use dextrose infusion-- infusion when you use insulin infusion?

Yes. Insulin requires dextrose to move insulin into the cells. So it needs an energy substrate. So we have to give them dextrose.

Perfect. Thank you. Do we have any other questions? Yes. In terms of using the term of refractory acidemia, when would you worry or consider bicarbonate?

Oh. I would only consider bicarbonate, if the pH is less than 7.1. So you might have smoldering depending on-- you may have animals for four, five, six days that have smoldering infection like a pyelonephritis or a pancreatitis, which is inflammation infection. But those animals could have ketoacidosis and 7.2 or 7.3, and they can be that way for several days.

But until you get rid of the underlying cause of insulin resistance, which is why we do the whole diagnostic workup with thoracic radiographs to rule out pneumonia or neoplasia and an abdominal ultrasound to rule out those things, then it could take days. But I only will give bicarbonate, if the pH is less than 7.1.

I could literally count probably on one hand. The number of times, I've given bicarbonate over the years. I actually just-- it has to be bad, bad. I say less than 7.1, but sometimes I'll stretch it those 6.9. But those animals are sick. But usually, I'll just start insulin with fluids and their pH will start coming up. May not normalize for a while, but they'll start coming up.

Very good to know. One more question. If I don't have a cemetery to check pH, is there another endpoint that you could aim for?

I'm sorry. Say again, you don't have what-- check pH?

If they don't have a way to check pH, is there some other endpoint that they could aim for?

I would say normalization of your electrolytes, if you can't maybe run a blood gas, but you could-- if you can do an electrolyte clip. So normalization of glucose and potassium would be beneficial.

Sounds good to me. Next question is, with magnesium supplement, are you giving it instead of potassium to start in order to get the potassium levels? And do you add it to the IV fluids?

Yeah. Sure. So when I'm giving magnesium supplementation, it's-- I only give it, if I've given potassium chloride and I'm seeing my electrolyte panel that my hypokalemia is not resolving. So I'm hypoglycemic and I'm giving more, and adding more and adding more KCL to the liter bag of fluids.

And so that's when I think-- gosh they're becoming refractory. And once I get above 60 milligrams per liter of potassium chloride, I continue that same dose of potassium chloride. And I add in the magnesium sulfate, as a constant infusion. Usually, I just add it to the back of fluids.

And then I run that along with the potassium chloride. Intravenously.

Thank you. And we have one last question. How often is it recommended to recheck electrolytes?

And so it depends how sick they are, and how low the potassium is or the phosphorus is. And so typically, in very sick animals, I'll recheck it every four to six hours. But then as things improve, then I'll check it less frequently every 6.0 to 8.0, and then every 8 to 12. But usually you're starting every four to six hours to start.

All right. I think, we'll go ahead and wrap it up with that. Thank you so much for joining us, we really appreciate it.

OK. Well, happy spring, everyone. And it's the end of my day, and now I'm all fired up and excited. And I have to go check on the hyperosmolar animals before I leave. So all right. Have a great night. Thank you guys!

Thanks. Have a great night, bye.

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