Canine and Feline Diabetes Mellitus

PACIFIC COAST VETERINARY SPECIALISTS

Our mission is to redefine and elevate your pet's health through collaborative, minimally-invasive, and compassionate care that supports the well-being of your pet and peace of mind for your family.

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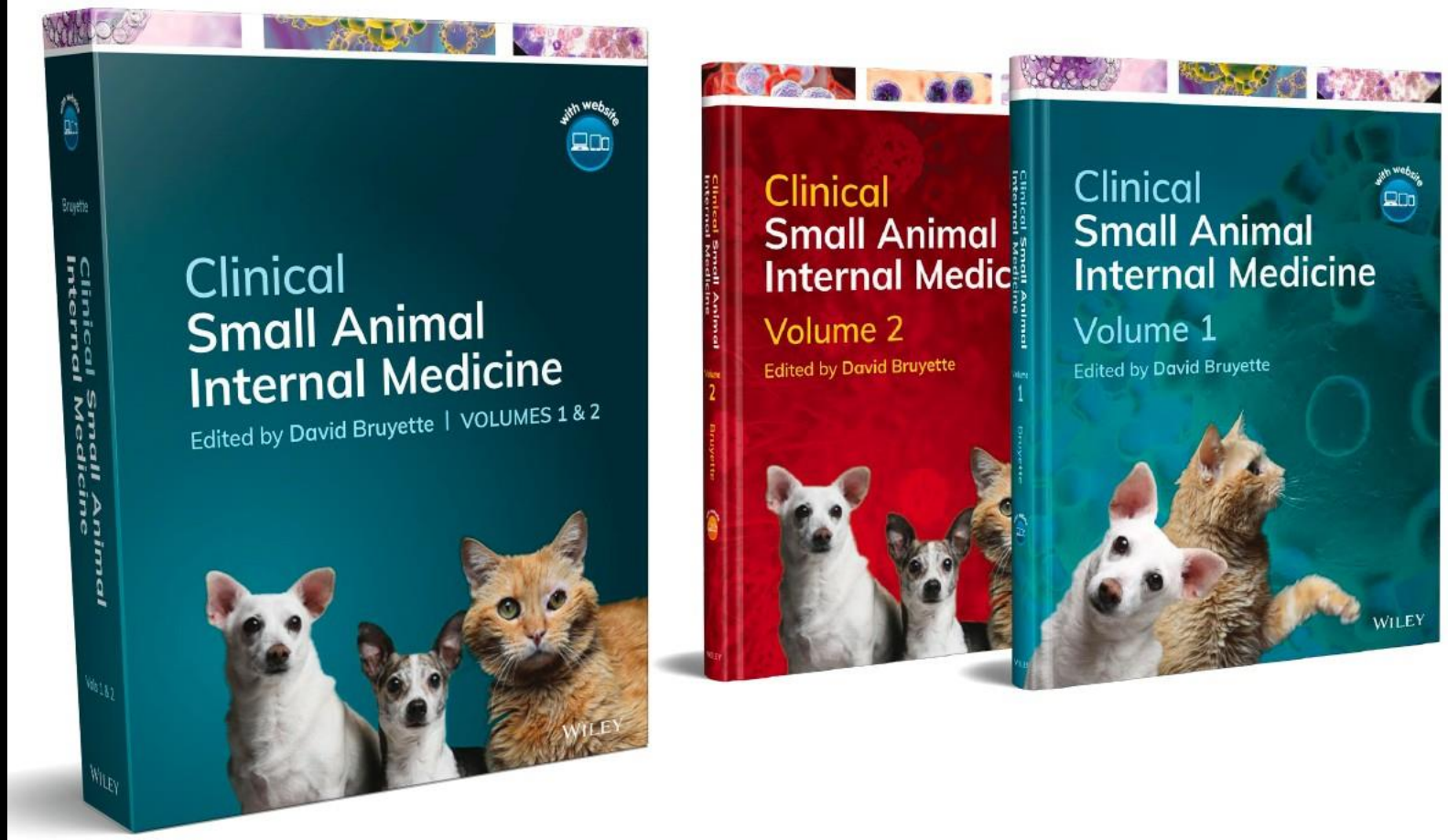
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PURITY
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ULTRA 34 PREMIUM
ORGANIC
DRY
DOLIN
VERMOUTH
DE CHAMBÉRY

Canine Diabetes

Goal: Control of clinical signs
Treatment: Lente insulin 0.5 units/kg BID
Diet: Consistent Diet
Monitoring: CBGM/fructosamine

Feline Diabetes

Goal: Remission
Treatment: Glargine insulin
1-3 units BID
Diet: High protein
Monitoring: CBGM/fructosamine

"Insulin is not a cure for diabetes, it is a treatment". Frederick Banting, Nobel Lecture, 1923

More than 38.4 million Americans have diabetes with another 97.6 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 2022, the cost of diagnosed diabetes was estimated to be $413 billion annually, with $307 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.

Table 2.1—Criteria for the diagnosis of diabetes in nonpregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results obtained at the same time (e.g., A1C and FPG) or at two different time points.

Table 2.2—Criteria defining prediabetes in nonpregnant individuals

A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose.

American Diabetes Association.
Connected for Life

Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. How old are you?
Less than 40 years (0 points)
40–49 years (1 point)
50–59 years (2 points)
60 years or older (3 points)

2. Are you a man or a woman?
Man (1 point) Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes?
Yes (1 point) No (0 points)

4. Do you have a mother, father, sister or brother with diabetes?
Yes (1 point) No (0 points)

5. Have you ever been diagnosed with high blood pressure?
Yes (1 point) No (0 points)

6. Are you physically active?
Yes (0 points) No (1 point)

7. What is your weight category?
See chart at right.

ADD UP YOUR SCORE.

Height	Weight (lbs.)		
4′ 10″	119–142	143–190	191+
4′ 11″	124–147	148–197	198+
5′ 0″	128–152	153–203	204+
5′ 1″	132–157	158–210	211+
5′ 2″	136–163	164–217	218+
5′ 3″	141–168	169–224	225+
5′ 4″	145–173	174–231	232+
5′ 5″	150–179	180–239	240+
5′ 6″	155–185	186–246	247+
5′ 7″	159–190	191–254	255+
5′ 8″	164–196	197–261	262+
5′ 9″	169–202	203–269	270+
5′ 10″	174–208	209–277	278+
5′ 11″	179–214	215–285	286+
6′ 0″	184–220	221–293	294+
6′ 1″	189–226	227–301	302+
6′ 2″	194–232	233–310	311+
6′ 3″	200–239	240–318	319+
6′ 4″	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower Your Risk

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

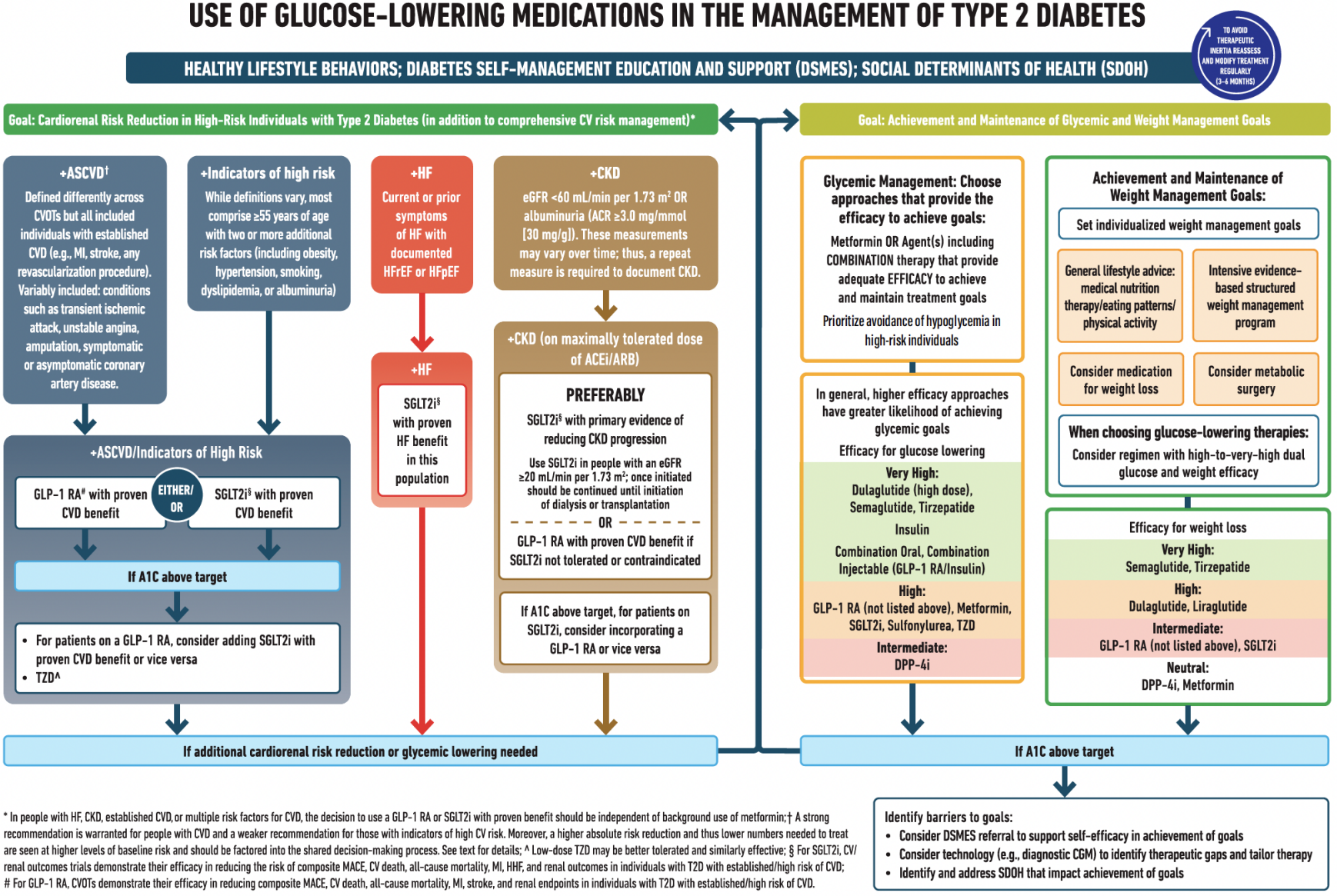
*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Table 9.2—Medications for lowering glucose, summary of characteristics

	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost	Clinical considerations
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*			
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m^2	Oral	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food • Potential for vitamin B12 deficiency; monitor at regular intervals
SGLT2 inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Counsel patients about potential for ileus • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
Dual GIP and GLP-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Not recommended for individuals with history of gastroparesis • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	Oral	High	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing): discontinue if suspected
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	Oral	Low	• Congestive HF (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Oral	Low	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) • Use with caution in persons at risk for hypoglycemia
Insulin Human	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	SQ; inhaled	Low (SQ)	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin Analogs								SQ	High	

CV, cardiovascular; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; NASH, nonalcoholic steatohepatitis; MACE, major adverse cardiovascular events; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes mellitus. *For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. [1]Tsapas et al. (104). [2]Tsapas et al. (152). Adapted from Davies et al. (84).

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/ renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (84).

Table 9.3—Median monthly (30-day) AWP and NADAC of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

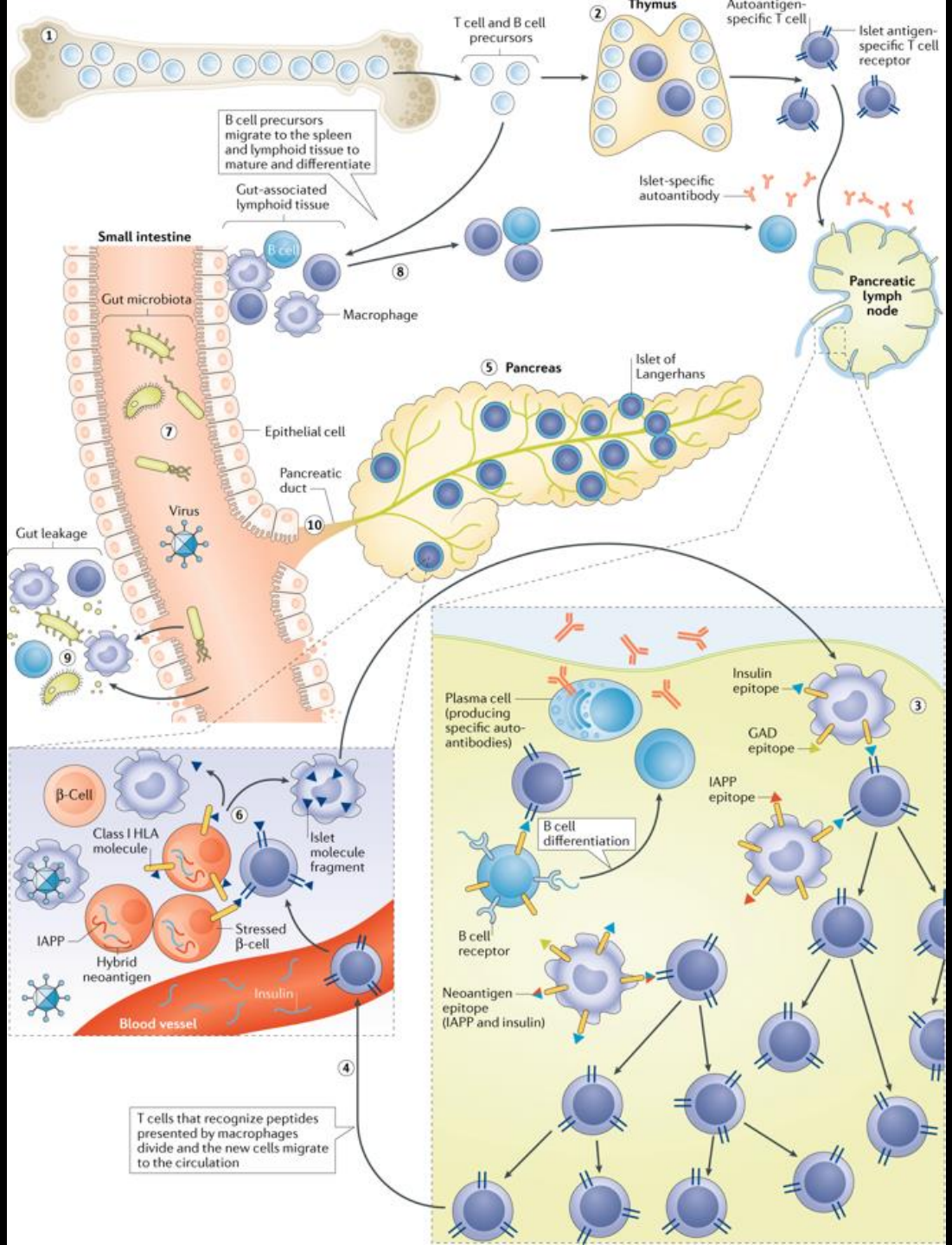
Class	Compound(s)	Dosage strength/ product (if applicable)	Median AWP (min, max)*	Median NADAC (min, max)*	Maximum approved daily dose†
Biguanides	• Metformin	500 mg (ER)	$89 ($45, $6,719)	$5	2,000 mg
		850 mg (IR)	$108 ($5, $189)	$2	2,550 mg
		1,000 mg (IR)	$87 ($3, $144)	$2	2,000 mg
		1,000 mg (ER)	$1,884 ($242, $7,214)	$31 ($31, $226)	2,000 mg
		500 mg (Sol)	$405 ($405, $739)	$535	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$73 ($72, $198)	$3	8 mg
	• Glipizide	10 mg (IR)	$72 ($67, $91)	$6	40 mg
		10 mg (XL/ER)	$48 ($46, $48)	$10	20 mg
	• Glyburide	6 mg (micronized)	$54 ($48, $71)	$12	12 mg
		5 mg	$82 ($63, $432)	$8	20 mg
Thiazolidinedione	• Pioglitazone	45 mg	$348 ($7, $349)	$4	45 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $378)	$27	300 mg
	• Miglitol	100 mg	$294 ($241, $346)	NA	300 mg
Meglitinides	• Nateglinide	120 mg	$155	$27	360 mg
	• Repaglinide	2 mg	$878 ($58, $897)	$31	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$161	25 mg
	• Linagliptin	5 mg	$630	$504	5 mg
	• Saxagliptin	5 mg	$524	$466	5 mg
	• Sitagliptin	100 mg	$657	$525	100 mg
SGLT2 inhibitors	• Canagliflozin	300 mg	$718	$574	300 mg
	• Dapagliflozin	10 mg	$678	$543	10 mg
	• Empagliflozin	25 mg	$712	$569	25 mg
	• Ertugliflozin	15 mg	$408	$328	15 mg
GLP-1 RAs	• Dulaglutide	4.5 mg pen	$1,117	$895	4.5 mg‡
	• Exenatide	10 μg pen	$964	$771	20 μg
	• Exenatide (extended release)	2 mg pen	$990	$793	2 mg‡
	• Liraglutide	1.8 mg pen	$1,340	$1,072	1.8 mg
	• Semaglutide	1 mg pen	$1,123	$903	2 mg‡
		14 mg (tablet)	$1,097 ($1,070, $1,123)	$899	14 mg
Dual GIP and GLP-1 receptor agonist	• Tirzepatide	15 mg pen	$1,228	$982	15 mg‡
Bile acid sequestrant	• Colesevelam	625 mg tabs	$711 ($674, $712)	$64	3.75 g
		3.75 g suspension	$674 ($673, $675)	$130	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$1,200	$965	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2,866	NA	120 μg/injection§

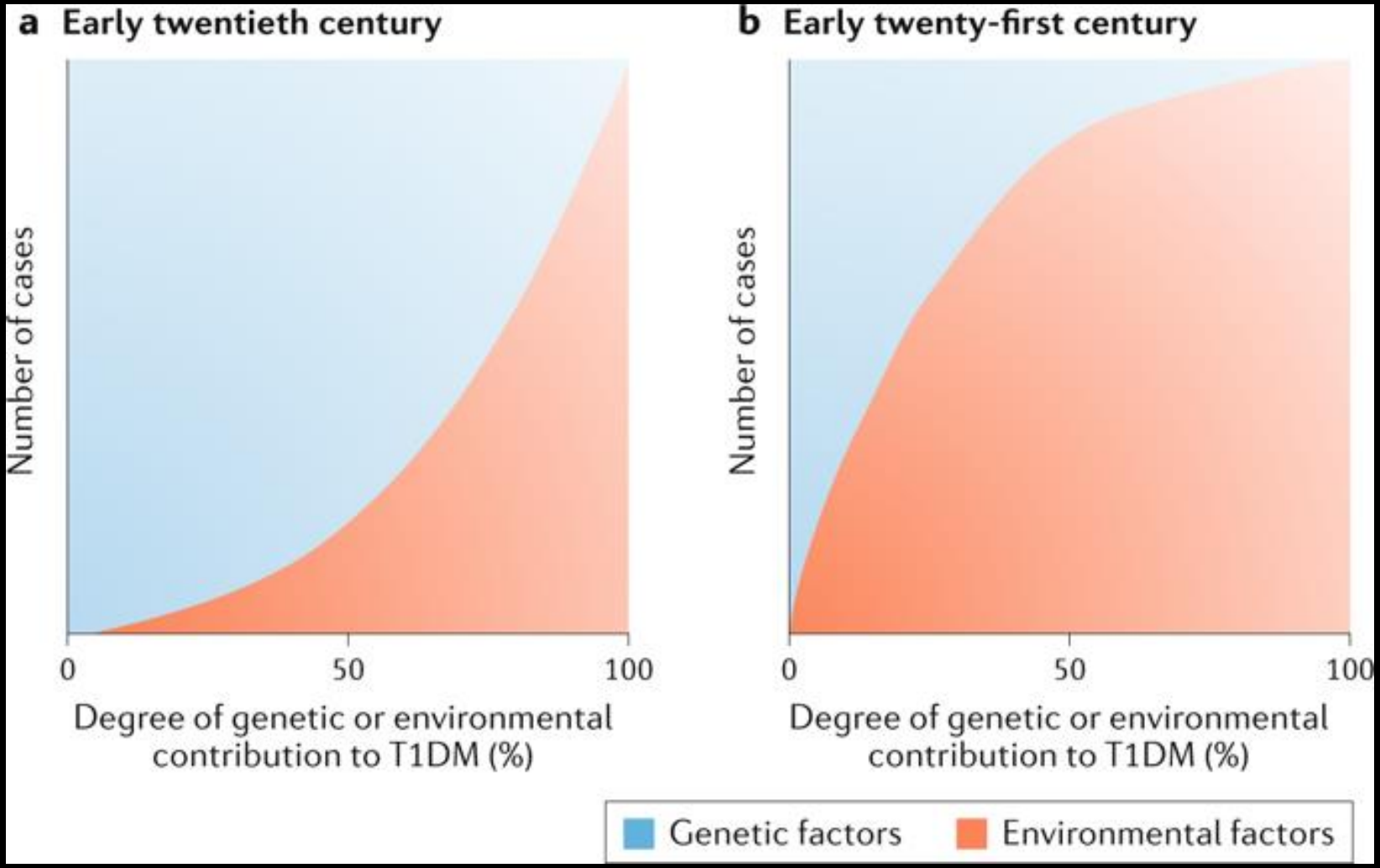
AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; NA, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. AWP and NADAC prices as of July 2023. *Calculated for 30-day supply (AWP [116] or NADAC [117] unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. †Used to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. Prices for bexagliflozin were not available at the time of this update. ‡Administered once weekly. §AWP and NADAC calculated based on 120 μg three times daily.

Table 9.4—Median cost of insulin products in the U.S. calculated as AWP and NADAC per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC*
Rapid-acting	• Aspart	U-100 vial	$174†	$139†
		U-100 cartridge	$215†	$172†
		U-100 prefilled pen	$224†	$179†
	• Aspart ("faster acting product")	U-100 vial	$347	$277
		U-100 cartridge	$430	$344
		U-100 prefilled pen	$447	$357
	• Glulisine	U-100 vial	$341	$273
		U-100 prefilled pen	$439	$351
	• Inhaled insulin	Inhalation cartridges	$1,503	NA
	• Lispro	U-100 vial	$30†	$24†
		U-100 cartridge	$408	$326
		U-100 prefilled pen	$127†	$102†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	$261
		U-100 prefilled pen	$424	$339
		U-200 prefilled pen	$424	$338
	• Lispro follow-on product	U-100 vial	$118	$94
		U-100 prefilled pen	$151	$121
Short-acting	• Human regular	U-100 vial	$172 ($165, $178)‡	$137 ($132, $142)‡
		U-100 prefilled pen	$208	$166
Intermediate-acting	• Human NPH	U-100 vial	$172 ($165, $178)‡	$137 ($132, $143)‡
		U-100 prefilled pen	$208 ($208, $377)	$234 ($166, $303)
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$142
		U-500 prefilled pen	$230	$184
Long-acting	• Detemir	U-100 vial; U-100 prefilled pen	$370	$295
	• Degludec	U-100 vial	$142†	$327
		U-100 prefilled pen	$142†	$114†
		U-200 prefilled pen	$85†	$113†
	• Glargine	U-100 vial; U-100 prefilled pen	$136†	$109†
		U-300 prefilled pen	$363	$290
	• Glargine biosimilar/ follow-on products	U-100 prefilled pen	$190 ($74, $323)	$95†
		U-100 vial	$118†	$95†
Premixed insulin products	• Aspart 70/30	U-100 vial	$180†	$145†
		U-100 prefilled pen	$224†	$179†
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$341
	• Lispro 75/25	U-100 vial	$342	$274
		U-100 prefilled pen	$127†	$102†
	• NPH/regular 70/30	U-100 vial	$172 ($165, $178)‡	$138 ($132, $143)‡
		U-100 prefilled pen	$208 ($208, $377)	$234 ($166, $302)
Premixed insulin/GLP-1 RA products	• Degludec/liraglutide	100/3.6 μg prefilled pen	$991	$795
	• Glargine/lixisenatide	100/33 μg prefilled pen	$679	$543

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NA, data not available; NADAC, National Average Drug Acquisition Cost. AWP (116) and NADAC (117) prices as of July 2023. *AWP or NADAC calculated as in **Table 9.3**. †Unbranded product prices used when available. ‡AWP and NADAC data presented do not include vials of regular human insulin and NPH available at Walmart for approximately $25/vial; median listed alone when only one product and/or price.


1
T cell and B cell precursors
2
Thymus
Autoantigen-specific T cell
Islet antigen-specific T cell receptor
B cell precursors migrate to the spleen and lymphoid tissue to mature and differentiate
Gut-associated lymphoid tissue
Small intestine
B cell
Macrophage
8
Islet-specific autoantibody
Pancreatic lymph node
Gut microbiota
5 Pancreas
Islet of Langerhans
7
Epithelial cell
Pancreatic duct
Virus
10
Gut leakage
9
Plasma cell (producing specific auto-antibodies)
Insulin epitope
3
GAD epitope
IAPP epitope
B cell differentiation
B cell receptor
Neoantigen epitope (IAPP and insulin)
β-Cell
6
Class I HLA molecule
Islet molecule fragment
IAPP
Hybrid neoantigen
Stressed β-cell
Insulin
Blood vessel
4
T cells that recognize peptides presented by macrophages divide and the new cells migrate to the circulation


a Early twentieth century
Number of cases
0
50
100
Degree of genetic or environmental contribution to T1DM (%)
b Early twenty-first century
Number of cases
0
50
100
Degree of genetic or environmental contribution to T1DM (%)
Genetic factors
Environmental factors

Mortality from Diabetes

1922

Mortality from Diabetes

1922	18.3/100,000

Mortality from Diabetes

1922 18.3/100,000

2022

Mortality from Diabetes

1922	18.3/100,000
2022	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.

What % 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) 75 %
4) 80 %

Goals of Therapy: Dog

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

Management of Diabetes

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

Insulin Therapy - Species of origin

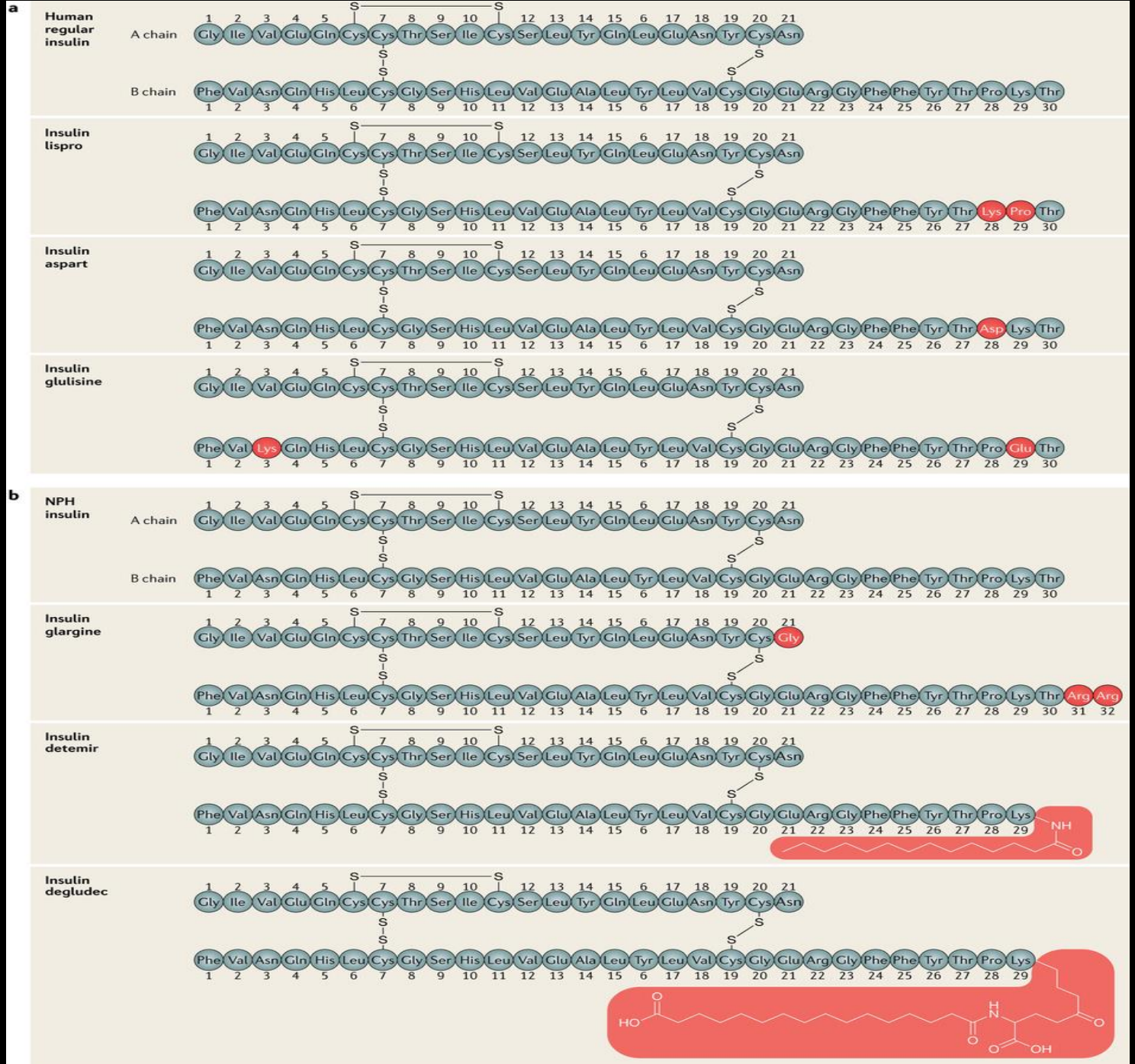
Beef, beef/pork, pork, human

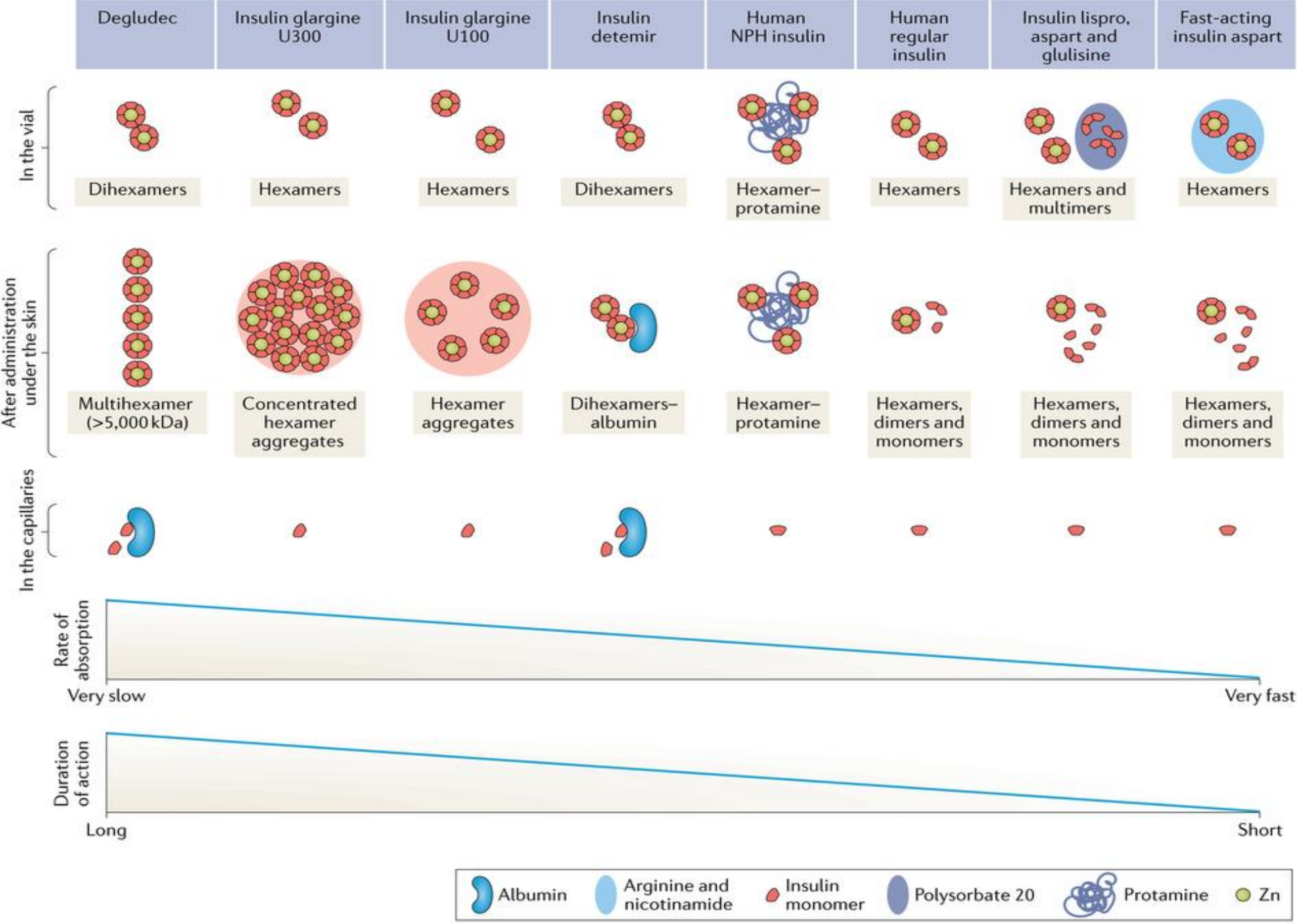
Increasingly difficult to obtain animal origin

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

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

FAST ACTING INSULINS

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

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

LONG ACTING INSULINS

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

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

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)

Glargine U300 (Toujeo)

Degludec (Tresiba)

Newly Diagnosed Canine Patients

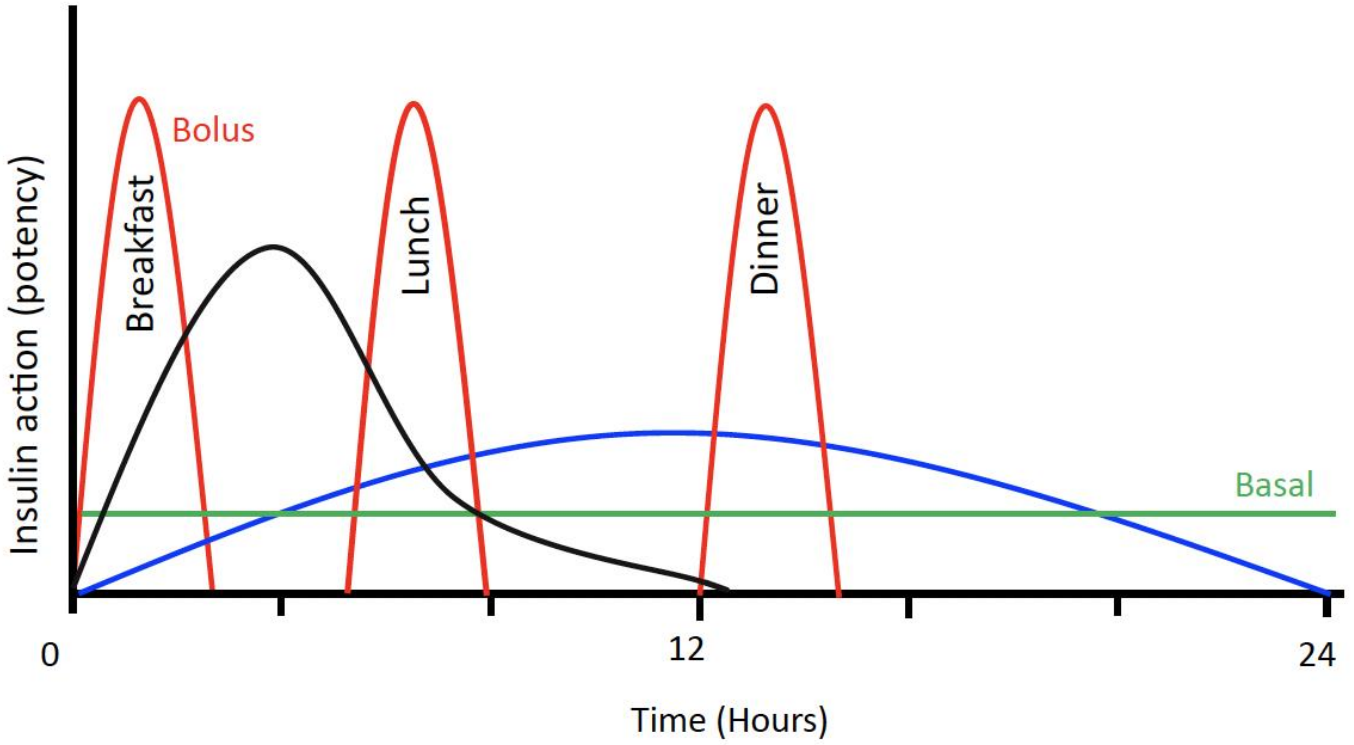


Fig. 1. Combination basal-bolus Insulin therapy: Red – bolus insulin requirement; Green – basal insulin requirement; Blue – Typical basal insulin kinetics; Black – Typical intermediate insulin kinetics.

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.

www.vetsulin.com

Vetsulin; Merck

40 IU/ml

Porcine origin

Lente insulin

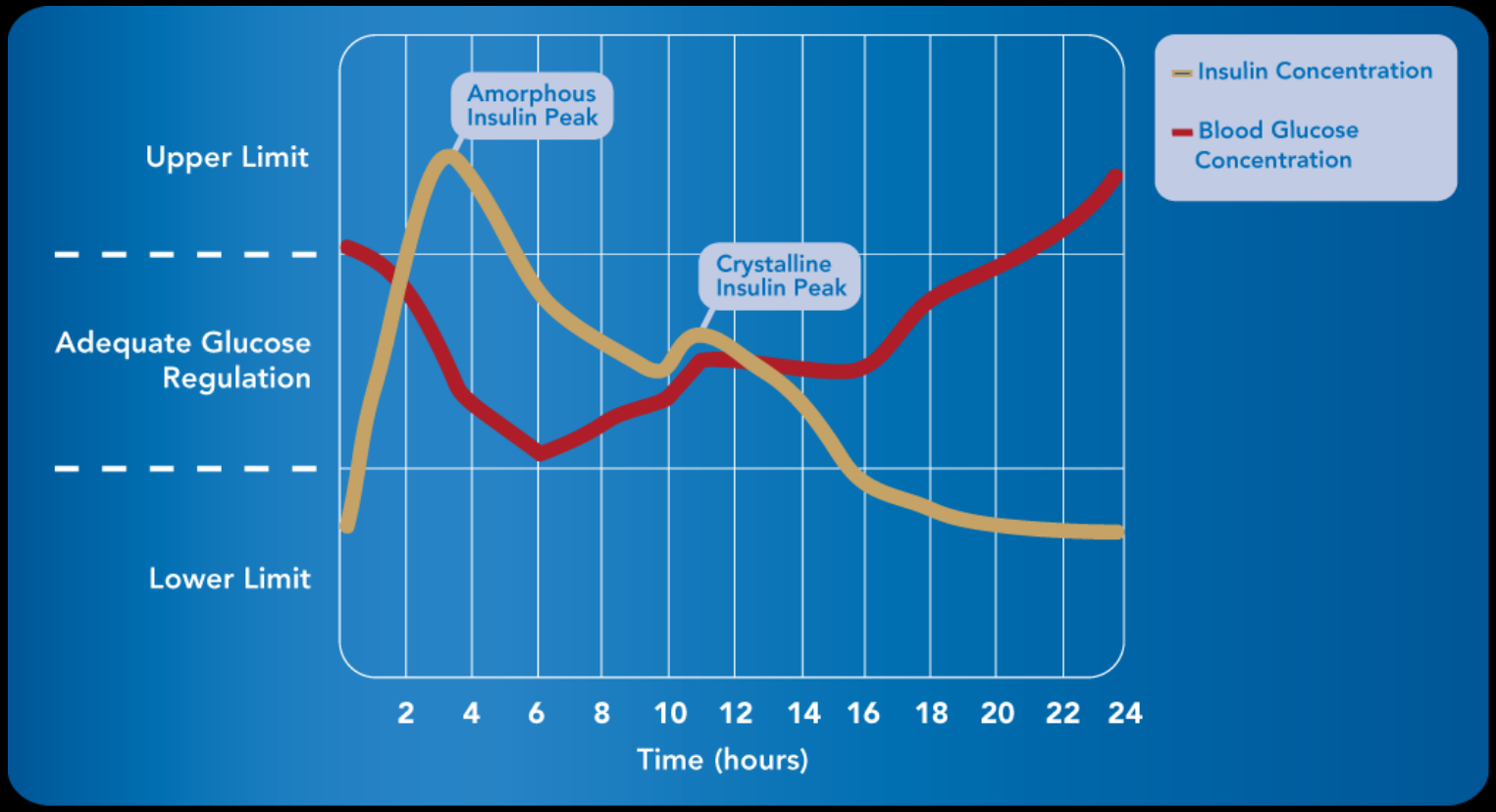
- Intermediate-acting
- 30% amorphous & 70% crystalline insulin

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

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; Merck



Vetsulin; Merck

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®
For Dogs
VetPen
Automatic Insulin Delivery Pen for Animal Use only
Starter kit
VetPen 8
28
VetPen™ Needles
MERCK

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.

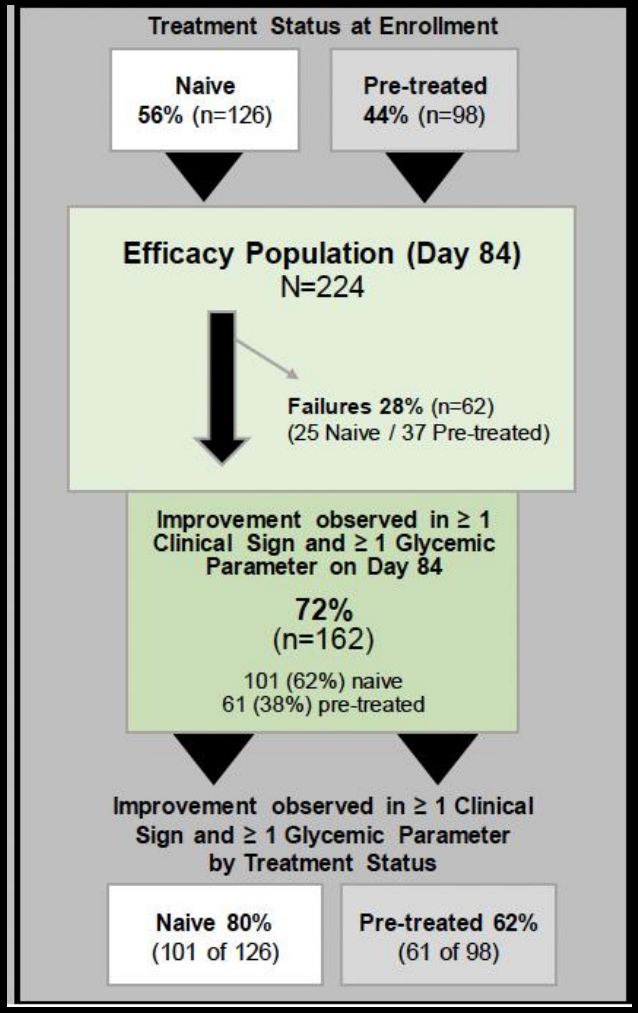
Newly Diagnosed Canine Patients

Field efficacy and safety of protamine zinc recombinant human insulin in 276 dogs with diabetes mellitus. Ward CR, Christiansen K, Li J, Bryson WL, Jerrentrup KA, Kroh C. Domest Anim Endocrinol. 2021 Apr;75:106575.

PZI Insulin in Dogs

Two hundred seventy-six client-owned dogs with naturally occurring DM (naïve or pre-treated with insulin) were enrolled in the study. Insulin treatment was initiated at 0.5–1.0 IU/kg SID. An improvement in at least one lab parameter related to DM (mean BG, min BG, Fructosamine) and one clinical parameter (PU/PD, body weight) was achieved in 72% of dogs (80% of naive, 62% of pretreated). Dogs treated SID and BID showed improvement in 71% and 74% of cases, respectively. In naïve dogs, mean and minimum BG and fructosamine were significantly decreased ($P < 0.05$) by d 7 and 21, respectively, and in pre-treated dogs by d 63. By d 84, PU/PD improved in 90% and 88% of dogs, respectively, and the mean successful insulin dose was 1.4 IU/kg/d. Safety parameters were measured in 276 dogs for up to 182 d; clinical hypoglycemia occurred in 8.9% of dogs. We conclude that PZIR safely and effectively improved glycemic parameters and clinical signs in naïve and pre-treated diabetic dogs. The significant percentage of dogs on SID treatment with improvement in hyperglycemia and clinical signs confirms the prolonged action of PZIR in many dogs.

PZI Insulin in Dogs



Glargine; Sanofi

Use of insulin glargine in dogs with diabetes mellitus.

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.

Vet Rec. 2012 Jan;170(2):52.

Glargine; Sanofi

Glargine insulin for treatment of naturally occurring diabetes mellitus in dogs.

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.

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.

This product has been discontinued in the United States as of Dec 2024.

Insulin Glargine U-300 ; Toujeo

Likely requires CGMS and can only be accurately administered using the manufacturer's injection pen delivering 1 U unit increments.

DOI: 10.1111/jvim.17106

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

A dose titration protocol for once-daily insulin glargine 300 U/mL for the treatment of diabetes mellitus in dogs

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Abstract

Background: In purpose-bred dogs, insulin glargine 300 U/mL (IGla300) has long duration of action, peakless time-action profile, and low potency, making it suitable for use as a basal insulin.

Hypothesis: To evaluate IGla300 in client-owned diabetic dogs monitored using a flash glucose monitoring system (FGMS).

Animals: Ninety-five client-owned diabetic dogs, newly diagnosed or previously treated with other insulin formulations, with or without concurrent diseases.

Methods: Prospective multi-institutional study. Clinical signs and standardized assessment of FGMS data, using treatment and monitoring guidelines established a priori, guided dose adjustments and categorization into levels of glycemic control.

Results: The initial IGla300 dose was 0.5 U/Kg q24h for newly diagnosed dogs and (median dose [range]) 0.8 U/Kg (0.2-2.5) q24h for all dogs. Glycemic control was classified as good or excellent in 87/95 (92%) dogs. The IGla300 was administered q24h (1.9 U/kg [0.2-5.2]) and q12h (1.9 U/kg/day [0.6-5.0]) in 56/95 (59%) and 39/95 (41%) dogs, respectively. Meal-time bolus injections were added in 5 dogs (0.5 U/kg/injection [0.3-1.0]). Clinical hypoglycemia occurred in 6/95 (6%) dogs. Dogs without concurrent diseases were more likely to receive IGla300 q24h than dogs with concurrent diseases (72% vs 50%, respectively; $P = .04$).

Conclusions and Clinical Importance: Insulin glargine 300 U/mL can be considered a suitable therapeutic option for once-daily administration in diabetic dogs. Clinicians should be aware of the low potency and wide dose range of IGla300. In some dogs, twice-daily administration with or without meal-time bolus injections may be necessary to achieve glycemic control. Monitoring with FGMS is essential for dose titration of IGla300.

Abbreviations: BCS, body condition score; BGCs, blood glucose curves; DM, diabetes mellitus; FGMS, flash glucose monitoring system; IG, Interstitial glucose concentration; IGla100, insulin glargine 100 U/mL; IGla300, insulin glargine 300 U/mL; NPH, neutral protamine Hagedorn; PZI, protamine zinc insulin.

The preliminary results of this study were presented in abstract form as an oral presentation at the 2022 ACVIM Forum, Austin, Texas.

Insulin Degludec; Tresiba

Likely requires CGMS and come U100 and U200.

Overall glycemic control was better with insulin degludec, vs NPH as a result of lower blood glucose during time intervals preceding meals

The Journal of Veterinary Medical Science

NOTE

Internal Medicine

Time-action profiles of insulin degludec in healthy dogs and its effects on glycemic control in diabetic dogs

Hitomi ODA[1)], Akihiro MORI[1)]*, Satoko ISHII[1)], Saori SHONO[1)], Eri ONOZAWA[1)] and Toshinori SAKO[1)]

[1)]School of Veterinary Nursing & Technology, Faculty of Veterinary Science, Nippon Veterinary and Life Science University, 1-7-1 Kyonancho, Musashino, Tokyo 180-8602, Japan

J. Vet. Med. Sci.
80(11): 1720–1723, 2018
doi: 10.1292/jvms.17-0714

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Accepted: 13 September 2018
Published online in J-STAGE: 11 October 2018

ABSTRACT. Insulin degludec (IDeg) is a new insulin formulation that facilitates long-term control of glucose level in humans. In this study, we investigated the effects of IDeg on glycemic control in dogs. Its time-action profiles were monitored in healthy dogs using an artificial pancreas apparatus under euglycemic conditions. At 9.0–13.5 hr post-IDeg injection, an indistinct peak of glucose level was detected. Moreover, the action of IDeg was persistent for >20 hr. Both IDeg and neutral protamine Hagedorn insulin (NPH) lowered blood glucose concentrations in diabetic dogs, but IDeg caused postprandial hyperglycemia and a somewhat lower preprandial glucose level than that caused by NPH. IDeg might be ineffective in concurrently preventing postprandial hyperglycemia and preprandial hypoglycemia in a single-agent administration.

KEY WORDS: glucose infusion rate, glucose-lowering effect, long-acting insulin

In this sample of dogs with well-controlled diabetes mellitus, addition of lispro (Humalog) insulin, 0.1 U/kg, to an existing treatment regimen of NPH insulin and dietary management significantly decreased postprandial BGCs. Further study of BBIT for dogs with diabetes mellitus is warranted.

	BGC (mg/dL)	
Time (h)	NPH insulin	BBIT
0	337 (246–418)	290 (160–438)*
0.5	378 (263–490)*	247 (50–391)*†
1	313 (187–376) *†§	117 (42–307)†
1.5	239 (166–332)†‡§	94 (48–197)
2	191 (61–301)‡	112 (48–186)
4	136 (50–293)	103 (71–261)
6	127 (62–279)	94 (44–311)
8	191 (74–303)	122 (39–365)
10	213 (66–320)§	91 (46–320)
12	254 (108–287)	96 (51–297)

Effects of treatment with lispro and neutral protamine Hagedorn insulins on serum fructosamine and postprandial blood glucose concentrations in dogs with clinically well-controlled diabetes mellitus and postprandial hyperglycemia. Am J Vet Res 2020;81:153–158

Dietary Management of Canine Diabetes

- For dogs, a diet that will correct obesity, optimize body weight, and minimize postprandial hyperglycemia is recommended. For dogs, diets that contain increased quantities of soluble and insoluble fiber or that are designed for weight maintenance in diabetics or for weight loss in obese diabetics can:
- Improve glycemic control by reducing postprandial hyperglycemia.
- Restrict caloric intake in obese dogs undergoing weight reduction.
- Some clinicians recommend that owners supplement with canned pumpkin, green beans, or commercial fiber supplements containing psyllium or wheat dextrin. Additionally, regular and appropriate exercise should be considered an adjunct of any diet-based weight-loss program.

Diabetes Management: Dietary therapy AAHA 2018

Client Education

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

Glycated Blood Proteins

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

Feline Diabetes

- 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): Discontinued

Glargine U300 (Toujeo)

Degludec (Tresiba)

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

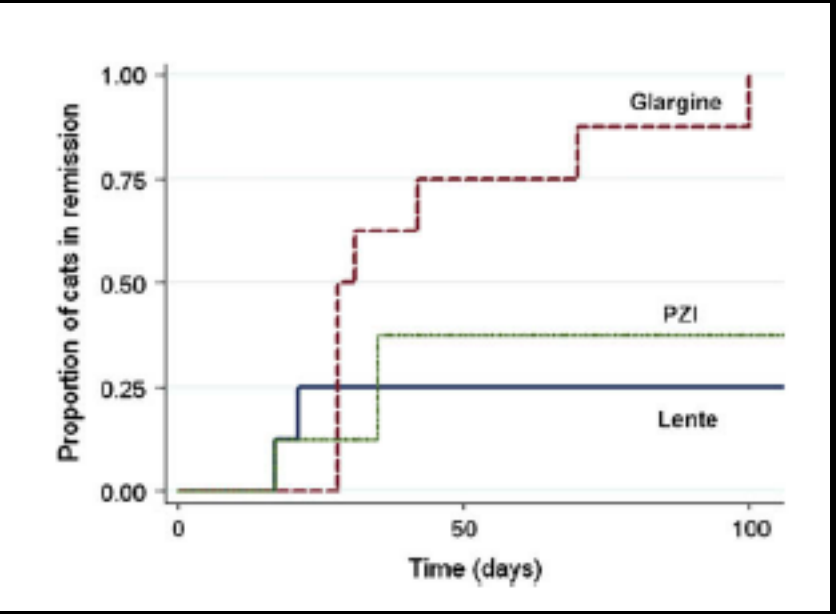
J Fel Med and Surg 11: 683-691, 2009

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.

Semglee and Basaglar

The expense of human insulin has come to be extreme in the U.S. It is helpful to know that Basaglar® pens are typically around 2/3 the cost of Lantus®and Semglee® products are typically approximately half the cost of Lantus®.

Semglee (insulin glargine-yfgn) and Rezvoglar (insulin glargine-aglr) are biosimilars to Lantus. Basaglar (insulin glargine) is considered a follow-on biologic version of Lantus.

Semglee and Basaglar

Biosimilar products are biological products that are manufactured to resemble reference biological products. The BPCIA (Biologics Price Competition and Innovation Act) permits the FDA, following a period of market exclusivity for reference products, to approve biological products if they have the same primary amino acid sequence and mechanism of action as the reference product and there are no clinically meaningful differences between the reference product and the biosimilar. Because each reference product's manufacturing process is proprietary information, the manufacturer's biosimilar product always differs slightly from the reference product. This is in contrast to generic medications, which are identical to brand medications.

Semglee and Basaglar

Follow-on insulins are designated as follow-on biologics rather than biosimilars because they undergo an older approval pathway. Abbreviated New Drug Applications for follow-on biologics are submitted through Section 505(b)(2) of the Food, Drug, and Cosmetic Act. After March 23, 2020, all biologics will be regulated through Section 351(k) under the Public Health Service Act and will be referred to as biosimilars.

An interchangeable biosimilar product is a biosimilar that meets additional requirements outlined by the law that allows for the FDA to approve biosimilar and interchangeable biosimilar medications.

An interchangeable biosimilar product may be substituted without the intervention of the health care professional who prescribed the reference product, much like how generic drugs are routinely substituted for brand name drugs.

Semglee and Basaglar

Glargine and detemir are available in a 3 ml (300 unit) pen ejectors and in 10ml (1,000 unit) bottles. (Brand name Lantus® is available in either vial or pen as is Semglee® but Basaglar® is only available in the pen format). In order to be cost effective, vials and pens must be refrigerated after they are opened. Glargine insulin has been formally studied and found to retain activity for 6 months if refrigerated. The 10 ml bottle of glargine will expire in one month if it is not kept refrigerated. Detemir has been studied by its manufacturer and the vial or pen will last 40 days whether it has been refrigerated or not. That said, refrigerated open pens or vials are commonly refrigerated for 3-4 months and appear to maintain strength.

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.

Toujeo, Insulin glargine (300 units/ml)

IGla-U300 seems effective and safe for the treatment of feline diabetes, but more long- term and comparative clinical trials are needed.

Original Article

Journal of Feline Medicine and Surgery
2022, Vol. 24(2) 168–176

DOI: 10.1177/1098612X211013018
journals.sagepub.com/home/jfm

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SAGE

Insulin glargine 300 U/ml for the treatment of feline diabetes mellitus

Guido Linari[1], Linda Fleeman[2], Chen Gilor[3], Lucia Giacomelli[1] and Federico Fracassi[1]

Abstract

Objectives This study aimed to evaluate the efficacy and safety of insulin glargine 300 U/ml (IGla-U300) in cats with variable duration of diabetes mellitus (DM).

Methods Thirteen client-owned cats with DM completed a prospective clinical trial. Four cats were highly suspected of hypersomatotropism and excluded from the insulin efficacy evaluation. All cats were treated with IGla-U300 SC at a starting dosage of 0.5 U/kg q12h and fed with a low carbohydrate diet. Cats were monitored for 8 weeks with a once-weekly at-home 16 h blood glucose curve (BGC) and a questionnaire evaluating the presence of DM-related clinical signs. In-clinic evaluations, including serum fructosamine measurement, were scheduled within 3 days of the first, third, sixth and eighth BGC. Glycemic variability was assessed by calculating the SD of each BGC.

Results Excluding four cats suspected of hypersomatotropism, at the time of the eighth BGC, improved or absent polyuria, polydipsia, polyphagia, weight loss, lethargy and improved or normal general demeanor were reported in 8/9 (88%), 8/9 (88%), 7/9 (77%), 7/9 (77%), 7/9 (77%) and 8/9 (88%) cats, respectively. Two cats achieved remission after 29 and 53 days. Another two cats went into remission after the end of the study (days 82 and 96). All cats that achieved remission were newly diagnosed diabetics. Median (range) serum fructosamine concentration significantly decreased when comparing the time of enrollment (604 [457–683] µmol/l) with the eighth week of treatment (366 [220–738] µmol/l) ($P = 0.02$). In all 13 cats, biochemical hypoglycemia (blood glucose <60 mg/dl; <3.3 mmol/l) was detected in 13/104 (12.5%) BGCs, while clinical signs suggesting hypoglycemic episodes were not reported. Glycemic variability was significantly lower at the fifth BGC when comparing cats that achieved remission with cats that did not achieve remission ($P = 0.02$).

Conclusions and relevance IGla-U300 seems effective and safe for the treatment of feline diabetes, but more long-term and comparative clinical trials are needed.

Keywords: Glucose; remission; therapy; blood glucose curve; fructosamine

Accepted: 6 April 2021

Introduction

Long-acting insulin products are currently considered the first choice for feline diabetes mellitus (DM) treatment.[1,2] Glargine insulin 100 U/ml (IGla-U100) has been evaluated previously in diabetic cats, resulting in effective glycemic control.[3,4] Recently, a new insulin glargine product with an increased concentration of 300 U/ml (IGla-U300) was approved for treatment of human type 1 diabetes mellitus (T1DM) and type 2 DM (T2DM).[5] IGla-U300 formulation comprises the same molecule as IGla-U100 that is delivered in a third of the original volume, which results in a smaller subcutaneous depot and reduced surface area, leading to a slower re-dissolution rate, lower bioavailability and increased daily dose in human patients.[6] These features probably explain the flatter and more prolonged insulin profiles that were obtained with IGla-U300 when

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Insulin Degludec; Tresiba

Likely requires CGMS and is available as U100 and U200.

In cats, compared with insulin degludec, insulin glargine 300 U/mL is longer acting and has a flatter time-action profile, making it more suitable for use as basal insulin.

The Journal of Veterinary Medical Science

NOTE

Internal Medicine

The effect of Insulin Degludec on glycemic control in diabetic cats over a 12-month period

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20 April 2020

ABSTRACT. Insulin degludec (IDeg) is a long-acting basal insulin recently developed for use in humans. This study aimed to investigate the effects of IDeg on glycemic control in diabetic cats. Changes in body weight, IDeg dosage, and glycated albumin (GA) were evaluated at 0, 1, 3, 6, 9, and 12 months following initiation of IDeg. A significant decrease in GA was observed and a mean GA level below 25% was achieved between 3 and 12 months. Furthermore, a significant increase in body weight was observed between 3 and 12 months. The mean IDeg dose was 0.75 ± 0.68 IU/kg/day at 12 months. Taken together, long-term glycemic control was successfully achieved in diabetic cats using IDeg.

KEY WORDS: diabetes, feline, glucose lowering effect, ultra-long-acting insulin

Insulin degludec (IDeg) is a new basal form of insulin that generates soluble multihexamers following subcutaneous injection, resulting in an exceptionally long duration of action (>42 hr), thus effectively reducing blood glucose levels in individuals with diabetes mellitus [17, 19, 21]. In human studies, the half-life of IDeg is longer than that of insulin glargine following subcutaneous administration (25 vs. 12 hr, respectively) [3–5].

There has been a marked increase in the number of cats with diabetes mellitus (DM) [6]. Currently, diabetic cats are treated with insulin injections, oral hypoglycemic drugs, and/or prescription diets [2]; however, diabetic cats with severe hyperglycemia (>350–500 mg/d*l*) generally require daily insulin administration [7]. Protamine zinc insulin is the current gold standard for the treatment of feline diabetes in Japan as it is the only commercially available insulin for cats in this region. Furthermore, long-acting human insulins, including insulin glargine and insulin detemir, are often used in the long-term management of feline diabetes [1, 2, 13]. Previously, a clear difference among four different insulin preparations for dogs was demonstrated by examining their time-action profiles [9, 14, 18]. The action of IDeg was persistent for >20 hr, representing its long profile [14] as well as insulin detemir (IDet), and insulin glargine (IGla) [9, 14, 18]. However, the effects of IDeg have not yet been investigated in cats; therefore, in the current study, the effects of IDeg upon long-term glycemic control in diabetic cats were studied.

Eight cats with DM brought to the Nippon Veterinary and Life Science University Veterinary Medical Teaching Hospital from April 2016 to April 2018 were monitored for 12 months of IDeg treatment. The profiles of the eight cats are presented in Table 1. All diabetic cats were defined by clinical signs (polyuria and polydipsia) and the documentation of persistent fasting hyperglycemia (>250 mg/d*l*), over 20% glycated albumin (GA) and glucosuria. A serum GA of over 20% was considered abnormal and a normal reference range of GA was 7.5–13.9% for GA (%) (95% C.I.) in normal healthy cats [8]. Five of the eight cats were newly diagnosed as diabetic and had not had insulin administered prior to this investigation. The remaining three cats were previously diagnosed and had been treated with insulin prior to this investigation (Table 1). However, as these three cats had fair to poor glycemic control (GA; cat 1 for 28%, cat 7 for 30% and cat 8 for 33%), changing their insulin preparation was allowed by the owners. Informed consent was obtained from the owners following the review of the purpose, nature, potential risks, and benefits of the study. All cats were injected with IDeg (Tresiba, Novo Nordisk Pharma Ltd., Tokyo, Japan) once or twice daily with dietary feeding twice daily. The initial dosages administered to the previously untreated diabetic cats were 0.5–2.0 units/cat/once or twice a day depending upon clinical signs and GA levels. These doses were adjusted throughout the treatment period according to the clinical condition of each individual (such as improvement in polyuria/polydipsia and increasing body weight) and the serum GA level for maintaining 11.9–25.6% (between excellent to fair glycemic control) [8]. The cats were fed individual diets by their respective owners, which provided a daily calorie intake of 0.8–1.6 × resting energy requirement (Ideal Body Weight$^{0.75}$ × 70). Feeds were provided twice daily. Owners were educated on the potential complications of this investigation, which included

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.

Feline DKA and Lantus

- **Measurements and main results:** The main outcome measure was time (h) to resolution of ketonemia. Secondary outcome measures were time until first improvement of hyperglycemia and ketonemia, decrease of glucose to ≤13.9 mmol/L (250 mg/dL), resolution of acidosis, consumption of first meal, and discharge from hospital. Additionally, occurrence of treatment-associated adverse events and death were compared. Seventeen cats (85%) survived to discharge, with no difference in survival between groups (P = 1.0). Median times to β-OHB < 2.55 mmol/L were 42 (CRI-group) and 30 (glargine-group) hours, respectively (P = 0.114). Median times to first improvement of hyperglycemia (glargine-group: 2 h; CRI-group: 6 h; P = 0.018) and until discharge from hospital (glargine-group: 140 h; CRI-group: 174 h; P = 0.033) were significantly shorter in the glargine-group. No significant differences were observed in any other parameter under investigation (P > 0.05).
- **Conclusions:** Basal-bolus administration of glargine insulin appears to be an effective and safe alternative to the current standard CRI-protocol for the management of DKA in cats. The positive outcomes and simplicity make it a viable option for the treatment of feline DKA.

Glargine versus regular insulin protocol in feline diabetic ketoacidosis
J Vet Emerg Crit Care (San Antonio). 2021 Jul;31(4):459-468.

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.

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.

Dietary Management of Feline Diabetes

Dietary carbohydrates, within nutritionally balanced diets, do not appear to have adverse effects in healthy cats.

However, low-carbohydrate, high-fat diets have been identified as increasing the risk for development of obesity in cats.

Depending on the specific formulation, we suggest that diets for healthy cats should not exceed 40% to 50% of calories from carbohydrates to assure all other nutrient needs are met.

While higher compared to lower carbohydrate diets may lead to greater postprandial blood glucose concentrations, there is no evidence that the concentrations reported are detrimental rather than physiological.

There is no evidence to conclude that high carbohydrate diets lead to diabetes mellitus in cats.

However, although the evidence is very limited, it appears that low-carbohydrate diets (≤ 26% of ME) may help diabetic cats improve glucose control and achieve remission.

Laflamme DP, Backus RC, Forrester SD, Hoenig M. Evidence does not support the controversy regarding carbohydrates in feline diets. J Am Vet Med Assoc. 2022 Jan 28;260(5):506-513.

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

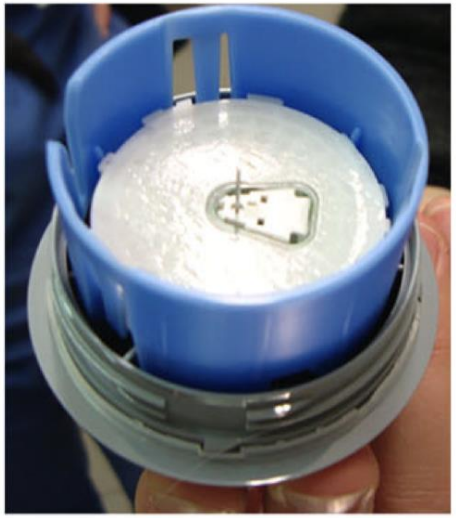
Improved glycemic control

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

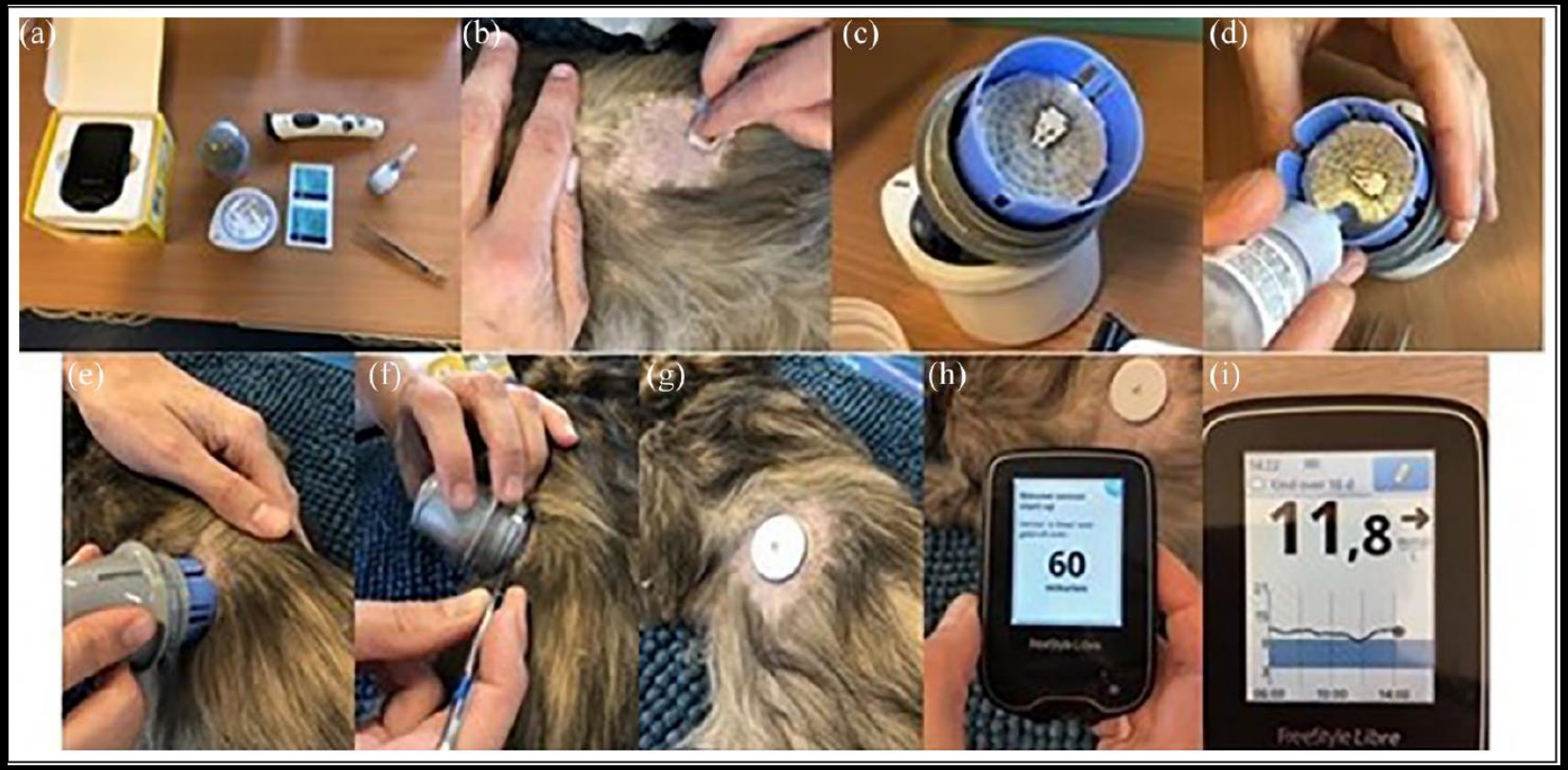


Knies M, Teske E, Kooistra H. Evaluation of the FreeStyle Libre, a flash glucose monitoring system, in client-owned cats with diabetes mellitus. J FelineMed Surg. 2022 Aug;24(8):e223-e231. doi: 10.1177/1098612X221104051. Epub 2022 Jun 28. PMID: 35762266; PMCID: PMC9315169.

Placing the device was easy, with 70% of cats showing no reaction. Most sensors were placed on the thoracic wall. Skin reactions at the attachment site were not present or mild in almost all cats. Owners were very satisfied with the use of the FreeStyle Libre. Median functional life of the sensor was 10 days (range 1–14). Good correlation was found between interstitial and blood glucose measurements (rho[r]=0.88, P <0.0001). Fifty- three percent of interstitial glucose concentrations were within a maximum deviation of 15% from blood glucose concentrations and 92.7% were within the safe risk zones 0 and 1 of the surveillance error grid.

The flash glucose monitoring system was easy to use and owners of diabetic cats were satisfied with its use. Although the device did not completely fulfil ISO requirements, it is sufficiently accurate for glucose monitoring in diabetic cats.

Knies M, Teske E, Kooistra H. Evaluation of the FreeStyle Libre, a flash glucose monitoring system, in client-owned cats with diabetes mellitus. J FelineMed Surg. 2022 Aug;24(8):e223-e231. doi: 10.1177/1098612X221104051. Epub 2022 Jun 28. PMID: 35762266; PMCID: PMC9315169.

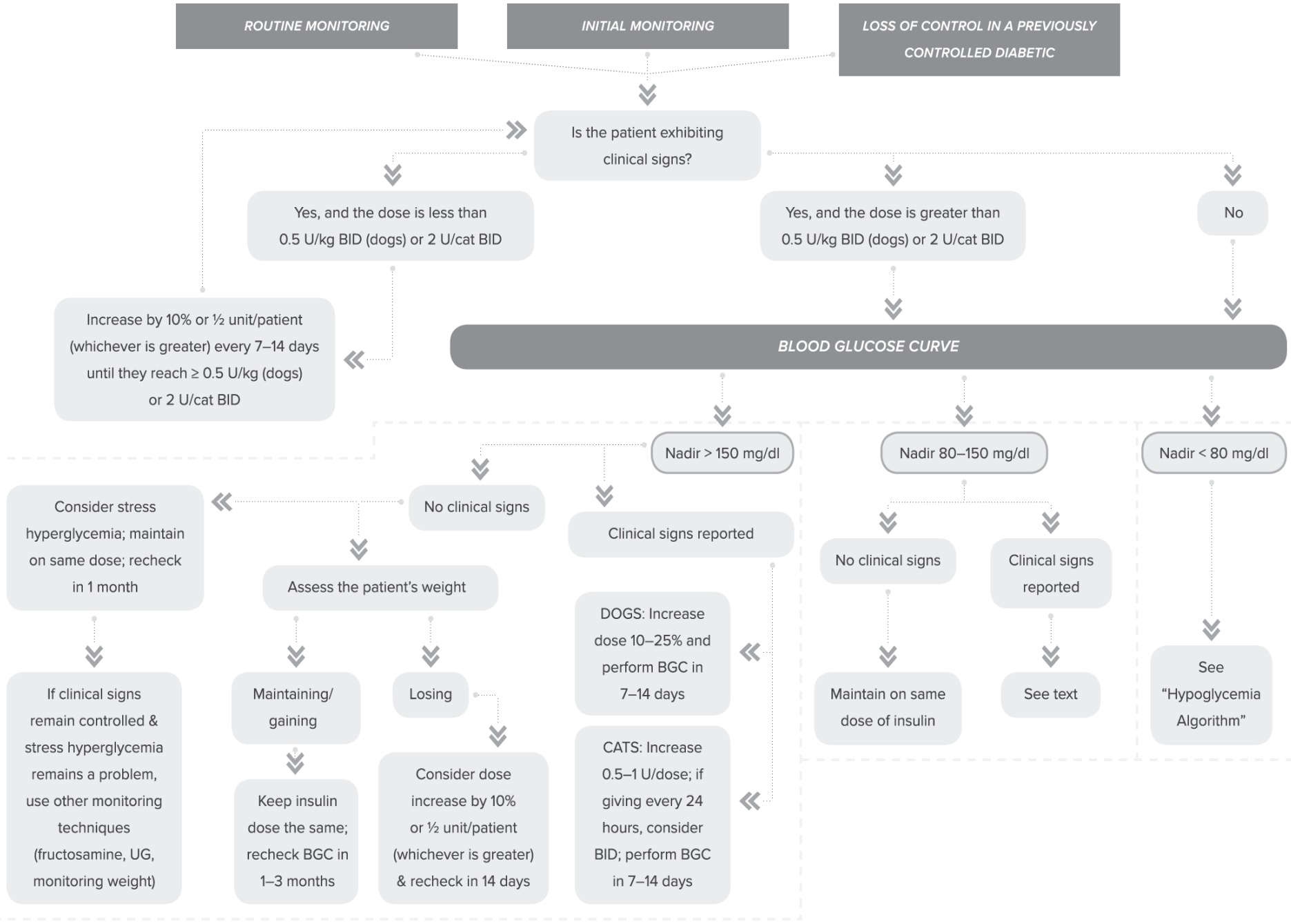


1) Pre-prandial and pre insulin

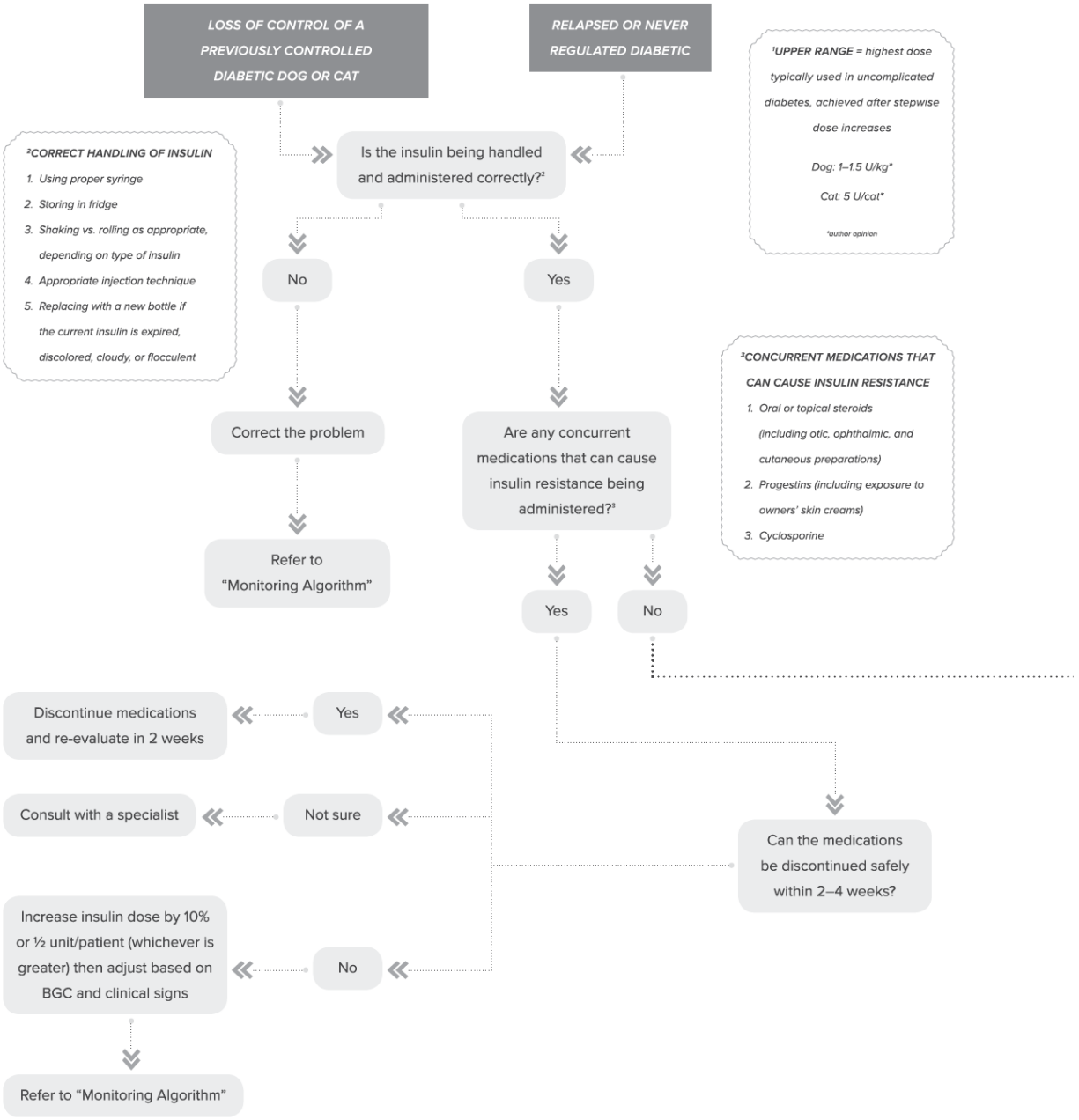
2) Every 2 hours (dogs; cats on NPH, ProZinc or Vetsulin) or 4 hours (cats on glargine) post prandial/insulin

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

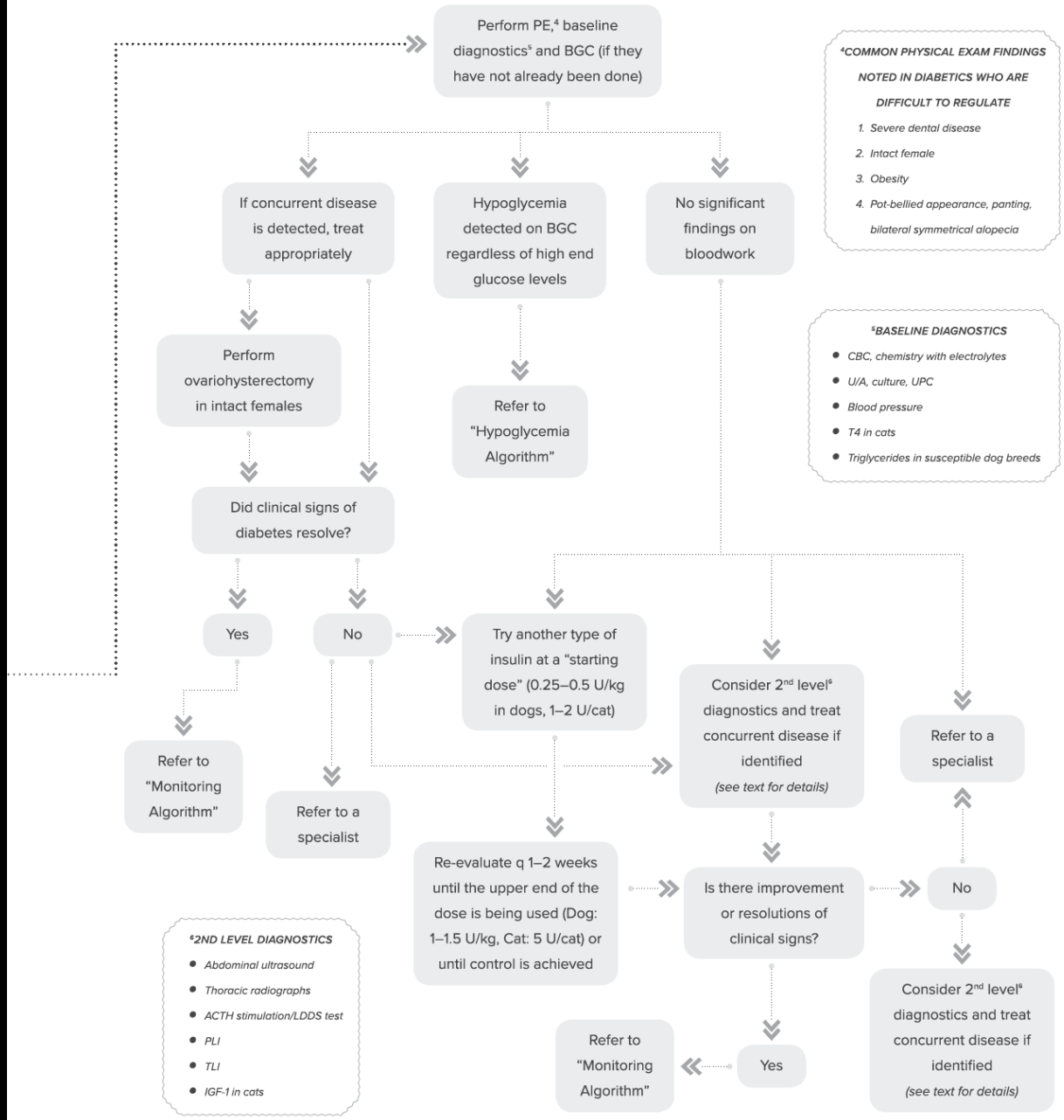
MONITORING BLOOD GLUCOSE LEVELS IN DIABETIC DOGS AND CATS



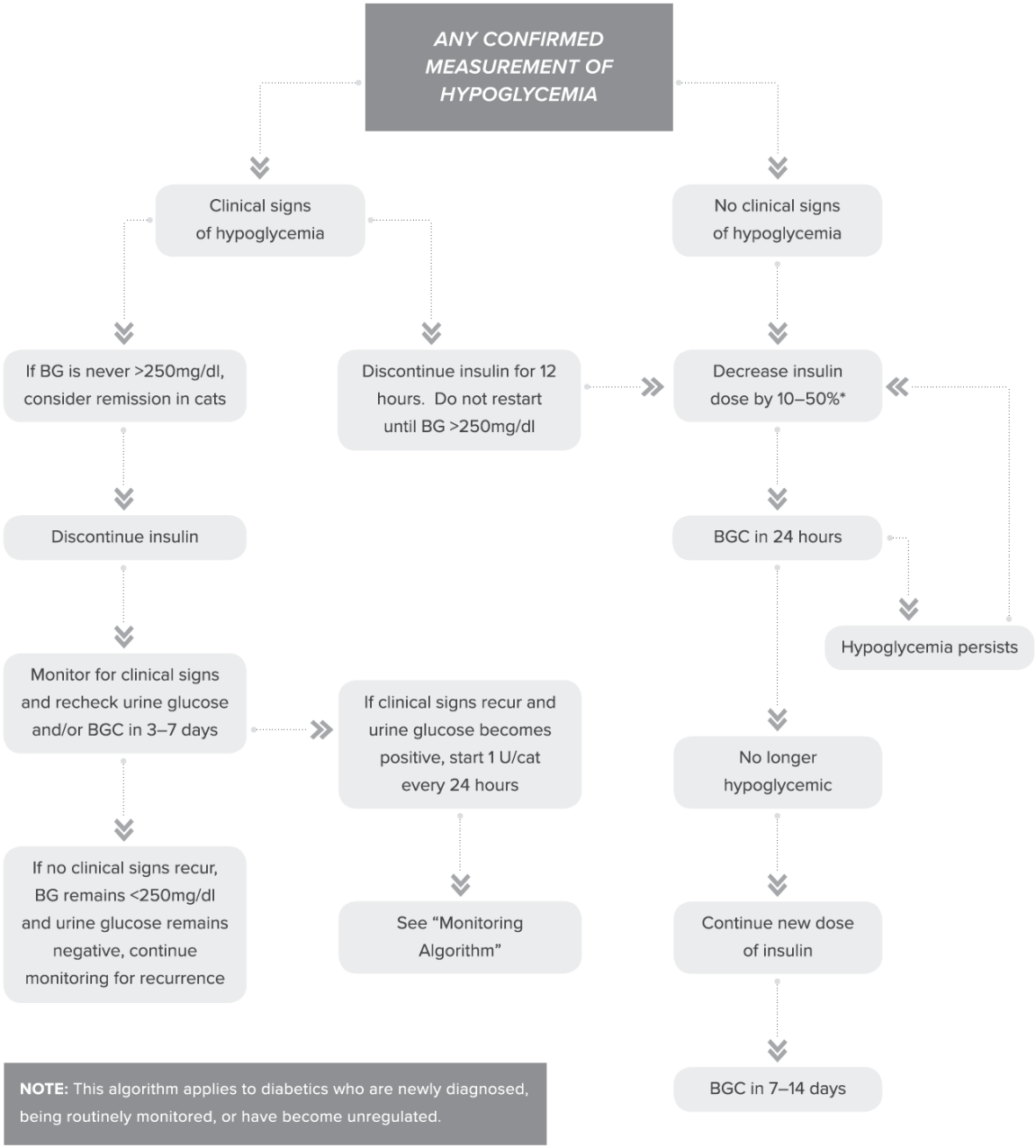
TROUBLESHOOTING DIABETIC DOGS AND CATS RECEIVING THE "UPPER RANGE"[1] OF INSULIN DOSES



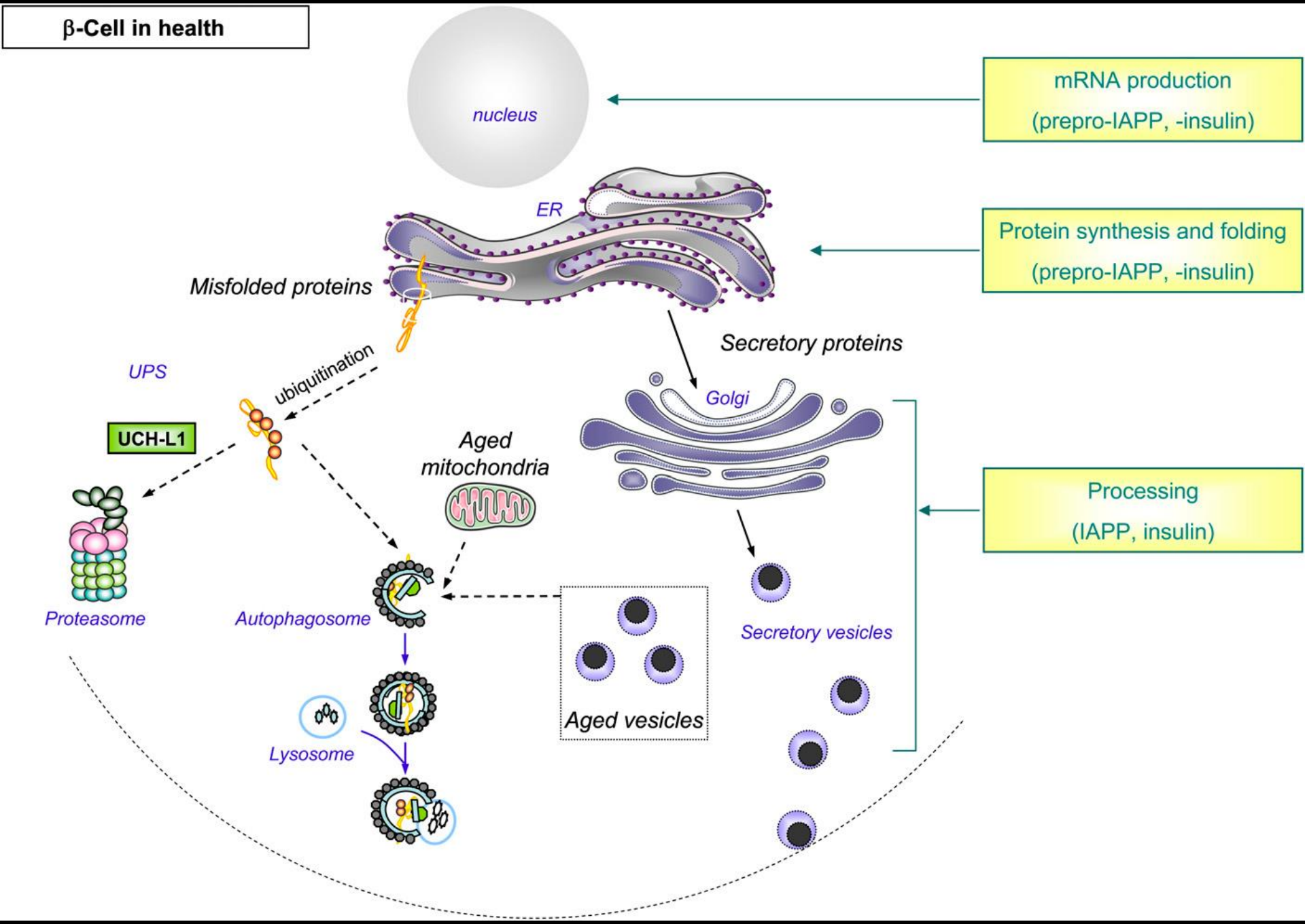
TROUBLESHOOTING DIABETIC DOGS AND CATS RECEIVING THE "UPPER RANGE"[1] OF INSULIN DOSES



MANAGING HYPOGLYCEMIA IN DIABETIC DOGS AND CATS



NOTE: This algorithm applies to diabetics who are newly diagnosed, being routinely monitored, or have become unregulated.

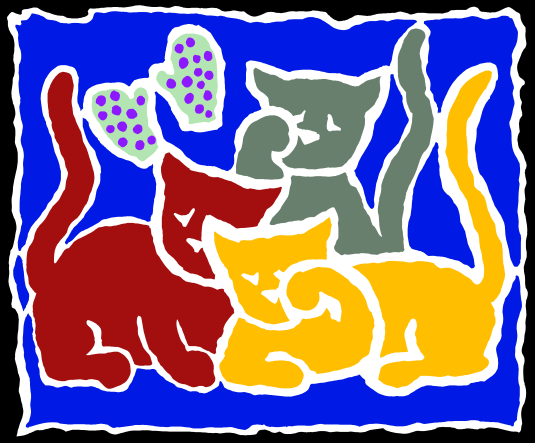

β-Cell in health
nucleus
mRNA production
(prepro-IAPP, -insulin)
ER
Protein synthesis and folding
(prepro-IAPP, -insulin)
Misfolded proteins
Secretory proteins
UPS
ubiquitination
Golgi
UCH-L1
Aged
mitochondria
Processing
(IAPP, insulin)
Proteasome
Autophagosome
Secretory vesicles
Aged vesicles
Lysosome

Feline Insular Amyloid

Concentration increases with age

Number of affected islets

Extent of deposition



Feline Insular Amyloid

Islet Amyloid (IA)

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

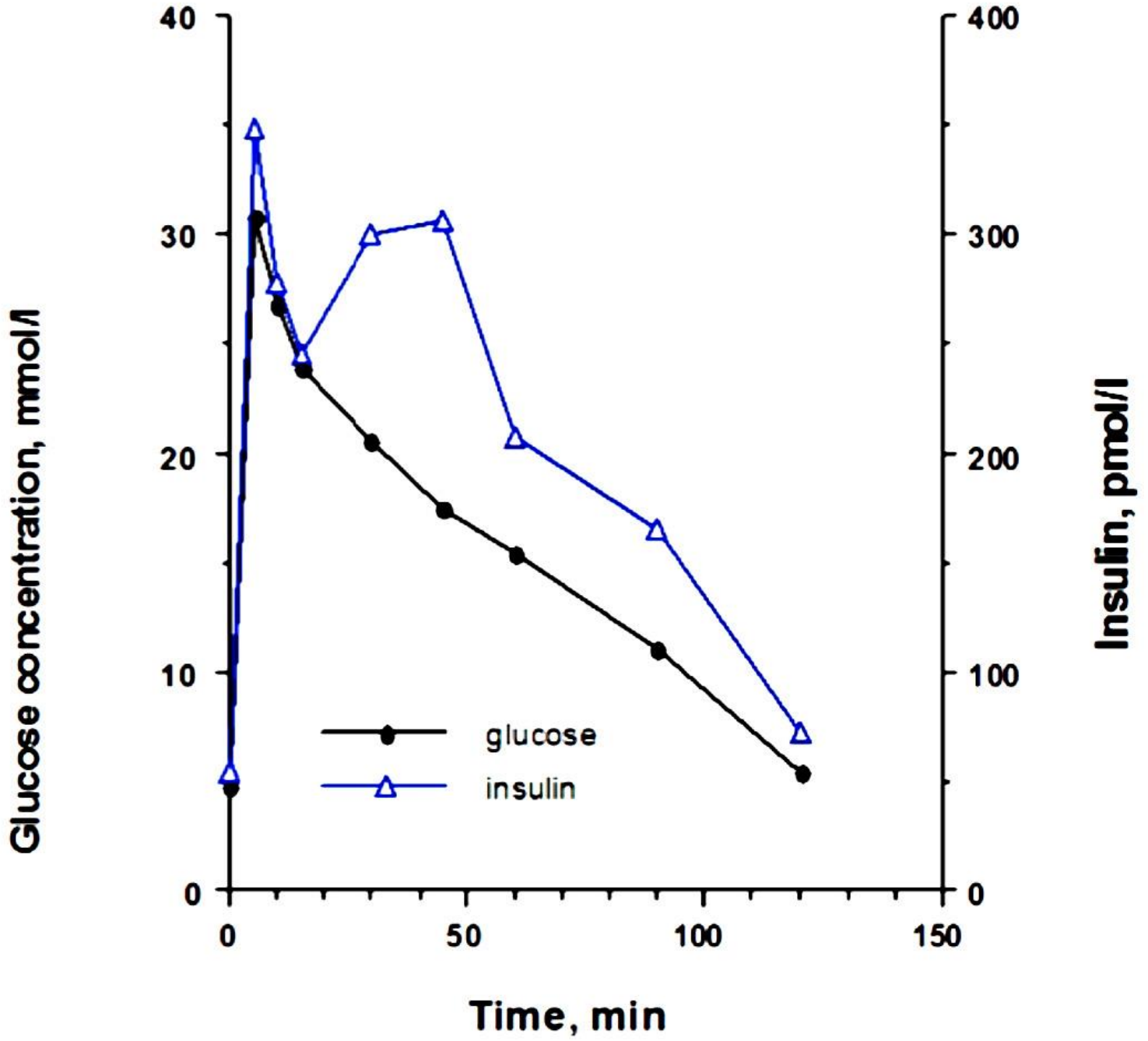
Feline Insular Amyloid

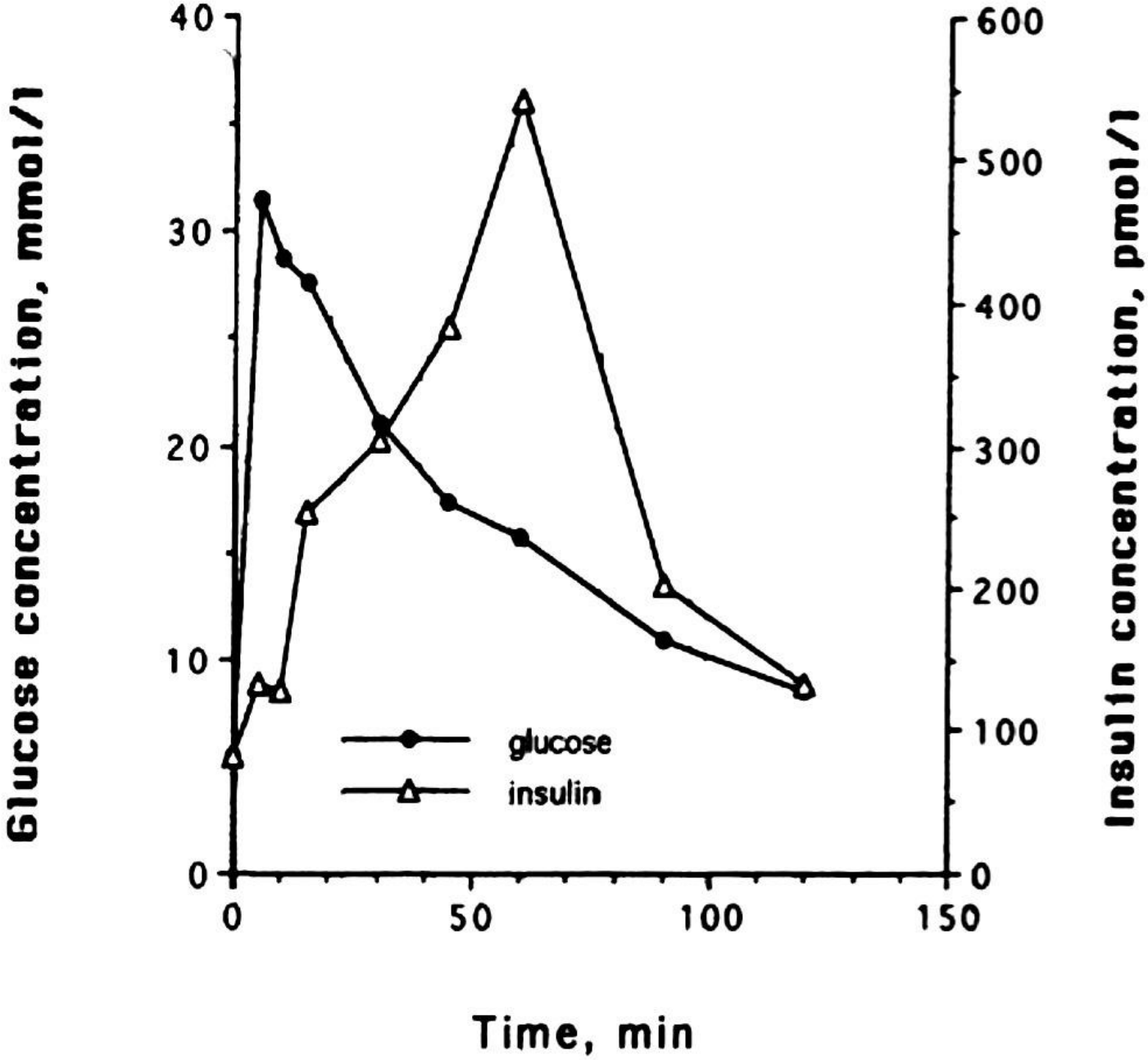
Role of IA and IAPP in Diabetes

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
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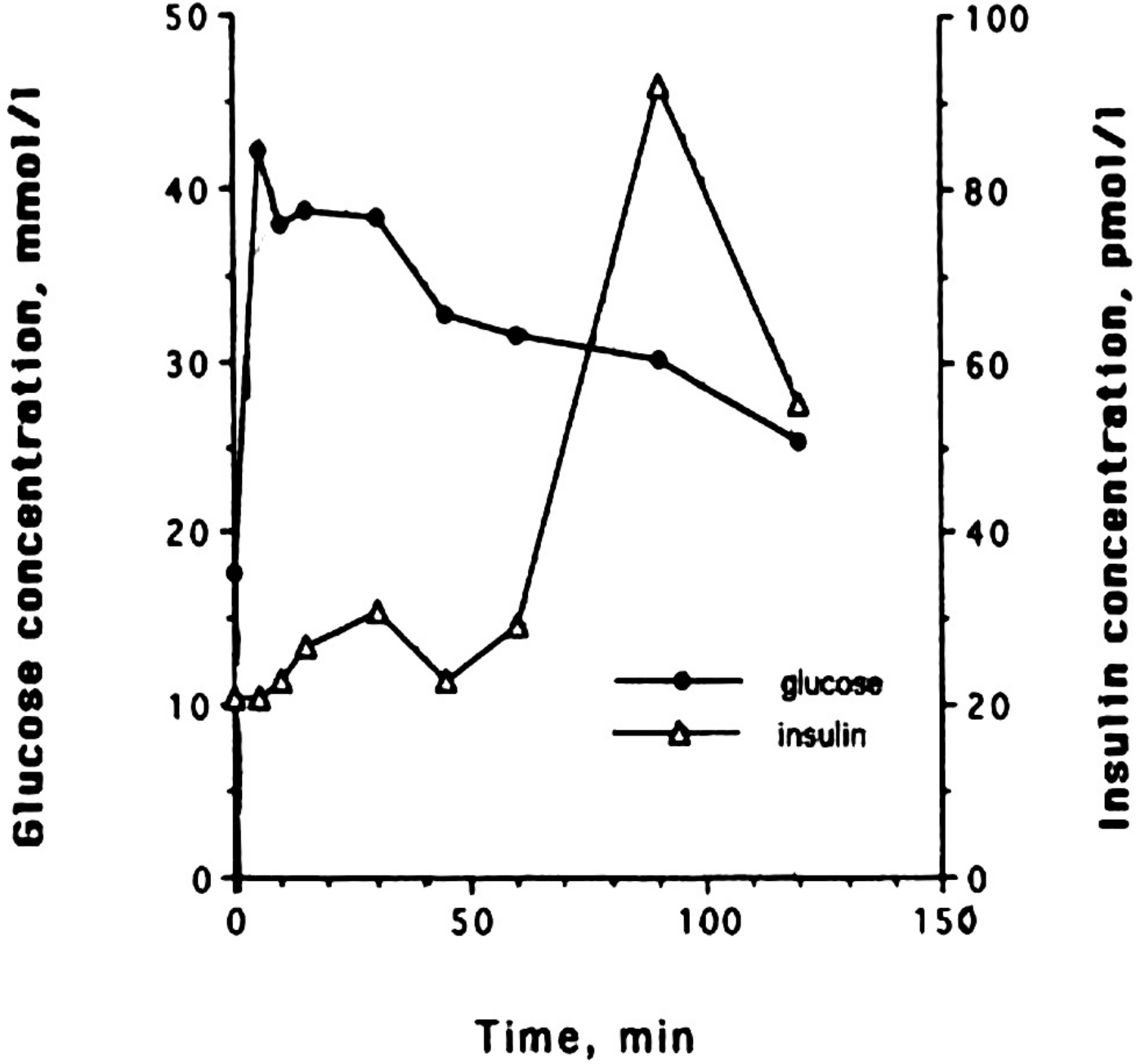
30
40
0
100
200
300
400
500
600
0
50
100
150


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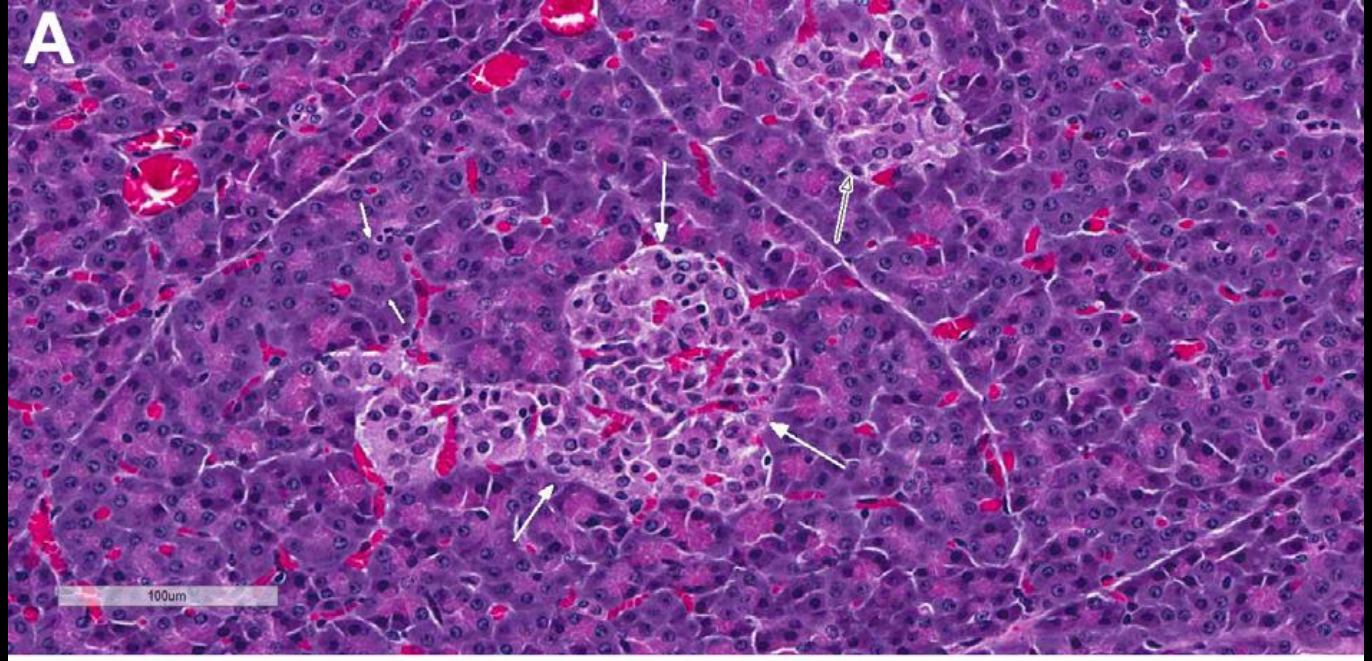
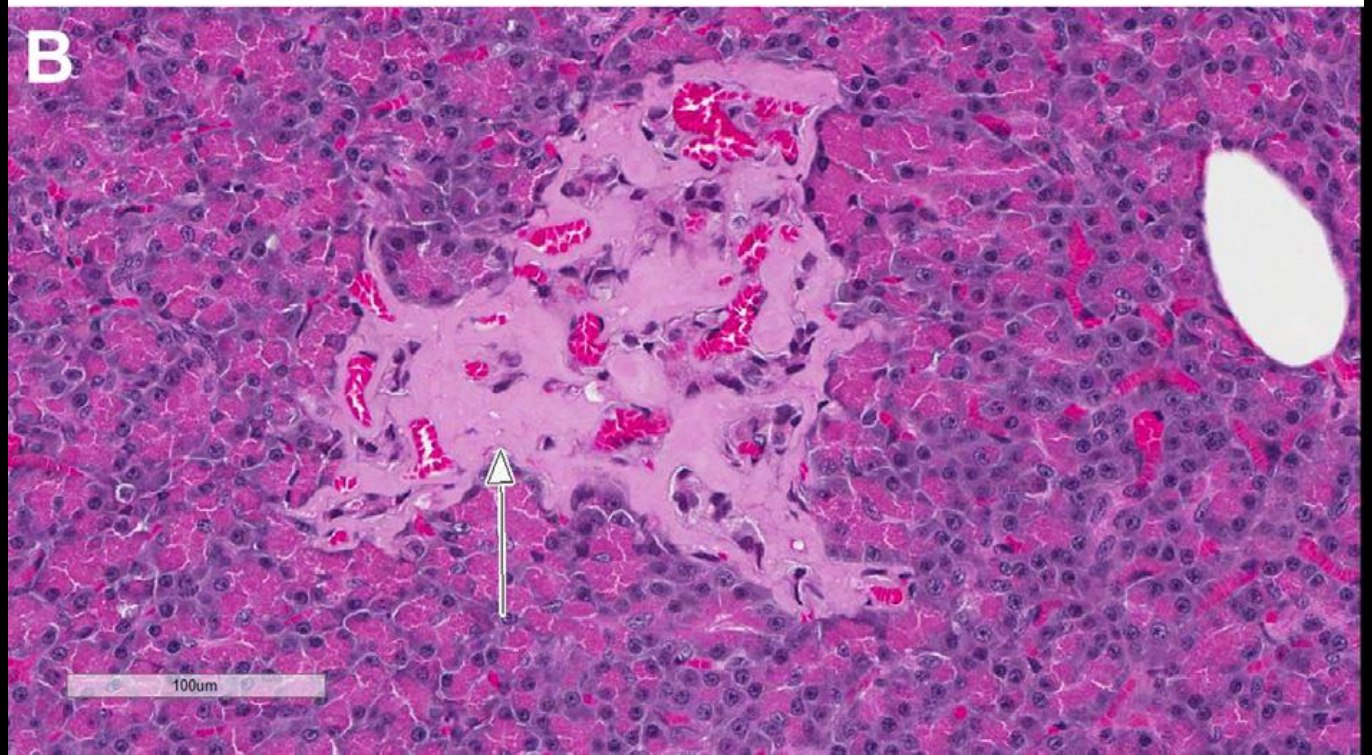
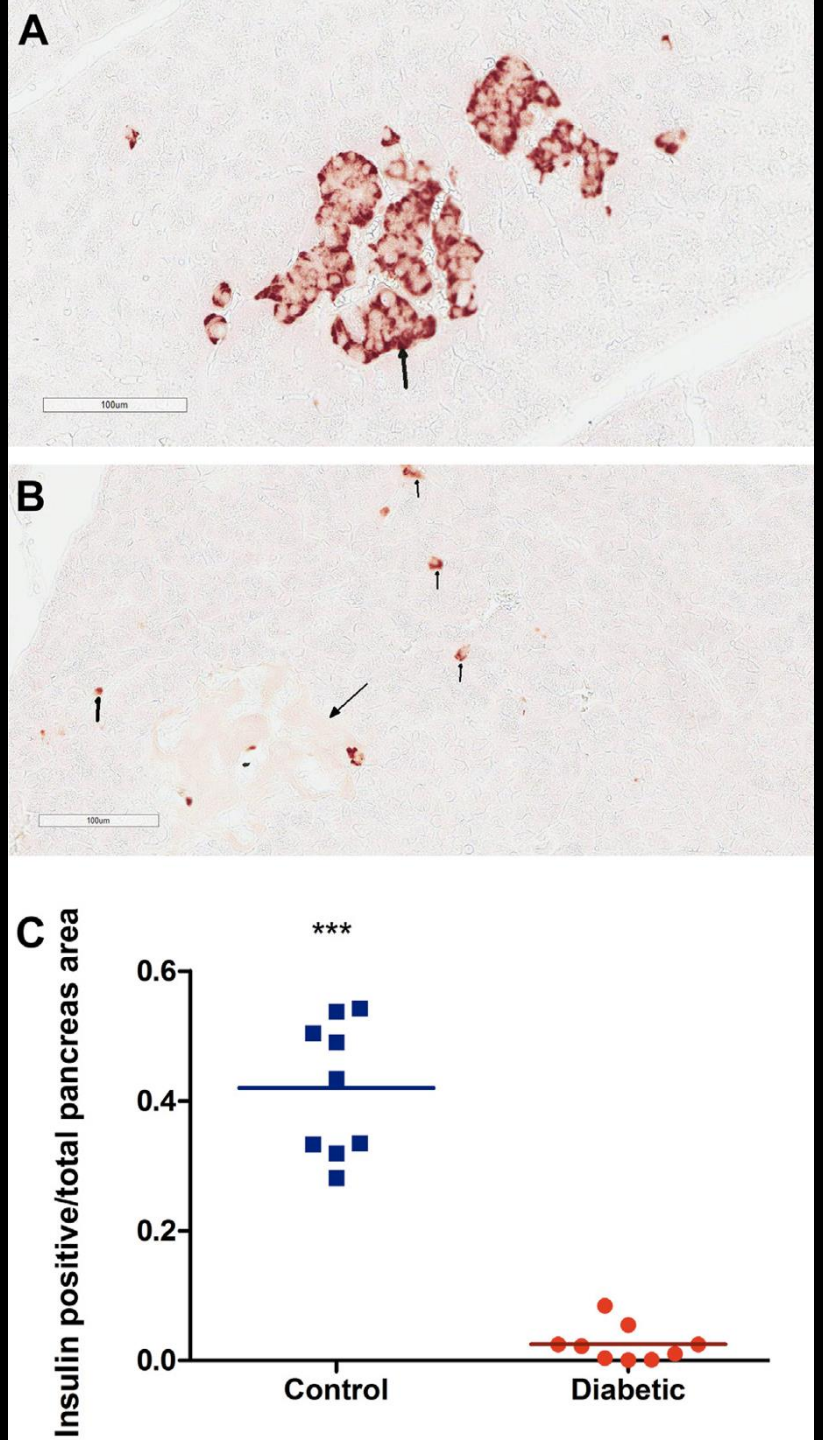
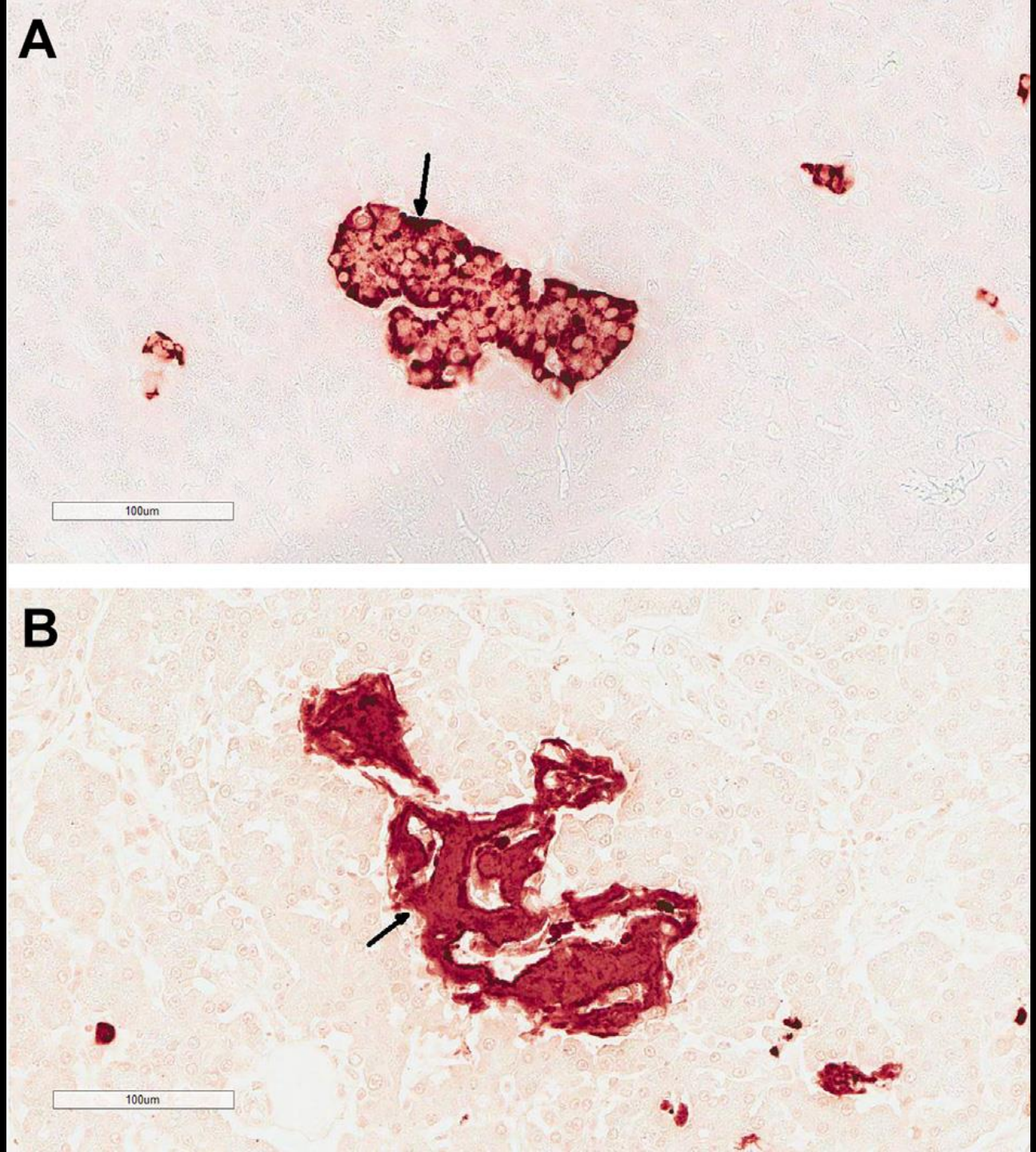
30
40
50
0
20
40
60
80
100
0
50
100
150


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
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B
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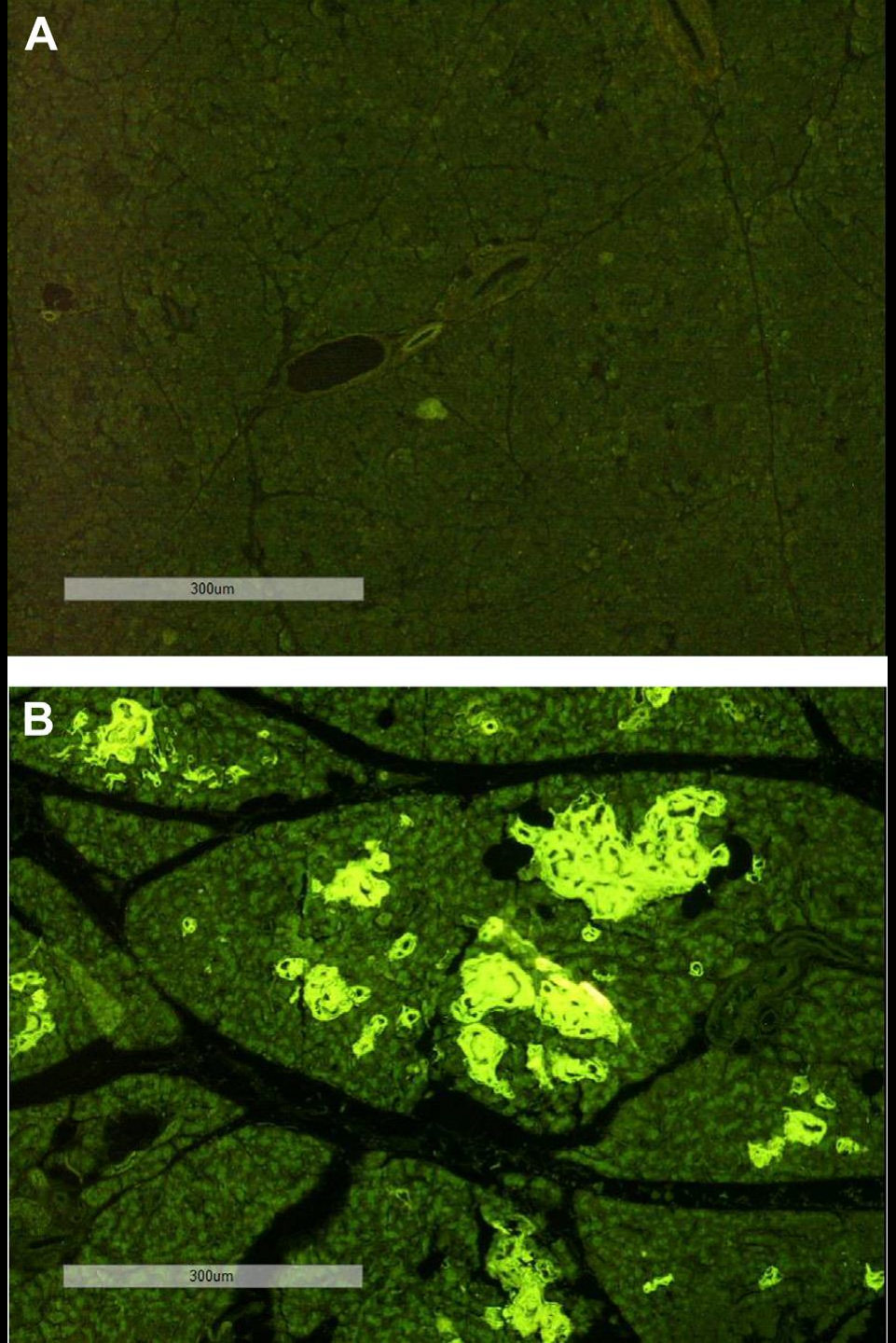
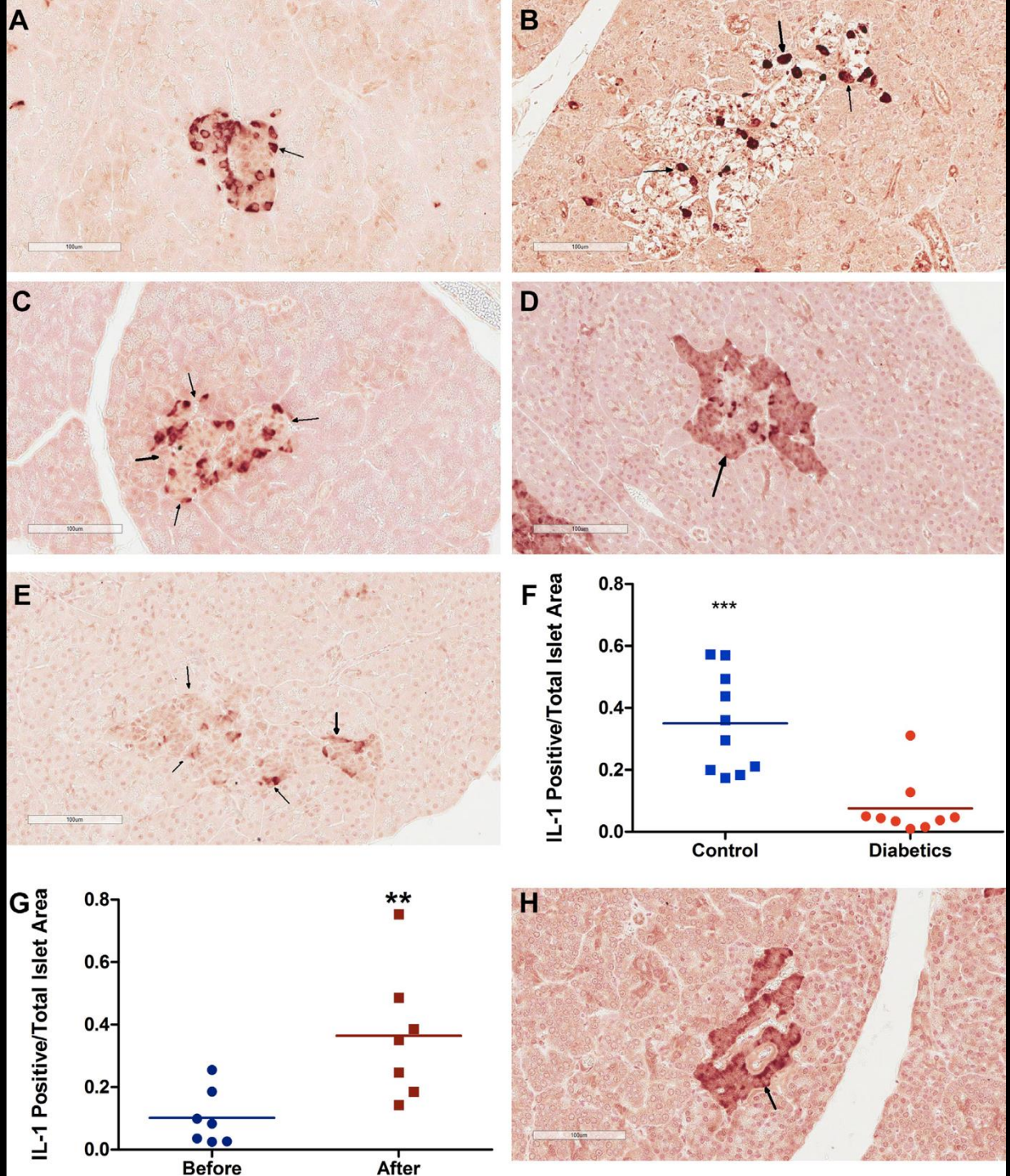
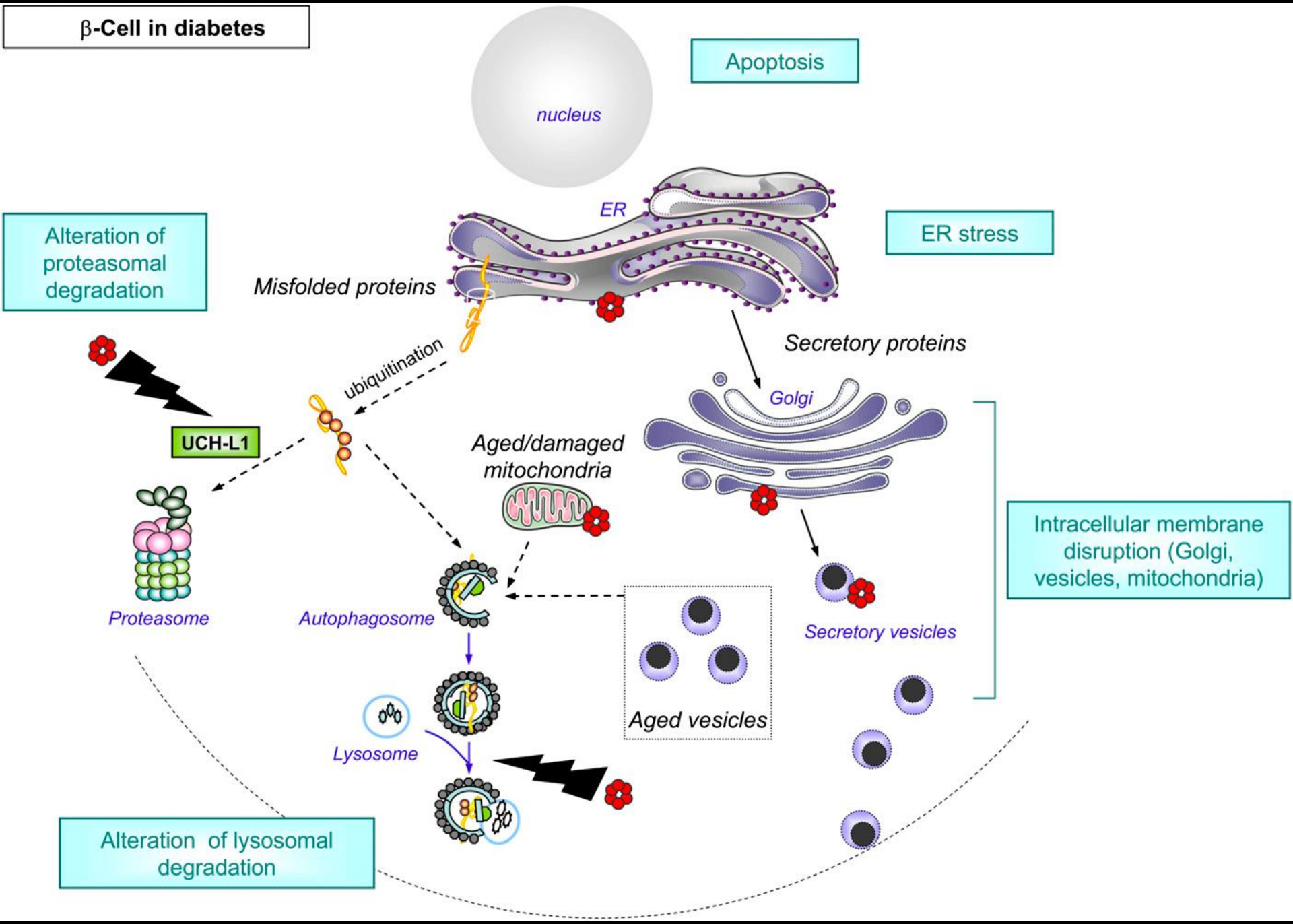
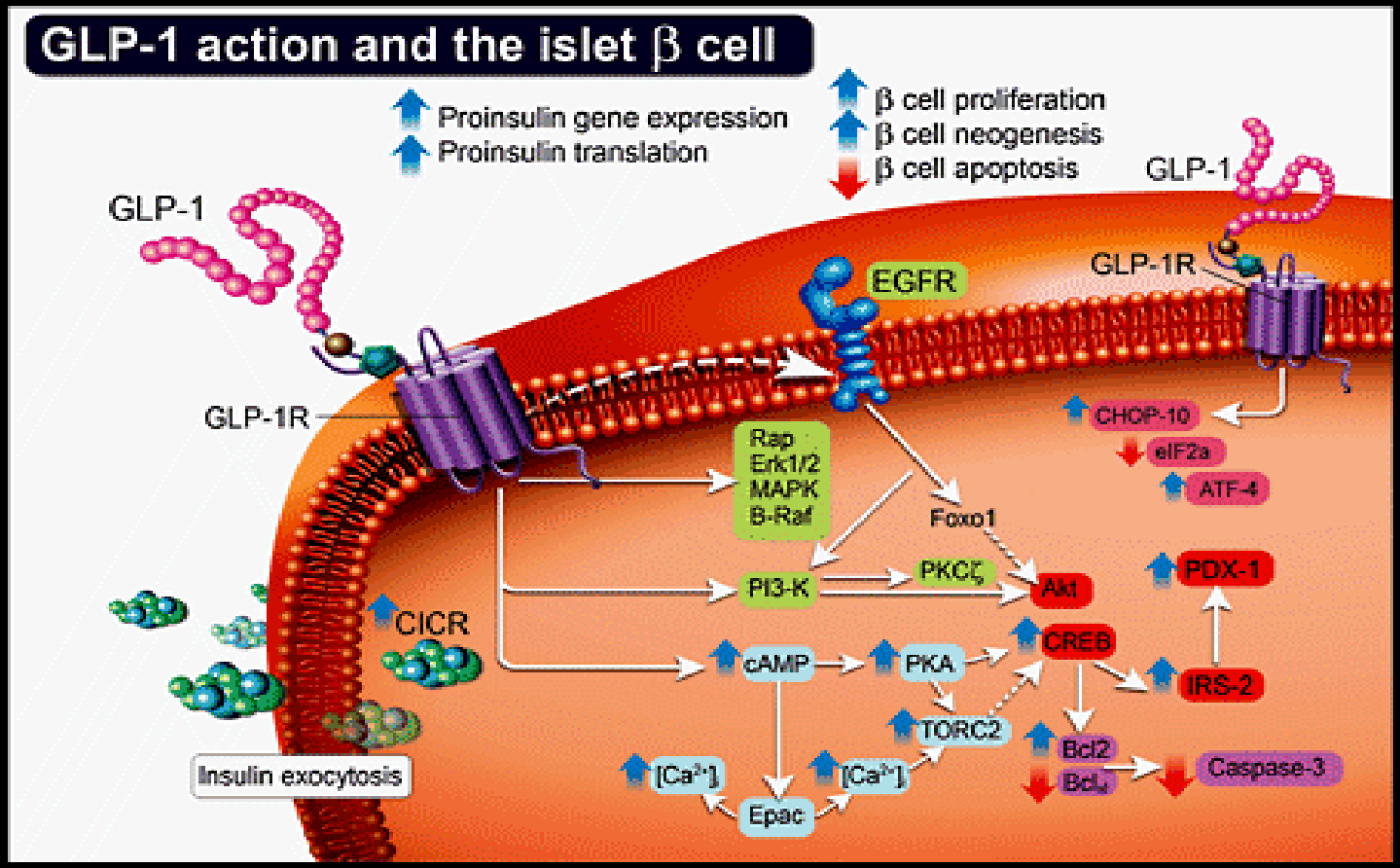

A
300um
B
300um


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

Moving Beyond Insulin



Moving Beyond Insulin

Byetta (exenatide)

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

Moving Beyond Insulin

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.

Moving Beyond Insulin

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.

Moving Beyond Insulin

Exenatide in Cats

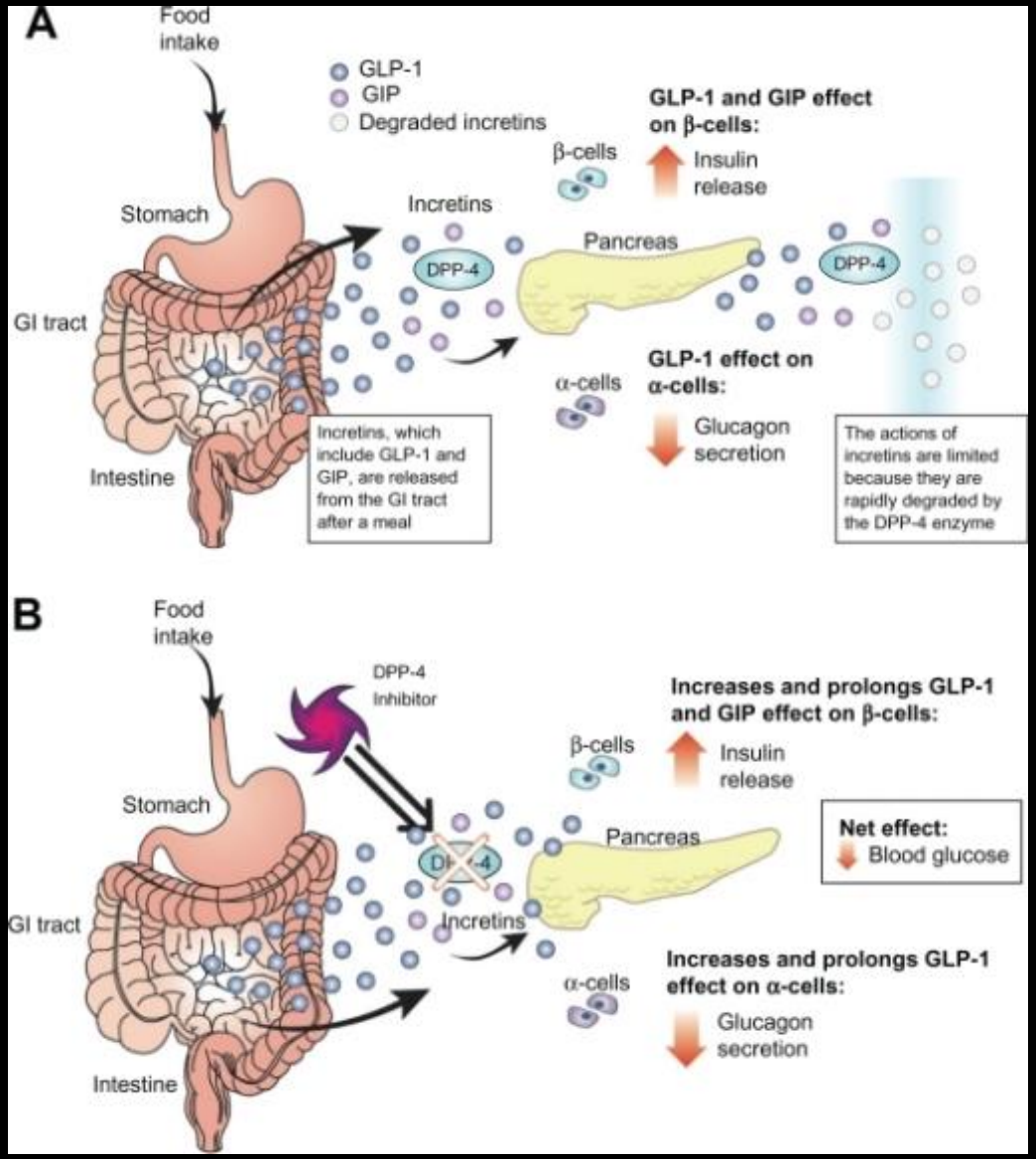
Recently, exenatide-ER was assessed in a group of normal and newly diagnosed diabetic cats treated with insulin glargine and fed a diabetic diet. Cats in this study were treated with once-weekly injection of placebo or exenatide-ER at a dose of 0.2 mg/kg. Despite using what seems in retrospect like a 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.

Moving Beyond Insulin

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.

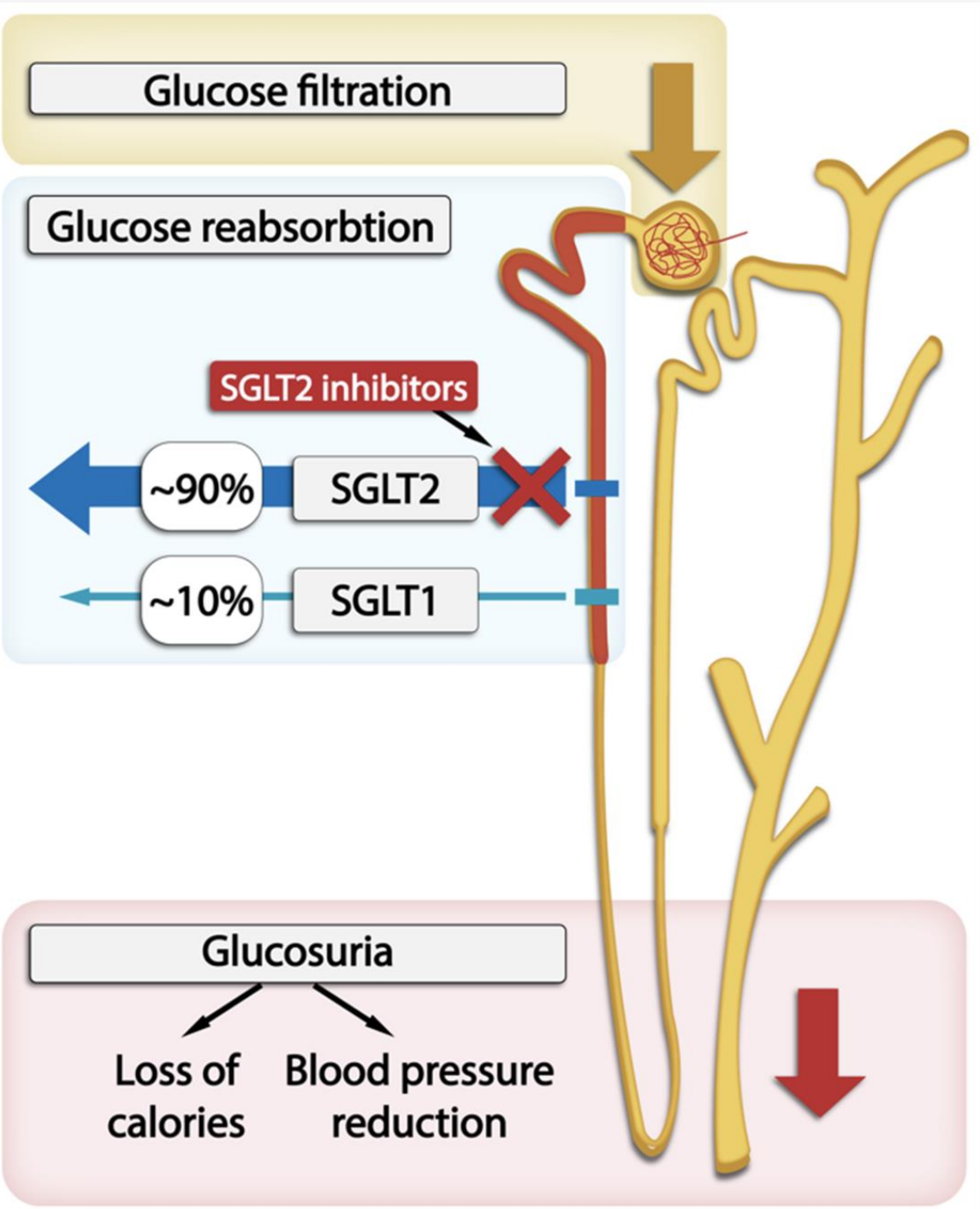
Moving Beyond Insulin



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


Glucose filtration
Glucose reabsorbtion
SGLT2 inhibitors
~90%
SGLT2
~10%
SGLT1
Glucosuria
Loss of calories
Blood pressure reduction

JAVMA

Velagliflozin, a once-daily, liquid, oral SGLT2 inhibitor, is effective as a stand-alone therapy for feline diabetes mellitus: the SENSATION study

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OBJECTIVE
To investigate safety and effectiveness of velagliflozin oral solution as sole therapy in naïve and previously insulin-treated diabetic cats.

ANIMALS
252 client-owned cats receiving ≥ 2 doses of velagliflozin; 214 (85%) naïve diabetics and 38 (15%) insulin-treated diabetics.

PROCEDURES
Prospective, baseline-controlled, open-label clinical field trial. Cats received velagliflozin orally, once daily. Physical examinations and blood collections were performed days 0, 3, 7, 30, 60, 120, and 180.

RESULTS
Data are median (range). Screening blood glucose (BG) was 436 mg/dL (272 to 676 mg/dL). On days 30, 60, 120, and 180, single BG after receiving velagliflozin was 153 mg/dL (62 to 480 mg/dL), 134 mg/dL (64 to 414 mg/dL), 128 mg/dL (55 to 461 mg/dL), and 125 mg/dL (77 to 384 mg/dL), respectively. Screening fructosamine was 538 µmol/L (375 to 794 µmol/L). On the same recheck days, fructosamine was 310 µmol/L (204 to 609 µmol/L), 286 µmol/L (175 to 531 µmol/L), 269 µmol/L (189 to 575 µmol/L), and 263 µmol/L (203 to 620 µmol/L). At day 180, 81% of 158 cats remaining had BG and/or fructosamine within reference ranges; 88.6% (124 of 140) and 87.7% (121 of 138) showed improvement in polyuria and polydipsia, respectively. Ketonuria developed in 35 cats (13.9%), including 18 (7.1%) that had ketoacidosis. Ketoacidosis was less common in naïve diabetic cats (11 of 214 [5.1%]) compared to insulin-treated diabetic cats (7 of 38 [18.4%]). At ketoacidosis diagnosis, 14 of 18 cats (77.8%) were euglycemic (ie, BG < 250 mg/dL). Most episodes of ketosis or ketoacidosis (30 of 35 [85.7%]) occurred within the first 14 days of treatment. Insulin-treated diabetic cats were less likely to complete the trial. No clinical hypoglycemia occurred.

CLINICAL RELEVANCE
Velagliflozin improved glycemic parameters and clinical signs in diabetic cats. Velagliflozin provides an alternative to insulin as a stand-alone treatment of diabetic cats.

Keywords: hyperglycemia, cat, diabetes mellitus, oral hypoglycemic agent, SGLT2 inhibitor

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The prevalence of feline diabetes mellitus (DM) is rising, with a reported range of 0.12% to 0.6%.[1–3] Feline DM is similar to type 2 DM in people, characterized by a combination of peripheral insulin resistance and inadequate insulin secretion.[4,5] With continued hyperglycemia, pancreatic β cells undergo

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STANDARD ARTICLE

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Safety and effectiveness of the sodium-glucose cotransporter inhibitor bexagliflozin in cats newly diagnosed with diabetes mellitus

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Abstract

Background: Bexagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. A pilot study has shown that bexagliflozin can decrease dependence on exogenous insulin in cats with diabetes mellitus (DM).

Objective: To evaluate the safety and effectiveness of bexagliflozin as a monotherapy for DM in previously untreated cats.

Animals: Eighty-four client-owned cats.

Methods: Historically controlled prospective open-label clinical trial. Cats were dosed PO with 15 mg bexagliflozin once daily for 56 days, with a 124-day extension to evaluate safety and treatment effect durability. The primary endpoint was the proportion of cats experiencing a decrease in hyperglycemia and improvement in clinical signs of hyperglycemia from baseline on day 56.

Results: Of 84 enrolled cats, 81 were evaluable on day 56, and 68 (84.0%) were treatment successes. Decreases in mean serum glucose, fructosamine, and β-hydroxybutyrate (β-OHB) concentrations were observed, and investigator assessments of cat neurological status, musculature, and hair coat quality improved. Owner evaluations of both cat and owner quality of life were favorable. The fructosamine half-life in diabetic cats was found to be 6.8 days. Commonly observed adverse events included emesis, diarrhea, anorexia, lethargy, and dehydration. Eight cats experienced serious adverse events, 3 of which led to death or euthanasia. The most important adverse event was euglycemic diabetic ketoacidosis, diagnosed in 3 cats and presumed present in a fourth.

Conclusion and Clinical Importance: Bexagliflozin decreased hyperglycemia and observed clinical signs in cats newly diagnosed with DM. As a once-daily PO medication, bexagliflozin may simplify management of DM in cats.

Abbreviations: ANOVA, analysis of variance; BGC, blood glucose curve; CI, confidence interval; DM, diabetes mellitus; FDA, Food and Drug Administration; FPL, feline pancreatic lipase; IGF-1, insulin-like growth factor 1; IVP, investigational veterinary product; SAE, serious adverse event; SDMA, symmetrical dimethylarginine; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus; T4, thyroxine; VeDDRA, Veterinary Dictionary for Drug Regulatory Activities; β-OHB, β-hydroxybutyrate.

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.

Moving Beyond Insulin

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