Diabetes Mellitus

(Do we really know what's going on?)

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GSLVMA
11.13.2018

Affiliated with:
ANTECH DIAGNOSTICS


BWAHAHAHAHA

Diabetic Types

DOGS

- Type 1
  - Idiopathic
  - Immune-mediated?
- Type 2
  - Rare
  - Associated w/ obesity

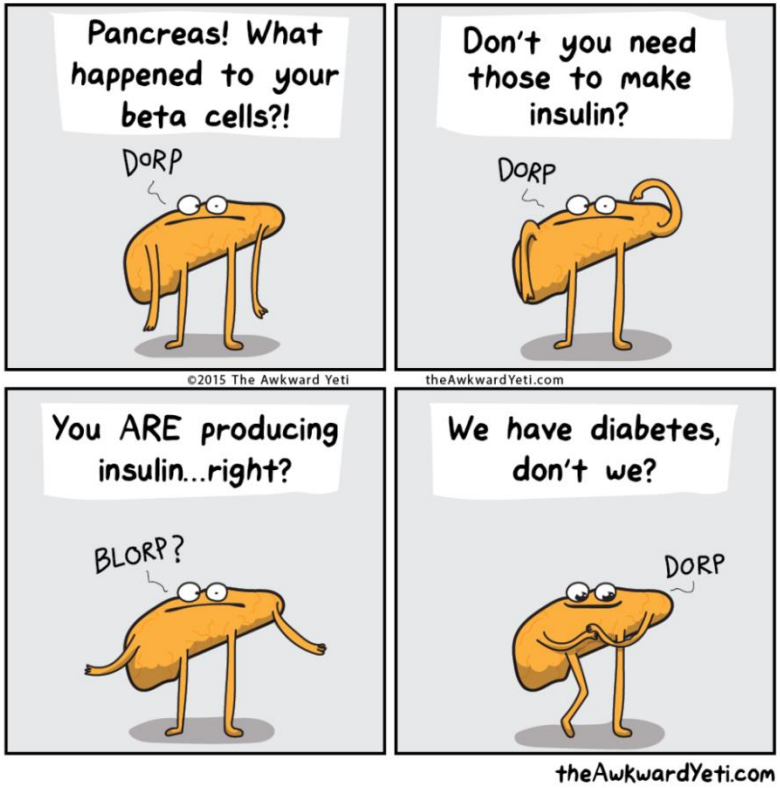
CATS

- Type 1
- Type 2
  - Predominantly

Type	Description
1	B-cell destruction
2	Relative insulin deficiency • Decreased insulin secretion • Peripheral insulin resistance
3	Disease of exocrine pancreas Genetic defects • B-cell function • Insulin action Endocrinopathies • HAC • Hypersomatotropism
Gestational	Increased resistance w/ β-cell dysfunction or loss
Pre-diabetes	??

The Insulins

- NPH (intermediate)
- Vetsulin® (intermediate)
- Prozinc (intermediate)
- Glargine (long)
- Detemir (long)
- Degludec (long)



Goals of Management

- Diabetic remission
- Decrease clinical signs
- Blood glucose
  - DOG: 80-200 mg/dL
  - CAT: 80-300 mg/dL
- Avoiding hypoglycemia
- Fructosamine
- Glycated hemoglobin

Remission predictors

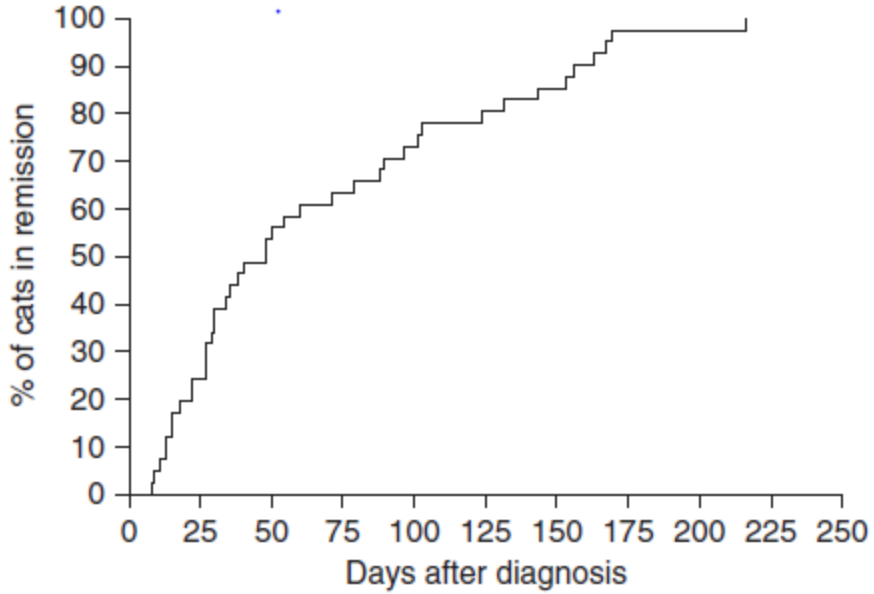
- Positive
  - Well managed DM w/in 6 months
  - Prior glucocorticoid therapy
- Negative
  - Diabetic neuropathy

J Vet Intern Med 2010;24:1314–1321

Predictors of Clinical Remission in Cats with Diabetes Mellitus

E. Zini, M. Hafner, M. Osto, M. Franchini, M. Ackermann, T.A. Lutz, and C.E. Reusch

- Remission 50%
- 48 days until remission
  - Range: 8-216 days
- ~25-30% relapse
- Median remission
  - 114 days (3-3,370 days)
  - 151 day (28-1,180 days)

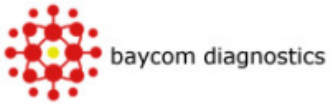


Prediction of Remission

Age, body weight, cholesterol, glucose levels

Diagnostics Available

- Fructosamine
  - Average of previous 1-3 weeks
  - Hypoproteinemia, hyperlipidemia, azotemia may effect results
- Glycated hemoglobin
  - Average of previous 3-4 months



The Rankings…

DOG

- Vetsulin®
- NPH
- Detemir
- Glargine
- ProZinc

Detemir
NPH/Vetsulin®

Unsure where degludec fits in hierarchy

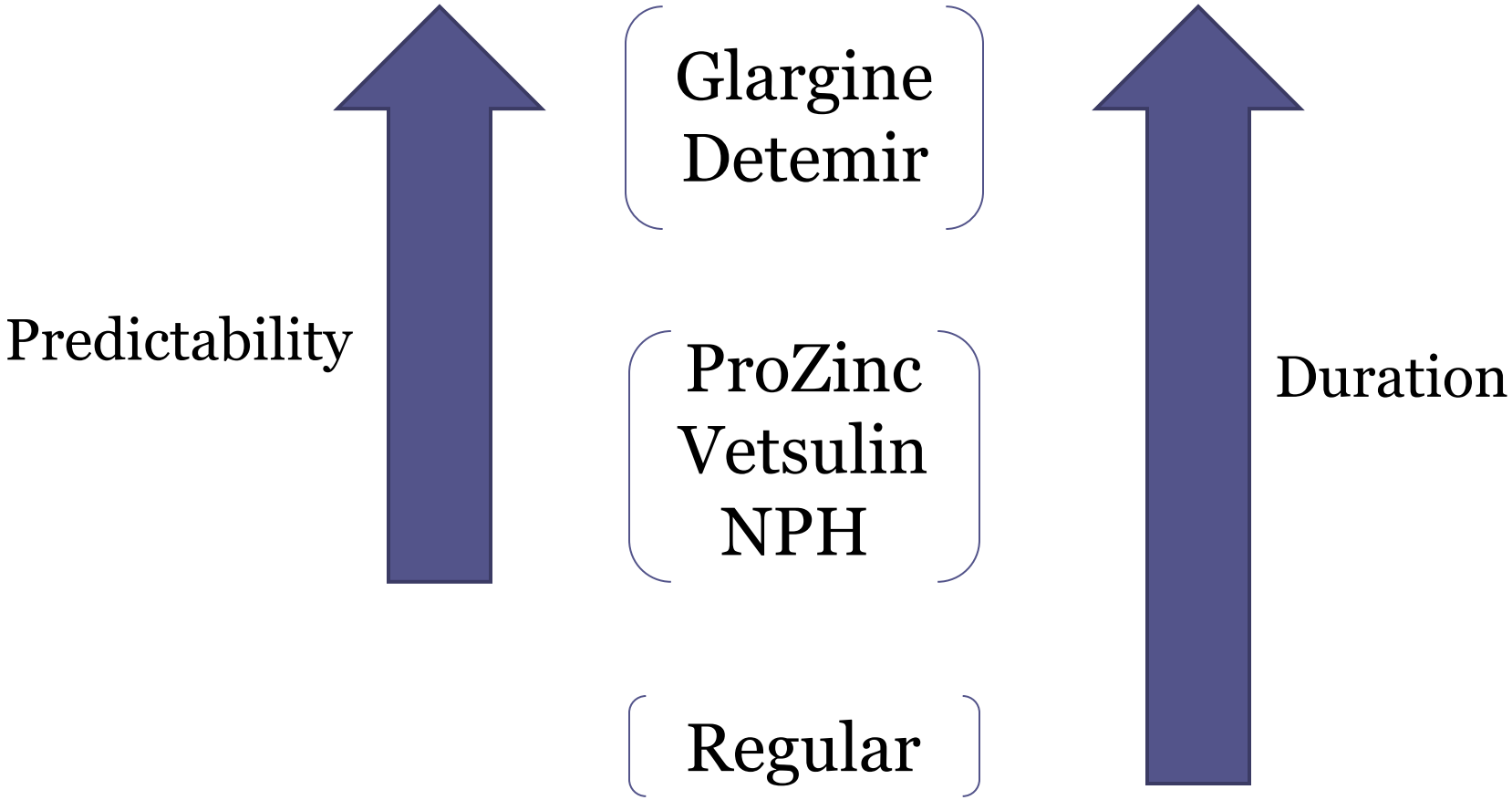
Cost standpoint
Vetsulin/NPH
Detemir
Degludec
Toujeo®/Lantas®

CAT

- Glargine = Prozinc
- Detemir
- Vetsulin®
- NPH

Toujeo®
Prozinc
Lantus®
Detemir
Vetsulin/NPH

Predictability and Duration



The Newbies…

Toujeo® (glargine)

300 U/mL

Tresiba® (degludec)

100 U/mL
200 U/mL

Insulin Breakdown

- Glargine
  - Lantus®
  - Basalglar® (bio-similar)
  - Toujeo®
- Detemir (Levemir®)

Insulin	Concentration (units/mL)	Vial	Pen
Lantus®	100	10 mL	3.0 mL
Basalglar®	100	NA	3.0 mL
Toujeo®	300	NA	1.5 mL
Levemir®	100	10 mL	3.0 mL

$188

$58

$47

$98

~$75

Prices based on www.goodrx.com search (11.2018)

Biosimilar Insulin

- Lantus® ≠ Basalglar®

- Grown in batches
  - Not manufactured by combining chemicals
- Grown using yeast or bacteria cells
- Rigorous QC protocols but there can be changes in cells over time
  - Translate into very small changes from batch to batch
- Manufacturing process is similar to the original BUT not an exact copy
  - Slight differences in the way it could affect a patient

Insulin Degludec

- Tresiba®
- Little bit more like detemir
  - More like ‘super-strong detemir’
- Humans: very long acting
  - Actually given SID at any time (b/c actually reaches a steady state)
- Cats: does not appear long-acting
- Dogs: may be a once a day option

Studies ongoing

ACVIM 2018 Abstract (Chen Gilor):

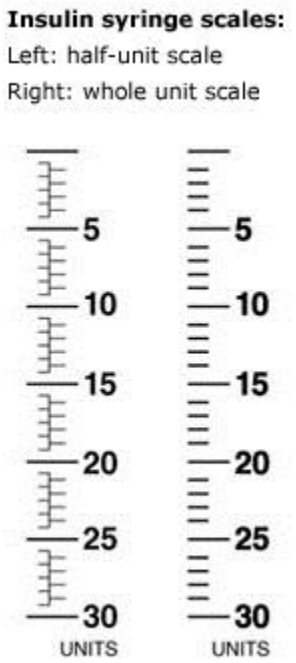
Comparison of Pharmacodynamics between Insulin Degludec and Insulin Glargine 300U/mL in Healthy Cats

- Onset of action was similar
  - Toujeo: 79 ± 27 minutes
  - Tresiba: 60 ± 21 minutes
- End of action
  - Toujeo: 907 ± 135 minutes (15.1 hours)
  - Tresiba: 679 ± 127 minutes (11.3 hours)
- Duration of action
  - Toujeo: 828 ± 130 minutes (13.8 hours)
  - Tresiba: 620 ± 148 minutes (10.3 hours)

BG Curve Variability

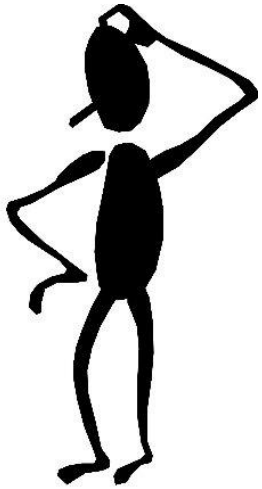
- Injection site
  - Vasculature
  - Temperature
- Injection technique
- Dose inaccuracies (syringes are less accurate)
- Insulin absorption
  - For example: Vetsulin (dog) nadir is 2-12 hours
- External factors
  - Meal composition and size
  - Physical and emotional stress
  - Activity level/exercise

Dose Inaccuracies



- Veterinary medical personnel
- 6 syringes of particular dose
  - U100: 1.0U, 2.5U, 4.0U, 10.0U
  - U40: 1.0U, 2.5U, 4.0U
- Inaccuracy was worse for low doses using U100
  - >60% were inaccurate at 1.0U
- >40% individuals were at least 10% off their personal average on particular dose

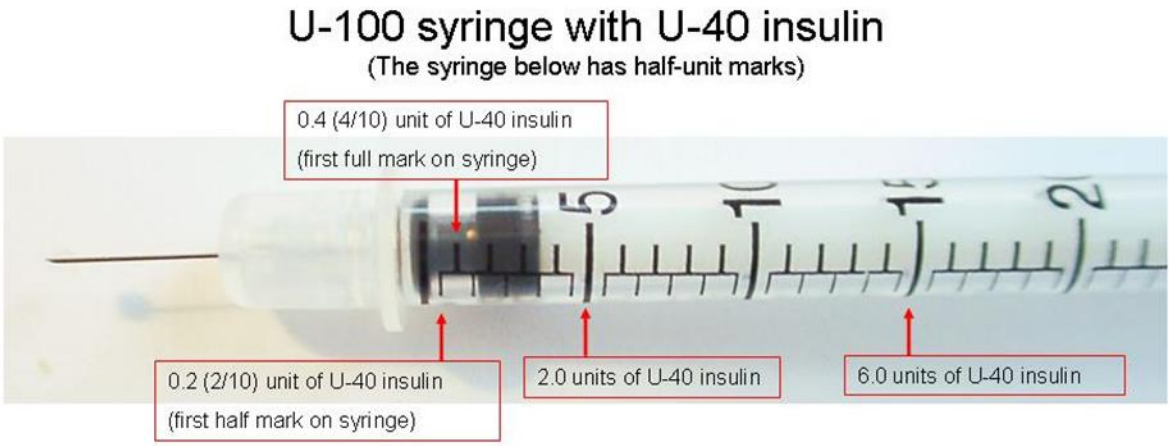
U-40 and U-100 Conversion

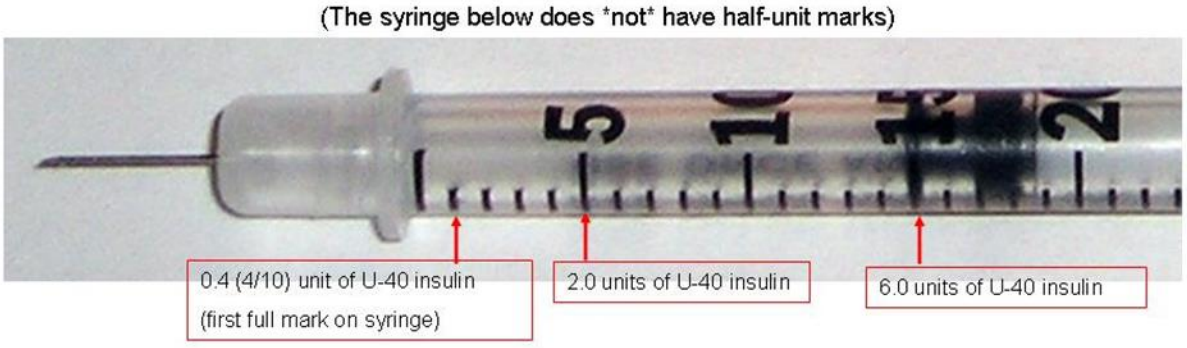


- Why make life more difficult?
  - Confusion
  - Increases risk of mistakes/inaccurate dosing
  - Over-dosing!!!!
  - Risk vs Benefit (IMO – not worth it)

- Conversion
  - U-40 (units) x 2.5 = ‘units’ on U-100 syringe
  - U-100 (units) ÷ 2.5 = ‘units’ on U-40 syringe

U-100 and U-40 Conversions





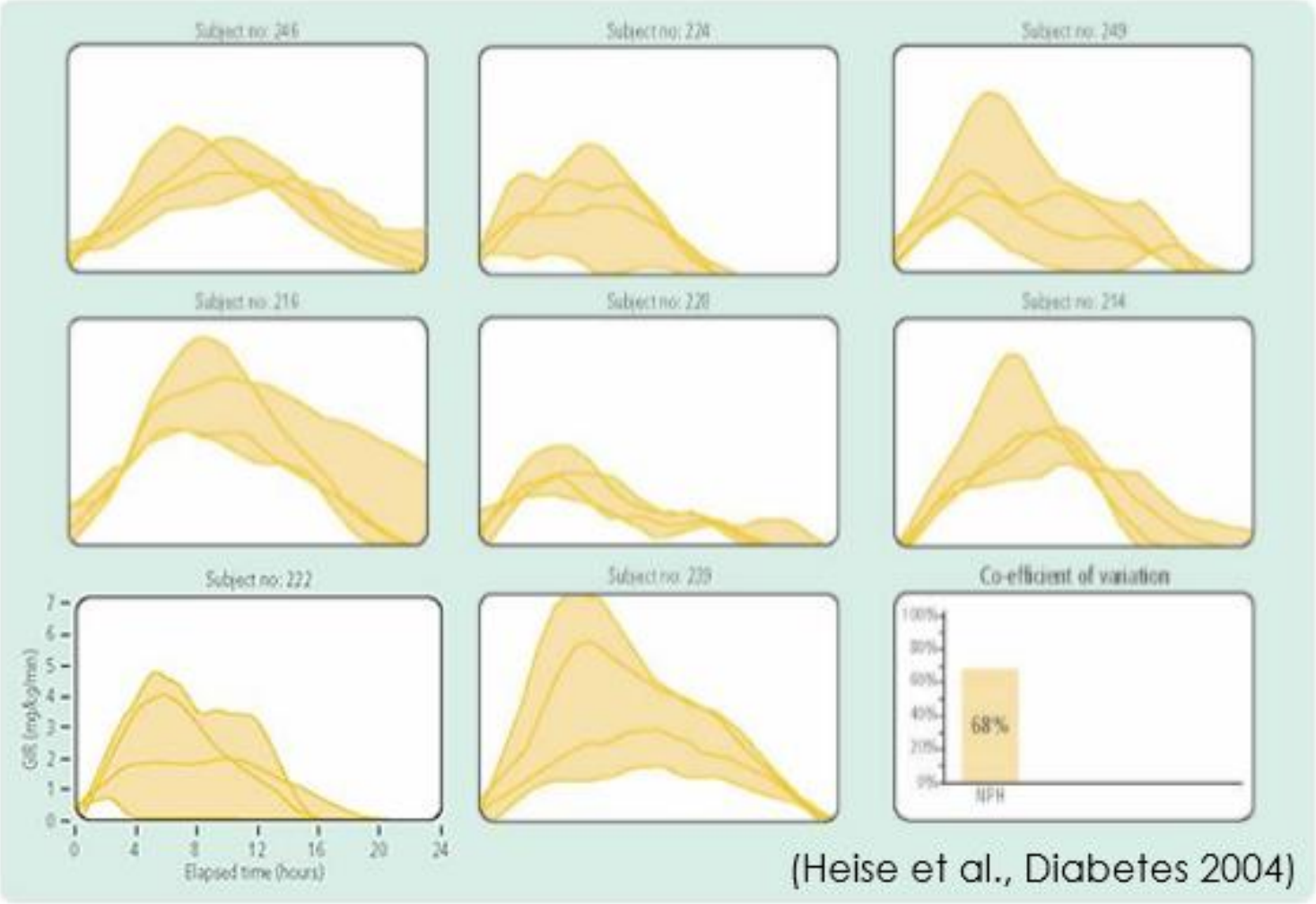
Is there a situation where this may be worthwhile?

I'll entertain the idea but probably wouldn't sleep well at night

Insulin Absorption

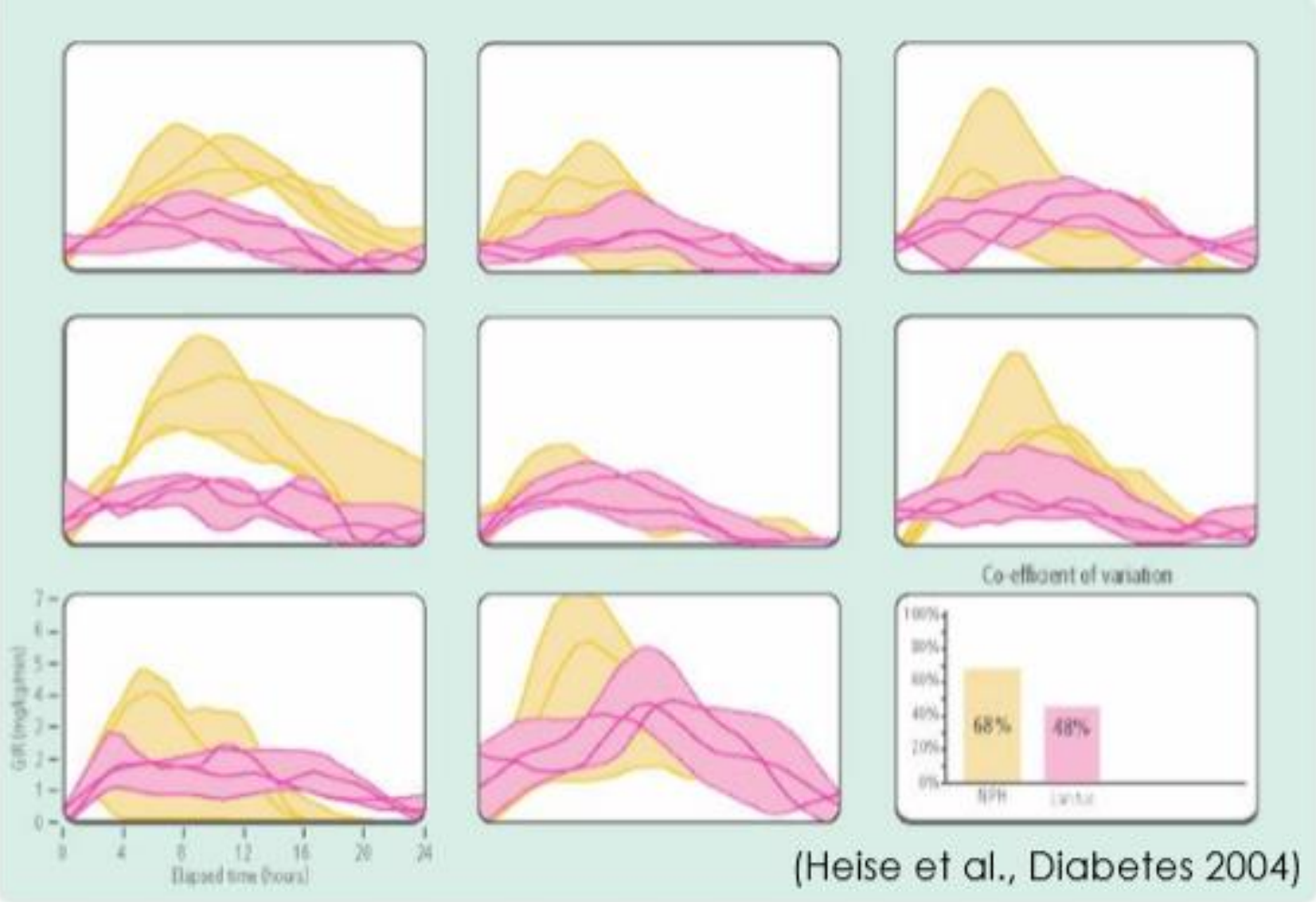
- Human study (bed rest during procedure)
- Different absorptions
- Variable b/t individuals
- Variable w/in same individual
  - Dose to dose
  - Day to day

Pharmacodynamic Variability - NPH

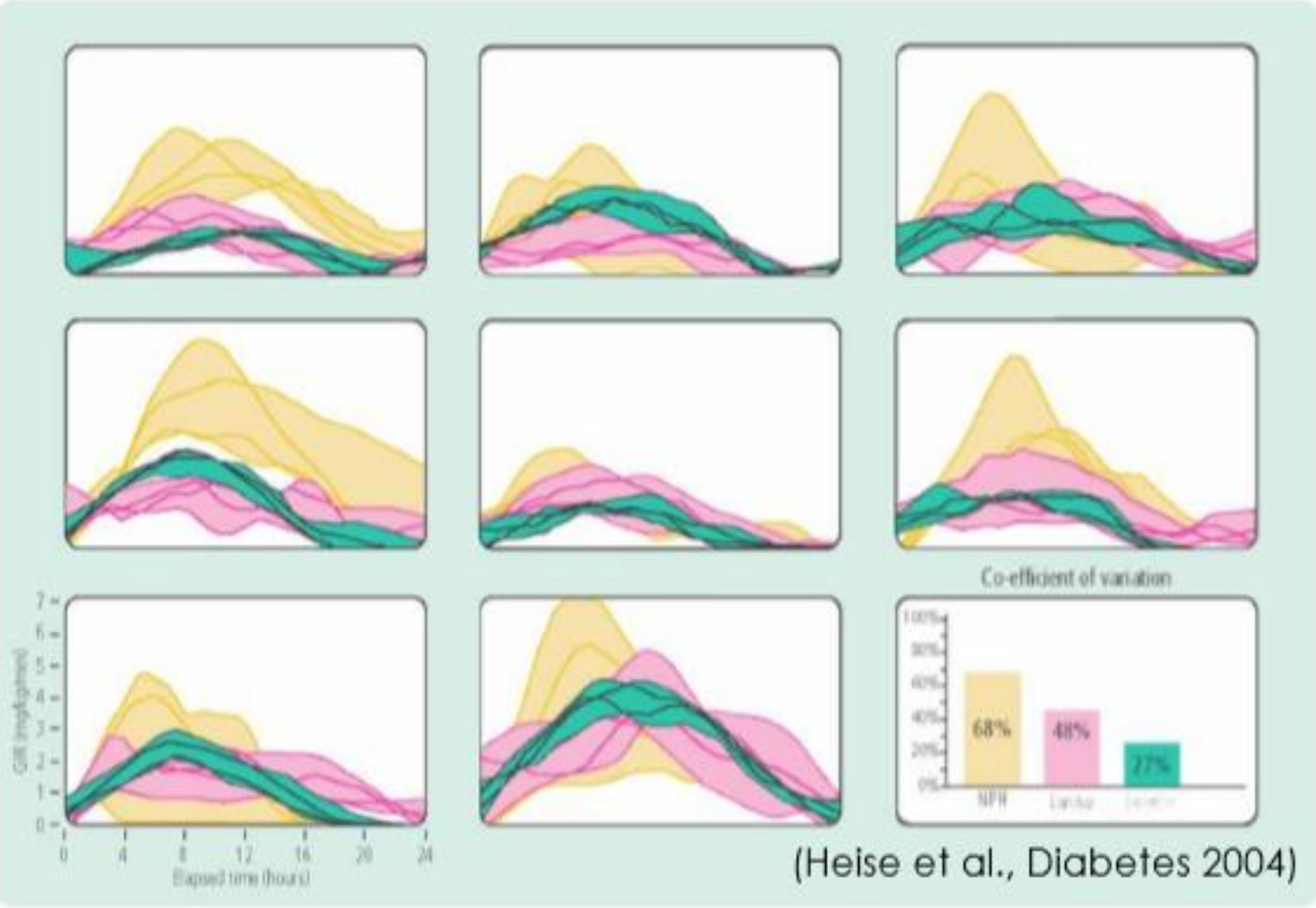


(Heise et al., Diabetes 2004)

Pharmacodynamic Variability NPH vs Glargine (Lantas)

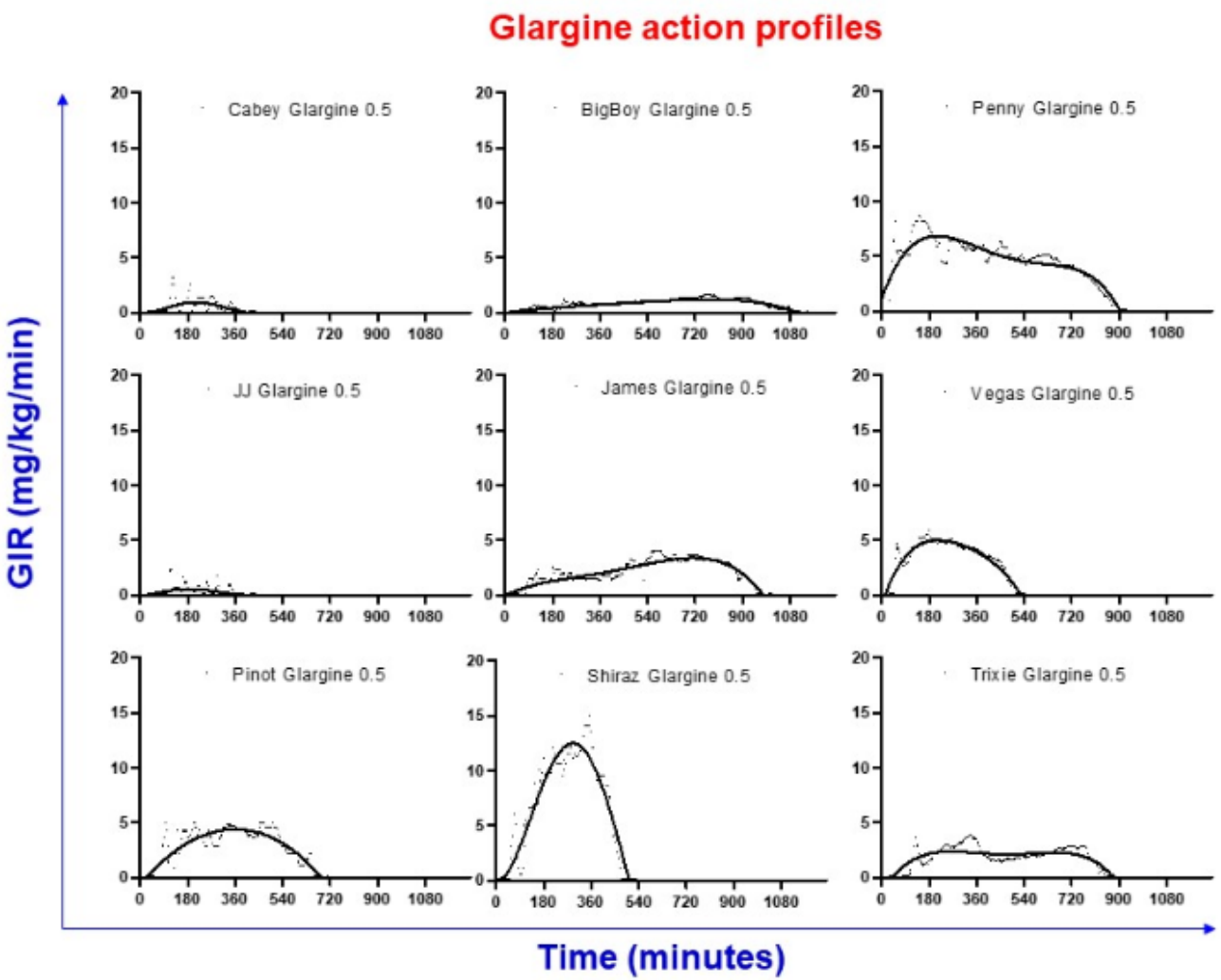


Pharmacodynamic Variability
NPH vs Glargine vs Detemir



(Heise et al., Diabetes 2004)

Glargine - Cats



Healthy cats: given insulin, normalized blood glucose by infusing dextrose and changing rate of dextrose infusion over time

Huge amount of variation b/t cats

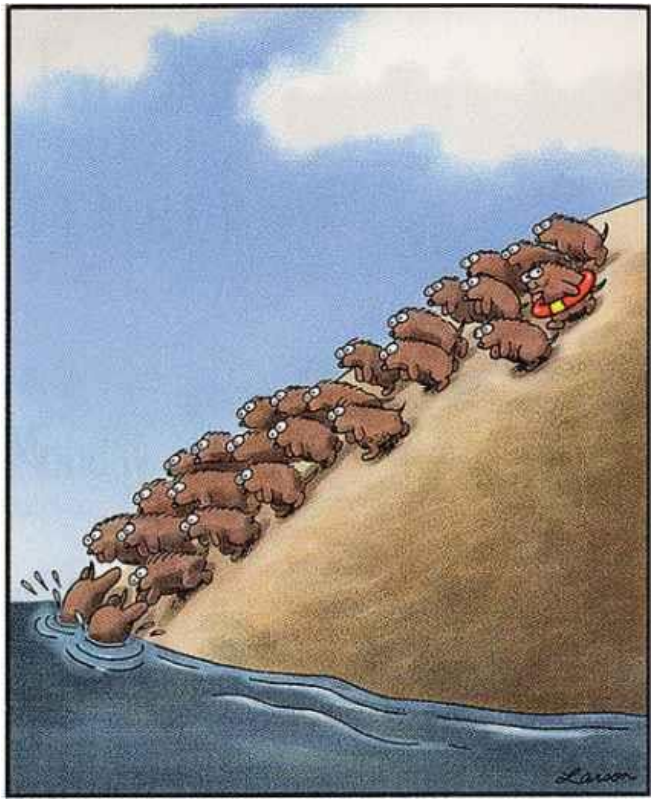
Duration of action ~9 hours

What can a BG curve tell us?

- Identifies hypoglycemic events
  - Specific BUT not really sensitive
- All else: only if repeatable
- More data points
  - Decreased effect of day-to-day variability
- Continuous Glucose Monitoring (CGM)
- Home monitoring

Continuous Glucose Monitoring (CGM)

- This is likely the direction we are heading



…this will actually be a good thing…

FreeStyle Libre

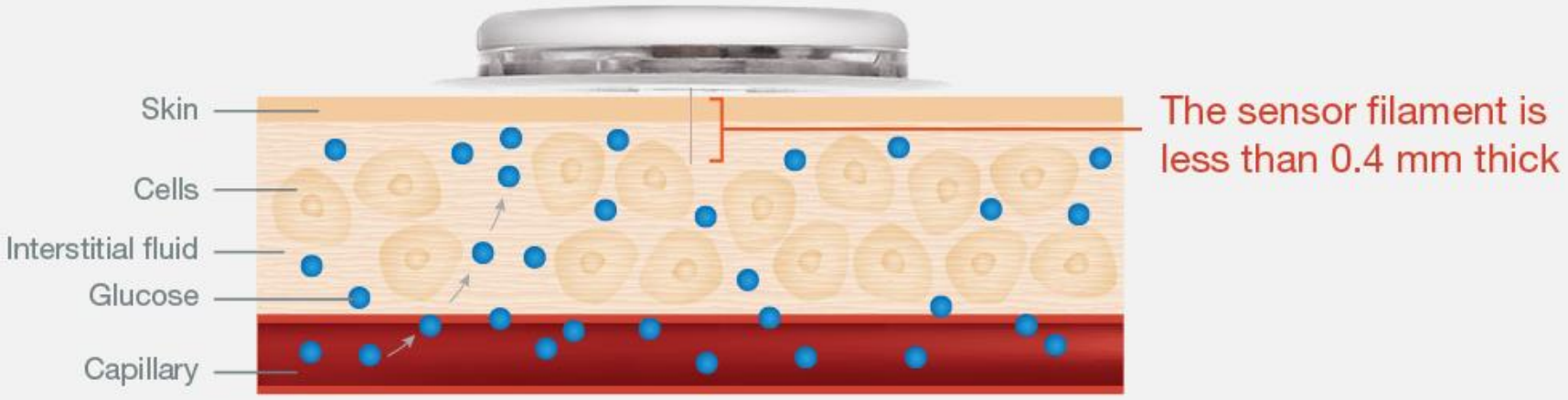
- Interstitial glucose (IG)
- Validated for use in dogs
- Validation in progress for cats
  - Excellent clinically so far
- Accuracy – similar to human glucometers
- DO NOT expect the same absolute values
- Excellent for trends
- Range: 40-500 mg/dL (graphs < 350 mg/dL)

Corradini et al. JVIM 2016

FreeStyle Libre

- 12 hour initiation
- IG every 15 minutes x 10 days
- $40/sensor (disposable)
- $90/reader

- User friendly
- Easy application (no sedation)
- No pain
- Data transfer (USB)
  - To software or website



FreeStyle Libre

COMPLICATIONS

- Early removal
  - Especially cats
- Inconsistent data acquisition
- Local irritation

USES

- Replace BG curve?
- Replace fructosamine?
  - Periodical
- Quicker and safer adjustments in doses
- Tighter control
  - Constant

Counter-Regulatory Mechanisms

- Healthy: release of multiple counter-regulatory hormones is triggered when [BG] decreases towards hypoglycemic range
  - Glucagon, cortisol, epinephrine
  - Increase insulin resistance (prevent further decrease in BG)
- Response is often deficient in diabetics
  - Neuroglycopenia results if counter-regulatory response to insulin overdose is inadequate

Glycemic Variability

- Hypoglycemic events are more common than previously realized
  - Unaware of 75% of hypoglycemic events (CGM)
- Most hypoglycemic events are associated w/ no clinical signs
  - Can induce impaired glucose counter-regulation which increases risk of neuroglycopenia

Insulin Resistance

- > 1.5 U/kg
- Main differential diagnoses
  - Error in insulin handling or administration
  - Obesity
  - Concurrent disease or drug therapy
  - Insulin-induced hyperglycemia
    - Previously the 'somogyi effect'
- Response to decreased insulin dose
- Changing to less potent, longer-acting insulin, or restriction of dietary CHO can be considered

Major Cause of Glycemic Variability

- Rapid increases in insulin dose to 'stabilize' DM
- Animals response to insulin dose adjustment should be monitored for 1-2 weeks before another increase is considered
- Increased when:
  - Some improvement in clinical signs (pu, pd, weight gain, decreased pp, and/or increased activity/interaction)
  - Some clinical signs of DM are still present (pu, pd, lethargy, pp)
  - Evidence of BG often above renal threshold

Oral Hypoglycemia Agents

- Sulfonylurea (glipizide, glyburide, glimepiride)
  - Increases insulin secretion and reduces insulin resistance
  - May promote progression of pancreatic amyloidosis
- Biguanides (metformin)
  - Inhibits hepatic glucose release and improves peripheral insulin sensitivity
- Thiazolindinediones (troglitazone)
  - Facilitate insulin-dependent glucose disposal and inhibit hepatic glucose output thru attenuation of gluconeogenesis and glycogenolysis
- α-glucosidase inhibitors (acarbose)
  - Impair glucose absorption form intestine by decreasing fiber digestion (and hence glucose production from food sources)
- Transition metals (chromium, vanadium)
  - Insulin-like properties BUT exact mechanism not known
- Incretins (exenatide)

Oral Hypoglycemics - Dosing

Drug	Dose	Frequency	Side Effects	Mechanism of Action
Glipizide	2.5-5.0 mg/cat	q8-12h, PO	Hepatotoxicity, hypoglycemia, vomiting	Increases insulin secretion and sensitivity
Glimepiride	1-2 mg/cat	q24h, PO	Same as glipizide but lower incidence	Same as glipizide
Metformin	2 mg/kg	q12h	Anorexia, vomiting	Inhibits hepatic glucose production
Acarbose	12.5mg/cat	q8-12h	Flatulence, soft stools/diarrhea	A1-glucosidase inhibitor, impairs glucose absorption from GIT
Troglitazone	20-40 mg/kg	q12-24h	Mild increases in WBC, platelet, and Hb counts	Increases insulin Rc sensitivity
Chromium	200mcg	q24h	Anorexia at high doses	Increases insulin Rc sensitivity
Vanadium	0.2 mg/kg/day	q24h in canned food	Anorexia, vomiting	Increases insulin Rc sensitivity

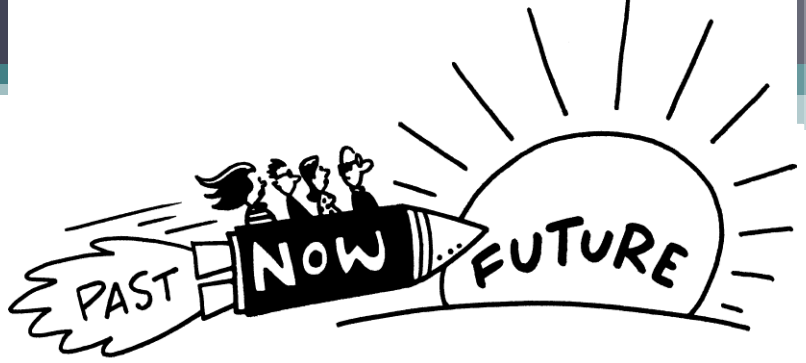
What's in the future?

- Incretins

Fun fact

Exenatide originally derived from the salivary secretions of the Gila monster

Incretins

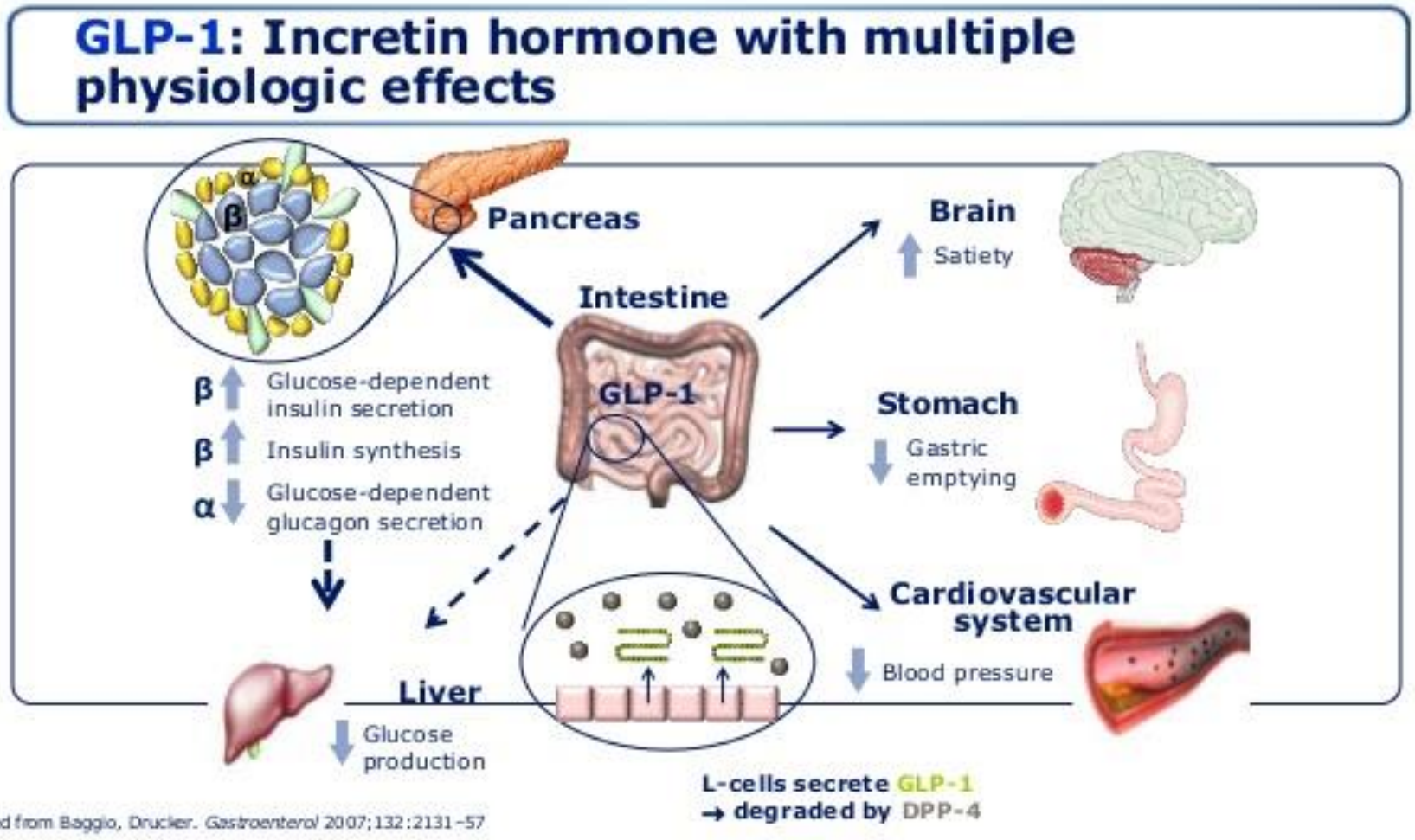


- Hormones that are released in response to nutrients and that potentiate nutrient-induced pancreatic insulin secretion
  - GLP-1: glucagon-like peptide
  - GIP: glucose-dependent insulintropic polypeptide
- Enteroendocrine derived
- Inactivation: depeptidyl peptidase -4 (DDP-4)

Pharmacologic Forms

- GLP-1 mimetic
  - Exenatide (Byetta)
  - Liraglutide (Victoza)
  - Albiglutide (Tanzeum)
  - Exenatide ER(Budureon)
- DDP-4 inhibitors
  - Sitagliptin (Januvia)
  - Vildagliptin (Galvus)

GLP-1: MOA


GLP-1: Incretin hormone with multiple physiologic effects
α
β
Pancreas
Brain
Satiety
Intestine
GLP-1
β Glucose-dependent insulin secretion
β Insulin synthesis
α Glucose-dependent glucagon secretion
Stomach
Gastric emptying
Cardiovascular system
Blood pressure
Liver
Glucose production
L-cells secrete GLP-1
→ degraded by DPP-4
Adapted from Baggio, Drucker. Gastroenterol 2007;132:2131–57

J Vet Intern Med 2016;30:92–100

Effect of the Glucagon-like Peptide-1 Analogue Exenatide Extended Release in Cats with Newly Diagnosed Diabetes Mellitus

A. Riederer, E. Zini, E. Salesov, F. Fracassi, I. Padrutt, K. Macha, T.M. Stöckle, T.A. Lutz, and C.E. Reusch

- n = 30 cats
- Placebo-controlled
  - Glargine, low-CHO diet
  - 16 weeks (4 weeks beyond remission)
- Exenatide ER/Placebo
  - Remission: 40%/20%
  - Good control: 89%/58%

Byetta® (exenatide) injection

Diabetic Dietary Management

- Several studies DO NOT support carbohydrates as diabetogenic or as factors increasing insulin resistance
- Dry food easily increase the number of calories consumed
- Avoid soft moist products (food/treats)
  - Free sugars and humectants

What is the Glycemic Index (GI)?

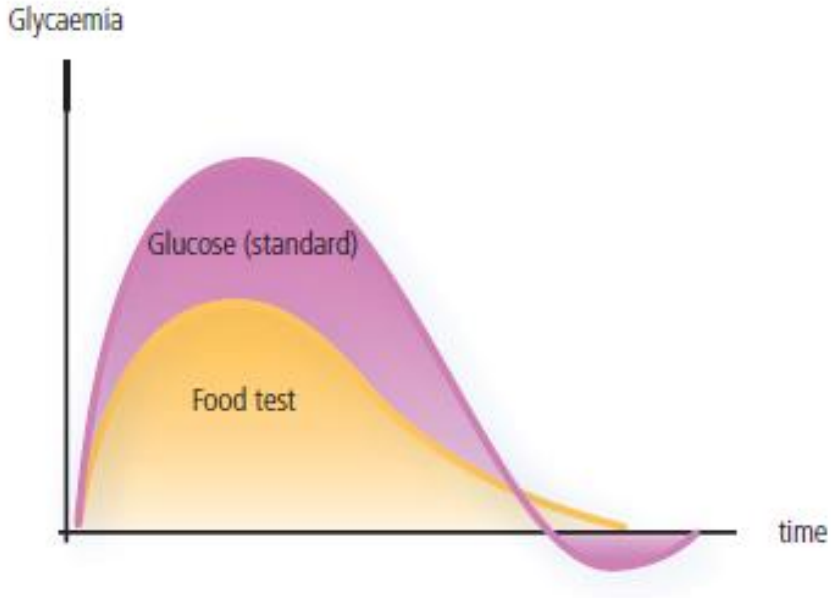
How Evaluated (humans)

- Amount of food, equivalent to 50g CHO eaten w/in 13 minutes
- BG levels are measured in the next 2-3 hours: measurement of the 'area under curve' (AUC)
- Trial replicated in 8-10 people
- GI = ratio of curve integrals compared to a control (glucose = 100%)

- Classification:
  - <55: low GI
  - Between 55-70: medium GI
  - > 70: high GI

Unfortunately, studies in people have found an ingredients' GI is not always reflective of the glycemic response when incorporated into a mixed meal and vary depending on the manner in which the food is prepared.

The value of the GI would really be in the comparison of complete diets, not the individual ingredients.



Dietary Management: DOG

- Total CHO content of diet is major determinant of glycemic response
  - Moderately CHO-restricted diet (<30% ME)
  - Meals should have consistent CHO content
- Low glycemic CHO sources
  - Legumes
  - Sorghum
  - Barley
  - Corn
- Nutrient requirements for concurrent diseases have priority over those for diabetes

Dietary Management: DOG

Recommended Ranges of Key Nutrients				
Nutrient	**% DM**	**g/100 kcal**	**% DM**	**g/100 kcal**
	Recommended dietary level		**Minimum dietary requirement***	
Protein	25-50	6-10	18	5.1
Fat≠	8-12	3-5	5	1.4
Carbohydrate	0-40	0-8	n/a	n/a
Crude Fiber	5-15	2-4	n/a	n/a

*Nutrient requirement for adult animals as determined by the Association of American Feed Control Officials

≠Dietary fat restriction is recommended for diabetic dogs w/ concurrent chronic pancreatitis or persistent hypertriglyceridemia. Dietary fat restriction should not be routinely recommended for diabetic dogs w/ thin body condition.

Dietary Management: CAT

Recommended Ranges of Key Nutrients				
Nutrient	**% DM**	**g/100 kcal**	**% DM**	**g/100 kcal**
	Recommended dietary level		**Minimum dietary requirement***	
Protein	40-60	10-17	26	6.5
Carbohydrate	0-20	0-5	n/a	n/a
Fat	10-35	3-7	9	2.3

*Nutrient requirement for adult animals as determined by the Association of American Feed Control Officials

Dietary Management: CAT (Simplified)

Carbohydrate Content

< 20% DMB

< 5.0 g/100 kcal

New Approaches to Feline Diabetes Mellitus: Glucagon-like peptide-1 analogs.

Language: English

J Feline Med Surg. September 2016;18(9):733-43.

DOI: 10.1177/1098612X16660441

Chen Gilor 1, Adam J Rudinsky 2, Melanie J Hall 3

CLINICAL RELEVANCE:
Incretin-based therapies are revolutionizing the field of human diabetes mellitus (DM) by replacing insulin therapy with safer and more convenient long-acting drugs.

MECHANISM OF ACTION:
Incretin hormones (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic peptide [GIP]) are secreted from the intestinal tract in response to the presence of food in the intestinal lumen. GLP-1 delays gastric emptying and increases satiety. In the pancreas, GLP-1 augments insulin secretion and suppresses glucagon secretion during hyperglycemia in a glucose-dependent manner. It also protects beta cells from oxidative and toxic injury and promotes expansion of beta cell mass.

ADVANTAGES:
Clinical data have revealed that GLP-1 analog drugs are as effective as insulin in improving glycemic control while reducing body weight in people suffering from type 2 DM. Furthermore, the incidence of hypoglycemia is low with these drugs because of their glucose-dependent mechanism of action. Another significant advantage of these drugs is their duration of action. While insulin injections are administered at least once daily, long-acting GLP-1 analogs have been developed as once-a-week injections and could potentially be administered even less frequently than that in diabetic cats.

OUTLINE:
This article reviews the physiology of incretin hormones, and the pharmacology and use of GLP-1 analogs, with emphasis on recent research in cats. Further therapies that are based on incretin hormones, such as DPP-4 inhibitors, are also briefly discussed, as are some other treatment modalities that are currently under investigation.

Realistic Goals:

- Avoid hypoglycemia
- Stable weight (unless intentional weight loss)
- Happy dog/cat
- Reasonable curve
  - 100-300 mg/dL range most of day
- Some glucose in urine
- Diet
  - DOG: consistent feedings
  - CAT: individual
    - Low CHO vs higher fiber

Thank You!

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