Diabetes Mellitus

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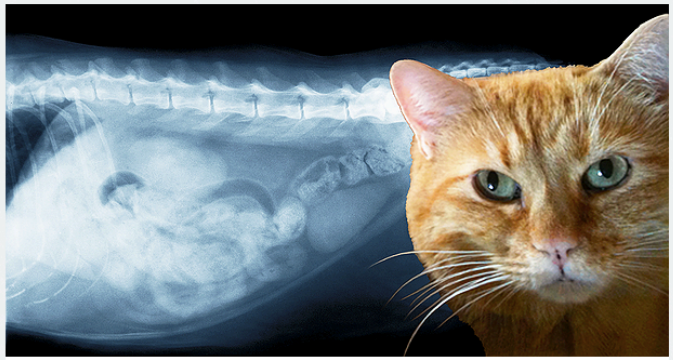

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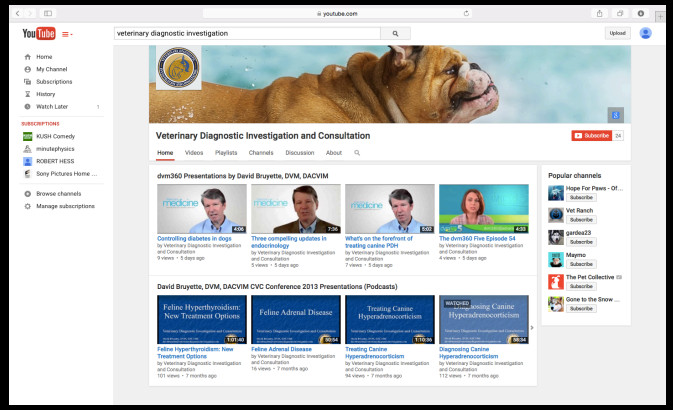

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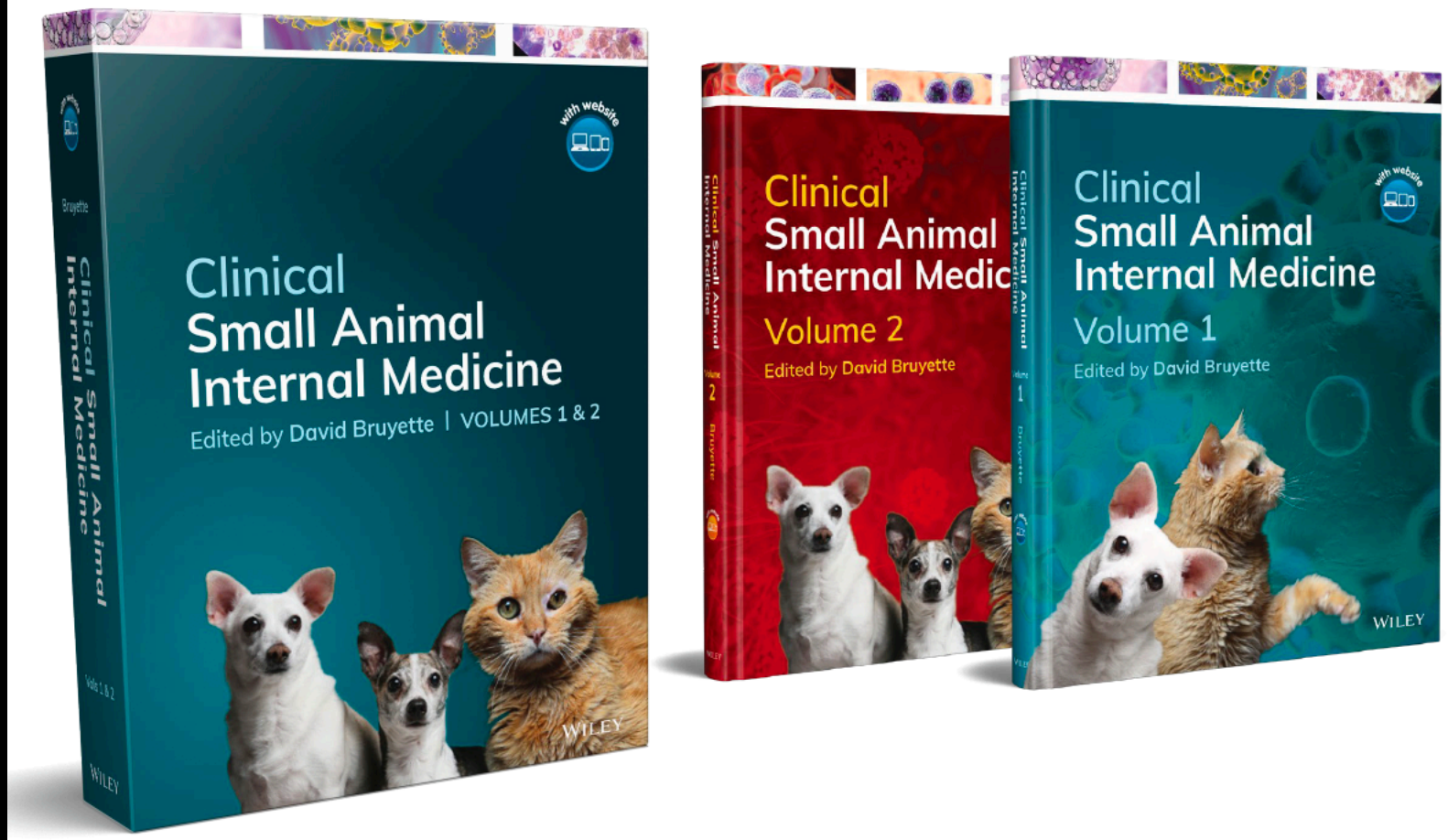
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“We dance round a ring and suppose, but the Secret sits in the center and knows.”

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

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.

Table 2.2—Criteria for the diagnosis of diabetes

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
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
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Table 2.5—Criteria defining prediabetes*

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)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *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.

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.

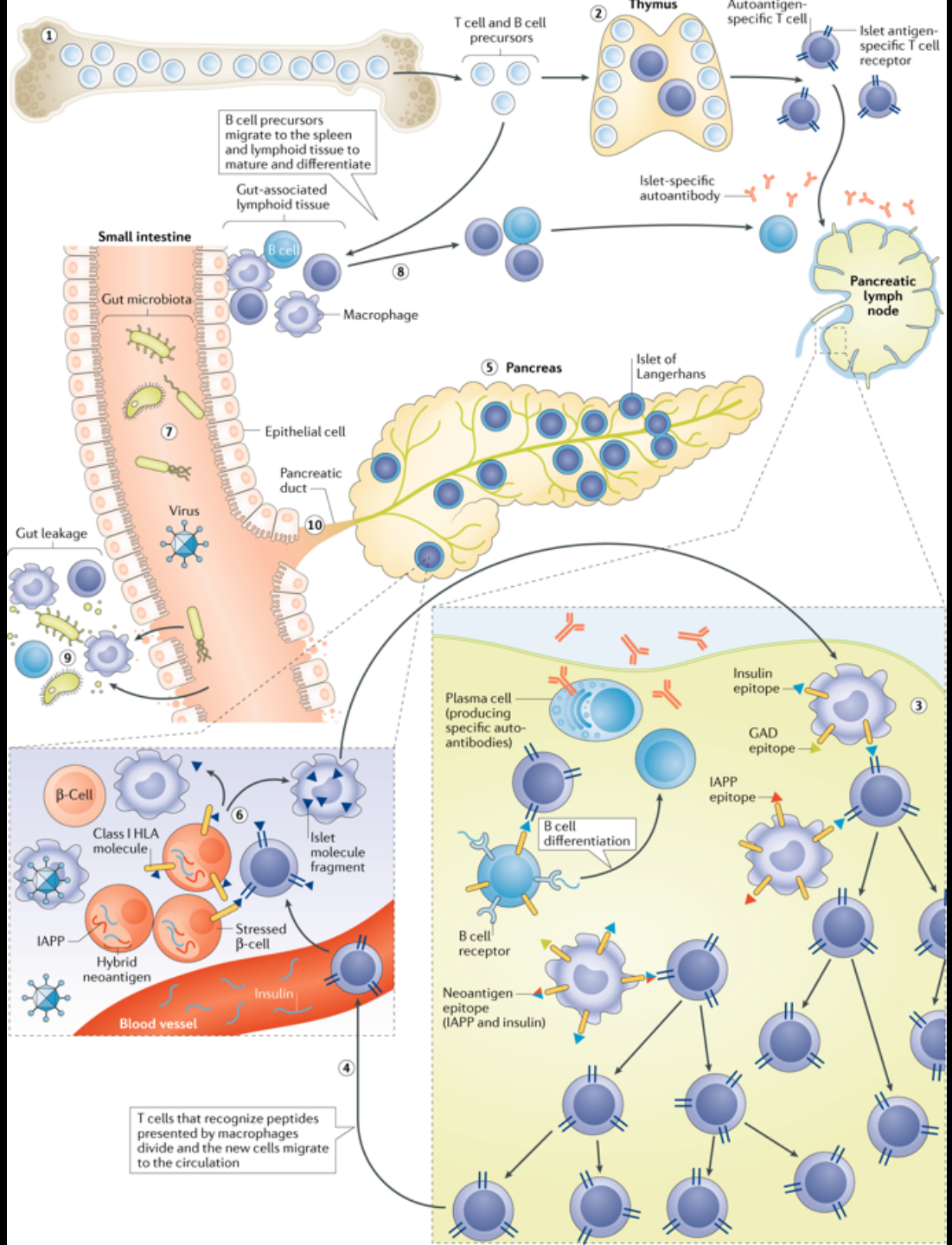
If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

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.


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
Class I HLA molecule
6
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

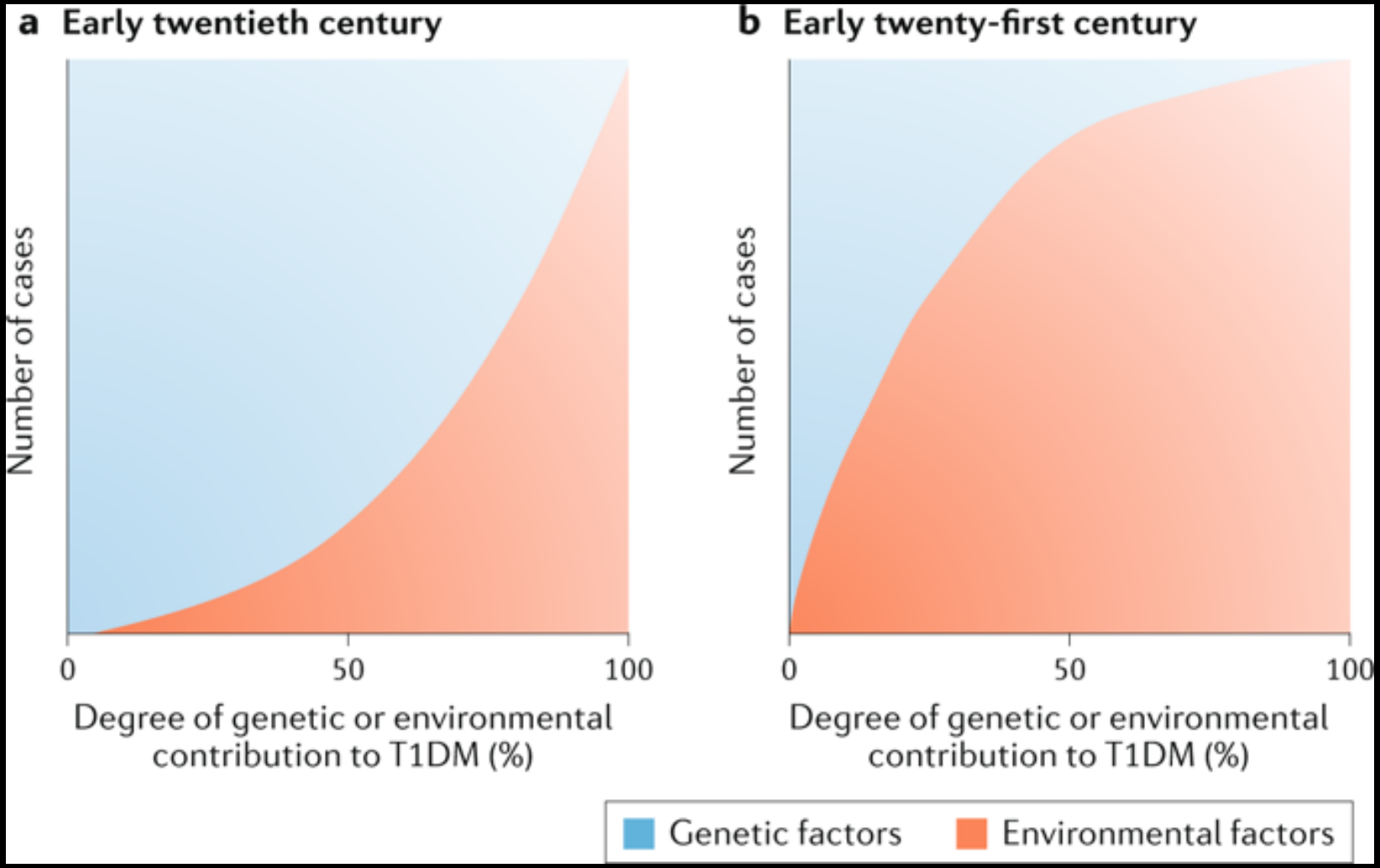
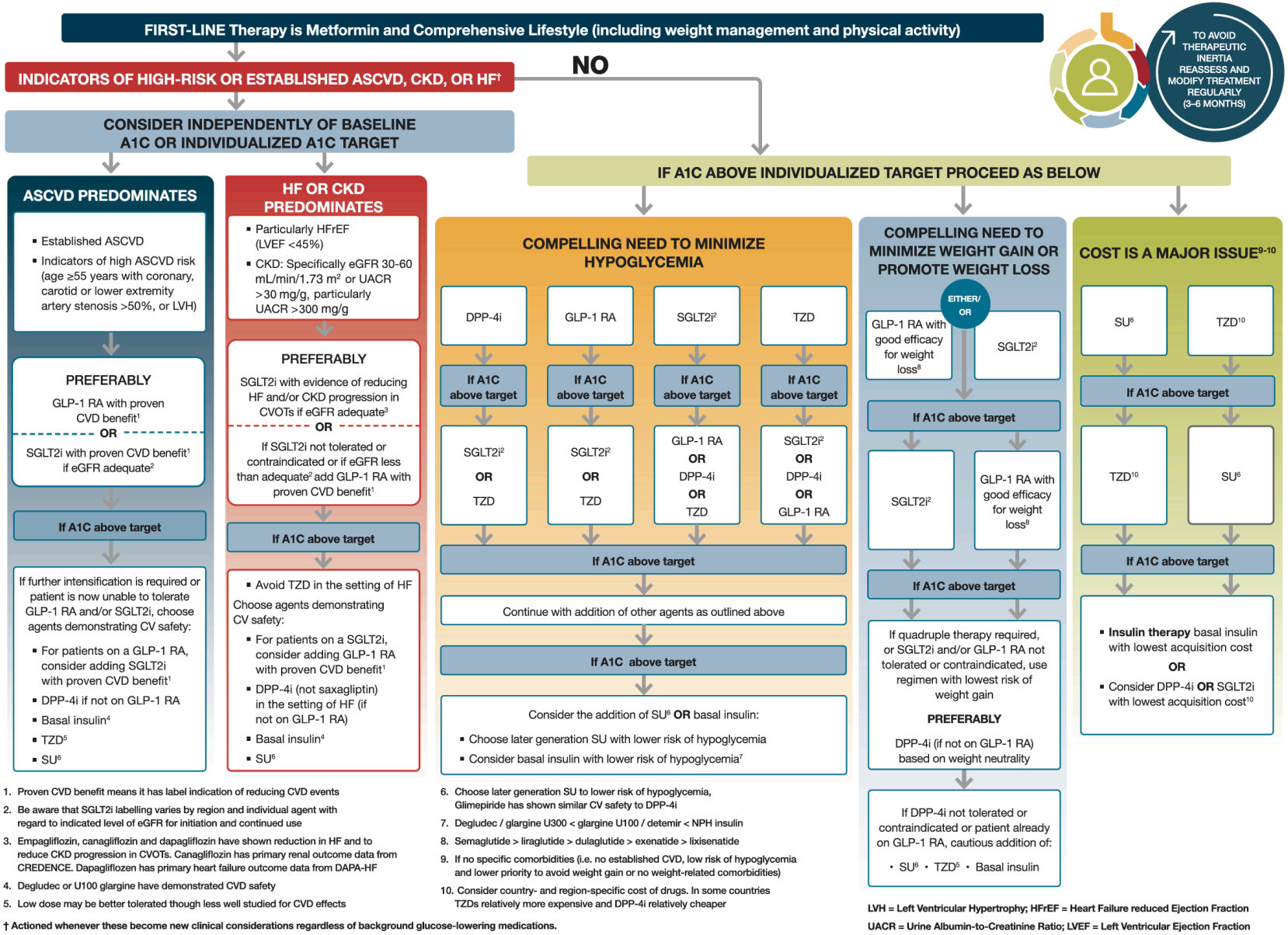

a Early twentieth century
Number of cases
0
50
100
Degree of genetic or environmental contribution to T1DM (%)
b Early twenty-first century
Number of cases
0
50
100
Degree of genetic or environmental contribution to T1DM (%)
Genetic factors
Environmental factors

Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m²	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: See label indication of reducing CVD events	Neutral	High	SQ; oral (semaglutide)	Benefit: liraglutide	▪ Renal dose adjustment required (exenatide, lixisenatide) ▪ Caution when initiating or increasing dose due to potential risk of acute kidney injury	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — Analogs						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. ‡FDA-approved for heart failure indication; §FDA-approved for CKD indication. CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see **Fig. 4.1**. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies and colleagues (33,34).

Table 9.2—Median monthly (30-day) cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

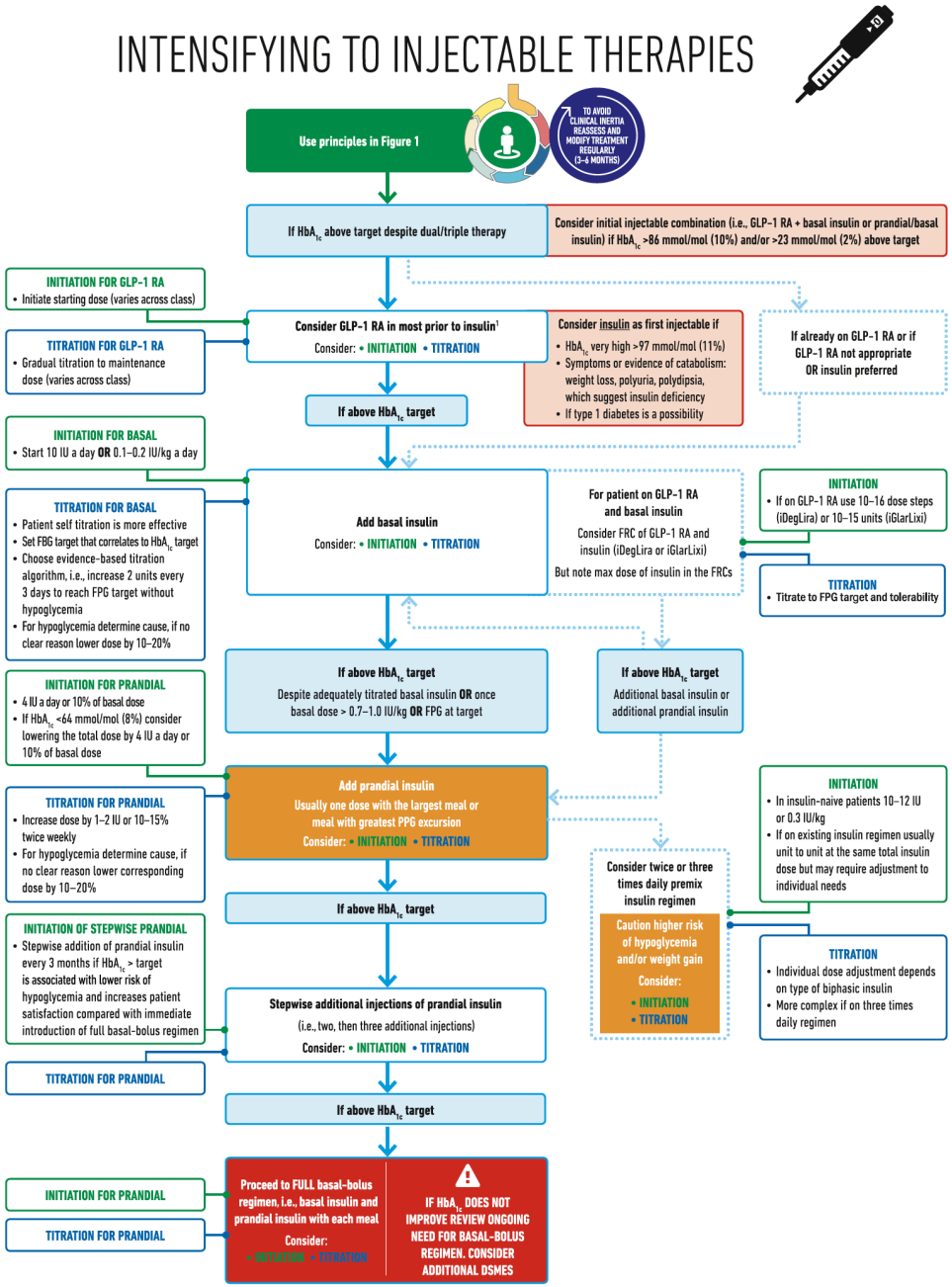
Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Median NADAC (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	500 mg (IR)	$84 ($4, $85)	$2	2,000 mg
		850 mg (IR)	$108 ($6, $109)	$3	2,550 mg
		1,000 mg (IR)	$87 ($4, $88)	$2	2,000 mg
		500 mg (ER)	$89 ($87, $7,412)	$5 ($5, $988)	2,000 mg
		750 mg (ER)	$74 ($65, $74)	$4	1,500 mg
		1,000 mg (ER)	$242 ($242, $7,214)	$224 ($224, $910)	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$74 ($71, $198)	$4	8 mg
	• Glipizide	10 mg (IR)	$75 ($67, $97)	$5	40 mg (IR)
		10 mg (XL)	$48	$15	20 mg (XL)
	• Glyburide	6 mg (micronized)	$50 ($48, $71)	$4	12 mg (micronized)
		5 mg	$93 ($63, $103)	$11	20 mg
Thiazolidinediones	• Pioglitazone	45 mg	$348 ($283, $349)	$4	45 mg
	• Rosiglitazone	4 mg	$407	$330	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $106)	$23	300 mg
	• Miglitol	100 mg	$241	$311	300 mg
Meglitinides (glinides)	• Nateglinide	120 mg	$155	$39	360 mg
	• Repaglinide	2 mg	$878 ($162, $897)	$39	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$168	25 mg
	• Saxagliptin	5 mg	$505	$403	5 mg
	• Linagliptin	5 mg	$523	$419	5 mg
	• Sitagliptin	100 mg	$541	$433	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	$338	$271	15 mg
	• Dapagliflozin	10 mg	$591	$473	10 mg
	• Empagliflozin	25 mg	$591	$473	25 mg
	• Canagliflozin	300 mg	$593	$475	300 mg
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	$840	$672	2 mg**
	• Exenatide	10 μg pen	$876	$730	20 μg
	• Dulaglutide	1.5/0.5 mL pen	$911	$730	1.5 mg**
	• Semaglutide	1 mg pen	$927	$745	1 mg**
		14 mg (tablet)	$927	N/A	14 mg
	• Liraglutide	18 mg/3 mL pen	$1,106	$886	1.8 mg
	• Lixisenatide	300 μg/3 mL pen	$744	N/A	20 μg
Bile acid sequestrant	• Colesevelam	625 mg tabs	$712 ($674, $712)	$177	3.75 g
		3.75 g suspension	$675	$415	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$906	$729	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2,623	$2,097	120 μg/injection†††

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; N/A, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. †Calculated for 30-day supply (AWP [54] or NADAC [55] 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. *Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. **Administered once weekly. †††AWP and NADAC calculated based on 120 μg three times daily.

Table 9.3—Median cost of insulin products in the U.S. calculated as AWP (54) and NADAC (55) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC (min, max)*
Rapid-acting	• Lispro follow-on product	U-100 vial	$157	$126
		U-100 prefilled pen	$202	$162
	• Lispro	U-100 vial	$330	$264
		U-100 3 mL cartridges	$408	$327
		U-100 prefilled pen; U-200 prefilled pen	$424	$340
	• Glulisine	U-100 vial	$341	$273
		U-100 prefilled pen	$439	$353
	• Aspart	U-100 vial	$347†	$278†
		U-100 3 mL cartridges	$430	$345
		U-100 prefilled pen	$447†	$358†
	• Inhaled insulin	Inhalation cartridges	$924	$606
Short-acting	• human regular	U-100 vial	$165 ($165, $178)††	$134 ($134, $146)††
Intermediate-acting	• human NPH	U-100 vial	$165 ($165, $178)††	$135 ($135, $146)††
		U-100 prefilled pen	$377	$304
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$144
		U-500 prefilled pen	$230	$184
Long-acting	• Glargine follow-on product	U-100 prefilled pen	$261	$210
	• Glargine	U-100 vial; U-100 prefilled pen	$340	$272
		U-300 prefilled pen	$346	$280
	• Detemir	U-100 vial; U-100 prefilled pen	$370	$295
	• Degludec	U-100 vial; U-100 prefilled pen; U-200 prefilled pen	$407	$326
Premixed insulin products	• NPH/regular 70/30	U-100 vial	$165 ($165, $178)	$134 ($134, $145)
		U-100 prefilled pen	$377	$303
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$338
	• Lispro 75/25	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$340
	• Aspart 70/30	U-100 vial	$360	$289
		U-100 prefilled pen	$447	$358
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 prefilled pen	$565	$454
	• Degludec/Liraglutide	100/3.6 prefilled pen	$832	$668

AWP, average wholesale price; GLP-1, glucagon-like peptide 1; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in **Table 9.2**. †Inclusive of both the original and "faster-acting" products. ††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. Consider choice of GLP-1 RA considering: patient preference, HbA_{1c} lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit

Figure 7—Intensifying to injectable therapies. FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide 1 receptor agonist; FBG, fasting blood glucose; FPG, fasting plasma glucose; max, maximum; PPG, postprandial glucose.

Table 2—Glucose-lowering medications and therapies available in the U.S. or Europe and specific characteristics that may guide individualized treatment choices in nonpregnant adults with type 2 diabetes

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
Lifestyle					
Diet quality	• Mediterranean type • DASH • Low carbohydrate • Vegetarian • Others	• Depends on diet	• Inexpensive • No side effects	• Requires instruction • Requires motivation • Requires lifelong behavioral change • Social barriers may exist	Intermediate
Physical activity	• Running, walking • Bicycling (including stationary) • Swimming • Resistance training • Yoga • Tai chi • Many others	• Energy expenditure • Weight management • ↑ Insulin sensitivity	• Inexpensive • ↓ Fall risk by increasing balance/strength • ? Improves mental health • ↑ Bone density • ↓ Blood pressure • ↓ Weight • Improves ASCVD risk factors	• Risk of musculoskeletal injury • Requires motivation • Risk of foot trauma in patients with neuropathy • Requires lifelong behavioral change	Intermediate
Energy restriction	• Individual energy restriction with or without energy tracking • Programs with counseling • Food substitution programs	• Energy restriction • Weight management • ↓ Hepatic and pancreatic fat • ↑ Insulin sensitivity	• Lowers glycemia • Reduces need for diabetes and other medications • No serious side effects • Improves ASCVD risk factors	• Requires motivation • Requires lifelong behavioral change	Variable, with potential for very high efficacy; often intermediate
Oral medications					
Biguanides	• Metformin	• ↓ Hepatic glucose production • Multiple other non-insulin-mediated mechanisms	• Extensive experience • No hypoglycemia • Inexpensive	• GI symptoms • Vitamin B_{12} deficiency • Use with caution or dose adjustment for CKD stage 3B (eGFR 30–44 mL min^{-1} [1.73 m]$^{-2}$) • Lactic acidosis (rare)	High
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin • Empagliflozin • Ertugliflozin	• Blocks glucose reabsorption by the kidney, increasing glucosuria • ? Other tubulo-glomerular effects	• No hypoglycemia • ↓ Weight • ↓ Blood pressure • Effective at all stages of T2DM with preserved glomerular function • ↓ MACE, HF, CKD with some agents (see text)	• Genital infections • UTI • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • Dose adjustment/avoidance for renal disease • ↑ Risk for amputation (canagliflozin) • ↑ Risk for fracture (canagliflozin)	Intermediate–high (dependent on GFR)

Continued on p. 2682

Table 2—Continued

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
				• ↑ Risk for DKA (rare) • Fournier's gangrene (rare) • Expensive	
DPP-4 inhibitors	• Sitagliptin • Vildagliptin[a] • Saxagliptin • Linagliptin • Alogliptin	• Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion	• No hypoglycemia • Weight neutral • Well tolerated	• Rare urticaria/angioedema • ↑ HF hospitalization (saxagliptin) • Dose adjustment/avoidance for renal disease depending on agent • ? Pancreatitis • ? Arthralgia • ? Bullous pemphigoid • Expensive (U.S.); variable in Europe	Intermediate
Sulfonylureas	• Glibenclamide/glyburide • Glipizide • Gliclazide[a] • Glimepiride	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS) • Inexpensive	• Hypoglycemia • ↑ Weight • Uncertain cardiovascular safety • Dose adjustment/avoidance for renal disease • High rate of secondary failure	High
TZDs	• Pioglitazone • Rosiglitazone[b]	• ↑ Insulin sensitivity	• Low risk for hypoglycemia • Durability • ↑ HDL-C • ↓ Triacylglycerols (pioglitazone) • ↓ ASCVD events (pioglitazone: in a poststroke insulin-resistant population and as secondary end point in a high-risk-of-CVD diabetes population) • Lower cost	• ↑ Weight • Edema/heart failure • Bone loss • ↑ Bone fractures • ↑ LDL-C (rosiglitazone) • ? Bladder cancer • ? Macular edema	High
Meglitinides (Glinides)	• Repaglinide • Nateglinide	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility • Safe in advanced renal disease with cautious dosing (especially repaglinide) • Lower cost	• Hypoglycemia • ↑ Weight • Uncertain cardiovascular safety • Frequent dosing schedule	Intermediate–high
α-Glucosidase inhibitors	• Acarbose • Miglitol	• Slows carbohydrate digestion/absorption	• Low risk for hypoglycemia • ↓ Postprandial glucose excursions • Nonsystemic mechanism of action • Cardiovascular safety • Lower cost	• Frequent GI side effects • Frequent dosing schedule • Dose adjustment/avoidance for renal disease	Low–intermediate
Bile acid sequestrants	• Colesevelam[b]	• ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• No hypoglycemia • ↓ LDL-C	• Constipation • ↑ Triacylglycerols • May ↓ absorption of other medications • Intermediate expense	Low–intermediate

Continued on p. 2683

Table 2—Continued

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
Dopamine-2 agonists	• Quick-release bromocriptine[b]	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• No hypoglycemia • ? ↓ ASCVD events	• Headache/dizziness/syncope • Nausea • Fatigue • Rhinitis • High cost	Low–intermediate
Injectable medications					
Insulins					
Long acting (basal)	• Degludec (U100, U200) • Detemir • Glargine (U100, U300)	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • Theoretically unlimited efficacy • Once-daily injection	• Hypoglycemia • Weight gain • Training requirements • Frequent dose adjustment for optimal efficacy • High cost	Very high
Intermediate acting (basal)	• Human NPH	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • Theoretically unlimited efficacy • Less expensive than analogs	• Hypoglycemia • Weight gain • Training requirements • Often given twice daily • Frequent dose adjustment for optimal efficacy	Very high
Rapid acting	• Aspart (conventional and fast acting) • Lispro (U100, U200) • Glulisine	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • Theoretically unlimited efficacy • ↓ Postprandial glucose	• Hypoglycemia • Weight gain • Training requirements • May require multiple daily injections • Frequent dose adjustment for optimal efficacy • High cost	Very high
Inhaled rapid acting	• Human insulin inhalation powder[b]	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • ↓ Postprandial glucose • More rapid onset and shorter duration than rapid-acting analogs	• Spirometry (FEV_1) required before initiating, after 6 months, and annually • Contraindicated in chronic lung disease • Not recommended in smokers • Hypoglycemia • Weight gain • Training requirements • May require multiple inhalations daily	High

Continued on p. 2684

Table 2—Continued

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
				• Frequent dose adjustment for optimal efficacy; limited options in dosing interval • High cost • Respiratory side effects (e.g., bronchospasm, cough, decline in FEV_1)	
Short acting	• Human regular (U100, U500)	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • Theoretically unlimited efficacy • ↓ Postprandial glucose • Less expensive than analogs	• Hypoglycemia • Weight gain • Training requirements • Frequent dose adjustment for optimal efficacy • May require multiple daily injections	Very high
Premixed	• Many	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • Theoretically unlimited efficacy • Fewer injections than basal/bolus before every meal • Recombinant human analogs are less expensive	• Hypoglycemia • Weight gain • Training requirements • Frequent dose adjustment for optimal efficacy • High cost (except human insulin premix) • Can lead to obligate eating	Very high
GLP-1 RA					
Shorter acting	• Exenatide • Lixisenatide	• Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• No hypoglycemia as monotherapy • ↓ Weight • Excellent postprandial glucose efficacy for meals after injections • Improves cardiovascular risk factors	• Frequent GI side effects that may be transient • Modestly ↑ heart rate • Training requirements • Dose adjustment/avoidance in renal disease • Acute pancreatitis (rare/uncertain) • Very high cost	Intermediate–high
Longer acting	• Dulaglutide • Exenatide extended-release • Liraglutide • Semaglutide	• Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion • ↑ Satiety	• No hypoglycemia as monotherapy • ↓ Weight • ↓ Postprandial glucose excursions • Improves cardiovascular risk factors • ↓ MACE with some agents (see text) • ↓ Albuminuria with some agents (see text)	• GI side effects, including gallbladder disease • Greater ↑ heart rate • Training requirements • Dose adjustment/avoidance for some agents in renal disease • Acute pancreatitis (rare/uncertain)	High–very high

Continued on p. 2685

Table 2—Continued

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
			• Greater lowering of fasting glucose vs. short-acting preparations • Once-weekly dosing (except liraglutide, which is daily)	• C-cell hyperplasia/medullary thyroid tumors (rare/uncertain; observed in animals only) • Very high cost	
Other injectables					
Amylin mimetics	• Pramlintide[b]	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • ↓ Weight	• Hypoglycemia • Frequent dosing schedule • Training requirements • Frequent GI side effects • Very high cost	Intermediate
Fixed-dose combination of GLP-1 RA and basal insulin analogs	• Liraglutide/degludec • Lixisenatide/glargine	• Combined activities of components	• Enhanced glycemic efficacy vs. components • Reduced adverse effects (e.g., GI, hypoglycemia) vs. components	• Less weight loss than GLP-1 receptor agonist alone • Very high cost	Very high
Weight loss medications	• Lorcaserin[b] • Naltrexone/bupropion • Orlistat • Phentermine/topiramate[b] • Liraglutide 3 mg	• Reduced appetite • Fat malabsorption (orlistat)	• Mean 3–9 kg weight loss vs. placebo	• High discontinuation rates from side effects • <50% achieve ≥5% weight loss • Drug-specific side effects • Limited durability • High cost	Intermediate
Metabolic surgery	• VSG • RYGB • Adjustable gastric band • BPD	• Restriction of food intake (all) • Malabsorption (RYGB, BPD) • Changes in hormonal and possibly neuronal signaling (VSG, RYGB, BPD)	• Sustained weight reduction • ↑ Rate of remission of diabetes • ↓ Number of diabetes drugs • ↓ Blood pressure • Improved lipid metabolism	• High initial cost • ↑ Risk for early and late surgical complications • ↑ Risk for reoperation • ↑ Risk for dumping syndrome • ↑ Nutrient and vitamin malabsorption • ↑ Risk for new-onset depression • ↑ Risk for new-onset opioid use • ↑ Risk for gastroduodenal ulcer • ↑ Risk for hypoglycemia • ↑ Risk for alcohol use disorder	Very high

More details available in ADA's *Standards of Medical Care in Diabetes—2018* (3). Glucose-lowering efficacy of drugs by change in HbA_{1c}: >22 mmol/mol (2%) very high, 11–22 mmol/mol (1–2%) high, 6–11 mmol/mol (0.5–1.5%) intermediate, <6 mmol/mol (0.5%) low. [a]Not licensed in the U.S. for type 2 diabetes. [b]Not licensed in Europe for type 2 diabetes. BPD, biliopancreatic diversion; DKA, diabetic ketoacidosis; FEV_1, forced expiratory volume in 1 s on pulmonary function testing; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; RYGB, Roux-en-Y gastric bypass; VSG, vertical sleeve gastroplasty; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection.

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

BMJ. 2020 Dec 10;371:m4337. doi: 10.1136/bmj.m4337.

The shared risk of diabetes between dog and cat owners and their pets: register based cohort study

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Affiliations + expand

PMID: 33303475 PMCID: PMC7726310 DOI: 10.1136/bmj.m4337

Free PMC article

Abstract

Objective: To investigate whether dog and cat owners and their pets share a risk of developing diabetes.

Design: Cohort study.

Setting: Register based longitudinal study, Sweden.

Participants: 208 980 owner-dog pairs and 123 566 owner-cat pairs identified during a baseline assessment period (1 January 2004 to 31 December 2006).

Main outcome measures: Type 2 diabetes events in dog and cat owners and diabetes events in their pets, including date of diagnosis during the follow-up period (1 January 2007 to 31 December 2012). Owners with type 2 diabetes were identified by combining information from the National Patient Register, the Cause of Death Register, and the Swedish Prescribed Drug Register. Information on diabetes in the pets was extracted from veterinary care insurance data. Multi-state models were used to assess the hazard ratios with 95% confidence intervals and to adjust for possible shared risk factors, including personal and socioeconomic circumstances.

Results: The incidence of type 2 diabetes during follow-up was 7.7 cases per 1000 person years at risk in dog owners and 7.9 cases per 1000 person years at risk in cat owners. The incidence of diabetes in the pets was 1.3 cases per 1000 dog years at risk and 2.2 cases per 1000 cat years at risk. The crude hazard ratio for type 2 diabetes in owners of a dog with diabetes compared with owners of a dog without diabetes was 1.38 (95% confidence interval 1.10 to 1.74), with a multivariable adjusted hazard ratio of 1.32 (1.04 to 1.68). Having an owner with type 2 diabetes was associated with an increased hazard of diabetes in the dog (crude hazard ratio 1.28, 1.01 to 1.63), which was attenuated after adjusting for owner's age, with the confidence interval crossing the null (1.11, 0.87 to 1.42). No association was found between type 2 diabetes in cat owners and diabetes in their cats (crude hazard ratio 0.99, 0.74 to 1.34, and 1.00, 0.78 to 1.28, respectively).

Conclusions: Data indicated that owners of a dog with diabetes were more likely to develop type 2 diabetes during follow-up than owners of a dog without diabetes. It is possible that dogs with diabetes could serve as a sentinel for shared diabetogenic health behaviours and environmental exposures.

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)70 %
4)80 %

Goals of Therapy

- 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

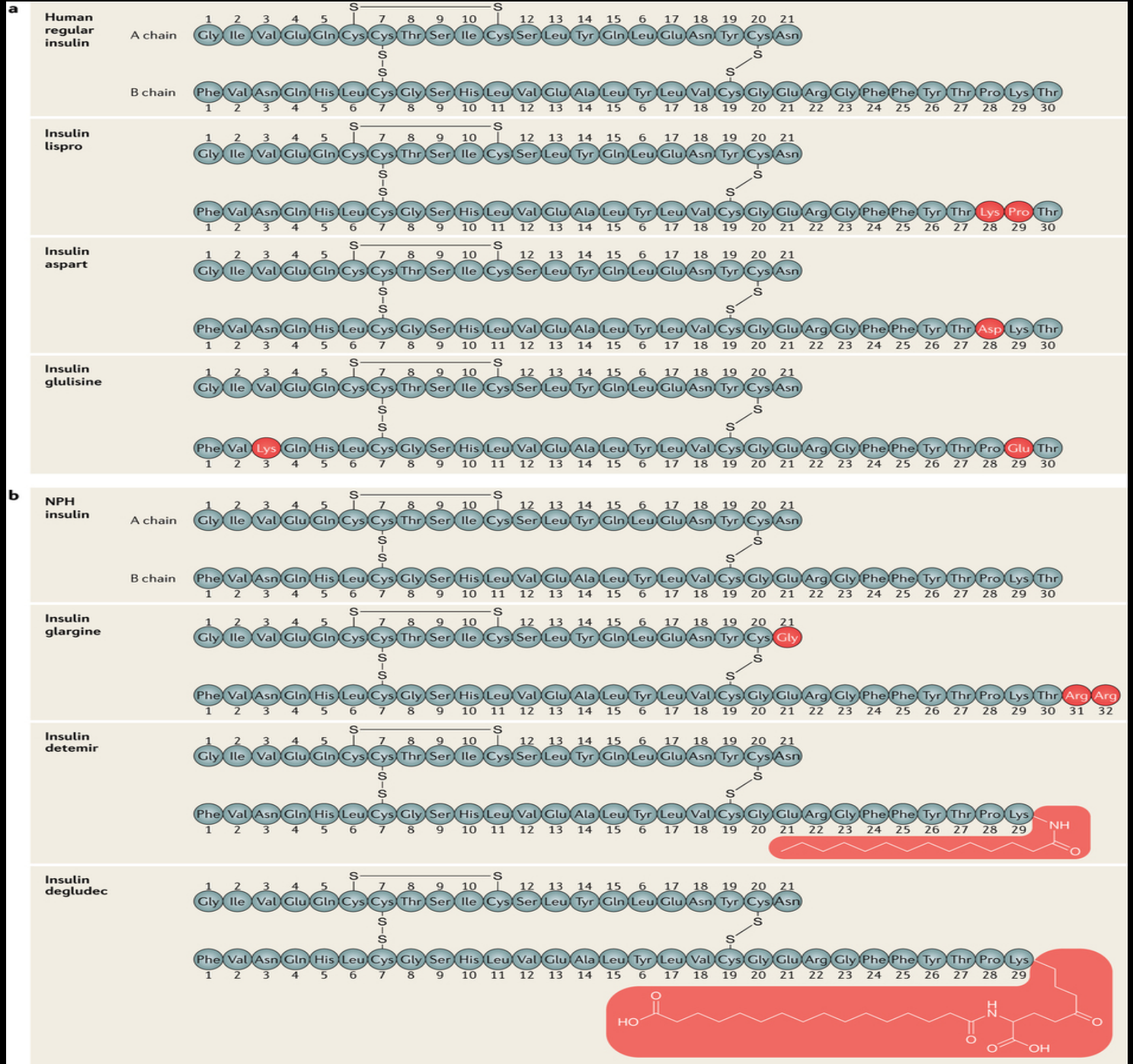
Beef, beef/pork, pork, human

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
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
B chain
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
Insulin lispro
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Lys Pro Thr
Insulin aspart
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Asp Lys Thr
Insulin glulisine
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
Phe Val Lys Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Glu Thr
b
NPH insulin
A chain
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
B chain
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
Insulin glargine
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Gly
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg
Insulin detemir
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys
NH
O
Insulin degludec
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys
HO
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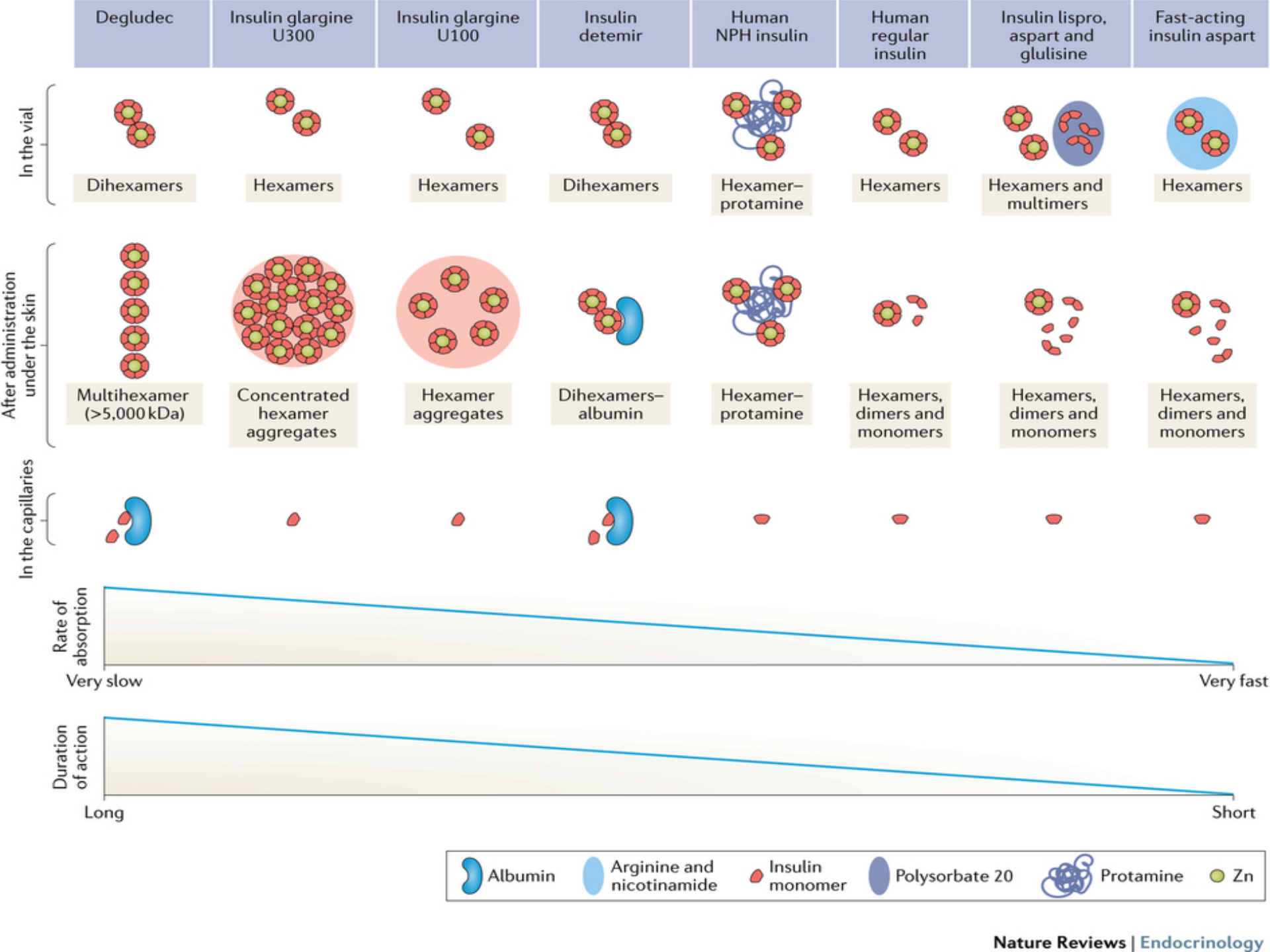
OH


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)

Newly Diagnosed Canine Patients

Humulin N or Novolin N (human origin)

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

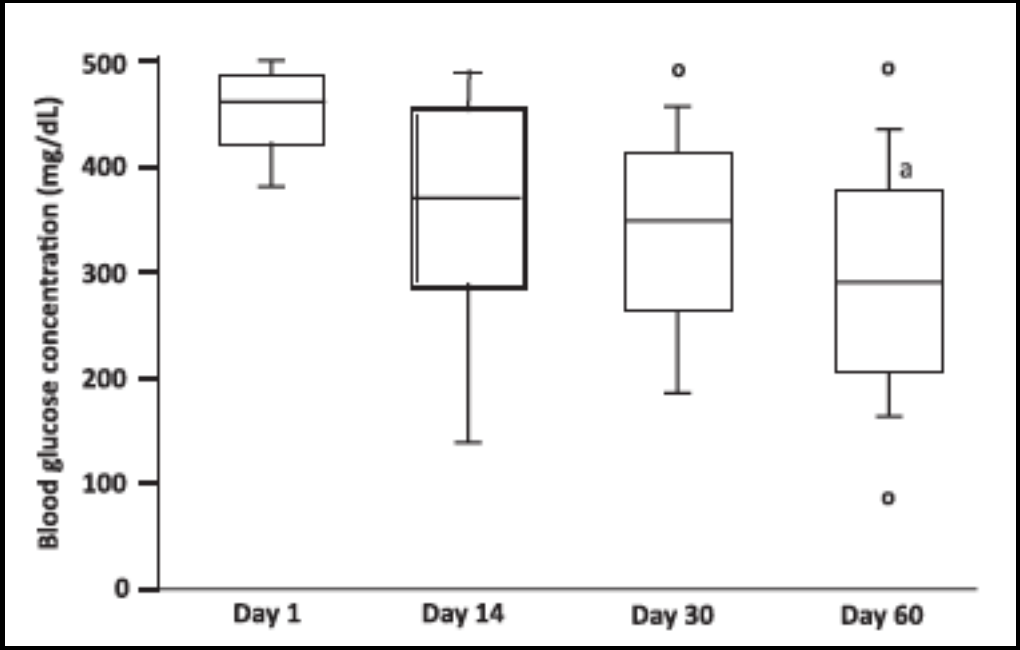
An investigation of the action of Neutral Protamine Hagedorn human analogue insulin in dogs with naturally occurring diabetes mellitus.

Newly Diagnosed Canine Patients

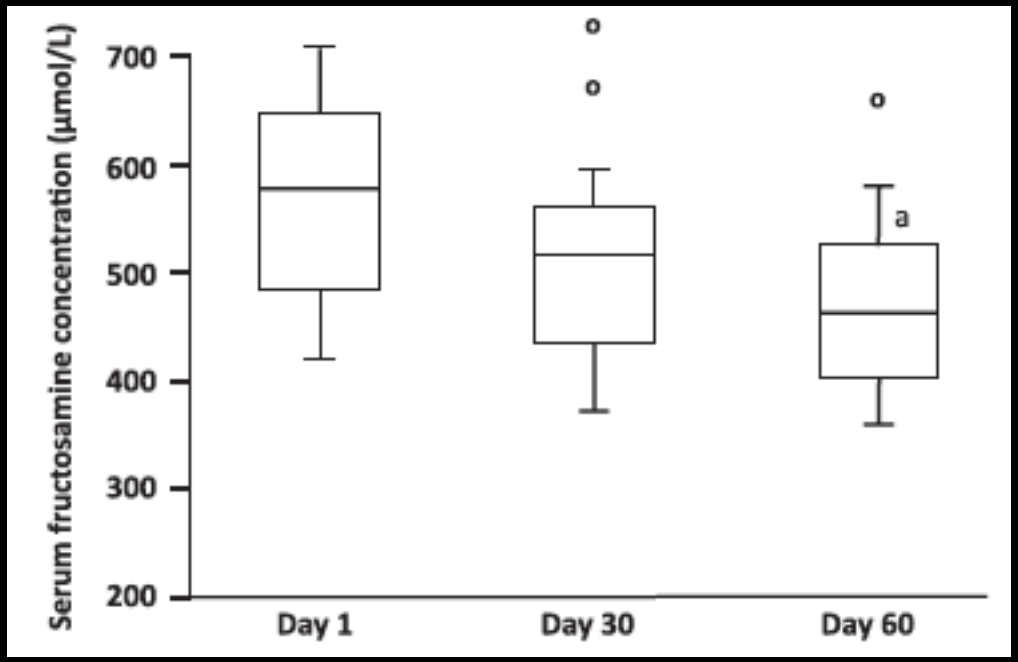
Efficacy of Protamine Zinc Recombinant Human Insulin for Controlling Hyperglycemia in Dogs with Diabetes Mellitus

J Vet Intern Med 2012;26:109–115

PZI Insulin in Dogs



PZI Insulin in Dogs



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

Contents lists available at ScienceDirect

Domestic Animal Endocrinology

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Field efficacy and safety of protamine zinc recombinant human insulin in 276 dogs with diabetes mellitus

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Posology
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ABSTRACT

Twice-daily (BID) insulin injections are a major deterrence to owners treating dogs with diabetes mellitus (DM). The hypothesis for this study was that Protamine Zinc Recombinant Human Insulin (PZIR) is safe and efficacious as a once-daily (SID) treatment for canine DM. This was a prospective, baseline-controlled, multi-center study over 182 ± 5 d. Two hundred seventy-six client-owned dogs with naturally occurring DM (naïve or pre-treated with insulin) were enrolled in the study. Enrollment was based upon demonstration of hyperglycemia, glycosuria, and ≥1 diabetic clinical sign (polyuria (PU), polydipsia (PD), or weight loss). 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 pre-treated). 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.

1. Introduction

Diabetes mellitus (DM) is a common disease in dogs with a reported worldwide prevalence of 0.3%–0.6% [1–3]. Similar to human type 1 DM, DM in dogs requires insulin supplementation ideally alongside dietary modification, exercise, and weight control [4]. Treatment goals for dogs include control of clinical signs, maintenance of good physical condition, and avoidance of hypoglycemia and ketosis [4]. Insulin therapy has been shown to be effective in controlling clinical signs and elevated blood glucose (BG) associated with DM in dogs. Insulins differ in the insulin source material, repository form, and concentration. Insulin types most often used to treat canine DM include porcine lente and neutral protamine Hagedorn (NPH), although the use of protamine zinc recombinant human insulin (PZIR), detemir, and glargine insulins has also been reported [4–7]. Insulins licensed for veterinary use in the USA are limited to porcine lente and PZIR. The lack of large controlled studies in dogs has left the practitioner without a clear choice in optimal insulin therapy, relying instead on product familiarity or licensing requirements. Regardless of which insulin is chosen, previous studies indicate that optimal DM control requires twice-daily (BID) injection [4,8].

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E-mail address: crward@uga.edu (C.R. Ward).

www.vetsulin.com

Vetsulin; Merck

40 IU/ml

Porcine origin

Lente insulin

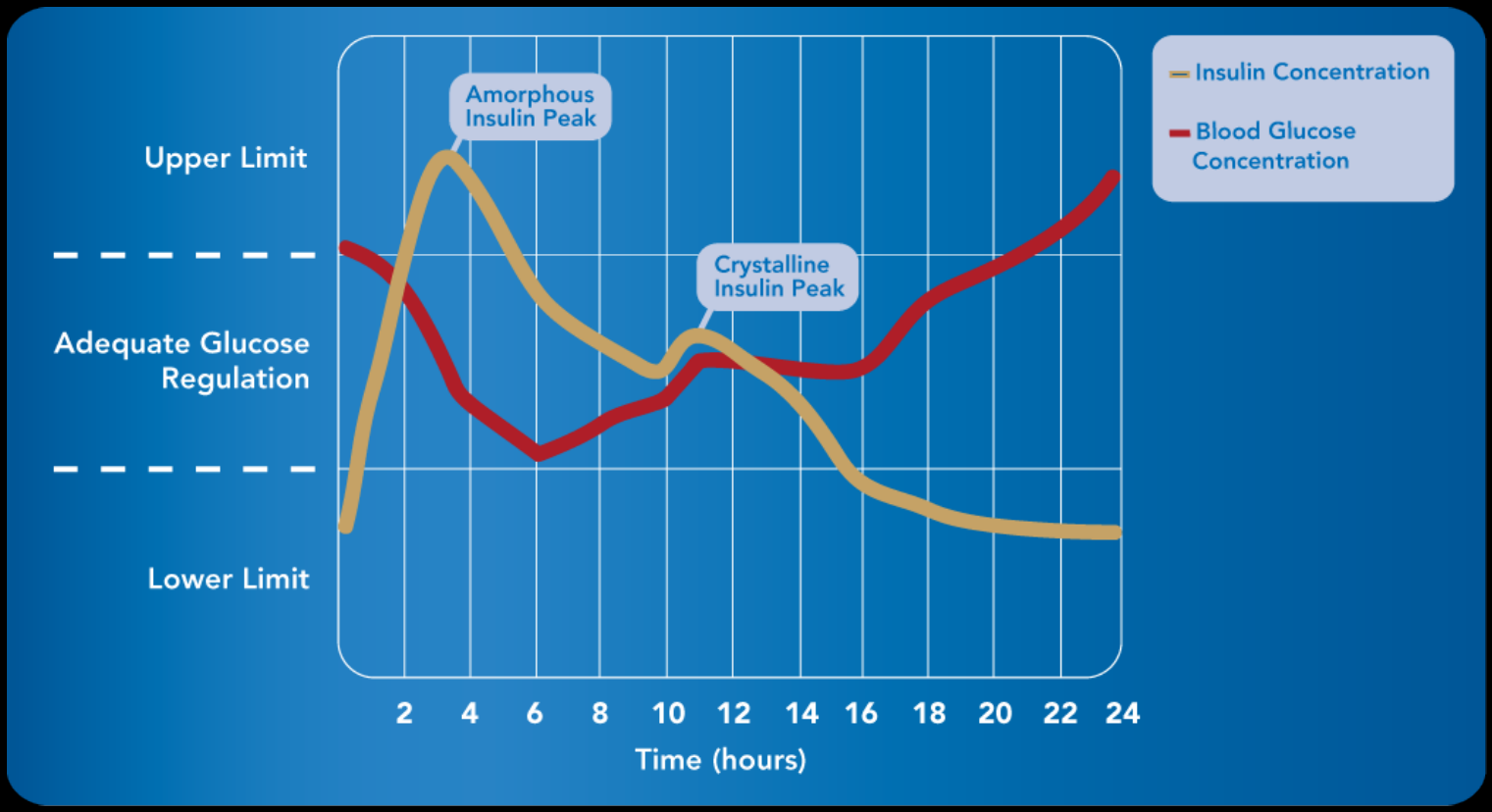
- Intermediate-acting
- 30% amorphous & 70% crystalline insulin

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® STARTER KIT

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.

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

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)

Client Education

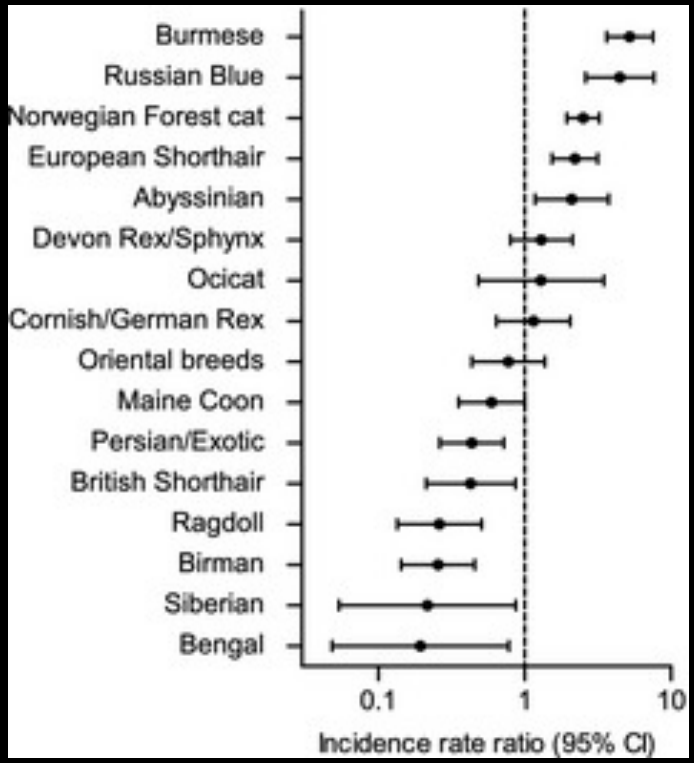
- Clinical signs
- Injection techniques
- Handling, storage and mixing of insulin, syringes
- Signs of hypoglycemia
- Urine monitoring
  - Trends
  - Not used to adjust dose

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

ANIVIVE TRIAL

basepaws

JOIN THE MOVEMENT TO **ADVANCE CAT HEALTHCARE.**

A new partnership between Anivive Lifesciences and Basepaws has formed to study the genetics of diabetes in cats. Patients meeting the study criteria are eligible to receive complementary genetic testing. Your participation in this study is an opportunity to support scientific exploration of the genes thought to be involved with diabetes. This information will help researchers develop new diagnostic tests, suggest possible preventative measures and explore new treatments for this common feline disease.

BASEPAWS

www.basepaws.com

A pet genetics company that has developed the first consumer genetics test for cats. With a mission to improve the lives of cats everywhere and help foster stronger bonds between humans and their pets, Basepaws offers pet owners' insights into their cat's unique background, including detailed information about breeds, traits, health, and genetic markers for potential hereditary disease. With new data from each CatKit completed, Basepaws' database continues to provide new and valuable information into genetic correlations and cat-specific diseases.

ANIVIVE

www.anivive.com

A veterinary pharmaceutical company focused on reshaping pet healthcare by bringing together experts in software development, veterinary medicine, and clinical research to accelerate the development of novel pet therapeutics. Currently, only 15% of pet diseases and conditions have an approved veterinary treatment. We create therapeutics for the other 85%. Anivive, "Smarter for pet health".

www.Anitrial.com/CatDNA

Visit our website for details about the study and instruction on how to sign up.

Accelerating the discovery of
novel therapeutics through pet genetics

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

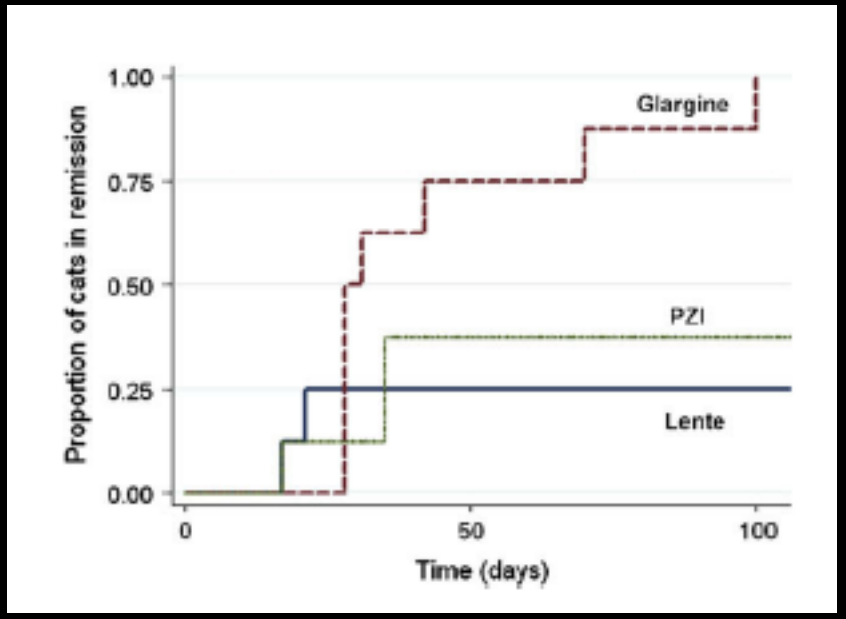
J Fel Med and Surg 11: 683-691, 2009

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.

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

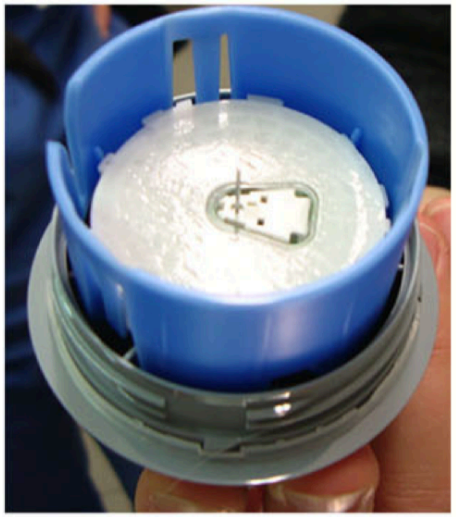
Improved glycemic control

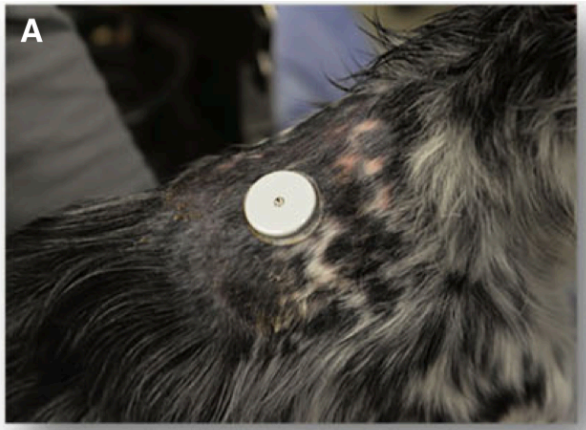
Indications:

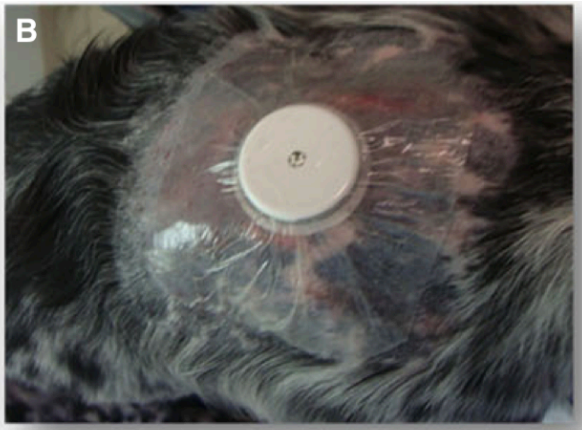
Initial management
Whenever the animal is ill or shows progression in clinical signs
Change in insulin dose
Aggressive insulin protocols (cats)

Accuracy of a Flash Glucose Monitoring System in Diabetic Dogs

J Vet Intern Med 2016;30:983–988







J Vet Intern Med. 2021 Feb 1. doi: 10.1111/jvim.16046. Online ahead of print.

Assessment of postprandial hyperglycemia and circadian fluctuation of glucose concentrations in diabetic dogs using a flash glucose monitoring system

Emily K Shea [1], Rebecka S Hess [1]

Affiliations + expand

PMID: 33522022 DOI: 10.1111/jvim.16046

Abstract

Background: Postprandial hyperglycemia (PPH) and circadian glucose concentration fluctuations recorded in the home environment of dogs with naturally occurring diabetes mellitus (DM) have not been reported.

Objectives: To determine if a flash glucose monitoring system (FGMS; FreeStyle Libre) can detect PPH and circadian fluctuations in glucose concentrations in dogs with variably controlled DM.

Animals: Fourteen client-owned dogs with DM.

Methods: Prospective observational study. Interstitial glucose (IG) concentrations measured by the FGMS during a 13-day study period were analyzed.

Results: A total of 17, 446 FGMS IG concentrations were analyzed. For all dogs analyzed together, median IG concentration measured within 30 (288 mg/dL), 60 (286 mg/dL), 90 (285 mg/dL), and 120 (285 mg/dL) minutes of meals was each significantly higher than the median IG concentration at all other times (260 mg/dL, 259 mg/dL, 258 mg/dL, and 257 mg/dL, respectively; range, 40-500 mg/dL; $P < .001$ for each). Median night-time IG concentration measured from all dogs on 3,547 samples recorded between 1:00 am and 6:00 am (268 mg/dL; range, 40-500 mg/dL) was significantly higher than median IG measured on 13, 899 samples at all other time points (259 mg/dL; range, 40-500 mg/dL; $P < .001$).

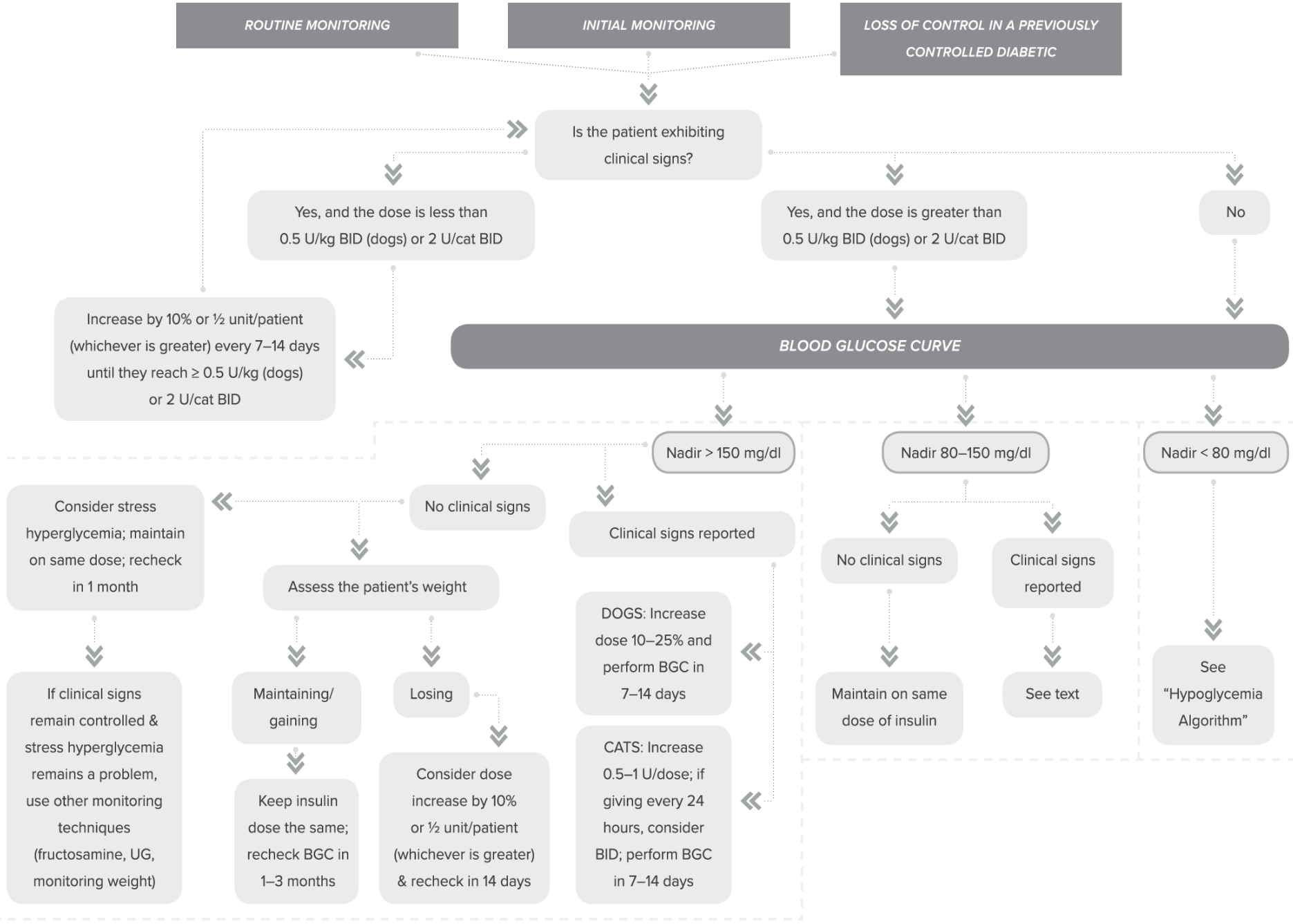
Conclusions and clinical importance: The FGMS can be used for future studies of PPH and circadian fluctuations of glucose concentrations in dogs with DM in their home environment.

1) Pre-prandial and pre insulin

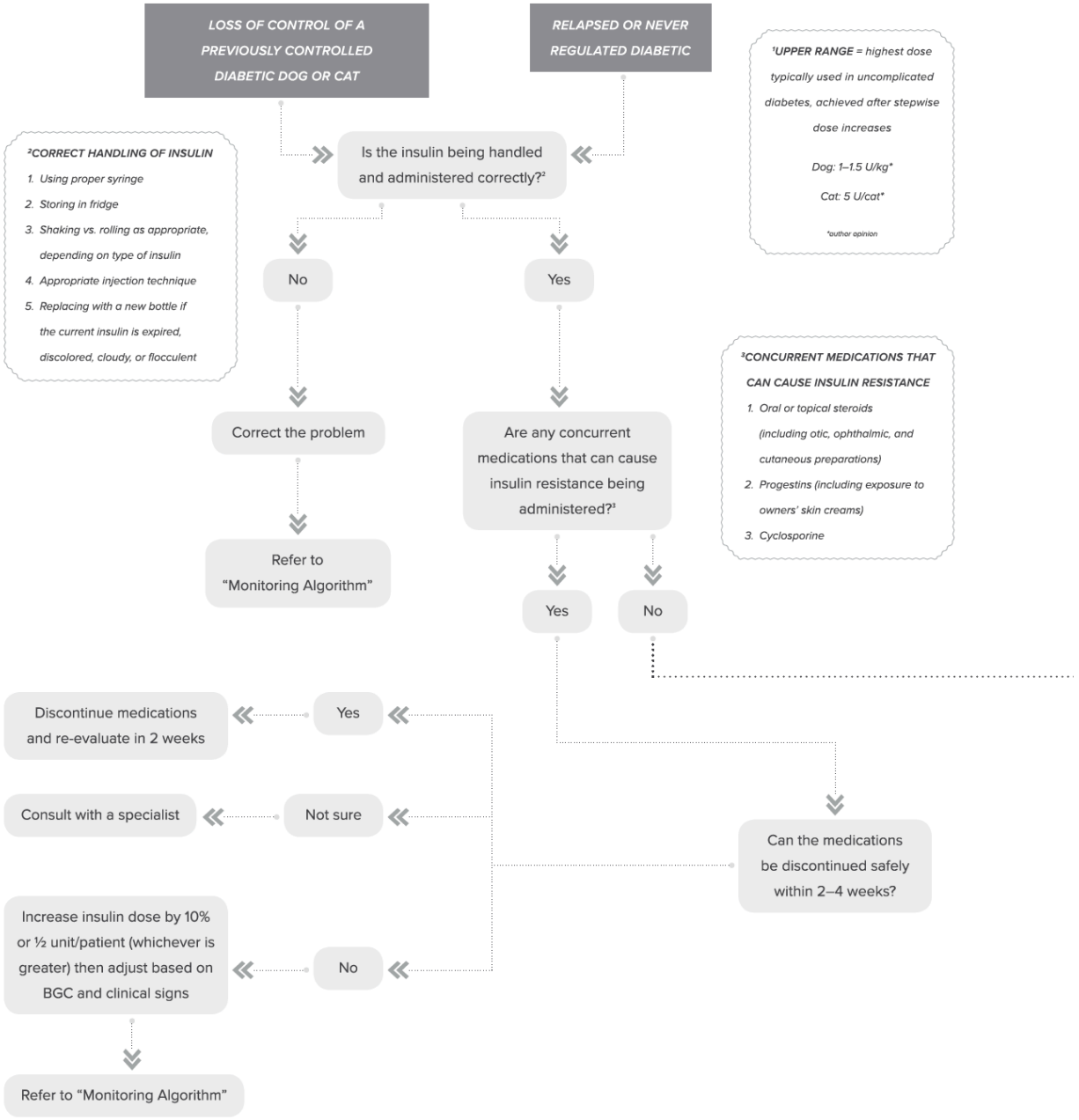
2) Every 2 hours (dogs; cats on NPH, ProZinc or Vetsulin) or 4 hours (cats on glargine) post prandial/insulin

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

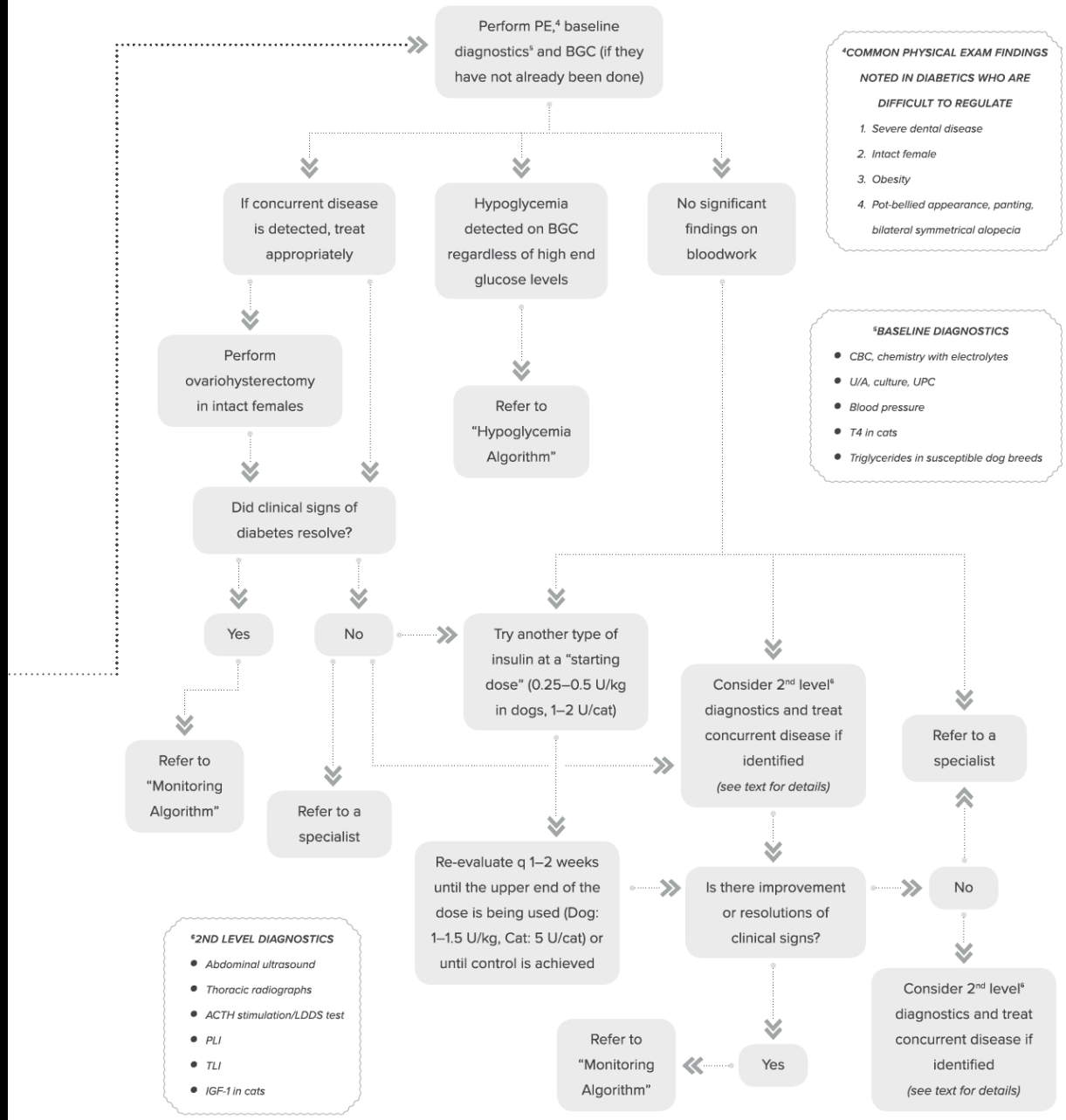
MONITORING BLOOD GLUCOSE LEVELS IN DIABETIC DOGS AND CATS



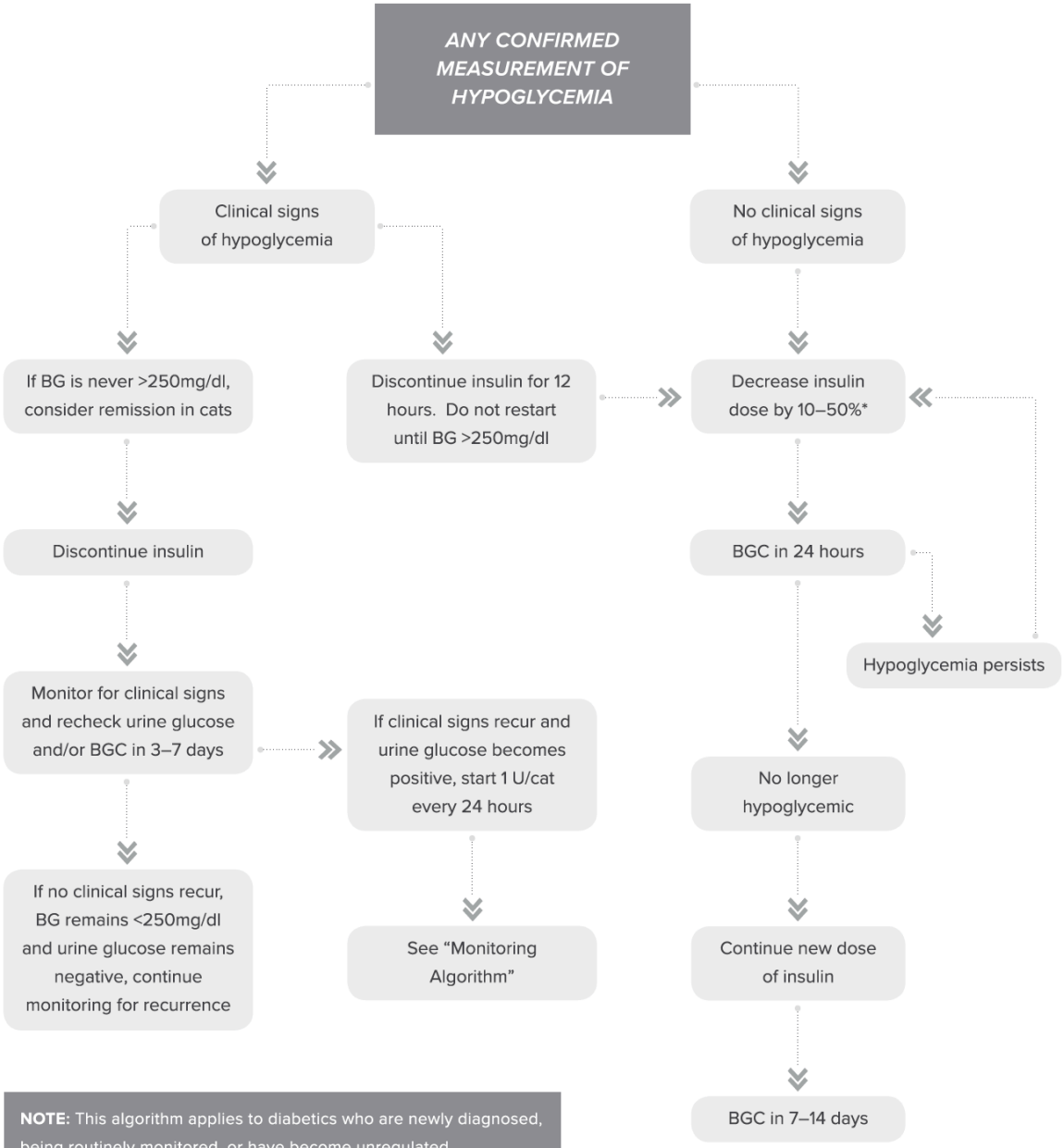
TROUBLESHOOTING DIABETIC DOGS AND CATS RECEIVING THE "UPPER RANGE"[1] OF INSULIN DOSES



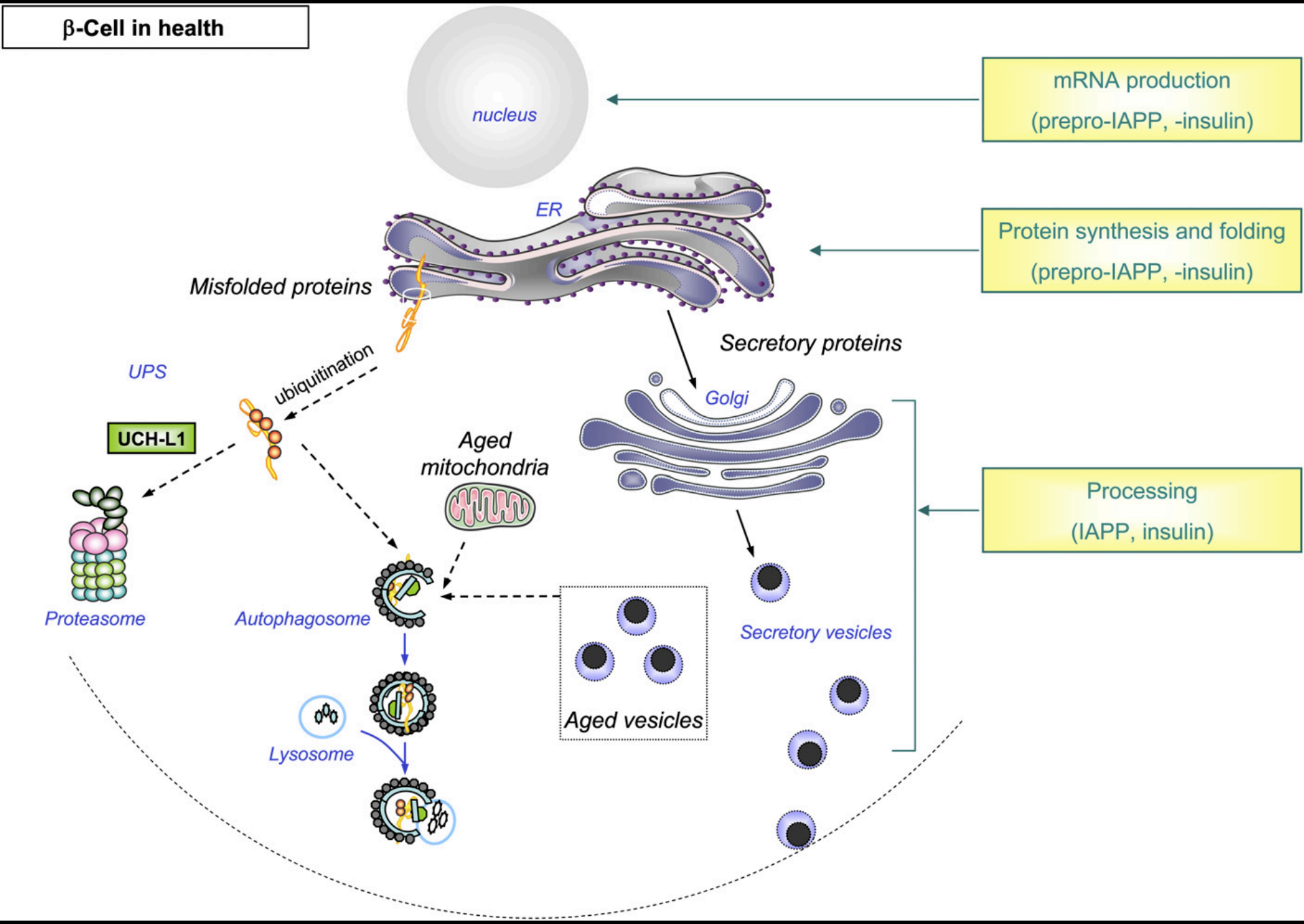
TROUBLESHOOTING DIABETIC DOGS AND CATS RECEIVING THE "UPPER RANGE"[1] OF INSULIN DOSES



MANAGING HYPOGLYCEMIA IN DIABETIC DOGS AND CATS

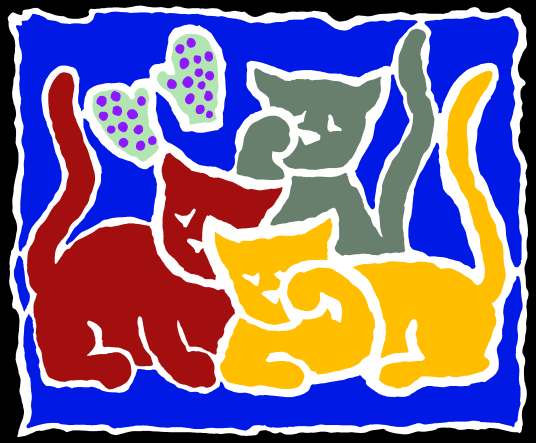


NOTE: This algorithm applies to diabetics who are newly diagnosed, being routinely monitored, or have become unregulated.


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

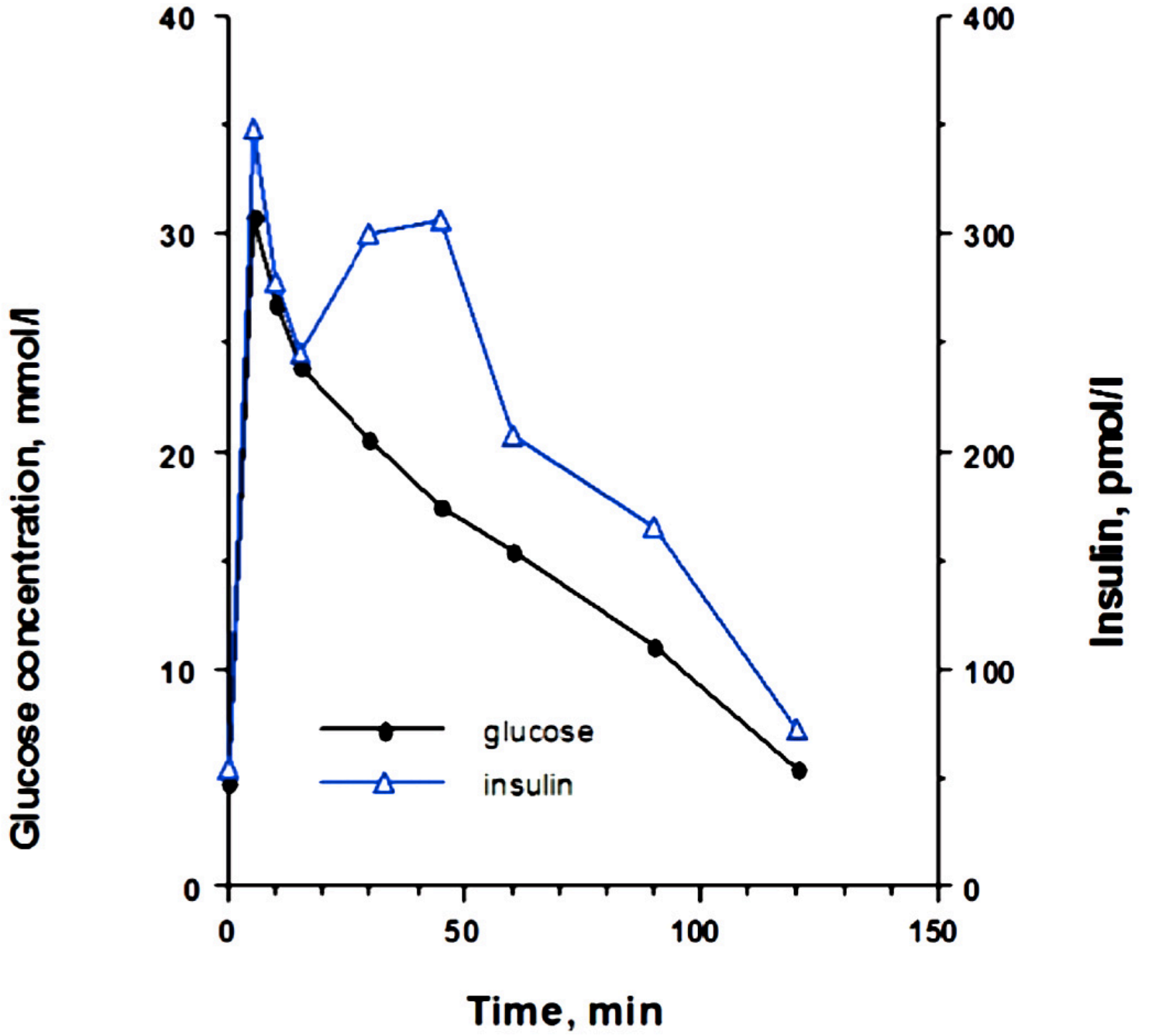
Feline Insular Amyloid

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
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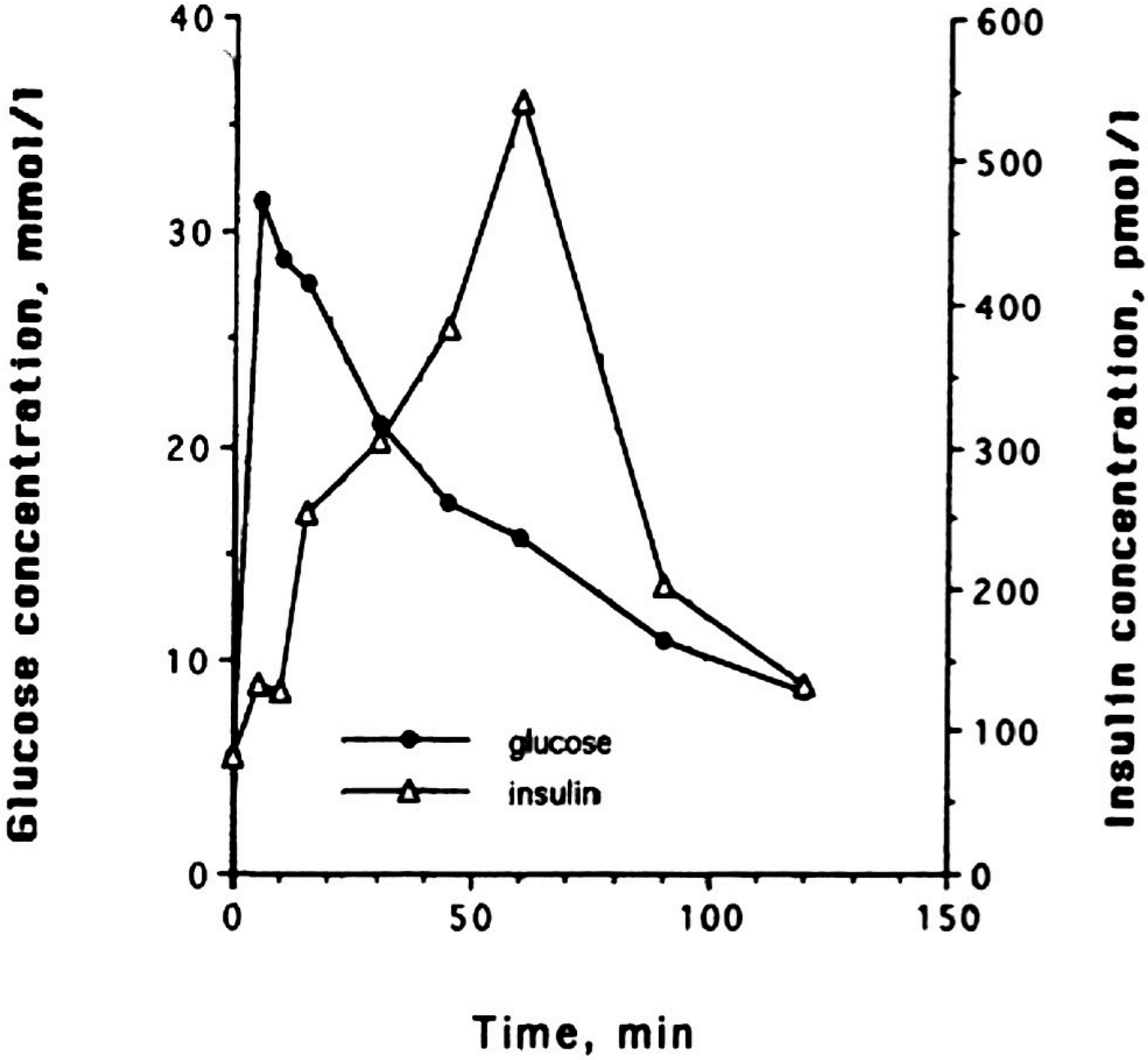
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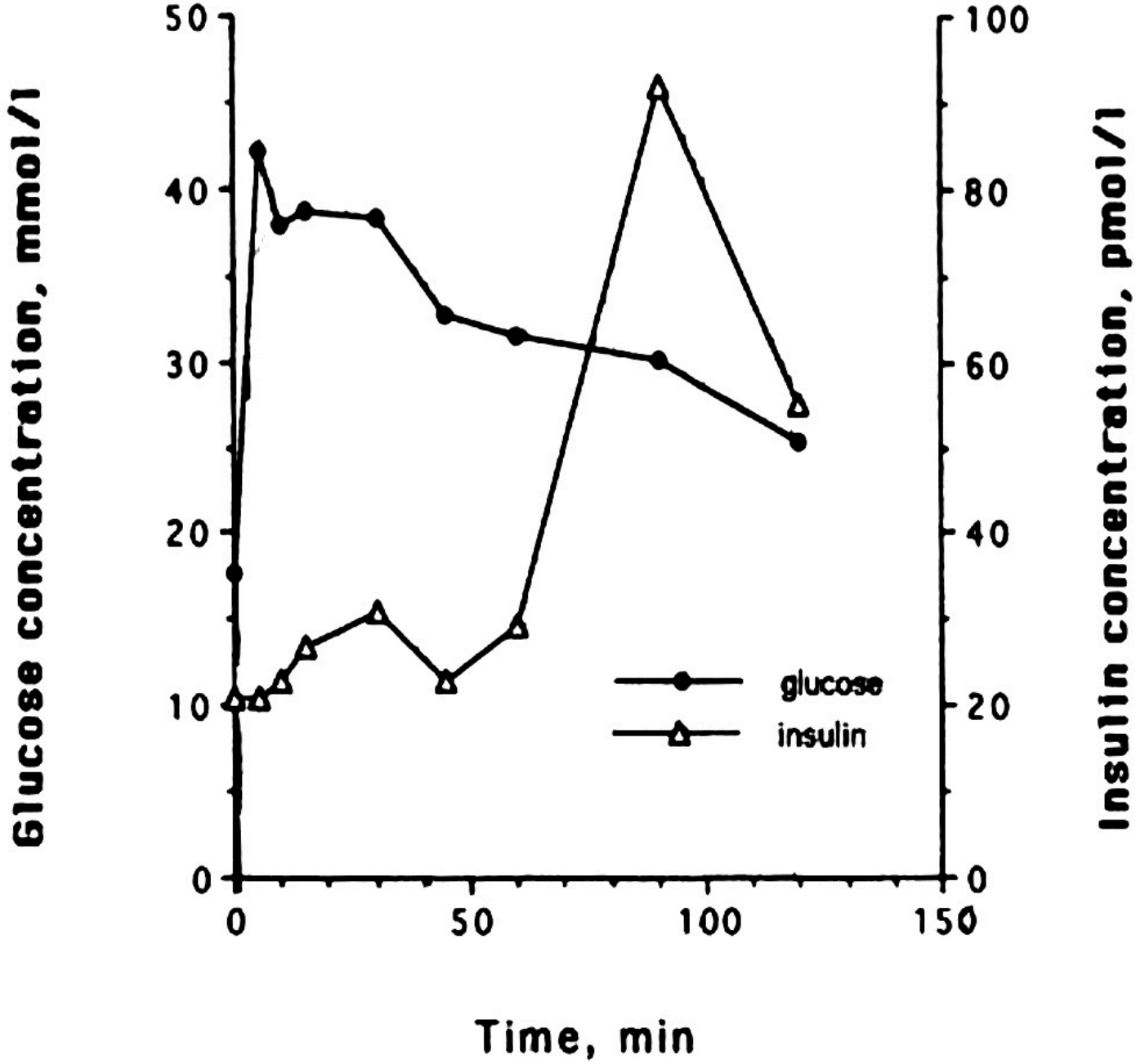
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Insulin concentration, pmol/l
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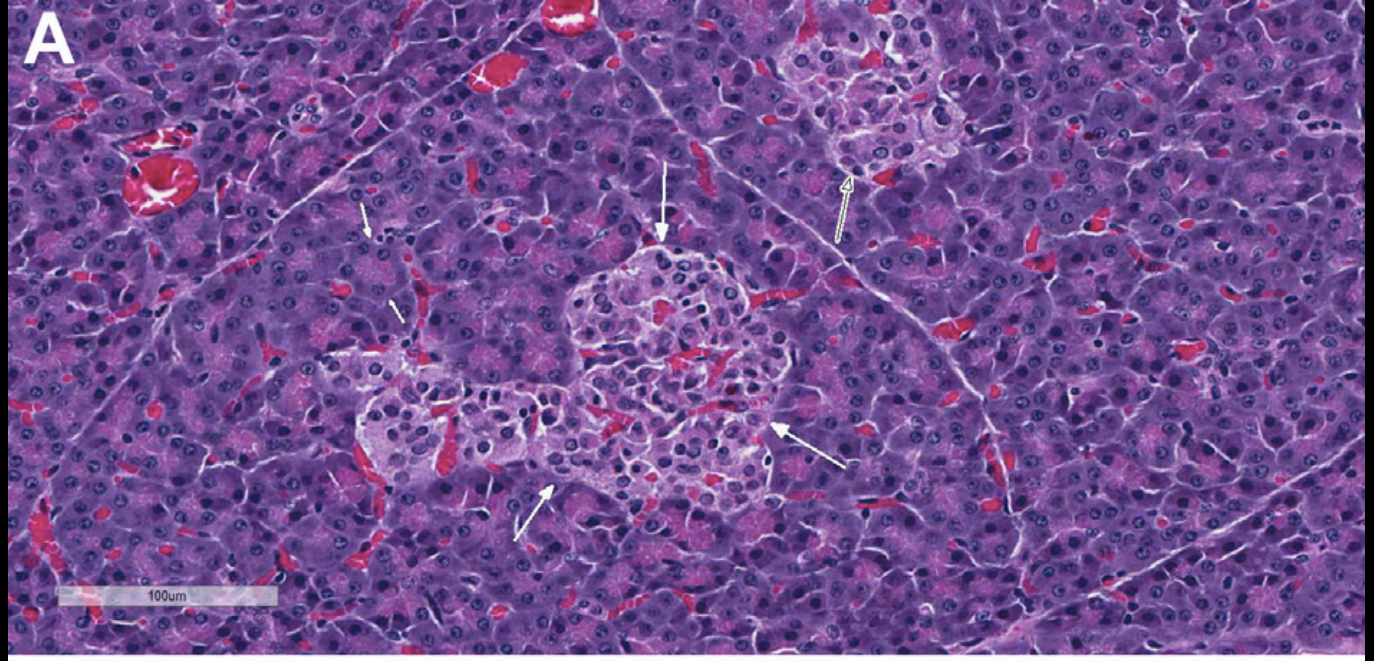
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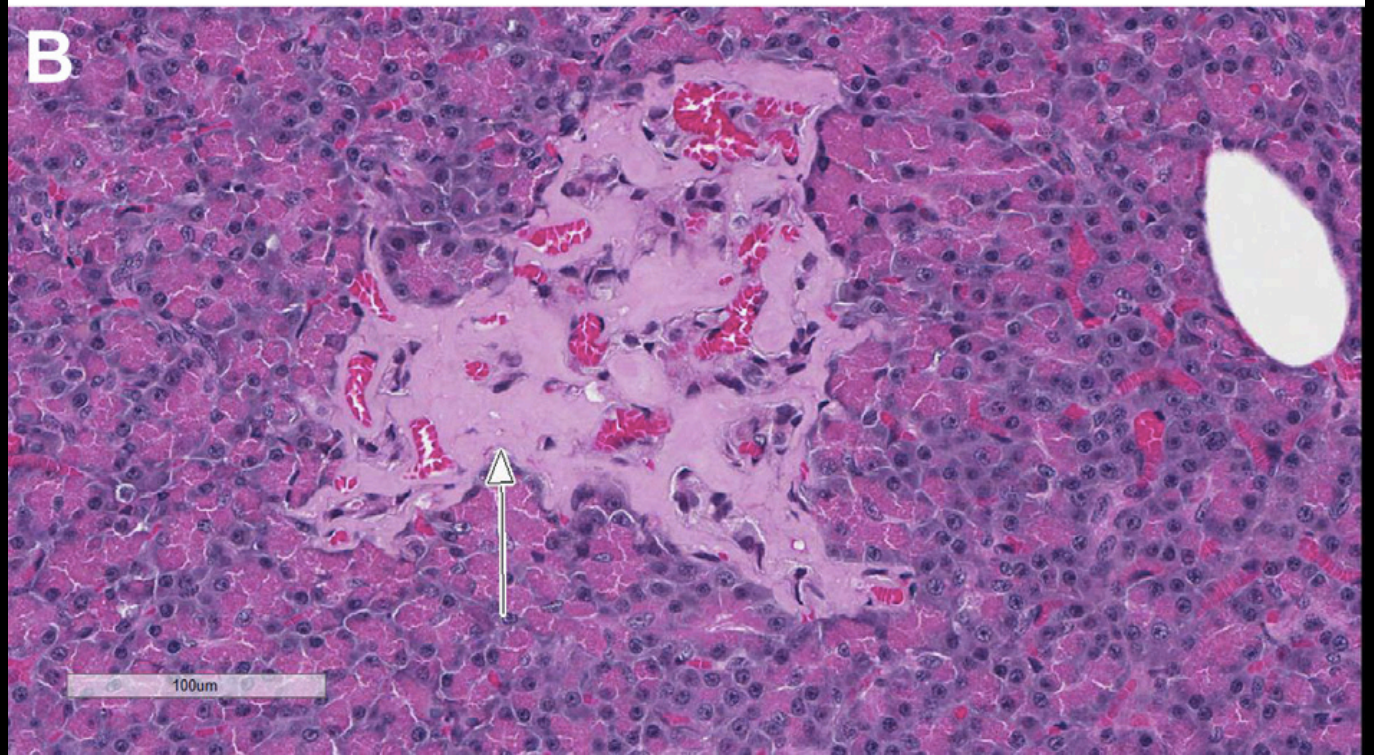
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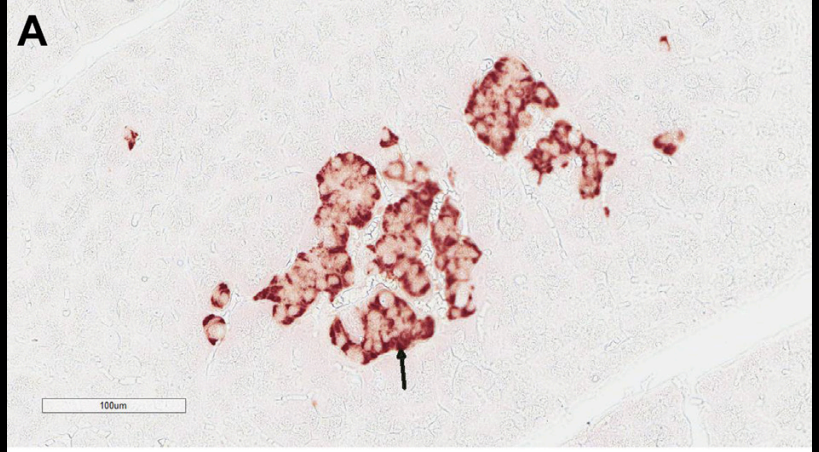
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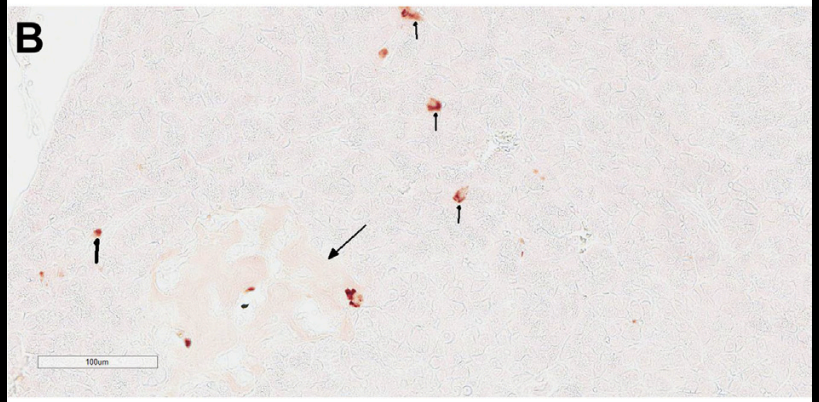
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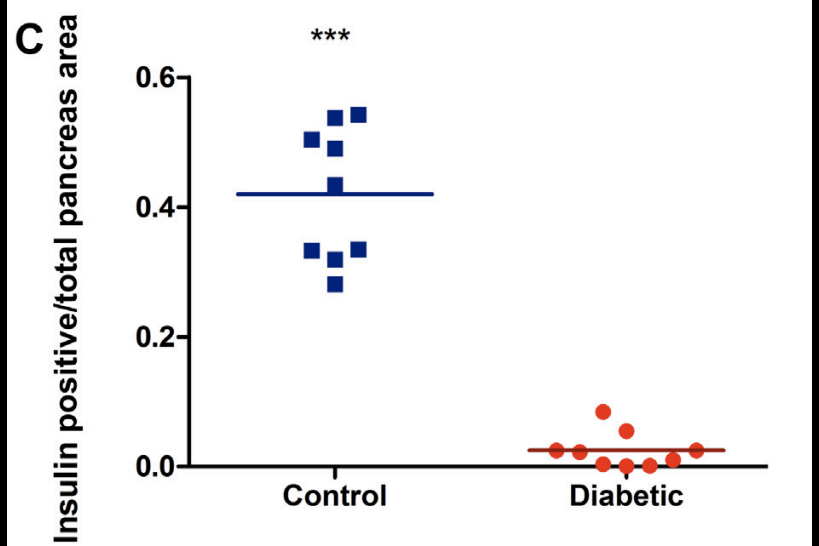
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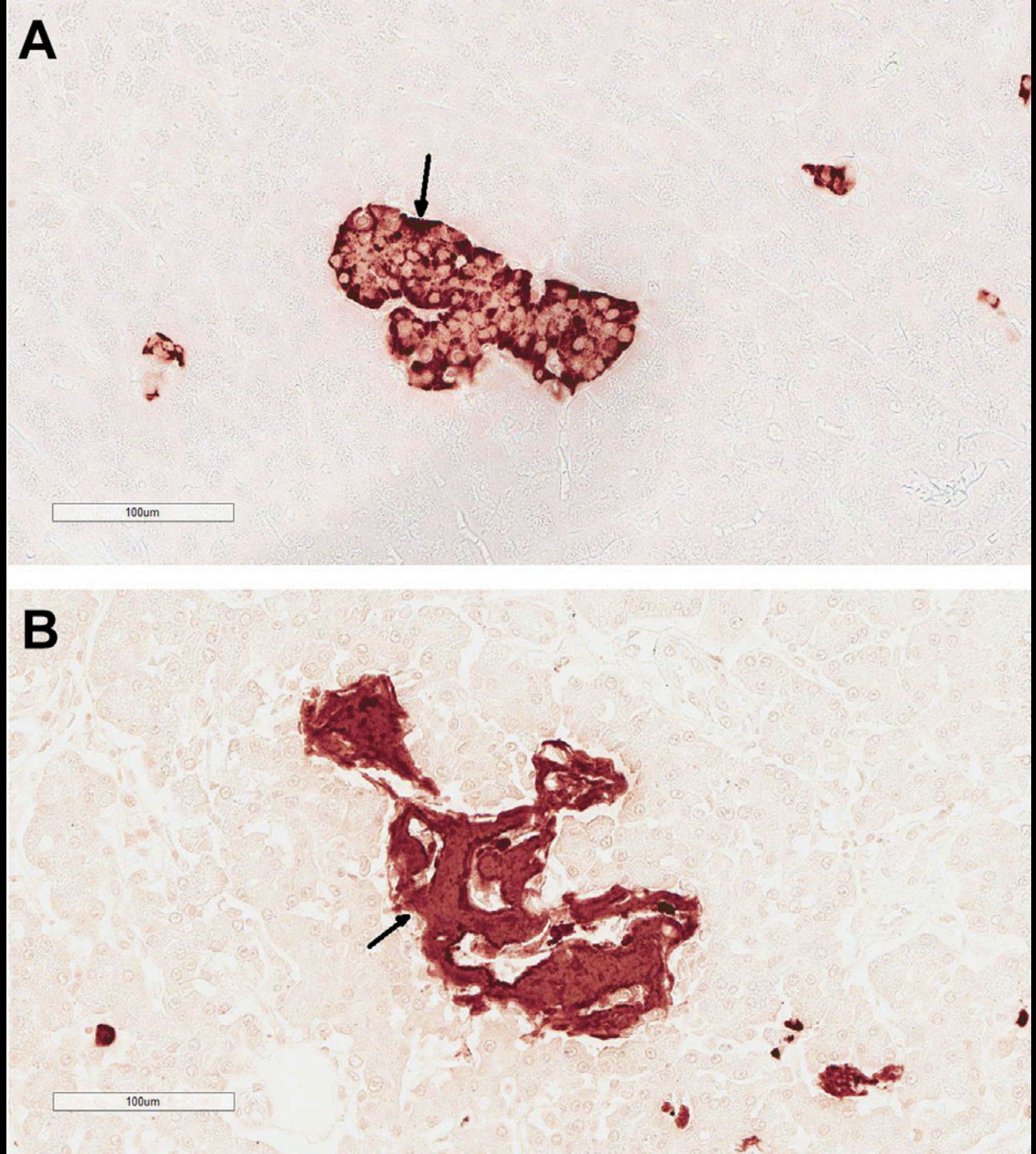
Diabetic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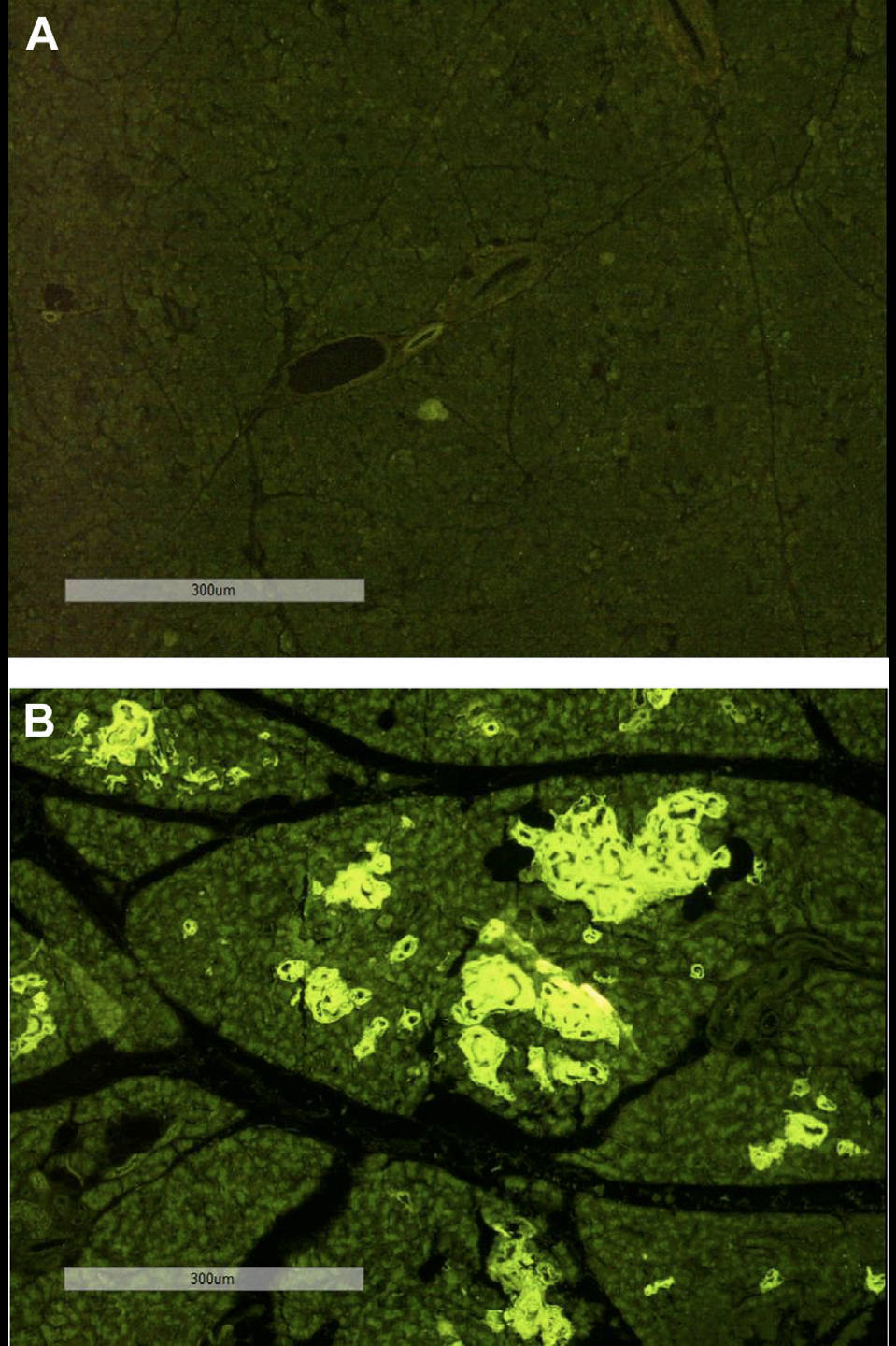
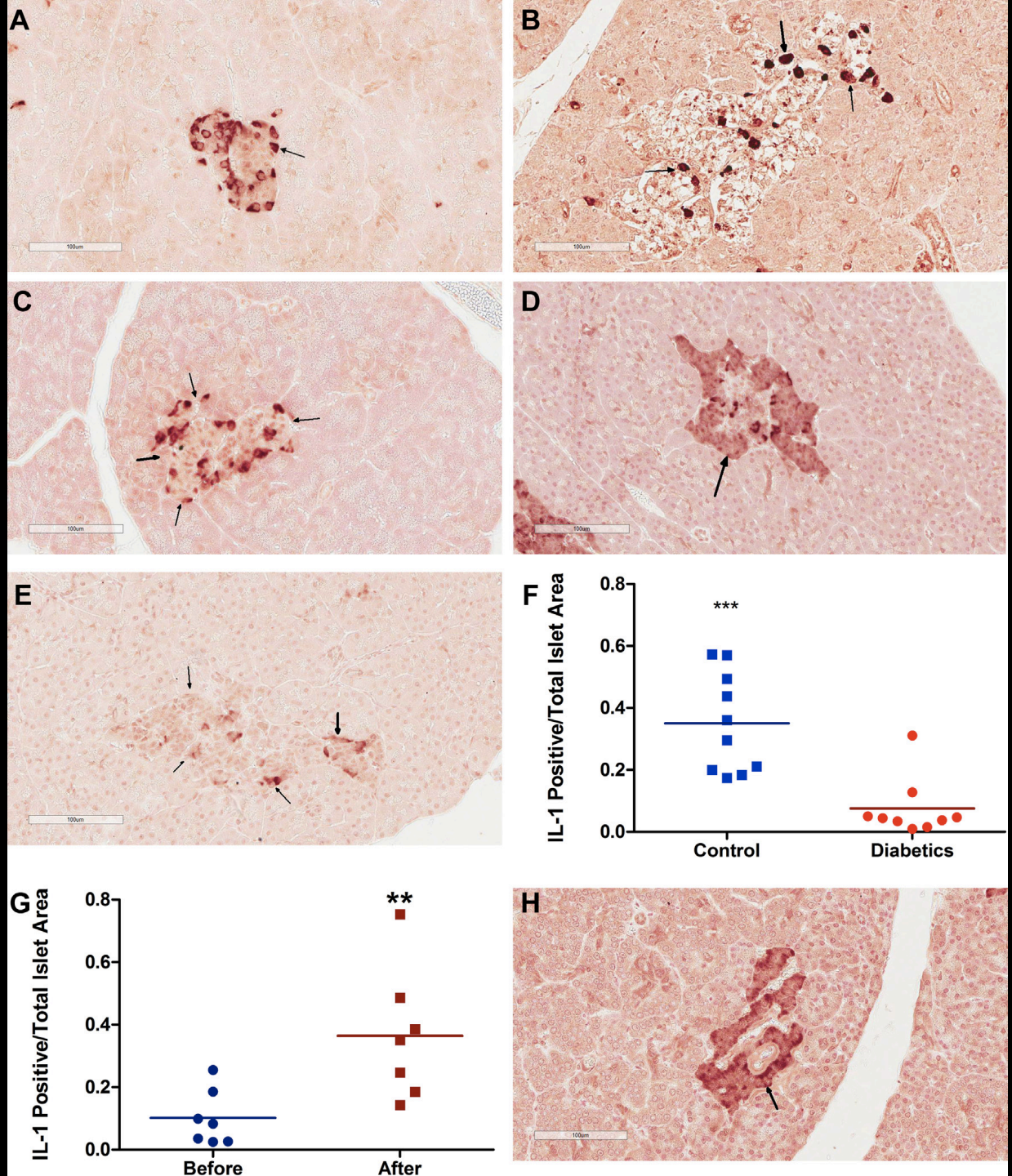
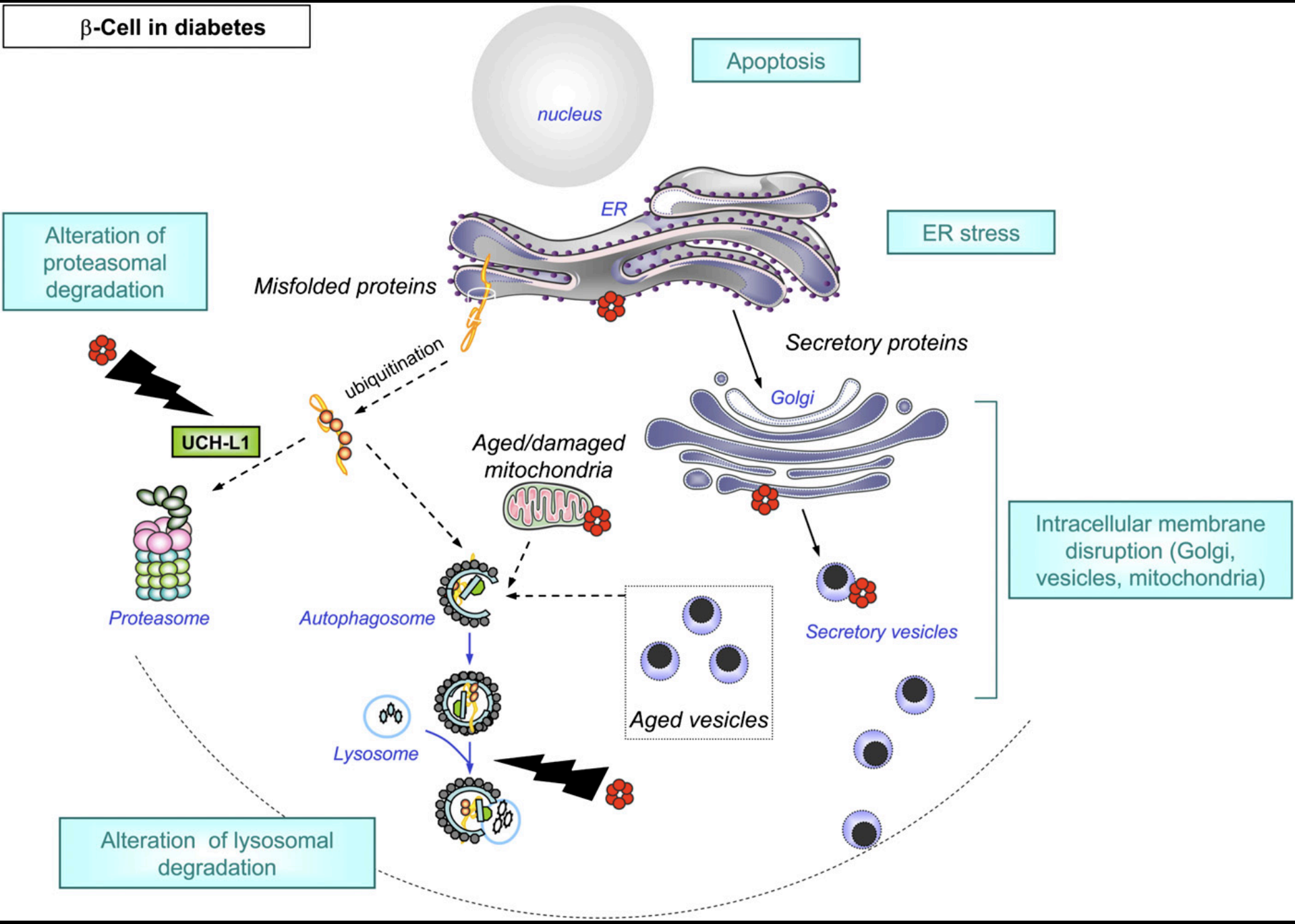
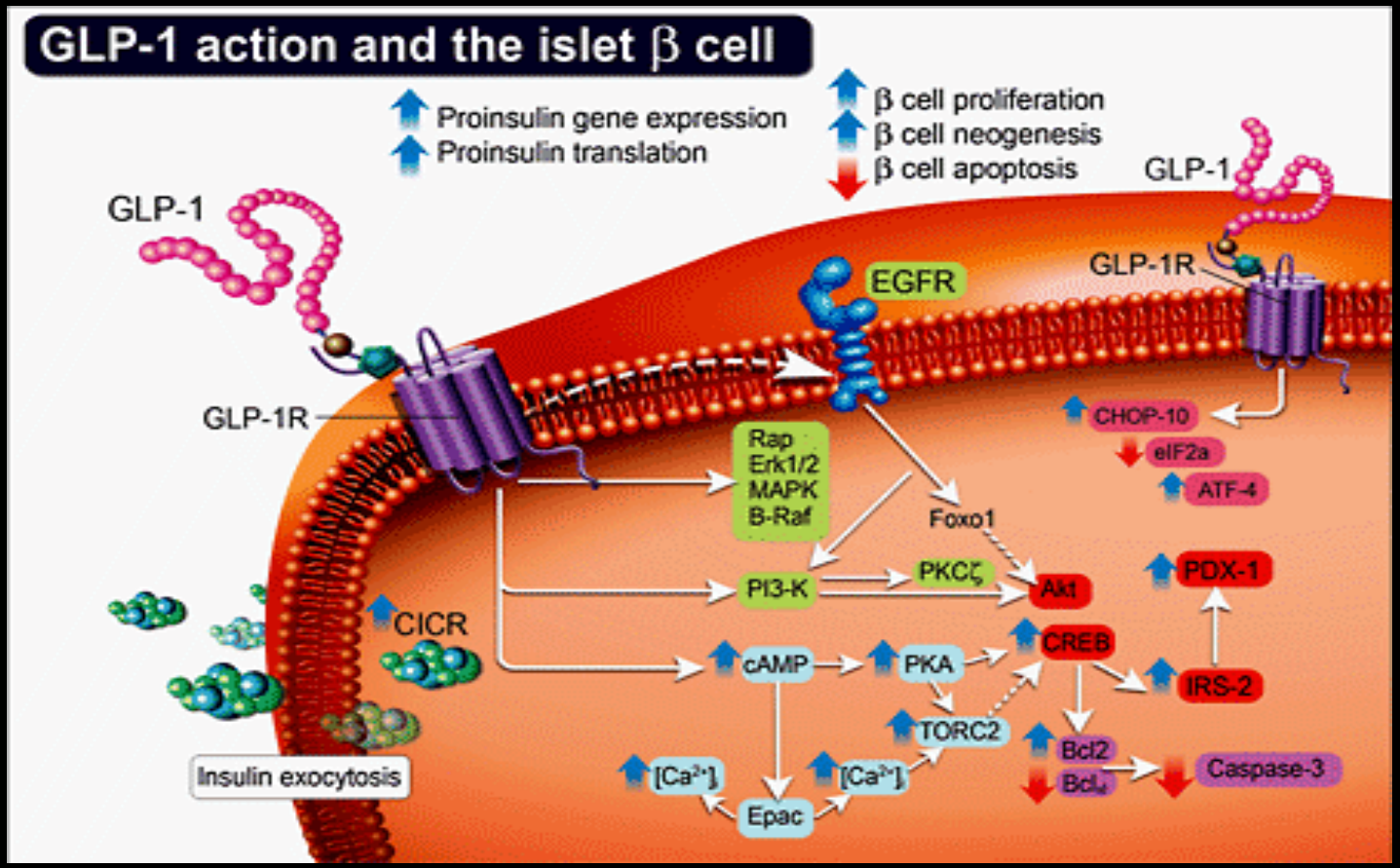
B
100um


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

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

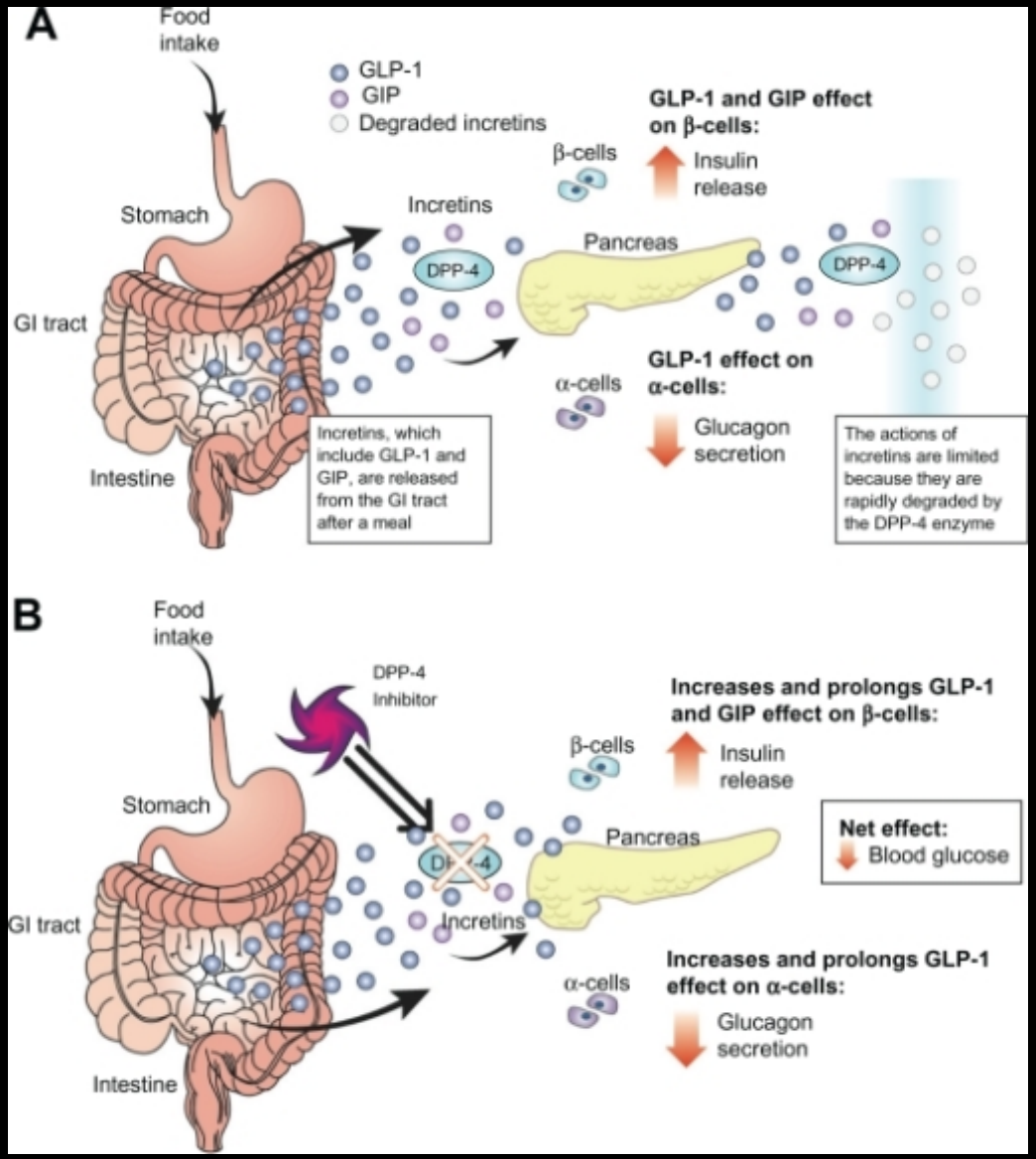
Recently, exenatide-ER was assessed in a group of normal and newly diagnosed diabetic cats treated with insulin glargine and fed a diabetic diet. Cats in this study were treated with once-weekly injection of placebo or exenatide-ER at a dose of 0.2 mg/kg. Despite using what seems in retrospect like a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

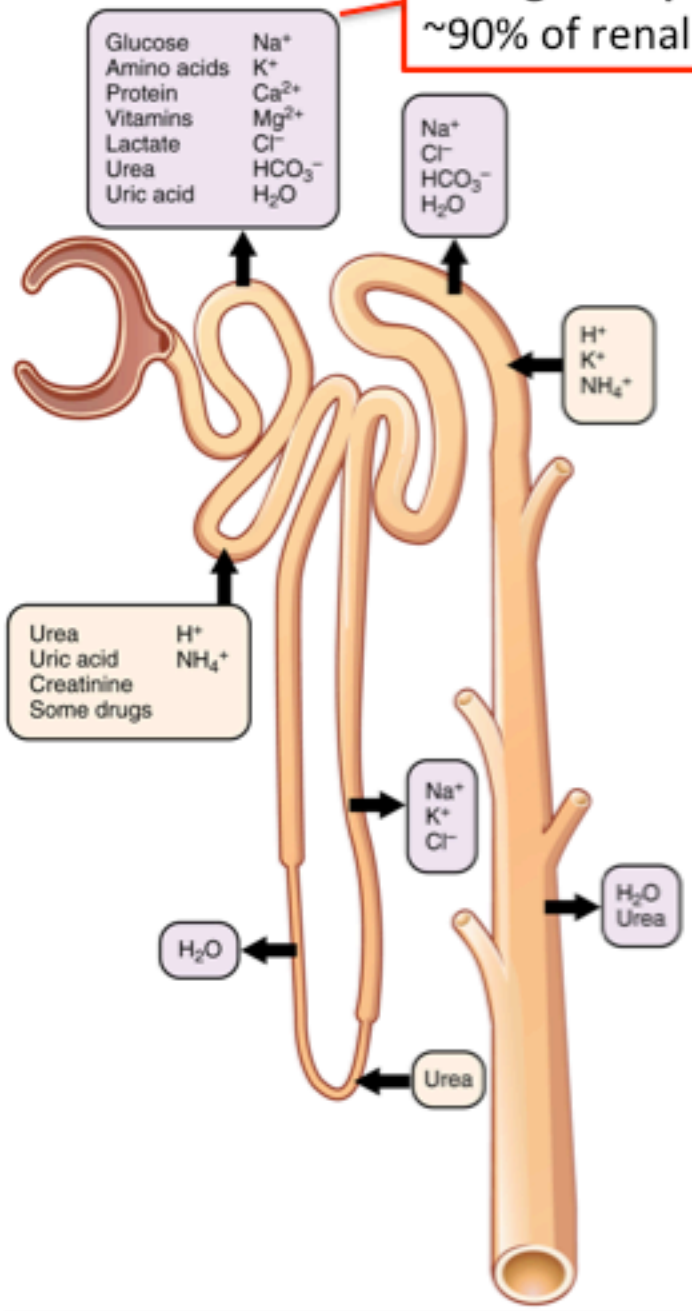


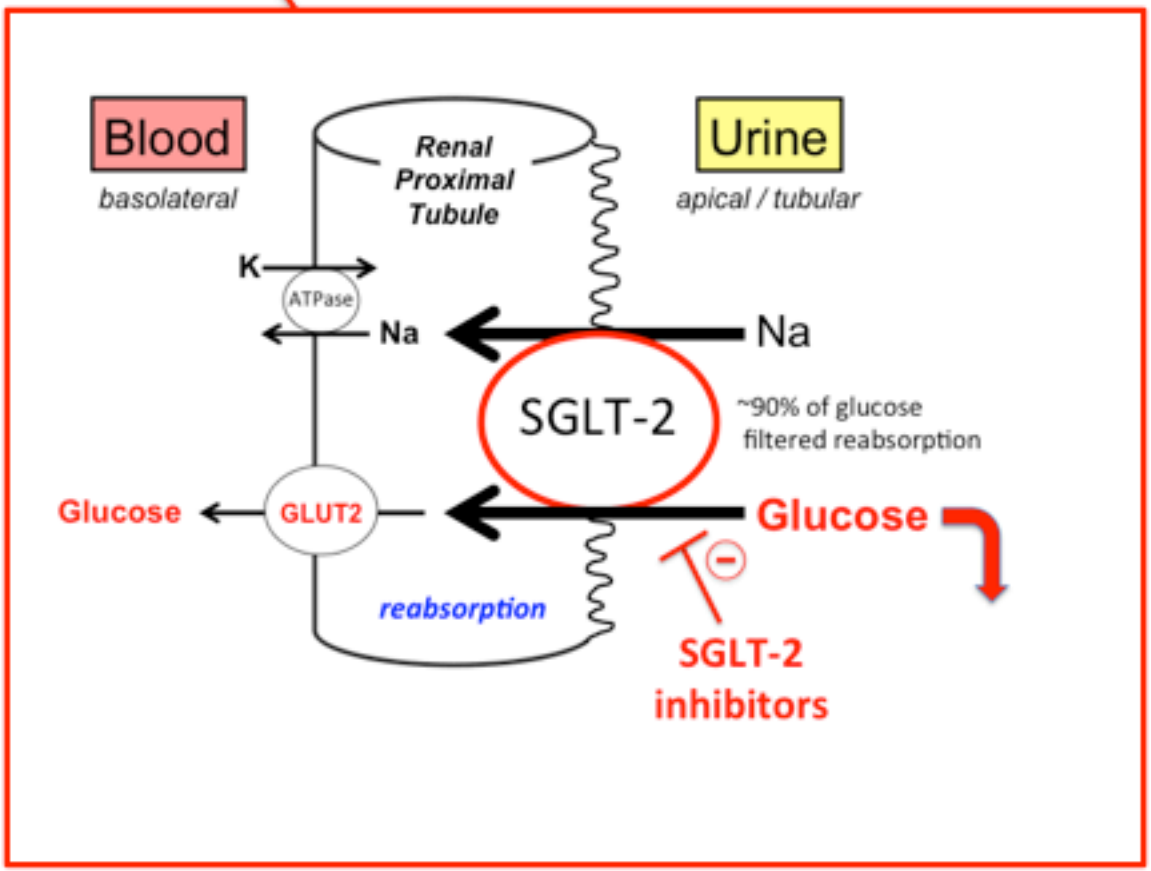
DPP IV Inhibitors

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

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.

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