Diabetes Mellitus

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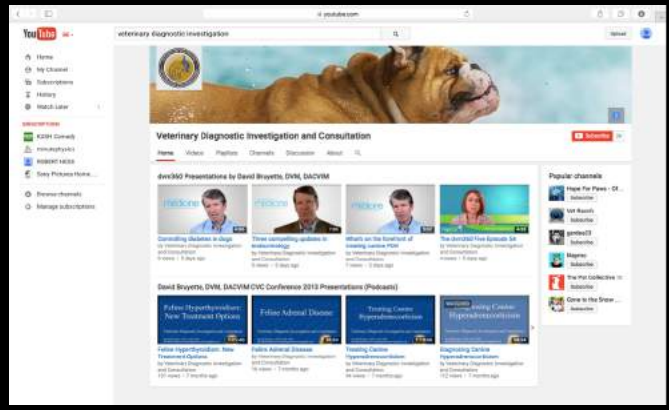

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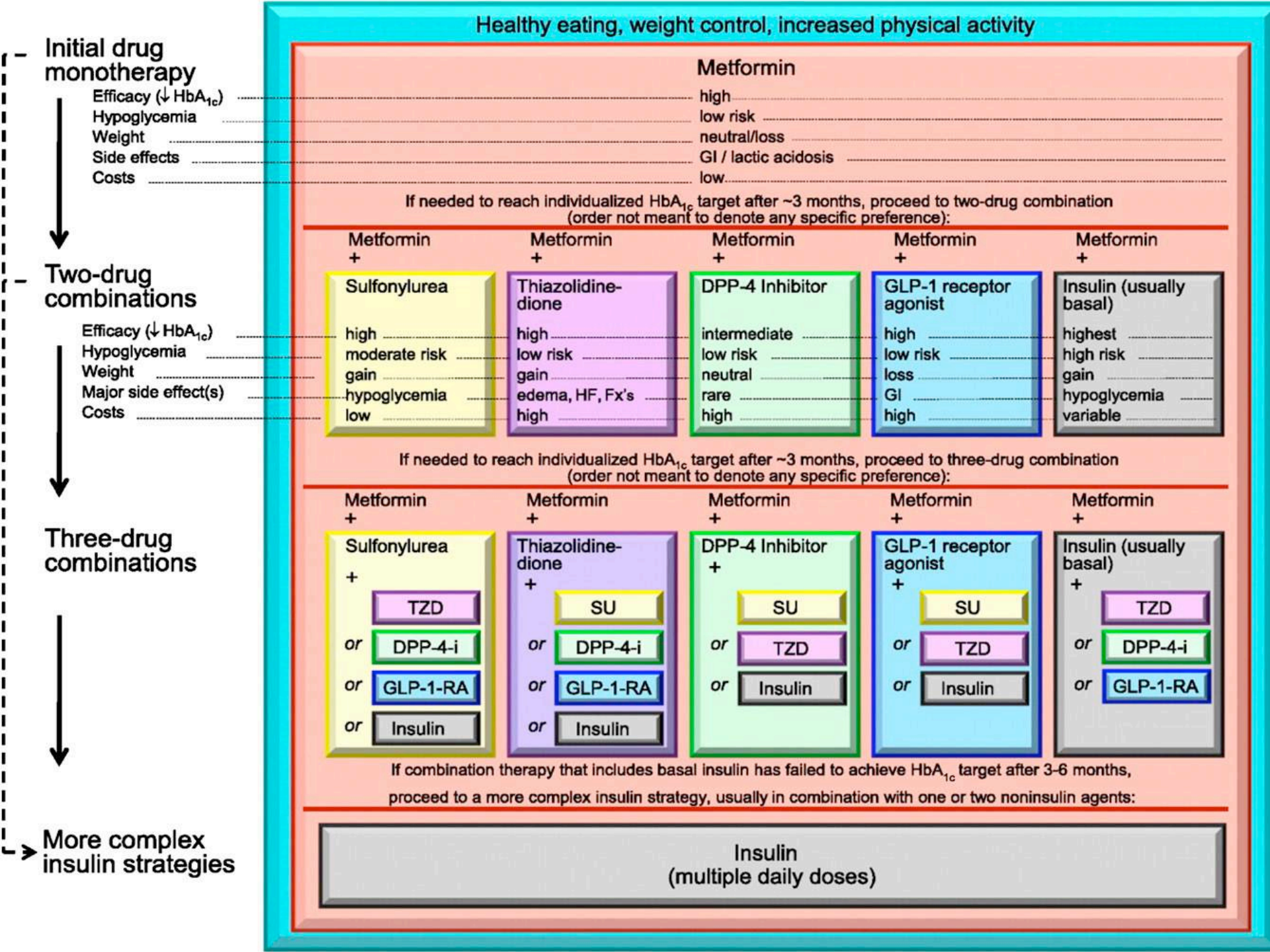
More than 30 million Americans have diabetes with another 84 million at risk for developing the disease. Having diabetes increases one's risk for serious health problems including heart attack, stroke, blindness, kidney failure, amputations, and death.

Diabetes is also the most expensive chronic condition in the United States. Average medical expenses are 2.3 times higher for people with diabetes. In 2017, the cost of diagnosed diabetes was estimated to be $327 billion annually, with $237 billion in direct medical costs. This equates to one-in-four health care dollars being spent on people with diagnosed diabetes. And since one-in-four are unaware they have the disease, costs to the healthcare system are even higher than estimated.


Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Side effects
Costs
Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low
If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination
(order not meant to denote any specific preference):
Two-drug combinations
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Major side effect(s)
Costs
Metformin + Sulfonylurea
high
moderate risk
gain
hypoglycemia
low
Metformin + Thiazolidinedione
high
low risk
gain
edema, HF, Fx's
high
Metformin + DPP-4 Inhibitor
intermediate
low risk
neutral
rare
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (usually basal)
highest
high risk
gain
hypoglycemia
variable
If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination
(order not meant to denote any specific preference):
Three-drug combinations
Metformin + Sulfonylurea + TZD or DPP-4-i or GLP-1-RA or Insulin
Metformin + Thiazolidinedione + SU or DPP-4-i or GLP-1-RA or Insulin
Metformin + DPP-4 Inhibitor + SU or TZD or Insulin
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin
Metformin + Insulin (usually basal) + TZD or DPP-4-i or GLP-1-RA
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months,
proceed to a more complex insulin strategy, usually in combination with one or two noninsulin agents:
More complex insulin strategies
Insulin
(multiple daily doses)

MORTALITY FROM DIABETES

1922

MORTALITY FROM DIABETES

1922	18.3/100,000

MORTALITY FROM DIABETES

1922	18.3/100,000
1998	

MORTALITY FROM DIABETES

1922	18.3/100,000
1998	24/100,000

COMMUNICATING WITH OWNERS OF DIABETIC PETS

The number one cause of death in diabetic dogs and cats is …

1)Renal failure

2)Pancreatitis

3)Owner elected euthanasia

4)Heart disease

COMMUNICATING WITH OWNERS OF DIABETIC PETS

Importance of Effective Communication

1) # 1 cause of death = owner elected euthanasia

2) Concerns over time commitment and expense

3) Diabetes as a chronic disease

4) Potential for excellent long term quality of life

COMMUNICATING WITH OWNERS OF DIABETIC PETS

Owner Experience in Treating Dogs and Cats Diagnosed with Diabetes Mellitus in the United States. JAAHA 50: 247-253, 2014.

Treated with insulin

97% Dogs 82% Cats

Twice daily insulin

87% Dogs 73 % Cats

Insulin types

Lente and NPH: Dogs Glargine and PZI: Cats

Most not fed a prescription diet

COMMUNICATING WITH OWNERS OF DIABETIC PETS

Owner Experience in Treating Dogs and Cats Diagnosed with Diabetes Mellitus in the United States. JAAHA 50: 247-253, 2014.

Satisfied with Diabetic Control

Dogs:

COMMUNICATING WITH OWNERS OF DIABETIC PETS

Owner Experience in Treating Dogs and Cats Diagnosed with Diabetes Mellitus in the United States. JAAHA 50: 247-253, 2014.

Satisfied with Diabetic Control

Dogs: 50%

COMMUNICATING WITH OWNERS OF DIABETIC PETS

Owner Experience in Treating Dogs and Cats Diagnosed with Diabetes Mellitus in the United States. JAAHA 50: 247-253, 2014.

Satisfied with Diabetic Control

Dogs: 50% Cats:

COMMUNICATING WITH OWNERS OF DIABETIC PETS

Owner Experience in Treating Dogs and Cats Diagnosed with Diabetes Mellitus in the United States. JAAHA 50: 247-253, 2014.

Satisfied with Diabetic Control

Dogs: 50% Cats: 66%

COMMUNICATING WITH OWNERS OF DIABETIC PETS

Owner Experience in Treating Dogs and Cats Diagnosed with Diabetes Mellitus in the United States. JAAHA 50: 247-253, 2014.

How many felt treatment was “expensive” ?

COMMUNICATING WITH OWNERS OF DIABETIC PETS

Owner Experience in Treating Dogs and Cats Diagnosed with Diabetes Mellitus in the United States. JAAHA 50: 247-253, 2014.

How many felt treatment was “expensive” ?

80%

COMMUNICATING WITH OWNERS OF DIABETIC PETS

What can I expect and how is this disease like diabetes in people ?

1) Differences in pathogenesis

2) Differential diagnosis in dogs and cats

3) Long term side effects in humans

Nephropathy, retinopathy, neuropathy, vascular disease

COMMUNICATING WITH OWNERS OF DIABETIC PETS

What percentage of dogs develop diabetic induced cataracts with the first 2 years of treatment ?

1)25 %
2)60 %
3)70 %
4)80 %

DIABETES MELLITUS

Goals of Therapy

- Remission of clinical signs
- Slow or delay progression of cataracts
  - 75 % within 2 years
- Maintenance of body weight
- Avoidance of hypoglycemia

DIABETES MELLITUS

Management of Diabetes

- Diet
- Insulin
- Oral hypoglycemic agents
- Concurrent illness
- Owner consultation

DIABETES MELLITUS

Insulin Therapy - Species of origin

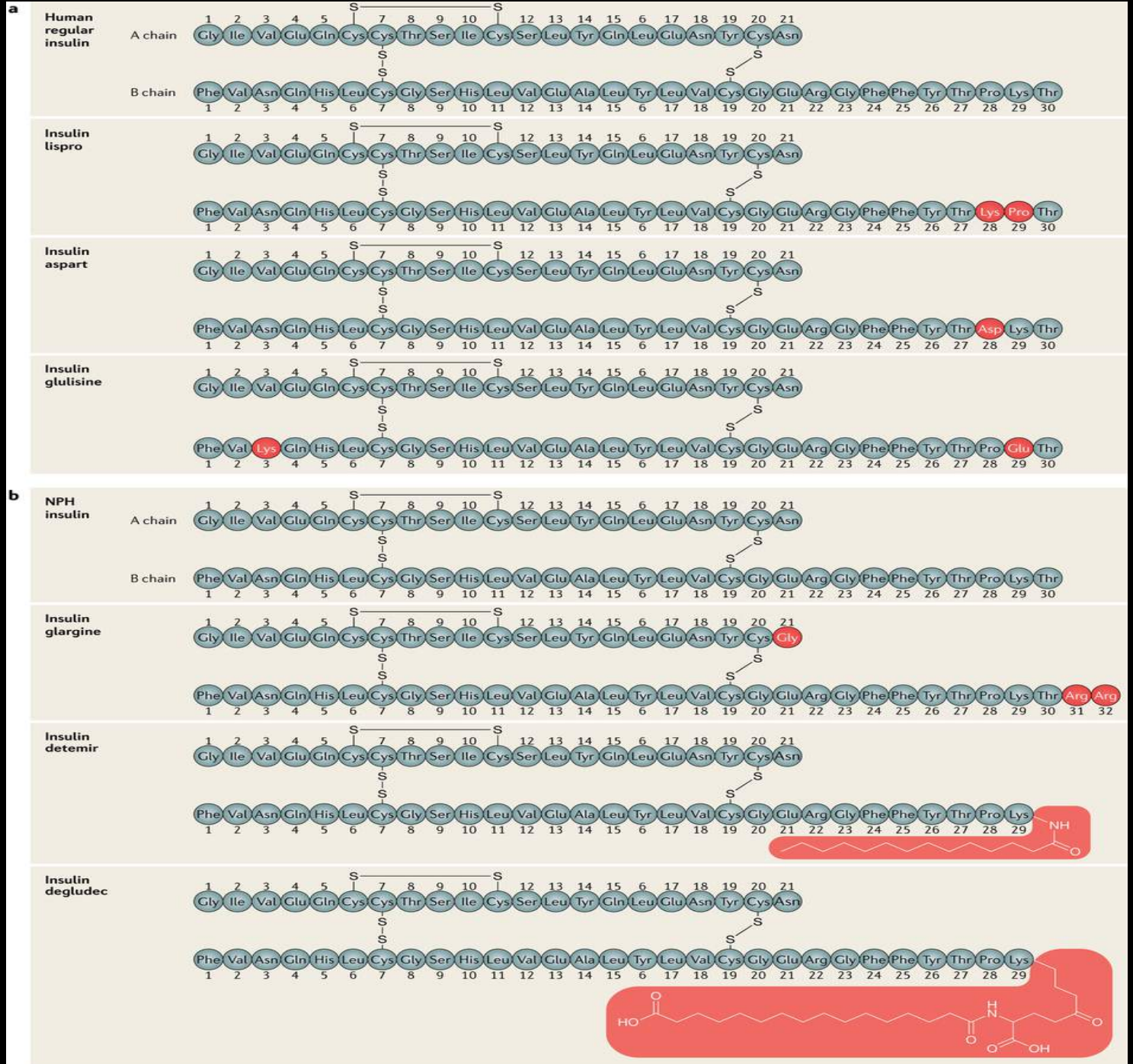
Beef, beef/pork, pork, human

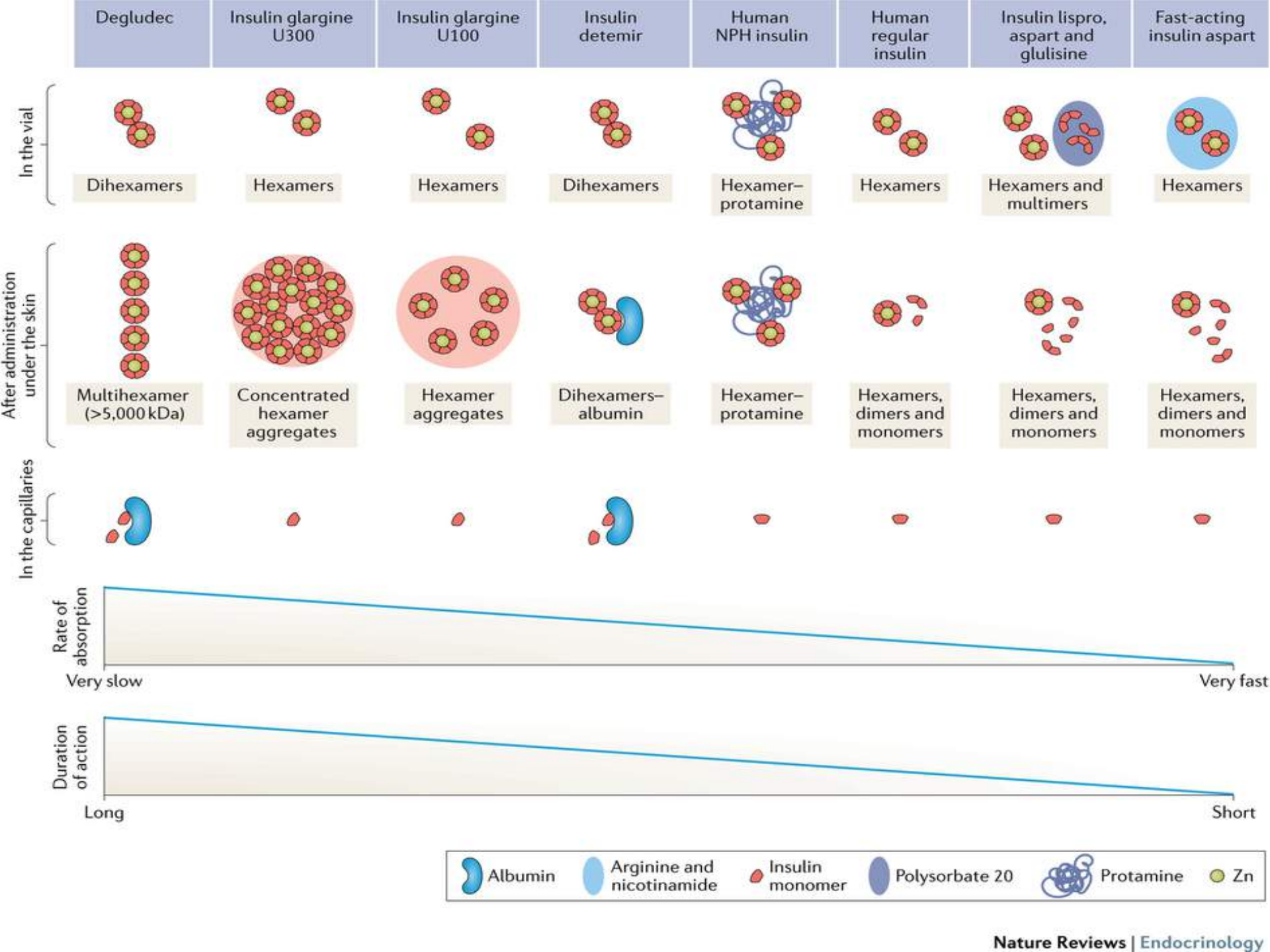
Increasingly difficult to obtain animal origin

Focus on use of human origin products

Role of antibodies and duration of action

Pork > human > beef/pork


a
Human regular insulin
A chain
B chain
Insulin lispro
Insulin aspart
Insulin glulisine
b
NPH insulin
A chain
B chain
Insulin glargine
Insulin detemir
Insulin degludec


Degludec
Insulin glargine U300
Insulin glargine U100
Insulin detemir
Human NPH insulin
Human regular insulin
Insulin lispro, aspart and glulisine
Fast-acting insulin aspart
In the vial
Dihexamers
Hexamers
Hexamers
Dihexamers
Hexamer–protamine
Hexamers
Hexamers and multimers
Hexamers
After administration under the skin
Multihexamer (>5,000 kDa)
Concentrated hexamer aggregates
Hexamer aggregates
Dihexamers–albumin
Hexamer–protamine
Hexamers, dimers and monomers
Hexamers, dimers and monomers
Hexamers, dimers and monomers
In the capillaries
Rate of absorption
Very slow
Very fast
Duration of action
Long
Short
Albumin
Arginine and nicotinamide
Insulin monomer
Polysorbate 20
Protamine
Zn

DIABETES MELLITUS
ULTRA FAST ACTING INSULINS

Brand Name	Onset	Peak	Duration	Structure
Humalog (Insulin lispro; Lilly)	5-15 minutes	45-90 minutes	3-4 hours	Lysine – proline substitution
Novolog (Insulin aspart; Novo)	5-15 minutes	45-90 minutes	3-4 hours	Aspartate-proline substitution

DIABETES MELLITUS
FAST ACTING INSULINS

Brand Name	Onset	Peak	Duration	Structure
Humulin-R Novolin-R	30-60 minutes	2-5 hours	5-8 Hours	Regular insulin

DIABETES MELLITUS
INTERMEDIATE ACTING INSULINS

Brand Name	Onset	Peak	Duration	Structure
Vetsulin (Merck)	1-3 hours	2-10 hours	6-24	Porcine
Humulin-N Novolin-N				Addition of protamine and zinc

DIABETES MELLITUS
LONG ACTING INSULINS

Brand Name	Onset	Peak	Duration	Structure
PZI (BI)	1-3 hours	14-24	24-26	Human

DIABETES MELLITUS
ULTRA LONG ACTING INSULINS

Brand Name	Onset	Peak	Duration	Structure
Detemir				Lysine at B29
Lantus (insulin glargine; Aventis)	1 hour	No peak	Constant concentration over 24 hours	Addition of arginine and asparagine-glycine substitution

Rising Insulin Costs

The true cost of insulin can be difficult to pinpoint because of a lack of transparency in financial agreements between stakeholders in the supply chain, geographical differences in cost, and insurance coverage.[12] From 2001-2016, the list price of Novolog, a commonly used insulin, increased by 353% per vial.[13] Humulin U500 increased from $170 to more than $1,400 since 1987.[14] From 2001-2015, the price of Humalog increased 585% for a vial of insulin.[15] GoodRx.com, a website that aggregates claims data to estimate the average list price of medications (the price of insulin without the negotiated discounts or rebates), published cost information per vial (1000 units) for commonly prescribed insulins in August 2018. The following prices are averaged from Walgreens and CVS pharmacies:

- Lantus: $302
- Humalog: $322
- Novolog: $336
- Humulin N: $180
- Novolin N: $155
- Basaglar: $261*
- Levemir: $394
- Toujeo: $338*
- Humulin R: $180
- Novolin R: $155
- Humulin 70/30: $177
- Novolin 70/30: $156
- Novolog 70/30: $338
- Humalog 75/25: $351
- Tresiba: $388*
- Apidra: $368
- Admelog: $254

*cost based on conversion to 1000 units

Newly Diagnosed Canine Patients

Vetsulin (porcine origin lente)

Humulin N or Novolin N (human origin)

ProZinc (human recombinant)

Glargine (long acting insulin analogue)

Detemir (long acting insulin analogue)

Newly Diagnosed Canine Patients

Humulin N or Novolin N (human origin)

J Vet Intern Med. Jan-Feb;23(1):50-5, 2009.

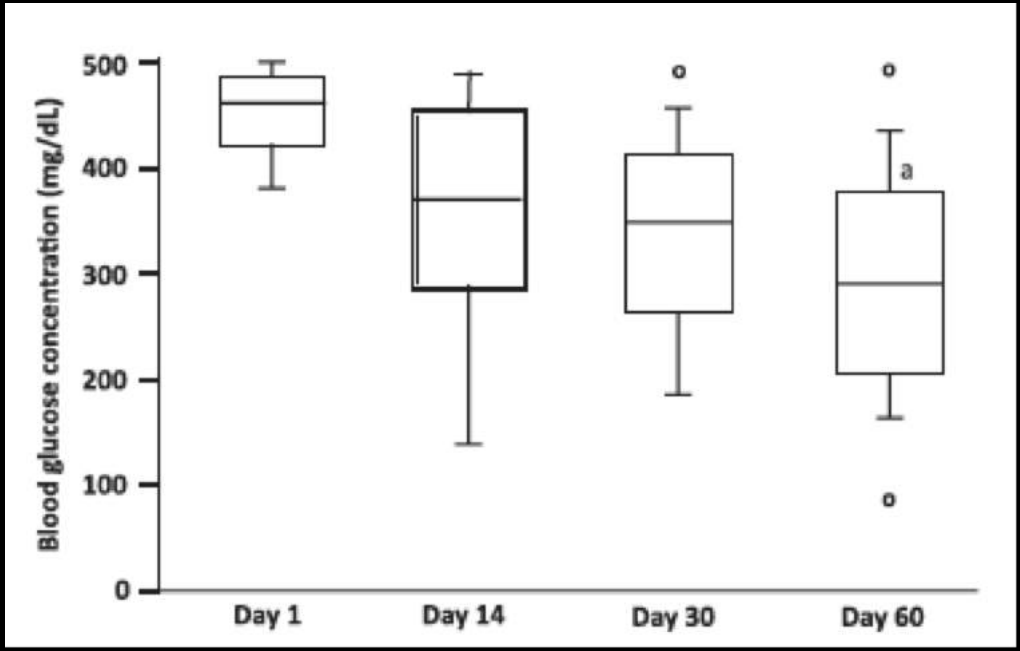
An investigation of the action of Neutral Protamine Hagedorn human analogue insulin in dogs with naturally occurring diabetes mellitus.

Newly Diagnosed Canine Patients

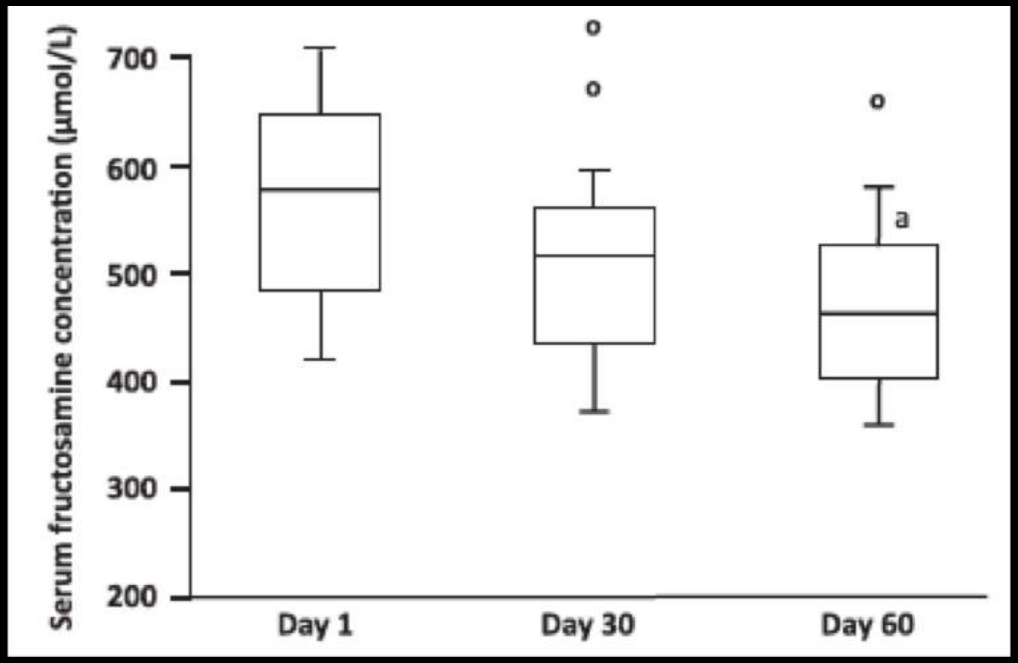
Efficacy of Protamine Zinc Recombinant Human Insulin for Controlling Hyperglycemia in Dogs with Diabetes Mellitus

J Vet Intern Med 2012;26:109–115

Newly Diagnosed Canine Patients



Newly Diagnosed Canine Patients



Starting dose is 0.5 u/kg BID but many required 1 u/kg BID

www.vetsulin.com

VETSULIN (MERCK)

40 IU/ml

Porcine origin

Lente insulin

- Intermediate-acting
- 30% amorphous & 70% crystalline insulin

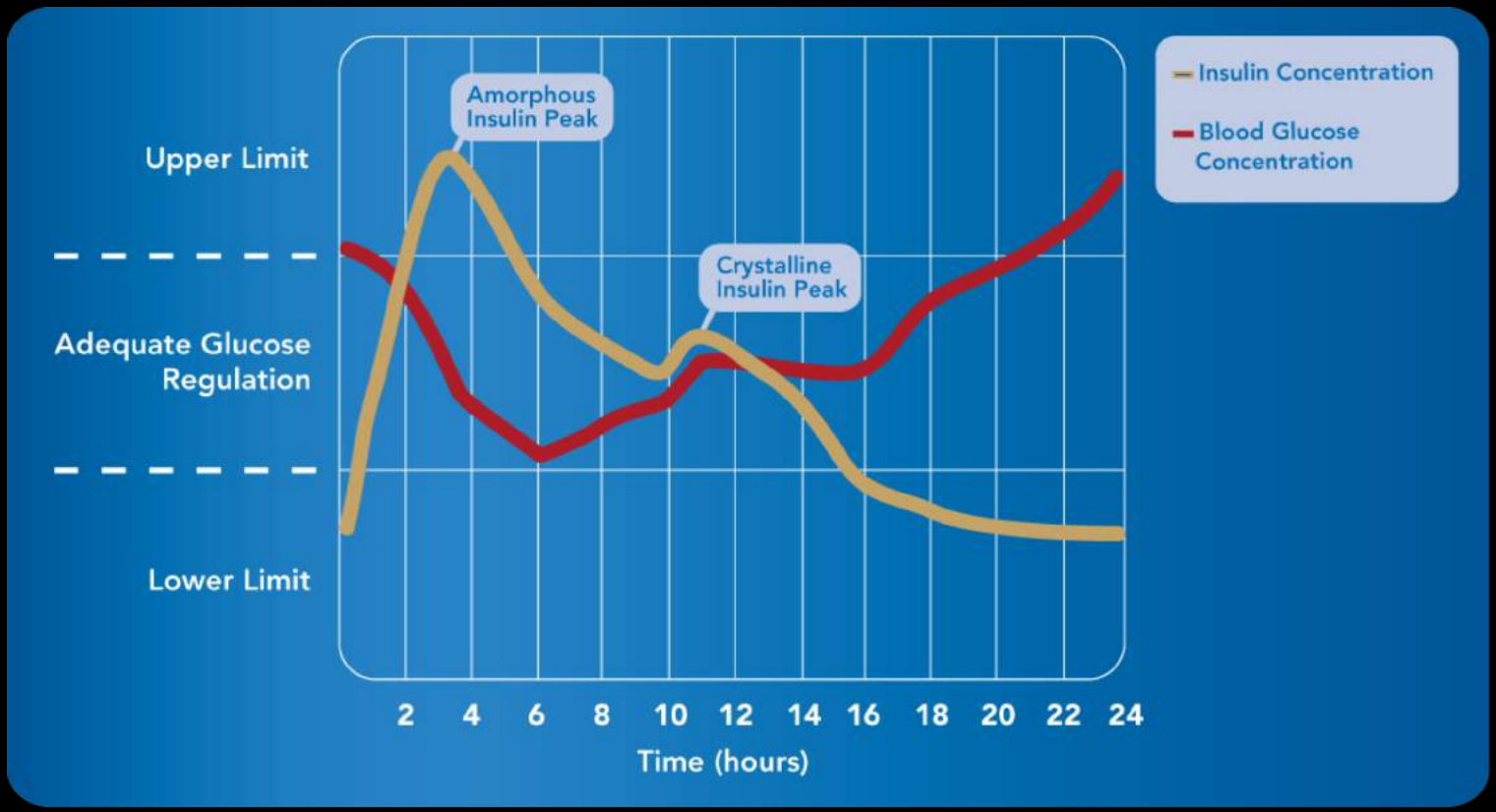
Anti-insulin antibodies in diabetic dogs before and after treatment with different insulin preparations. J Vet Intern Med Nov-Dec;1317-25, 2008

VETSULIN

Fifty-three dogs were treated for 60 days after an initial dose determination period. The means of the blood glucose concentrations during 12-hour glucose curves and the means of the blood glucose nadir concentrations during 12-hour glucose curves for all dogs were determined before beginning insulin therapy (time 0), at the end of the dose determination period (time 1), 30 days after time 1 (time 2), and 60 days after time 1 (time 3). The means of the blood glucose concentrations during 12-hour glucose curves and the means of the blood glucose nadir concentrations during 12-hour glucose curves for all dogs at times 1, 2, and 3 were significantly lower compared with time 0 ($P < .0001$). There was a reduction in the proportion of dogs with polyuria, polydipsia, and ketonuria of 82, 86, and 80%, respectively. All of the dogs had adequate glycemic control at time 1, 66% at time 2, and 75% at time 3. At time 3, 66% of dogs required insulin injections q12h.

JVIM 2005 Sep-Oct;19(5):675-82

VETSULIN


Amorphous Insulin Peak
Crystalline Insulin Peak
Upper Limit
Adequate Glucose Regulation
Lower Limit
Insulin Concentration
Blood Glucose Concentration
2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)

VETSULIN

One important change that occurred with the re-launch of Vetsulin is the manufacturers recommendations regarding handling of the insulin. Vetsulin should be **shaken thoroughly** until a homogeneous, uniformly milky suspension is obtained. Foam on the surface of the suspension formed during shaking should be allowed to disperse before the product is used and, if required, the product should be gently mixed to maintain a homogeneous, uniformly milky suspension before use.

Clumps or white particles can form in insulin suspensions: do not use the product if visible clumps or white particles persist after shaking thoroughly. The product has a shelf life of 12 months and is usable for 42 days once the vial has been opened.

VETPEN® STARTER KIT

- ▶1 pen (8 IU or 16 IU)
- ▶1 instruction leaflet
- ▶1 box of 28 x needles (29G/12 mm)
- ▶1 travel pouch
- ▶1 needle remover
- ▶1 dose selector adaptor
- ▶1 release button adaptor

VETPEN®

A recent study comparing the precision and accuracy of the VetPen to U40 syringes demonstrated that even when doses were drawn up by trained laboratory technicians, syringes were found to deliver at least 20% to 25% more insulin than needed for a 1-unit dose.

Burgaud S, Riant S, Piau N. Comparative laboratory evaluation of dose delivery using a veterinary insulin pen. Proceedings World Congress ASAVA/FECAVA/BSAVA 2012;567.

GLARGINE; SANOFI

Twelve client-owned dogs were included.

Mean blood glucose concentrations were significantly lower after two weeks of treatment and remained significantly lower for the duration of the study.

By week 24, polyuria/polydipsia had improved in 91 per cent of the dogs.

No clinical signs that could have been caused by hypoglycemia were observed.

Based on BGCs and remission of the clinical signs for judging the success of the treatment, 58, 33 and 8 per cent of the dogs attained good, moderate and poor glycemic control by week 24 of the study, respectively.

Use of insulin glargine in dogs with diabetes mellitus. Vet Rec. 2012 Jan;170(2):52.

GLARGINE; SANOFI

10 dogs had well-regulated diabetes mellitus at a mean of 38 days following study enrollment.

At the time diabetes mellitus was well regulated, mean glargine insulin dosage was 0.5 twice daily, and 3 dogs were receiving a dosage < 0.4 U/kg (0.18 U/lb).

Results of the present study suggested that, in diabetic dogs fed a diet high in insoluble fiber, glargine insulin is a peakless insulin that does not induce a distinct blood glucose concentration nadir. For glargine insulin, 0.3 U/kg (0.136 U/lb) SC twice daily is recommended as an initial dosage.

Glargine insulin for treatment of naturally occurring diabetes mellitus in dogs.
J Am Vet Med Assoc. 2013 Oct 15;243(8):1154-61.

LEVEMIR; NOVO NORDISK

In contrast to glargine, detemir is a newer synthetic insulin analogue with long duration of action through modification of the insulin molecule via addition of an acylated fatty acid chain.

This modification facilitates reversible binding to plasma proteins, particularly albumin, from where it is released slowly into plasma. The modification also prolongs self-association in the injection depot, which prolongs absorption from subcutaneous tissue at the injection site and contributes to the long duration of action.

LEVEMIR; NOVO NORDISK

Dogs were treated with insulin detemir SC every 12 hours for 6 months. Follow-up evaluations were done at 1, 2, 4, 12, and 24 weeks and included evaluation of clinical signs and measurement of blood glucose concentration curves and serum fructosamine concentrations.

Insulin detemir administration resulted in a significant decrease in blood glucose and serum fructosamine concentrations at 6 months, compared with pretreatment values. Median insulin dosage at the end of the study was 0.12 U/kg (0.055 U/lb; range, 0.05 to 0.34 U/kg [0.023 to 0.155 U/lb], SC, q 12 h). Hypoglycemia was identified in 22% (10/45) of the blood glucose concentration curves, and 6 episodes of clinical hypoglycemia in 4 dogs were recorded. On the basis of clinical signs and blood glucose concentration curves, efficacy of insulin detemir at the end of the study was considered good in 5 dogs, moderate in 3, and poor in 2.

Detemir insulin for the treatment of diabetes mellitus in dogs: JAVMA July 1, 2015, Vol. 247, No. 1, Pages 73-78

LEVEMIR; NOVO NORDISK

Results indicate that insulin detemir has a greater effect than either NPH insulin or insulin glargine in canines, requiring a lower dose than other insulin preparation. However, using insulin detemir also carries a higher risk of inducing hypoglycemia as compared to either NPH insulin or insulin glargine. I generally start at a dose of 0.1 unit/kg BID in dogs that have not been well controlled with NPH or lente insulins.

Time-action profiles of insulin detemir in normal and diabetic dogs. Res Vet Sci. 2011 Jun;90(3):396-403.

DIABETES MELLITUS

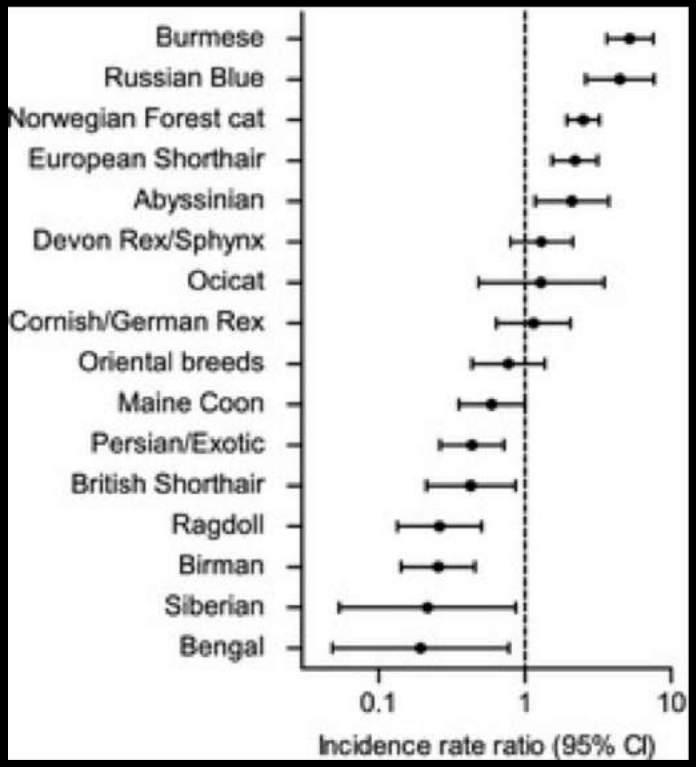
Client Education

- Clinical signs
- Injection techniques
- Handling, storage and mixing of insulin, syringes
- Signs of hypoglycemia
- Urine monitoring
  - Trends
  - Not used to adjust dose

DIABETES MELLITUS

- Glycated Blood Proteins
  - Fructosamine
    - Glycation of serum proteins (albumin)
    - Reflection of glycemic control over the past 2 - 3 weeks

INCIDENCE & RISK FACTORS



- 1:80 – 1:200
- Male > Female
- Domestic > Purebred
- Higher incidence Burmese, Russian Blue, Norwegian Forest Cat, Abyssinian, Tonkinese
- Higher incidence in higher BCS, older age (7), obesity, renal transplantation, and insured cats

Newly Diagnosed Feline Patients

Vetsulin (porcine origin lente)

Humulin N or Novolin N (human origin)

ProZinc (human recombinant)

Glargine (long acting insulin analogue)

Detemir (long acting insulin analogue)

Newly Diagnosed Feline Patients

Insulin glargine (Lantus): Glargine is a modified, recombinant, long acting insulin analog. Several studies demonstrate a very high rate of remission 80-90 % in feline diabetics with the use of glargine and a low carbohydrate-high protein diet.

Treatment of newly diagnosed diabetic cats with glargine insulin improves glycaemic control and results in higher probability of remission than protamine zinc and lente

insulins

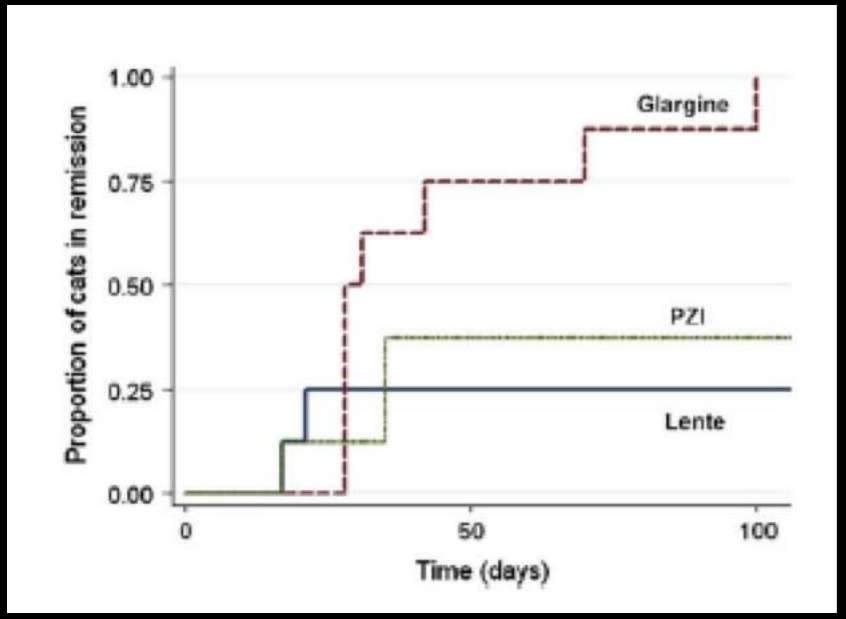
J Fel Med and Surg 11: 683-691, 2009

Table 5. Serum fructosamine concentrations from day 0 to day 112 in a controlled trial comparing glycaemic control and remission in 24 newly diagnosed diabetic cats treated with either glargine, PZI or lente insulin

Day	Lente	*n*	Glargine	*n*	PZI	*n*	*P* value
0	573	8	554	8	568	8	*
28	465 ± 49	8	343 ± 38	8	444 ± 42	8	0.125
56	539 ± 31[a]	6	**342 ± 31**[b]	2	543 ± 35[a]	5	0.019
84	517 ± 24[a]	6	**182**[b]	1	540 ± 32[a]	5	0.002
112	479 ± 17	6		0	562 ± 65	5	0.210

Table 6. Proportion of cats going into remission and time from initiation of treatment to remission in a controlled trial comparing glycaemic control and remission in 24 newly diagnosed diabetic cats treated with either glargine, PZI or lente insulin

	Lente	Glargine	PZI	*P* value
Proportion of cats going into remission by day 42 (number of eight cats)	0.25 (2)	0.75 (6)	0.38 (3)	0.014
Proportion of cats going into remission by day 112 (number of eight cats)	0.25 (2)	1.00 (8)	0.38 (3)	
Median time (days) from initiation of treatment to remission for cats that achieved remission (range)	19 (17–21)	28 (28–100)	35 (17–35)	


1.00
0.75
0.50
0.25
0.00
Proportion of cats in remission
Glargine
PZI
Lente
0
50
100
Time (days)

Newly Diagnosed Feline Patients

The recommended starting dose is 0.5 units/kg BID if the fasting blood sugar is greater than 360 mg/dl and 0.25 units/kg BID if the initial fasting blood glucose is less than 360 mg/dl.

Newly Diagnosed Feline Patients

Recheck blood glucose in 7 days

Pre meal/pre insulin

4 hour post

Preferably at home

If the preinsulin blood glucose concentration is

> 360 mg/dl and/or the 4 hour post blood glucose concentration is > 180 mg/dl the dose of insulin is increased by 0.5 to 1 unit BID.

If the preinsulin blood glucose concentration is 270 to 360 mg/dl and/or the 4 hour post glucose concentration is 90 - 180 mg/dl the dose of insulin is maintained.

If the preinsulin blood glucose concentration is 190 - 270 mg/dl and/or the 4 hour post glucose concentration is 54 - 90 mg/dl use clinical signs and the next preinsulin glucose concentration to determine if the dose is decreased or maintained.

If the preinsulin blood glucose concentration is < 180 mg/dl and/or the 4 hour post glucose concentration is < 54 mg/dl the dose of insulin is decreased by 0.5 to 1 unit BID. If the total insulin dose is already 0.5 – 1 unit BID, stop the insulin and check for diabetic remission.

Feline DKA and Lantus

Fifteen cats diagnosed with DKA were initially administered IM glargine (1-2 U) and in most cats (12/15 cats) this was combined with SC glargine (1-3 U). All 15 cats survived and were discharged from hospital (median 4 d; range 2-5 d) and one-third (5/15) of cats subsequently achieved remission (median time 20 d; range 15-29 d). Complications included hypokalemia and hypophosphatemia.

Intramuscular glargine with or without concurrent subcutaneous administration for treatment of feline diabetic ketoacidosis. J Vet Emerg Crit Care (San Antonio). 2013 Mar 26.

Prozinc (Boehringer Ingelheim)

In a large clinical trial 132 cats were treated with PZI twice daily for 45 days. PZI administration resulted in a significant decrease in 9-hour mean blood glucose (199+/-114 versus 417+/-83 mg/dL, X+/-SD, P<.001) and serum fructosamine (375+/-117 versus 505+/-96 micromol/L, P<.001) concentration and a significant increase in mean body weight (5.9+/-1.4 versus 5.4+/-1.5 kg, P=.017) in 133 diabetic cats at day 45 compared with day 0, respectively.

Prozinc (Boehringer Ingelheim)

By day 45, polyuria and polydipsia had improved in 79% (105 of 133), 89% (118 of 133) had a good body condition, and 9-hour mean blood glucose concentration, serum fructosamine concentration, or both had improved in 84% (112 of 133) of the cats compared with day 0. Hypoglycemia (<80 mg/dL) was identified in 151 of 678, 9-hour serial blood glucose determinations in 85 of 133 diabetic cats.

Field safety and efficacy of protamine zinc recombinant human insulin for treatment of diabetes mellitus in cats. J Vet Intern Med. 2009 Jul-Aug;23(4):787-93

Porcine - Lente

46 cats with diabetes mellitus during treatment with porcine lente insulin for 16+/-1 weeks (stabilization phase), with additional monitoring of some cats (n=23) for a variable period.

Insulin treatment was started at a dose rate of 0.25-0.5 IU/kg body weight twice daily, with a maximum starting dose of 2 IU/injection. Twenty-eight of the cats were classed as reaching clinical stability during the study. Seven cats went into remission during the stabilization phase and one of the cats in week 56 (17%). Clinical signs of hypoglycemia, significantly associated with a dose of 3 units or 0.5 IU/kg or more per cat (twice daily), were observed in nine of the 46 cats. Biochemical hypoglycemia, recorded in 6% of the blood glucose curves performed during the stabilization phase, was significantly associated with a dose rate of 0.75 IU/kg or more twice daily.

Treatment of 46 cats with porcine lente insulin-a prospective, multicentre study. J Feline Med Surg. 2008 Oct;10(5):439-51.

Levemir – Novo Nordisk

Eighteen cats diagnosed with diabetes and previously treated with other insulins were included in the study. The overall remission rate was 67%. For cats that began the protocol before or after 6 months of diagnosis, remission rates were 81% and 42%, respectively (P = 0.14). No significant differences were identified between the outcomes for the glargine and detemir patients, with the exception of three possibly interrelated factors: a slightly older median age of the detemir cohort at diabetes diagnosis, a higher rate of chronic renal disease in the detemir cohort and lower maximal dose for insulin detemir. In contrast to dogs, detemir does not appear to be more potent than glargine so the starting dose is the same for both insulins.

Evaluation of detemir in diabetic cats managed with a protocol for intensive blood glucose control. J Feline Med Surg. 2012 Aug;14(8):566-72.

Insulin Products Commonly Used in Dogs and Cats

Insulin Products	Product Description	Brand Name (Manufacturer)	Veterinary FDA Approval Status	Peak Action (Nadir) and Duration of Effect	Starting Dose	Concentration	Comments
Lente (intermediate-acting)	Porcine insulin zinc suspension	Vetsulin (Merck Animal Health)	Dogs, cats	**Cats** Nadir 2–8 hr. Duration 8–14 hr.[19] **Dogs** Nadir 1–10 hr.[20] Duration 10–24 hr.[20]	**Cats** 0.25–0.5 U/kg *q* 12 hr (not to exceed 3 U per cat).[5] **Dogs** 0.25–0.5 U/kg *q* 12 hr.	U-40	Commonly used in dogs; injection pens (in either 0.5 U or 1 U increments) available for dogs and cats. **Shaking insulin bottle is required.** NOTE: In dogs, the manufacturer recommends a starting dose of 0.5 U/kg *q* 24 hr.
Glargine (long-acting)	Recombinant DNA origin human insulin	Lantus (Sanofi)	Not approved	**Cats** Nadir 12–14 hr. Duration 12–24 hr. **Dogs** Nadir 6–10 hr.[21] Duration 12–20 hr.	**Cats** 0.5 U/kg *q* 12 hr if BG > 360 mg/dL and 0.25 U/kg *q* 12 hr if BG < 360 mg/dL. **Dogs** 0.3 U/kg *q* 12 hr.	U-100, U-300	Commonly used in cats; use only U-100 (U-300 available); potential option in dogs
PZI (long-acting)	Recombinant DNA origin human insulin	Prozinc (Boehringer Ingelheim Animal Health)	Cats	**Cats** Nadir 5–7 hr. Duration 8–24 hr.[14] **Dogs** Nadir 8–12 hr.[22]	**Cats** 1–2 U per cat *q* 12 hr. **Dogs** 0.25–0.5 U/kg *q* 12 hr.[22]	U-40	Commonly used in cats; not commonly used in dogs. Some clinicians believe that for dogs, a starting dose of 0.25 U/kg is appropriate and 0.5 U/kg should be reserved for potentially challenging diabetics.
NPH (intermediate-acting)	Recombinant human insulin	Novolin (Novo Nordisk) Humulin (Lilly)	Not approved	**Dogs** Nadir 0.5–8.5 hr.[15] Duration 4–10 hr.	**Dogs** 0.25–0.5 U/kg *q* 12 hr.[15]	U-100	Option for dogs; rarely recommended for cats due to short duration of effect. Consider using the lower end of the starting dose for a large dog and higher end for a small dog.
Detemir (long-acting)	Recombinant DNA origin human insulin	Levemir (Novo Nordisk)	Not approved	**Cats** Nadir 12–14 hr. Duration 12–24 hr.[16,17]	**Cats** 0.5 U/kg *q* 12 hr if BG > 360 mg/dL, and 0.25 U/kg *q* 12 hr if BG < 360 mg/dL.[17] **Dogs** 0.10 U/kg *q* 12 hr.[18]	U-100	Very potent in dogs (caution required); used in dogs and cats; suitable for dogs in which NPH and lente have short duration of activity.

COMMUNICATING WITH OWNERS OF DIABETIC PETS

Can I monitor my pet's blood glucose's at home?

Numerous studies have shown that pet owners can reliably obtain blood samples from cats and dogs

More accurate due to lack of stress response

Improved glycemic control

COMMUNICATING WITH OWNERS OF DIABETIC PETS

Indications:

Initial management
Whenever the animal is ill or shows progression in clinical signs
Change in insulin dose
Aggressive insulin protocols (cats)

Accuracy of a Flash Glucose Monitoring System in Diabetic Dogs

J Vet Intern Med 2016;30:983–988

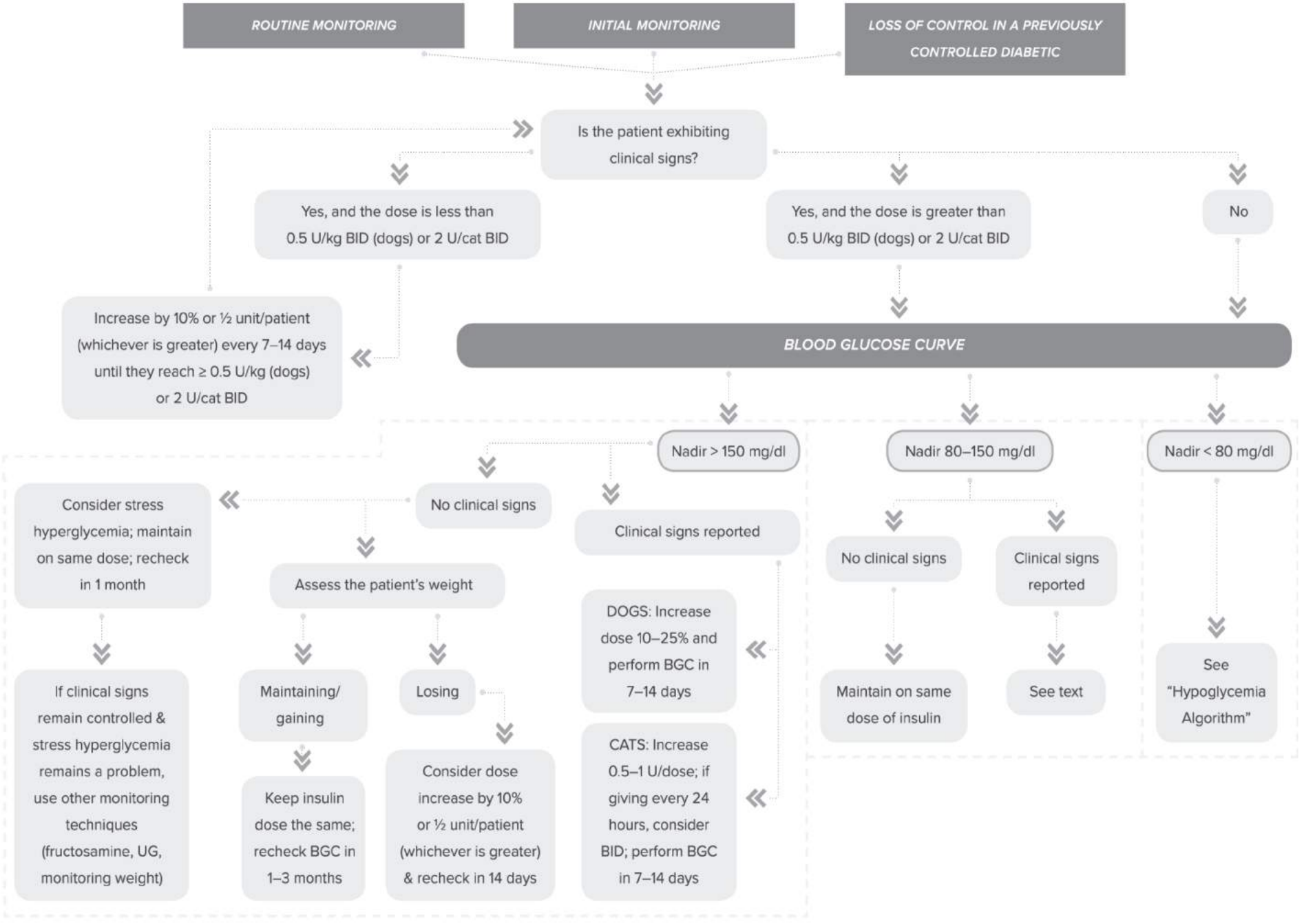
COMMUNICATING WITH OWNERS OF DIABETIC PETS

1) Pre-prandial and pre insulin

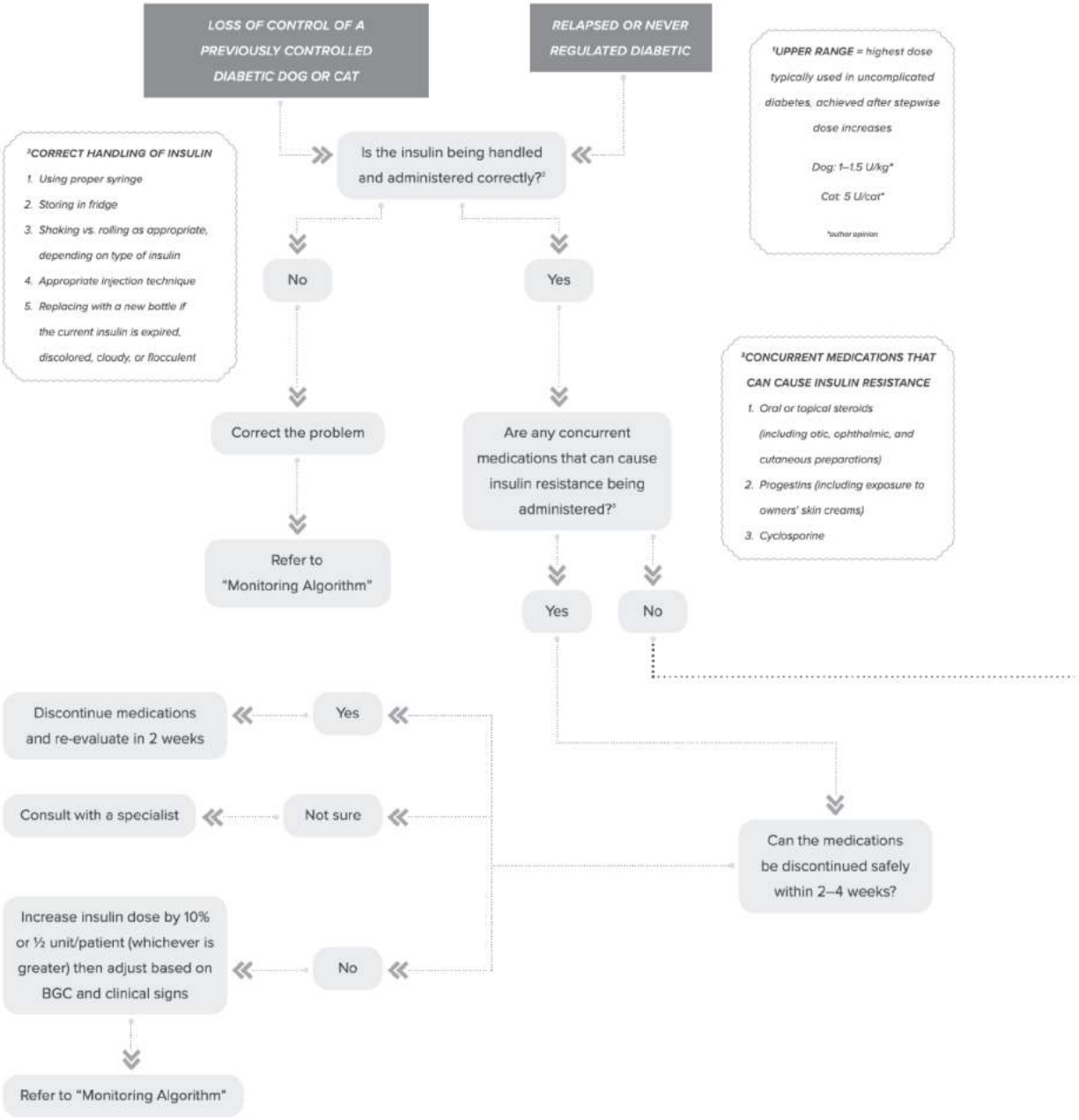
2) Every 2 hours (dogs; cats on NPH, ProZinc or Vetsulin) or 4 hours (cats on glargine) post prandial/insulin

3) Samples should be obtained for 12 hours or until the nadir (lowest glucose concentration) is observed

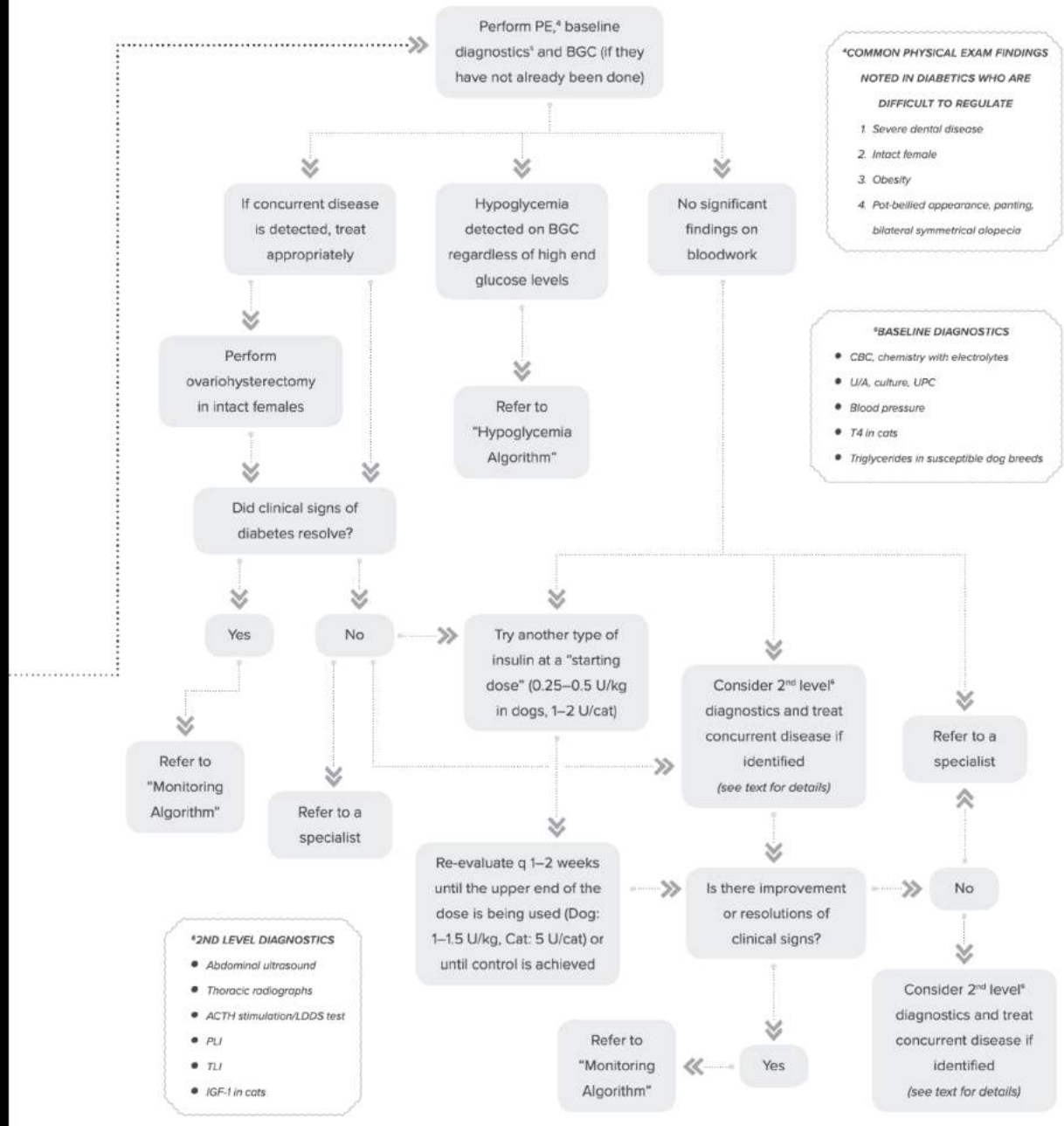
MONITORING BLOOD GLUCOSE LEVELS IN DIABETIC DOGS AND CATS



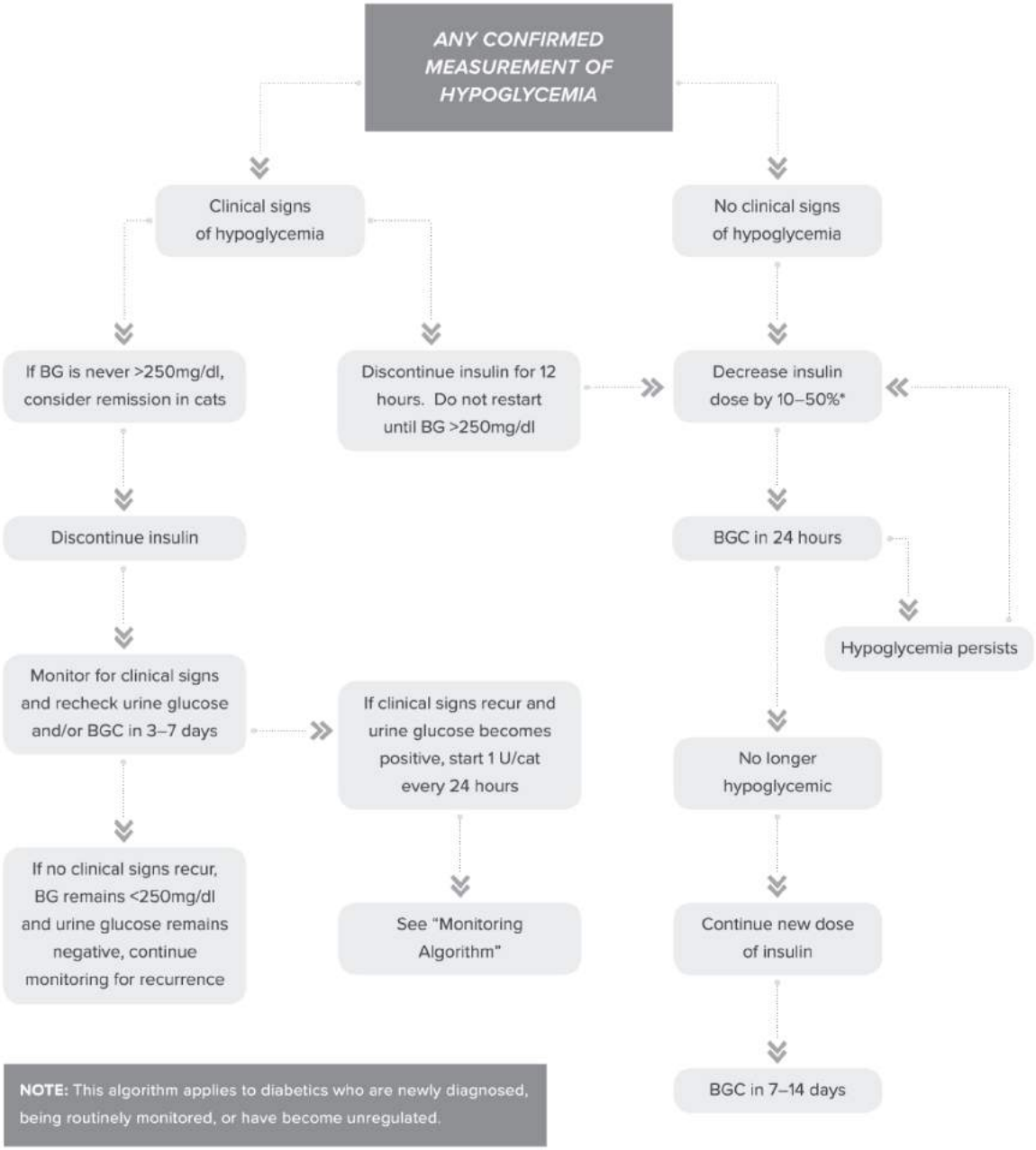
TROUBLESHOOTING DIABETIC DOGS AND CATS RECEIVING THE "UPPER RANGE"[1] OF INSULIN DOSES

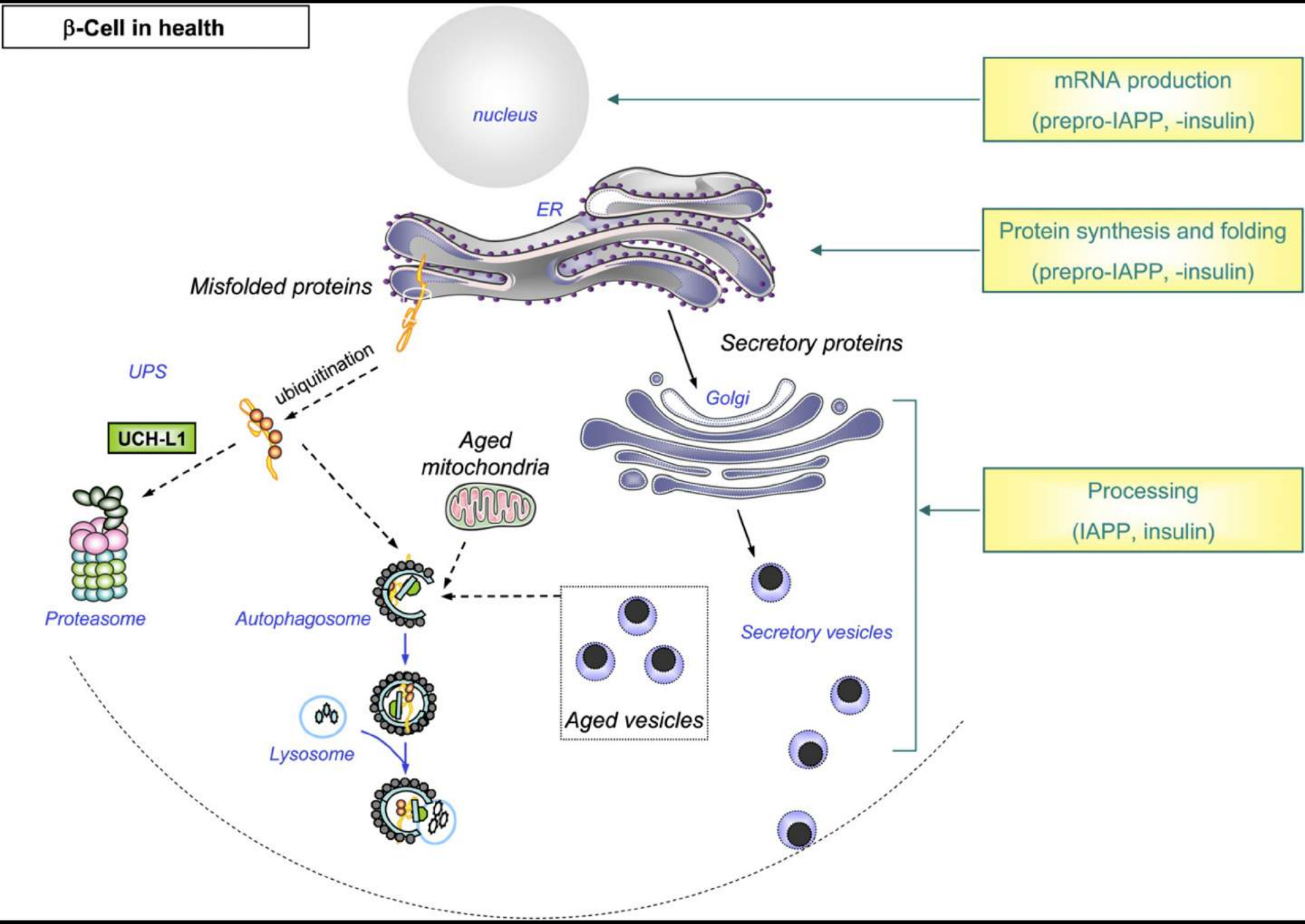


TROUBLESHOOTING DIABETIC DOGS AND CATS RECEIVING THE "UPPER RANGE"[1] OF INSULIN DOSES



MANAGING HYPOGLYCEMIA IN DIABETIC DOGS AND CATS

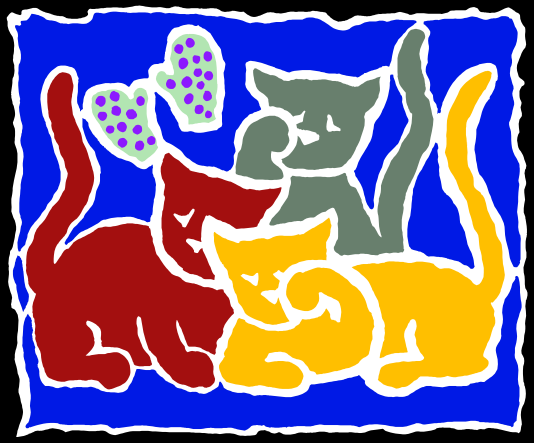



β-Cell in health
nucleus
mRNA production
(prepro-IAPP, -insulin)
ER
Protein synthesis and folding
(prepro-IAPP, -insulin)
Misfolded proteins
Secretory proteins
UPS
ubiquitination
Golgi
UCH-L1
Aged
mitochondria
Processing
(IAPP, insulin)
Proteasome
Autophagosome
Secretory vesicles
Aged vesicles
Lysosome

DIABETES MELLITUS

Feline Insular Amyloid

- Concentration increases with age
- Number of affected islets
- Extent of deposition



DIABETES MELLITUS

Feline Insular Amyloid

- Islet Amyloid (IA)
  - Product of Islet Amyloid Polypeptide (IAPP)
  - Co-produced in beta cell
  - Co-secreted with insulin

DIABETES MELLITUS

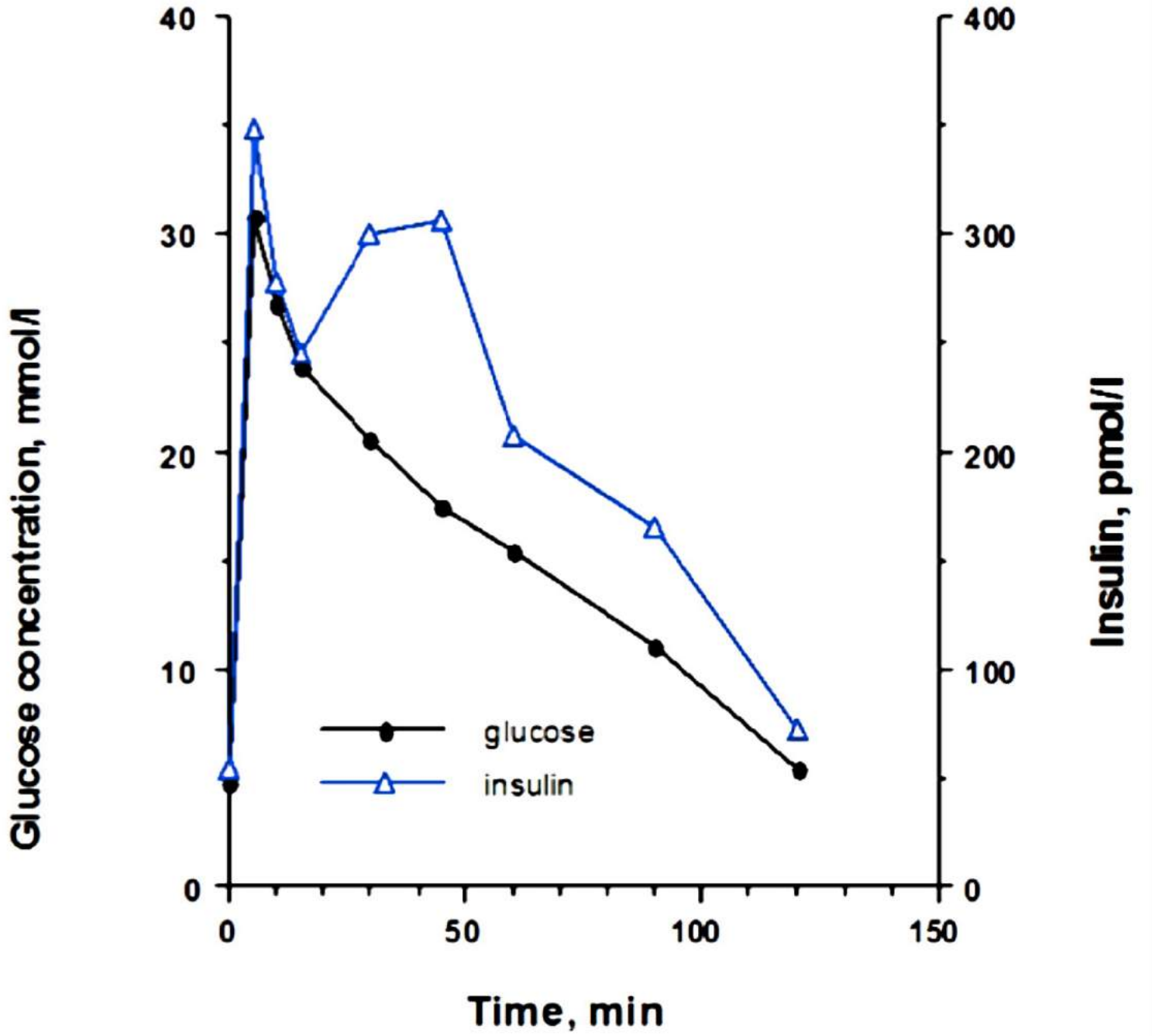
Feline Insular Amyloid

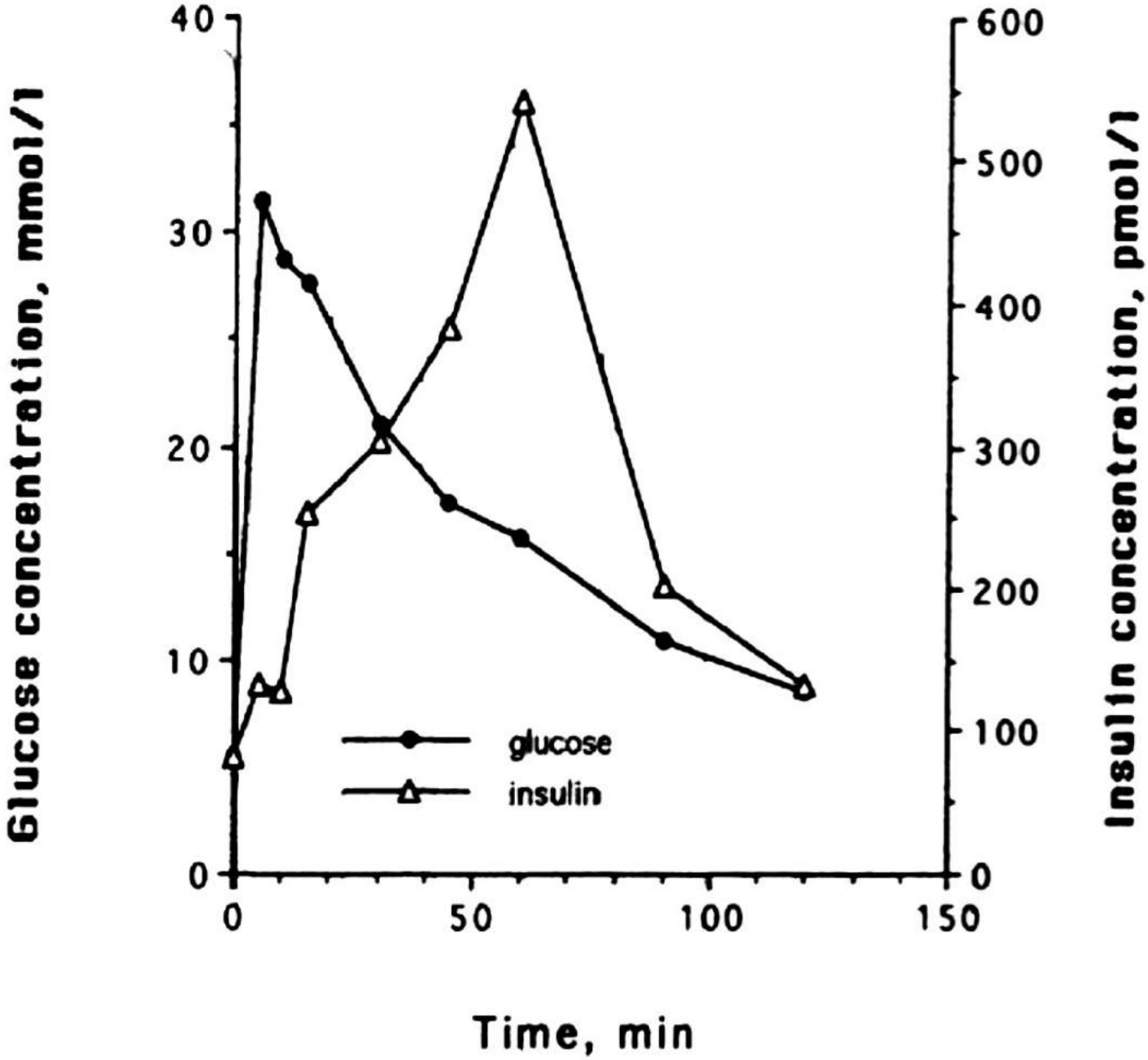
Role of IA and IAPP in Diabetes

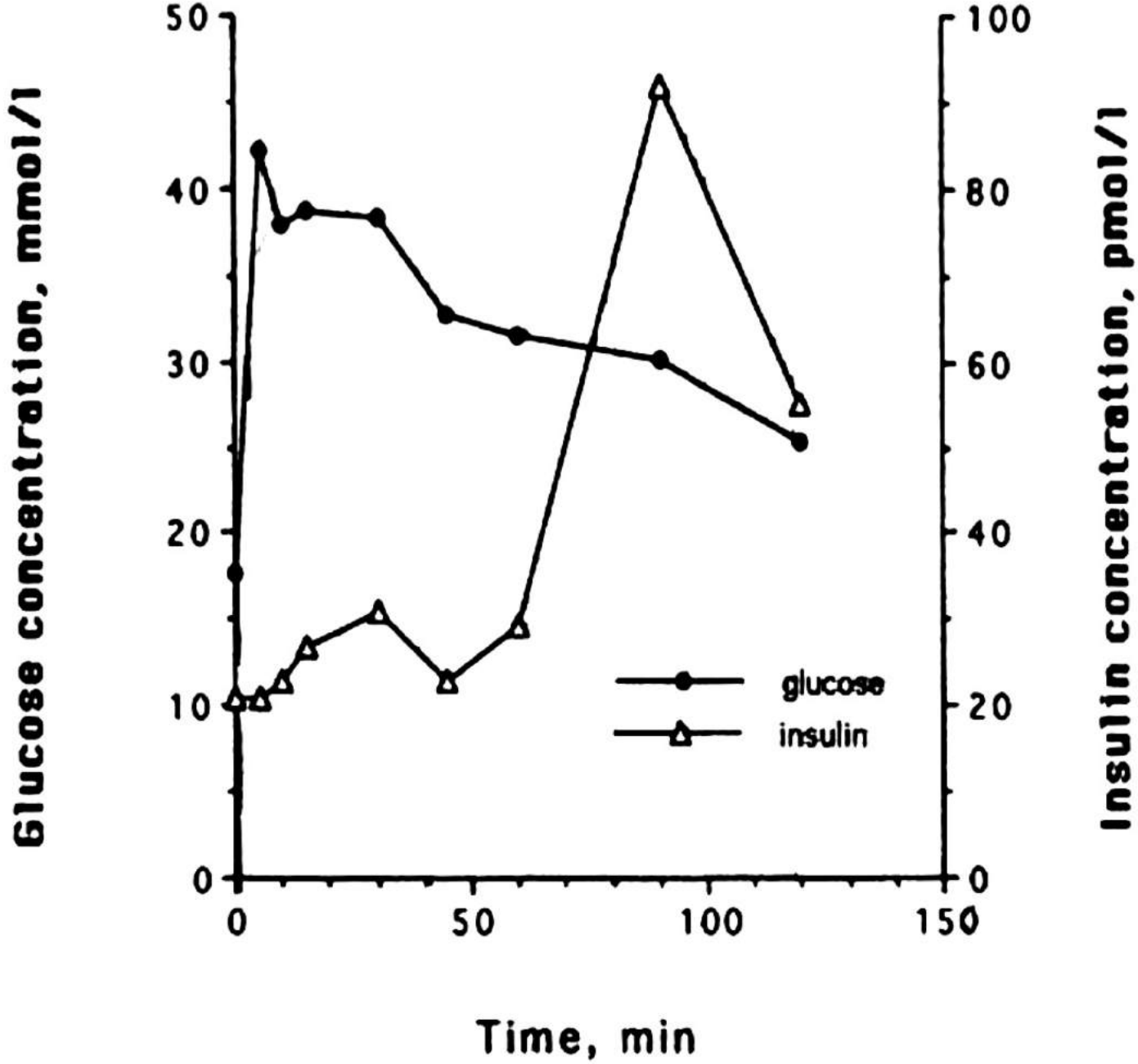
Physical injury to beta cells

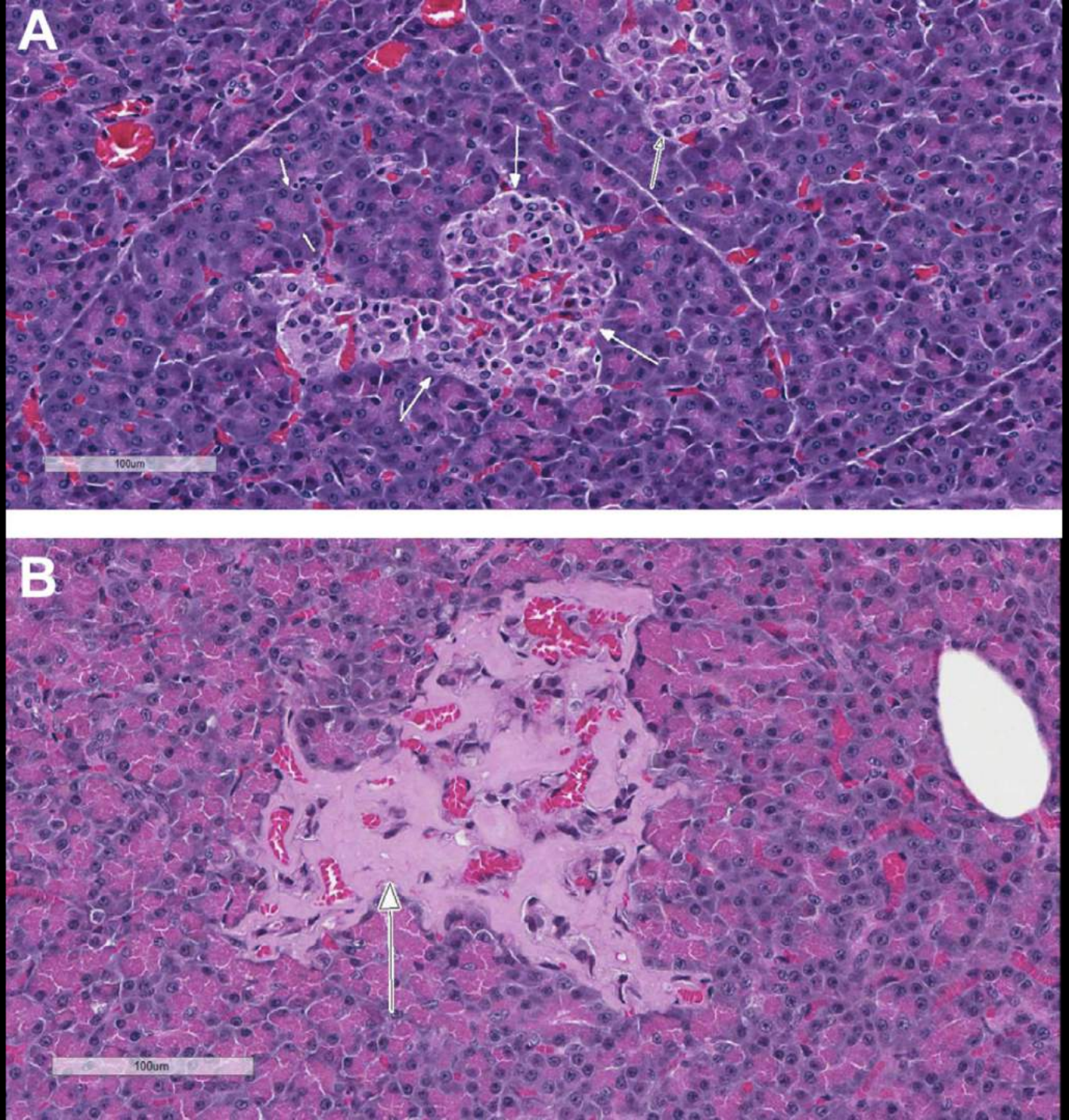
Biological activity of IAPP

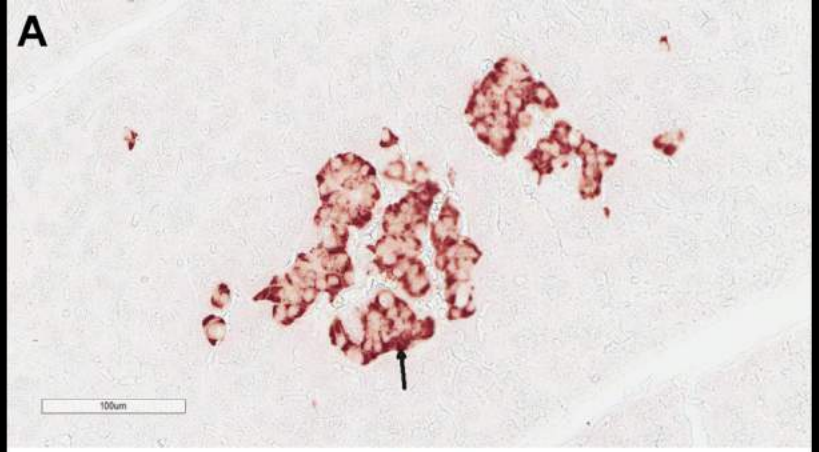
Islet cell membrane effects
glucose and insulin transport
“Glucose toxicty”

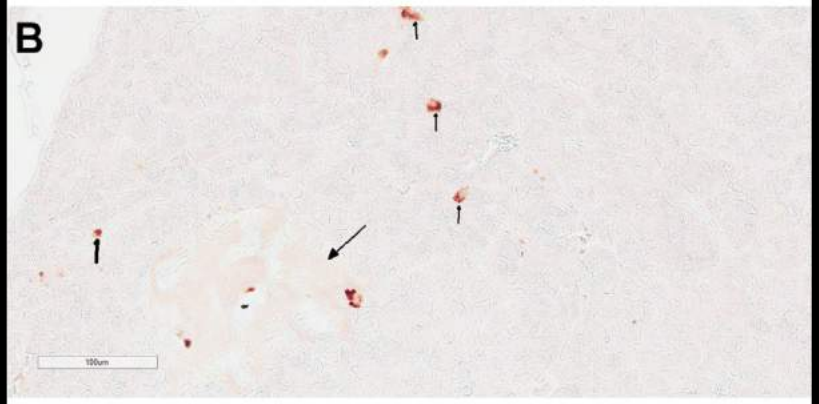

Glucose concentration, mmol/l
Insulin, pmol/l
Time, min
glucose
insulin
0
10
20
30
40
0
100
200
300
400
0
50
100
150

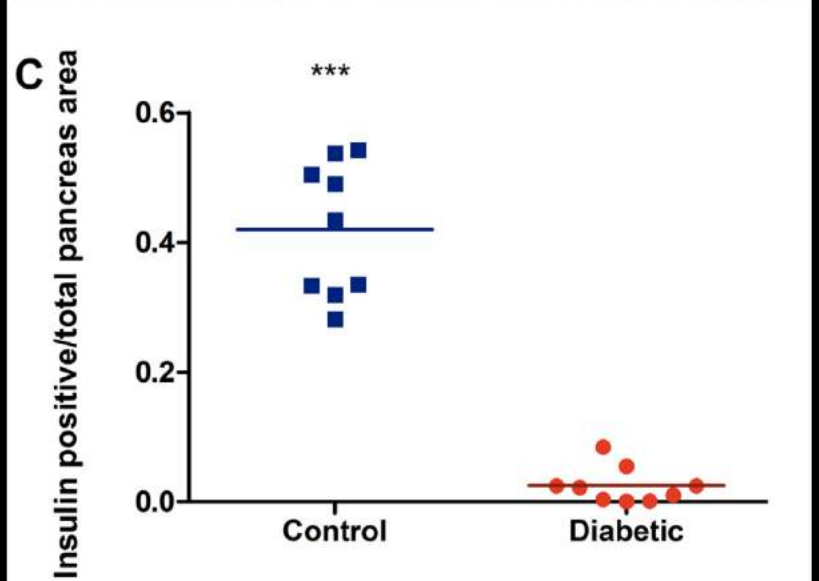

Glucose concentration, mmol/l
Insulin concentration, pmol/l
Time, min
glucose
insulin
0
10
20
30
40
0
100
200
300
400
500
600
0
50
100
150

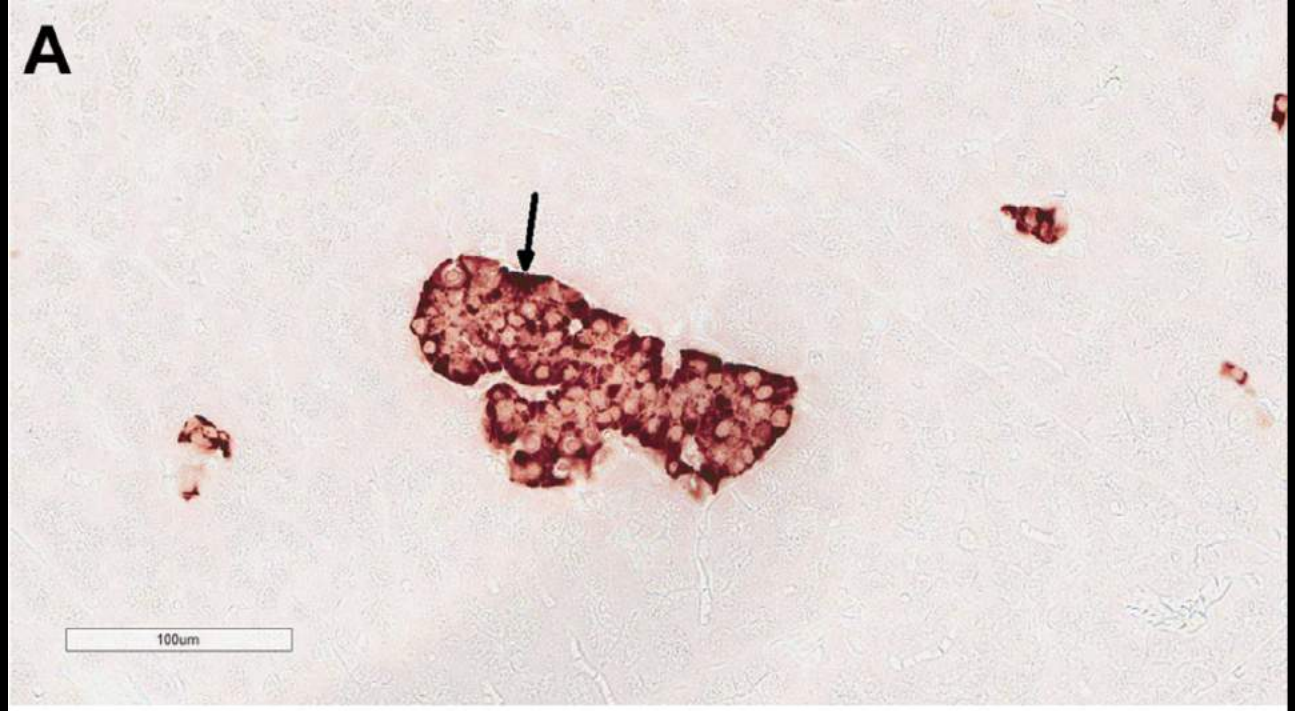

Glucose concentration, mmol/l
Insulin concentration, pmol/l
Time, min
glucose
insulin
0
10
20
30
40
50
0
20
40
60
80
100
0
50
100
150

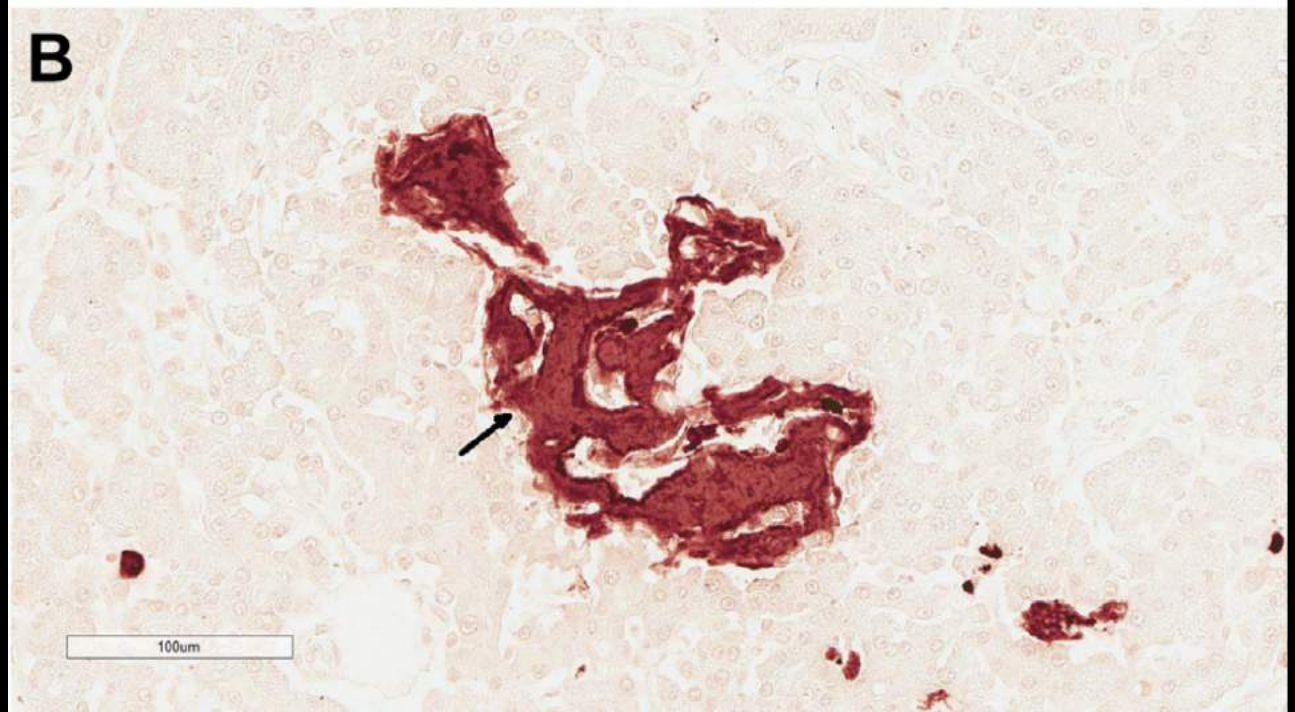

A
100um
B
100um

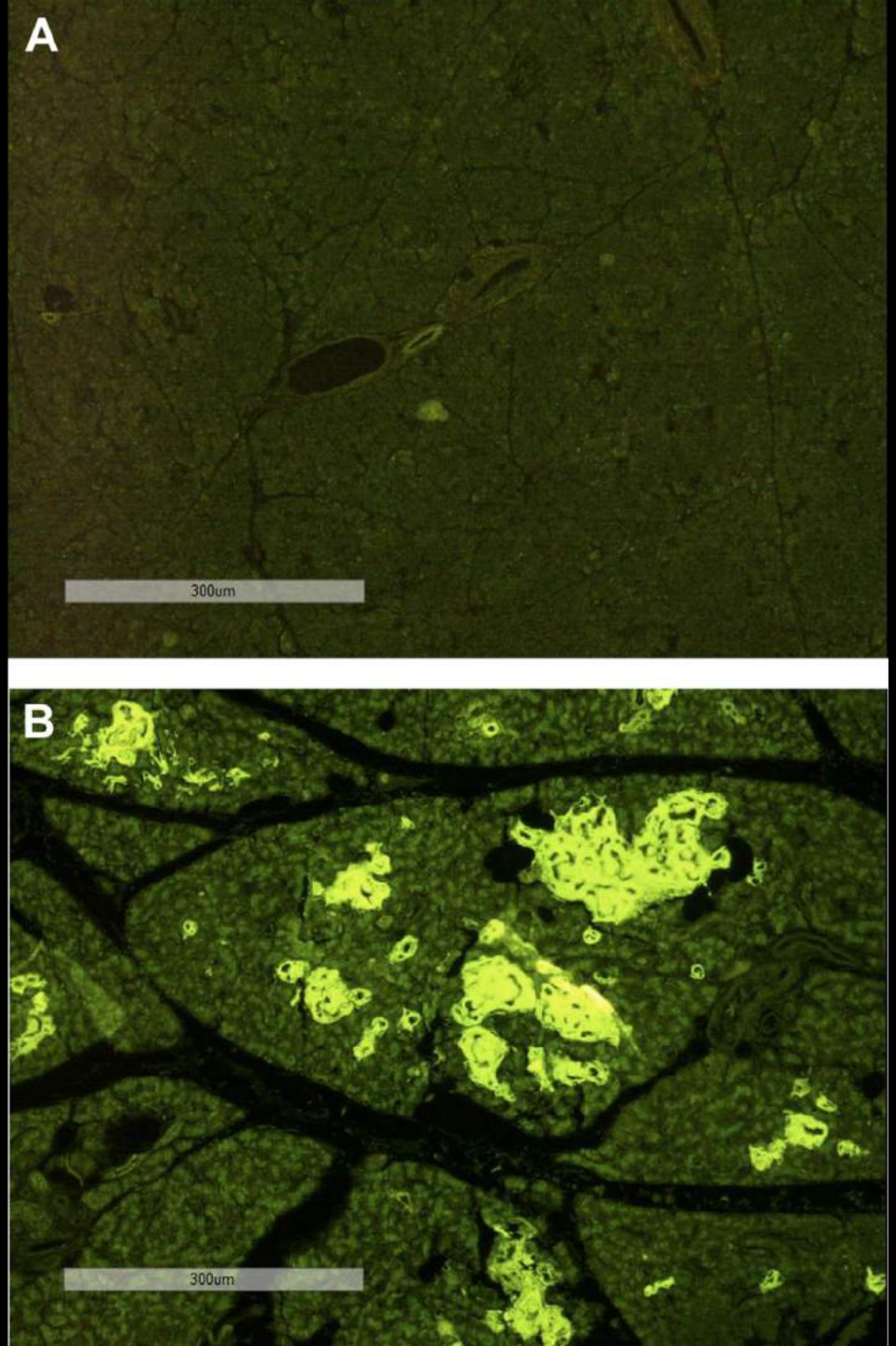

A
100um

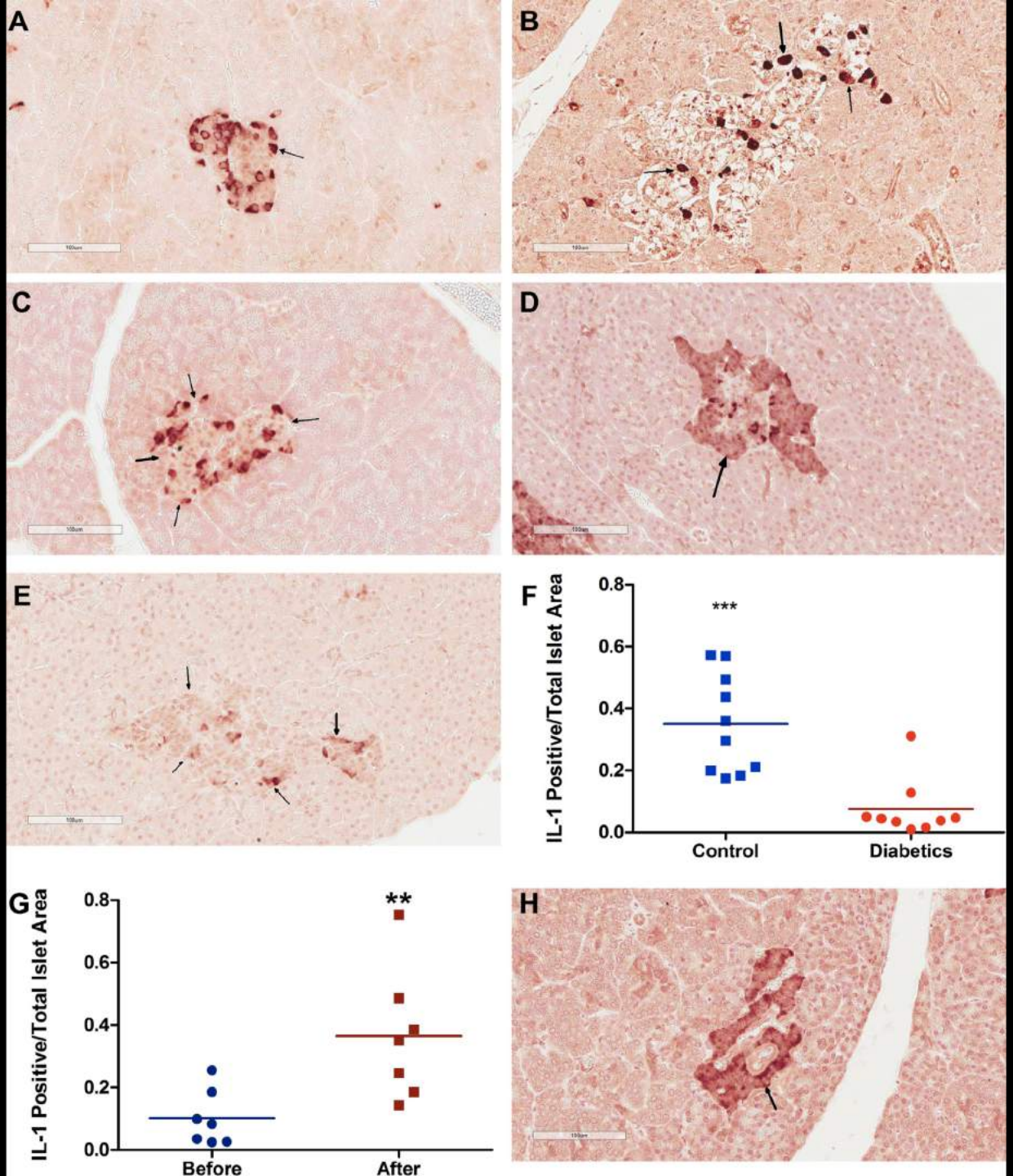

B
100um

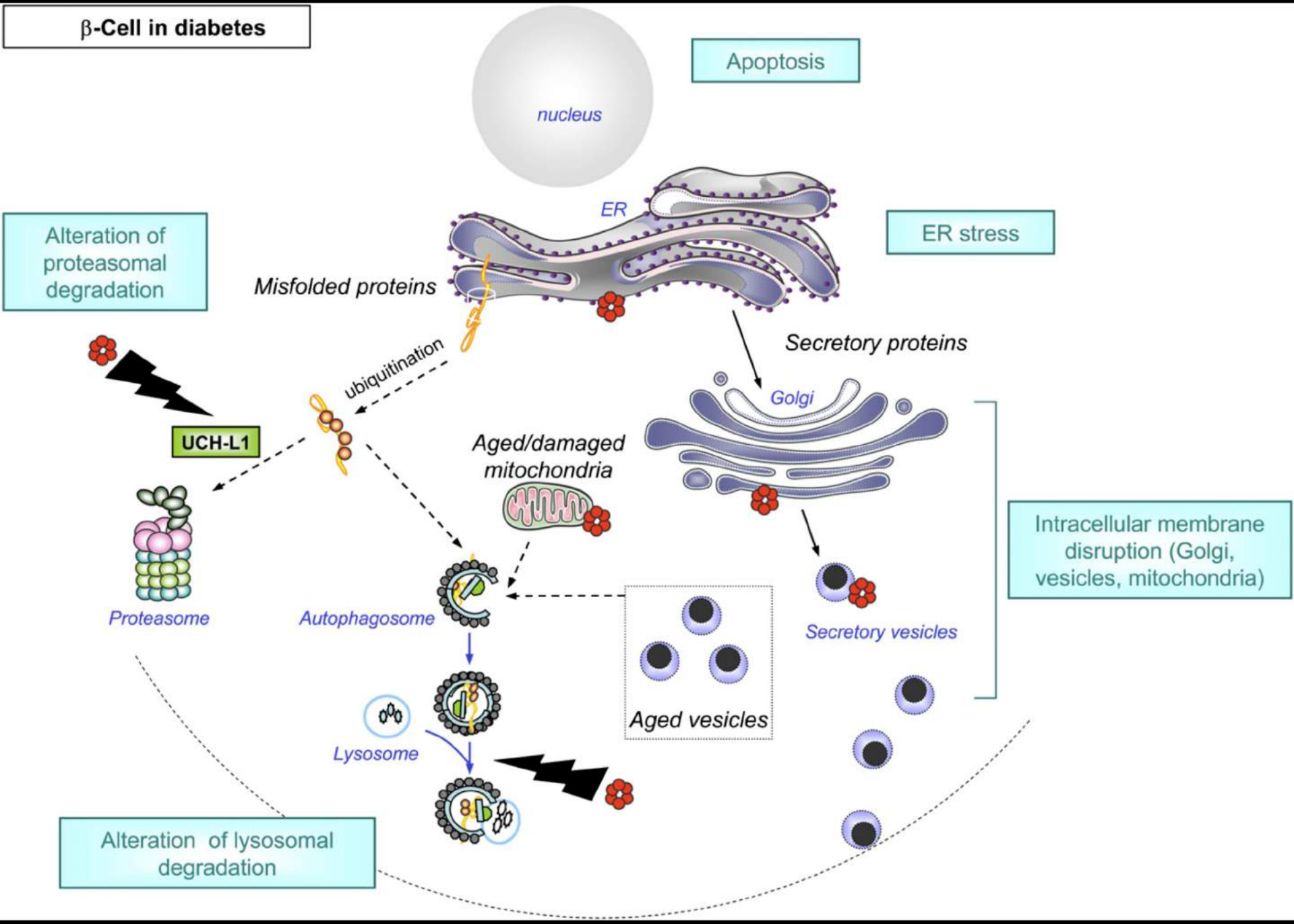

C
***
Insulin positive/total pancreas area
0.6
0.4
0.2
0.0
Control
Diabetic


A
100um

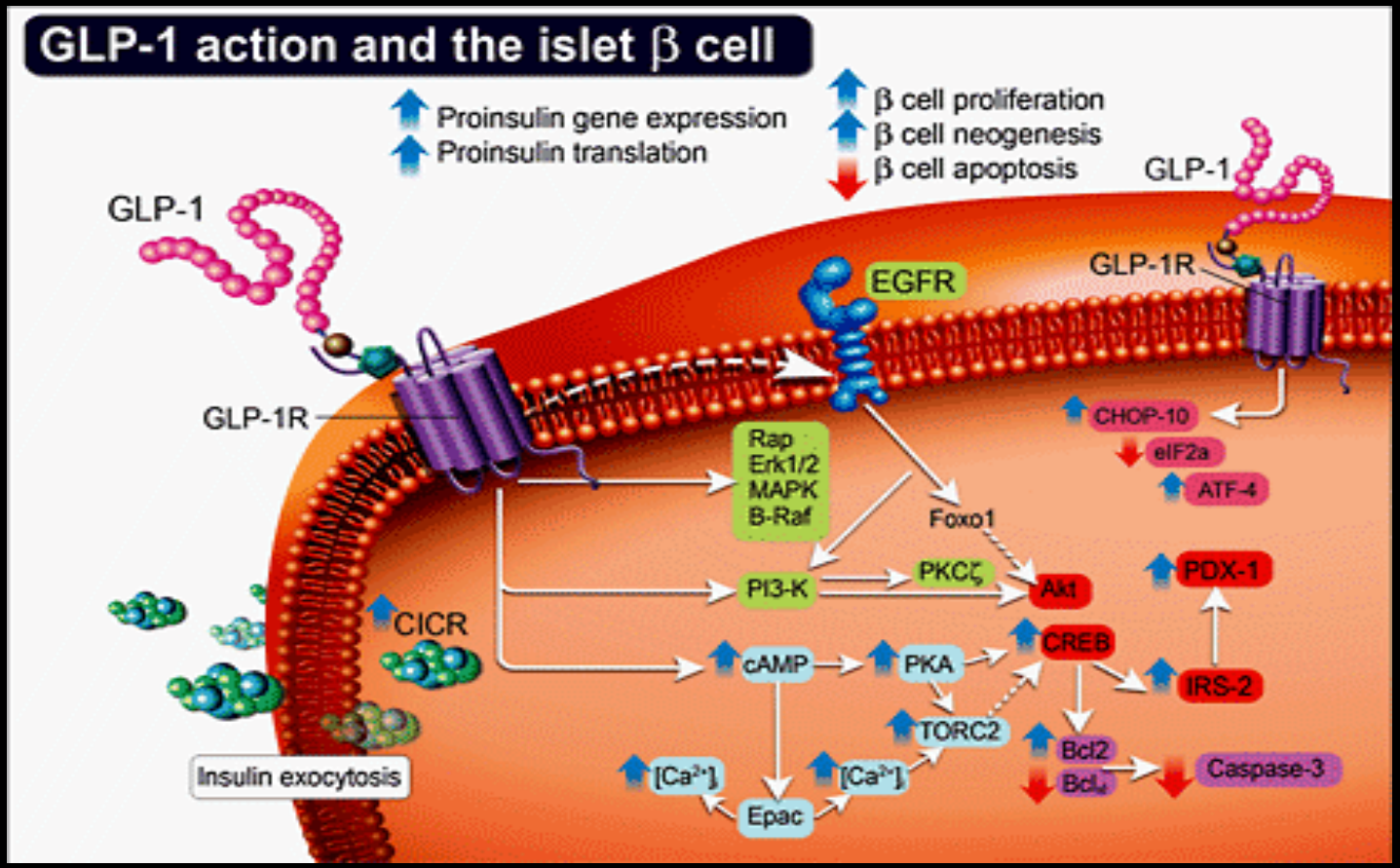

B
100um


A
300um
B
300um


A
B
C
D
E
F
IL-1 Positive/Total Islet Area
0.8
0.6
0.4
0.2
0.0
***
Control
Diabetics
G
IL-1 Positive/Total Islet Area
0.8
0.6
0.4
0.2
0.0
**
Before
After
H


β-Cell in diabetes
Apoptosis
nucleus
ER
ER stress
Alteration of proteasomal degradation
Misfolded proteins
ubiquitination
Secretory proteins
Golgi
UCH-L1
Aged/damaged mitochondria
Intracellular membrane disruption (Golgi, vesicles, mitochondria)
Proteasome
Autophagosome
Secretory vesicles
Aged vesicles
Lysosome
Alteration of lysosomal degradation

DIABETES MELLITUS



DIABETES MELLITUS

Byetta (exenatide)

- Incretin mimetic
- Binds to GLP-1
  - Stimulates insulin secretion
  - Normalizes hypersecretion of glucagon
  - Decreases gastric emptying
  - Improves satiety

DIABETES MELLITUS

Byetta (exenatide and exenatide XR)

After exenatide injection, insulin serum concentrations increased significantly (2.4-fold; range 1.0- to 9.2-fold; P = 0.004) within 15 min. This was followed by a mild decrease in BG concentration and a return of insulin concentration to baseline despite a continuous increase in serum exenatide concentrations. No adverse reactions to exenatide were observed. In conclusion, exenatide affects insulin secretion in cats in a glucose-dependent manner, similar to its effect in other species. Although this effect was not accompanied by a greater ability to dispose of an intravenous glucose infusion, other potentially beneficial effects of exenatide on pancreatic β cells, mainly increasing their proliferation and survival, should be investigated in cats.

The GLP-1 mimetic exenatide potentiates insulin secretion in healthy cats. Domest Anim Endocrinol. 2011 Jul;41(1):42-9.

DIABETES MELLITUS

Exenatide in Cats

In healthy cats, exenatide was quickly absorbed after a SQ injection and caused glucose-dependent insulin secretion.

At a dose of 1.0 mcg/kg SQ (about 10 times the dose that is used in diabetic people), exenatide injection did not cause any side effects in healthy cats, except for hypoglycemia in 1 out of 9 cats. Exenatide has led to significant weight loss in healthy cats of 7.0 ± 4.9% (from 4.78 ± 1.5 kg to 4.48 ± 1.5 kg) with a dose of 1.0 mcg/kg SQ BID for 28 days.

DIABETES MELLITUS

Exenatide in Cats

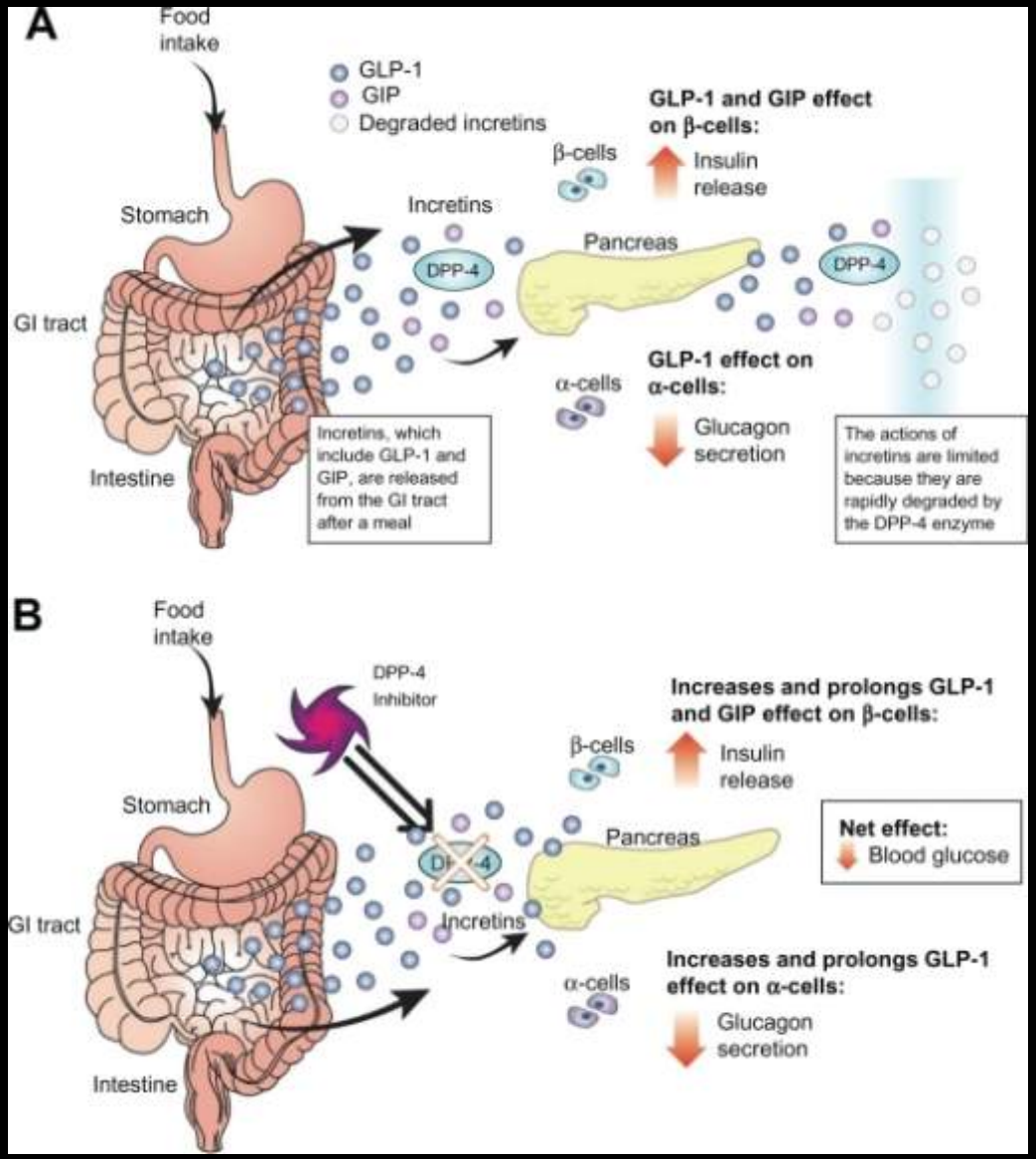
Recently, exenatide-ER was assessed in a group of normal and newly diagnosed diabetic cats treated with insulin glargine and fed a diabetic diet. Cats in this study were treated with once-weekly injection of placebo or exenatide-ER at a dose of 0.2 mg/kg. Despite using what seems in retrospect like a very high dose, this study found only a trend towards a small effect of exenatide-ER on remission rates and improved glycemic control. At first glance these are disappointing results because they suggest lack of efficacy in diabetic cats. However, it is possible that a more obvious positive effect would have been seen if the target population was more similar to the target population used in exenatide studies in people (i.e., non-insulin dependent type 2 diabetics) (relatively early in the course of the disease). No side effects were observed in cats in the two studies described above.

DIABETES MELLITUS

Liraglutide in Cats

Liraglutide in healthy cats has been studied at a dose of 0.6 mg/cat once daily for 7 days. Liraglutide caused significant weight loss in all cats at day (9 ± 3%). Appetite was subjectively decreased in all cats and one cat was withdrawn on day 4 because of 48 hours of anorexia. During a hyperglycemic clamp, liraglutide was associated with a trend towards improved glucose tolerance, higher insulin concentrations and lower glucagon concentrations. Fasting glucose concentrations were not affected.

DIABETES MELLITUS

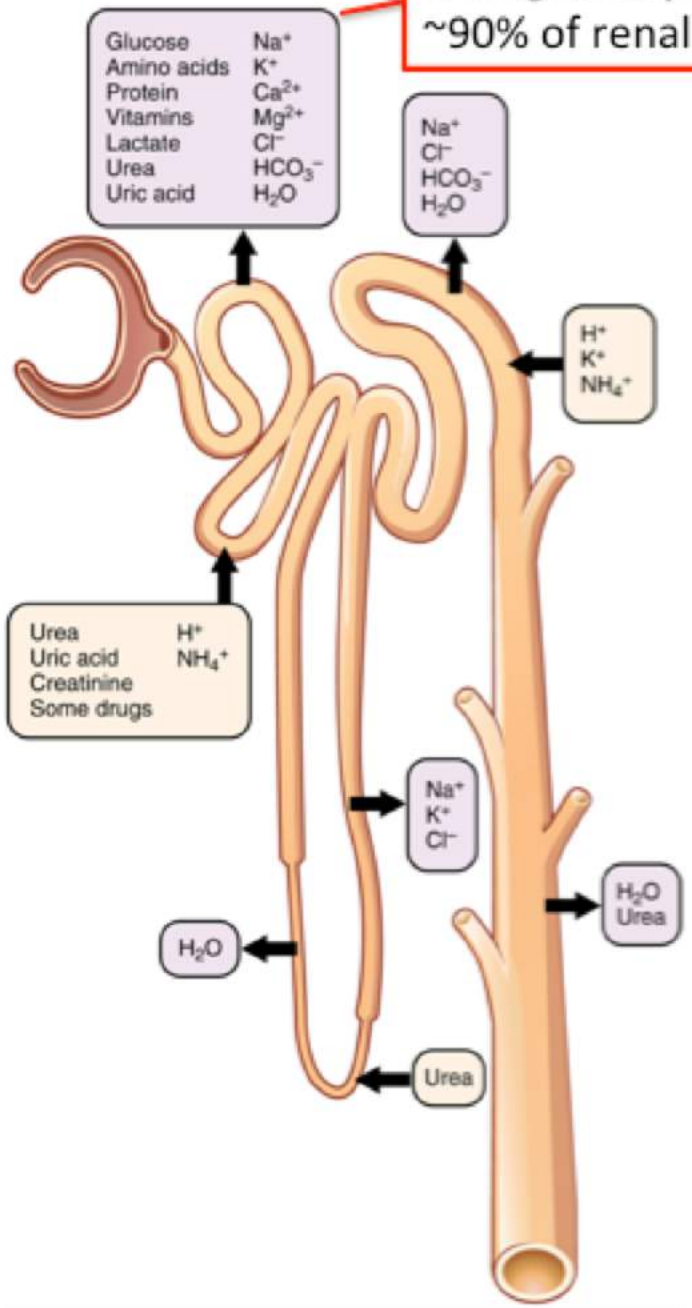


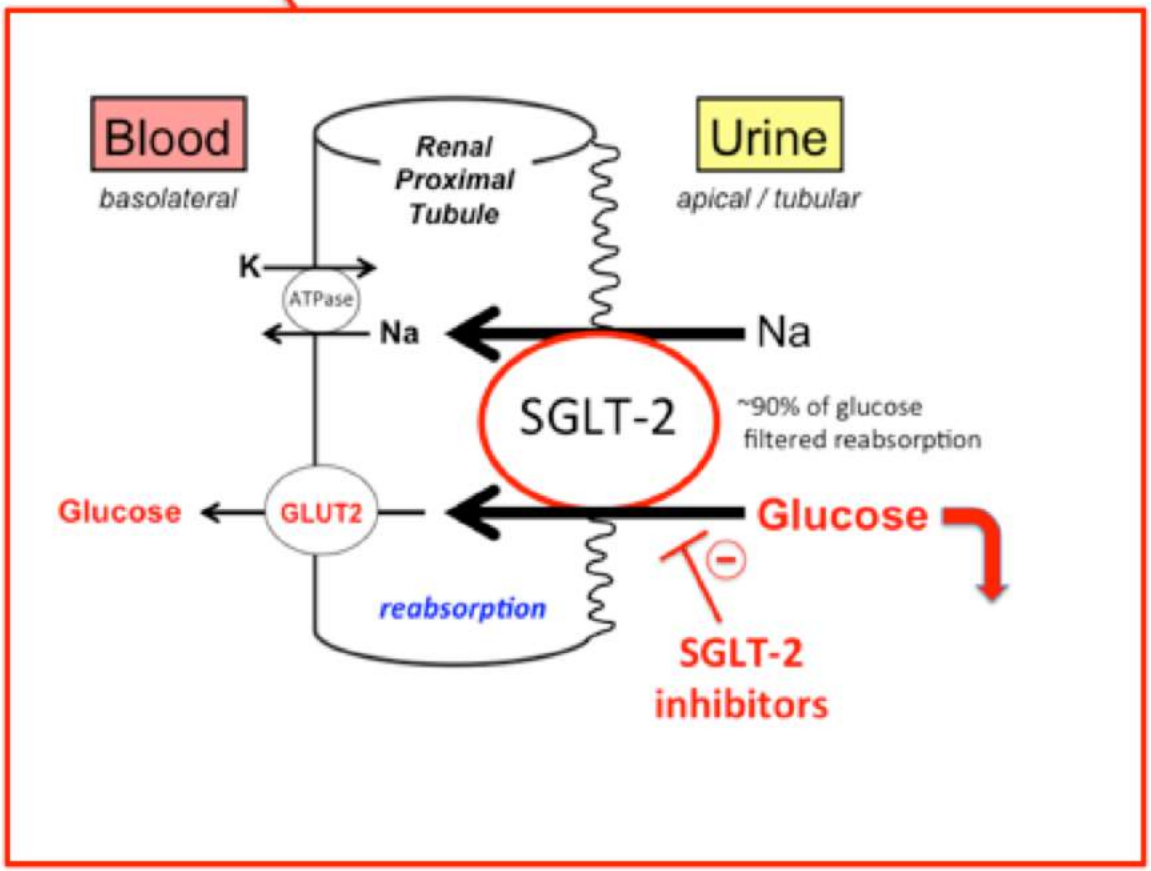
DPP IV INHIBITORS

Intravenous glucose tolerance tests (ivGTT; 0.5 g/kg glucose after 12 h fasting) and a meal response test (test meal of 50% of average daily food intake, offered after 24 h fasting) were performed in healthy non-diabetic cats. NVP-DPP728 (0.5-2.5 mg/kg i.v. or s.c.) significantly reduced glucagon output in all tests and increased insulin output in the ivGTT. Follow-up studies will investigate the potential usefulness as therapy in diabetic cats.

The dipeptidyl peptidase IV inhibitor NVP-DPP728 reduces plasma glucagon concentration in cats. Vet J. 2010 Mar;183(3):355-7

S1 segment proximal tubule:
~90% of renal glucose reabsorption





Non-Insulin Therapeutic Agents Used to Treat Canine and Feline Diabetes Mellitus

Therapeutic Class	Examples	Mode of Action	Used with Insulin Cotherapy	Comments
Sulfonylureas	Glipizide	Stimulates insulin secretion from the pancreas.	No	Only recommended for owners who refuse to use insulin in cats. Not for use in dogs.
α-glucosidase inhibitors	Acarbose	Inhibits intestinal glucose absorption and reduces postprandial hyperglycemia.	Yes	Can be used in dogs and cats. Useful when peak activity of insulin occurs too soon (2 hr after administration).
Incretins	Glucagon-like peptide-1; Exenatide (Byetta); Exenatide ER (Bydureon); Liraglutide (Victoza)	Stimulates insulin secretion from pancreas, delays gastric emptying, increases satiety, protects beta cells, promotes expansion of beta cell population, suppresses glucagon.	Yes	Promising results with exenatide ER in cats and liraglutide in dogs.[24,25] The mode of action is seen most commonly in healthy animals and possibly, diabetic cats, but not in dogs with classic diabetes.

DIABETES MELLITUS

Chromium and Vanadium

- Transition metals
- Insulinomimetic properties
- NIDDM and IDDM
- Acts at post-receptor sites
  - Chromium 100 ug BID
  - Vanadium 200 ug/day in food