DIABETES MELLITUS

Rob Presley, DVM, MS, DACVIM
Upstate Veterinary Specialists
TCTC Technician Program
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Diabetes mellitus

- Insulin deficiency
  - Absolute
  - Relative

- Causes abnormal metabolism
  - Glucose → hyperglycemia

Pancreatic function

- Exocrine function
  - Digestive enzymes
    - Trypsin
    - Amylase
    - Lipase

- Endocrine function
  - Islets of Langerhans
    - Beta cells
    - Produce insulin

Insulin

- Half life of 10 minutes

- Promotes
  - Glucose uptake by cells
  - Glucose storage by the liver and muscle
    - Glycogen
  - Fat storage
  - Protein production

Insulin

- Inhibits
  - Gluconeogenesis
    - Production of glucose by liver
  - Glycogenolysis
    - Breakdown of glycogen in liver and muscle
  - Breakdown of fats
  - Production of ketones
  - Breakdown of protein

- Promotes anabolic processes
  - Storage
    - Glycogen
    - Fat
    - Protein

- Prevents catabolic processes
  - Breakdown of other nutrients into glucose

- Insulin deficiency
  - Hyperglycemia
Diabetes mellitus

• Type I
  – Previously called Insulin dependent
  – Absolute insulin deficiency
  – Destruction of Beta cells
    • Immune mediated
      • Idiopathic
      • <25% of beta cells remaining
    – Most common in dogs
      • Immune mediated
      – Anti-beta cell antibodies
      – Idiopathic
      – Pancreatitis
  – Immune mediated
  – Idiopathic
  – <25% of beta cells remaining
  – Most common in dogs

• Type II
  – Previously Non-insulin dependent
  – Relative insulin deficiency
    • Peripheral resistance
    • Impaired insulin secretion
    • Increased gluconeogenesis
  – Most common in cats
    • 90% humans

Diabetes mellitus

• Type II
  – Obesity plays a major role
    • Obese 4x risk
  – B cell dysfunction
    • Decreased insulin release
      • <25% of beta cells
    • Secondary to
      – Amyloid deposition
      – Lipid toxicity
      – Glucose toxicity

• Dogs
  – Older dogs
    • 7-9 years
    • Juvenile form
      – <1 yr old
      – Rare
    – Females > males
    – Breeds
      • Miniature Poodles
      • Miniature Schnauzers
      • Bichon

Diabetes mellitus

• Cats
  – Older cats
    • 10 years +
    • Neutered males > females
      • 70-80% male
    • 50-60% obese

Clinical signs

• Polyuria / polydipsia
  – Osmotic diuresis
  – Renal threshold
    • 200 mg/dl dog
    • 250 mg/dl cat

• Polyphagia
  – Insulin promotes glucose movement into hypothalamus
    • Satiety center
Clinical signs

• Weight loss
  – Decreased cellular uptake
  – Catabolism
    • Fat
    • Muscle
  – “starving in the face of plenty”

Clinical signs

• Lethargy
• Weakness
  – Diabetic neuropathy
  – Decreased glucose uptake
• Hepatomegaly
• Vomiting / diarrhea
  – DKA

Clinical signs

• Cataracts
  – Dogs only
  – Excessive glucose converted to fructose and sorbitol
    • Osmotic water uptake in lens
  – Wide fluctuations in BG seem to be more important than just high BG levels
  – Can occur even in well controlled diabetics

Clinical signs

• Diabetic neuropathy
  – Changes in nerves occur in 90% of dogs and cats
    • Dogs typically non-clinical
      – Demyelination
      – Degeneration of axon
      – Vascular pathology

Clinical signs

• Diabetic neuropathy
  – Plantigrade stance
    • Muscle weakness
    • Proprioceptive deficits
      • Can be seen with hypokalemia
  • Occasionally seen in front legs

Other signs

• Pancreatitis
  – Cause / effect
  – Hyperlipidemia may contribute

• Infection
  – Skin
  – Respiratory
  – Urinary tract
Diagnosis

• Typically straightforward
  – Routine bloodwork
  – Urinalysis
  – Fructosamine
  – Glycosylated hemoglobin

Routine bloodwork

• Complete blood count
  – Usually normal
  – Elevated WBC

• Serum Chemistries
  – Elevated liver values
  – Increased triglycerides
  – Increased cholesterol

• Abnormal lipid metabolism

• cPLI / IPI
  – If pancreatitis present in dogs

Fasting glucose

• Fasting glucose
  – < 200 mg/dl

• Stress hyperglycemia
  – n=106 cats
    • Range 146-592 mg/dL
    • Most <300
      – Only 2/106 were > 300
  – Dogs less affected

Urinalysis

• Glucosuria
  – BG
    • > 200 dog
    • >250 dog

• Ketonuria
  – Acetoacetic acid
  – Dipstick
    – Beta hydroxybutyrate
      • Produced in highest volumes in DKA
      • Does not read on standard dipstick
      • Add hydrogen peroxide and re-test

• Urinary tract infection
  – Must culture urine!!

Still not sure?

• Glycated proteins
  – Non-enzymatic binding of glucose to
    • Hemoglobin
    • Albumin

• Glycosylated hemoglobin
  – A1c
  – Control 2-3 months

Still not sure?

• Fructosamine
  – Glucose bound to albumin
  – Control over 2-3 weeks

  – Hypoglycemia
  – Elevated triglycerides
    • May affect measurement

• Not affected by acute stress!!!
Dietary therapy

- Weight loss
  - Obesity = insulin resistance
  - Feed 60-70% of maintenance calories
    - Slow, controlled weight loss
- Minimize glucose fluctuations
  - Feed multiple small meals
  - Avoid simple carbohydrates

• Dogs
  - High fiber
  - Complex carbohydrates
    - Slow absorption of glucose
    - Hills w/d
    - Hills r/d
    - Royal canin diabetic HF
    - Purina DCO

Diabetic therapy

• Cats
  - Carnivores
    - Not omnivores
  - High protein
  - Low carbohydrate
    - Lack salivary amylase
    - Low levels of intestinal / pancreatic amylase
    - High capacity of gluconeogenesis from proteins

• Antigenicity
  - Cats
    - Bovine is similar
  - Dogs
    - Porcine and human similar
  - Anti-insulin antibodies
    - Change in insulin duration
    - Poor diabetic control
    - Insulin resistance
  - Dogs develop antibodies to beef insulin
    - PZI
  - Use of human insulin usually not problematic in either species

Dietary management

• Diets
  - Canned varieties
    - lower carbohydrates
  - Purina DM
  - Evo 95
  - Friskies "classic" varieties
  - Catinfo.org
    - List of appropriate diets
  - Hills MD
    - High fiber
    - Do not use!!!
Insulin

- Numerous types
  - Full time job keeping up with what’s available
  - discontinued
  - backorder

Insulin therapy

- Currently available
  - (may change in 10 minutes)
    - Ultrashort
      - Insulin Lispro
      - Insulin Aspart
      - Insulin Glulisine
    - Regular
    - NPH
    - PZI
    - Glargine
    - Detemir

Insulin therapy

- Classified based on duration of action
  - Ultrashort
    - Not really used in veterinary patients
  - Short
    - Regular
  - Intermediate
    - NPH, Glargine, Detemir
  - Long
    - PZI

- Concentration
  - Units per milliliter
    - U-40
    - U-100

Insulin therapy

- Which type to start?
  - DKA
    - Regular insulin
  - Dogs
    - NPH
    - 0.25 U/kg SQ q12
  - Cats
    - Glargine
    - Best chance of remission
    - 1-3 U / CAT SQ q 12

Insulin therapy

- Ideally hospitalize on day 1
  - Start glucose curve
    - q 2 hours
  - Goal is to ensure BG is not getting too low
    - DO NOT increase dose
      - Takes several days for insulin to equilibrate
**Insulin therapy**

- Recheck in 1 week for BG curve

**Monitoring therapy**

- Typically cannot rely on one technique
  - Glucose curves
  - Home glucose curves
  - Glycosylated hemoglobin
  - Fructosamine
  - Urine samples

**Glucose curves**

- Perform
  - After initiating therapy
  - Following equilibration after dose change
  - If clinical signs recur
  - If suspicious of hypoglycemia
  - Concurrent illness that could affect BG

**Glucose curve**

- Alpha trak
  - Veterinary only glucometer
  - Plasma glucose percentages
    - Dog: 87.5%
    - Cat: 93%
    - Human: 58%
    - 42% in RBCs
  - Human meters will underestimate true BG
  - Seem better controlled than they are

**Glucose curves**

- Maintain normal routine
  - Owners to feed and give insulin at home
  - Some animals will not eat in hospital
  - Bring in for curve during day

- Obtain blood glucose q2 hours
  - Even with glargine / detemir

**Glucose curve**

- If on once daily insulin
  - 24 hour curve
- Twice daily
  - 12 hour curve
Glucose curve

- **Onset of action**
  - Time until insulin effect occurs
- **Nadir**
  - Lowest BG concentration
- **Duration**
  - Time from administration through nadir until BG >250 mg/dl

**Goals**

- Eliminate clinical signs
- Avoid major BG fluctuations
- Maintain BG 80-200 mg/dl for 24 hour
  - Rarely achieved

- To limit complications
  - <300 mg/dl in cats
  - 200-250 mg/dl in dogs
  - Similar to renal threshold?

**Glucose curve**

- Always maintain BG <80 mg/dl
  - Ideal nadir
    - 80 – 150 mg/dl

**Glucose curves**

- “Spot” checks
- Random samples
  - COMPLETELY WORTHLESS!!!!!!!

**Home monitoring**

- **Clinical signs**
  - Water consumption
  - Easy to measure
  - Appetite
  - Attitude
  - Weight
  - Urine glucose
    - If clinical signs are normal
      - Usually well controlled
Home monitoring

- Urine glucose
  - Can be used to help determine control
    - If persistently negative
    - Insulin dose may be too high
  - If persistently glucosuric, insulin dose may be too low
  - Do not use alone to adjust insulin

- Glucose curves
  - Owners can perform curves at home
    - "Choose clients wisely"
  - Not trying to achieve fine control
    - Prevent owners from being too overzealous
    - NOT adjusting insulin daily

Glycated proteins

- Glycosylated hemoglobin
  - Not used frequently
  - Time frame too long for adjusting insulin dose

- Fructosamine
  - 2-3 weeks
  - Helpful
    - Data conflicting
    - Stressed animals
    - Suspect somogyi effect

Somogyi phenomenon

- Hypoglycemia
  - BG <60

- Causes release of epinephrine / glucagon
  - Rebound hyperglycemia
  - Can remain elevated for hours to days

- Can be very difficult to diagnose
- Decide if:
  - Inadequate insulin dose
  - Somogyi

- Fructosamine
  - If normal
    - May suggest significant periods of hypoglycemia

Insulin resistance

- > 2.2 units / kg / per injection
- Become suspicious when
  - Marked hyperglycemia persists despite > 1.5 u / kg dose
Insulin resistance

- Always rule out technical issues first
  - Patient management
  - Owner technique
    - Improper insulin handling
      - Mixing
      - Storage
    - Incorrect syringe
      - U-40 vs. U-100
    - Improper injection technique
      - Expired insulin

- If resistance is suspected
  - Buy new bottle of insulin
  - Change injection site
  - Monitor owners perform injection

Insulin resistance

- Anti-insulin antibodies
  - Actual incidence unknown
  - No commercial test
  - Switch to different insulin
    - Beef for cats (PZI)
    - Pork for dogs (vetsulin)
  - Should improve control within 2 weeks

- Intact females
  - Progesterone / growth hormone

- Hormone dysfunction
  - Acromegaly
  - Thyroid disorders
  - Hyperadrenocorticism

Insulin resistance

- Infection
  - Urinary tract infection
  - Dental disease
- Neoplasia
- Hyperlipidemia
- Renal failure
- Pancreatitis
- Congestive heart failure

Prognosis

- Guarded long term
  - Concurrent disease
  - Owner commitment
    - Education is paramount
    - Consistency
      - Injections
      - Feeding
    - Clinical signs of both hyper and hypoglycemia
**Diabetic ketoacidosis**

- Absolute emergency!!
  - Check for ketones anytime diabetic sick
- Caused by
  - Absolute insulin deficiency
  - Stress hormone production
    - Glucagon
    - Epinephrine
    - Cortisol
    - Growth hormone
- Ketones produced by liver from free fatty acids
  - Incomplete burning of fat
  - Promoted by glucagon
  - Acetoacetic acid
  - Beta-hydroxybutyrate
  - Acetone

**Diabetic ketoacidosis**

- Lack of insulin
  - Hyperglycemia
    - Osmotic diuresis
      - Hypovolemia
      - Free water loss
      - Hypokalemia
      - Hypoglycemia
    - Ketone production
      - Acidosis
      - High anion gap acidosis
      - Underestimated on routine dipstick
        - Up to 20:1 ratio
        - BHB: acetoacetic acid

**Diabetic ketoacidosis**

- Place IV catheter
  - Preferably central line
- Aggressive fluid therapy
  - Correct dehydration
    - 6-8 hours
  - Correct electrolytes
  - Ongoing losses from severe osmotic diuresis
    - May need to supplement potassium
      - Intracellular shift
    - Correction of acidosis
    - Insulin therapy

**Diabetic ketoacidosis**

- Insulin therapy
  - Regular insulin ONLY
- Subcutaneous method
  - Only for non-dehydrated patients
  - Dogs
    - 0.5 - 1 unit / kg q 6-8 hours
  - Cat
    - 0.25 units / kg q 6-8 hours
  - Measure BG every 2 hours

**Diabetic ketoacidosis**

- IM technique
  - 0.2 u/kg IM initially
  - 0.1 u / kg hourly
    - Until BG < 250 mg/dl
  - Then switch to SQ method
    - q6-8 hours

**Insulin CRI**

- DKA dogs and cats
  - Easiest way to manage
  - Confusing initially
  - Simply following a chart
Insulin CRI

- Dogs
  - 250 ml NaCl
  - 2.2 units R insulin / kg

- Cats
  - 250 ml NaCl
  - 1.1 u/kg
  - 10 ml/hr
  - Waste first 50mL
  - Insulin binds to tubing
  - Monitor glucose q 1-2 h

Insulin CRI

- Pros
  - Very easy
  - Vet students can use it
  - Not as time consuming
  - Keeps you from calling me every 2 hours for a dose of insulin

- Cons
  - Makes you responsible for therapy
  - Also a pro!!!
  - Requires multiple fluid bags
    - Saline
    - 2.5% dextrose
    - 5% dextrose
    - Often have to switch between several times

Diabetic ketoacidosis

- Continue regular insulin until
  - Urine ketone free
  - Patient is eating

- Switch to longer acting insulin
  - NPH (dogs)
  - Glargine (cats)
    - May develop low amount ketones once on longer acting insulin

Diabetic ketoacidosis

- Hypokalemia common
  - Intracellular shift
  - Insulin
  - Correction of acidosis
  - Often need KCL CRI
    - < 0.5 mEq / kg / hour

- Hypophosphatemia
  - Catabolism of fat and muscle
    - Phosphorus wasting
    - 0.01 – 0.03 mmol /kg / hour over 6 hours
Hyperosmolar diabetes

- Glucose > 600
- Osmolality > 350
- Ketone negative
  - CNS depression
  - Ataxia
  - Nystagmus
  - Coma
  - Seizures
- Treatment is similar to DKA
  - Avoid rapid fluid loading
  - Rehydrate over 24 hours
  - Insulin CRI ideal
  - Lower rate (1.1 u / kg / day)