Diabetes in Dogs

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Outline

- Pathophysiology
- Can diabetes be prevented in dogs?
- Initial diagnosis
- Types of insulin available
- Monitoring treatment
- Insulin resistance
The Endocrine Pancreas

The endocrine pancreas is comprised of the islets of Langerhans & contains 4 cell types

• Alpha cells secrete glucagon
• Beta cells secrete insulin
• Delta cells secrete somatostatin
• F cells secrete pancreatic polypeptide
Hyperglycemia

- Definition: Blood glucose (BG) > ref range
- Clinical signs occur when the renal threshold is exceeded
  - 180-220 mg/dl in dog
  - Results in glucosuria → osmotic diuresis
  - → Polyuria-polydipsia
Ruleouts for Hyperglycemia

- Diabetes Mellitus
  - Primary Islet Destruction
    - Immune-mediated
    - Pancreatitits
  - Insulin Resistance
    - Hyperadrenocorticism
    - Acromegaly
    - Drugs (steroids most commonly)
      - Hyperglycemia from glucocorticoids not always accompanied by glycosuria
Definition of Diabetes

- Fasting hyperglycemia
- Glucosuria
- Elevated fructosamine or glycosylated hemoglobin
- This is a very conservative definition
Pathophysiology

• Type 1
  – Destruction/loss of beta cells
  – May be partial

• Type 2
  – Insulin resistance/dysfunctional beta cells
  – Can be obesity-related

• Sometime classified as IDDM or NIDDM

• Dogs are more like Type 1, and cats more like Type 2, but all fall somewhere on a continuum between the two
Causes of DM in dogs

• Genetic predispositions
• Immune-mediated
  – Anti-islet antibodies
  – Anti-insulin antibodies
• Pancreatitis
• Insulin-antagonistic drugs and diseases
• Obesity can cause insulin resistance but not glucose intolerance in dogs
• Concurrent illnesses and infections
DM in Dogs

• Incidence is approx. 70/10,000 cases
• Age
  – 2.2% <1 year
  – 0.67% 1–2 years
  – 2.8% 3–4 years
  – 15.4% 5–7 years
  – 37.1% 8–10 years
  – 39.2% 11–15 years
  – 1.8% >15 years
DM in Dogs

- Female 2x more likely than male
- Dogs weighing less than 23 kg greater risk
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Breeds at lowest risk

- Boxer (OR = 0.07)
- German Shorthaired Pointer (0.14)
- Airedale Terrier (0.15)
- German Shepherd Dog (0.16)
- Pekingese (0.18)
- Collie (0.19)
- Shetland Sheepdog (0.23)
- Bulldog (0.23)
- Great Dane (0.24)
- Cocker Spaniel (0.25)
Can Type I Diabetes be Prevented?

• First would have to know which animals are at risk?
  – Are there genetic markers?
  – Studies of anti-insulin and anti-islet antibodies are needed.

• Experimental evidence that cyclosporine can prevent immune-mediated islet destruction

• Diet cannot prevent diabetes
Clinical Signs

• Increased thirst (polydipsia)
• Increased urination (polyuria)
• Increased appetite (polyphagia)
• Weight loss
DM- Clinical Features

• Peripheral tissues are not able to use glucose → breakdown of muscle & fat leads to weight loss

• Increased appetite b/c satiety center has insulin-mediated uptake of glucose
Diabetic cataracts

• The lens is freely permeable to glucose
• In diabetics, there may be saturation of the pathways which metabolize glucose
• The sorbitol pathway will then metabolize glucose to sorbitol & fructose
• Sorbitol & fructose draw H₂O into the lens which disrupts the fibers
Diabetic neuropathy

- Seen in cats but not in dogs
- Plantigrade posture with the hocks touching the ground
- Cause is not known
Neuropathy does not always resolve or improve with treatment of diabetes
Initial Diagnostics

- Urinalysis
- CBC
- Chemistry profile
- Urine culture
- +/- Fructosamine
Urinalysis

- Glycosuria
- Proteinuria
- Ketonuria
  - May find small amounts in otherwise healthy diabetic
- Bacteriuria
  - Always culture given high prevalence of occult infections
CBC

• ↑ HCT if dehydrated
• ↑ WBC w/ infection or inflammation
Chemistry Panel

- Liver enzyme abnormalities
  - Due to lipidosis and pancreatitis
  - Changes in function tests may be noted
- Pre-renal azotemia may be seen
- Electrolyte abnormalities, esp. w/ DKA
- ↑ Cholesterol
Treatment of Diabetes
Therapy-Dietary

• Minimize post-prandial fluctuations in blood glucose
  – High fiber
    • Promotes weight loss
    • Slows glucose absorption from GI tract
  – Complex carbohydrates
  – Avoid excessive amounts of protein
  – Avoid excessive amounts of fat
Exercise

- Promotes weight loss
- Glucose lowering effect
Insulin

- Different types of insulin are available
- Protamine and zinc are typically used to prolong the duration of action
Insulin

• Similarity of insulin structure

100% homology
Insulin

- Similarity of insulin structure:

\[ 1 \text{ aa difference} \]
Insulin

Potency

Detemir*****
Glargine
PZI
Vetsulin
NPH
Regular

Duration

*****Detemir is very potent in dogs
Point to Remember:

Every patient responds differently to a given insulin preparation. What works for one dog might not work for another.
Regular Insulin

- Rapid onset
- Short acting
- Used at mealtime
- Used for emergency
NPH Insulin

- Similar to Vetsulin in terms of kinetics
- May be shorter acting
- Contains protamine
Vetsulin

- Porcine Insulin
- Contains zinc to bind insulin
- U-40
- Moderate onset and action
PZI

- Moderately long-acting
- Doesn’t work in all dogs
- U-40
Insulin Analogs
Human Insulin
Insulin Glargine

• Recombinant human insulin analog
• Long-acting, “peakless”
Properties of Glargine

- AA mutations shift isoelectric point
- Completely soluble at pH4
- Acid is neutralized in subcutaneous tissue
- Insulin crystals precipitate (hexamers)
- Hexamers are slowly broken down
In the bottle . . .

In the body . . .

(monomer)

(hexamer)
Insulin Detemir
Insulin detemir

• Liquid depot – detemir does not precipitate into hexamers at the site of injection
• No mixing required
• Buffered by albumin
• Less weight gain in people
• In people detemir is more predictable than glargine → decreased frequency of hypoglycemic events
In the bottle . . .

In the body . . .

Albumin

(bound to albumin)
Variability in insulin curves with NPH

Variability in insulin curves with NPH vs. glargine

Variability in insulin curves: NPH vs. glargine vs. detemir

Oral Hypoglycemic Drugs

- Increase insulin secretion
  - Sulfonylureas (glipizide)
- Inhibit glucose release
  - biguanide drugs (metformin)
- Decrease glucose absorption
  - acarbose
- Increase sensitivity to insulin
  - thiazolodinediones
- Vanadium and Chromium
Acarbose

• Mild glucose lowering effect if used as single agent
• May be combined with sulfonylureas or transition metals
• Give with meals
• Dose: 100-200 mg PO bid
Glucose curves

• For a diabetic dog without cataracts, glucose values should range between 100-250 mg/dL

• For diabetic dogs with cataracts, glucose values should range between 100-300 mg/dL
Glucose curve

- Interpretation:
  - Was insulin effective in lowering BG?
    - Establish highest BG
    - Establish lowest BG
Glucose curve

Was insulin effective in lowering BG?

What is the lowest BG?

How long does insulin last?

How would you adjust insulin therapy?
Insulin type or dosing frequency

Insulin dose
Blood Glucose
Blood Glucose Target
Somogyi Phenomenon

• Result of too much insulin
• Insulin-induced hyperglycemia
• Response to either hypoglycemia (BG<65) or too rapid a decline in BG
• Secretion of diabetogenic hormones
  – Catecholamines
  – Glucagon
• ↑↑↑ hepatic glycogenolysis
Blood Glucose Target
Blood Glucose Target
Bailey is PU/PD, eats canned Pedigree, serum fructoasamine is 640 μM
Still PU/PD  serum fructosamine = 545 uM
Bailey 9yo FS Yorkie 5.5 U Humulin U BID

Still PU/PD serum fructosamine = 560 μM
Are blood glucose curves useful?

- Fleeman and Rand JAVMA 2003
  - Paired BGC’s 2 weeks apart
  - High CVs (68% - 100%) for mean, min, max, pre-insulin glucose and glucose nadir

- Casella et al. JSAP 2003
  - Compared home vs. hospital
  - Mean and max glucose sometimes highest at home
  - Treatment decision would have been different 42% of the time based on home vs. clinic
Monitoring

• Owners perceptions of pet’s quality of life
  – Weight
  – Water intake & urination frequency
  – Food intake
Monitoring

• Fructosamine
  – Serum proteins that have undergone glycosylation
  – Reflects glycemic control over 2-3 weeks

• Glycosylated hemoglobin
  – Irreversible binding of glucose to hemoglobin in RBC
  – Reflects glycemic control over 2-3 months
Monitoring Insulin Therapy

• Clinical Signs
• Signs of Hypoglycemia
• PU/PD
• Spot BG can document hypoglycemia or hyperglycemia
• Fructosamine
• Glucose curves?
What if insulin is not working?
Insulin Resistance

- This term usually refers to the pathogenesis of type 2 diabetes mellitus in people, but is used differently in clinical vet med.
  - Diet and obesity are associated with ineffective action of insulin at the cellular level.
  - Leads to inappropriate insulin secretion and, eventually, to exhaustion of beta cell function and overt diabetes.
Insulin Resistance

• Clinical definition used in veterinary medicine:
  – Insulin dose > 1.5 U/kg in dog
  – Insulin dose > 6-8 U/cat
  – Apparent insulin resistance must be differentiated from true insulin resistance.
Apparent Insulin Resistance

• Is it really insulin resistance, or are owners not giving insulin properly?
  – Watch owners administer injection
  – Type of syringe
  – Site of injection?
  – Check type and dose of insulin
  – If using a diluted insulin, switch to non-diluted
  – Handling of insulin & syringe
  – Storage of insulin
  – Expiration date of insulin
Causes of Insulin Resistance

• Problems with a Specific Insulin
• Problems with Endocrine Organs
  – Adipose
  – Adrenal
  – Pituitary
  – Thyroid
  – Pancreas
  – Ovary
• Drugs
• Others
Insulin Problems

• Rapid Metabolism of Insulin
  – Response to a given insulin is unpredictable

• Somogyi Phenomenon
Obesity

• Reversible insulin resistance
  – Impaired insulin secretion
  – Down-regulation of receptors
  – Impaired receptor binding affinity
  – Post-receptor defects
  – Decreased adiponectin
  – Increased resistin
  – Pro-inflammatory cytokines
Glucocorticoid Excess

• Causes
  – Stress
  – Hypercortisolism
  – Exogenous administration

• Effects of Glucocorticoids
  – Increased hepatic gluconeogenesis
  – Decreased tissue utilization of glucose
  – Decreased receptor affinity for insulin
  – Decreased number and affinity of glucose transporters
  – Increased glucagon and free fatty acid concentrations
Clinical Signs -- Urinary System

• Polyuria/Polydipsia (90%)
  – Due to ADH antagonism
  – Concurrent diabetes mellitus
  – Decreased renal tubular water permeability
  – Decreased vasopressin secretion
  – Increased GFR?

• Urinary Tract Infection
  – Associated with steroids
  – Dilute urine predisposes
  – Can show signs of lower urinary tract disease
Clinical Signs: Skin

- Bilaterally symmetrical alopecia (55 – 90%)
- Thin skin
- Hyperpigmentation
- Comedones
Clinical Signs -- Muscle

Muscle atrophy
  direct effect of glucocorticoids

Pot Belly
  Abdominal muscle weakness
  Redistribution of fat
  Hepatomegaly

Myotonia
  Uncommon
  Non-inflammatory degenerative myelopathy
Clinical Signs

• Respiratory System
  – Panting is common
  – Dyspnea due to pulmonary embolism

• Endocrine System
  – Insulin resistance
  – Diabetes is common in dogs with hypercortisolism

• Nervous System
  – Seizures, blindness, circling due to macroadenoma
Growth Hormone Excess

• Acromegaly
• Only occurs in intact bitches
• Different from the disease in cats and people
• Effects
  – Glucose transport inhibition
  – Increased glucose production
  – Decreased insulin receptor numbers
  – Effects downstream of receptor
  – Increased lipolysis
Thyroid Hormone Excess

• Uncommon in dogs unless on thyroid supplementation
• Feline hyperthyroidism and diabetes are sometimes seen as co-morbid conditions

Effects of thyroid hormone
- Lower insulin production
- Insulin receptor binding defects
- Abnormal glucose transport?

Clinical effects
- Hyperthyroid patients may need less insulin after treatment of thyroid disease
- Human hyperthyroid patients commonly have glucosuria
- Hyperthyroidism associated with lower fructosamine
Glucagon Excess

- Associated with…
  - Bacterial infection
  - Pancreatitis
  - Trauma
  - Congestive heart failure
  - Renal failure
  - Glucagonoma

- Effects of Glucagon
  - Increased hepatic gluconeogenesis
  - Increased hepatic glycogenolysis
Progesterone Excess

• Cause of hyperprogesteronism
  – Diestrus/pregnancy
  – Use of pregestagens (eg. megestrol acetate)
  – Adrenal tumors?

• Effects of progesterone
  – Reduced insulin binding
  – Reduced glucose transport in tissues
Catecholamine Excess

• Causes
  – Stress
  – Pheochromocytoma
  – Hyperthyroidism?

• Effects of epinephrine
  – Stimulation hepatic and renal glucose production
  – Decreased glucose utilization
  – Decreased insulin secretion
  – Stimulation glucagon secretion
  – Gluconeogenesis
Insulin Resistance

• Other things to consider:
  – Administration of any drugs which antagonize insulin (eye, ear Rx common culprits)
  – Heat cycles?
Common Causes of Insulin Resistance

• Dogs
  – Cushing’s disease
  – Bacterial infections
Anti-Insulin Antibodies

- Result of continued exposure to a foreign protein (insulin)
- Low levels may be beneficial in prolonging the duration of effect of insulin
- High levels may cause insulin resistance
- High levels may cause erratic fluctuations in blood glucose (Δ in binding affinity)
- Not a lot of evidence that these are important in veterinary patients
Work-Up of Insulin Resistance

- Glucose curve?
- Full medical work-up
- Blood Pressure
- Urinalysis and culture
- Tests for Cushing’s disease?
13-year-old Shih Tzu x Bichon
June 09

• On Vetsulin for 3 years
• Presented for evaluation of neuro signs
• Owner reports dog is on 15 U BID
• Medical record says dog is on 5 U BID
• Diet of people food. Dog doesn’t always eat well.
• Exam:
  – 16 pounds
  – Thin skin and bad hair
  – BCS 3/9
  – Severe dental disease
  – Cataracts
June 09

• Top ruleouts for neurological signs?
  – Hypoglycemia
  – Other metabolic disorders
  – Neoplasia
  – Vascular
June 09

- Owner declines medical work-up other than spot BG.
- BG = 49 mg/dl
- Plan: Decrease insulin dose to 4 U BID.
August 09

- Owner reports dog is very PU/PD.
- Blood Glucose Curve
  - 8 a.m. 204 mg/dl
  - 10 a.m. 180 mg/dl
  - Noon 166 mg/dl
  - 2 p.m. 230 mg/dl
  - 4 p.m. 291 mg/dl
- Because of persistent PU/PD, Vetsulin dose was increased to 5 U BID
October 09

- Owner reports dog is still very PU/PD.
- Blood Glucose Curve
  - 8 a.m.        367 mg/dl
  - 10 a.m.       280 mg/dl
  - Noon         310 mg/dl
  - 2 p.m.        297 mg/dl
  - 4 p.m.        253 mg/dl
- Vetsulin dose was increased to 5.5 U BID
November 09

- Vetsulin alert issued by FDA
- Dog transitioned to Humulin-N
- Recommended dose of 3 U BID
- Owners ignored recommendation and gave 5 U BID
Later That November

- Owners report seizures.
- DVM recommends decreasing Humulin-N to 4 U BID
December 2009

- Owner reports dog is still very PU/PD.
- UA – glucose 1000, inactive sediment
- Blood Glucose Curve
  - 8 a.m. 192 mg/dl
  - 10 a.m. 297 mg/dl
  - Noon 304 mg/dl
  - 2 p.m. 297 mg/dl
  - 4 p.m. 266 mg/dl
- Vetsulin dose was increased to 5 U BID
January 2010

• Owner reports dog is still very PU/PD.
• UA – gluc 500, inactive sediment, SG = 1.030
• Blood Glucose Curve
  – 8 a.m. 319 mg/dl
  – 10 a.m. 265 mg/dl
  – Noon 328 mg/dl
  – 2 p.m. 242 mg/dl
  – 4 p.m. 351 mg/dl
• Now what???
Questions

• Why did the dog have seizures on 5 U BID in November, and persistent hyperglycemia in January?

• Why was the dog better controlled on 4 U of Vetsulin BID than on 5 U of Vetsulin BID?

• Should you trust BG curves?

• If the owners would agree to a more aggressive work-up, what should you do?
Recommendations

- Measure blood pressure
- Start a diet that makes sense for a diabetic dog.
- Chemistry profile to look for causes of difficult regulation of insulin therapy
- Consider fructosamine rather than BG curves.
- Use 0.3-ml Lo-dose syringes for more consistent dosing of insulin
- Dental
- Urine Culture
- Are there other insulin options?
- Imaging studies (chronic pancreatitis, neoplasia, etc.)
And a little about hypothyroidism . . .

- Many veterinarians and breeders think that hypothyroidism is common in dogs.
- From ATCA website—
  - “..with a deficient endocrine system come other related disorders such as Cushing’s disease, Addison’s disease, thyroid abnormalities . . . “
"Hypothyroidism is the most frequently diagnosed endocrinopathy found in the dog. Whether these diagnoses accurately reflect the true incidence of hypothyroidism in dogs is clouded by the controversy concerning the best means of diagnosis, and by the pitfalls of early recognition of the disease, which are caused by the variety and subtleness of hypothyroidism’s presenting signs. Even so, there is little doubt that hypothyroidism is a common endocrine disease of the dog."

Chastain and Ganjam, Clinical Endocrinology of Companion Animals, 1986
Compared 233 dogs with non-thyroidal disease and 150 normal dogs

Total T4, Free T4, and Total T3 were significantly lower in sick dogs

TSH was significantly higher in sick dogs

Conclusion TT4, FT4, and TT3 can be in the hypothyroid range in sick dogs

TSH is more likely to be in the normal range for sick dogs, but can be high
• 18% of healthy euthyroid dogs had low T4
• 24% of hypothyroid dogs had normal TSH
• TSH had a low sensitivity for hypothyroidism
No difference in free T4 concentrations comparing hypothyroid dogs and dogs with diseases that look like hypothyroidism (Cushings, peripheral neuropathy, etc.)

Sick dogs with normal thyroid glands have low free T4 (17%) and low T4 (20%)
Many drugs affect thyroid testing

- NSAIDS
- Glucocorticoids
- Anticonvulsants
- Sulfonamides
- Radioccontrast agents
Breeds with lower T4

- Greyhound
- Scottish Deerhound
- Siberian Husky
- Others likely
Diabetes and Hypothyroidism

• Dogs with diabetes usually have low T4 even with normal thyroid glands
• There is no known association between diabetes and hypothyroidism
• Hypothyroidism is mistakenly diagnosed in diabetic dogs
• Thyroid hormone supplementation could make diabetes more difficult to control.
Diabetes and Cushing’s Disease

• These two disease can occur together
• Uncontrolled diabetes can result in false-positive tests for Cushing’s disease
• Diabetes is extremely difficult to control unless Cushing’s disease is controlled first.
• The clinical signs of the two diseases are similar.