Diagnosis and Management of Diabetes Mellitus and Diabetic Ketoacidosis

How to Treat and When to Refer

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Outline

- Review
  - Anatomy and physiology of the pancreas
  - Function and regulation of insulin
- Diabetes mellitus
  - Pathophysiology
  - Diagnosis
  - Management
- Diabetic ketoacidosis
  - Pathophysiology
  - Diagnosis
  - Management

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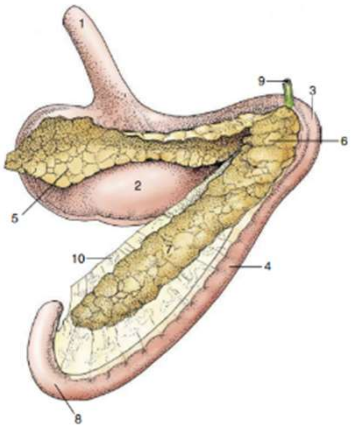
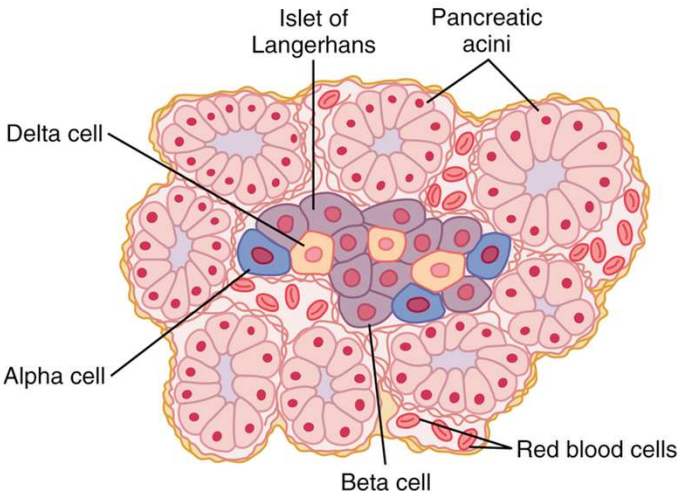
Anatomy and Physiology Review

- Pancreas
- Insulin
- Glucagon
- Glucose, Fatty Acid, and Amino Acid regulation

Pancreas

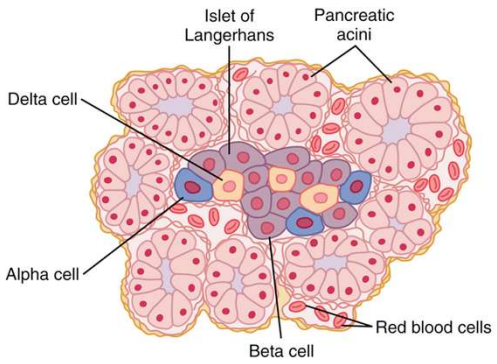




(Dyce, Sack, & Wensing, 2010)(Hall & Hall, 2021)

- Pancreas is found in the cranial abdominal cavity, made up of a body and two lobes (right and left) the body is closely associated with the cranial flexure of the duodenum with the right lobe caudally with the mesoduodenum and the left lobe extending over the dorsal surface of the stomach toward the spleen located within the greater omentum. Blood supply comes from the cranial and caudal pancreaticoduodenal arteries which are branches off the celiac and cranial mesenteric arteries. Pancreatic veins drain to the portal vein. There is both sympathetic and parasympathetic innervation. (Dyce, Sac, & Wensing, 2010)
- Made up of primarily exocrine tissue acini (~99%) and endocrine tissue, Islet of Langerhans (~1%).

Islet of Langerhans



Three major endocrine cells:

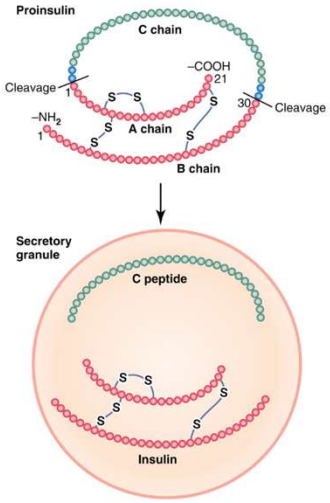
Alpha cells – secrete glucagon

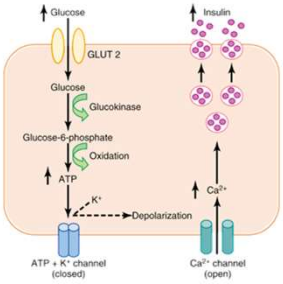
Beta cells – secrete insulin & amylin

Delta cells – secrete somatostatin

(Dyce, Sack, & Wensing, 2010)(Hall & Hall, 2021)

Insulin





(Hall & Hall, 2021)

- Insulin synthesis: Protein made by and cleaved in the ribosomes & endoplasmic reticulum to produce proinsulin, Proinsulin is cleaved by the golgi apparatus to insulin and C peptide, Packaged in secretory granules in equimolar amounts of insulin and c peptide (5-10% still as proinsulin);
    - insulin is stored in hexamers surrounding zinc molecules (Camara, et al., 2020)
    - C peptide can be used (in humans) to measure how much endogenous insulin is made while on insulin therapy
- Insulin secretion in response to abundance of energy (primarily glucose, fatty acids and/or amino acids that are converted to ATP can also stimulate insulin release, other hormones or neural input);
    - insulin hexamers don't enter the blood stream easily, when the zinc is diluted allowing the hexamers to break down to dimers and monomers that enter the blood stream (Camara, et al., 2020)
- Insulin enters portal circulation unbound (~50% cleared by the liver via insulinase), then systemic circulation and delivery to target tissues. Half life 6 minutes and usually cleared within 10-15min

Basal vs Bolus Insulin Secretion

2 phases of endogenous insulin secretion in homeostasis

1. Basal phase – insulin is secreted at a constant rate
   - This helps limit lipolysis and hepatic glucose production while fasting
   - Increase and decreases in response to insulin sensitivity
2. Bolus phase – occurs in response to post-prandial nutrient elevations
   - Combats post-prandial hyperglycemia by stimulating use of glucose by cells and limiting hepatic production
   - Amount released determined by nutrient content of the meal, GI transit time, and hormones

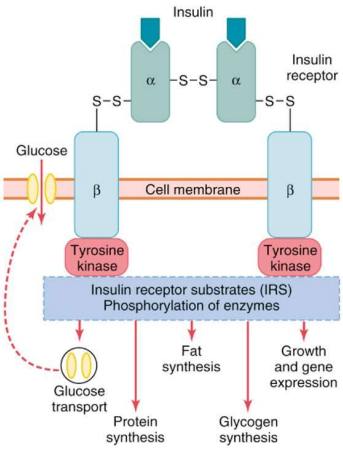
Table 1
Comparison of "bolus" insulin secretion in people, dogs, and cats

	Duration of Bolus Insulin Secretion	Magnitude of Increase of Insulin During Bolus Insulin Secretion
Human	2–4 h	5-fold
Dog	6–9 h	5–7-fold
Cat	6 - >12 h	0–3-fold

(Fleeman & Gilor, 2023)

This study was designed with cats being fasted for 24h then fed a single meal. A more recent study with 4 feedings per day in cats showed a minimal increase in plasma insulin and was sustained throughout the 24-h period. (Camara, et al., 2020) Bear in mind that the magnitude and shape of the curve created will vary based on the nutrient content and size of the meal.

Insulin Receptor



- Membrane bound
- Enzyme linked
  - (begins cellular cascades)

(Hall & Hall, 2021)

- Insulin receptor is a membrane bound protein with 2 extracellular subunits and 2 transmembrane units connect by disulfide bonds
- Insulin receptor is enzyme linked receptor: When insulin binds, it causes autophosphorylation of the beta-units → activate local tyrosine kinase to start cellular cascades with extensive and not fully understood consequences

Insulin Main Effects

Fast effects
- Increases glucose uptake by cells
- Makes cell membranes more permeable to amino acids, potassium, and phosphate ions to increase transport

Slow effects
- Changes activity of intracellular enzymes via phosphorylation

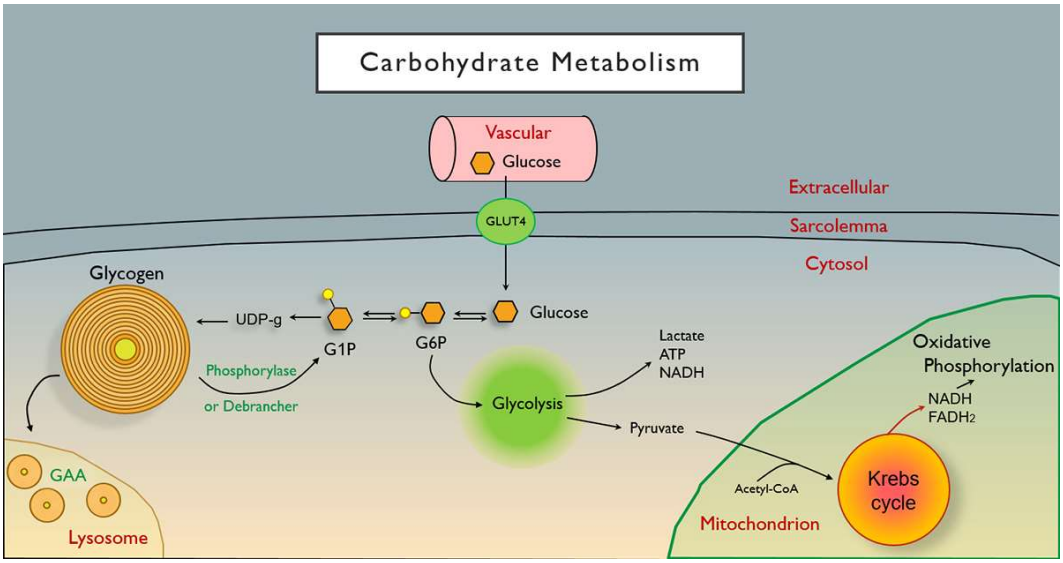
Much slower effects
- Changes rate of translation of messenger RNA to form proteins (even slower changes rates of transcription of DNA in the cell nucleus)

- Potassium via N-K-ATPase pump activity
- Phosphorus uptake increases to meet excessive demand – insulin induces phosphorylation intermediates intracellularly and Pi shift to keep up the balance

Insulin Effects on Carbohydrate Metabolism

- Rapidly **increases glucose uptake** in the cells
  - Via translocation of vesicles containing glucose transport proteins to the cell surface
  - After insulin is broken down, vesicles separate within ~3-5 minutes returning glucose transport to basal levels
  - Once in the cell, glucose → glucose-6-phosphate
    - Glucose-6-phosphate → ATP by glycolysis and oxidative phosphorylation
    - Excess can be converted to glycogen and stored (**glycogenesis**)
- **Inhibits glycogenolysis** via inhibition of phosphorylase which breaks down glycogen to glucose-6-phosphate
- **Inhibits gluconeogenesis** by decreasing enzyme activity in the liver and preventing release of precursors from cells (amino acids)

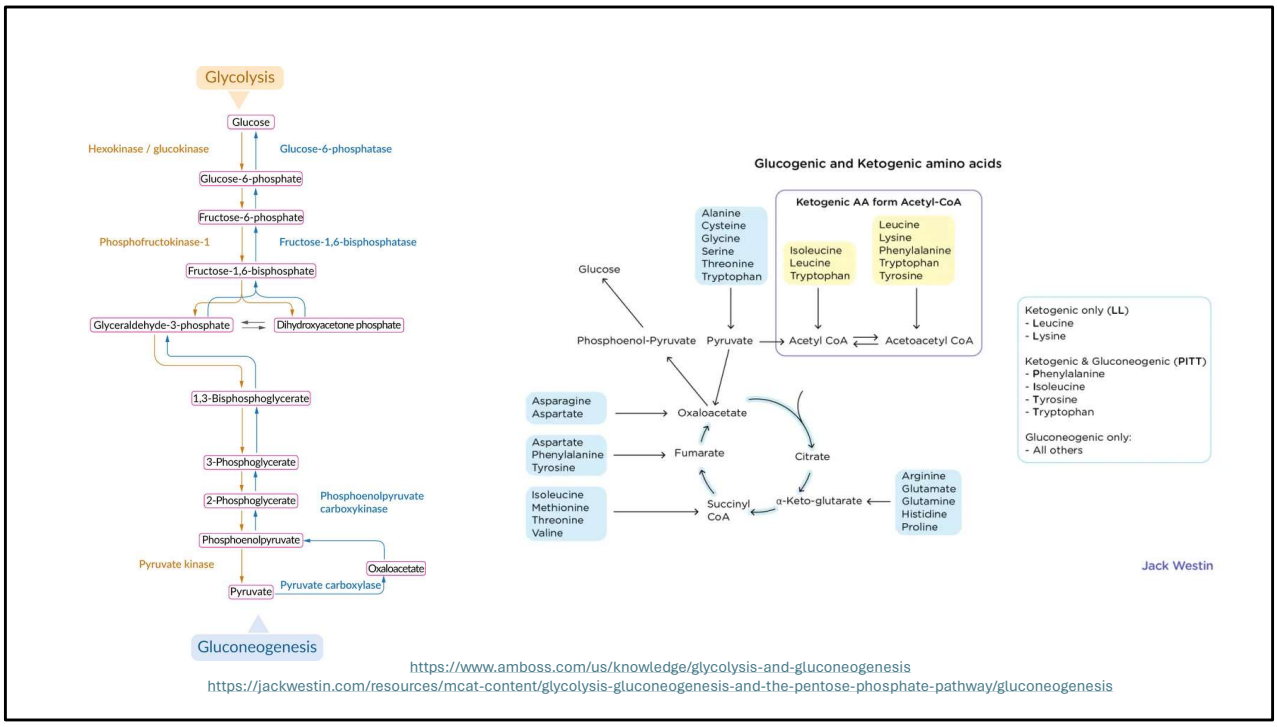
- increased glucose uptake, primarily in the muscles, liver, and fat; Insulin is not necessary for glucose use by neurons in the brain, retinal cells
- Once in the cell, glucose is phosphorylated to glucose phosphate by glucokinase, trapping it in the cells as glucose-6-phosphate



- Once in the cell, glucose is phosphorylated to glucose phosphate by glucokinase, trapping it in the cells as glucose-6-phosphate

    Glucose-6-phosphate can either undergo glycolysis and oxidative phosphorylation to make ATP

    Or excess can be converted to glycogen and stored in the cell (**glycogenesis**)



https://www.amboss.com/us/knowledge/glycolysis-and-gluconeogenesis
https://jackwestin.com/resources/mcat-content/glycolysis-gluconeogenesis-and-the-pentose-phosphate-pathway/gluconeogenesis

Insulin Inhibits gluconeogenesis by decreasing enzyme activity in the liver and preventing release of precursors from cells (amino acids)

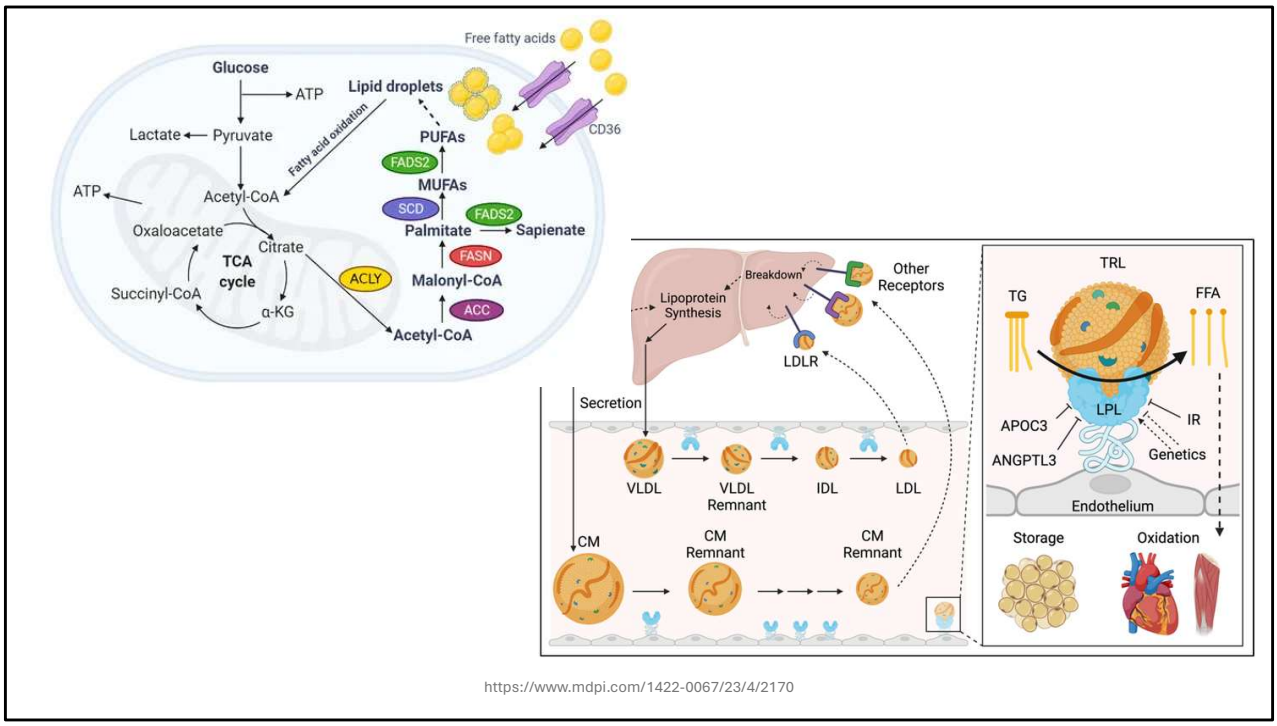
Insulin Effects on Fat Metabolism

- Increased glucose uptake by the cells → increased glucose utilization and thereby **decreased fat utilization**
- **Increased fatty acid synthesis** from excess glucose that cannot be used for local metabolism or glycogen production packaged as triglycerides → lipoproteins
  - Insulin activates lipoprotein lipase in capillary walls of the adipose tissue to convert back to fatty acids that can be absorbed into adipose and stored as triglycerides
  - Insulin **increases uptake of fatty acids** by increasing translocation FA transport proteins to the cell membrane from vesicles (Varlamov, et al., 2010)
- Inhibits hormone-sensitive lipase, **preventing the breakdown of triglycerides** in adipose tissue and thereby release of fatty acids from the cell

- Fatty acid synthesis primarily in the liver: excess glucose split to pyruvate → acetyl-CoA → citrate and isocitrate by the TCA cycle; citrate and isocitrate ions directly activate acetyl CoA carboxylase to convert acetyl CoA → malonyl CoA (1st step in fatty acid synthesis)

    - This is also regulated likely to prevent hepatic lipidosis! Insulin reduces hepatic fatty acid synthesis via phosphorylation of carcinoembryonic antigen

- Fatty acid created in the liver are used to form triglycerides and then secreted as lipoproteins



https://www.mdpi.com/1422-0067/23/4/2170

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- Insulin increases uptake of fatty acids by increasing translocation FA transport proteins to the cell membrane from vesicles (Varlamov, et al., 2010)

Insulin Effects on Protein Metabolism

- Stimulates transport of **amino acids into the cells**
- Increases translation of mRNA by turning on/off ribosomal machinery, leading to **formation of new proteins**
- Over a longer period of time, insulin **increases transcription rate of select DNA sequences in the nuclei**, particularly those associated with enzymes responsible for storage of fats, carbohydrates, and proteins
- **Inhibits catabolism**
- **Decreases rate of gluconeogenesis** in the liver

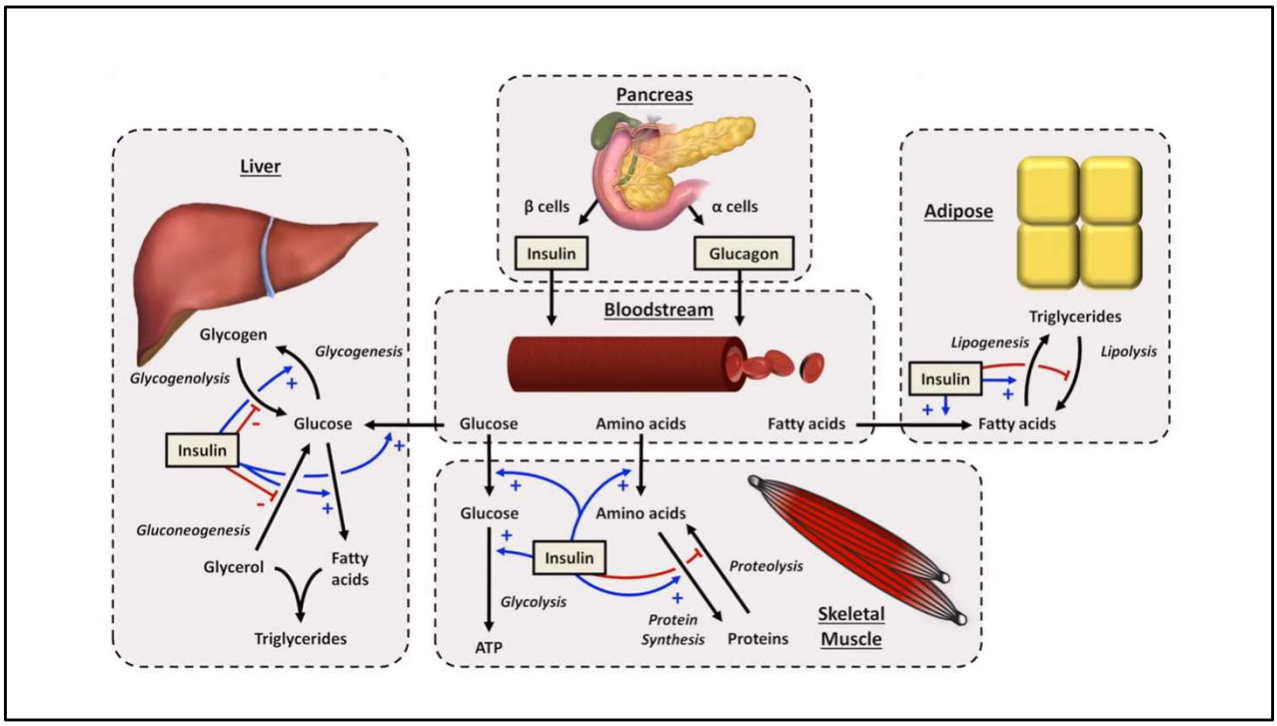
- Effects of insulin on protein synthesis aren't as well documented as fats and CHO and there is a lot of conflicting information very dependent on how studies are performed. There are very rapid effects (increased substrate uptake), fast effects within a few minutes (increased protein synthesis probably from translation of preformed mRNA, and slow effects over hours to days (DNA transcription)
- A.As: different amino acids than growth hormone, primarily valine, leucine, isoleucine, tyrosine, & phenylalanine
- Gluconeogenesis: remember substrates are amino acids (ex. On slide 12)

Insulin Functions Review

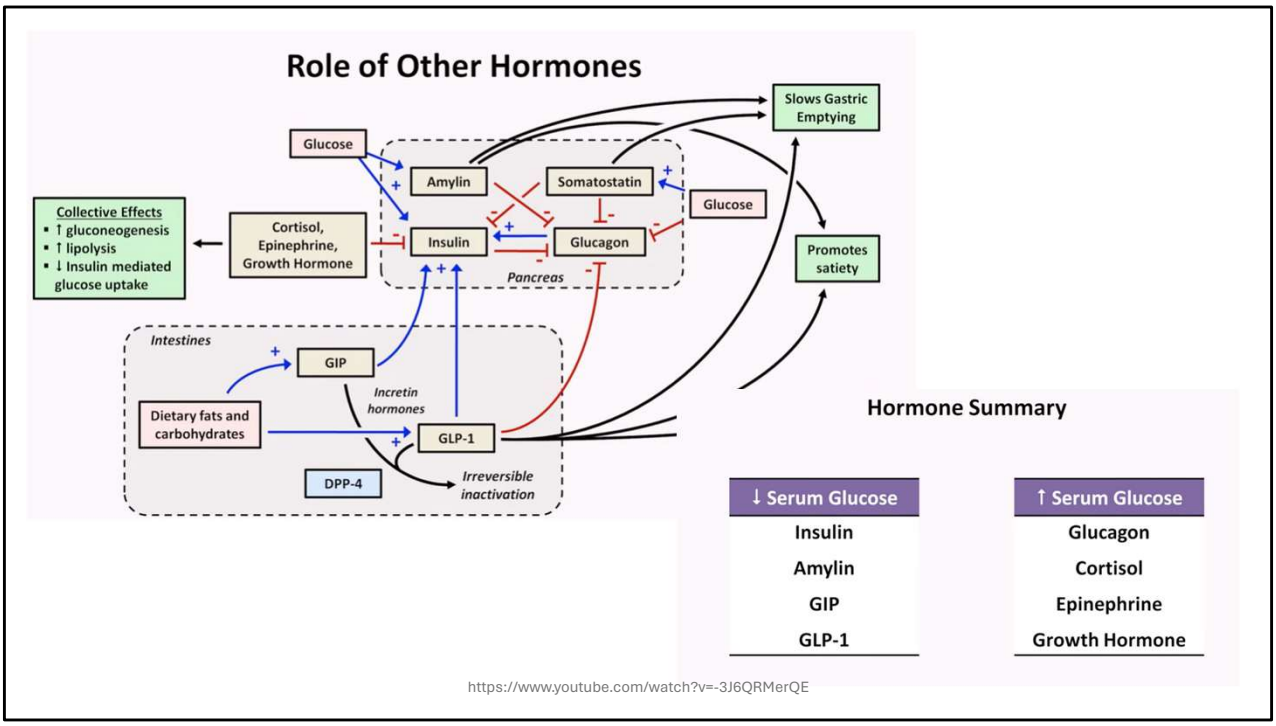
- Carbohydrates
  - Supports uptake and use of glucose by cells with additional being stored as glycogen
- Fat
  - Supports fat synthesis and storage
- Protein
  - Promotes formation and inhibits catabolism of proteins
- Growth
  - Synergistic with growth hormone to facilitate growth
- CNS (Petersen & Shulman, 2018)(Soto, Cai, Konishi, & Kahn, 2019)
  - Suppresses appetite
  - Regulates actions of insulin in other tissues
  - Affects mood, behavior, learning, and memory

- CNS insulin can regulate hepatic insulin activity independent of energy balance, changes uptake in muscles, change lipolysis, suppress glucagon While this list is certainly exhausting, it is by no means exhaustive.

Glucagon is secreted by alpha cells in response to dropping BG, its most dramatic effect is on glycogenolysis in the liver. Each successive step in the glycogenolysis pathway can is amplified so a very small amount of glucagon can raise the blood sugar significantly in a short period of time



Insulin pathways, glucagon is the opposite, not specific only to these tissues



- Insulin is the major switch between CHO and fat metabolism, but other hormones have roles in this
- growth hormone & cortisol secreted in response to low BG, inhibit cellular glucose use, and promote fat utilization, but these effects are SLOW (hours)
- epinephrine increases BG during stress via glycogenolysis when the sympathetic nervous system is excited, but also increases fatty acid concentration at the same time via LIPOLYSIS (greater of the 2 effects)

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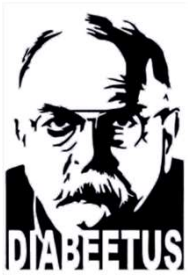
Consequences of Insulin Deficiency/Dysfunction

- Can't utilize/store Carbohydrates, Proteins, Fats
- Hyperglycemia
  - Glucosuria resulting in PU/PD and dehydration and electrolyte loss: potassium, phosphorus, magnesium
  - Vascular changes
- Altered fat metabolism
  - Increased utilization of fats and formation of cholesterol
  - Increased ketoacid production that could result in metabolic acidosis (more severe with dehydration)
  - Hyperlipidemia, increased risk for hepatic lipidosis
- Depletion of body proteins
  - Increased protein catabolism → hyperglycemia, negative nitrogen balance, cachexia
  - Rapid weight loss and lack of energy despite polyphagia
- Polyphagia from negative caloric balance

Glucosuria: Renal threshold in Humans 200mg/dL; Dogs: 180-200; Cats: 250-290
Dehydration: first on a cellular level from increased osmotic draw in the ECF, then further dehydration from osmotic diuresis drying out the ICF (vicious cycle)

Diabetes Mellitus

- "Syndrome of impaired carbohydrate, fat, and protein metabolism caused by either a lack of insulin secretion or decreased sensitivity of the tissues to insulin." (Hall & Hall, 2021)
- "Endocrine disorder characterized by chronic hyperglycemia resulting from a deficit in insulin production, action, or both." (Ettinger, Feldman, & Cote, 2017)
  - Type 1: insulin deficiency
  - Type 2: insulin resistance



Type I DM

- Hypoinsulinemia with no increase in serum [Insulin] or [C-peptide] with administration of insulin secretagogue
- Beta cells are unable to produce insulin
  - Damage can be from viral infection or auto-immune disorders
  - Hereditary changes making the beta-cells more susceptible to damage
- Absolute need for exogenous insulin

Type II DM

- Tissues are **resistant** to insulin from
  - Obesity
  - Excess glucocorticoids
  - Excess growth hormone
  - Pregnancy
  - Auto-antibodies to insulin receptor
  - Etc.
- Hyperinsulinemia as a compensatory mechanism from beta cells to insulin resistance
- Prolonged or severe insulin resistance leads to insufficient glucose regulation
  - In later stages, beta cells can become 'exhausted' or damaged leading worsening of hyperglycemia
- The point where the pancreas can no long keep up with the body's need for insulin is when type-2 diabetes develops

Relative insulin deficiency progresses to an absolute deficiency

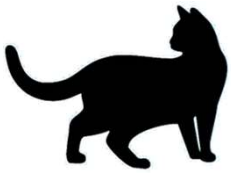
Canine DM

- Most closely resembles type-I with insulin deficiency from beta cell loss/destruction or dysfunction
  - Can see insulin resistance, but type-II is extremely rare in dogs
  - Transient or reversible DM is uncommon in dogs
- Can have initial good response to insulin with good glycemic control that changes over time as residual beta-cell function decreases
- Typically diagnosed in middle aged dogs (may Dx during diestrus)
- Females are over-represented

Causes of insulin deficiency/beta cell loss: Congenital beta cell hypoplasia/abiotropy, immune-mediated destruction, beta cell loss from pancreatitis or disorders that diffusely injure the pancreas (EPI, pancreatitis, etc.), beta cell exhaustion/glucose toxicity/lipotoxicity secondary to insulin resistance

- insulin resistance typically from antagonism of insulin function by other hormones but can be exacerbated by infection or inflammation; maybe by diestrus/pregnancy, concurrent endocrine disease, iatrogenic, steroids, progestogens, carbohydrate intolerance secondary to obesity, concurrent illness, CKD, heart disease, hyperlipidemia…

Feline DM



- Most commonly resembles type-II
- Pancreatitis is present in as many as 60% of cats at the time of diagnosis with DM
- Remission is possible
- Risk factors
  - Old age
  - Male
  - Obesity, physical inactivity, indoor confinement
    - each kg increase in BW over ideal causes a ~30% decrease in insulin sensitivity
  - Repeated long-acting steroid use
- Can see phenotypes similar to atypical DM in humans!

Type-1 is rare in cats but does happen
Other types include secondary loss of islets to pancreatitis or neoplasia, insulin resistance and DM secondary to acromegaly
Pancreatitis in up to 60% at time of diagnosis **with or without symptoms**, chronic is most common based on histology
Risk factors: things that cause reduced sensitivity to insulin!!
Atypical DM: PU/PD, wt. loss, relatively high BGs, susceptible to ketosis but go into remission within a few weeks or starting insulin!! Associated with several genetic loci!!

Feline DM

- 2 Key features of DM in cats
  - reduced insulin sensitivity
  - reduced insulin secretion secondary to beta-cell failure
    - Why do beta-cells fail?
- Relative insulin deficiency progresses to absolute deficiency

Feline DM

E-Box 305-1

Mechanisms Contributing to Beta-Cell Failure by Impairing Insulin Secretion, Reducing Beta-Cell Capacity to Proliferate and Increasing Beta-Cell Dedifferentiation and Beta-Cell Death[33,59,67,71,72,246,251]

Mechanisms

Accumulation of misfolded IAPP oligomers as aggregates and fibrils in beta-cells, and as amyloid within islets, leads to beta-cell death. Intracellular aggregation is particularly toxic and triggers apoptosis. It also contributes to islet inflammation by recruiting and activating macrophages and beta-cell production of chemokines and cytokines.

Generation of reactive oxygen species (ROS) secondary to nutrient overload. Chronic hyperglycemia increases glucose metabolism through oxidative phosphorylation, which induces mitochondrial dysfunction and production of ROS. ROS are also increased in chronic hyperlipidemia. Oxidative stress results in down-regulation of insulin and amylin production, and up-regulation of pro-inflammatory and apoptotic pathways.

Beta-cell endoplasmic reticulum (ER) stress occurs secondary to conditions that require prolonged high insulin production such as insulin resistance and high glucose concentrations, and with lipotoxicity and inflammatory conditions. ER stress results in reduced protein folding capacity of the ER, and accumulation and aggregation of unfolded proteins, including insulin. If the accumulation of unfolded protein is in excess of what can be managed by the unfolded protein response (UPR), it reduces insulin secretion and triggers apoptosis.

Increased glucose flux through the hexosamine biosynthetic pathway results in alteration in protein function, changes in gene expression, and decreased insulin secretion.

Exposure of beta-cells to overabundant supply of nutrients—glucose, free fatty acids and branched chain amino acids—associated with insulin resistance and obesity leads to beta-cell dysfunction and death.

Chronically increased glucose leads to **glucotoxicity,** which has a central role in beta-cell failure by decreasing both beta-cell function and mass.

Increased long chain free fatty acids (FFAs) and lipid intermediates associated with obesity lead to **lipotoxicity.**

Enhanced toxicity occurs when both glucose and free fatty acids are increased (glucolipotoxicity).

Increased branched-chain amino acids may have a role in beta-cell failure—for example, increased leucine results in decreased beta-cell function and insulin resistance.

Advanced glycation end products (AGEs) form secondary to increased glucose concentrations and result in damage to tissues including beta-cells.

Inflammation is initiated when there is over-nutrition and obesity resulting in high concentrations of glucose, free fatty acid and branched chain amino acids, but the mechanism is not fully characterized. Beta-cell induction of proinflammatory cytokines and chemokines results in immune cell infiltration into islets, including macrophages. Islets respond to glucolipotoxicity by generating inflammatory factors such as IL-1 and IL-6. IL-1 release is stimulated by hyperglycemia and IL-1 blockade improves beta-cell function.

Beta-cell dedifferentiation: Beta-cells progressively lose beta-cell characteristics, which to a certain degree is reversible. Dedifferentiation is triggered by glucolipotoxic conditions, ER and oxidative stress, and inflammation, but the relative contribution to beta-cell dysfunction and loss in type 2 diabetes is unknown.

Beta-cell death through apoptosis, necrosis and autophagy (programmed cell death) is triggered by many of the mechanisms above.

Diagnosis of DM

- Clinical signs consistent with DM
  - Polyphagia
  - Polyuria/Polydipsia
  - Weight loss
- Persistent hyperglycemia (with glucosuria) – why do you need both?
  - Causes of hyperglycemia: DM, stress, pancreatitis, post-prandial, Cushing's, Acromegaly, Diestrus, Pheochromocytoma, Steroids, Progestagens, Thiazide diuretics, alpha-2 agonists, dextrose in fluids, parenteral nutrition, head trauma
  - Causes of glucosuria: DM, renal tubular dysfunction (Fanconi syndrome, primary renal glycosuria, AKI, nephrotoxins, Lepto), dextrose in fluids
    - False positives for glucosuria
      - Vitamin C or pigment in urine
      - Glucose in collecting cup (jam jars)

Diagnosis of DM

- Check for comorbidities on newly diagnosed diabetics!
  - Cause or consequence?
    - Cushing's, pancreatitis, UTIs, weight loss, weakness
- Minimum database
  - CBC, Chem, UA/UCS
  - Ideally fructosamine
  - Abdominal ultrasound
  - Consider PLI
  - Serum [Pg] if intact female

Absolute dos:
- CBC: usually normal
- Chem: elevated: BG, Chol, ALT (<500), ALKP (<500); lipemia
- UA: USG usually >1.025, + Glucose and proteins, +/- ketones or bacteria (in a new diabetic, ketones are common, but it may not mean DKA)

If you can:
- Fructosamine makes sense, especially if you have an acute condition that causes insulin resistance
- Abdominal ultrasound is always on the list to check for comorbidities, this isn't strictly emergent and can be scheduled for near future if you don't have concerns for active pancreatitis or other comorbidities that need more acute treatments (if they're sick enough to be hospitalized, this should be done)
- PLI – needs to be fasted, if hyperlipemic I would wait, preference is for the TAMU panel (can now use the + cortisol panel) – snap cPL is not a reliable test (too many other things cause abnormal readings), quantitative specPSL is an option but still can be falsely elevated by CKD or conditions so interpret with care
- Prostaglandins [Pg] – this is academic and while listed, I wouldn't prioritize this largely because what are you going to do with this result

Management of DM

- Goals of Management
  - Resolve/minimize clinical signs
  - Glycemia control (Ettinger, Feldman, & Cote, 2017)
    - Dogs: [Glucose] 90-250 mg/dL, [Fructosamine] 350-450 umol/L
    - Cats: [Glucose] 72-180 mg/dL, [Fructosamine] 321-400 umol/L
  - Prevent, detect, and treat complications
- Treatments
  - Insulin
  - Diet
  - Exercise
  - Other drugs

Goals: no PU/PD, no polyphagia, normal body weight
Glycemic control: ***this is ideal, not always realistic***, tighter control increases the risks of hypoglycemia
Dogs: Nadir 90, Highest 250 (JAHAA nadir recommendation is btw 80-150)
Cats: tighter glycemic control because of glucose toxicity, lipotoxicity also occurs so managing lipid metabolism is also important – we care about this because tighter control increases chances for remission!

Insulin

- Goal is to make up for the deficiency (relative or absolute) by providing exogenous insulin
- Regular insulin is short acting, so it must be altered chemically to extend the duration and change the frequency of dosing to adjust the effects of insulin to avoid hypoglycemia and maintain euglycemia as much as possible

Remember basal vs bolus endogenous insulin secretion and high first pass effect in the liver

- regular insulin is short acting (remember endogenous half life of ~6m, cleared within 10-15m)
- Important limitation from SQ insulin injections:
    - remember the early hepatic removal of ~50% of secreted insulin – this creates a concentration gradient with high insulin concentrations in the portal circulation to the liver that manages glucose output by the liver which is a major player in maintaining euglycemia and lower concentrations to the other tissues to combat lipolysis, with SQ injections this doesn't happen so you can either have sufficient delivery of insulin to the liver with 'too much' insulin delivery to tissues leading to excess storage of nutrients (weight gain) but adequate glycemic control, or you can have appropriate delivery to the tissue with too little to the liver leading to poor glycemic control (Camara, et al., 2020)

Insulin Formulations

- Suspensions:
  - Lente (Vetsulin): porcine origin, U-40, 30% short-acting amorphous insulin/70% long-acting
  - Neutral Protamine Hagedorn (NPH): recombinant human, U-100
  - PZI: recombinant human, U-40
- Analogs:
  - Glargine: recombinant human, U-100 (also available U-300)
  - Detemir: recombinant human, U-100

- Suspensions take advantage of Insulin's natural tendency to precipitate in the presence of zinc or protamine to cause precipitation at the injection site which slows onset of action and prolongs duration. Zinc slowly diffuses and protamine is broken down, allowing insulin to go into solution (this process is variable to the individual! And leads to variability in response)
  - Vetsulin (Lente): zinc; NPH: protamine; PZI: both protamine and zinc
- Suspensions have to be resuspended prior to injection: vetsulin is shaken, not stirred; everyone else is gently rolled or inverted. This can lead to inconsistent or inaccurate dosing if not performed sufficiently/consistently.
- Analogs have amino acid additions or substitutions to affect insulin's tendency to form hexamers without changing the ability to bind insulin receptors. There are both short acting (faster than regular insulin, not routinely used in vet med) and long acting (increased hexamer association or lipophilic interactions to decrease absorption and flatten peaks)
- Analogs have more predictable responses because: **they don't need to be resuspended**, and absorption is more predictable. In human medicine they are used to mimic basal insulin needs with the addition of short acting insulin to mimic bolus needs depending on the nutrient content and size of a meal.

- Glargine is soluble at pH 4.0 (in vial), and precipitates strongly at neutral pH (SQ) slowing its absorption. Because it is pH dependent, it should never be diluted. U-300 is 3x more concentrated, so the same number of units is delivered as a small amount with less surface area which further slows absorption, extending duration, and as a result has an even flatter profile in humans.
- Detemir is bound to a fatty acid residue causing strong hydrophobic interaction between the fatty acid components. The fatty acid residue also binds reversibly to albumin. This interaction with albumin helps increase availability to the liver which may do a better job overall of mimicking endogenous insulin behavior in humans. This effect hasn't been demonstrated in companion animals.

Insulin Formulations

- U-40 vs U-100: not a true concentration but a measure of efficacy at lowering blood glucose
  - 1 'unit' of insulin is expected to lower BG by 30-50 mg/dL
  - U-100 = 100 units per milliliter
    - 1ml of Lantus = 100 units = 3.6378 mg of glargine insulin
    - 1ml of Levemir = 100 units = 14.2 mg of detemir insulin

Unit was calibrated for humans
Wrong syringe? You can calculate the volume needed for the other type. DO NOT LET OWNERS DO THIS
ex. (7u Vetsulin) /(40u/ml) = 0.175ml; (0.175ml) x (100u/ml) = 17.5u with a u-100 syringe

Insulin Formulations

- Duration – time from injection through the nadir until [glucose] exceeds 250
  - Too short → symptoms persist
  - Too long → risk for hypoglycemia or Somogyi
- Nadir – the lowest point on the glucose curve

Reported duration of action is most often **assessed in healthy cats**, often using a technique called the euglycemic clamp but not always (the point is the information isn't always consistent apples to apples so the following lists may be misleading). **This may not be reflected in a diabetic patient's true duration!** Given as ranges and medians. Ranges can vary widely (this is partly because there is a very individual response to absorption/metabolism of these medications by the body).
- May also see onset of action or end of action reported.

Insulin

TABLE 304-2

Commonly Used Insulin Preparations for Treating Uncomplicated Diabetes Mellitus in Dogs

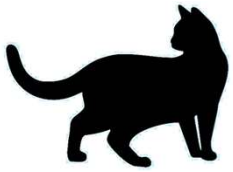
INSULIN	PRODUCT	ORIGIN	CONCENTRATION (U/mL)	DURATION OF EFFECT (hours)	FREQUENCY OF ADMINISTRATION	STARTING DOSAGE (U/kg/injection)	MEDIAN (RANGE) INSULIN DOSAGE (U/kg) PER INJECTION PER kg OF BODY WEIGHT TO ATTAIN CONTROL OF GLYCEMIA (U/kg/injection)
Lente	Vetsulin/Caninsulin	Porcine	40	8-14	q 12h	0.25	0.8 (0.3-1.4)[52]
NPH	Humulin N, Novolin N	Recombinant human	100	4-10	q 12h	0.25	0.8 (0.4-1.9) *[53] 0.4 (0.3-0.8) +[53]
PZI	ProZinc	Recombinant human	40	10-16	q 12h	0.25-0.5	0.9 (0.4-1.5)[54]
Glargine	Lantus	Recombinant human	100	8-16	q 12h (q 24h)	0.3	0.6 (0.1-1.1)[55] 0.5 (0.32-0.67)[56]
Detemir	Levemir	Recombinant human	100	8-16	q 12h (q 24h)	0.1	0.12 (0.05-0.34)[57]

(Ettinger, Feldman, & Cote, 2017)

Start with intermediate acting (NPH or Vetsulin, dealers choice unless mandated by law to use a labelled product)

Levemir is going to be discontinued December 2024

Insulin



Commonly Used Insulin in Cats

Insulin	Product	Concentration	Duration	Frequency	Starting Dose
Glargine	Lantus	U-100	10-24 h	Q12 h	~~0.25-0.5u/kg~~ **1u/cat**
Detemir	Levemir	U-100	9.1-14 h	Q12 h	0.25-0.5u/kg
PZI	Prozinc	U-40	21h	Q12 h	0.25-0.5u/kg
~~**Lente**~~	~~**Vetsulin**~~	~~**U-40**~~	~~**8-10h**~~	~~**Q12 h**~~	~~**0.25-0.5u/kg**~~

(Ettinger, Feldman, & Cote, 2017)

- Glargine: no sig. difference in duration between 0.25u/kg BID vs 0.5u/kg SID; recommended q12h with low carb diet to minimize postprandial increases in BG (if BG >360 can start at 0.5u/kg)

Realistically, start all cats at 1u/cat on glargine, titrate up by effect!!!

- Detemir has similar action but less variability in humans; later onset of action compared to glargine (1.8h vs 1.3h), duration 13.5h; may have an initial increased sensitivity to detemir (transient over 24-48)
- These (glargine and detemir) are choice #1 & 2 respectively because they have higher rates of remission, than PZI, then vetsulin
- PZI: biphasic action in healthy cats (1st nadir ~4h, 2nd ~14h), 1st nadir in DM cats was 5-7h
- Lente: nadir 3-6h **Don't use vetsulin unless you have to go through this due to regulations or have no other choice**

Diet

- Consistent feeding schedule and calorie intake
  - Dogs should be meal fed at time of insulin if possible
  - Cats **don't** require meal feeding because of differences in digestion and post-prandial glucose rise
- Diet composition
  - Comorbidities take priority for diet composition!
  - Dogs: High fiber, complex carbohydrates, low fat
  - Cats: High protein, low carbohydrate

Eating is more important that what they eat specifically Prescription diets only work if patients eat them and owners are compliant!

Other Treatments

- Exercise
  - Consistent duration, intensity, and scheduling
- Stop drugs that may interfere with insulin function/secretion
  - Glucocorticoids, Progestins, Estrogens, beta-adrenergic agonists, etc.
- Spay intact bitches as soon as possible
- Identify and treat comorbidities
  - Remember that many of these conditions alter insulin sensitivity

- OHE removes progesterone rise during diestrus (i.e. removes a source of insulin resistance)
- Common comorbidities that alter insulin sensitivity: obesity, Cushing's, pancreatitis (may be intermittent), infection, hypothyroid, etc.

Other Treatments

- Other drugs used in diabetes
  - Thiazolidinediones (increase insulin sensitivity)
  - Metformin (decreases liver glucose production)
  - Sulfonylurea drugs (increase endogenous insulin release)
  - SGLT-2 Inhibitors (reduce renal glucose absorption)
  - Incretins (stimulate insulin release, inhibit glucagon release)
  - Alpha-glucosidase inhibitors (inhibit intestinal glucose absorption)

Sulfonylureas – (glipizide)
there are studies for some of these showing they don't work well in vet med (metformin in cats), some of these are labeled for use with variable responses

Monitoring DM

- Glucose Curve
- Fructosamine
- Urine Monitoring

May take a few months to establish stable glycemic control, some never do
Glucose curve: wait a week to readjust, it can take a few days to reach equilibrium

Glucose Curve

- Glucose curves reflect not only exogenous insulin, but also endogenous insulin, stress hormones, diet, and exercise! Day-to-day variations are expected.
- Curve should be started in the morning just before the first insulin dose. [BG] should be monitored every 1-2 hours until the next dose of insulin is due.
- Home monitoring of [BG] should be encouraged with the appropriate tools
- What are you using to measure?

(Ettinger, feldman, & Cote, 2017)

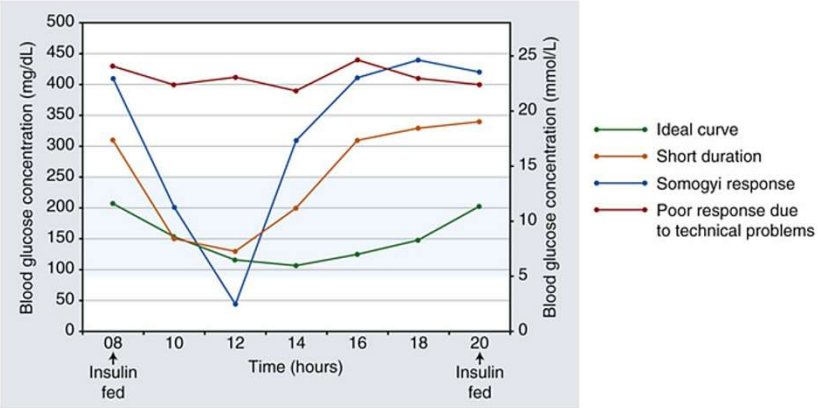
- Remember glucose curves reflect not only exogenous insulin (how we're use to interpreting them), but also endogenous insulin, stress hormones, diet, and exercise! (Camara, et al., 2020)
- 24-hour curves can be done if there are concerns, but most animals respond well to the same dose morning and night and studies show no significant difference between BGs day vs night. (Ettinger)

Glucose Monitors

- Portable glucose monitors are easy to use at home with lancets to collect blood from ears or paw pads
  - AlphaTrak: glucose monitors should be appropriately calibrated for the species, tends to overestimate BGs.
    - Less accurate if PCV < 30%
- Continuous glucose monitors are easy to apply and give more consistent results
  - Measures interstitial blood glucose, lags behind peripheral by ~10-20m
  - Less accurate with hypoglycemia

- Most human portable glucose monitors give lower results than lab reference methods
- AlphaTrak is less accurate with PCV <30% (increased PCV may cause decreased BG measurement and vice versa)
- CGMs don't work well in very thin patients, capillaries break easily and they rarely stay on for the full time but you still may get some really good data so prep owners accordingly (may still be cheaper and better information, also far less work for you)
    - Can use tac wipes and tac away to help make CGMs stay better without using surgical glue that will far outlast your monitor
    - Don't rely on the CGM to tell you if the BG is too low, if there are signs of hypoglycemia either treat anyway with dextrose or check peripherally!

Glucose Curve



- Goal is for [BG] to stay between 90 and 250-300 mg/dL throughout the curve.
- Ideally the nadir would be between 90-150 mg/dL.

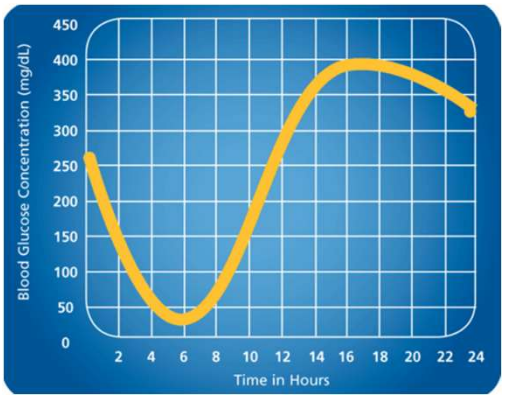
(Ettinger, feldman, & Cote, 2017)

Again, these goals are academic and may be too tight of a goal range, recommend a nadir between 100-200, if we can keep the high end of the range below 250-300 we're thrilled

Figure 304-3 (Ettinger): Representative blood glucose curves in dogs treated with an intermediate-acting insulin q 12 h. The blue area is the preferred range of blood glucose concentration in treated diabetic dogs (90 to 250 mg/dL). Green line: ideal curve. Orange line: short duration of insulin effect. Blue line: Somogyi response with counterregulation after rapid decrease in blood glucose concentration. Red line: poor response due to technical problems, the counterregulatory phase of the Somogyi response, insulin resistance, poor insulin absorption, or insulin antibodies.

- Looking for the nadir, degree of fluctuation [BG], and duration of effect

Somoygi Response

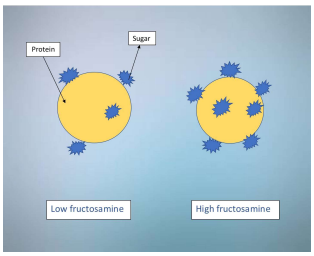


- Rebound hyperglycemia after insulin overdose and hypoglycemic event cause by counter-regulatory hormones that raise the BG and cause insulin resistance that may last for days
- Dx requires evidence of hypoglycemia within hours of hyperglycemia
- Fructosamine is not a reliable marker (usually high)

https://www.merck-animal-health-usa.com/vetsulin/dogs/the-somogyi-effect

- Acute response triggered if BG <65 or if the BG drops rapidly over a short period of time (2-3h) regardless of the nadir – glucagon and epinephrine are secreted, they stimulate growth hormone and cortisol for longer acting response.
- May look similar to insulin with too short a duration of action

Fructosamine



- Glycated proteins produced by an irreversible, non-enzymatic reaction between glucose and plasma proteins
- Estimates glycemic control over preceding 2-3 weeks
- Not affected by acute changes like stress hyperglycemia
- Poor glycemic control does not help you differentiate why

Glycemic control	Fructosamine (µmol/L)
Poor	>550
Moderate	450-550
Good	360-450

Available for in hospital or reference lab measurements
Lower Fructosamine can develop independent of BG with: low proteins/albumin, azotemia, hyperlipidemia, and hemolysis
Higher fructosamine can be from hypothyroid or hyperglobulinemia from multiple myeloma
****This is the least important monitoring measure and should not be used to adjust insulin on its own****

Urine monitoring

- Can be monitored by owner daily at home
- Check on any sick diabetic in hospital
- Ketonuria is never normal and should be evaluated by vet
  - Does not measure the most common ketone in small animals
- Occasional lack of glucose is a normal, if glucose is persistently absent, either the control is very good or there is concern for hypoglycemia

- Cheap and easy, available at nearly all pharmacies
- Ketonuria is never normal in **managed diabetics**, it is seen frequently in new DM, this doesn't necessarily mean they are DKA
- Monitors glucose and acetoacetic acid and acetone, does not detect BHOBs (beta-hydroxybutyrate) which are the most common ketone in small animals. (more on this later)
- BHOB is formed from acetoacetic acid in the presence of hydrogen ions, therefore the more acidotic the animal, the more BHOB are formed

When to recheck what?

- Week 1: BG curve, ~~fructosamine~~, recheck exam and review history
- Weeks 2 & 3: repeat in hospital checks as above; consider starting at home monitoring
  - Fasting BG 2x/week, generate BG curve twice a month
- Week 6-8: repeat in hospital checks, may not need full curve if spot check prior to insulin is in good range and fructosamine is in desired range
- Week 10-12: repeat 6-8wk recheck
- Recheck every 4 months

(Ettinger, Feldman, Cote, 2017)

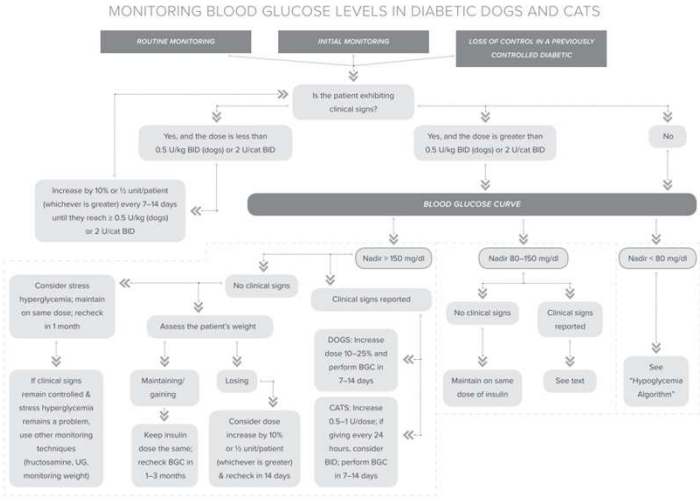
Reminder of goals:
BG: ideally between 250 (before insulin) and 90 (nadir) ***again this may be unrealistic and too much risk for hypoglycemia***, ideally highest point under 250-300 with nadir in the 100s
Fructosamine is the LEAST important! Ideal 350-450

Adjusting Insulin Dosing

- Insulin doses shouldn't be changed more often than every 5-7 days unless there is concern for hypoglycemia.
- Insulin should never be adjusted on single glucose readings unless there is hypoglycemia
  - If hypoglycemia is confirmed or suspected, decrease the dose by 50%
- Increase by **10-25%** at a time until adequate glycemic control is achieved
  - Ideal nadir between 90-150
  - Ideal curve should stay under 250-300
- **Insulin Resistance >1.5u/kg per injection to maintain [BG] <300**
- Remember that many comorbidities of DM cause insulin resistance and the insulin dose may need to be adjusted as those conditions are addressed.

(Ettinger, Feldman, & Cote, 2017)

Adjusting Insulin Dosing



2018 AAHA Diabetes Management Guidelines for Dogs and Cats

Client Education!!!

- Demonstrate as many times as necessary how to handle insulin, draw up injection, how to give injection, where to give
- Provide owners written instructions for them to reference
- Have links available to videos
- Don't have owners start glucose curves at home right away
- Discuss complications and what to look for
- Discuss when they should come back to see you vs when they need to seek emergency care, this will vary based on your ability and comfort level in your individual practices!

When to Refer

- Complicated DM
  - Suspected insulin resistance
    >1.5u/kg per injection to maintain [BG] <300
  - Poor or variable glycemic control
  - Significant comorbidities

- Referrals can be sent to:
  - CCVS
  - Angell
  - Tufts
  - VCA SouthShore
  - OSVS

Referrals need to be sent to internal medicine, not through ER on complicated DM cases

Outline

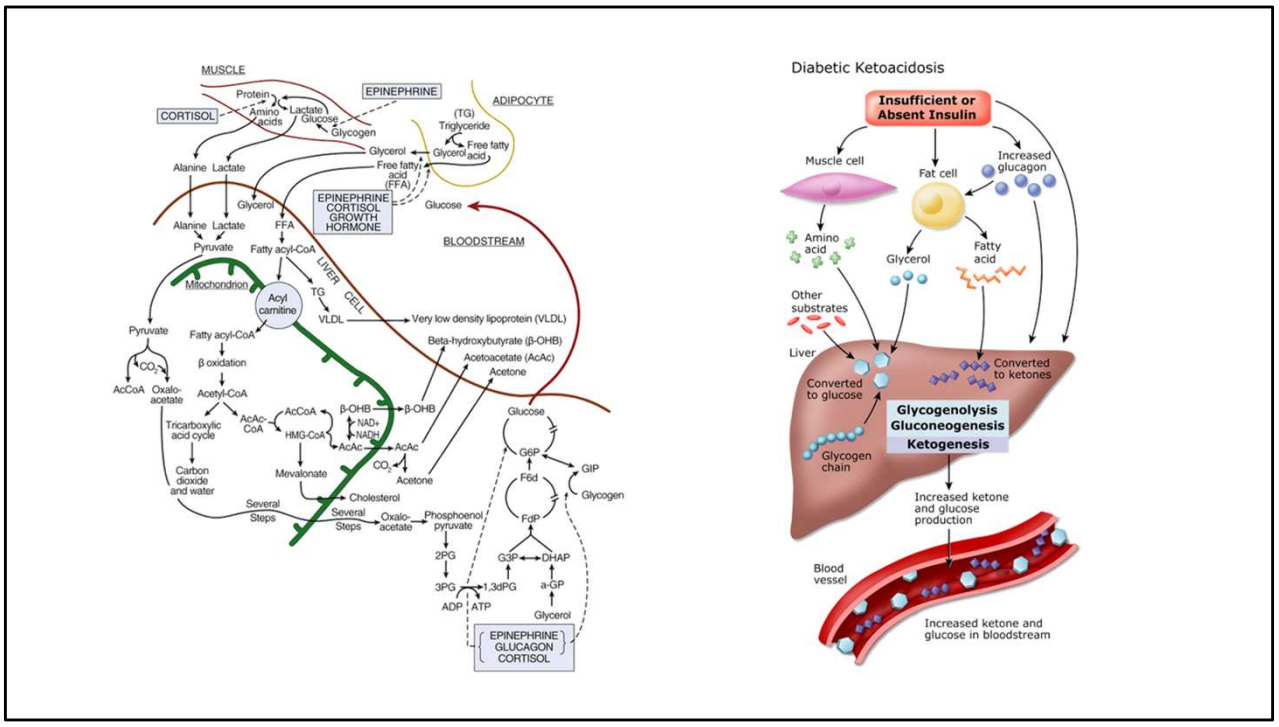
- Review
  - Anatomy and physiology of the pancreas
  - Function and regulation of insulin
- Diabetes mellitus
  - Pathophysiology
  - Diagnosis
  - Management
- Diabetic ketoacidosis
  - Pathophysiology
  - Diagnosis
  - Management

CCVS
CAPE COD VETERINARY SPECIALISTS

Pathophysiology of DKA

- Lack of/insufficient insulin → increased [BG]
- Despite elevated blood glucose, cells are unable to utilize glucose for energy in the absence of insulin → shifts in metabolism to allow FFAs to be utilized for energy & increased release of glucagon to stimulate glycogenolysis and gluconeogenesis
- Absence of insulin also allows lipolysis to continue → increased serum [FFA]s
- FFAs are then converted to ketones by the liver

This cycle happens in diabetics all the time without moving to full blown DKA. Counter-regulatory hormones are the deciding component. Glucagon increases in this scenario **due to perceived hypoglycemia** leading to worsening of hyperglycemia and facilitating greater increases in lipolysis and ketone body production



Simplified diagram on the right, the left shows more of the counter-regulatory hormone contributions

Pathophysiology of DKA

- Comorbidities contribute to or trigger the pathogenesis of DKA by increasing counter-regulatory hormones like epinephrine and cortisol and inflammatory cytokines
- When ketones overwhelm the TCA cycle, ketosis prevails and eventually overwhelms the body's buffering capacity leading to acidemia
- Acidemia → worsening electrolyte shifting, causes insulin resistance, has body wide consequences
- These effects culminate in a complex, potentially fatal disorder that is complicated to manage

Effects of Acidemia: including respiratory changes (tachypneic, decreased oxygen binding and consequently delivery to tissues), decreased cardiac output, arrhythmias, vasodilation (hypotension, increased intracranial pressure), exacerbates diuresis, decreased gastric emptying/nausea/vomiting, coagulopathies, etc.

Hyperglycemia Hyperosmolar Syndrome

- Syndrome of severe hyperglycemia (>600 mg/dL) and serum osmolality (>320 mOsm/kg, range variable dependent on species)
  - This can only develop if there is reduced GFR
- May or may not have ketones present
- Most are not acidotic, less electrolyte losses as a result
- More profound free water loss in urine, but intravascular volume is maintained because of the increased osmolarity

$$Osm_T = 2(Na^+ + K^+) + {}^{Glucose}/_{18} + {}^{BUN}/_{2.8}$$

Hyperosmolality >325 mOsm/kg dogs, >330-350mOsm/kg cats

- This is here to remind you that this is a separate condition and has different prognosis, recognition is important. These should be referred for treatment.
- Effective osmoles are Na and Glucose (create an osmotic gradient because they cannot cross the cell membrane), outside of severe elevations, the contribution of K and BUN can be left out
- RI: (Ettinger, Feldman, Cote, 2017) – the reference intervals will vary dramatically sometimes based on source

Diagnosis

- Presence of hyperglycemia, glucosuria, ketonemia or ketonuria with an increased anion gap metabolic acidosis
  - [BG]
  - Ketonemia >3.5mmol/L (RI 0.02-0.15 mmol/L) dogs, >2.4 mmol/L (RI 0-0.1 mmol/L) cats consistent with DKA (Chong & Reineke, 2016)
    - In DKA, ketones are primarily beta-hydroxybutyrate in dogs and cats, these are not measured by **urine ketone strips**.
      - Can you use peroxide? Study found that addition of hydrogen peroxide does urine not improve urinary ketone detection (Smith, Manini, Szekely, & Hoffman, 2008)
      - Use serum or plasma on the urine strips to improve sensitivity/specificity (Chong & Reineke, 2016)
    - Point of care ketone meters detect beta-hydroxybutyrate and glucose on whole blood, improved sensitivity over urine test strips
  - Blood gas
    - Metabolic acidosis in DKA is from the addition of an acid (in this case ketones) that dissociate to release H^+ which bind to bicarb to titrate and lower the [bicarb] as a result, the anion that dissociated from the H^+ accumulates → increased 'anion gap'
    - Can use serum or plasma on the urine dipstick to measure pH

$$\text{Anion Gap} = ([Na^+] + [K^+]) - ([HCO_3^-] + [Cl^-])$$

RI: 12-24mEq/L (dogs), 13-27mEq/L (cats) (Dibartola, 2012)

BG
Ketones
- Normal serum BHA: AcAc ratio is 3:1, in DKA this can increase up to 10:1
- pH (how can you measure this without blood gas) – the urinalysis dipstick has litmus paper, use serum or plasma on that to get a good estimate
- Anion gap is a reflection of the unmeasured ions (i.e. not Cl or bicarb); other causes of anion gap metabolic acidosis = uremia, ethylene glycol, lactic acidosis, methanol tox, salicylate ingestion
- Other 'unmeasured anions' that affect acidemia – albumin and phosphous!, if low albumin, the calculated anion gap may be normal in the face of significant ketosis; also hyperalbuminemia will increase the anion gap
- TCO2 approximates HCO3, so if you have one but not the other you can substitute it in this equation

Other Diagnostics

- PCV/TS
- Chemistry (need to monitor phosphorus)
- Electrolytes (need to monitor potassium) +/- Magnesium
- Blood gas
- CBC, UA , urine culture
- Abdominal Ultrasound, thoracic radiographs
- Blood pressure

Treatments

- Fluids
- Fluids
- Fluids
- Correct/supplement electrolytes
- Supportive care for symptoms and comorbidities
- Then insulin after intravascular volume and electrolytes are stabile

- Why fluids first?: fluid will decrease BGs and may correct substantial amount of acidosis, insulin may: worsen hypovolemia, decreasing effective osmolarity and potentially causing cerebral edema, worsening hypokalemia/hypophosphatemia which may be potentially life threatening

Fluid Therapy

- Balanced Crystalloids
- Correct shock
- Correct dehydration
- Provide maintenance while correcting dehydration
- Re-assess frequently
  - Urine outputs
  - Weights
  - Dehydration estimates

- Avoid Normal saline so as not to contribute to acidosis, lactated ringers solution is not a problem because of lactate, but because of calcium incompatibility with phosphorus!! If LRS is what you have use it, just remember it may not be able to share the same catheter as phosphorus supplementation

Fluid Therapy

- Hypovolemic shock secondary to severe dehydration is common in DKA. If they are compensating, the symptoms may be subtle, but they are still critically ill
  - Prolonged CRT, poor pulse quality/peripheral vasoconstriction, altered mental status, tachycardia (bradycardia in cats), tachypnea, hypotension, hypothermia
- Total shock bolus: 90ml/kg (60ml/kg in cats)
  - Balanced crystalloids, give 1/4th shock bolus and **reassess**

'ism': 10-20mls/kg over 10-15 minutes

- Crystalloids will redistribute into the dehydrated tissues over time. They may respond well, then become hypotensive again when this happens.

Remember that other things contribute to hypotension

- Hypovolemia is not the same as dehydration, we're concerned about circulating volume to maintain cardiovascular tone/function.
- Dogs will also become bradycardic as shock progresses
- Shock doses: ¼ shock bolus (60ml/kg in cats, 90mls/kg in dogs) – ism: 10-20mls/kg over 10-15 min; then reassess
  - do not give a shock bolus over an hour, this isn't a bolus, its just a high fluid rate and won't accomplish what you're needing it to, they idea is you are expanding the intravascular volume to correct vascular tone!!

***remember that fluids redistribute w/in 30m, frequently reassess, give them more when they're saying they need it**

keep in mind other things contribute to hypotension, like temperature, don't use BP alone to decide what they need

- why are these important notes? If your patient isn't euvolemic, they likely need more fluids, if they are euvolemic, maybe they need hypertonic fluids or oncotic support, or potentially pressors; if you're patient is euvolemic but cold and you're still fighting BP, warm them up! Are they taking other medications that could worsen their pressure, can you stop these?

Do you need the pressure to be completely normal? There isn't a solid consensus on what blood pressure is necessary to maintain renal perfusion (we

arbitrarily set MAP of 60mmHg as the minimum goal because of the pressures at bowman's capsule and it's a good one to aim for) if you have a really quiet patient, a systolic of 90 or 100 may be more than sufficient to keep their perfusion up. (permissive hypotension)

Fluid Therapy

- Correct Dehydration in addition to maintenance fluids
  - (% dehydration)(kg) = liters
  - 10% dehydration, 20kg dog
  - (0.10)(20kg) = 2 liters
  - Corrected over 24h = 83mls/hr
- Can your patient tolerate this fluid rate?
- Reassess dehydration often
  - Are the clinical signs resolving as expected
  - Are they gaining weight appropriately

Estimated % Dehydration	Physical Exam Findings
<5%	Not detectable
5-6%	Tacky mucous membranes +/- skin turgor changes
6-8%	Mild decreased skin turgor Dry mucous membranes
8-10%	Obvious decreased skin turgor Retracted globes within orbits
10-12%	Persistent skin tent due to complete loss of skin elasticity Dull corneas Evidence of hypovolemia
>12%	Hypovolemic shock Death
(Silverstein & Hopper, 2023)	

- Correct dehydration as quickly as safe to do so (6-24h) – take in mind cardiovascular and neurologic health, osmolality, etc.
- Remember acute weight gains and losses are from dehydration, this is the fastest and most reliable way to assess response to fluids before signs of fluid overload like increased respiratory rate/abnormal respiratory sounds/nasal discharge/tissue edema

Fluid Therapy

- Provide maintenance fluids in addition to correcting dehydration:
  - Maintenance
    - Dogs: 60mls/kg/day, 2.5mls/kg/hr
    - Cats: 45mls/kg/day, 1.875mls/kg/hr
    - RER ($kg^{0.75}$ x 70)
- + insensible losses 20mls/kg/day
- + ongoing losses in urine, diarrhea, vomit

****Remember diabetics have ongoing glycosuria, they will have increased urinary losses and as a result, have higher maintenance needs****

Maintenance doesn't refer to a specific number but a concept, no one agrees. Pick one, make sure you document it so people know what you are giving and reassess your patient's tolerance of what you are giving and adjust accordingly.
JUST PICK ONE
- insensible losses—is your patient panting like crazy because of its acidemia? Increased respiratory losses
- Higher maintenance due to osmotic diuresis in unregulated diabetics: more isms: 1.5-2x maintenance, DM maintenance 100mls/kg/day (dog)
- When you are calculating your fluid rates, if you aren't at least matching their urine output, you aren't going to be keeping up with their fluid needs or correcting dehydration so these are really important losses to consider in your patient's overall fluid plans. After their condition improves, remember to challenge them by stepping back on matching outputs to see when they are able to come back down to meet you. Otherwise you may be driving the polyuria.

Be Flexible and Reassess Frequently

The most important thing to remember with IV fluids therapy

Electrolytes

- Glycosuria leads to wasting of electrolytes
- Acidemia leads to shifting intracellular to extracellular, continued glycosuria leads to even further wasting
- Body wide depletion is common, sometimes their values are falsely elevated initially from acidemia, these levels will drop as fluids are given and acidemia improves, insulin supplementation will also drive intracellular shifting further dropping serum levels
- Most important:
  - Potassium
  - Phosphorus
  - Magnesium

Potassium

- May initially be normokalemic at time of diagnosis, remember that acidosis causes extracellular shifting of potassium and with glucosuria comes electrolyte wasting so they are body wide deplete
- Fluids will help with acidosis allowing intracellular shifting which drops the serum levels, diuresis will continue contributing to ongoing urinary losses which further drops the serum levels
- Consequences of hypokalemia depend on severity
  - Varying levels of muscle weakness (begins <3.0), ventroflexion is common
  - Can impair urine concentration → PU/PD
  - <2.0 can cause rhabdomyolysis and respiratory muscle paralysis
- Consequences of hyperkalemia (may see due to comorbidities or over supplementation):
  - Bradycardia, loss of P waves, 'tented' T waves, shortened QT intervals, prolonged P wave and PR interval durations prior to disappearance
  - **may not see these changes in the face of acidosis or other electrolyte derangements!**

IV Potassium Supplementation

Current [K^+]	Added to Fluids	Max Fluid Rate (ml/kg/hr)
3.6-5.0 mEq/L	20 mEq/L	26
2.6-3.5 mEq/L	40 mEq/L	12
2.1-2.5 mEq/L	60 mEq/L	9
<2.0 mEq/L	80 mEq/L	7

Kmax 0.5mEq/kg/hr, don't forget to consider the contribution from fluids and KPO_4

- In life-threatening hypokalemia, exceeding Kmax is possible but should be on ECG
- Oral supplementation is not recommended for severe hypokalemia, but can be used concurrently once patient is eating

- If >Kmax, must run continuous ECG monitoring and recheck a1h to decrease to safer rate of administration and avoid hyperkalemia **can cause acute cardiac arrest
- Oral supplementation can also be used at discharge or once eating for mild derangements

Phosphorus

- May be high, normal, or low at time of presentation depending on comorbidities
- Just like potassium, fluids and insulin will cause further decreases in serum levels either from intracellular shifting or diuresis
- Consequences of hypophosphatemia:
  - Mild to moderate (1-2.5 mg/dL) changes are typically asymptomatic, severe depletion (<1.0mg/dL) causes cellular dysfunction via lack of ATP and 2,3-DPG
    - Severe depletion can cause hemolysis (<1.0mg/dL in dogs, <2.5mg/dL in cats) (Weiss & Tvedten, 2012) secondary to osmotic swelling when lack of ATP shuts down the Na-K-ATPase pumps in the cell membranes
    - Lack of 2,3-DPG causes a left shift in the oxygen dissociation curve → harder for oxygen to leave hemoglobin for the tissues → tissue hypoxia (Jacob & Amsden, 1971)(Silverstein & Hopper, 2023)
    - Both lack of ATP and 2,3-DPG contribute to red cell fragility
    - Ileus, weakness, metabolic encephalopathy, rhabdomyolysis, decreased contractility, platelet dysfunction have also been reported

IV Phosphorus Supplementation

Current [Phosphorus]	Rate of administration
1-2 mg/dL	0.03 mmol/kg/hr
<1.0 mg/dL	0.06-0.12 mmol/kg/hr

Remember to check Potassium contribution

- Alternate rule of thumb: give half of the necessary potassium as KPO_4 and half as KCl
- If phosphorus isn't elevated, start KPO_4 at least at a maintenance rate of 0.01-0.03 mmol/kg/hr. It will drop when you start giving insulin.
- Phosphorous must be diluted and is not compatible with calcium containing fluids
  - Rapid or undiluted IV administration can result in thrombosis, vasculitis, seizures, arrhythmias, cardiac arrest, and death

- icterus can cause falsely low phosphorus readings on chemistry analyzers
- hyperphosphatemia from over supplementation can cause hypocalcemic tetany, hypotension, renal failure, tissue mineralization
- dilute sufficiently to not exceed 10mEq/100mls for peripheral administration, 28.2 mEq/100ml for central administration (FDA) – hypertonic solutions can cause thrombosis and vasculitis

Magnesium

- Hypomagnesemia is the most common electrolyte abnormality in the ambulatory diabetic patient, commonly seen with DKA (Sheehan, 1991)
  - Consequence of osmotic diuresis from glycosuria
- Can be low or normal on initial checks, may still need supplementation if normal
- Consequences of hypomagnesemia:
  - Dysfunctions of platelets, immune system, nervous tissue, cardiovascular systems, electrolyte balance
  - In diabetics: impairment of insulin secretion, insulin resistance, increased macrovascular risk in humans

- Mg is a cofactor for ATPase, DNA/RNA polymerase, production of glutathine, glutamine, cAMP, and thiamine; ATP cannot be transported into mitochondria for use without it, also has roles in T cell activation, myocardial and nerve cell depolarization, contractility of the vascular endothelium; its present is required to prevent programmed cell death (Humphrey, Kirby, & Rudloff, 2015)

- In critically ill dogs, hypomagnesemia was associated with double the length of hospitalization of those with normal [Mg++] (Humphrey, Kirby, & Rudloff, 2015)

- Mg will also shift extracellularly in response to acidemia

- Mg supplementation increases insulin receptors and GLUT4 levels in rat skeletal muscle & increases insulin-dependent glucose uptake in adipocytes (Oost, et al.,2022)

IV Magnesium Supplementation

Current [Mg^{2+}]	Rate of Administration
<1.2 mg/dL	0.75-2 mEq/kg/day

Use for Refractory Hypokalemia or Hypocalcemia

- Monitor ECG and BP while giving
- Consider fluid contributions from Plasmalyte or Normasol
- $MgSO_4$ needs to be diluted in D5W or Saline to 20% or less prior to administration
- Dedicated IV catheter
- Signs that its too much/too fast: vomiting, diarrhea, hypotension, weakness, respiratory depression, bradycardia, QT interval prolongation, PR interval prolongation, QRS complex widening

Sodium

- Decreases in Na follow hyperglycemia, every 100mg/dL increase in [BG] above 'normal' is associated with 1.6mmol/L decrease in [Na^+]

$$\text{Corrected sodium} = [Na^+]_{\text{measured}} + \left(1.6 \times \left({}^{[BG]-10}/_{100}\right)\right)$$

- Sodium plays an important role in maintaining osmolality, when there are increases in osmolality in the vascular space, the body makes idiogenic osmoles to help maintain fluid composition of cells, rapidly correcting osmolality (in DKA either by rapidly dropping glucose levels or sodium levels) can lead to fluid shifting and osmotic swelling of cells

$$\text{Osm} = 2(Na^+ + K^+) + {}^{Glucose}/_{18} + {}^{BUN}/_{2.8}$$

- Use the corrected sodium to calculate osmolality

- sodium correction of 1.6 likely underestimates glucose's effect on sodium, corrections as high as 2.4 (AmFamPhysician 1999;60(6):1821) have been suggested

Insulin Therapy

****Do not start until [K^+] >2.5-3.5 mEq/L****

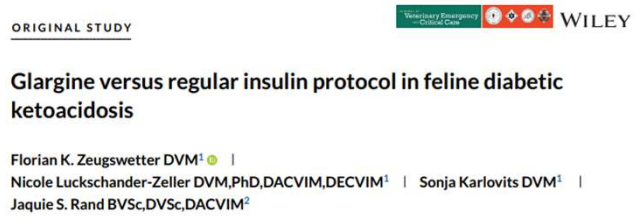
- Wait 4-6 hours? after starting fluid therapy to improve hydration
  - Delaying insulin prolongs treatment and severity of ketonuria (Difazio & Fletcher, 2016)
  - Make sure patients are intravascularly stable prior to starting
- Options:
  - Long acting
  - Short acting: Intermittent vs CRI? Fixed rate vs Variable rate?
    - IM may not be well absorbed in dehydration
  - Long acting + short acting

The long and short is, insulin fixes the ketosis, just pick one!

- There aren't specific studies saying when is ideal to start insulin therapy! Use your best judgement based on your patient. Are you seeing signs of improve hydration and cardiovascular status? - - - Early is defined as <6h in the study referenced
- In humans, insulin started as early as 1h (after sufficient intravascular volume expansion)

Insulin Therapy Intermittent Option

- R Insulin Intermittent protocol:
  - Initial dose 0.2 U/kg IM
  - then 0.1 U/kg q1h until [BG] <300 mg/dL
  - Then 0.1-0.4 U/kg q4-6h
- Intermittent long-acting protocol:



ORIGINAL STUDY

WILEY

Glargine versus regular insulin protocol in feline diabetic ketoacidosis

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- In human studies, starting **SQ long acting (glargine) early in the treatment process in addition to the IV CRI R insulin shortened length of stay and lead to faster resolution of DKA without increasing risks of hypoglycemia and hypokalemia** (Thammakosol & Sriphrapradang, 2022), **this basal-bolus protocol has been shown effective in cats** (Gallagher, Mahony, Rozanski, Buob, & Freeman, 2015) and in multiple human studies
- Glargine vs CRI study (2022): prospective over ~3.5y: 2u Glargine SQ at time of rehydration regardless of body weight & 1u IM 2h afterward, 1u IM repeated q4h if BG>250mg/dL & SQ glargine continued q12h at 0.25u/kg rounded to next half unit; dextrose added in fluids at 2.5-5% to keep BG 180-250 vs Fixed rate CRIs – both switched to just SQ glargine when hydrated, eating, and ketosis resolved; 20 cats in the study, 17 survived to discharge (8 in the CRI, 9 in the glargine) (Zeugswetter, Luckschander-Zeller, Karlovits, & Rand, 2021)

Insulin CRI (Gal & Odunayo, 2023)

$[Glucose]_{blood}$	Dextrose supplementation	Rate of insulin CRI administration	Dose of insulin administered
>250 mg/dL	None	10mls/hr	0.09 u/kg/hr
200-250 mg/dL	2.5% dextrose	7mls/hr	0.064 u/kg/hr
150-199 mg/dL	2.5% dextrose	5ml/hr	0.045 u/kg/hr
100-149 mg/dL	5% dextrose	5mls/hr	0.045 u/kg/hr
<100mg/dL	5% dextrose	Discontinue	Discontinue

Add 2.2u/kg of R insulin to 250mls of 0.9% NaCl (1.1-2.2 u/kg in cats)

- Change the bag q24h, run at least 50mls of the CRI through the tubing prior to administration
- Changing the volume of diluent will change the fluid rates!
- Continue until ketonemia resolves and eating. Start subcutaneous insulin 3-4h before stopping CRI.

This is an option, this isn't the only option and it isn't one that I specifically use. If you go with lower amounts of insulin you may need higher rates of fluids (may overload your patient) to resolve your ketosis or it may just not be sufficient. If it isn't working like you, don't be afraid to readjust the formulation for higher/lower concentrations.
- 2.2 U/kg/day is the total daily insulin dose **these are suggestions for starting points, may not be sufficient for any one animal**
- check BG q2h
- Insulin binds to plastic tubing
- Be mindful of your total fluid rates, particularly in cats!!!!!
- Don't have to start long-acting prior to stopping CRI (Ettinger recommends starting 6h later), but I would! Study mentioned on the previous page, I start long acting from the very beginning.

***We add dextrose so we can continue to give insulin. Remember the insulin is what is resolving the ketosis, we need to give insulin and we don't want them to become hypoglycemic. The dextrose is just to facilitate continue use of aggressive insulin treatment. Please remember that we don't want our patients to be hyperglycemic because it is damaging to the tissues and particularly to the

pancreas. We adjust the dextrose accordingly to no drive glucosuria or prolonged hyperglycemia***

Supportive Care for Comorbidities

- Comorbidities can be a driving cause of the counter-regulatory hormonal control that leads to development of DKA. Treating them is pivotal to successful resolution of DKA.
- Common conditions: pancreatitis, UTI, neoplasia, Cushing's, hepatic lipidosis, cholangiohepatitis, other infection
- Taylor treatment to your patients needs, consider:
  - GI meds
  - Pain
  - Antibiotics
  - Nutrition

Gastrointestinal Support

- Nausea, vomiting:
  - Maropitant
  - Ondansetron
  - Metoclopramide
- Gastroprotectants:
  - Pantoprazole
  - Sucralfate
- Appetite stimulants:
  - Mirtazapine
  - Capromorelin
- Nasogastric tube to reduce gastric residual volume?

Acid reducers: What are you treating? Remember that stomach pH is protective against infection, use these if you have strong suspicion for ulceration, otherwise this may not be beneficial

Pain Control

- Gabapentin
  - Use with caution in very old patients or kidney disease
  - May cause sedation (can be profound) but unlikely to cause/exacerbate GI upset
- Opioids: May exacerbate or cause ileus, may cause respiratory changes
  - Butorphanol is more sedating than analgesic
  - Buprenorphine binds strongly to receptors and lasts a long time, may interfere with our ability to escalate pain control
  - Fentanyl is short acting (needs CRI), titratable and less likely to cause ileus and vomiting
  - Methadone: less nausea/vomiting than hydro, just as much ileus
  - Hydromorphone: GI side effects common
- Anxiety meds
  - Remember that pain is about perception, they may hurt worse if they are stressed out in the hospital than they would at home
  - Gabapentin: better anxiolytic in cats than dogs
  - Trazodone

Acepromazine is not an anxiolytic!! May also cause hypotension in this patient population.

Antibiotics

- UTIs:
  - 20% of dogs with DKA had positive growth aerobic culture despite lack of pyuria (Ettinger, Feldman, Cote, 2017)
  - Remember that a very dilute urine sample isn't going to have high yield of cells and debris on urine sediment, don't rely on these to rule out infection
  - Treat the treatable while waiting on confirmation
- Cholangiohepatitis?
- Pancreatitis?

We treat the treatable, if there is concern for a UTI, start the antibiotics while waiting for your culture results. A 3-5 day course of Unasyn or ampicillin is not likely to cause major problems. Keep in mind that oral antibiotics may exacerbate your GI upset or appetite, so start with IV when possible to do so safely.

UTI: start with amoxicillin/ampicillin for first time UTIs, may use fluroquinolones in cats with bacterial rods (be **very** careful with IV enro in cats!!, give pradofloxacin when able to give PO)
Cholangiohep: Unasyn/enro (or maybe Unasyn/metro)
Panc: most published reports show no infection, possible that we're not getting the right sample or using the right culture media, use your best judgement on if this is necessary (probably worth trying on the more severe cases), similar choice to cholangiohep

Nutrition

- Get them eating
  - Prolonged inappetence should be avoided, use enteral nutrition via feeding tubes if necessary
    - Start slow (1/4th of RER?) and increase slowly as tolerated
    - Some food is better than no food
    - Parenteral nutrition is an option, but may complicate electrolytes/glycemia treatment/monitoring
- Eating is more important than what they eat
- Offer food frequently, transition to meal feeding with insulin only after ketosis has resolved and they are eating reliably (dogs only)
- Transition to prescription diets if able after the patient is eating reliably again at home, remember that comorbidities take precedence

Allow free access to water if patients are neurologically appropriate and not causing regurgitation by drinking excessively. If they are drinking to this point, still offer PO but limit the amount in one sitting!
If your patient is drinking excessively despite IV fluids, you likely aren't meeting their fluid needs!

Nursing Care

- Frequent walks
  - May tire easily, consider gurneys or carrying small patients
  - May need frequent bedding changes if too sick to go out
  - Consider urinary catheters or rectal foley catheters for very depressed patients
- Recumbency
  - Physical therapy?
- Monitoring
  - Mentation
  - Pain
  - Respiratory changes

Remember that **you can't manage what you don't measure**
- record positioning and mentation frequently so you can document that they are able to move themselves around appropriately and can identify patients that need more interventions!
  - If they're sick enough that you're having to flip them, they could benefit from PROM
- Train your nurses what to look for and listen to them when they come to you with concerns, they are an invaluable resource in the ICU

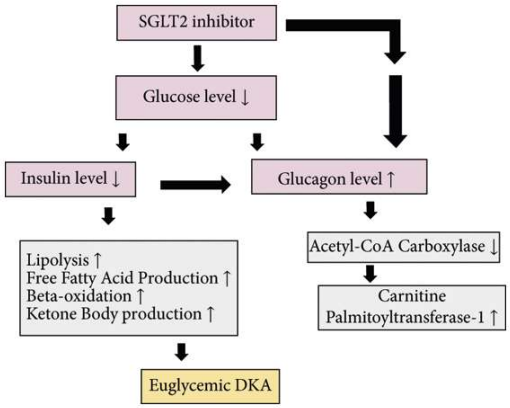
Monitoring

- Vitals (TPR, weight)
- BG
- Electrolytes: Potassium, Phosphorus, Magnesium, Sodium
- PCV/TS
- Blood pressures
- Ketones
- Dehydration
- Osmolality?

BHOB concentration decrease faster than AcAc with treatment and resolution of acidemia, remember that how your measuring may change how you interpret

Euglycemic Diabetic Ketoacidosis

- DKA in patients with 'near normal or lower than anticipated' blood glucose ≤200-250 mg/dL
- Known complication of SGLT2 inhibitors in humans
  - Used to improve glycemic control by causing ↑ glucosuria
- 2022 pilot study of bexagliflozin in cats found decreased insulin dose requirement and decreased mean [BG] measured (Benedict, Mahoney, McKee, & Bergman, 2022)



(Wojtas, Rasarmos, & Naddaf, 2023)

Bexacat: 2022 pilot study found decreased insulin dose requirement and decreased mean [BG] measured by serial inpatient sampling over a 10h period on day 0, 14, 28. Insulin was discontinued in 2 cats, no episodes of hypoglycemia and mild adverse effects reported. ***ONLY HAD 5 CATS***

Another labeled option in the same drug class is Senvelgo (velagliflozin), this one is liquid instead of tablets

We aren't recommending these medications be used. There is concern that the clients that are unable to given injections are less likely to be compliant with the very aggressive monitoring necessary to make sure these are being utilized safely and the complications associated with these are very severe.

Bexacat (bexagliflozin) tablets

- **Field study:** 72/84 cats completed the study. **2 cases of euglycemic DKA**, 3 cases of DKA, 2 hepatic lipidosis in the adverse reactions. 9 serious adverse reactions reported, 3 cats died or were euthanized. 2 of the 3 became sick within 5 doses. One of the 3 developed euglycemic DKA and hepatic lipidosis and was euthanized because it didn't respond despite treatment. Another of the 3 died despite supportive treatment for hepatic lipidosis.
- **Pilot study:** 89 cats, 6 died, **2 euglycemic DKA**, 2 DKA, 6 hepatopathy cases, 2 hemolytic anemias. Deaths were from necrotizing pancreatitis and abscessation, pancreatitis and hepatic lipidosis, euglycemic DKA and severe hepatic lipidosis, pancreatitis and hepatic abscesses, DKA, and 1 QOL concern (persistent PU/PD)
- **Extended Field Use Study:** 125 cats, 49 were withdrawn from the study due to adverse reactions, severe adverse reactions, death/euthanasia, lack of effectiveness, suspected remission, withdrawal of owner consent, or lost to follow up. 20 serious adverse reactions were documented, all resulting in death or euthanasia – **8 euglycemic DKA**, 4 DKA, 5, hepatic lipidosis, 3 pancreatic necrosis, etc.

(Elanco)

- **JAVIM 2022: Safety and effectiveness of the sodium-glucose cotransporter inhibitor bexagliflozin in cats newly diagnosed with diabetes mellitus:** 84 cats enrolled, 8 cats experienced serious adverse events (35 SAEs reported in study), 3 diet or were euthanized, **3 euglycemic DKA**

- From the drug inserts: Extended field use study: 16% mortality (4% and 6% for the others respectively)

Bexacat (bexagliflozin) tablets

Monitoring

- Sudden onset of hyporexia/anorexia, lethargy, dehydration, or weight loss in cats receiving Bexacat should prompt immediate discontinuation of Bexacat and assessment for diabetic ketoacidosis, regardless of blood glucose level.
- During treatment with Bexacat, blood glucose, fructosamine, serum β-hydroxybutyrate (BHBA), serum feline pancreas-specific lipase (fPL), liver parameters, serum cholesterol and triglycerides; and body weight and clinical signs should be routinely monitored.
  - Increasing or persistently elevated feline pancreas-specific lipase or liver parameters should prompt further evaluation for pancreatitis and/or hepatic disease and consideration for discontinuing Bexacat.
  - BHBA is the predominate ketoacid in diabetic ketoacidosis, Bexacat should be discontinued if a notable reduction in BHBA is not observed after initiation of Bexacat, or if BHBA persistently rises after an initial reduction.
  - Cats with increasing or persistently elevated cholesterol and triglyceride levels may be at an increased risk for developing diabetic ketoacidosis or euglycemic diabetic ketoacidosis.
  - Bexacat should be discontinued if poor glycemic control, as described below, develops.
- During the first 8 weeks after initiation of Bexacat, assessment of glycemic control and clinical improvement should be evaluated.
  - A physical examination, an 8-hour blood glucose curve, serum fructosamine and body weight should be assessed at 2, 4 and 8 weeks.
  - Cats demonstrating poor glycemic control, including weight loss, an average blood glucose concentration from an 8-hour blood glucose curve ≥ 250 mg/dL, and/or a fructosamine indicating poor glycemic control should be closely monitored.
  - Bexacat should be discontinued, and initiation of insulin considered in cats demonstrating poor glycemic control, as described above, at 8 weeks.
- Cats may present with diabetic ketoacidosis and a normal blood glucose concentration (euglycemic diabetic ketoacidosis). Delay in recognition and treatment of diabetic ketoacidosis and euglycemic diabetic ketoacidosis may result in increased morbidity and mortality.
- Development of diabetic ketoacidosis and euglycemic diabetic ketoacidosis requires the following actions:
  - Discontinuation of Bexacat
  - Prompt initiation of insulin therapy
  - Administration of dextrose or other carbohydrate source, regardless of blood glucose concentration
  - Appropriate nutritional support should be promptly initiated to prevent or treat hepatic lipidosis.

For more information refer to **CONTRAINDICATIONS** and **WARNINGS.**

WARNING: DIABETIC KETOACIDOSIS/EUGLYCEMIC DIABETIC KETOACIDOSIS

- **Cats treated with Bexacat may be at an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis (see Adverse Reactions). As diabetic ketoacidosis and euglycemic diabetic ketoacidosis in cats treated with Bexacat may result in death, development of these conditions should be treated promptly, including insulin administration and discontinuation of Bexacat (see Monitoring).**
- **Due to the risk of developing diabetic ketoacidosis or euglycemic diabetic ketoacidosis, do not use Bexacat in cats with diabetes mellitus who have previously been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus (see Contraindications).**
- **Bexacat should not be initiated in cats with anorexia, dehydration or lethargy at the time of diagnosis of diabetes mellitus or without appropriate screening tests (see Animal Safety Warnings).**

- “Do not use Bexacat in cats with diabetes mellitus who have previous been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus. The use of Bexacat in cats with insulin-dependent diabetes mellitus, or the withdrawal of insulin and initiation of Bexacat, is associated with an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis and death.”

Remember that we aren’t monitoring at what point these patients are no longer producing sufficient insulin to meet their needs!

What cases need to transfer to a referral center?

- To Internal Medicine:
  - Complicated DM
    - Suspected insulin resistance
    - Poor or variable glycemic control
    - Significant comorbidities
- To Emergency Critical Care:
  - Any DKA
    - Exceptions?
      - Diabetic Ketosis with no Acidemia – are they eating? May not need referral
      - Potentially early/mild DKA at time of diagnosis –depends on your hospital's capabilities
  - Euglycemic DKA
- Owners that can't afford referral, what is most important?
  - Fluids, electrolytes, insulin, get them eating!
  - Recheck frequently!

Prognosis of DKA: Mortality 16-30% in dogs, 26-41% in cats, recurrence rates ~42% (Gal & Odunayo, 2023);
- 2 most important factors predicting mortality in humans was severe concurrent illness and blood pH <7.0 (Ettinger, Feldman, & Cote, 2017)

DKA Exceptions:
- If you have an early DKA (very mild acidemia) without major electrolyte derangements that is still eating and reasonably well hydrated you **may** be able to safely treat them on an outpatient basis **with frequent rechecks**, but this depends on your hospital's capabilities and comfort level.

Remember that you can call to talk to the ECC team or email the Internal Medicine service (internalmedicine@capecodvetspecialists.com) if you have a DKA or DM case respectively that you aren't sure about. If it needs referral, we can let you know how to prep your owners, or if they can't come to us for care, we may be able offer guidance on how you can manage the case yourselves.

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QUESTIONS?

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