Diabetic Ketoacidosis

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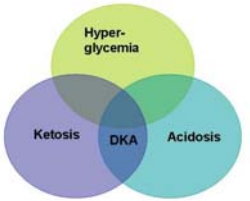
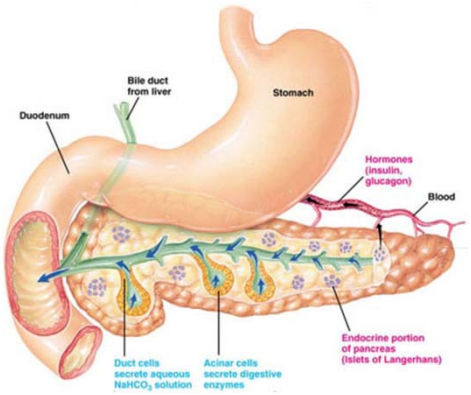
Presentation Overview

- Physiology/pathophysiology
- Treatment overview
- Prognosis

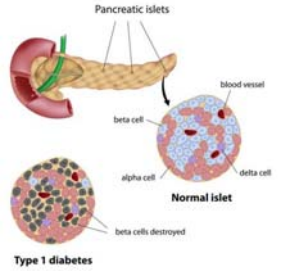


The Pancreas



Diabetes

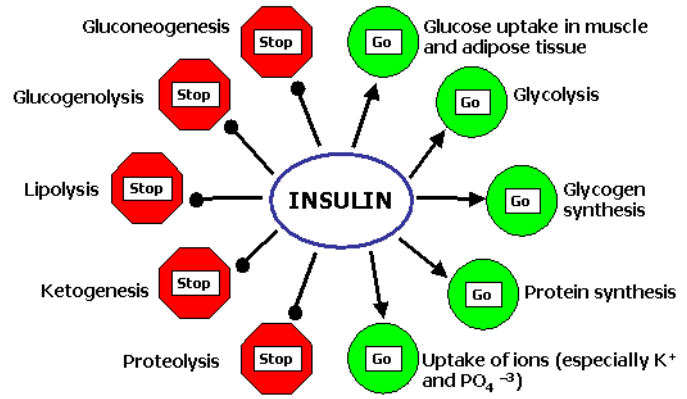
- Insulin dependent DM (Type I)
  - Beta cell destruction
- Noninsulin dependent DM (Type II)
  - Insulin receptor resistance
    - Causes
      - Obesity
      - Counter regulatory hormones



Human classification of DKA

- Ketosis prone diabetes (KPD)
  - 4 groups:
    - KPD type 1A
      - Permanent beta cell failure
      - Markers of islet cell autoimmunity
    - KPD type 1B
      - Permanent b-cell failure
      - No serologic markers of islet cell autoimmunity
    - KPD type 2A
      - B-cell function present
      - Serologic markers of islet cell autoimmunity
    - KPD type 2B
      - B-cell function present
      - No serologic markers of islet cell autoimmunity

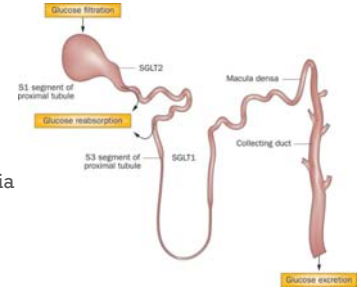
Actions of Insulin



Modified from Clinical Biochemistry, A. Gaw et al, Churchill Livingstone, Edinburgh, 1995.

Pathophysiology

- Hypoinsulinemia
- Glycosuria
  - 180-220mg/dL in dogs
  - 200-280mg/dL cats
- Polyuria→ compensatory polydipsia
- Weight loss despite polyphagia

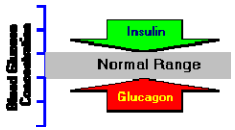


Diabetic Ketoacidosis

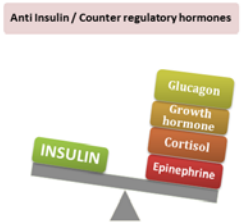
- Classic signs of DM but also SICK!
- Diagnostic criteria
  - Hyperglycemia, glycosuria
  - Ketonemia, ketonuria
  - Metabolic acidosis

Diabetic ketoacidosis

- Develops in patients with
  - An absolute insulin deficiency
  - Relative insulin deficiency
    - Increase in counter regulatory hormones
    - Exogenous administration of progestins or steroids
    - Release of cytokines
      - IL-18/resistin higher pre treatment



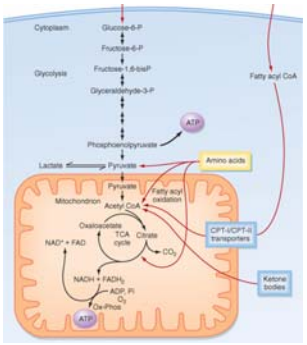
Role of counter regulatory hormones



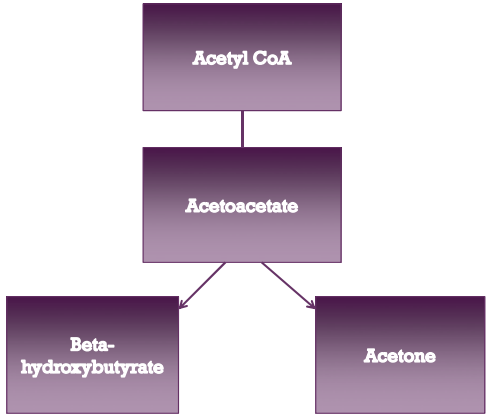
- Insulin resistance
- Stimulate gluconeogenesis
- Stimulation of lipolysis
- Generation of FFAs in circulation

Generation of ketone bodies

- FFA build up on the blood stream
  - FFA broken down in mitochondria to Acetyl CoA
  - Acetyl CoA normally enters krebs → ATP production
  - Krebs cycle overwhelmed = build up of Acetyl CoA→ ketone body production



Ketone bodies



Physiologic manifestations

- Osmotic diuresis
  - Due to ketones and glucose
  - Cations lost with ketones
    - Sodium, calcium, magnesium, potassium
    - Medullary solute washout
    - Excessive sodium lost→ volume contraction, hypoperfusion
- Acidosis
  - Consumption of buffer bases
  - Hypovolemia/hypoperfusion→ lactic acidosis
  - Decreased elimination of accumulated acids

Clinical Presentation

- History
  - PU/PD
  - Anorexia
  - Lethargy
  - Vomiting
  - Weight loss

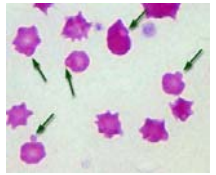
- Physical examination
  - Dehydrated
  - Tachycardia
  - Weak
  - Poor pulses
  - Cervical ventroflexion
  - Plantigrade stance
  - Cataracts
  - Kussmauls respiration
  - Acetone odor to breath?

Diagnostics to consider

- Triage diagnostics
  - Blood glucose
  - Urine glucose
  - Ketones (urine or serum)
  - Blood gas
  - Blood pressure
- Ideal
  - CBC
  - Chemistry profile
  - Electrolytes
  - Lactate
  - Urinalysis
  - Urine culture
  - Abdominal ultrasound
  - +/- thoracic imaging, PLI

Complete blood count

- Leukocytosis
  - Neutrophilia +/- left shift
- Non regenerative anemia
  - Heinz bodies seen in cats
    - Oxidative damage on RBC due to membrane protein glycosylation
    - Correlated to b-hydroxybutyrate levels



Chemistry profile

- Hyperglycemia
- Elevated triglycerides/cholesterol
- Increased hepatocellular and cholestatic liver enzymes
- Azotemia
  - Pre-renal or renal
  - Severe hyperglycemia → decreased GFR

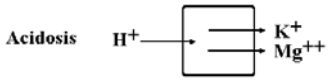
GFR	BG
108	400
72	600
56	800
36	1200
27	1600

Electrolyte abnormalities

- Sodium
  - Hyponatremia
    - Urinary/GI losses
  - Pseudohyponatremia
    - For each 100mg/dL increase in glucose above the reference range results in a 1.6mEq/L decrease in sodium
    - Due to movement of intracellular water into the intravascular space
    - Reversible with insulin administration
  - Hypernatremia

Potassium

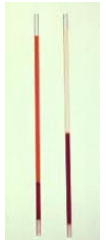
- Hyperkalemia
  - Transcellular shift
  - Decreased GFR



- Normal
  - Total body potassium depletion very common
- Hypokalemia
  - Causes
    - Renal/GI loss
    - Treatment
  - Consequences
    - Profound muscle weakness
  - Can increase morbidity

Phosphorous

- Can plummet with treatment
  - If < 1-1.5mg/dL can see
    - Hemolytic anemia
      - Decreased RBC ATP→altered RBC membrane lipid→ hemolysis
    - Neuromuscular signs
      - Weakness, ataxia, seizures, anorexia, vomiting (ileus)



Magnesium

- Important cofactor for enzymatic reactions involving ATP
  - Na-K ATPase pump
  - Essential for electrolyte homeostasis
- Hypomagnesemia common
  - Osmotic diuresis/insulin therapy
  - Total < 1mg/dL, ionized < 0.5mg/dL
  - Lethargy, anorexia, muscle weakness, arrhythmias, coma, ataxia, seizures
  - Refractory hypokalemia
  - Arrhythimas

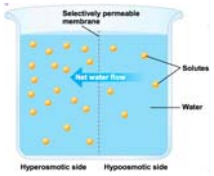
Blood gas

- Document metabolic acidosis
  - Decreased pH, negative BE, decreased bicarbonate

Rule of 4s	
Normal pH	7.4
Normal bicarb	24 +/- 4
Normal PCO2	40 +/- 4
Normal BE	0 +/- 4

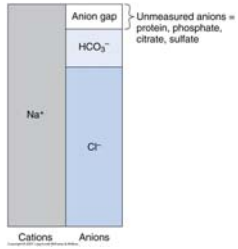
Osmolality

- Calculate osmolality
  - Hyperosmolality > 310-340mOsm/L (normal 280-300 mOsm/L)
  - Total osmolality = 2 (Na + K) + BUN/2.8 + glucose/18
  - Effective osmolality = 2(Na + K) + glucose/18
    - More closely reflects serum tonicity
    - Serum sodium more closely reflects changes in tonicity than BG

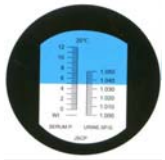


Anion Gap

- Anion gap (Na + K) – (HCO3 + CL)
  - Normal 17-24 mEq/L
  - Usually high gap acidosis due to ketones (20-35)
  - Can be normal due to retention of chloride

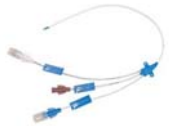


Urinalysis



- Glucosuria
- Ketonuria
  - Urine ketone sticks measure acetone/acetoacetate
    - Detection of b-hydroxybutyrate/addition of H202?
- Detection of serum b-hydroxybutyrate more sensitive than urine
  - Portable blood ketone meters available
- +/- pyuria, bacteriuria, hematuria
- USG
  - Glycosuria falsely increases USG
  - 4+ glucose increases USG 0.008-0.010

Treatment



- Vascular access
  - Peripheral for resuscitation
  - Central ideal for blood draws, CVPs etc
- Replace intravascular volume if poorly perfused to meet end points of resuscitation
  - Normal HR, mm/CRT, pulse quality
  - Improved mentation
  - Resolved lactic acidosis
  - BP > 90 mmHg, CVP 4-9cmH20 (dog), 3-5cmH20 (cat)

Treatment

- IV fluids
  - Replace dehydration deficit (% dehydration x bw kg)
  - Maintenance 40-60ml/kg/d
  - Ongoing losses
- Balanced isotonic solution
  - 0.9% NaCl often too acidifying
  - LRS, Normosol R, Plasmalyte A
- Delay insulin administration for 4-6 hours

Insulin therapy

- Routes of administration:
  - IV CRI
  - Intermittent IM injection
  - Subcutaneous injections
    - Inappropriate if dehydrated
  - Combined

Insulin Therapy

- Rapid acting insulin
  - Lispro/Apart/Glulisine
    - Works within 15min, peaks in 1 hour, lasts 2-4hr
    - Lispro studied in dogs with DKA (UPENN)
- Short acting
  - Regular—works in 30 mins, peaks in 2-3hrs, lasts 4-6 hrs
- Intermediate acting
  - Works in 2hrs, peaks in 4-12hrs, lasts 12-18hrs
  - NPH, Lente
- Long acting
  - Works in 2-4 hrs, peak less, lasts 24hrs
  - Glargine, determir

IV CRI

- Add 1.5unit/kg/day (dog or cat) to 0.9% NaCl
  - You chose the rate and volume

Blood glucose	Dextrose	Insulin
>200	0	ON
100-200	2.5%	ON
<100	5%	OFF

- If the BG is > 200mg/dL for > 6hr, the insulin dose OR rate is increased by 25%
- If BG is < 100mg/dL insulin is turned off until > 100mg/dL then dose OR rate is decreased by 25%
- Dextrose not removed from the bag (unless electrolytes significantly depleted), insulin CRI increased

IV CRI

Blood glucose (mg/dL	Fluid composition	Rate of administration (ml/hr)
>250	0.9% NaCl	10
200-250	0.45%NaCl + 2.5% dextrose	7
150-200	0.45% NaCl + 2.5% dextrose	5
100-150	0.45% NaCl + 5% dextrose	5
<100	0.45% NaCl + 5% dextrose	0

2.2 units/kg of regular insulin added to 0.9% NaCl

IV CRI

- First 50ml should be discarded since insulin binds to plastic
- Reduce rate or dose if significantly hypokalemic despite supplementation
- Can take 6-72 hours to resolve ketosis
- Decrease BG by 50-75mg/dL to avoid rapid changes in osmolality

Cerebral edema

- In human pediatrics
  - Related to rapid decrease in BG > 50mg/dl/hr?
    - Idiogenic osmoles
    - Cerebral edema occurs if osmolality outside the cell drops quickly = cytotoxic edema
  - Cerebral edema present before treatment of peds with DKA
  - Impaired cerebral blood flow autoregulation→ increased CBF→ vasogenic cerebral edema
  - Ketone bodies damage microvasculature

IV CRI dose cats vs. dogs

- JVECCS 2010, Comparison of regular insulin infusion doses in critically ill diabetic cats: 29 cases
  - Retrospective, Upenn
  - Compared traditional dose of 1.1u/kg/d to 2.2u/kg/d
  - Actual doses of insulin administered were actually lower than that prescribed (0.31-0.8 u/kg/d)
  - No adverse effects of increased dose noted
  - Theory that more neurologic events (cerebral edema)/electrolyte abnormalities would be seen
    - Neither identified

IM/SQ protocol

- 0.2unit/kg SQ loading dose then 0.1unit/kg hourly until BG <250mg/dL then 0.1-0.4u/kg q 4-6hr
  - IM more appropriate if dehydrated
- Monitor BG q 1-4hr
- Combined long and short acting protocol?
  - NPH, glargine q 12hr (dogs/cats)
    - 0.25-0.5unit/kg q 12hr
    - Monitor BG q 4hr (if BG >300mg/dL give ¼ unit/kg regular insulin SQ/IM) up to q 8hr

Glargine in cats with DKA

- JVECCs 23(3) 2013, Retrospective study of 15 cats
- Glargine substituted for regular insulin in IM protocol
- Doses given 1-2 units/cat IM and 1-3 units/cat SQ at initial presentation (median 3 units)
- No prescribed protocol adhered to
  - Repeated 0.5-1unit IM injections given q 2-22hr
  - SQ injections given q 12hr or longer to maintain BG between 180-250mg/dL
- Median combined (SC and IM) dose of insulin for cats 1.4u/kg/d for 1st 12hrs
- Median time for all 15 cats to be managed with SC glargine alone was 24 hours
- All 15 cats survived to discharge
- Recommendation—1-2units/cat SQ immediately and concurrent glargine IM (0.5-1unit) several hours after fluid resuscitation (q 4hr PRN)….

Intermittent glargine vs regular insulin

- *JVECCS 2014 00(0) 2014*
  - 16 cats, prospective, randomized clinical trial
  - Cats given 0.25units/kg glargine q 12hr SQ
  - Also given 1 unit regular insulin up to every 6 hours if BG > 250mg/dL
  - 69% survived to discharge
  - Significantly shorter times to normalization of pH, bicarbonate and resolution of hyperglycemia and ketonemia in SC/IM group
  - Cats in SC/IM group had significantly shorter hospitalization (3.8d vs 6d)
    - No specific criteria for when a cat could be discharged
  - Less rebound hyperglycemia when transition off CRI w/o increased risk of hypoglycemia

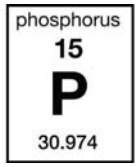
Hypokalemia

	Typical Guidelines	DKA Guidelines
Serum K+ (mEq/L)	K Supplementation/L IVF	K+ Supplementation/L IVF
>5.0	Wait	Wait
4.0-5.5	10	20-30
3.5-4.0	20	30-40
3.0-3.5	30	40-50
2.5-3.0	40	50-60
2.0-2.5	60	60-80
<2.0	80	80

Potassium supplementation

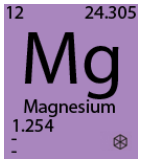
- If significant (<3.0mEq/L) can give high dose CRI
  - 0.5mEq/kg/hr, diluted 1:1 with saline IV over 4 hours
  - Label carefully –no flushing of this line!
  - Give with syringe pump
  - Recheck K+ after 4 hours
  - If > 0.5mEq/kg/hr required monitor ECG

Phosphorous



- Monitor q 8-24 hours
- Supplement if < 1.5-2 mg/dL
  - 0.01-0.12mmol/kg/hr
    - Ensure giving with calcium free fluids
- Can give 1/3 – ½ of potassium supplementation as KPhos
- Can cause
  - Iatrogenic hypocalcemia
  - Hypernatremia
  - Hypotension

Magnesium



- Identification of whole body magnesium depletion challenging
  - Supplement if
    - Refractory hypokalemia
    - Arrhythmias
    - Persistent lethargy/weakness
    - 0.75-1mEq/kg/d CRI in D5W
    - Reduce dose by 50% for patients with renal disease
    - Incompatible with bicarb, calcium, dobutamine
    - Can cause hypotension, bundle branch block, hypocalcemia, respiratory depression—calculate dose carefully

Sodium bicarbonate

- Controversial
- Usually corrected with improving perfusion/ketosis
- American diabetes association (if pH < 7.0 after 1hour of IVF)
- Dose (mEq) = body weight (kg) x 0.4 x (12-patient bicarb)
  - Give ½ dose IV as CRI over 6 hours
- Adverse effects
  - Ionized hypocalcemia
  - Hypokalemia
  - Paradoxical CNS acidosis
  - Prolonged ketone metabolism
- Poor prognosis if administered bicarb
  - Cause or consequence

Additional considerations

- Antiemetics
  - Cerenia 1mg/kg SQ/IV q 24hr
  - Anzemet 0.6mg/kg IV q 24hr
  - Reglan 1-2mg/kg/d IV CRI
- Antacids
  - Famotidine 0.5mg/kg IV q 12hr
  - Pantoprazole 1mg/kg IV q 12hr x 3 days then q 24hr
- Antibiotics
  - Unasyn 22mg/kg IV q 8hr
- Analgesics PRN

Nutrition

- NE tube/NG tube/E tube
  - Ensure, renacare, clinicare
- Parenteral nutrition if unable to tolerate enteral
  - May be more difficult to manage hyperglycemia
  - PPN (procalamine), TPN

Treatment monitoring

- BG q 1-4hr until stable
  - Continuous blood glucose monitoring?
- Electrolytes q 4-24 hours until stable
- Phosphorous at least daily
- Be careful with the #/amount of blood drawn!
- Hydration status 3-4 times daily
- Urine/serum ketones daily

Long acting insulin

- Acidosis/ketones resolved
- Patient eating
- Choices:
  - NPH
  - Vetsulin
  - Glargine
  - PZI
  - Detemir

Outcome

- Most are newly diagnosed diabetics
- Co morbid diseases common
  - 69% of dogs with DKA patients had concurrent disease
    - 27% had more than one concurrent condition
    - 41% had acute pancreatitis
    - 20% UTI
    - 15% hyperadrenocorticism
  - 90% of cats with DKA concurrent disease
    - Hepatic lipidosis
    - Chronic renal failure
    - Acute pancreatitis
    - Bacterial/viral infections
    - Neoplasia

Prognosis

- 70% of dogs and cats discharged from the hospital
  - Duration of hospitalization 6 days dog, 5 days cat
  - Recurrence in 7% dogs, 40% cats
- *JVIM* 2008; 22: 1326-1332. Remission of DM in cats with DKA
  - More likely to have a stress leukogram
  - More likely to have pancreatitis
  - Previous steroid administration
  - Remission in 7/12 cats

+

Questions?