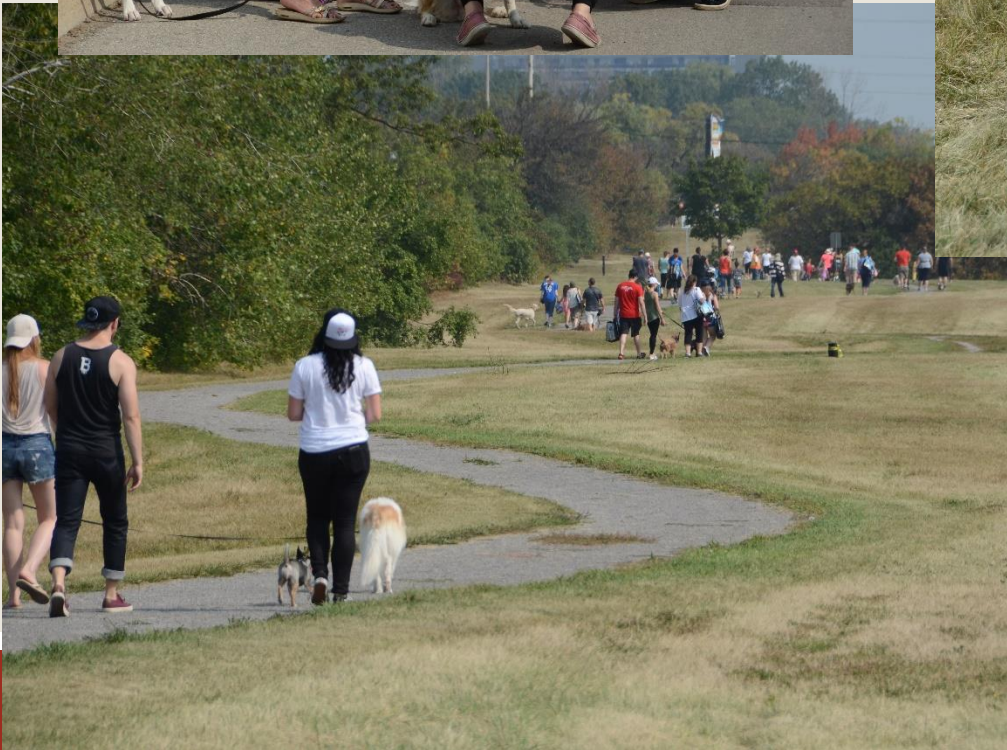




INSULIN THERAPY OPTIONS AND CASE STUDIES OF DIABETIC CATS AND DOGS

MOVEH WOOF WALK 2017



Overview

- Pathophysiology
- Diagnosis
- Treatment
- Follow-up care, in-clinic & at-home monitoring
- Case examples

Notes available:

www.vetemergency.ca

Pathophysiology

- Insulin is produced by the beta cells within the islets of Langerhans in the pancreas
- Lack of insulin results in the inability to uptake glucose from the blood into cells
- Result is hyperglycemia with glucose-starved cells
- Renal tubular threshold for glucose is exceeded, resulting in polyuria due to glucosuria
- Polyphagia due to starvation of cells and inability of glucose to enter satiety centre

Diagnosis

- Presence of significant hyperglycemia with glucosuria
- 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 diabetes mellitus in complicated cases

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

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

Insulin Therapy



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 diabetes mellitus may recur

Treatment Strategies

- Must be flexible
 - Kinetics vary markedly among species & individuals
- Duration of action of most insulins typically shorter in cats than dogs
 - Except short-acting insulin
 - Same duration in both

Insulin

- Should be started immediately in all dogs and probably all cats
- Almost all dogs and most cats 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 blood glucose
- Realistic goal = eliminate clinical signs

Insulin Products

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

- Fall into 3 categories
 - ▣ Short-acting
 - ▣ Intermediate-acting
 - ▣ Long-acting

Short Acting Insulin

- Reserved for diabetic ketoacidosis, clinically ill patients and occasionally for combination dosing
- Three methods of administration
 - ▣ Low-dose intravenous infusion technique
 - ▣ Intermittent intramuscular and subcutaneous technique
- Dosing schemes vary
 - ▣ CRI - 1.1 to 2.2 IU/kg/day
 - ▣ Intermittent IM – 0.1 to 0.2 IU/kg q1-4 hours
 - ▣ Intermittent SQ – 0.25 IU/kg q4-6 hours
 - Adjust based on serial measurements of blood glucose concentration

Short Acting Insulin

- Regular / Humulin R (U-100) is the short acting insulin of choice
- Lispro / Humalog (U-100) has a similar action to Humulin R
 - No benefit over Humulin R when giving intravenously
 - Less chance of hypoglycemia when given subcutaneously, so may be a better choice in combination with long acting insulin for long term use

Short Acting Insulin

- There are reports of using glargine insulin intravenously or intramuscularly to stabilize a clinically ill patient or a patient with diabetic ketoacidosis (J. Rand, 2012)
- Not reported by other internists or criticalists
- Insufficient data to recommend use, regular insulin should be used



Intermediate Acting Insulins

Caninsulin U-40

- Good first choice in dogs
- Good third choice in cats
- Porcine based

Onset of action	1/2 - 2 hours (dogs) <1 hour (cats)
Maximum effect	3 hours (dogs) 3 – 5 hours (cats)
Duration of action	8 hours (dogs) 8 – 12 hours (cats)

Caninsulin

- Twice-daily administration usually necessary
- Occasionally three times daily dosing required
- **Dogs** starting dose of 0.25-0.5 IU/kg lean weight twice daily
- **Cats** starting dose of 0.25-0.5 IU/kg lean weight usually twice daily
 - ▣ Can use pre-treatment blood glucose as a guide, use lower end of dosing if blood glucose is < 20 mmol/L

Caninsulin

- Able to dilute if needed
- Only available from vet clinics – encourages monitoring
- Previous concern with back-order resolved

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)

NPH U-100

- Good first choice in dogs
- Duration of action usually too short in cats
- Recombinant human insulin

Onset of action	1/2 - 2 hours (dogs and cats)
Maximum effect	2 - 10 hours (dogs) 2 - 9 hours (cats)
Duration of action	6 - 18 hours (dogs) 2 - 9 hours (cats)

NPH

- Twice-daily administration usually necessary
- Starting dose for **dogs**:
 - ▣ Some clinicians use starting dose of 0.25 IU/kg
 - ▣ Others recommend 0.5 IU/kg if BG >20 mmol/L and 0.25 IU/kg if <20 mmol/L
 - ▣ Both are acceptable protocols
 - ▣ Always round down to closest unit



Long Acting Insulins

Glargine U-100

- At acidic pH glargine insulin is in solution
- At the relatively neutral pH of SQ tissues, micro-precipitates form
 - Relatively constant systemic absorption rate
 - Up to 24 hours without significant peak
 - Cannot mix or dilute as micro-precipitates depend on solution's acidity

Onset of action 1 - 2 (cats)

Maximum effect 2 – 9 hours (cats)

Duration of action 8 – 16 hours (cats)

Glargine

- Good first choice in cats
- Glargine not recommended in dogs
 - ▣ Published data revealed good glycemic control in only 50% of dogs; concluded that other insulins have a better success rate
- Anecdotal reports claim that glargine seems ineffective in treating diabetic dogs
- Long duration of action could induce hypoglycemia in dogs

Glargine

- **Cats:** Very conservative starting dose, safer once daily at start however most will require twice daily
- 0.25-0.5 IU/**CAT** either once or twice daily
- More aggressive dosing at some institutions
 - ▣ 0.5 IU/**kg** lean weight if blood glucose \geq 20 mmol/l or 0.25/**kg** if blood glucose is $<$ 20 mmol/l
- Should not change dose in first week, other than reduction if hypoglycemia

ProZinc U-40

- Developed to prolong the effects of regular insulin
- Long-acting recombinant human insulin
- Contains insulin, zinc, protamine (fish protein)
- Forms poorly soluble precipitates which extends duration

Onset of action	1 - 4 (cats)
Maximum effect	4 – 12 hours (cats)
Duration of action	12 – 24 hours (cats)

ProZinc

Cats:

- Starting dose 0.2-0.5 IU/kg once daily
- 25% cats successfully managed with once-daily injections of ProZinc
- Now available in Canada
- Cannot dilute, always round down

ProZinc

- No studies evaluating ProZinc insulin in dogs
- Long-acting insulin so not recommended as a first line choice in diabetic dogs
 - ▣ Duration of action likely too long and risk of causing hypoglycemic episodes
 - ▣ The manufacturers of ProZinc report currently investigating its use in dogs
 - May become viable option for management of diabetic dogs in future

Detemir U-100

- Acylated fatty acid results in reversible binding of insulin to albumin
- Result is slow release of bound fraction, resulting in peakless insulin secretion
- Diluent available from manufacturer, although apparently very hard to obtain in North America

Onset of action	~3 hours (cats)
Maximum effect	8 – 12 hours (cats)
Duration of action	10 – 24 hours (cats)

Detemir

Cats:

- ❑ 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
- ❑ Starting dose of 0.25 IU/**CAT** once daily, may require twice daily
- ❑ More aggressive protocol of 0.25 IU/kg twice daily

Detemir

Dogs:

- Detemir not recommended in dogs
 - ▣ Lack of published data
- Anecdotal reports claim detemir is 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 q24h)
 - gradual, cautious increase
 - may require twice daily dosing

Degludec – 100 and 200 IU/ml

- Insulin degludec (Tresiba)
 - Similar properties to glargine and detemir
 - Very new insulin, no studies yet in animals

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

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

At Home Monitoring - Curves

- 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 and able to generate accurate at-home serial curves

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, blood glucose should nadir at 5.5-8.5 mmol/L in dogs & 7-10 mmol/L in cats
- Highest blood 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

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
- Currently use not permitted in pets in Canada

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 $\mu\text{mol/L}$ good control
 - 450-550 $\mu\text{mol/L}$ moderate control
 - >600 $\mu\text{mol/L}$ 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 glucosuria indicates the need for further evaluation of blood glucose levels
- High proportion of day with no glucosuria suggests periods of hypoglycemia

Goals

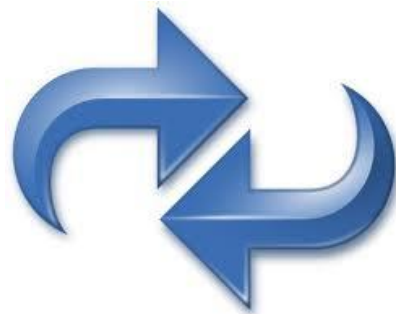
- Marked improvement of, or resolution of, PU/PD and polyphagia
 - ▣ Ensure no hypoglycemia if complete resolution
- Normalization of body weight
- BG between 15 mmol/L pre insulin to 5 mmol/L at nadir
 - ▣ Do not adjust insulin if these BG targets are not met but the animal is clinically doing well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

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

Switching insulin types

- Start as if newly diagnosed, based on recommended doses listed
- Ensure diet and exercise strategies are adequate
- Need for extra caution if using an insulin prone to cause hypoglycemia (glargine, detemir)



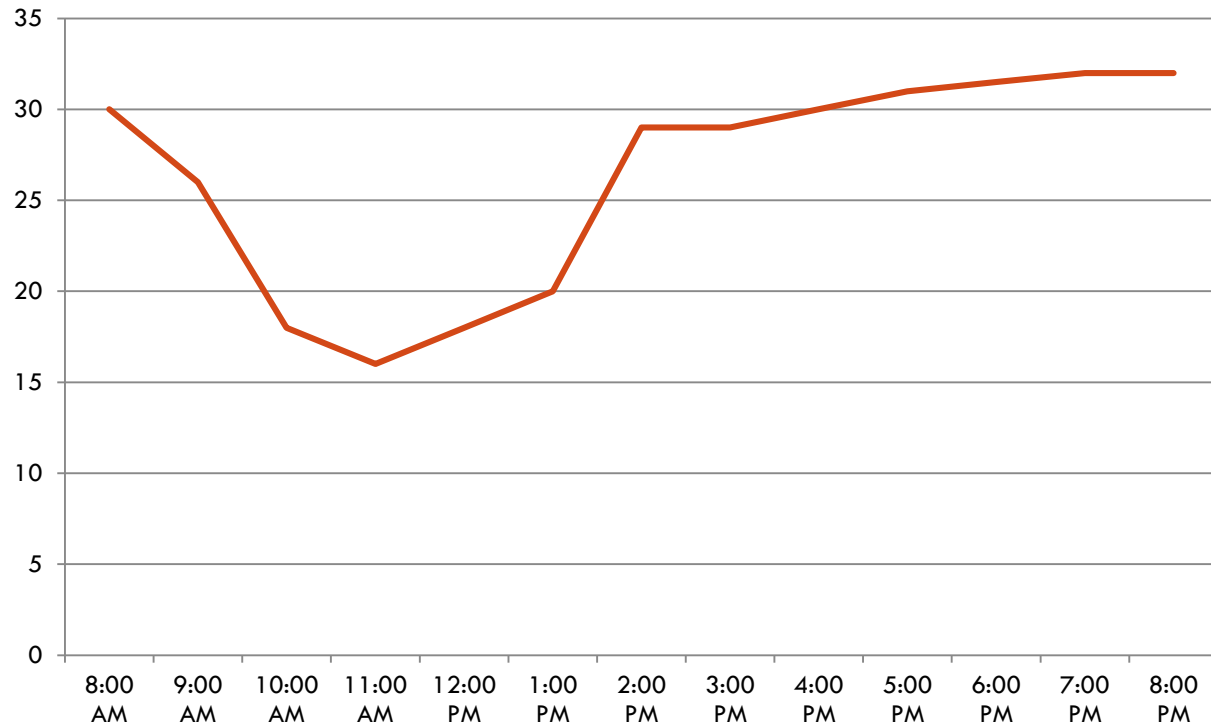
Prognosis

- 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

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

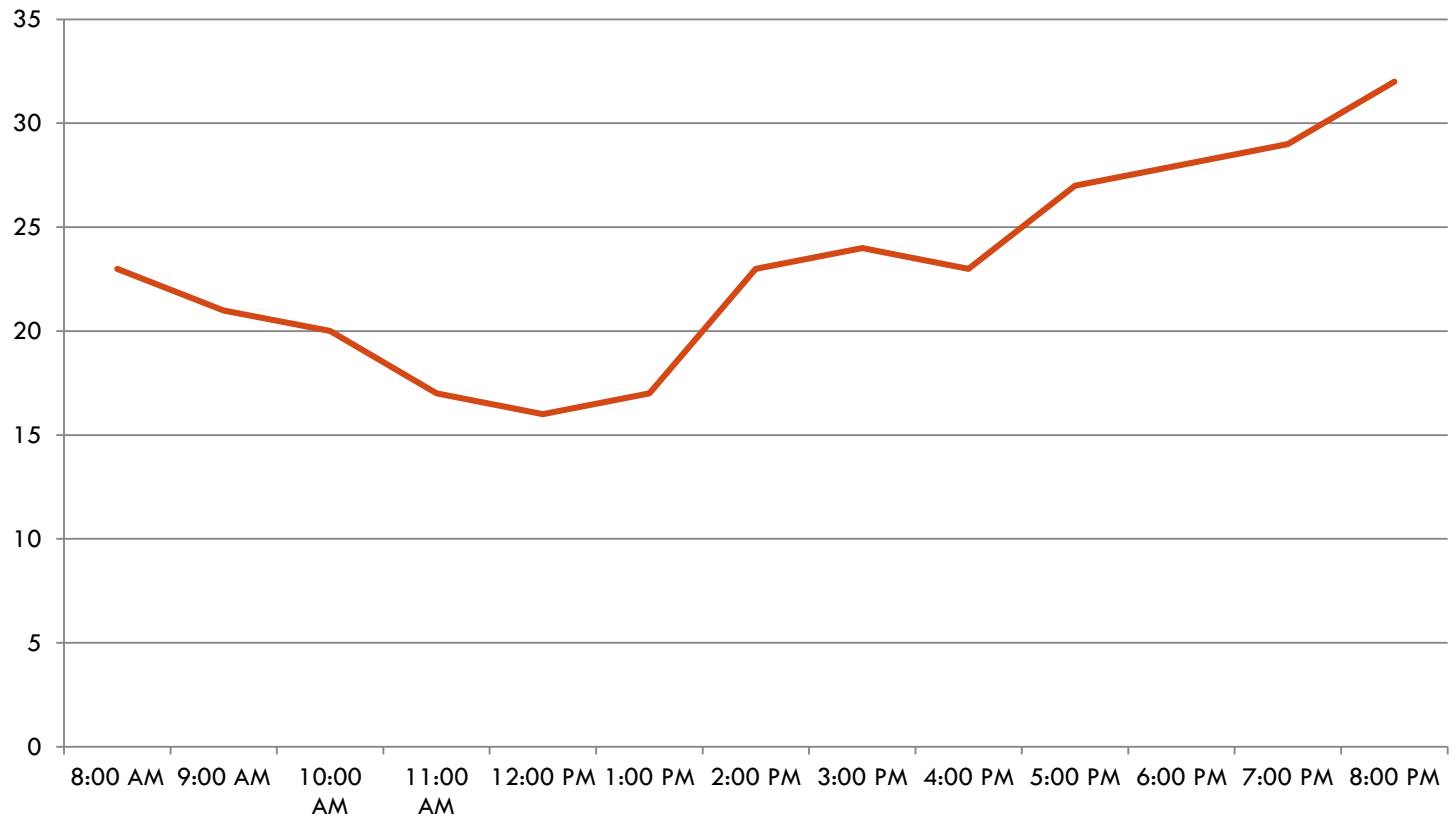
Cases - Snooky



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

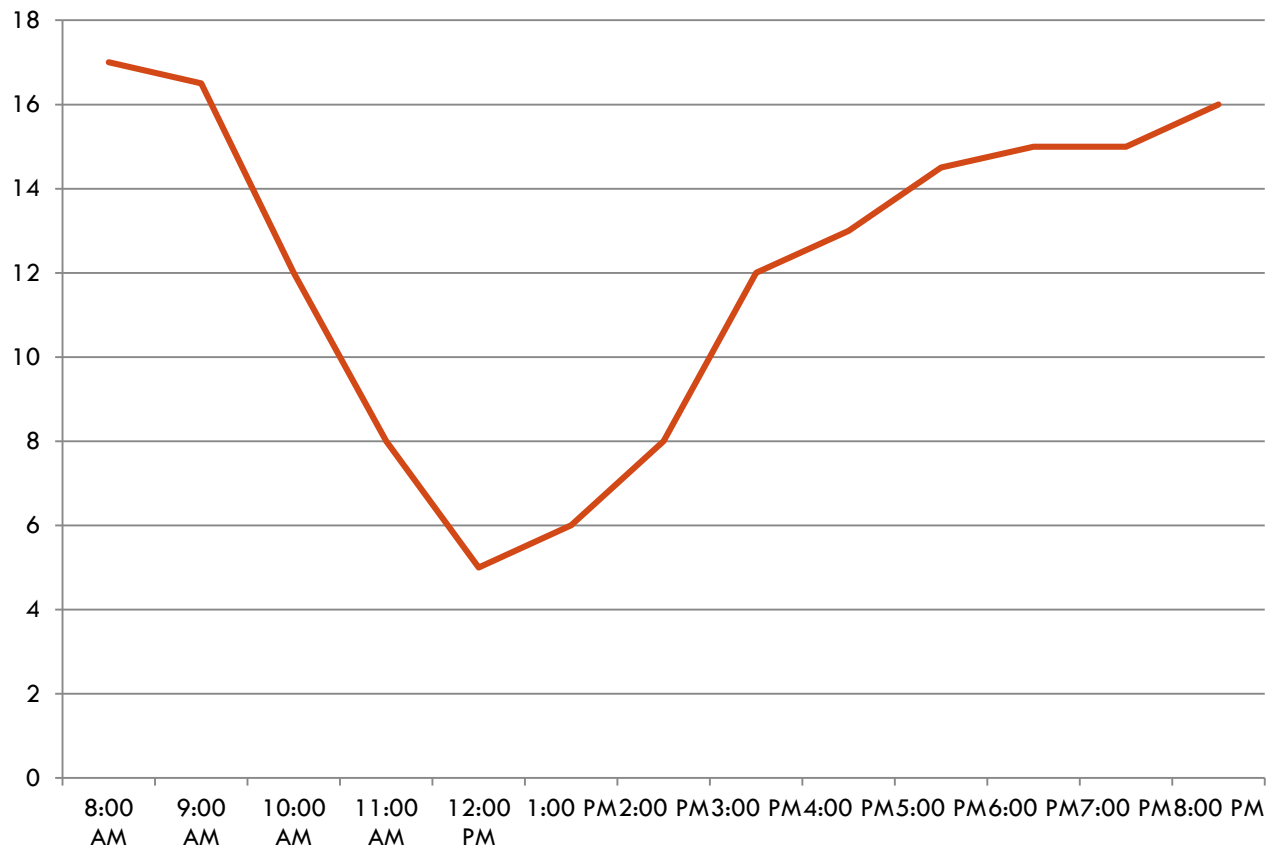
Cases - Snooky



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

- 4 yo MN DSH
- Diagnosed with DM in January 2011
- Initial diagnostics normal other than hyperglycemia and glucosuria
- Started on Caninsulin 7 units q 12 h
- Switched to Hill's w/d diet
- No change in PU/PD
- Regained all weight, now 3 pounds over previous stable weight

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 Bruno 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

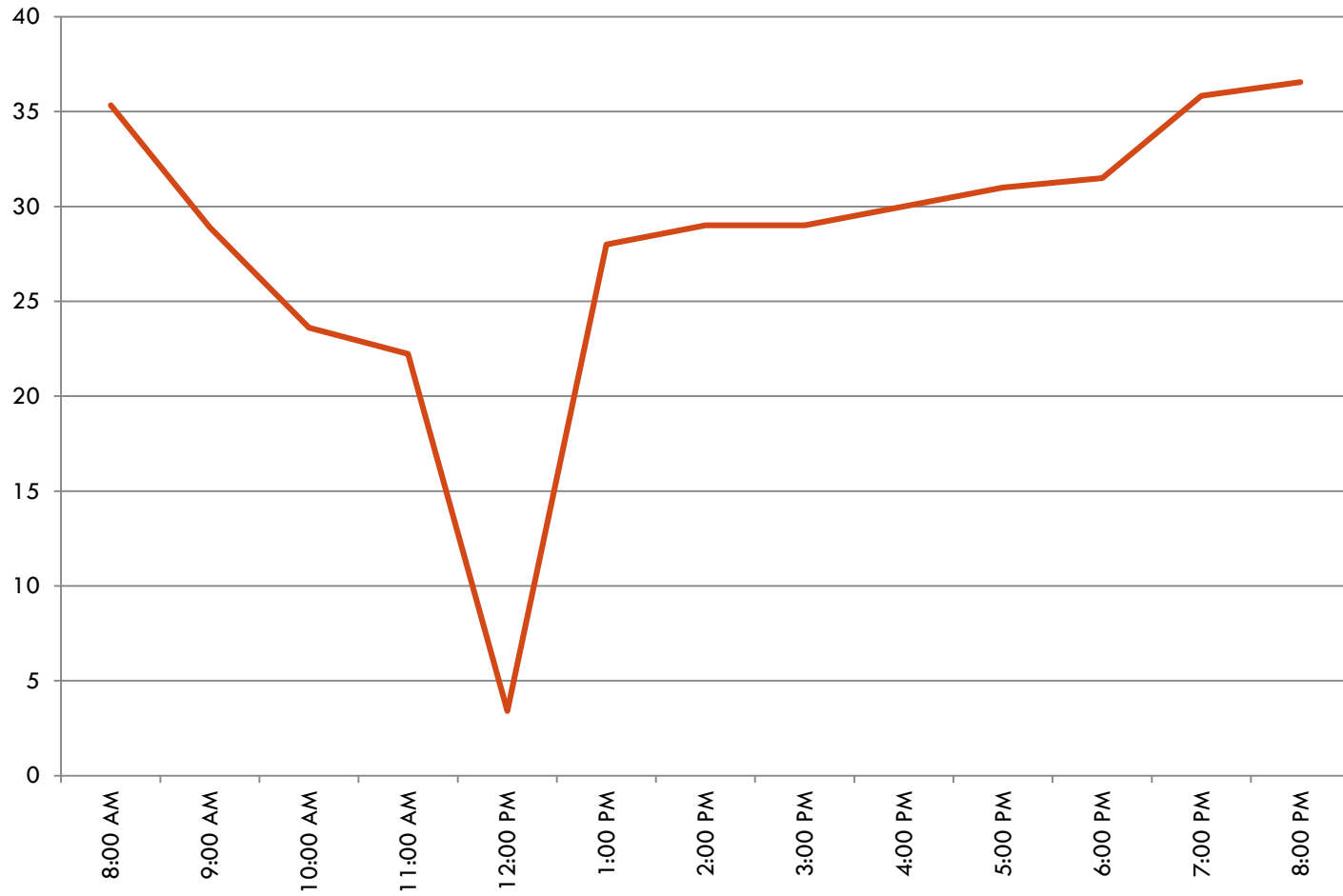
Cases - Bruno

- 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
 - In appropriate diet and feeding
 - Lack of exercise
- How well is our insulin working currently?
 - Glucose curve

Curves



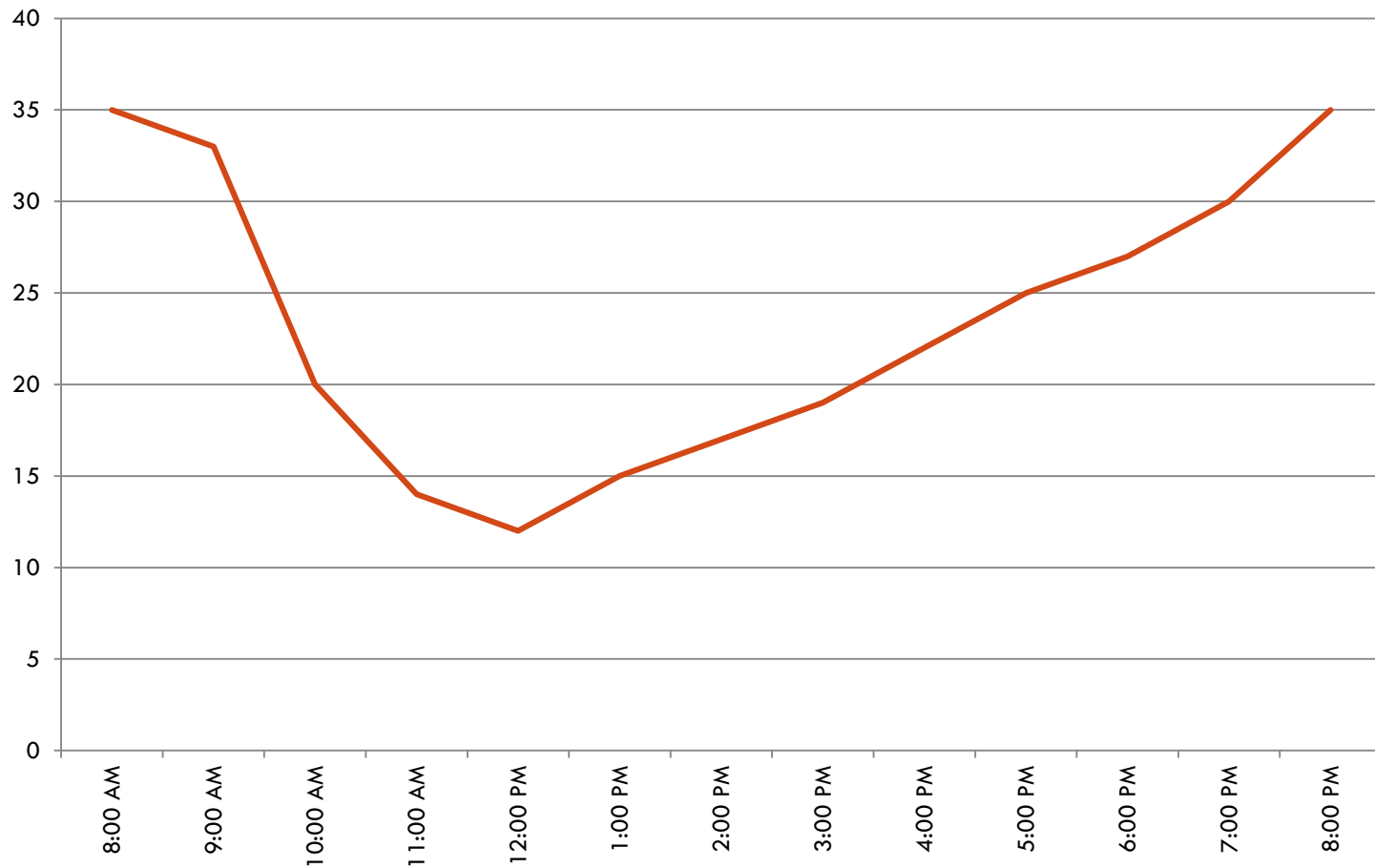
Cases - Bruno

- 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
 - ▣ Address diet and obesity
 - ▣ 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:

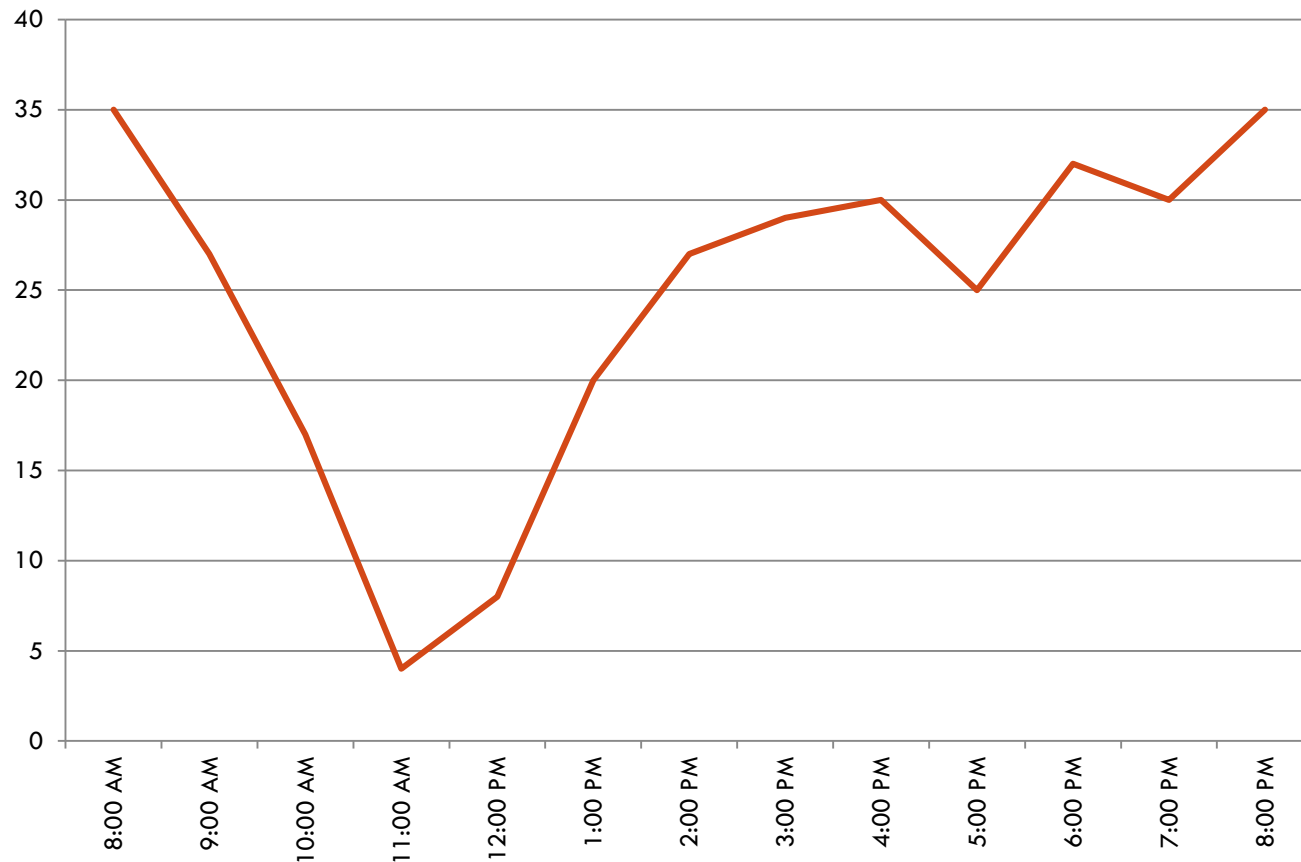
Cases - Kirby



Cases - Kirby

- Switched to Caninsulin 4 units q 12 h
- No change in PU/PD
- Fructosamine 689 $\mu\text{mol/L}$
- Glucose curve:

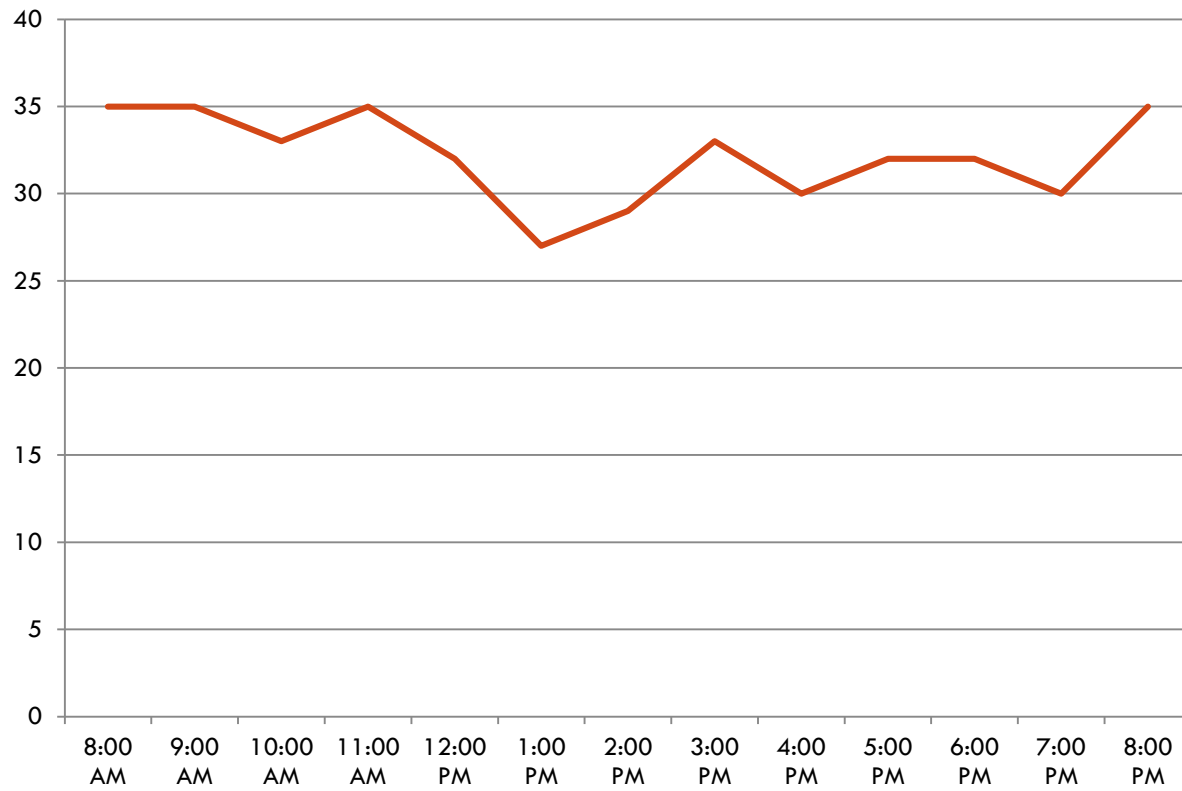
Cases - Kirby



Cases - Kirby

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

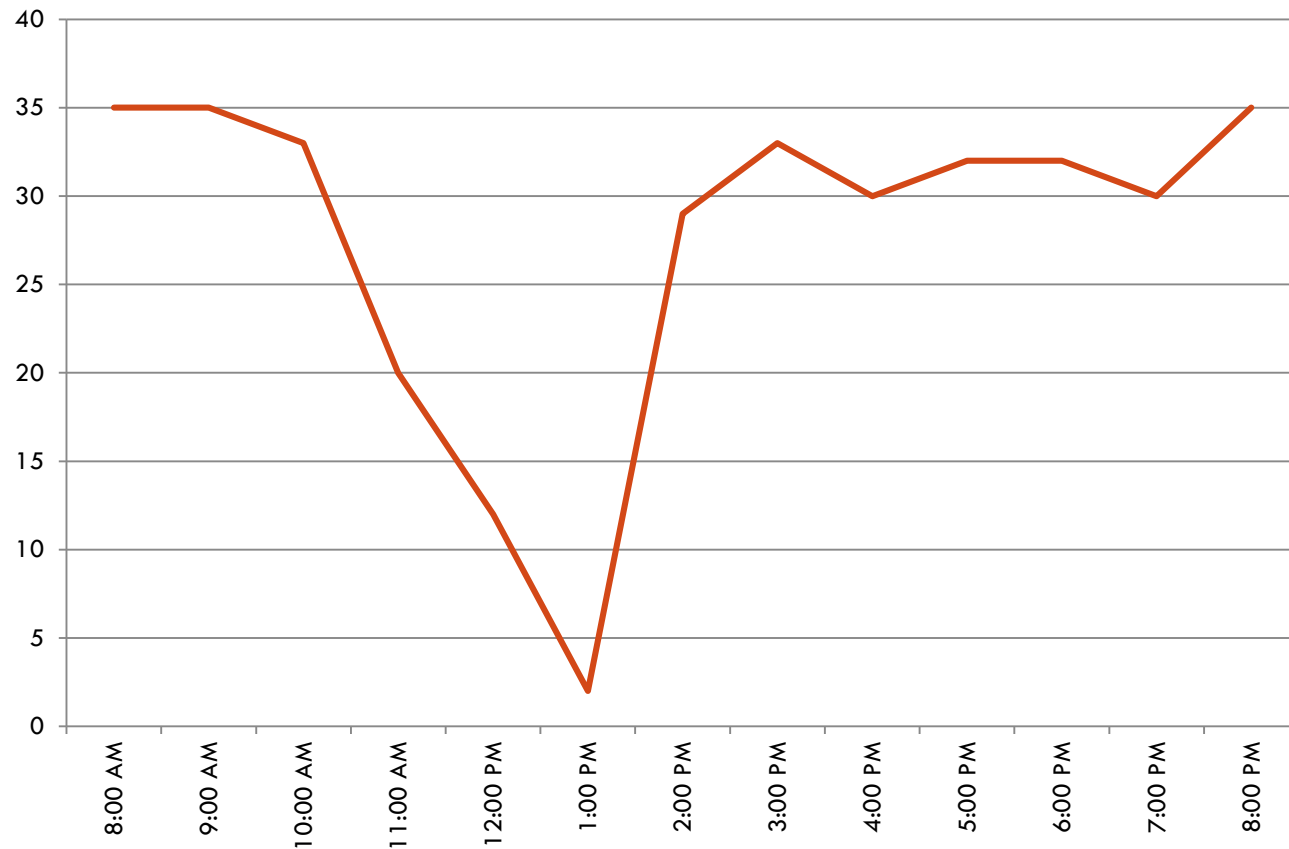
Cases - Kirby



Cases - Kirby

- Switched NPH 3 units q 12 h
- No change in PU/PD
- Fructosamine 700 $\mu\text{mol/L}$
- Glucose curve:

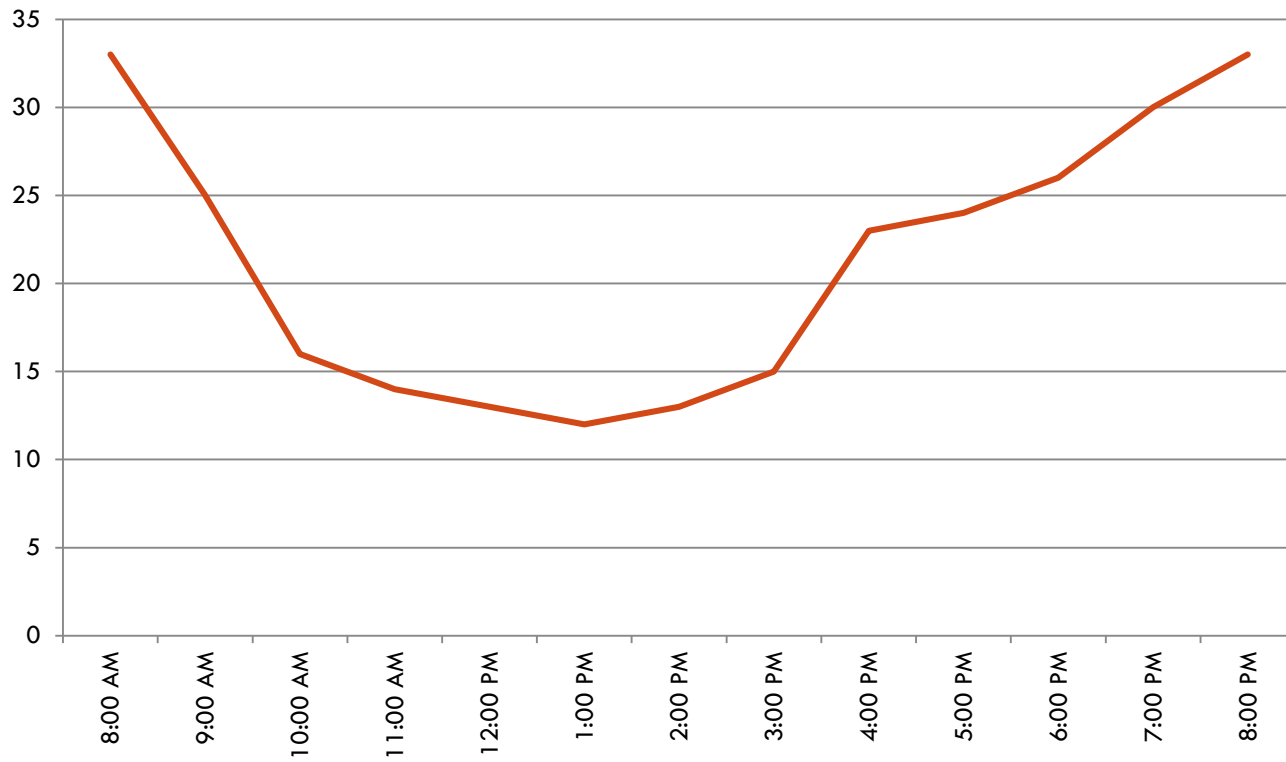
Cases - Kirby



Cases - Kirby

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

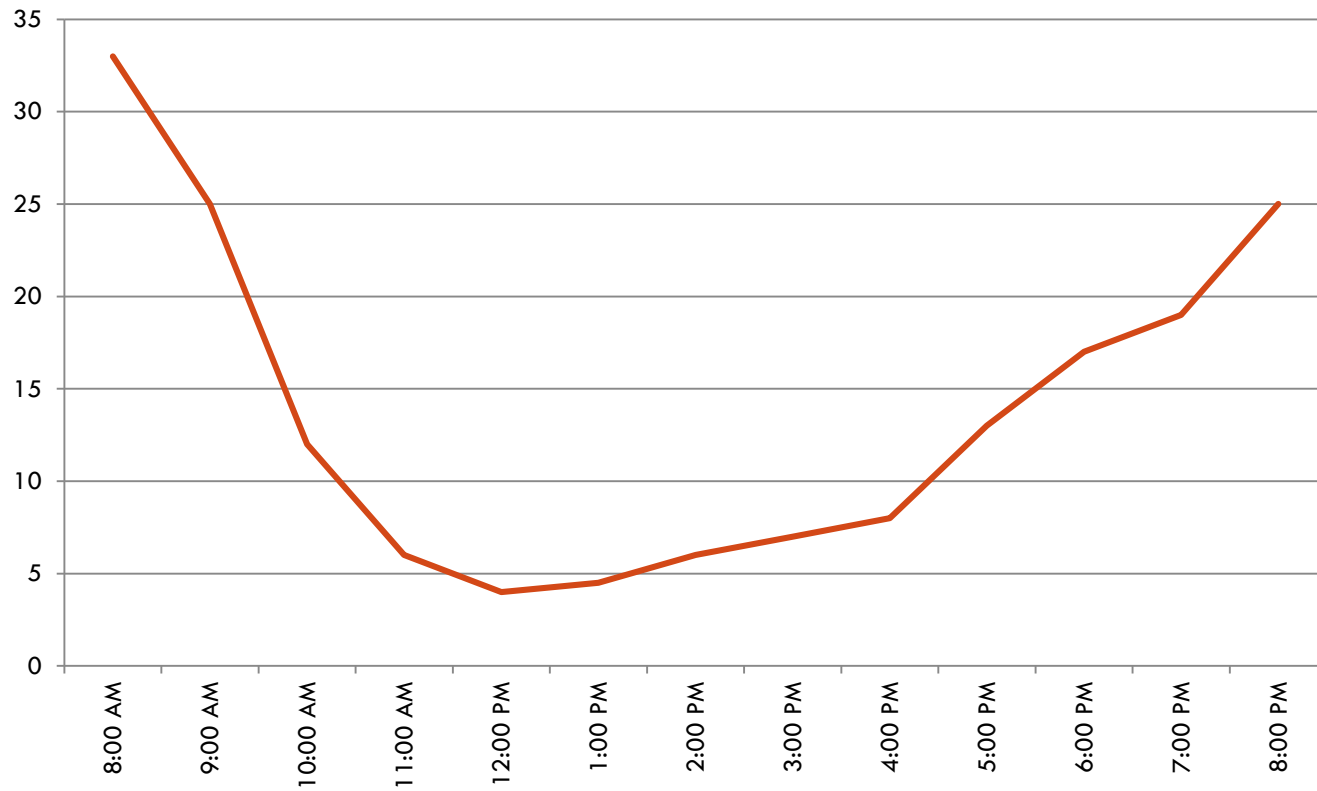
Cases - Kirby



Cases - Kirby

- Increased detemir to 2 units q 12 h
- Owners very happy with current clinical status
- Fructosamine 467 $\mu\text{mol/L}$
- Glucose curve:

Cases - 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

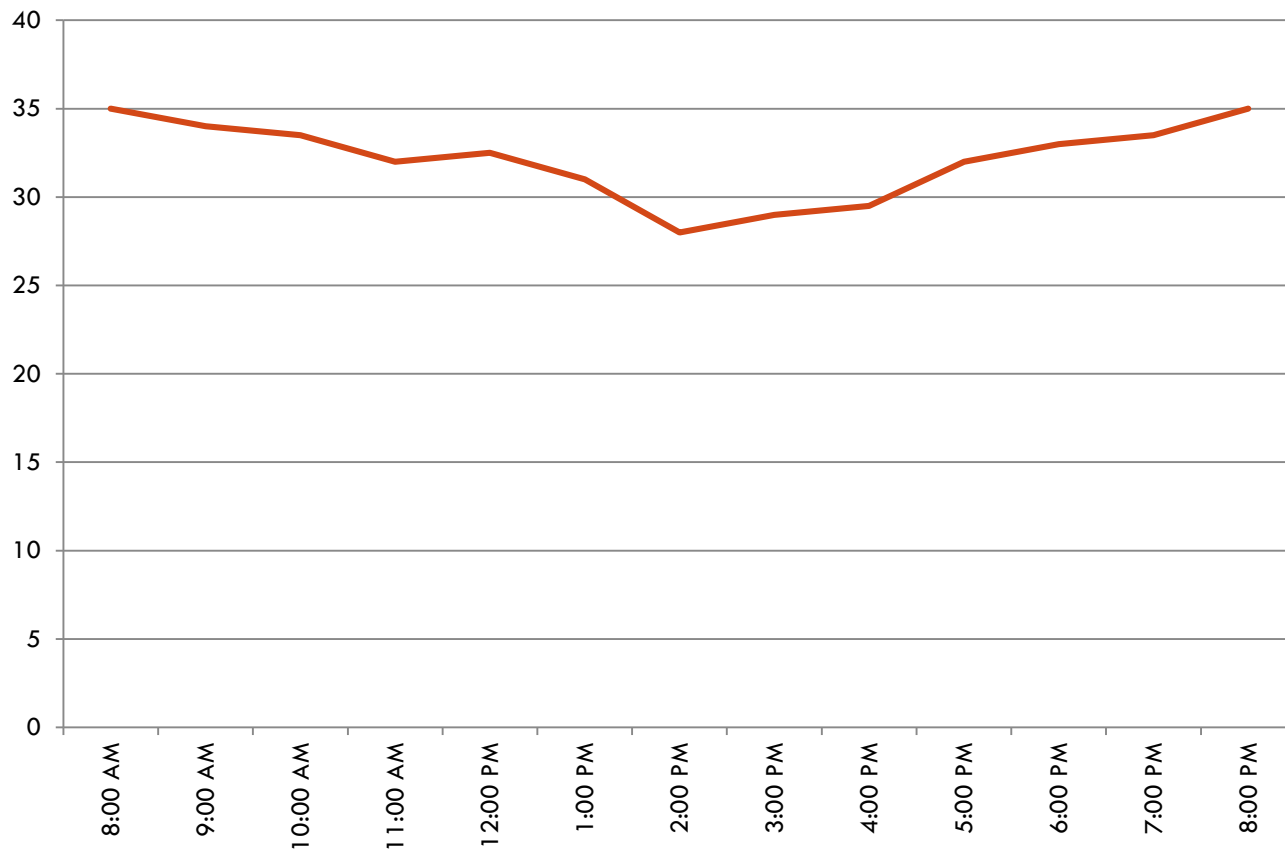
Cases - Precious

- 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?

