DIABETES MELLITUS IN THE DOG AND CAT

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Overview

- Pathophysiology
- Diagnosis
- Treatment
  - Diet & exercise in managing diabetics
  - The role of oral hypoglycemic agents
  - Different types insulin products
    - Canine & feline
- Follow-up care, in-clinic & at-home monitoring
- Case examples
Pathophysiology

- Insulin is produced by the beta cells within the islets of Langerhans in the pancreas.
- Immune-mediated destruction of cells (not usually immune-mediated destruction of insulin) or degeneration of cells results in reduced ability to produce insulin.
- Lack of insulin results in the inability to uptake glucose from the blood into cells.
- Result is hyperglycemia with glucose-starved cells.
Pathophysiology

- Insulin deficiency results in decreased tissue utilization of glucose, amino acids, fatty acids, accelerated hepatic glycogenolysis and glyconeogenesis, and subsequent hyperglycemia
- Renal tubular threshold for glucose is exceeded, resulting in osmotic diuresis and compensatory polydipsia
- Polyphagia due to starvation of cells and inability of glucose to enter satiety centre
Pathophysiology

- Histological changes in dogs
  - Reduction in size of pancreatic islets
  - Decreased beta cells within islets
  - Beta cell vacuolation and degeneration

- Congenital form (rare)
  - Pancreatic aplasia
  - Pancreatic hypoplasia
  - Absolute deficiency of beta cells – severe form
Etiology - Dogs

- Genetics (Australian Terrier, Schnauzer, Bichon, Terriers, Smaller Poodles, Samoyed, Keeshond, Maltese, Lhasa Apso, Spitz, Yorkie)
- Immune-mediated – suspected more in humans than dogs
- Obesity
- Drugs (glucocorticoids, progestagens)
- Infection
Etiology – Dogs continued

- Concurrent disease (chance of NIDDM)
  - Pancreatitis
  - Hyperadrenocorticism
  - Hypothyroidism
  - Other endocrine disease
  - Diestrus-induced increase in growth hormone
  - Renal insufficiency (?)
  - Cardiac disease
  - Hyperlipidemia (cause or effect)
Etiology - Cats

- Initially impaired insulin action in liver, muscle, fat which is defined as NIDDM (Type 2)
- Genetics suspected but not characterized
- Major risk factors:
  - Increasing age
  - Male gender
  - Neutered status
  - Physical inactivity
  - Glucocorticoid/progestin administration
  - Obesity
- Increased insulin secretion required due to insulin resistance, leading to beta cell loss
- Deposition of amyloid in pancreas also suggested to lead to beta cell loss
- Conversion to type 1 (IDDM) once loss of 80-90% of beta cells
Insulin resistance (muscle, fat, liver) → ↑Glucose

β cell

↑Insulin → Euglycemia

↓Insulin

Genes • Unknown

Environment • Obesity • Inactivity • Drugs • ↑Glucose

Genes • Unknown

Environment • Amyloid • ↑Glucose

Euglycemia → IGT → Diabetes mellitus
Diagnosis

- Presence of significant hyperglycemia with glucosuria
- Important to document hyperglycemia as glucosuria can occur due to renal disease (Fanconi syndrome)
- DDx for hyperglycemia:
  - Stress, post prandial, hyperadrenocorticism, diestrus, pheochromocytoma, pancreatitis, exocrine pancreatic neoplasia, drug therapy (glucocorticoids, progestagens, thiazide diuretic, dextrose IV fluids), head trauma
- Fructosamine can help diagnose DM
Clinicopathologic changes

- CBC – usually normal, can see neutrophilia
- Biochemistry – Hyperglycemia, fasting hypercholesterolemia, fasting hyperlipidemia, increased ALT (usually <500 IU/L), increased ALP (usually < 500 IU/L)
- Urinalysis – USG usually >1.025, glucosuria, proteinuria, bactiuria, can have ketonuria
Additional diagnostics

- Urine culture
- Abdominal ultrasound
- Thoracic radiographs
- fPL or spec cPL
Therapy
Goals of Therapy

- Reduce or eliminate owner-observed clinical signs
  - Polyuria and polydipsia most obvious change and easy to monitor
  - Polyphagia
- Prevent chronic complications of diabetes mellitus (reviewed later)
Diet and Exercise

- Obesity results in insulin resistance
- Weight loss can improve insulin sensitivity
- Essential to
  - Promote weight loss in all obese patients
  - Prevent obesity in patients with ideal body condition
Exercise

- Aim for loss of 1-2 % body weight every week
- Encourage a gradual increase in exercise
- Owners should aim for a daily routine of consistent, moderate exercise
- Strenuous and sporadic exercise should be avoided
- If strenuous exercise is to occur, reduce insulin by 50% to avoid hypoglycemia
Exercise Program Considerations

- Make clients aware of signs of hypoglycemia
  - Nervousness, shaking, weakness, seizures
- Have them keep a source glucose at home to administer orally if pet develops clinical signs
Physical Activity - Dogs

- Exercise strategies for dogs? What are you trying?
Diet and Exercise
Physical Activity
Physical Activity - Cats

Exercise strategies for cats?
Physical Activity

- Useful for weight control
  - Promotes fat loss
  - Preserve lean tissue
  - Prevent weight gain after successful weight loss?

- Exerts glucose-lowering effects in other ways
  - ↑ insulin absorption, delivery to tissues
  - ↑ glucose uptake by cells
Exercise Program Considerations

- Patient’s age, overall health, fitness level
- Concurrent medical conditions
  - Engage in different activities than otherwise healthy individuals
    - Labrador retriever with hip dysplasia may gain most from swimming or hydrotherapy
    - Overweight Border collie with healthy joints may retrieve ball for hours
Diet - Dogs

- Alterations in diet should correct or prevent obesity
- Maintain consistency in timing/caloric content of meals
- Minimize postprandial increase in blood glucose
- Increased fiber content can improve glycemic control
- This is more effective with soluble fiber compared to insoluble fiber
Mechanism with fiber

- Several proposed mechanisms
  - Delay
    - Gastric emptying
    - Intestinal absorption - fiber forms a viscous gel on the surface of the intestine, slowing glucose absorption
  - Fiber-induced effect on release of regulatory GI hormones into circulation
Diet - Dogs

- Most commercial diets have primarily insoluble fiber, however some are adding more soluble fiber.
- Ideally should have 3% or higher fiber, up to 25% in some diets.
- Diets $\geq 12\%$ insoluble or $\geq 8\%$ soluble & insoluble mixture best.
- Little information on adding soluble fiber to diet.
Complications of feeding high fiber

- Increased frequency of defecation (insoluble)
- Constipation (insoluble)
- Soft stools (soluble)
- Excessive flatulence (soluble)
- Hypoglycemia 1-2 weeks after starting (monitor)
- Do not feed in underweight dogs
Dietary Considerations - Dogs
Dietary Considerations - Cats

- **Goal of diet**
  - Provide nutritionally complete diet
  - Provide palatable food
  - Encourage ideal BCS

- Can avoid postprandial hyperglycemia with higher protein diet; cats are metabolically adapted to utilize protein and fat rather than carbohydrates

- Poorly adapted to deal with simple sugars
Dietary Considerations - Cats

- Previously, high-fiber, high-carb diets recommended for diabetic cats
  - Increased dietary fiber can improve glycemic control
  - Insoluble fiber in commercial high-fiber feline diets
- New research suggests high-protein, low-carb diets better
  - May help resolve feline diabetes & decrease insulin requirements
Some cats may achieve remission with diet change alone
- Most cases require exogenous insulin
- If remission achieved, maintain cat on high-protein, low-carb diet for life
- Exactly how diet helps glycemic control not fully elaborated
  - ↑ energy use in muscle, ↓ fat stores in body
    - Reverse some insulin resistant effects of adipocytes?
Dietary Considerations - Cats
Weight Control Program

- To successfully manage weight long-term
  - Encourage clients to continue
    - Monthly rechecks
    - Measuring their pet’s food
    - Monitoring weight
      - Even after pet reaches ideal weight
Insulin - Dogs
Insulin

- Should be started immediately in all dogs
- Essentially all dogs will require twice daily dosing
- Ideal goal - maintain blood [glucose] as close to physiologic levels as possible
  - Difficult to do, as administered as 1-2 large daily doses, not in response to [BG]
- Realistic goal in dogs = eliminate clinical signs
Goals of Insulin Therapy

- Prevent
  - Detrimental effects of hyperglycemia
  - Development of ketoacidosis
  - Hypoglycemia
Insulin Products

- Classified based on
  - Time of onset
  - Duration of action

- Fall into 3 categories
  - Short-acting
  - Intermediate-acting
  - Long-acting
Regular Insulin

- Reserved for DKAs
- Short-acting insulin of choice
  - Intermittent intramuscular technique
  - Low-dose intravenous infusion technique
- Dosing schemes vary
  - CRI - 1.1 to 2.2 U/kg/day, adjusted accordingly based on BG
  - Intermittently - 0.1 to 0.2 units/kg q1-4 hours
    - Based on BGs & route administration (i.e. IV, IM, or SQ)
NPH - 100 IU/ml

- Intermediate-acting insulin
- Recombinant human insulin
- Administered subcutaneously
- Onset of action
  - 30 minutes - 2 hours
- Maximum effect
  - 2 -10 hours (dogs)
- Duration of action
  - 6 -18 hours (dogs)
NPH

- Twice-daily administration usually necessary
  - Some clinicians use starting dose of 0.25 U/kg
  - Others recommend 0.5 U/kg if BG >20 mmol/L & 0.25 U/kg if <20 mmol/L
  - Both are acceptable protocols
  - Always round down to closest unit
Caninsulin – 40 IU/ml

- Intermediate-acting
- Porcine based
- Onset of action 1/2 - 2 hours
  - Maximum effect
    - 3 hours
  - Duration of action
    - 8 hours
Caninsulin

- Twice-daily administration usually necessary
- Occasionally three times daily dosing required
  - Starting dose of 0.25 U/kg twice daily
Caninsulin - VetPen™

- Only insulin pen designed for pets
- VetPen™ may minimize pet discomfort
  - 42% of cat owners reported that the cat’s response to injections improved after switching to VetPen™
- Some pet owners may find it less intimidating than a conventional insulin syringe
- It is likely to provide more accurate dosing consistently
- Can keep at room temperature for 28 days (vial labeled for 6 weeks)
Glargine – 100 IU/ml

- Long-acting insulin
- At acidic pH insulin in solution
- Relatively neutral pH of SQ tissues
  - Micro-precipitates form
    - Relatively constant systemic absorption rate up to 24 hours without significant peak
- Micro-precipitates depend on solution’s acidity
  - Cannot mix or dilute
Glargine

- Glargine not recommended in diabetic dogs
  - Recent published data revealed good glycemic control in only 50% of dogs; concluded that other insulins have a better success rate
- Anecdotal reports claim seems ineffective in treating diabetic dogs
- Long duration of action could induce hypoglycemia in dogs
Detemir – 100 IU/L

- Long-acting insulin
- Acylated fatty acid results in reversible binding of insulin to albumin
- Result is slow release of bound fraction, resulting in peakless insulin secretion
Detemir

- Detemir not recommended in diabetic dogs
  - Lack of published data
- Anecdotal reports claim ineffective in treating diabetic dogs
- Long duration of action and potency could induce hypoglycemia in dogs
- Last resort if all other insulins fail
  - start at very low dose (0.1 IU/kg q12h)
  - gradual, cautious increase
Degludec – 100 and 200 IU/ml

- Insulin degludec (Tresiba)
  - Similar properties to glargine and detemir
  - Very new insulin, no studies yet in animals
ProZinc – 40 IU/L

- Developed to prolong the effects of regular insulin
- Long-acting recombinant human insulin
- Contains
  - Insulin
  - Zinc
  - Protamine
    - Fish protein
- Form poorly soluble precipitates which extends duration
ProZinc

- One study evaluating PROZINC insulin in dogs; effective in the 11 dogs in study, but required a high dose for control
- Recently available in Canada
- Long-acting insulin so not recommended as top choice insulin in the diabetic dog
  - Duration of action likely too long and risks causing hypoglycemic episodes in these patients
  - The manufacturers of PROZINC report currently investigating its use in dogs
    - May become viable option for management of diabetic dogs in future, high cost due to dose required for control
Insulin - Cats
Insulin

- Most effective, fastest means of achieving glycemic control
  - Solid evidence cats started on insulin within first 6 months of diagnosis more likely achieve remission
    - No longer need exogenous insulin injections
    - Maintain euglycemia with high-protein, low carb diet alone
- Strongest argument for initiating insulin treatment at outset with your patients
Insulin

- Ideal goal - maintain blood [glucose] as close to physiologic levels as possible
  - Difficult to do, as administered as 1-2 large daily doses, not in response to [BG]
- Usual goal in cats = eliminate clinical signs
- Some centers advise very aggressive therapy early on in order to try to maximize chance of remission – cases must be closely monitored
Goals of Insulin Therapy

- Prevent
  - Detrimental effects of hyperglycemia
  - Development of ketoacidosis
  - Hypoglycemia

- In some cases
  - Reversal of diabetic state
  - These cases likely return to a prediabetic state so may recur
Regular Insulin

- Reserved for DKAs
- Short-acting insulin of choice
  - Intermittent intramuscular technique
  - Low-dose intravenous infusion technique
- Dosing schemes vary
  - CRI - 1.1 to 2.2 U/kg/day, adjusted accordingly based on BG
  - Intermittently - 0.1 to 0.2 units/kg q1-4 hours
    - Based on BGs & route administration (i.e. IV, IM, or SQ)
Glargine – 100 IU/ml

- Good first choice insulin in cats
- Very conservative starting dose recommended to avoid hypoglycemia
- 0.25-0.5 IU/CAT either once or twice daily
- Safer to start once daily however most cats require twice daily
- Should not change dose in first week
Caninsulin – 40 IU/ml

- Also a good starting choice in cats, currently my third choice behind glargine and ProZinc
- Twice-daily administration usually necessary
- Start at 0.25-0.5 IU/KG, dose on lean weight
- Can use pre-treatment blood glucose as a guide, use lower end of dosing if blood glucose is < 20 mmol/L
- Can use VetPen for certain clients
Detemir – 100 IU/ml

- Time to maximum effect 8-16 hours
- Published abstract (ACVIM 2009) indicated similar action to glargine
- Lower doses needed when compared with glargine
- Potential for hypoglycemia, need to be very conservative with dosing and start once daily
- Reserve for refractory cases
NPH – 100 IU/ml

- Intermediate-acting insulin
- Recombinant human insulin
- Administered subcutaneously
- Maximum effect
  - 2-8 hours (cats)
- Duration of action
  - 4-12 hours (cats)
- In most cats the duration of action is too short for use
ProZinc – 40 IU/ml

- In cats
  - Onset of action
    - 1 - 4 hours
  - Maximum effect
    - 4 - 14 hours
  - Duration
    - 12 - 24 hours
- 25% cats successfully managed with once-daily injections of protamine zinc
- Recently available in Canada
ProZinc

- One study evaluated use
- Good glycemic control in 85-90% of cats
- Mean dose 0.6 IU/kg
- Hypoglycemia occurred in 22% of cats, sometimes at very low dose of insulin
- Recommend conservative starting dose (1 IU per cat)
Hypoglycemic Agents
Hypoglycemic Agents

- Drugs used to treat diabetes
- Reduce level of glucose in bloodstream
- With exception of insulin, all taken orally
Oral Hypoglycemics

- Occasionally part of therapy
- Many types available
  - Varying mechanisms of actions
- Can be effective
- Typically only used in cats, as they are often type 2 DM
- Insulin remains mainstay of therapy; oral hypoglycemics should be reserved for owners who refuse insulin therapy
Sulfonylureas

- Stimulate insulin secretion, therefore must have enough remaining beta cells for production
- No parameters for selection of cases, currently have to use judgement of severity of disease
- Glipizide most commonly used
  - 2.5 mg/cat q12h with meal to start
  - Increase to 5 mg/cat q12h with meal in 2 weeks if still hyperglycemic
  - Re-evaluate after 2 more weeks, monitor routinely
  - Stop if hypoglycemia, switch to insulin if hyperglycemia
Sulfonylureas

- **Drawbacks**
  - Successful in only about 30% of cases
  - May accelerate beta cell loss
  - May increase amyloid deposition in pancreas
  - No benefit over insulin, so reserve for cases where owners refuse insulin therapy
  - May be difficult to obtain
Other agents

- **Metformin**
  - One report in cats with results of poor glycemic control

- **Meglitinides**
  - No reports on use, likely would not work in cats

- **Glitazones (Thiazolidinediones)**
  - Insulin sensitizer, theoretical benefit, no studies

- **Alpha-glucosidase inhibitors**
  - Delays glucose absorption, poor response in studies

- **Trace elements (chromium, vanadium)**
  - Lack of effect in studies other than one study with Vanadium
Treat concurrent diseases

- Antibiotics for urinary tract infection
- Therapy for stomatitis (cats)
- Pancreatitis
- Cardiac disease
- Difficulties obtaining definitive diagnosis:
  - Hyperadrenocorticism
  - Renal disease
Monitoring
Monitoring

- Marked variation in insulin kinetics, makes monitoring crucial

- Including
  - Serial blood glucose curves
    - Either in hospital or at home
  - Continuous subcutaneous glucose measurements
  - Measuring serum fructosamine concentrations
  - Monitoring presence and degree of glucosuria
  - Assessing clinical signs
Clinical signs

- Most important monitoring tool
- Remember first goal of insulin therapy is to improve or resolve owner-observed signs
- Best assessment of success of insulin therapy
- If complete resolution of clinical signs, ensure hypoglycemia is not occurring
Glucose Curves

- Long been gold standard
- Glucose curves demonstrate
  - Insulin effectiveness
  - Time to peak effect
  - Duration of effect
  - Blood glucose nadir
  - Degree of blood glucose fluctuation
- Identify Somogyi effect if present
  - Hypoglycemia-induced hyperglycemia
Glucose Curves

- Maintain normal feeding/insulin schedule
- Ideally, [glucose] should nadir at 5.5-8.5 mmol/L in dogs & 7-10 mmol/L in cats
- Highest [glucose] (peak) < 14 mmol/L in dogs & 17 mmol/L in cats
- Usually require glucose measurements every 2-4 hours, depending on insulin type
  - Every 2 hours for NPH, Caninsulin
  - Every 4 hours for glargine, detemir, ProZinc
- Up to every 30 minutes if looking for Somogyi
Glucose Curves

- Ideally 7-10 days after insulin dose change
- Next day if hypoglycemia is a concern
- When you assess BG curve ask three basic questions
  - Has insulin decreased [BG]?
  - If so, what was the nadir?
  - How long has insulin lasted?
- The answers will help you make logical changes in dosing regimen
Glucose Curves

- Measure blood glucose levels for one interval between injections
  - 12 hours if insulin twice daily (some need 24 hr curve)
  - 24 hours if insulin once daily
    - If impossible to obtain 24 hour curve, can start with a 12 hour curve
- If BG <7 mmol/L, measure hourly
- Maintain as normal an insulin and feeding schedule as possible
- If patient does not eat normal amount of usual food at usual time, postpone curve
Glucose Curves

- Perform curves on first day after you initiate or change insulin therapy if you suspect hypoglycemia may occur
- If patient develops hypoglycemia, decrease insulin dose 25%
- Perform another curve following day to check for hypoglycemia
- Do not increase insulin dose based on first day’s curve regardless of values
Glucose Curves

- Always interpret results in light of clinical signs
- Curves vary from day to day
  - Stress hyperglycemia can falsely elevate
  - Refusal to eat in hospital can falsely decrease
- If patient not polyphagia, polydipsia, or polyuria & body weight is stable or increasing, you’ve likely achieved good diabetic control
Glucose Curves

- If no acceptable nadir, adjust insulin dosage
  - Usually dose changes of about 10% are appropriate, more caution with glargine and detemir
- No matter what other [BG], if the nadir <4.5 mmol/L, decrease the dose by 25%
  - When decrease dose because of hypoglycemia, perform a curve the following day
    - Ensure hypoglycemia does not recur
- If hyperglycemia is the issue, repeat curve 7 - 10 days after insulin dose adjustment
Interpret blood glucose curves & adjust doses differently than for other insulin types

Recommendations for dose adjustments are based on pre-insulin blood glucose concentration
- Compared to other insulins where dose is altered based on the nadir

Ensures not substantial overlap from the previous injection
- Minimize the likelihood of causing hypoglycemia
BG Curves & Glargine

- Pre-insulin BG >16 mmol/L
  - Increase glargine dose by 0.25 IU/cat

- Pre-insulin BG 12-16 mmol/L
  - Dose not changed
    - In either of these first 2 scenarios, perform curve to ensure no hypoglycemia

- Pre-insulin BG 4.5-10 mmol/L
  - Dose decrease 0.5 IU/cat

- Biochemical hypoglycemia (BG <4.5 mmol/L) without C/S
  - Dose decrease 1 IU/cat or more
If clinical signs of hypoglycemia present

- Dose decrease to 0.25 IU/cat, or at least by 50%

Do not discontinue within 2 weeks of starting treatment even if normoglycemia present

- Decrease dose if needed, but do not stop
BG Curves & higher dose Glargine

- Perform 12-hour blood glucose curves for the first 3 days after initiating insulin treatment unless starting at very low dose (0.25-0.5 IU/cat)
  - Detect hypoglycemia, if present
    - Decrease dose as needed
  - Many cats require dose reduction within the first three days of glargine treatment
- After first three days, discharge & have return for BG curve in 7 days
- Perform subsequent BG curves at one, two, and four weeks, then PRN to monitor control
First glucose curve at 7-10 days
Follow recommendations for typical monitoring
Counsel owners about clinical signs of hypoglycemia
At Home Monitoring - Curves

- Allows you to maintain diabetic control
- At-home-generated glucose curves could help avoid some problems associated with in-clinic curves
  - Stress-induced hyperglycemia
  - Patients not eating
- Venous blood not necessary
  - Capillary blood is suitable
- Many studies show owners willing, able generate accurate at-home serial curves
Continuous SQ glucose curve

- Small electrode inserted in SQ, measures interstitial glucose concentrations which correlates closely to blood glucose
- Reading every 5 minutes sent to wireless monitor (must be within 2 metres of animal)
  - Attached to animal with jacket
  - Hung on cage door in hospital
- New models display results in real time on monitor
- Provides an on-going picture of glucose levels
Continuous SQ glucose curve

- Benefits over traditional glucose curve:
  - Catching Somogyi phenomenon and rapid changes in BG
  - Can send animal home and avoid hospital induced BG changes
  - Have used it to diagnose hypoglycemia due to insulinoma

- Challenges:
  - Requires calibration with blood glucose level every 8-12 hours
  - Sensor can only be left in place for 72 hours
  - Contact dermatitis has been noted
  - Occasionally loses data or sensor becomes dislodged
  - Expensive equipment and expensive sensors
Fructosamine

- Glycated proteins synthesized from irreversible binding of glucose
- Reflects mean glucose concentration in past 1-2 weeks
- Good for long term monitoring once stable
- Not affected by acute stress hyperglycemia
  - 360-450 umol/L good control
  - 450-550 umol/L moderate control
  - >600 umol/L poor control
- Hypoproteinemia and hyperthyroidism can lower fructosamine levels
Urine glucose sticks

- Monitoring that can be performed at home
- Should not alter insulin dose based on urine glucose
- Persistent glucouria indicates the need for further evaluation of blood glucose levels
Typical Monitoring Regime

- Evaluate at one week
  - Feed animal at home then bring immediately to clinic
  - Discuss history, resolution of clinical signs
  - Blood glucose curve, measure BG every 1-2 hours
  - Fructosamine level can also be performed
  - Adjust insulin by 0.5-1 IU if required, adjust by 0.25 IU if glargine
  - Adjust frequency if necessary
Typical Monitoring Regime

- Re-evaluate at 3 weeks
  - Vital signs, weight, glucose curve
  - Discuss at home monitoring
- Re-evaluate at 6-8 weeks
  - Vital signs, weight, glucose curve
  - May not need glucose curve if clinical signs indicate control
  - Otherwise aim for pre-insulin BG of 10-15 mmol/L and fructosamine of 350-450 umol/L
- Re-evaluate at 10-12 weeks, base monitoring on response to therapy
- Re-evaluate every 4 months
Goals

- Marked improvement of, or resolution of, PU/PD and polyphagia
  - Ensure no hypoglycemia if complete resolution
- Normalization of body weight
- BG between 15 mmol/L pre insulin to 5 mmol/L at nadir
  - Do not adjust insulin if these BG targets are not met but the animal is clinically doing well
- Fructosamine between 350-450 umol/L
Complications of Insulin Therapy

- Hypoglycemia
  - Complication of insulin therapy
  - Counsel owners on clinical signs, appropriate emergency therapy
  - Reason why we don’t achieve perfect glycemic control

- Stress hyperglycemia in hospital
  - Assumption of poor control
  - Inappropriate increase in insulin dose
  - Can lead to Somogyi phenomenon and vicious circle
Reasons for poor control

1. **Technical problems**
   a. Errors in handling, shaking, diluting, freezing, heating, outdated insulin, drawing up air, poor injection technique, wrong syringe

2. **Insulin underdose**
   a. Consider if insulin dose $\leq 1$ IU/kg unless glargine

3. **Insulin overdose and possible Somogyi Phenomenon**
   a. Suspicious if owners report days that seem well controlled then days that are poorly controlled
   b. Suspect if higher dose insulin with persistently elevated glucose levels ($> 1.5$ IU/kg q12h)
Reasons for poor control

3. Short duration of insulin effect
   a. Can be seen with twice daily insulin therapy, especially in cats with Caninsulin
   b. Perform glucose curve to evaluate
   c. Fructosamine usually moderately to severely elevated

4. Prolonged duration of insulin effect
   a. Not usually an issue with NPH or Caninsulin
   b. Can be seen in glargine used twice daily

5. Impaired absorption of insulin
   a. Rarely occurs, avoid by rotating sites (thickened skin)
   b. Consider if dehydrated, poor circulation
6. Binding of insulin by antibodies
   a. Amino acid sequence differs from human, porcine and bovine insulin
   b. Can result in production of anti-insulin antibodies
   c. Requirement for insulin extremely high
   d. If insulin dissociates from antibody, result in erratic insulin need
   e. Present in 14-37% of cats, but no correlation to glycemic control
   f. Likely not a factor in almost all cases
   g. Potentially more of a concern in dogs receiving beef source insulin
Reasons for poor control

7. Concurrent disorders
   a. Result is insulin resistance (>1.5 IU/kg unless glargine/detemir)
   b. Inflammatory, neoplastic, endocrine, drug use, infectious
      • Obesity
      • Chronic renal failure
      • Pancreatitis
      • Stomatitis, urinary tract infection
      • Hyperadrenocorticism
      • Hyperlipidemia
      • Acromegaly in cats
      • Inflammatory bowel disease
      • Hyperthyroidism/hypothyroidism
Stepwise work up — poor control

1. Review previous work up and therapy
2. Determine whether insulin is outdated, has been shaken, diluted, frozen, heated;
3. Review that correct syringes are being used
4. Assess owner’s method of drawing up insulin
5. Review diet and exercise regime
6. Increase insulin dosage every 5-7 days until 1 IU/kg q12h
7. Generate glucose curves to assess for Somogyi phenomenon
8. Diagnostic work up for diseases causing insulin resistance
9. Switch insulin type
Switching insulin types

- Start as if newly diagnosed, based on recommended doses listed
- Ensure diet and exercise strategies are adequate
- If transitioning due to inability to obtain current insulin type (for example Caninsulin backorder), dose of new insulin should be 75% of current insulin dose
- Need to reduce further if using an insulin prone to cause hypoglycemia (glargine, detemir)
Diabetic remission

- Resolution of clinical signs, normalization of blood glucose levels and fructosamine without therapy for one month
- Most likely to occur if rapid therapy for DM started early on, to reduce length of glucotoxicity and lipotoxicity
  - Damaging effect of chronic hyperglycemia on beta cells, and effect of increased use of fatty acids by beta cells
- Usually occurs within first 3 months of starting therapy
- Occasionally seen after more than a year
- Viability of beta cells may not fully recover, number of beta cells likely also permanently reduced
  - Pre-diabetic state
- Counsel owners to watch for recurrence of clinical signs
Diabetic remission

- Positive predictors of diabetic remission
  - Strict glycemic control
  - Administration of corticosteroids prior to diagnosis
  - Absence of polyneuropathy
  - Older age
  - Use of glargine

- Negative predictors of diabetic remission
  - Elevated cholesterol
  - Elevated urea and bilirubin
  - Anemia
Diabetic remission

- Predictors not related to remission
  - Glucose concentration
  - Fructosamine concentration
  - Serum concentrations of insulin, glucagon, insulin growth factor-1
  - Age
  - Sex
  - Body weight
  - Renal failure
  - Hyperthyroidism
  - Ketoacidosis
  - Presence of concurrent diseases
Complications of Diabetes Mellitus

- Cataract formation
  - 14% of dogs at diagnosis, 80% at 1.5 years after diagnosis
  - Blindness, anterior uveitis, irreversible
  - Altered osmotic relationship due to accumulation of sorbitol/fructose
  - High risk in dogs with poorly controlled DM
  - Vision can be restored in 80-90% of cases with cataract removal

- Diabetic neuropathy
  - Primarily distal, due to segmental demyelination and remyelination
  - Plantigrade stance, weakness, knuckling, muscle atrophy
  - Only treatment is improved glycemic control

- Chronic pancreatitis, chronic renal failure?
- Recurring infections
- Diabetic ketoacidosis
Prognosis

- Depends on owner commitment
- Mean survival time from diagnosis in dogs is 2-3 years
- Skewed by older population of pets, often succumb to other diseases
- Higher mortality rate in first 6 months, better longevity if stable after 6 months
- May be closer to mean survival time of 5 years if survive the first 6 months
Curves

- Now we will tackle some actual cases and look at BG curves
Questions

- What is the nadir?
- Is the nadir appropriate?
- What is the duration?
- Is the duration adequate?
- What are your recommendations?
Questions

- What is the nadir?
  - 22 mol/L
- Is the nadir appropriate?
  - No
- What is the duration?
  - 12 hours
- Is the duration adequate?
  - Yes
- What are your recommendations?
  - Increase dose
Curves
Questions

- What is the nadir?
  - 17 mmol/L

- Is the nadir appropriate?
  - No

- What is the duration?
  - 12 hour

- Is the duration adequate?
  - Yes

- What are your recommendations?
  - Increase dose
Curves
Questions

- What is the nadir?
  - 9 mmol/L
- Is the nadir appropriate?
  - Yes
- What is the duration?
  - 12 hours
- Is the duration adequate?
  - Yes
- What are your recommendations?
  - No change if acceptable clinical signs
Curves
Questions

- What are your recommendations?
  - Base on clinical signs and fructosamine
Curves
Questions

- What is the nadir?
  - 14 mmol/L
- Is the nadir appropriate?
  - No
- What is the duration?
  - > 12 hours
- Is the duration adequate?
  - Incomplete curve
- What are your recommendations?
  - 24 hour curve, consider q24h insulin, increase dose
Questions

- What is the nadir?
  - 3 mmol/L

- Is the nadir appropriate?
  - No

- What is the duration?
  - 12 hours

- Is the duration adequate?
  - Yes

- What are your recommendations?
  - Decrease dose by 25%, curve the following day
Questions

- What is the nadir?
  - 5 mmol/L

- Is the nadir appropriate?
  - Yes

- What is the duration?
  - 12 hours

- Is the duration adequate?
  - Yes

- What are your recommendations?
  - Depending on clinical signs; may need insulin change
Curves
Questions

- What is the nadir?
  - 7.5 mmol/L
- Is the nadir appropriate?
  - Yes
- What is the duration?
  - 12 hours
- Is the duration adequate?
  - Yes
- What are your recommendations?
  - No change
Cases - Snooky

- 4 yo MN Miniature Poodle
- Diagnosed with DM in October 2010
- Initial diagnostics normal other than hyperglycemia and glucosuria
- Started on Caninsulin 2 units q 12 h
- No change in PU/PD
- Glucose curve revealed hyperglycemia, Caninsulin increased to 3 units q12h
- No change in PU/PD
Cases - Snooky
Cases - Snooky

- Nadir too high
- Duration inappropriate
- Options:
  - Increase dose
  - Give three times daily
  - Change insulin
- Elected to change insulins given short duration of Caninsulin, started on 3 IU q12h of NPH
Cases - Snooky
Cases - Snooky

- Nadir too high
- Duration appropriate
- Options:
  - Increase dose
- Elected to increase NPH, increased to 5 IU q12h
Cases - Snooky
Cases - Snooky

- Appropriate nadir and duration
- Clinical signs resolved
- Appropriate diet and exercise regime
- Continue to monitor
Cases - Bruno

- Additional detailed history from owner
- Has 3 other cats, two of which are on free choice food
- Third cat has special diet, however Bruiser often chases him away and eats his food
- He is steadily gaining weight
- He used to play all the time, since diagnosis the owner does not play with him due to his disease, tries to keep him quiet
Cases - Bruno

- Additional diagnostic testing
- Repeat blood work (4 months after diagnosis) showed hyperglycemia and glucosuria, remainder normal
- Urine culture negative
- Remainder of diagnostic testing normal
Cases - Bruno

- Potential causes of insulin resistance in Bruno
  - Obesity
  - Inappropriate diet and feeding
  - Lack of exercise

- How well is our insulin working currently?
  - Glucose curve
Curves
Cases - Bruno

- Glucose curve reveals a Somogyi phenomenon

- Plan for Bruno
  - Reduce insulin by 25%, from 6 IU q12h to 4 IU q12h
  - Glucose curve the following day
  - May need a switch in insulin depending on response, next choice would be glargine
Cases - Kirby

- 9 yo MN Bichon Frise
- Diagnosed with DM November 2010
- Initial diagnostics revealed hyperglycemia, lipemic serum, glucosuria
- Started on Caninsulin 3 units q 12 h
- No change in PU/PD
- Glucose curve:
Cases - Kirby
Cases - Kirby

- Switched to Caninsulin 4 units q 12 h
- No change in PU/PD
- Fructosamine 689 umol/L
- Glucose curve:
Cases - Kirby
Cases - Kirby

- Switched NPH 2 units q 12 h
- No change in PU/PD
- Glucose curve:
Cases - Kirby
Cases - Kirby

- Switched NPH 4 units q 12 h
- No change in PU/PD
- Fructosamine 700 umol/L
- Glucose curve:
Cases - Kirby
Cases - Kirby

- Appropriate diet, insulin technique, exercise, no evidence of concurrent disease
- Owners contemplating euthanasia
- Switched detemir 1 unit q 12 h
- Marked improvement in PU/PD
- Glucose curve:
Cases - Kirby

![Graph showing daily cases of Kirby]

- X-axis: Time of Day (8:00 AM to 8:00 PM)
- Y-axis: Cases (0 to 35)

The graph illustrates the number of cases for Kirby throughout the day, with a peak in the evening.
Cases - Kirby

- Increased detemir to 2 units q 12 h
- Owners very happy with current clinical status
- Fructosamine 467 umol/L
- Glucose curve:
Cases - Kirby

![Graph showing cases over time for Kirby]
Cases - Kirby

- Not perfect control due to hyperglycemia prior to insulin administration
- Reasonable control, especially for a refractory case with no obvious cause for insulin resistance
Cases - Precious

- 12 yo 5 kg MN Miniature Poodle
- Diagnosed with DM in September 2010
- Initial diagnostics revealed hyperglycemia, moderate increase in ALP and ALT, lipemic serum, glucosuria, proteinuria
- Started on Caninsulin 1 unit q 12 h
- No change in PU/PD
- Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 2 units q12h
- No change in PU/PD
Cases - Precious

- Increased Caninsulin to 3 units q 12 h
- No change in PU/PD
- Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 4 units q12h
- No change in PU/PD
- Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 5 units q12h
- No change in PU/PD
Cases - Precious

- Increased Caninsulin to 6 units q 12 h
- No change in PU/PD
- Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 7 units q12h
- No change in PU/PD
- Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 8 units q12h
- No change in PU/PD
- Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 9 units q12h
- No change in PU/PD
Cases - Precious
Cases - Precious

- Level of insulin would indicate insulin resistance
- Repeat blood work revealed stable elevation in ALP, ALT, proteinuria
- Urine culture negative
- Mild dental disease
- Thoracic radiographs normal
- Abdominal ultrasound:
Cases - Precious
Cases - Precious

- Right adrenal mass present
- Diagnosed as functional adrenal tumour with provocative testing
- Increased glucocorticoid from functional adrenal tumour causing insulin resistance
- Recommended therapy for right adrenal mass
Questions?