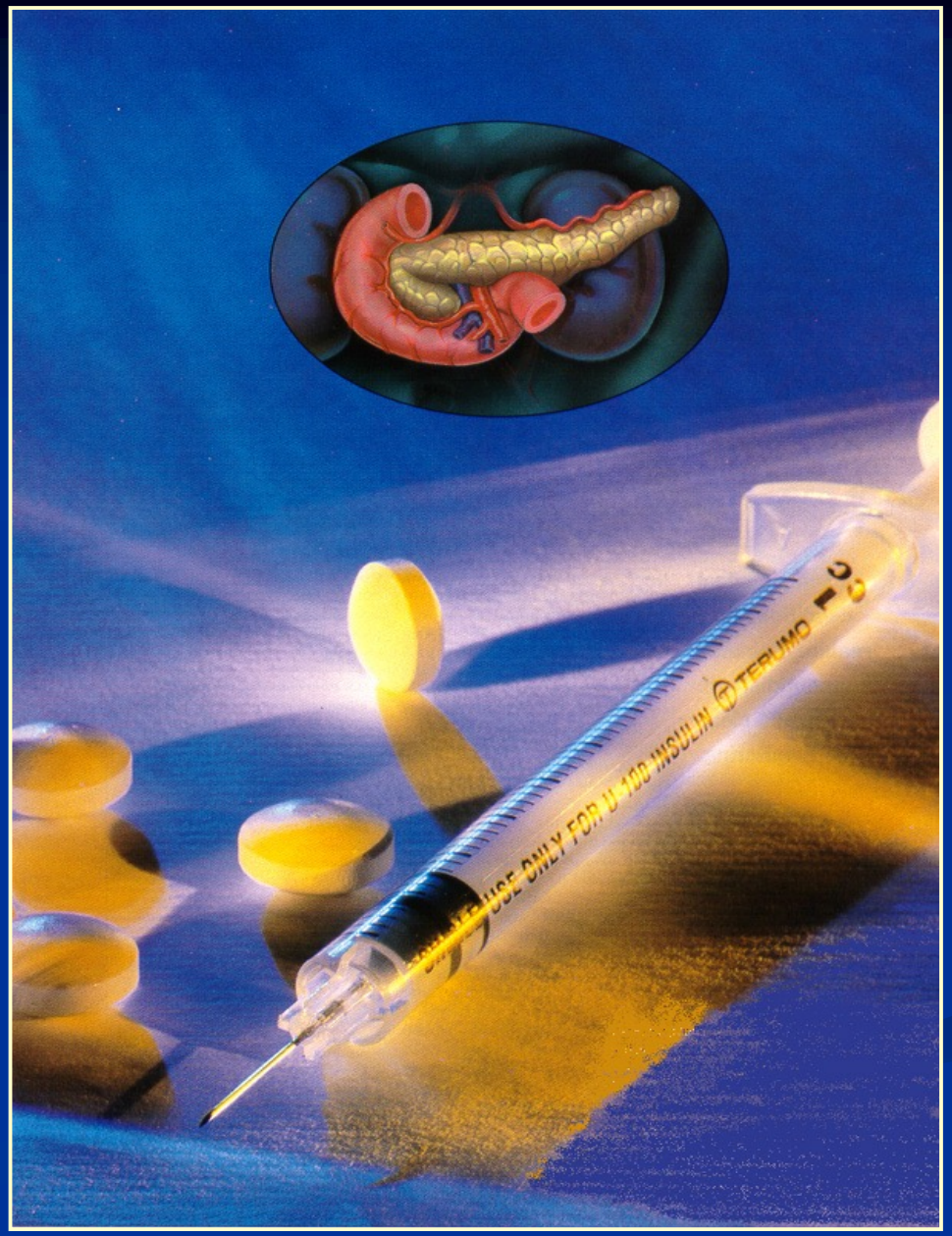
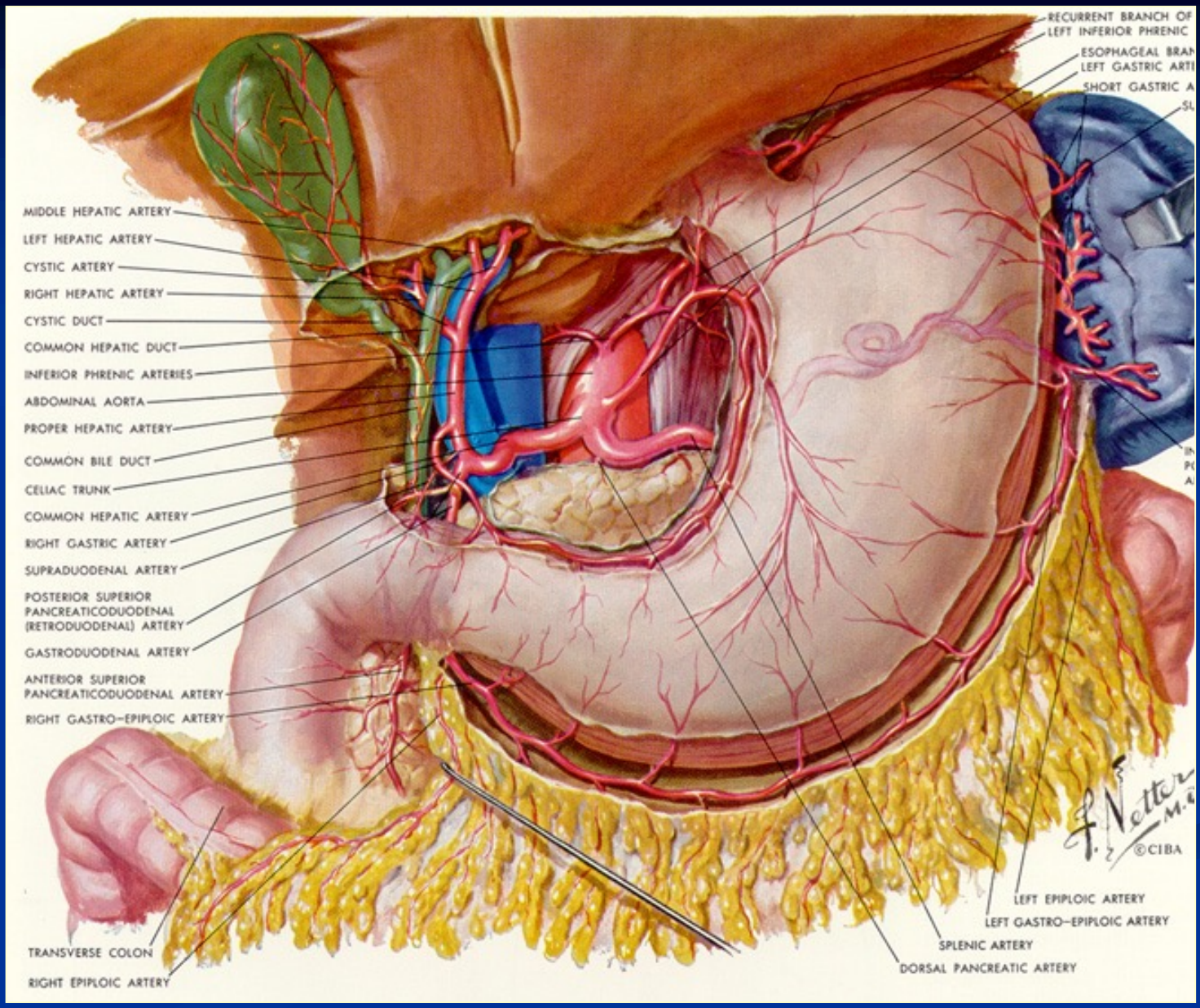
Pharmacologic Management of Diabetes Mellitus



MSPA Program
Southern California University of Health Science

ANATOMY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LEFT INFERIOR PHRENIC
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SHORT GASTRIC A
MIDDLE HEPATIC ARTERY
LEFT HEPATIC ARTERY
CYSTIC ARTERY
RIGHT HEPATIC ARTERY
CYSTIC DUCT
COMMON HEPATIC DUCT
INFERIOR PHRENIC ARTERIES
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PROPER HEPATIC ARTERY
COMMON BILE DUCT
CELIAC TRUNK
COMMON HEPATIC ARTERY
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RIGHT GASTRO–EPIPLOIC ARTERY
TRANSVERSE COLON
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SPLENIC ARTERY
DORSAL PANCREATIC ARTERY
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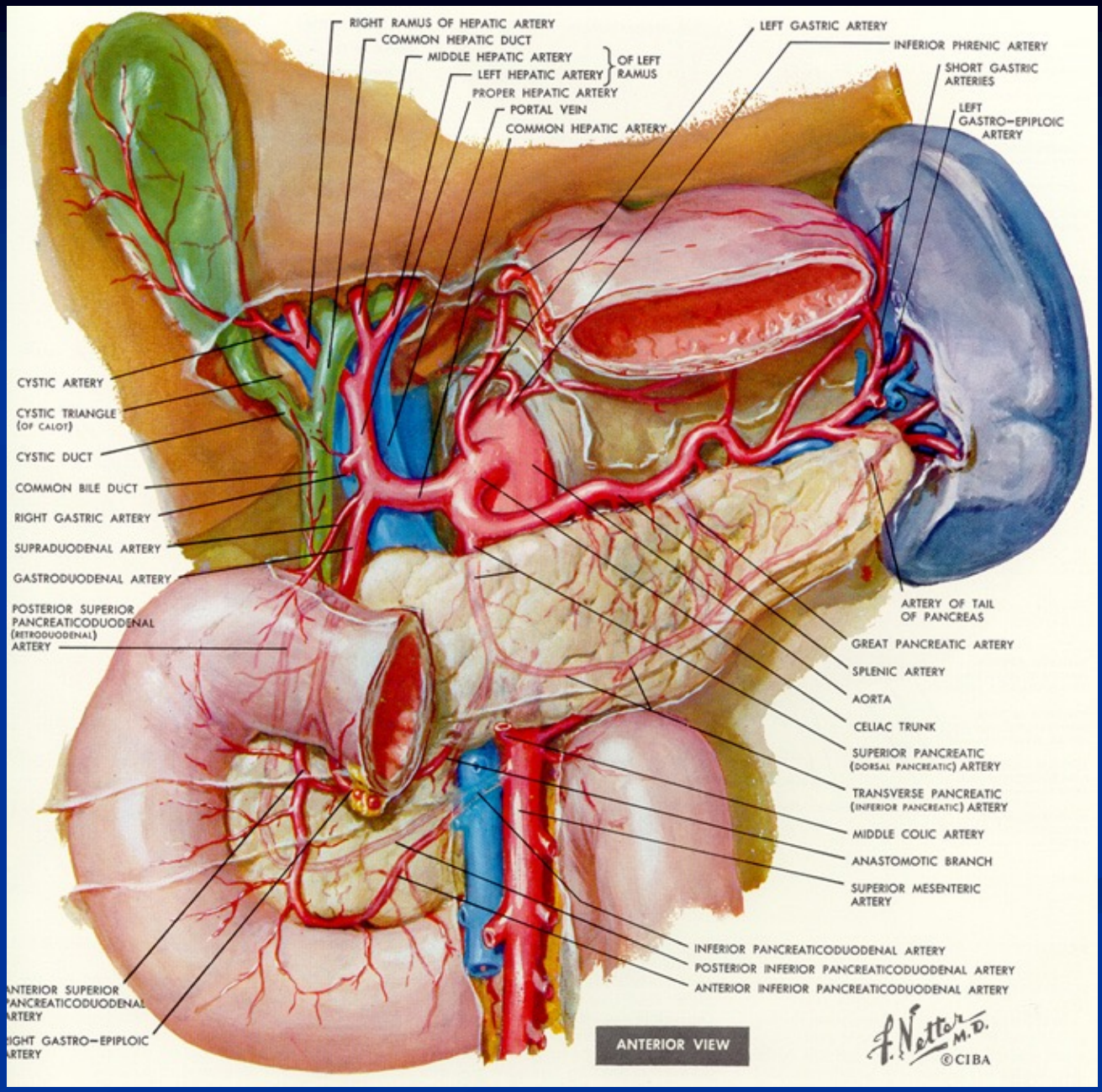
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LEFT GASTRIC ARTERY
INFERIOR PHRENIC ARTERY
SHORT GASTRIC ARTERIES
LEFT GASTRO-EPIPLOIC ARTERY
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SUPERIOR PANCREATIC (DORSAL PANCREATIC) ARTERY
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RIGHT GASTRO-EPIPLOIC ARTERY
ANTERIOR VIEW
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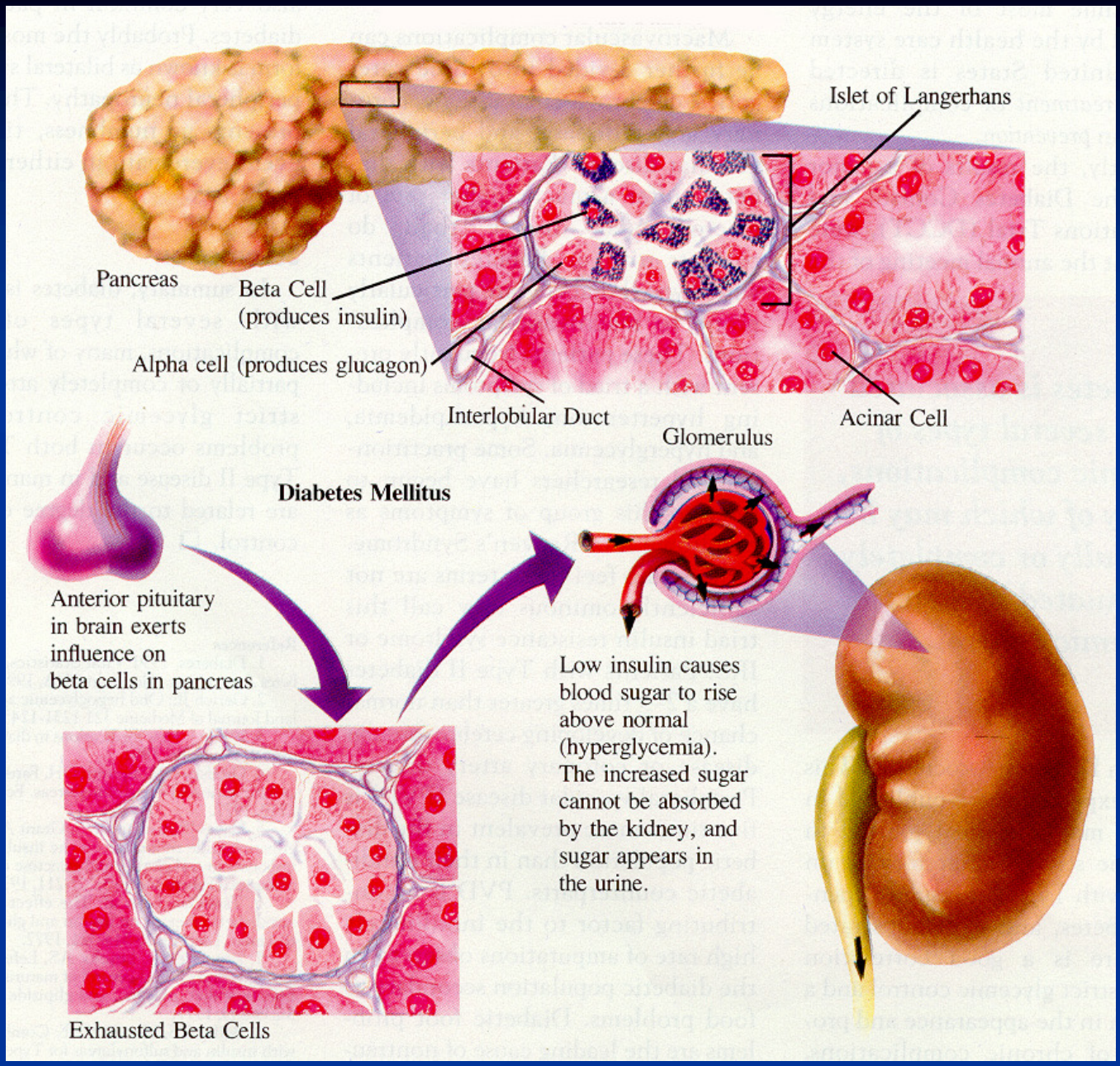
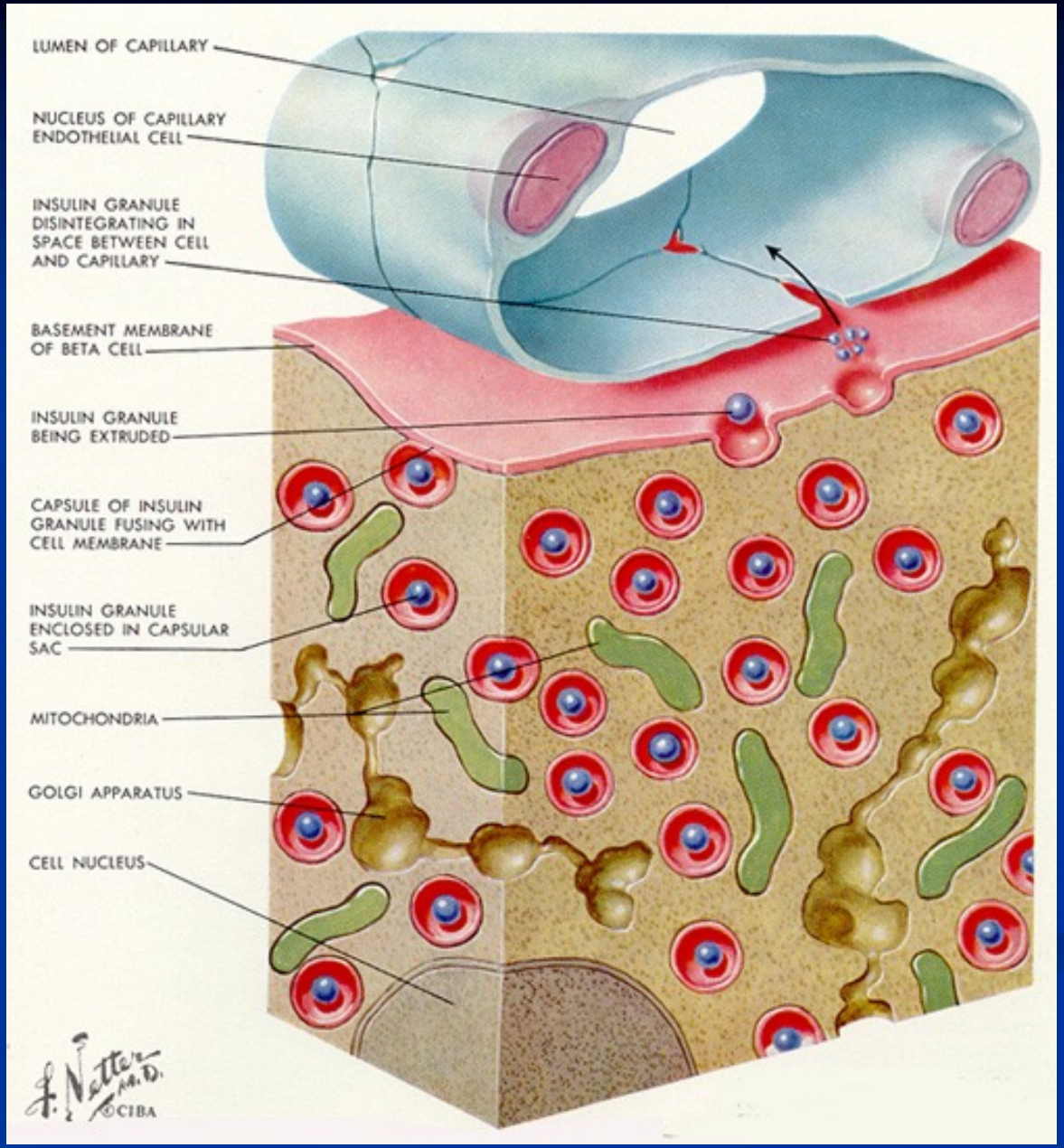
PHYSIOLOGY


Islet of Langerhans
Pancreas
Beta Cell
(produces insulin)
Alpha cell (produces glucagon)
Interlobular Duct
Acinar Cell
Glomerulus
Diabetes Mellitus
Anterior pituitary
in brain exerts
influence on
beta cells in pancreas
Low insulin causes
blood sugar to rise
above normal
(hyperglycemia).
The increased sugar
cannot be absorbed
by the kidney, and
sugar appears in
the urine.
Exhausted Beta Cells

PHYSIOLOGY


LUMEN OF CAPILLARY
NUCLEUS OF CAPILLARY ENDOTHELIAL CELL
INSULIN GRANULE DISINTEGRATING IN SPACE BETWEEN CELL AND CAPILLARY
BASEMENT MEMBRANE OF BETA CELL
INSULIN GRANULE BEING EXTRUDED
CAPSULE OF INSULIN GRANULE FUSING WITH CELL MEMBRANE
INSULIN GRANULE ENCLOSED IN CAPSULAR SAC
MITOCHONDRIA
GOLGI APPARATUS
CELL NUCLEUS
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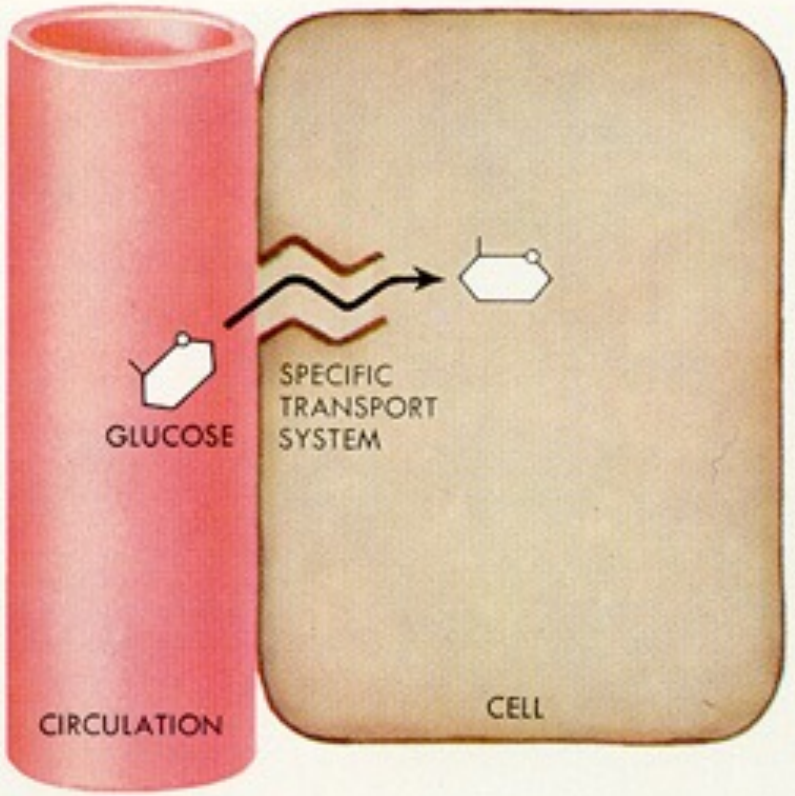
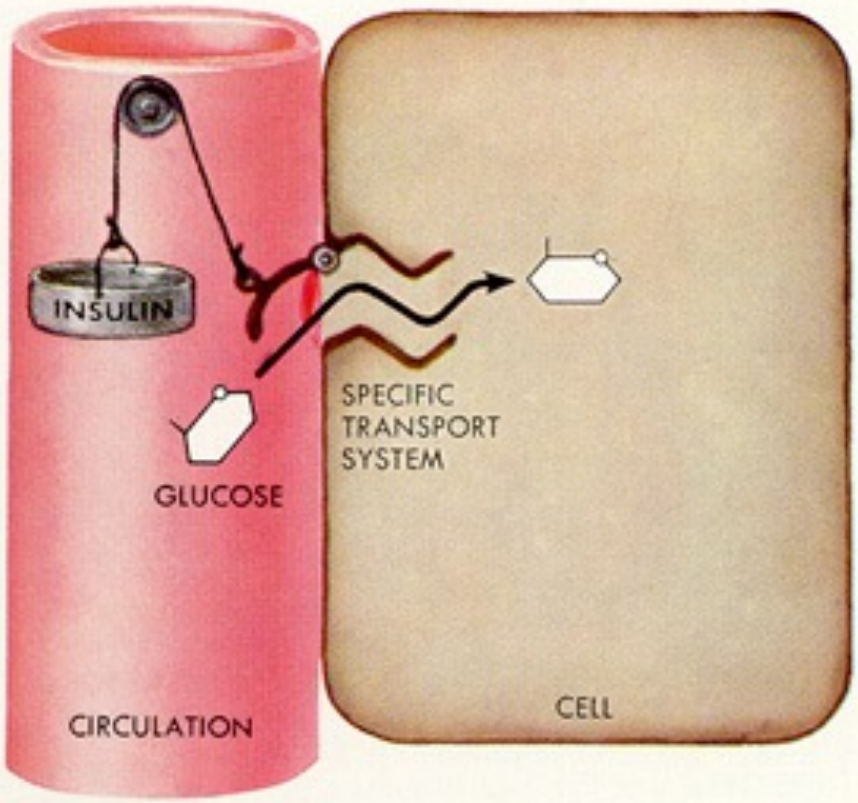
Function of Insulin



RED BLOOD CELLS; NEURONS

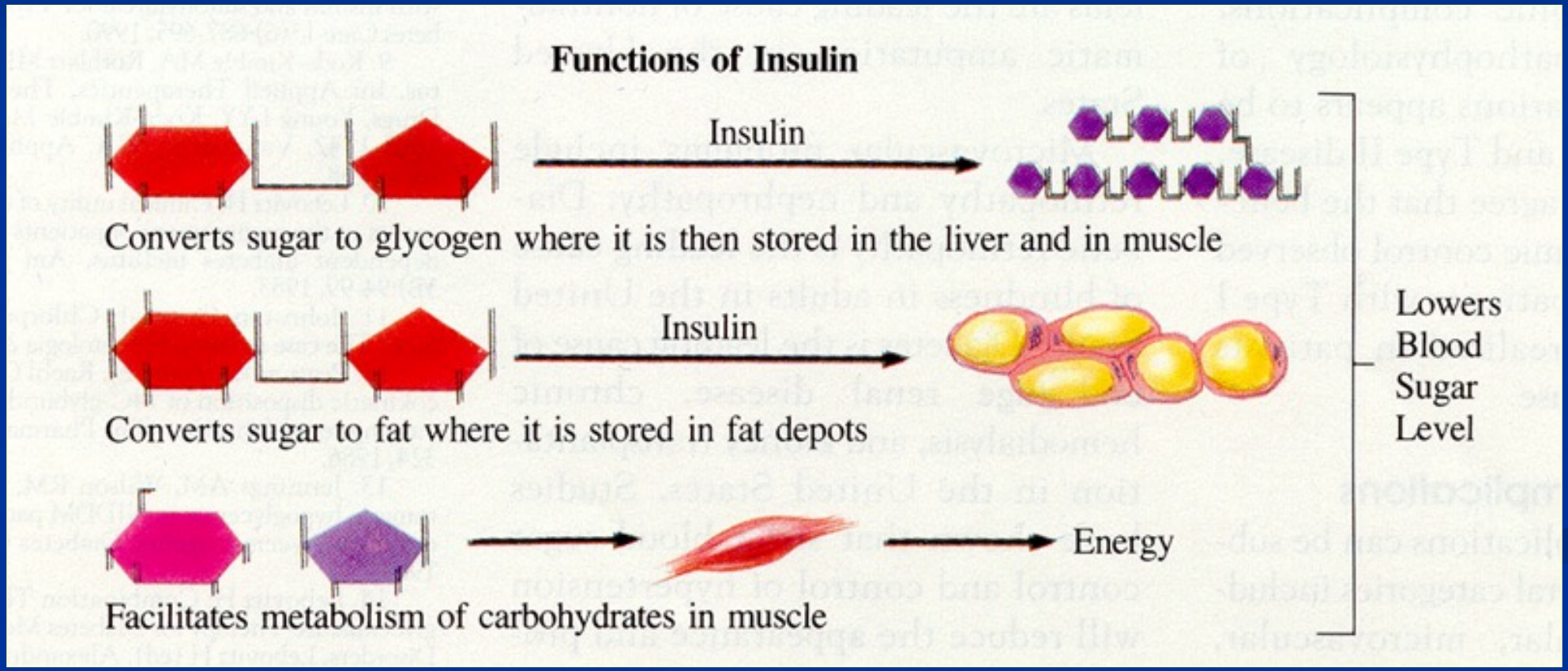
TRANSPORT (ENTRY) SYSTEM SPECIFIC
FOR CERTAIN SUGARS:
INSULIN HAS NO EFFECT ON RATE OF UPTAKE



FAT CELLS; MUSCLE CELLS

SPECIFIC TRANSPORT SYSTEM KEPT
INHIBITED OR COVERED:
INSULIN REMOVES COVER AND THUS
PROMOTES UPTAKE

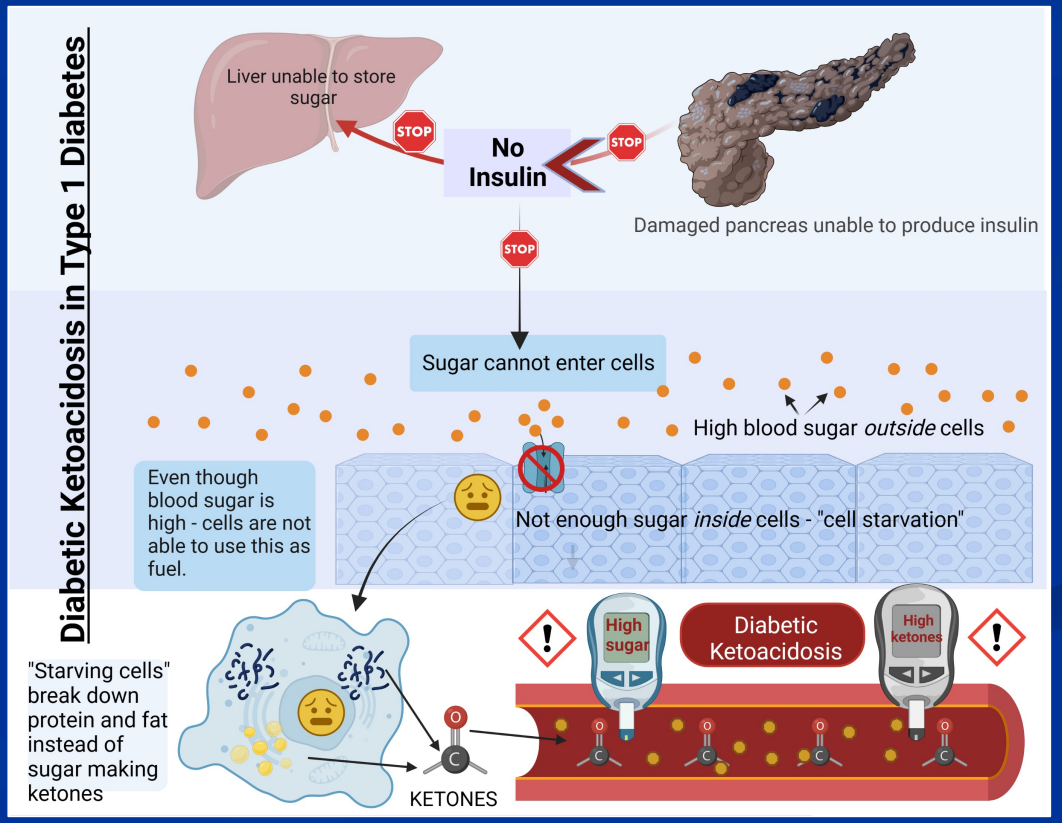
Function of Insulin



I. General Considerations

A. Type I ("Juvenile Onset" or IDDM)

- Type I diabetes represents 5-10% of adult diabetics
- Type I DM is characterized by autoimmune destruction of pancreatic beta cells
  → inability to produce and secrete insulin
  → IDDM
- Type I diabetics are subject to diabetic ketoacidosis (DKA)



I. General Considerations

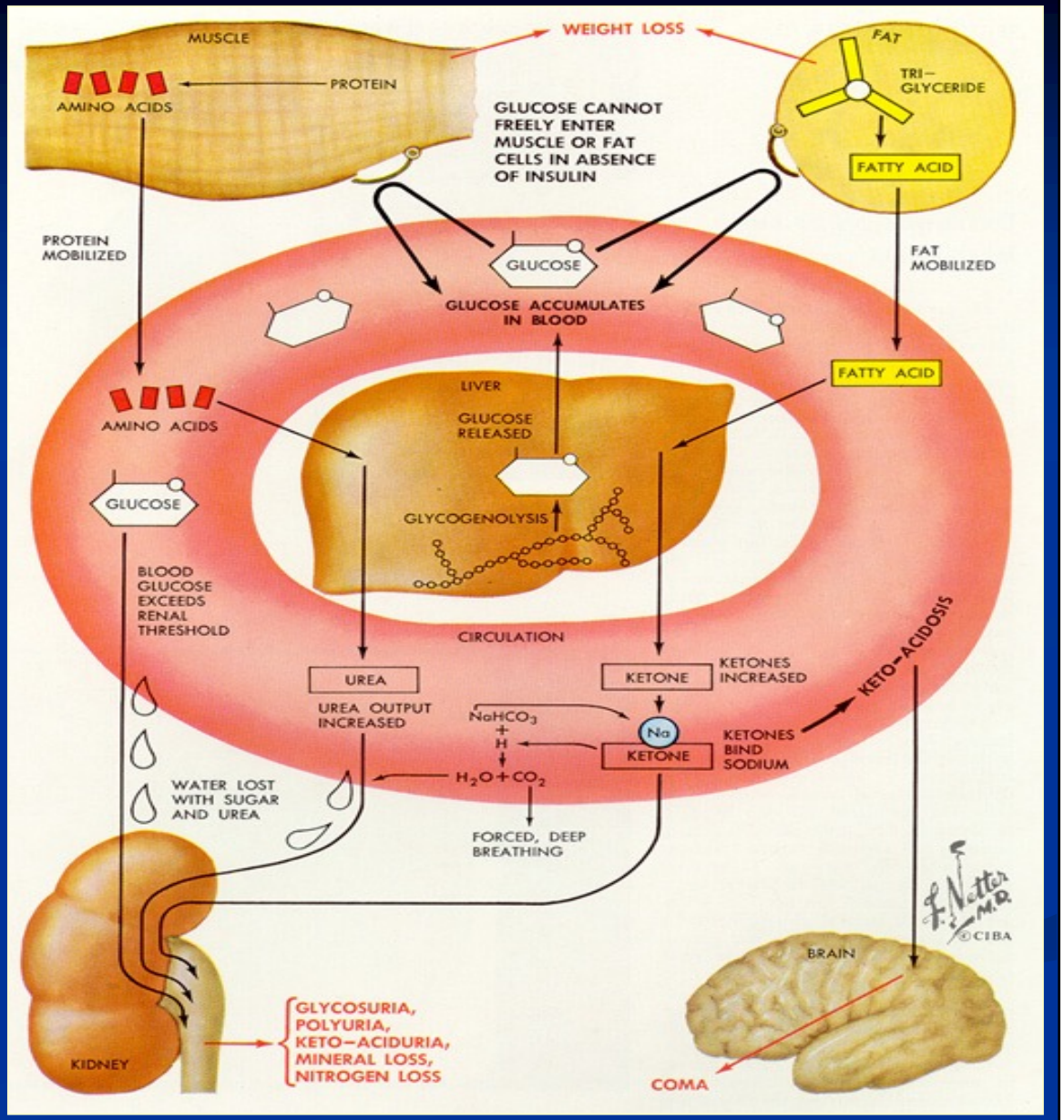
A. Type I DM

- Diabetic Ketoacidosis (DKA)

Diagnostic criteria for DKA

	DKA		
	Mild	Moderate	Severe
Plasma glucose(mg/dl)	More than 250	More than 250	More than 250
Arterial PH	7.25 – 7.30	7.00 – 7.24	Less than 7.00
Serum bicarbonate(mEq/L)	15 - 18	10 - 14	Less than 10
Urine ketones	+ve	+ve	+ve
Serum ketones	+ve	+ve	+ve
Effective serum osmolality(mOsm/kg)	Variable	Variable	Variable
Anion gap	More than 10	More than 12	More than 12
Alteration in sensoria	Alert	Alert / drowsy	Stupor / coma

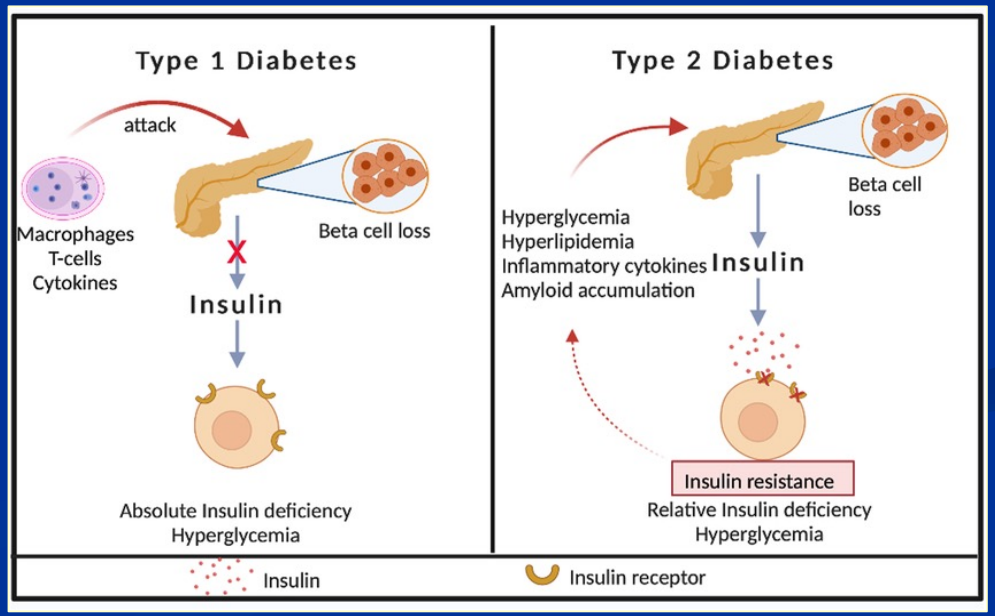
<u>Normal Values</u>
BG: 90-110 mg/dL
pH: 7.35-7.45
Bicarbonate: 21-28 mEq/L



I. General Considerations

B. Type II ("Adult Onset" or NIDDM)

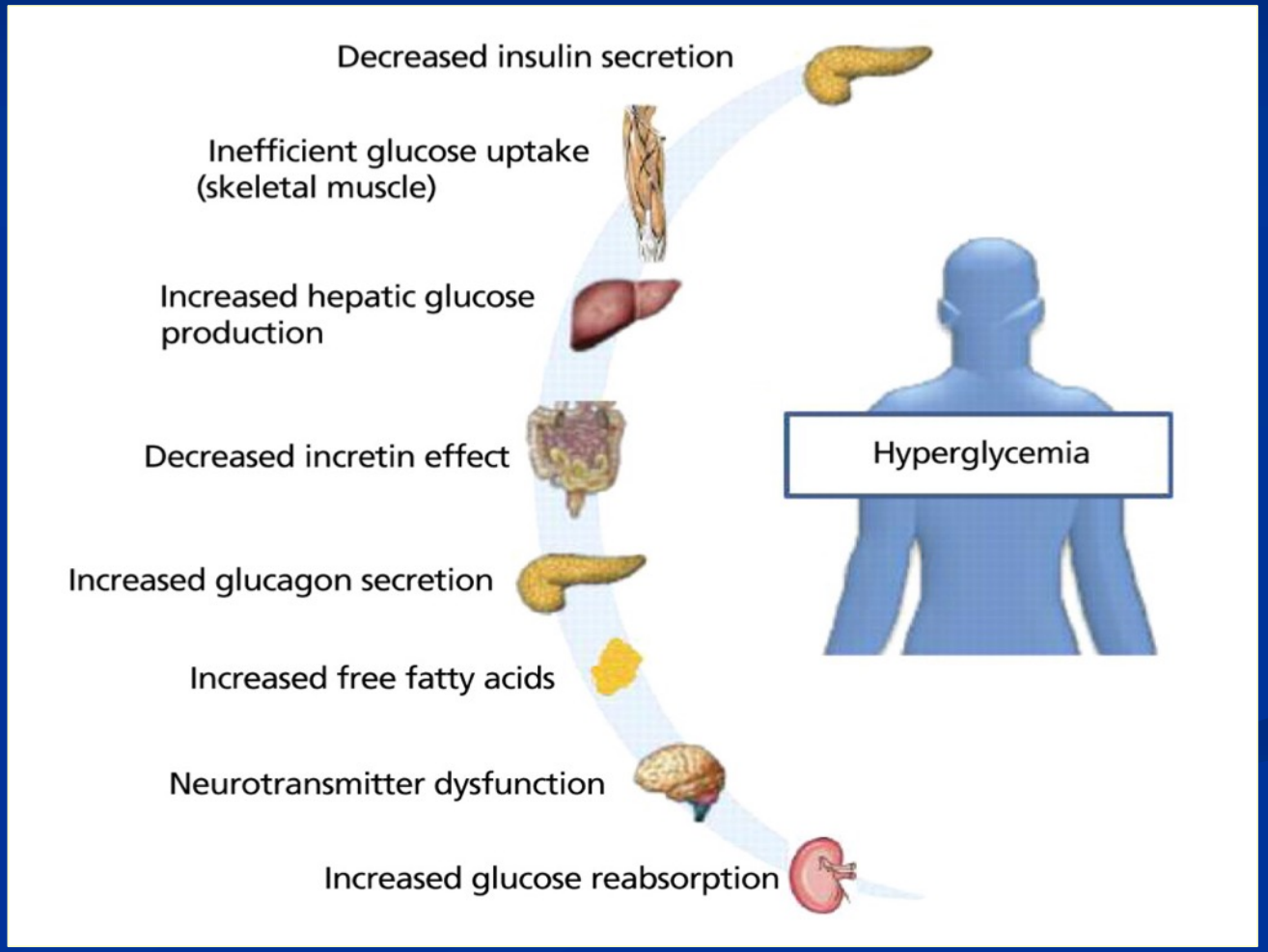
- Type II DM is characterized by a progressive deficiency of insulin secretion and insulin resistance → hyperglycemia.
- Type II diabetics are subject to hyperosmolar hyperglycemic state (HHS) → severe dehydration and obtundation.
- Although DKA is uncommon in Type II DM, it is more likely to occur during acute illnesses (e.g., sepsis, acute MI).



I. General Considerations

B. Type II Diabetes Mellitus (cont.)

- Type II DM is a complex disease involving many pathologic factors …



II. Acute Complications of Diabetes

- Acute Symptoms: polydipsia, polyuria, polyphagia, nocturia, hypoglycemia, fatigue, and blurred vision.
- Type I DM: Diabetic Ketoacidosis (DKA) → Coma
- Type II DM: Hyperosmolar Hyperglycemic State (HHS) → Non-Ketotic Coma

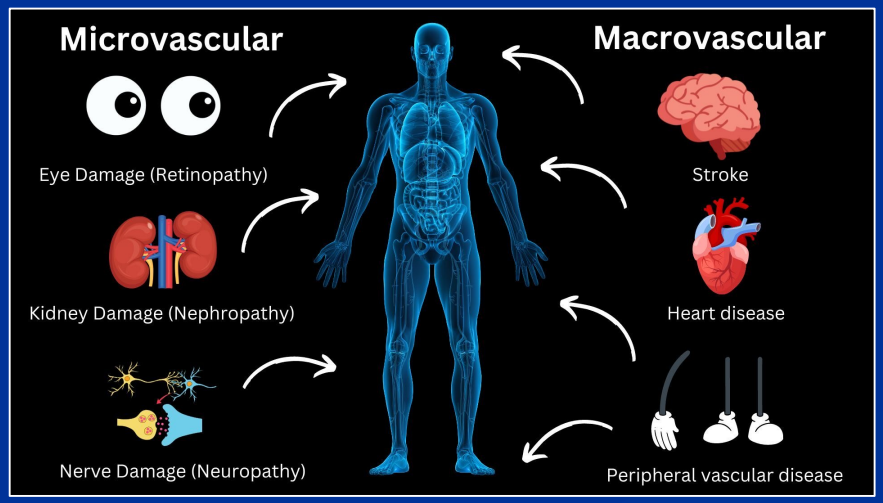
Diagnostic Criteria for Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycemic State (HHS)

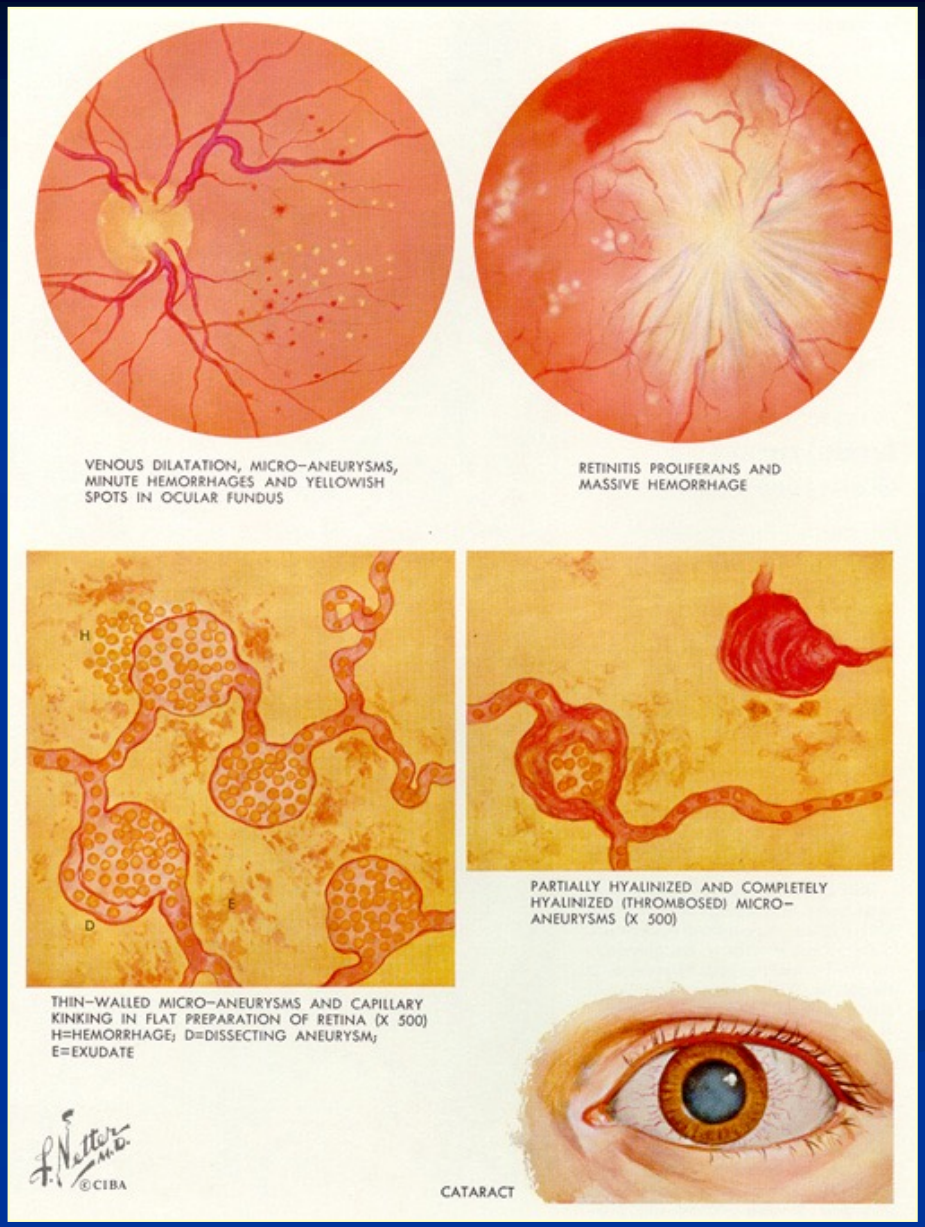
	Diabetic ketoacidosis			*Hyperosmolar hyperglycemic state*
Criterion	*Mild (serum glucose > 250 mg per dL [13.88 mmol per L])*	*Moderate (serum glucose > 250 mg per dL)*	*Severe (serum glucose > 250 mg per dL)*	*Serum glucose > 600 mg per dL (33.30 mmol per L)*
Anion gap*	> 10 mEq per L (10 mmol per L)	> 12 mEq per L (12 mmol per L)	> 12 mEq per L (12 mmol per L)	Variable
Arterial pH	7.24 to 7.30	7.00 to < 7.24	< 7.00	> 7.30
Effective serum osmolality*	Variable	Variable	Variable	> 320 mOsm per kg (320 mmol per kg)
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma
Serum bicarbonate	15 to 18 mEq per L (15 to 18 mmol per L)	10 to < 15 mEq per L (10 to < 15 mmol per L)	< 10 mEq per L (10 mmol per L)	> 18 mEq per L (18 mmol per L)
Serum ketone†	Positive	Positive	Positive	Small
Urine ketone†	Positive	Positive	Positive	Small

III. Chronic Complications of Diabetes Mellitus

A. Microvascular and Macrovascular Disorders

1. Microvascular Disorders: Retinopathy



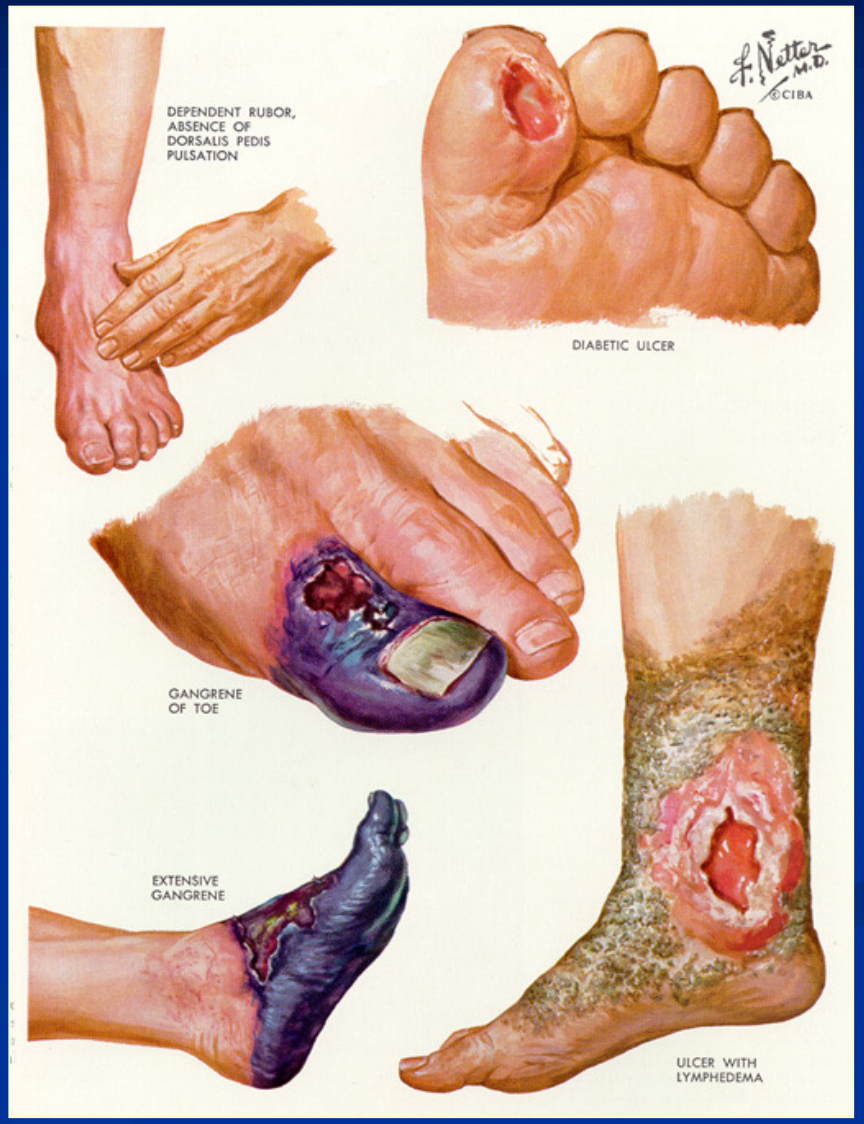


III. Chronic Complications of Diabetes Mellitus (cont.)

A. Microvascular and Macrovascular Disorders

2. Macrovascular Disorders

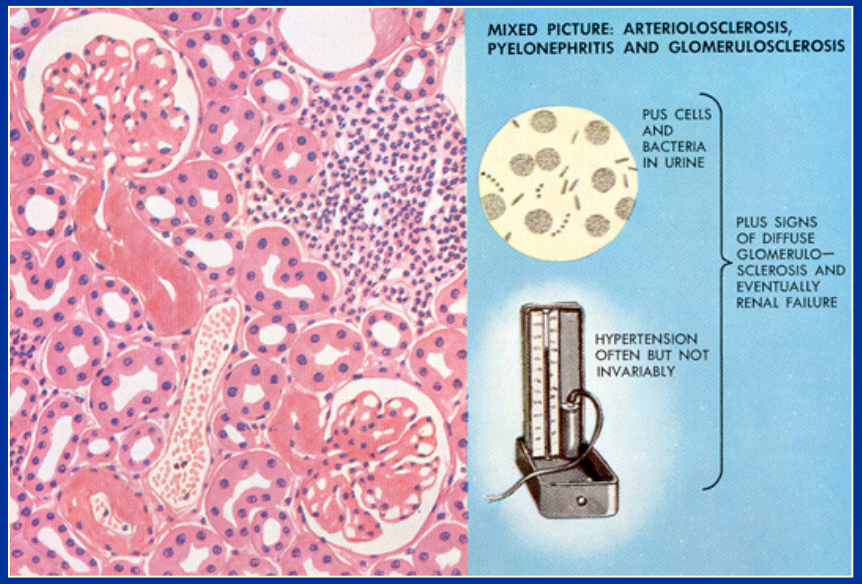
- Cerebrovascular Disease
  → CVA (Stroke)
- Cardiovascular Disease
  → CAD (coronary artery disease) → MI
- Peripheral Vascular Disease
  → Diabetic Foot Infections
  → Gangrenous Extremities
  → Limb Amputations

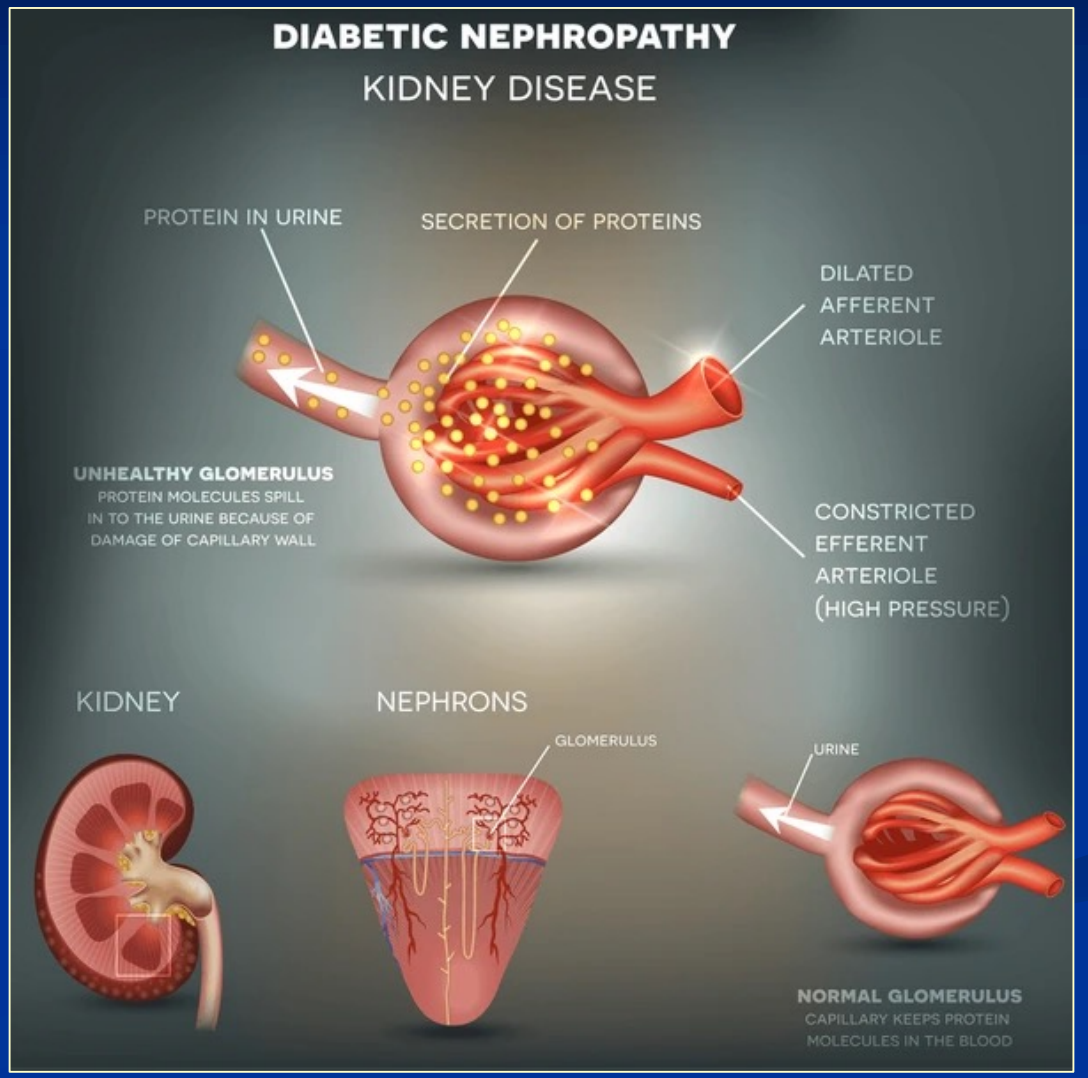


III. Chronic Complications of Diabetes Mellitus (cont.)

B. Kidney Disorders

1. Chronic Kidney Disease (CKD, DKD) →
2. Pyelonephritis ↓

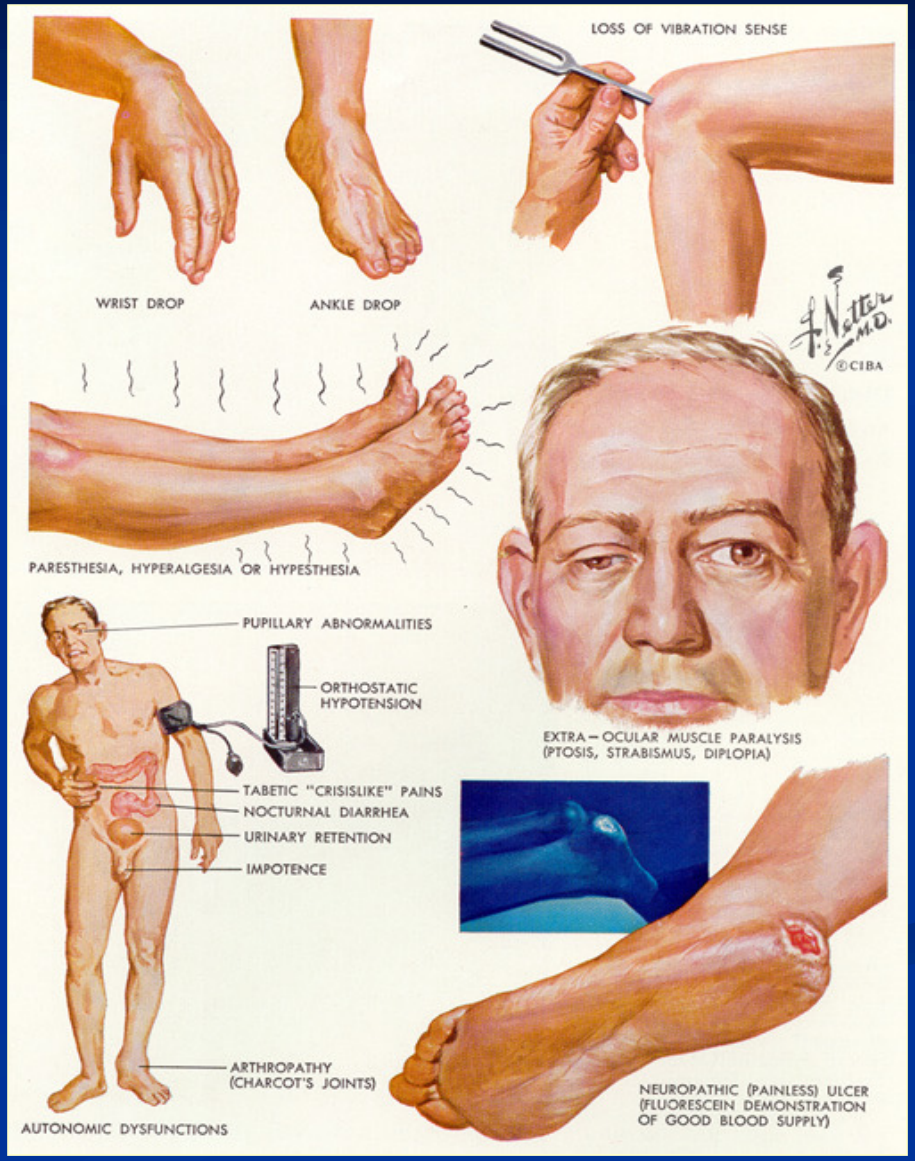




III. Chronic Complications of Diabetes Mellitus (cont.)

C. Diabetic Neuropathy

1. Chronic Neuropathic Pain
2. Paresthesia
3. Orthostatic Hypotension
4. Gastroparesis
5. Diabetic Foot Ulcers



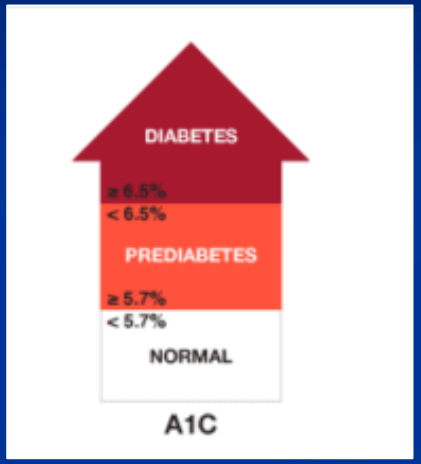
IV. Criteria for Diagnosis of PRE-DIABETES & DIABETES

Criteria for the Diagnosis of PREDIABETES
A1C ≥5.7%, but <6.5% **OR** Fasting plasma glucose ≥100 mg/dL (fasting is no food for at least 8 hours), but <126 mg/dL **OR** Two-hour plasma glucose ≥140 mg/dL during an oral glucose tolerance test, but <200 mg/dL
Criteria for the Diagnosis of DIABETES
A1C ≥6.5% **OR** Fasting plasma glucose ≥126 mg/dL (fasting is no food for at least 8 hours) **OR** Two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test **OR** Symptomatic patients with a random plasma glucose ≥200 mg/dL

IV. Criteria for Diagnosis of Pre-Diabetes and Diabetes (cont.)

- A1C may also be reported as "Estimated Average Glucose (eAG)"

A1C	eAG	
%	mg/dL	mmol/L
6	126	7.0
6.5	140	7.8
7	154	8.6
7.5	169	9.4
8	183	10.1
8.5	197	10.9
9	212	11.8
9.5	226	12.6
10	240	13.4



V. Treatment: Lifestyle Modifications

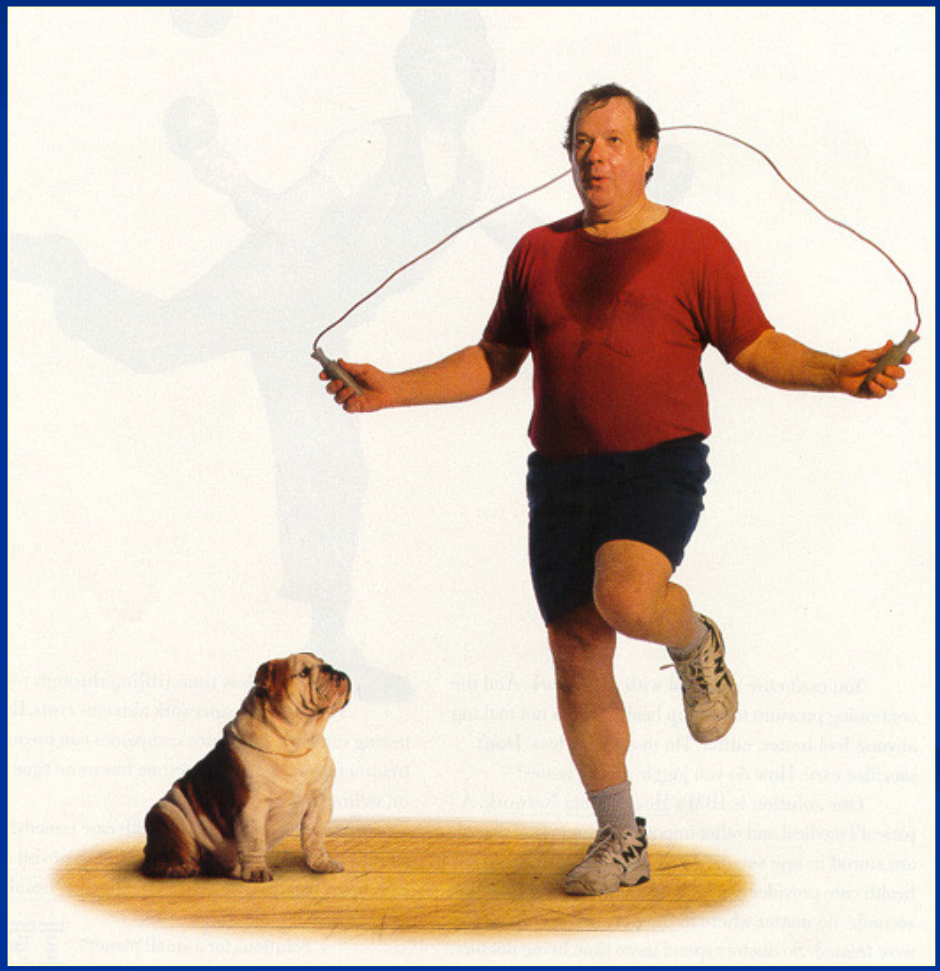
A. Nutrition

B. Timing of Meals

C. Body Weight Considerations

D. Exercise

   1. Exercise improves utilization of glucose.
   2. Exercise improves insulin utilization.
   3. Exercise improves lipid profile.



V. Treatment: Lifestyle Modifications

E. BEE (basal energy expenditure) formula allows us to estimate daily caloric requirements.

Sample Caloric Requirement (BEE) Calculation for Stressed Patients

Female: 655 + (9.6 x wt. in kg) + (1.85 x ht. in cm) – (4.7 x age)

Male: 66 + (13.7 x wt. in kg) + (5.00 x ht. in cm) – (6.8 x age)

Sample Calculation (based on patient-specific parameters: ht, wt, age, and disease state)

S.Y. is a 64 year-old female patient with major sepsis. Calculate her caloric requirement based on her pathologic condition. Her height is 5'4" and body weight is 140 pounds.

Conversion Factors:

- body weight from pounds to kg. : 140 lbs / 2.2 = 63.64 kg
- height from inches to cm. : 5'4" = 64 inches x 2.54 = 162.56 cm

BEE = 655 + (9.6 x **63.64**) + (1.85 x **162.56**) – (4.7 x **64**)

= (655 + 610.94 + 300.74) – (300.8)

= 1265.88 kcal / day

Multiply the BEE value by the appropriate "disease stress factor", which provides additional calories to account for the degree of physiologic stress (based on increased metabolic requirement during pathologic condition – i.e., major sepsis).

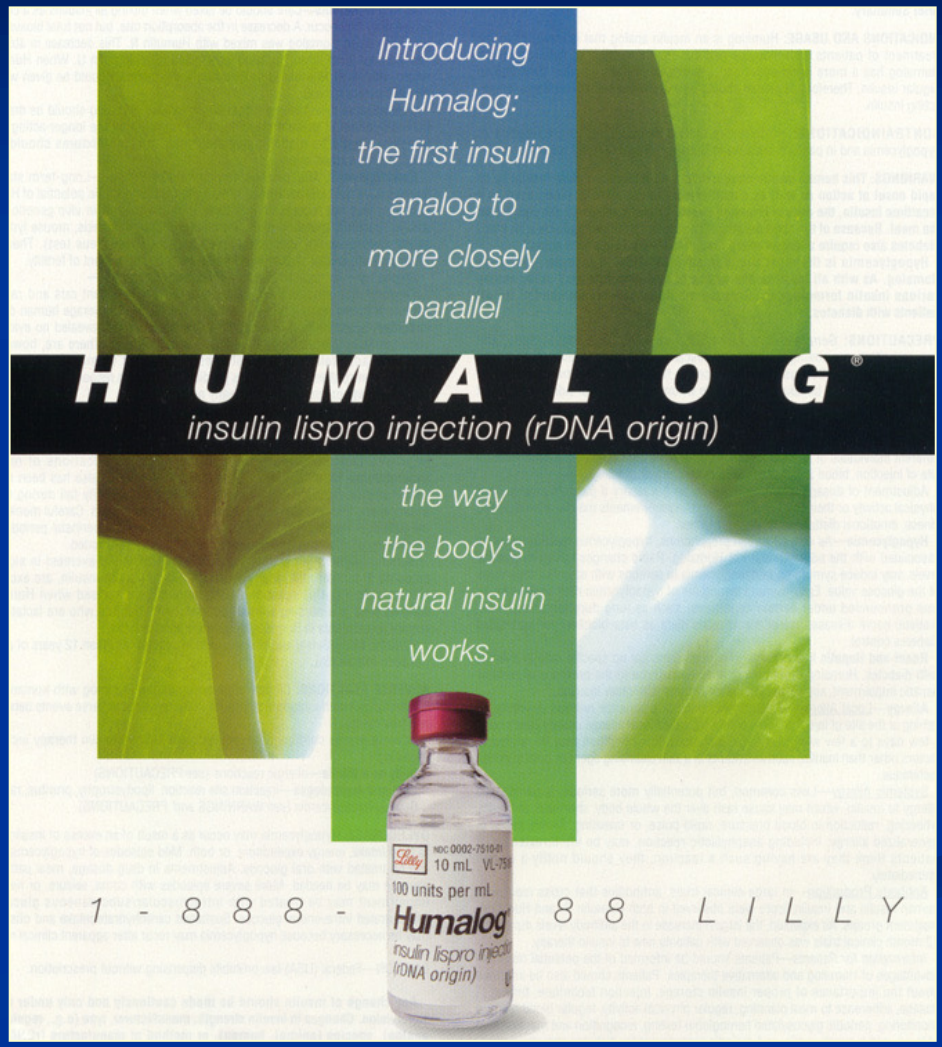
BEE for major sepsis = 1.5 x 1265.88

Answer → 1898.82 kcal / day

VI. Pharmacologic Management of IDDM

A. Insulin Products

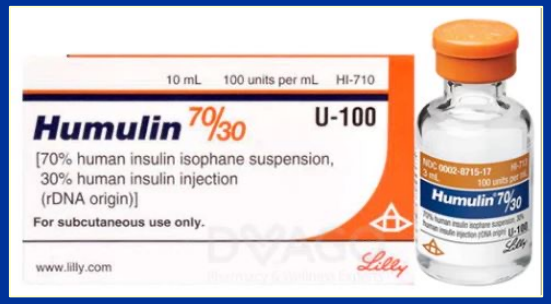
1. Rapid-Acting Insulin: Humalog (Lispro)
   - onset: 10 - 15 min
   - peak: 45 min - 1 hour
   - duration: 2 - 4 hours



VI. Pharmacologic Management of IDDM (cont.)

A. Insulin Products (cont.)

2. Short-Acting Insulin: Regular Insulin (Humulin R)
    - onset: 30 - 60 min → peak: 2 - 4 hours
    - duration: 4 - 8 hours
3. Intermediate-Acting Insulin: NPH (Humulin N)
    - onset: 2 – 4 hours → peak: 4 – 10 hours
    - duration: 10 – 18 hours



VI. Pharmacologic Management of IDDM (cont.)

A. Insulin Products (cont.)

3. Long-Acting Insulin:

a. Detemir (Levemir) → BID

- onset: 2 – 3 hours
- peak: 6 – 8 hours
- Duration: 5.7 – 23.2 hours

b. Glargine (Lantus) → Q24H (mostly) / BID

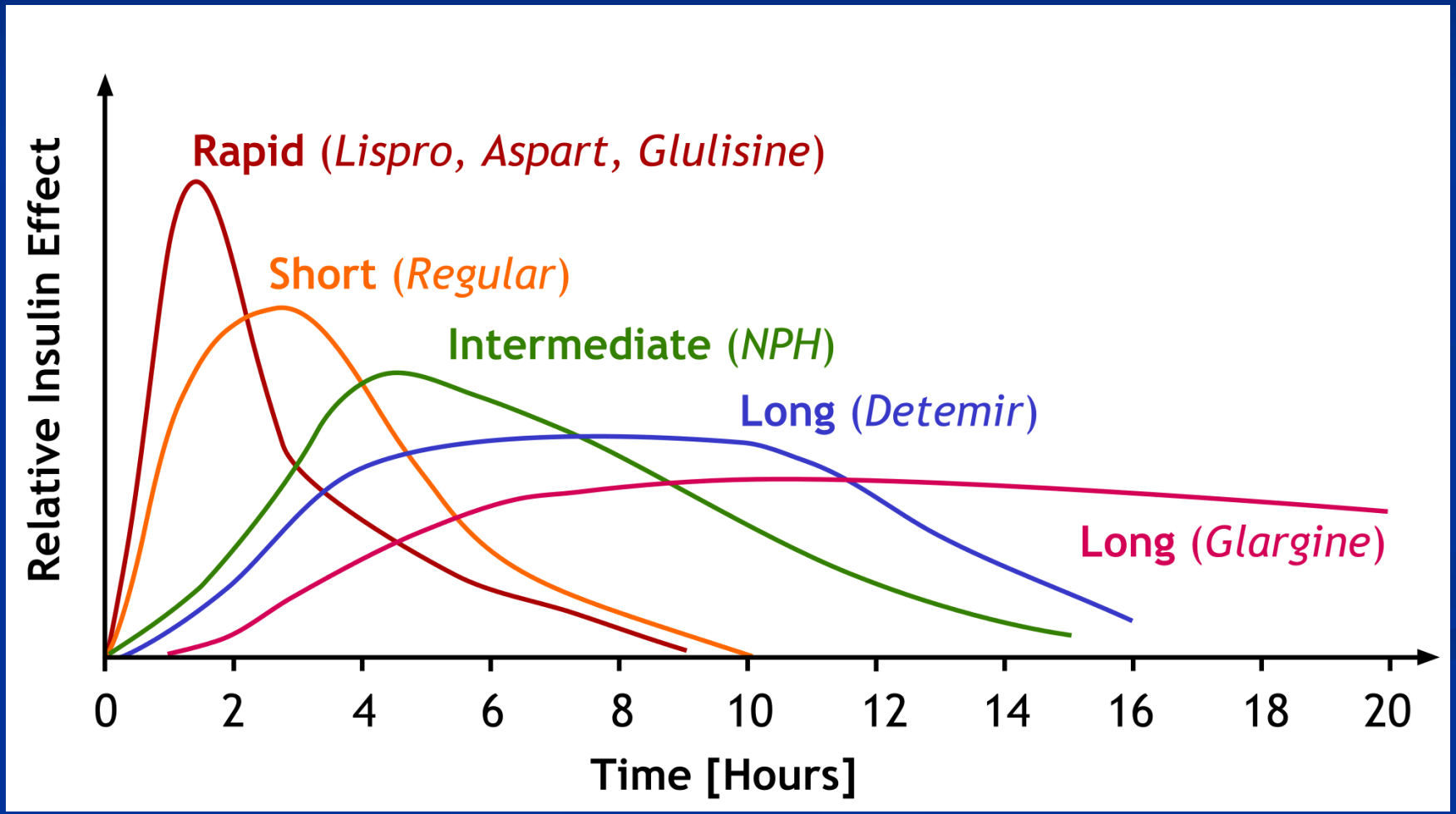
- onset: 4 - 6 hours →
- peak / duration: same
  action throughout the day for 24 hours

Insulin Comparison Chart

Insulin Name	When does it start working? (onset)	When will the effect be the greatest? (peak)	How long will it lower blood glucose? (duration)	Notes for Use	Cost estimate
Rapid Acting					
Lispro (Humalog™)	<15 minutes	0.5-3 hours*	3-5 hours	If mixing with NPH, rapid acting insulin should be drawn into syringe first. Mixture should be given immediately to avoid effects on peak action.	$96 (10 ml vial) $183 (5x3 ml pen cartridges)
Aspart (Novolog™)	<15 minutes	0.5-3 hours*	3-5 hours		$102 (10 ml vial) $205 (5x3 ml pen cartridges)
Glulisine (Apidra™)	<15 minutes	0.5-3 hour*	3-5 hours		$96 (10 ml vial) $184 (5x3 ml pen cartridges
Short Acting					
Regular (Novolin R™ or Humulin R™)	0.5-1 hour	2-4 hours	4-8 hours	May be mixed with NPH in same syringe. Mixing order should be the clear regular drawn up first, then the cloudy NPH (ie "clear to cloudy").	$53 (10 ml vial Humulin or Novolin) $121 (5x3 ml Novolin pen cartridges) $89 (5x3 ml Innolet cartridges)
Intermediate Acting					
NPH (Novolin N™ or Humulin N™)	2-4 hours	4-10 hours	10-18 hours	Available as pen or in vial to be used with syringe.	$52 (10 ml vial Humulin or Novolin) $121 (5x3 ml pen cartridges) $91 (5x3 ml Innolet cartridges)
Long Acting					
Glargine (Lantus™)	4-6 hours	Same action throughout the day	24 hours	Do not mix with other insulins. Available as pen or in vial. Duration (clinical trial data): 6 hrs (0.1 U/kg), 12 hrs (0.2 U/kg),20 hrs (0.4 U/kg), 23 hrs (0.8 U/kg and 1.6 U/kg)	$97 (10 ml vial) $177 (5x3 ml Solostar pen cartridges)
Detemir (Levemir™)	2-3 hours	6-8 hours	Dose-dependent 5.7-23.2 hours		$95 (10 ml vial) $182 (5x3 ml pen cartridges)
Combinations					
Humulin or Novolin 70/30	0.5-1 hour	2-10 hours	10-18 hours	70% NPH +30% regular insulin. Insulin action includes 2 peaks (1 from each formulation).	$54 (10 ml vial) $135 (5x3 ml pen cartridges) $94 (5x3 ml Innolet cartridges)
Novolog Mix 70/30 Humalog Mix 75/25 or 50/50	<15 minutes	1-2 hours	10-18 hours	Novolog Mix: aspart protamine 70% + aspart 30% Humalog mix: 75/25=75% lispro protamine + 25% lispro 50/50=50% lispro protamine + 50% lispro Insulin action includes 2 peaks (1 from each formulation).	Humalog Mix 75/25: $102 (10 ml vial), $174 (5x3 ml pen cartridges)

Time Profile Curves of Current Insulin Products

Lispro (Humalog), Aspart (Novolog), Glulisine (Apidra), Regular (Humulin R), NPH (Humulin N), Detemir (Levemir), and Glargine (Lantus)



VI. Pharmacologic Management of IDDM (cont.)

B. Insulin Regimens

- General Estimate of Daily Insulin Requirement:
  0.5 - 1.0 units insulin / kg body weight / day
- General Rule: 1 - 2 units insulin → ↓ 30-50 mg/dl BG

- Humalog Sliding Scale Regimen: QID (AC & HS)

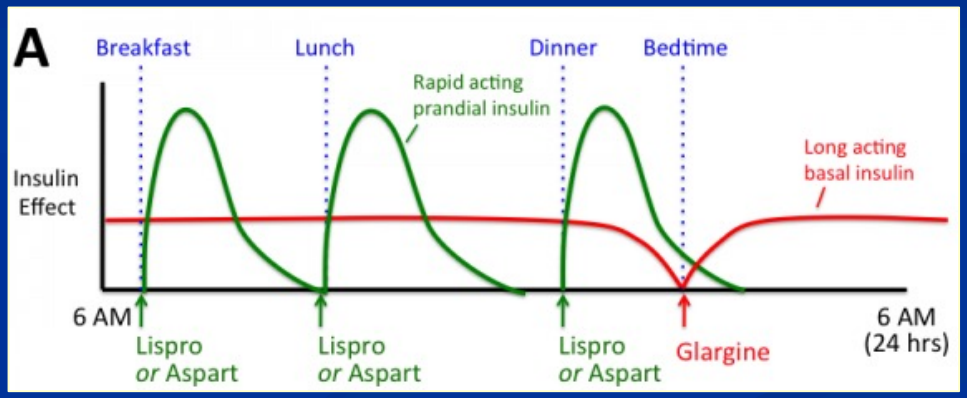
Glucose Level (mg/dL)	Low Dose Regimen (0-6 UNITS) AC & HS	Medium Dose Regimen (0-12 UNITS) AC & HS	High Dose Regimen (0-18 UNITS) AC & HS
< 70	25-50 ml Dextrose 50% IVP		
60 – 150	0	0	0
151 - 199	1	2	4
200 - 249	2	4	6
250 – 299	3	6	8
300 – 349	4	8	12
350 – 399	5	10	14
> 400	6 Call MD/PA	12 Call MD/PA	18 Call MD/PA

B. Insulin Regimens (cont.)

- Method A: Lispro (Humalog) + Glargine (Lantus)
- Method B: Regular Insulin (Humulin R) or Lispro + NPH (Humulin N)

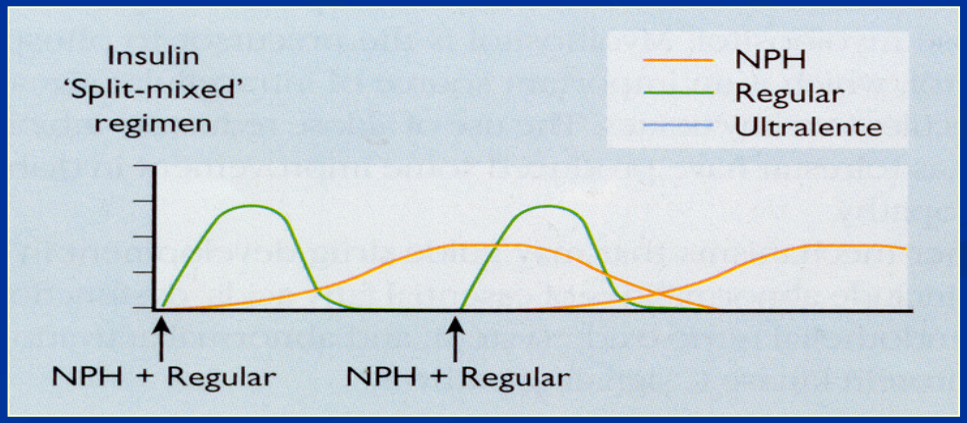
Method A: Basal/Bolus Regimen Mimics Normal Insulin Profile

- Short-Acting Insulin Bolus with Long-Acting Insulin Basal Coverage



Method B: Bolus/Intermediate Insulin Regimen

- 7AM: NPH:Reg (2/3 of daily insulin dose)
- 6 PM: NPH:Reg (1/3 of daily insulin dose)



VI. Pharmacologic Management of IDDM (cont.)

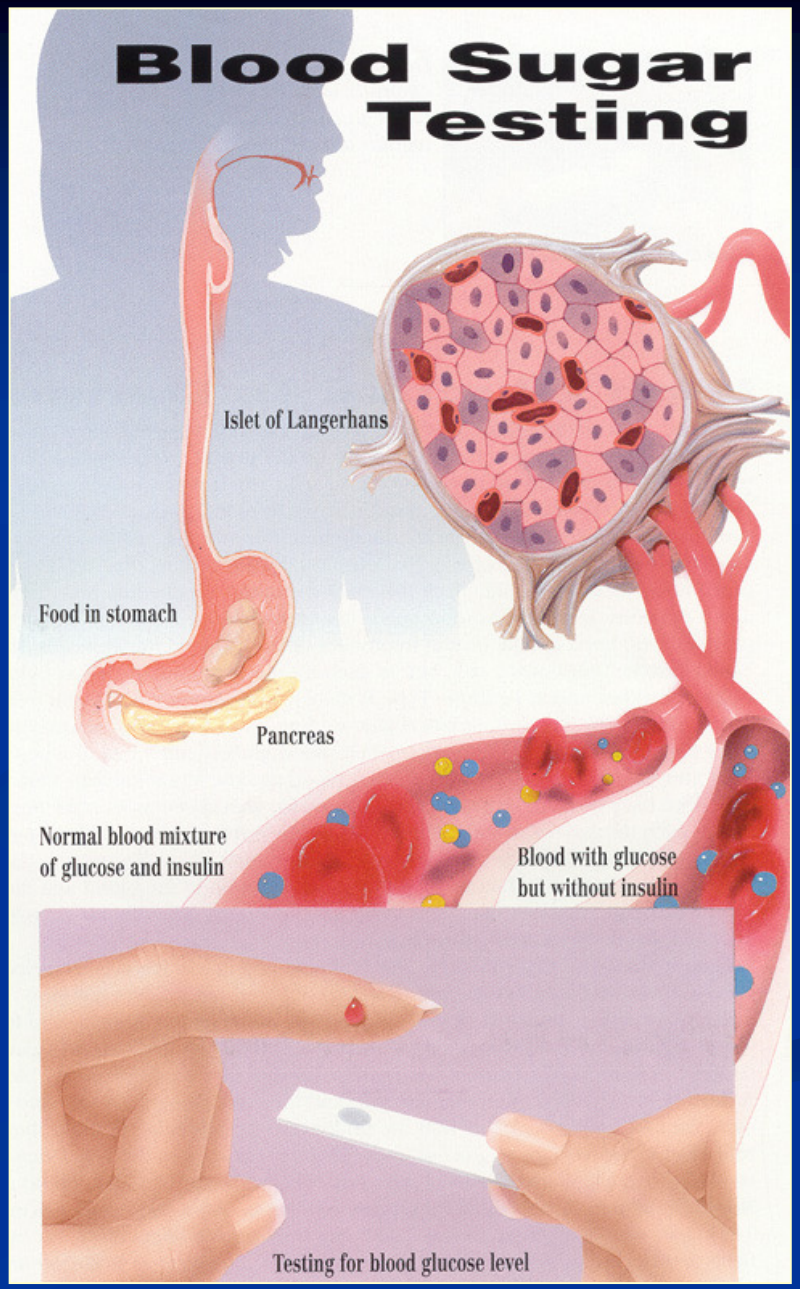
C. Biochemical Indices of Metabolic Control

Index	Normal	Intensive	Acceptable	Poor
Fasting	< 115	70-120	<140	>200
2 hrs pp	< 140	< 180	< 200	> 235
HgbA1c	4 – 6 %	< 6.5 %	< 7 %	> 10%
Urine Gluc	neg	rare	intermit	constant
Urine Keto	neg	rare	rare	intermit

VI. Pharmacologic Management of IDDM (cont.)

D. Monitoring Patients on Insulin Therapy

- AC & HS
  (before meals and at bedtime)
- occasionally at 0300 during periods of insulin dose adjustments
- whenever hypoglycemia is suspected



VI. Pharmacologic Management of IDDM (cont.)

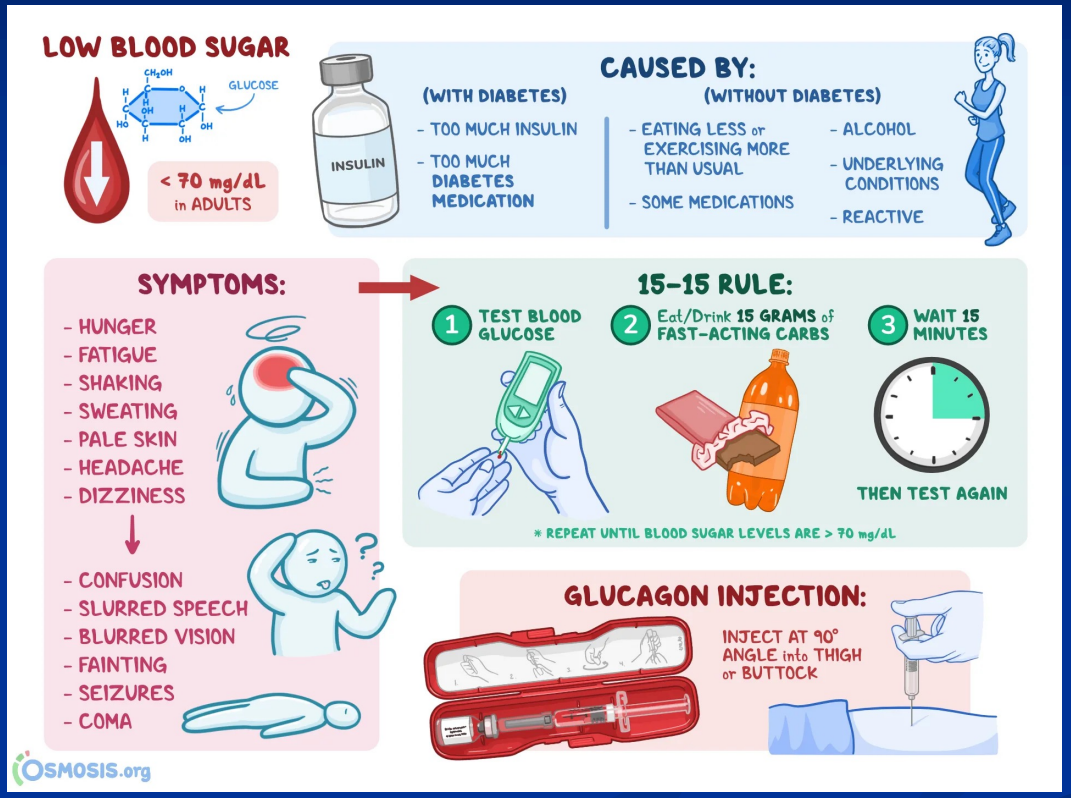
E. Signs & Symptoms of Hypoglycemia

- Palpitations, tachycardia, blurred vision, sweaty palms, generalized sweating, tremors, hunger, confusion, anxiety, irritability, headache, tingling and numbness, and seizures.
- Nocturnal hypoglycemia: nightmares, restless sleep, profuse sweating, and morning "hangover."

VI. Pharmacologic Management of IDDM (cont.)

F. Treatment of Hypoglycemia

- 15/15 rule: 15 gm rapidly absorbed carbohydrate (MR in 15 mins if BG<60 or if patient is still symptomatic)
    - Examples: OJ (1/2 cup), apple juice (1/3 cup), grape juice (1/4 cup), sugar (2 tsp or 2 cubes), Lifesavers (5-6 pieces), B/D glucose tabs (2 tabs)

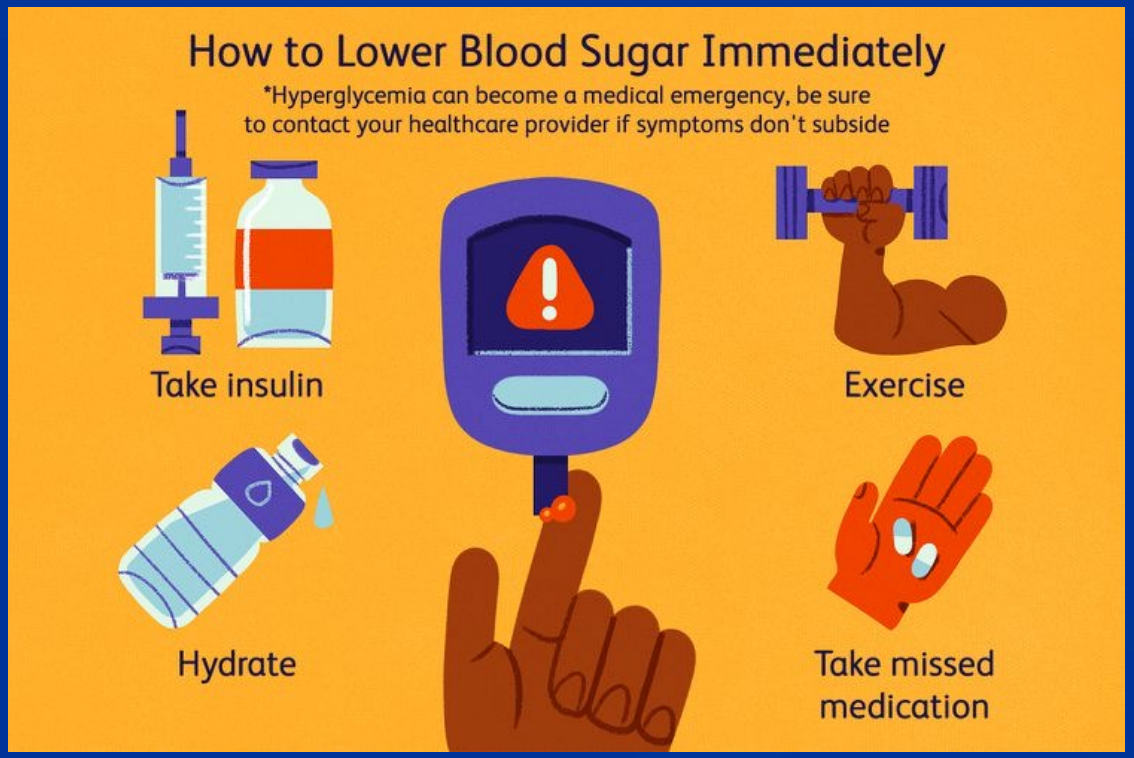


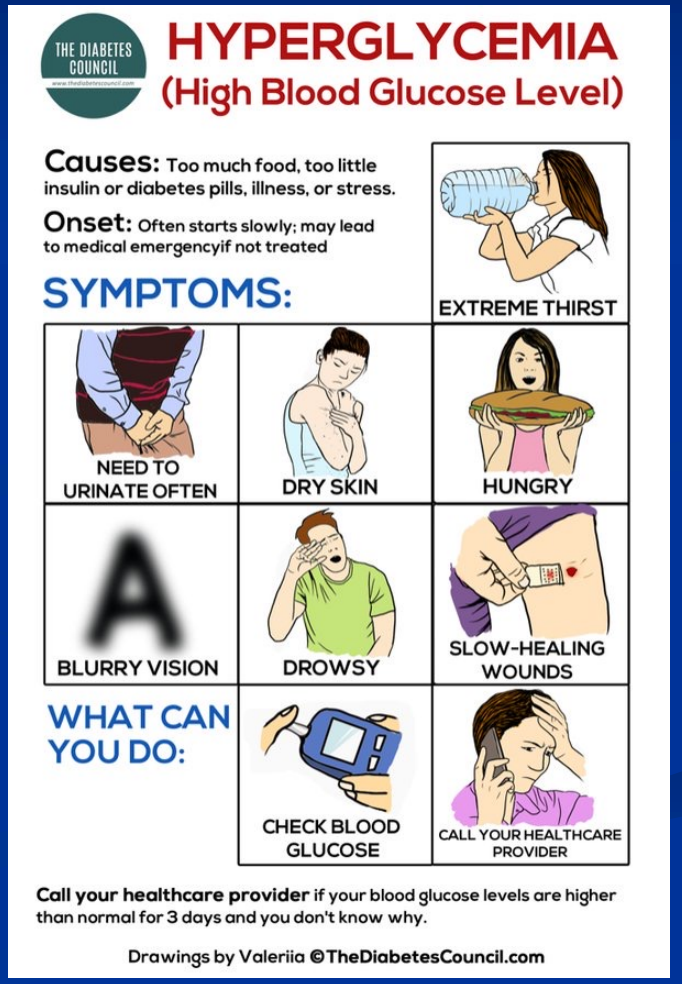
- If patient is unconscious, give glucagon 1 mg SC, IM, or IVP.
- In Clinical Settings: Dextrose 50% → 12.5-25 gm (25-50 ml) IVP

VI. Pharmacologic Management of IDDM (cont.)

G. Signs & Symptoms of Hyperglycemia

- polydipsia, polyuria, polyphagia, fatigue, blurry vision, …





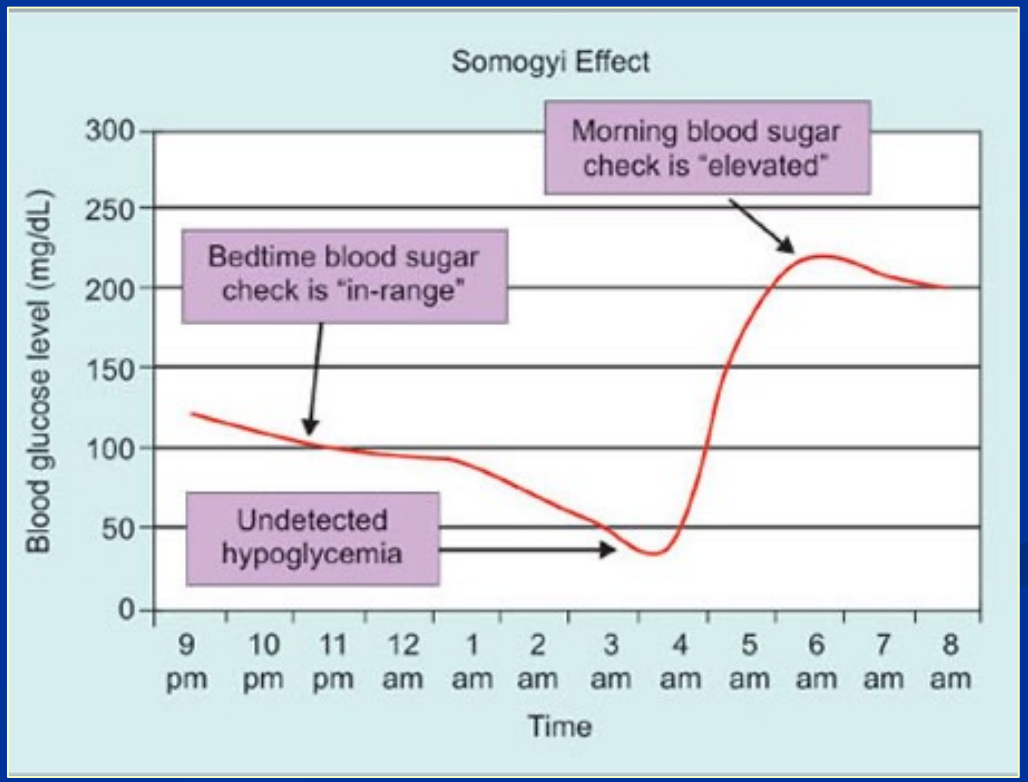
VI. Pharmacologic Management of IDDM (cont.)

G. Signs & Symptoms of Hyperglycemia

- Somogyi Effect: "post-hypoglycemic hyperglycemia" or "rebound hyperglycemia" that occurs at 3-4 AM

Treatment includes …

- reduction of evening regular insulin dose
- increase calories at evening meal
- increase evening NPH dose



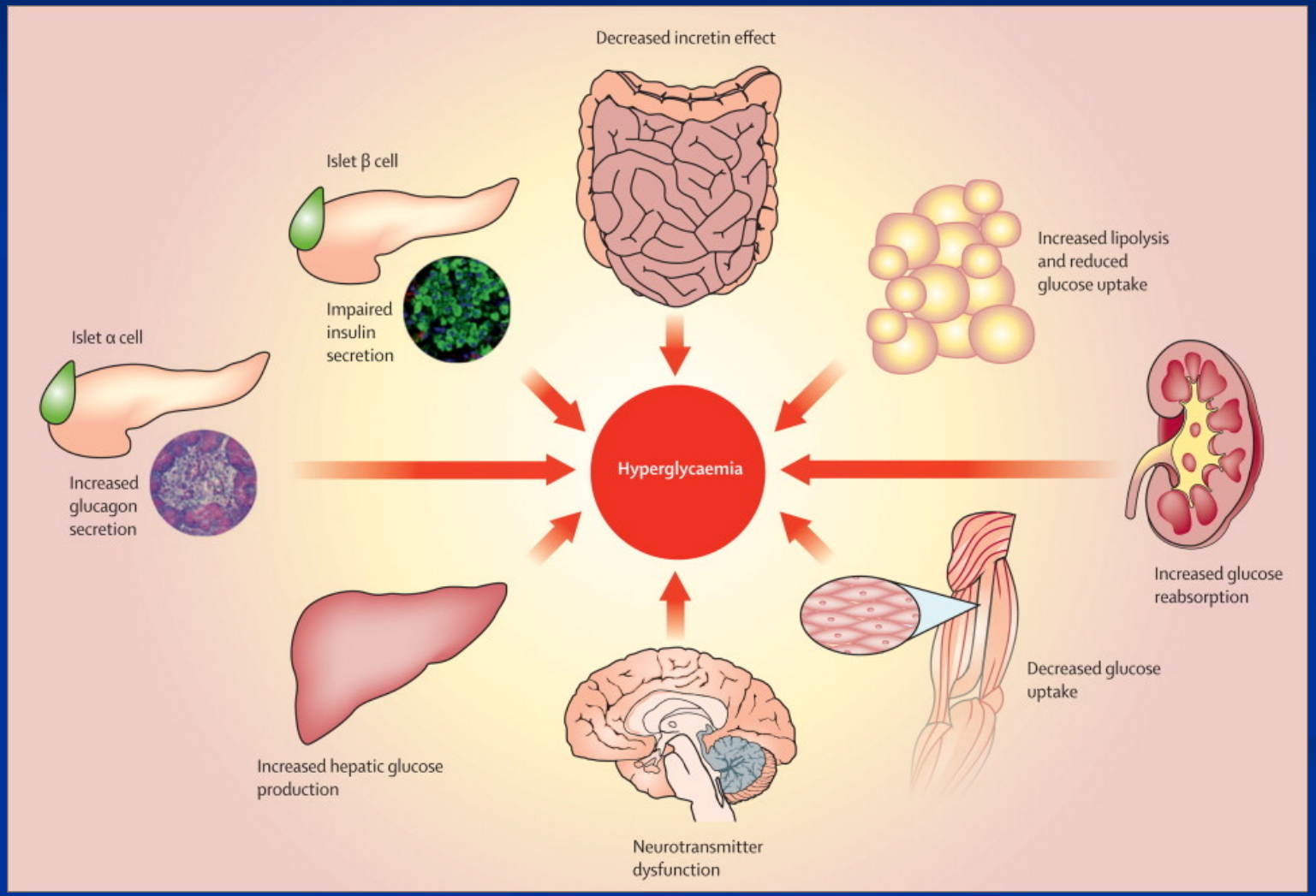
VI. Pharmacologic Management of IDDM (cont.)

H. Drugs Associated with Hypoglycemia

Drug	Effect	Mechanism
ethanol	+++	(-) gluconeogenesis (-) insulin secretion
beta-blockers	++	(-) glycogenolysis masks sx's hypoglycemia
salicylates	++	↑ insulin secretion/sensitivity ↑ serum sulfonylurea levels

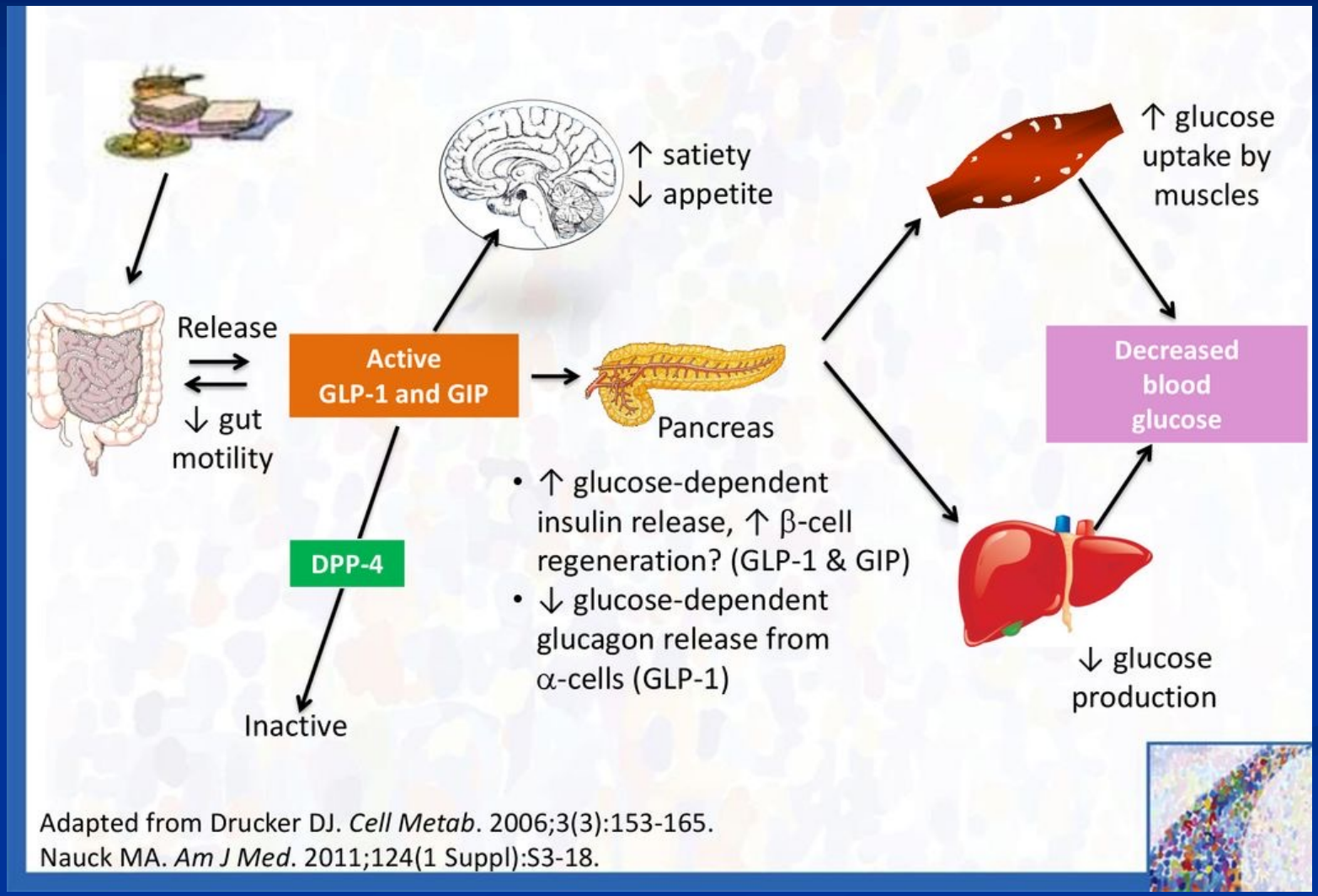
VII. Management of Type II DM

A. Pathogenesis of Type II Diabetes Mellitus



VII. Management of Type II Diabetes Mellitus

A. Pathogenesis of Type II Diabetes Mellitus



VIII. Pharmacologic Management of Type II DM

A. Sulfonylureas

1. MOA: Sulfonylureas increase insulin release by beta cells in the pancreas.

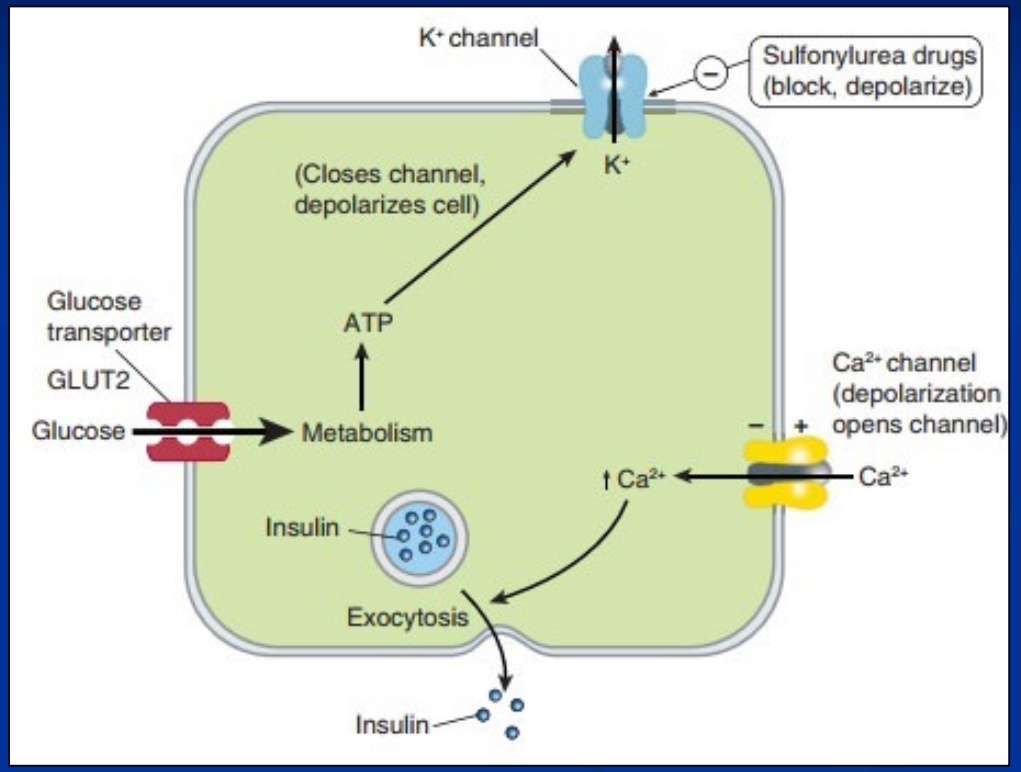
block K channels

↓

depolarizes beta cells

↓

↑ insulin release



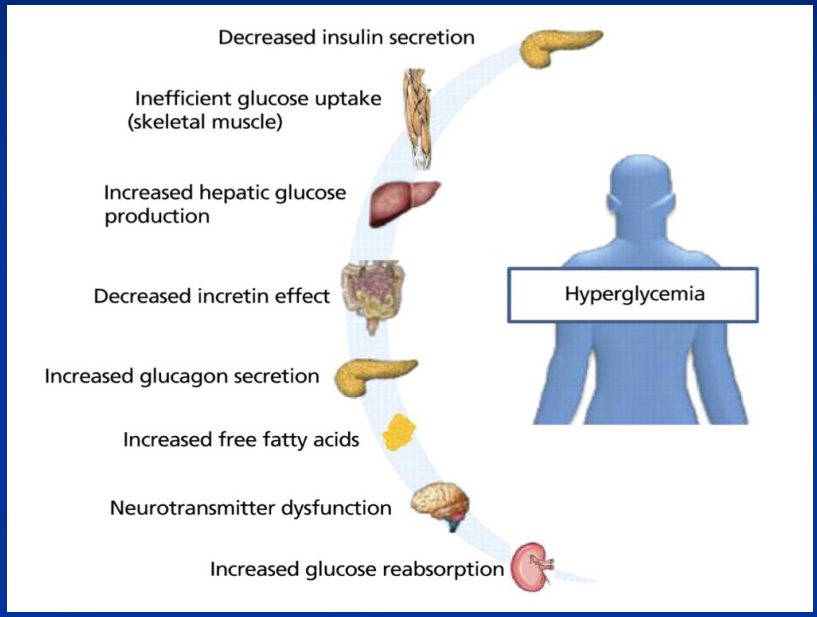
In the resting cell with normal (low) ATP levels, potassium diffuses down its concentration gradient through ATP-gated potassium channels, maintaining the intracellular potential at a fully polarized, negative level. Insulin release is minimal. If glucose concentration rises, AT production increases, potassium channels close, and depolarization of the cell results. As in muscle and nerve, voltage-gated calcium channels open in response to depolarization, allowing more calcium to enter the cell. Increased intracellular calcium results in increased insulin secretion. Insulin secretagogues close the ATP-dependent potassium channel, thereby depolarizing the membrane and causing increased insulin release by the same mechanism.

VIII. Pharmacologic Management of Type II DM

A. Sulfonylureas (cont.)

2. Other MOAs associated with sulfonylureas include …

   - reduction of serum glucagon → reduction of hepatic glucose output
   - increase insulin receptor sensitivity at peripheral target sites



3. First Generation Sulfonylureas

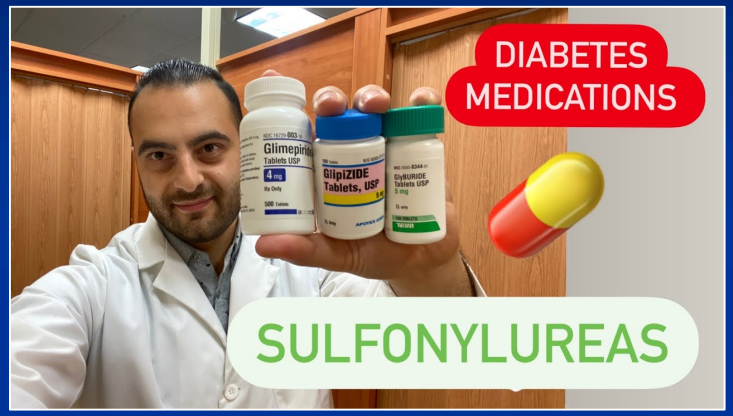
   - Tolbutamide (Orinase), Tolazamide (Tolinase), and Chlorpropamide (Diabinese)

VIII. Pharmacologic Management of Type II DM

A. Sulfonylureas (cont.)

4. Second Generation Sulfonylureas

- Glipizide (Glucotrol)
- Gyburide (Diabeta, Micronase)
- Glimepiride (Amaryl)



5. Side Effects

- Hypoglycemia
  - most common SE, esp. with glimerpiride
- Weight Gain
  - weight gain may be mitigated with exercise
  - if weight gain worsens rather than improves glycemic control, discontinue sulfonylurea

Sulfonylureas (2nd generation)

	Dose Size / Dose/day (mg)	Peak (hrs)	Dose Interval	Common side effects
Glyburide (Micronase®, DiaBeta®)	2.5, 5mg / 1.25mg – 20mg	4	QD – BID	Weight gain Low Blood Sugar
Glipizide (Glucotrol®)	5, 10mg / 2.5mg – 40mg	1 – 3	QD – BID	Weight gain Low Blood Sugar
Glimepiride (Amaryl®)	1, 2, 4mg / 1 – 8mg	2 – 3	QD	Weight gain Low Blood Sugar

VIII. Pharmacologic Management of Type II DM (cont.)

B. Metformin

1. MOA: decreases hepatic glucose production
2. Other MOAs associated with metformin include …
   - decreases intestinal absorption of glucose
   - improves insulin sensitivity (increases glucose uptake / utilization)
3. Side Effects (GI): diarrhea, nausea, vomiting, bloating, flatulence.
4. Dose: 500 mg – 2500 mg / day in divided doses (BID) with meals.
5. Cautions and Contraindications:

   GFR < 30 ml/min → contraindicated → risk of lactic acidosis
   GFR < 45 ml/min → caution: consider risks vs benefits

6. Metformin is a 1st line agent for newly diagnosed Type II diabetics.

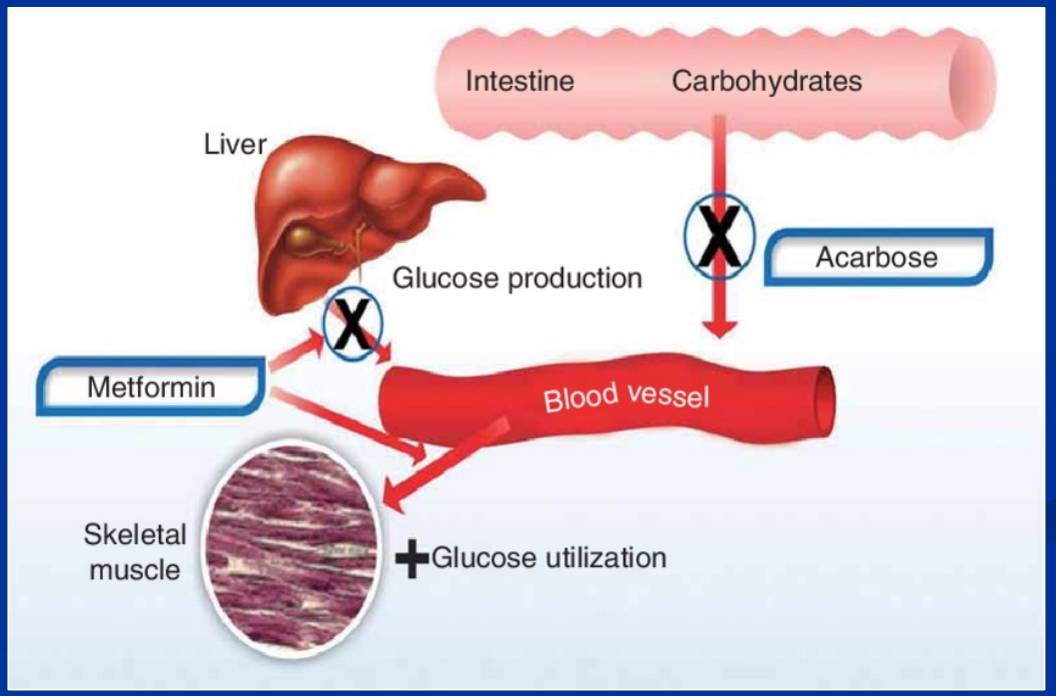
VIII. Pharmacologic Management of Type II DM (cont.)

C. Acarbose (Precose)

1. MOA: inhibits breakdown of carbohydrates by inhibiting alpha glucosidase (secreted by small intestine)

2. Side Effects (GI): abdominal pain, diarrhea, and flatulence (due to undigested carbohydrates in lower GI tract)

3. Dose: 50 – 100 mg TID with first bite of each meal



VIII. Pharmacologic Management of Type II DM (cont.)

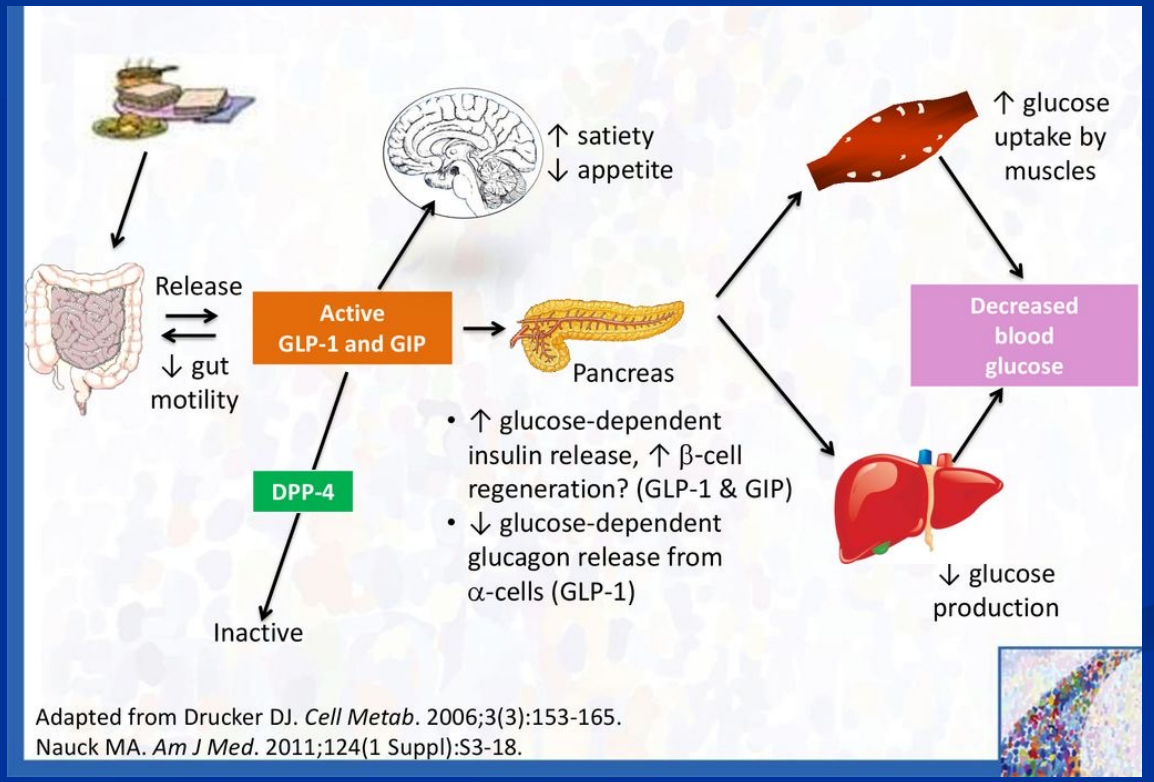
D. Thiazolidinediones (TZDs or Glitazones):
Rosiglitazone (Avandia) and Pioglitazone (Actose)

1. MOA: TZDs increase insulin receptor sensitivity and improve glucose transport in muscle and adipose tissue.
2. Other MOA associated with TZDs includes a decrease hepatic glucose production
3. Side Effects: weight gain, fluid retention, and osteopenia.
4. Pioglitazone (Avandia): 15-30 mg once daily.
5. Cautions and Contraindications:
    - TZDs should not be used in patients with heart failure or any evidence of fluid overload.
    - TZDs should not be used in patients with a history of fracture or at high risk for fracture (e.g., postmenopausal women with low bone mass).

VIII. Pharmacologic Management of Type II DM (cont.)

E. DPP-4 Inhibitors ("Gliptins"):
Sitagliptin (Januvia) and Linagliptin (Tradjenta)

1. MOA: inhibits DPP-4 enzyme → prolongs active incretin levels (GLP-1 and GIP).
2. Side Effects: nasopharyngitis (5%), URI (1%), nausea (2%), diarrhea (4%).
3. Sitagliptin (Januvia): 100 mg PO once daily.



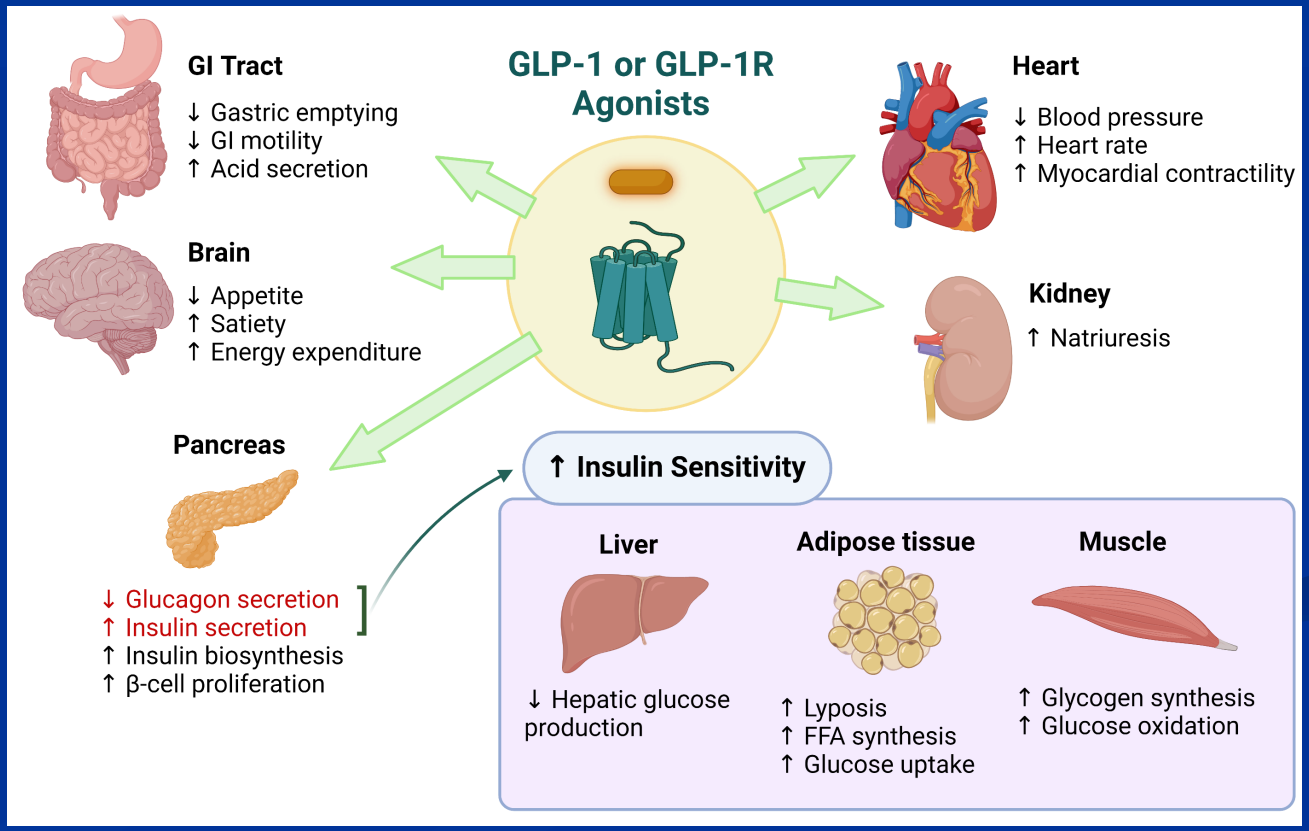
VIII. Pharmacologic Management of Type II DM (cont.)

F. GLP-1 Receptor Agonists

Semaglutide (Ozempic, Wegovy, Rybelsus): SC/PO
Dulaglutide (Trulicity) SC
Liraglutide (Victoza): SC
Exenatide (Byetta): SC
Tirzepatide (Mounjaro): SC

↓

Increase Insulin Release
+
Decrease Glucagon Release
+
Increase Satiety
+
Delay Gastric Emptying Time



VIII. Pharmacologic Management of Type II DM (cont.)

F. GLP-1 Receptor Agonists

Semaglutide (Ozempic, Wegovy, Rybelsus): SC/PO
Dulaglutide (Trulicity) SC
Liraglutide (Victoza): SC
Exenatide (Byetta): SC
Tirzepatide (Mounjaro, Zepbound): SC

1. General Considerations
   - GLP-1 receptor agonists are indicated for use in combination with metformin for patients with existing ASCVD when weight loss is a primary consideration and when cost of injectables formulations are not limiting factors.
   - GLP-1 receptor agonists may also be used in combination with basal insulin with or without metformin when HgbA1c levels remain persistently high.
   - Tirzepatide (Mounjaro) is a dual-acting GLP-1 and GI receptor agonist for Type II DM without ASCVD who may benefit from weight loss, since there is insufficient evidence yet that tirzepatide provides protection against ASCVD.
2. Adverse Effects (GI): nausea (26-50%), vomiting, and diarrhea.
   - Nausea is reduced with gradual dose titrations and wanes with continued use.

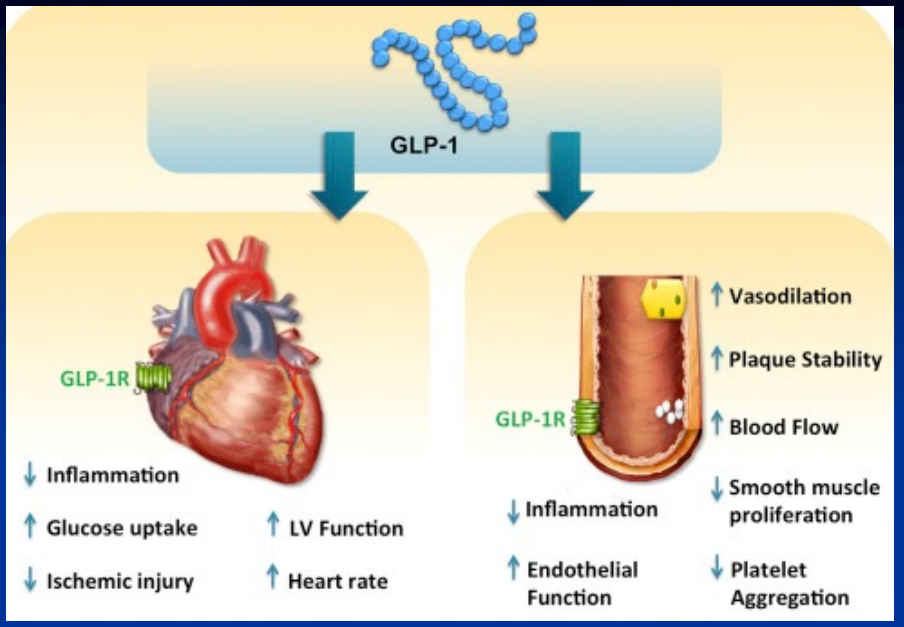
VIII. Pharmacologic Management of Type II DM

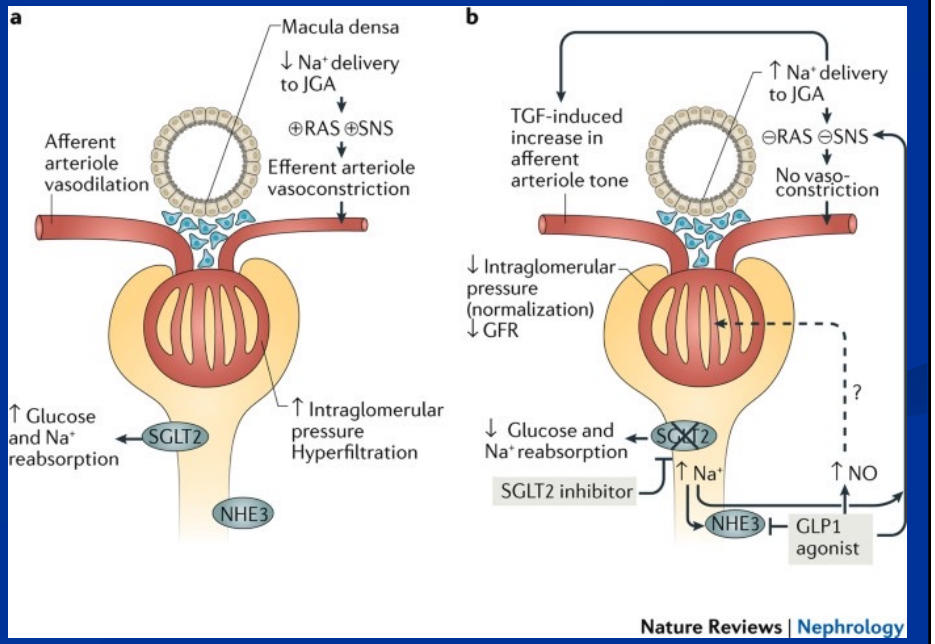
F. GLP-1 Receptor Agonists

3. GLP-1 Receptor Agonist Benefits in ASCVD (Atherosclerotic Cardiovascular Disease) and CKD

   - In CKD, GLP-1 RA induces natriuresis and diuresis by inhibiting the Na^+/H^+ exchanger-3 (NHE3) located in the renal proximal tubule → increases tubular Na^+ transport to the macular densa → reduces intraglomerular pressure and hyperfiltration → restores tubular glomerular feedback and improves kidney outcomes in CKD

   - In CKD, GLP-1 RA decreases circulating concentrations of angiotensin II → decreases BP and Na/H_2O retention.



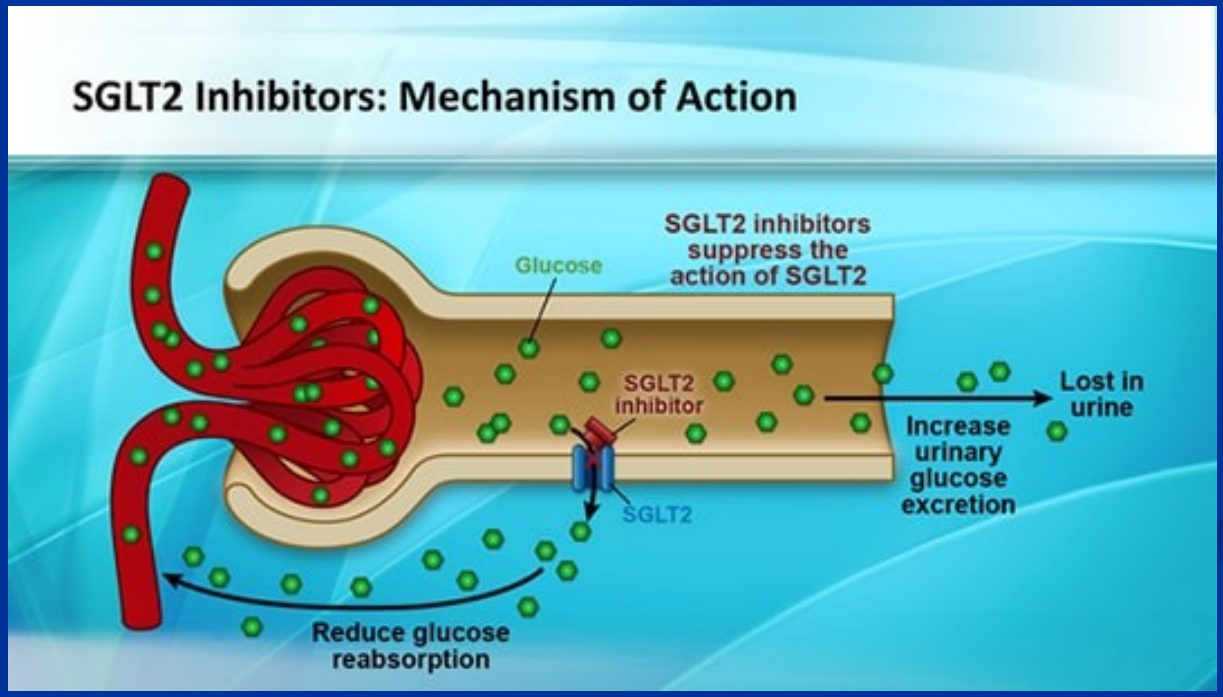


VIII. Pharmacologic Management of Type II DM (cont.)

G. SGLT2 Inhibitors (Sodium-Glucose Transport Inhibitors)

Canaglifozin (Invokana)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)

MOA: inhibit SGLT2 transport mechanism
→ lower blood glucose levels by increasing kidney excretion of glucose into the urine



VIII. Pharmacologic Management of Type II DM (cont.)

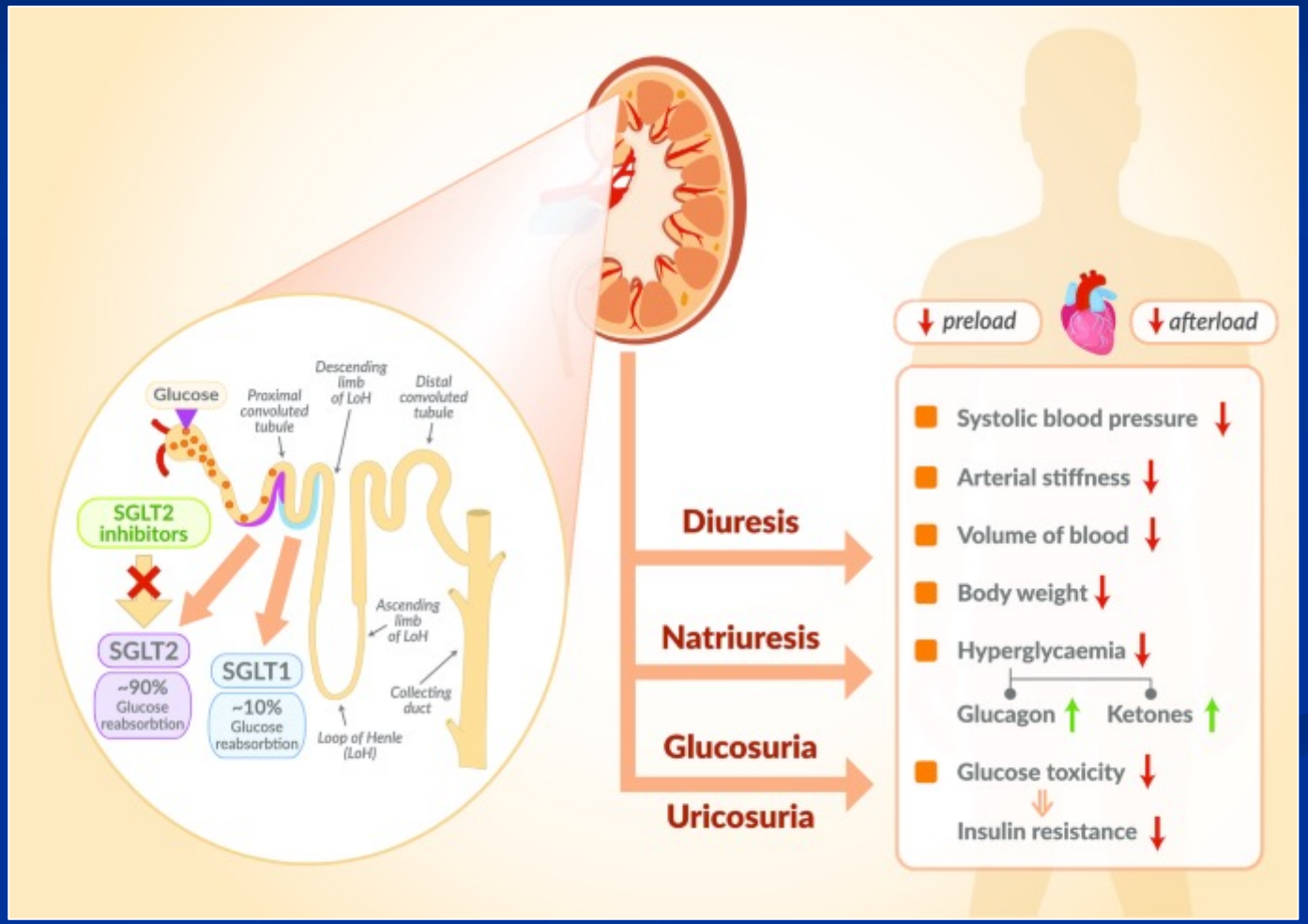
G. SGLT2 Inhibitors (Sodium-Glucose Transport Inhibitors)	Canaglifozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)

1. Adverse Effects: vaginal candidiasis (10-15%), UTIs (6-8%), dehydration → hypotension, DKA, necrotizing fasciitis of the perineum (Fournier's gangrene), bone fractures.
   - "Euglycemic" (BG < 250) DKA has been reported in pts with T2DM; therefore, serum ketones should be measured in patients with nausea, vomiting, malaise who are taking SGLT2 inhibitors.
2. Note: SGLT2 inhibitors only lower plasma glucose levels by blocking reabsorption of filtered glucose, which decreases as plasma levels decreases. Therefore, SGLT2 inhibitors do not cause hypoglycemia.
3. Note: SGLT2 inhibitors are less effective in pts with renal insuff and are not recommended in pts with CrCl < 30 ml/min.

VIII. Pharmacologic Management of Type II DM (cont.)

G. SGLT2 Inhibitors and Cardiovascular Protection

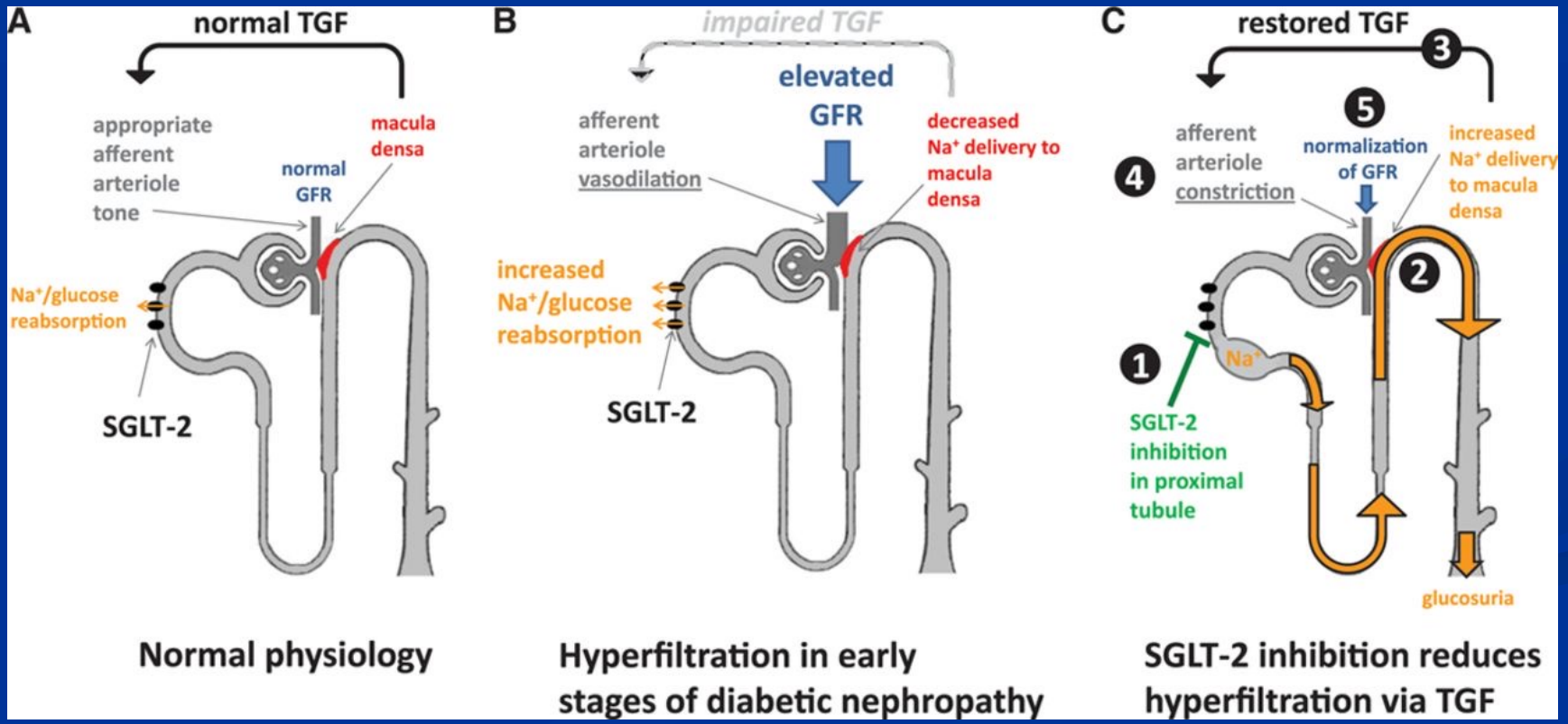
4. Empagliflozin and Canagliflozin have shown to decrease ASCVD morbidity and mortality in patients with T2DM and CVD.



VIII. Pharmacologic Management of Type II DM (cont.)

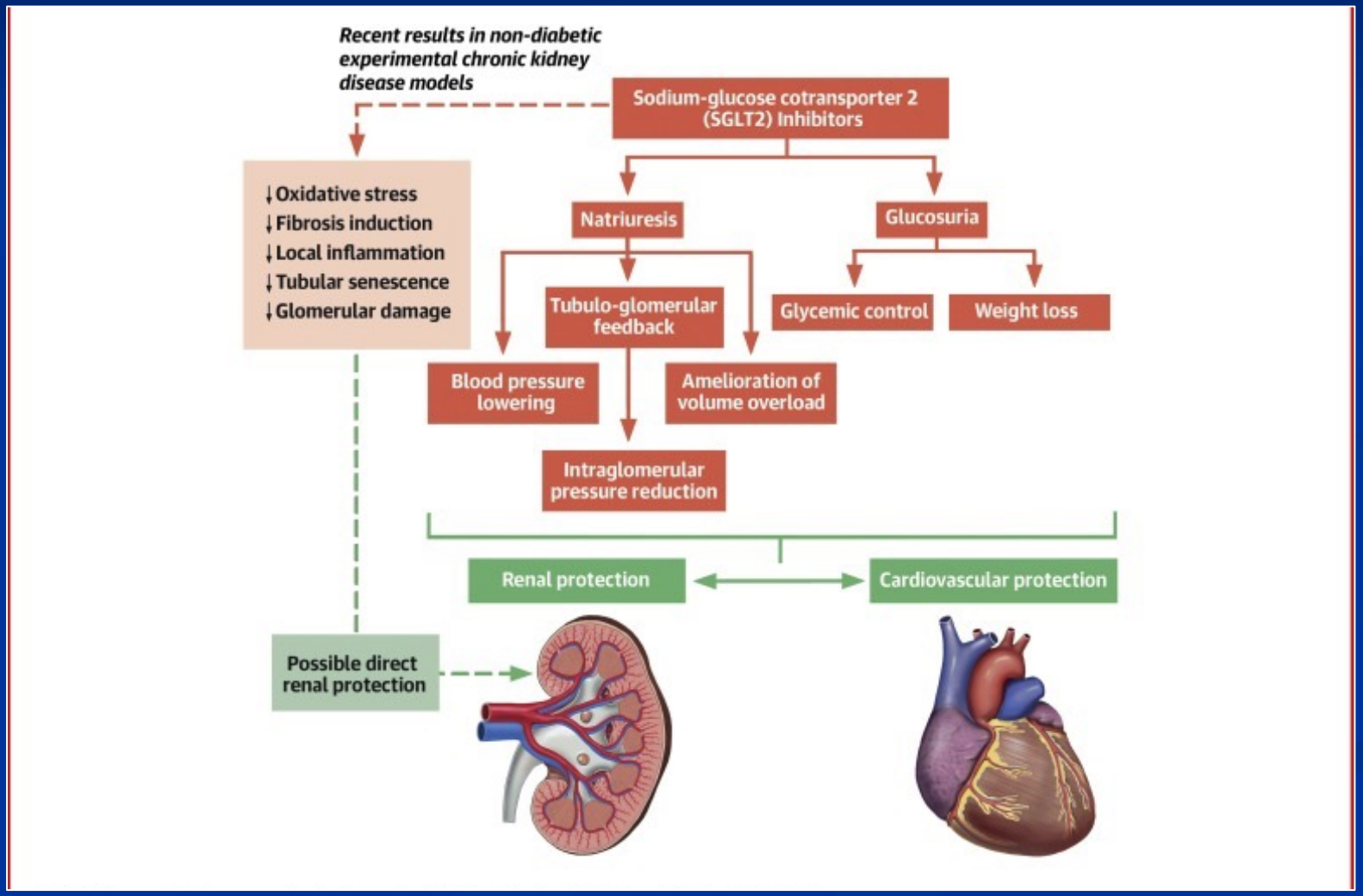
G. SGLT2 Inhibitors and Chronic Kidney Disease

5. SGLT-2 Inhibitors block sodium and glucose reabsorption in the renal proximal tubule → increase delivery of sodium to the macula densa → constrict abnormally dilated afferent arterioles → reduce intraglomerular pressure and reduce glomerular hyperfiltration → normalize GFR → lower progression of CKD



VIII. Pharmacologic Management of Type II DM (cont.)

G. SGLT2 Inhibitors and Cardiorenal Protection (Summary)



VIII. Pharmacologic Management of Type II DM (cont.)

S U M M A R Y

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

CV, cardiovascular; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; NASH, nonalcoholic steatohepatitis; MACE, major adverse cardiovascular events; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes mellitus. *For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. [1]Tsapas et al. (62). [2]Tsapas et al. (114). Reprinted from Davies et al. (45).

IX. ADA Algorithm: Management of T2DM (2023)

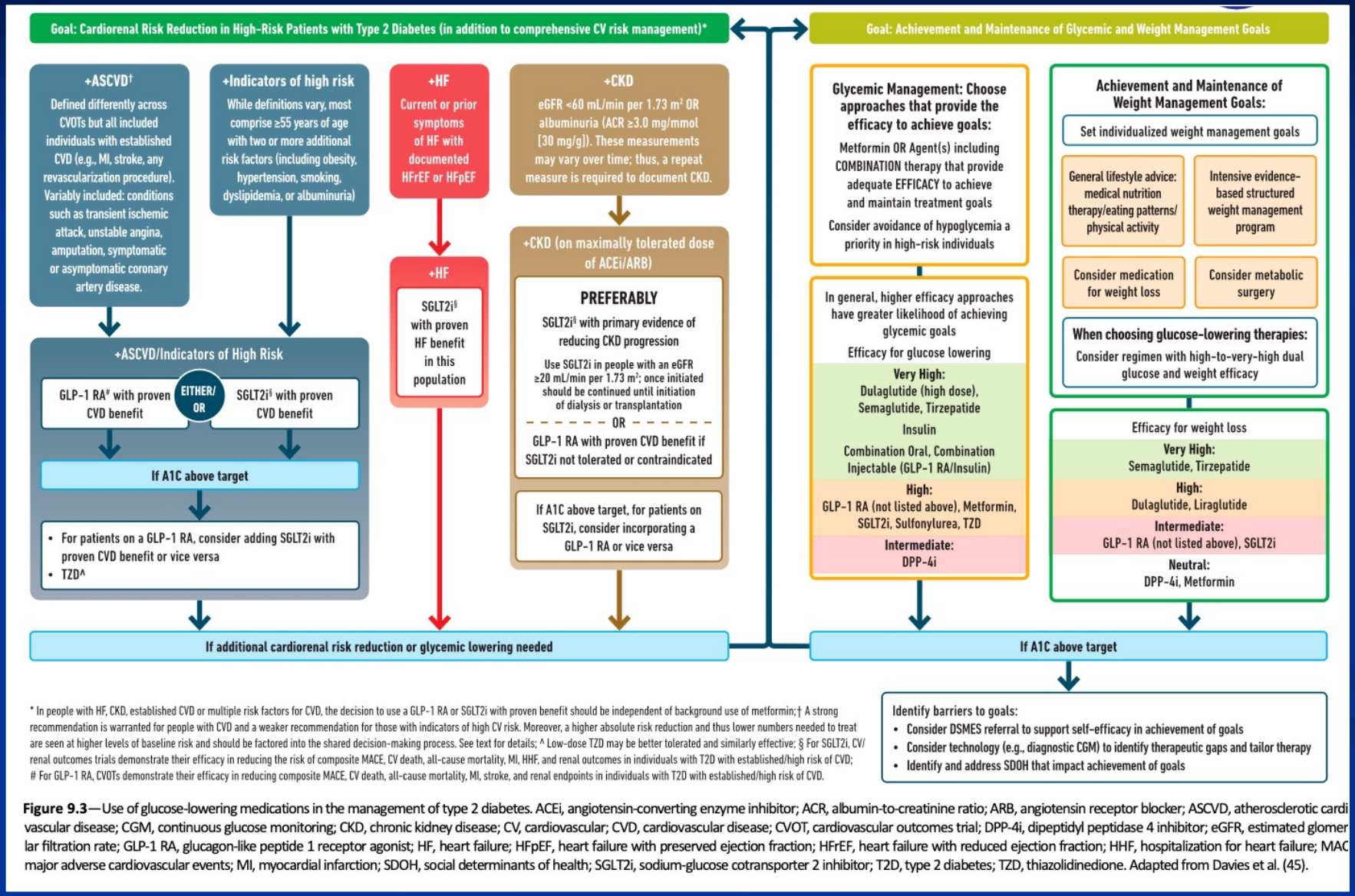


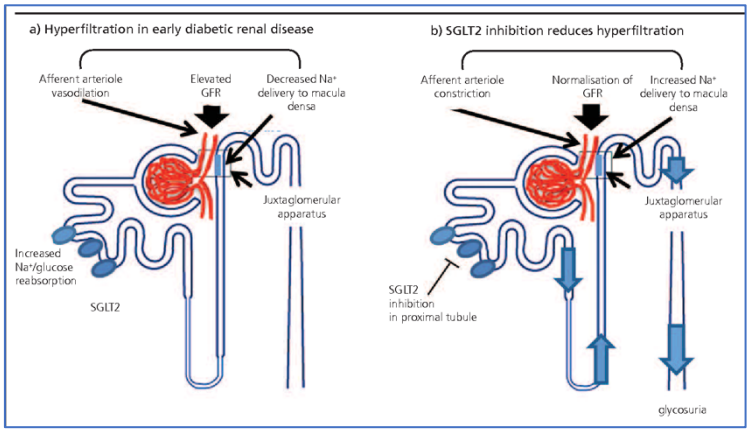
Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardi vascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomer lar filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MAC major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (45).

Compelling Pharmacologic Indications and Considerations (Type II DM)

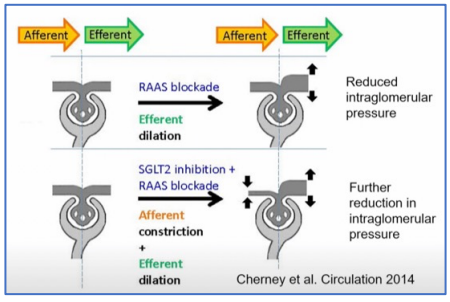
In the absence of specific contraindications (e.g., CrCl ≤ 30 ml/min, lactic acidosis), metformin is recommended in the initial therapy of newly diagnosed Type II diabetics.

- Metformin is effective in maintaining glycemic control and is well-tolerated with a favorable cost.
- Metformin starting dose: 500 mg PO daily with the evening meal and, if tolerated, add a second 500 mg dose with breakfast. The dose may be increased up to 2000 mg/day.
- Metformin extended-release formulations (e.g., metformin XL), dosed once daily with breakfast, may be better tolerated in patients with GI side effects (i.e., diarrhea, flatulence, bloating, nausea/vomiting).
- Metformin is associated with fewer episodes of hypoglycemia compared to the sulfonylureas and is associated with less edema and weight gain compared with the thiazolidinediones, such as pioglitazone (Actos) and rosiglitazone (Avandia).

Chronic Kidney Disease (CKD) / Diabetic Kidney Disease (CKD)

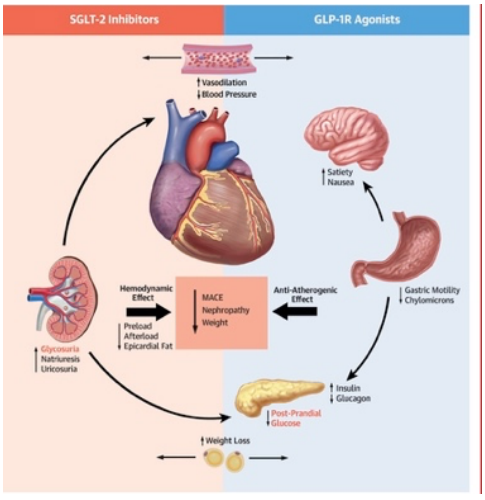


- For patients with CKD / DKD, use SGLT-2 inhibitors, since SGLT-2 inhibitors reduce progression of CKD by reducing glomerular hyperfiltration.
  - SGLT-2 Inhibitors: Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance)
  - SGLT-2 Inhibitors block sodium & glucose reabsorption in proximal tubule → increase delivery of sodium to the macula densa → constrict abnormally dilated afferent arterioles → reduce glomerular hyperfiltration → slow progression of CKD.
  - Note: SGLT-2 inhibitors are contraindicated in patients with CrCl ≤ 30 ml/min.
- RAAS blockers are also recommended in CKD, since ACE-I's and ARBs inhibit Angiotensin-II from constricting glomerular efferent arterioles → reduce hyperfiltration.



Weight Loss Considerations

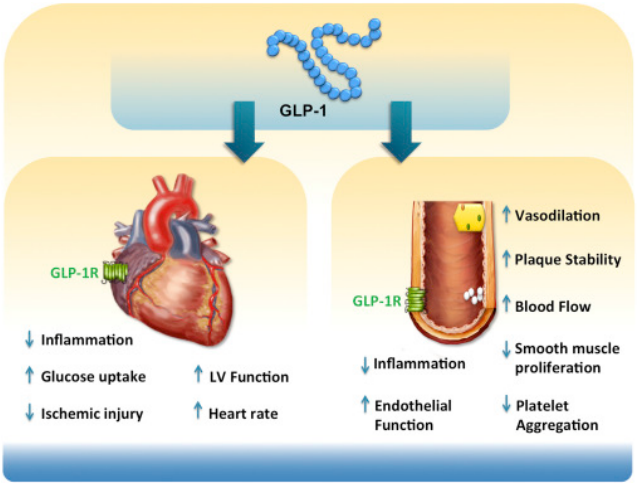
- If weight loss is a priority, GLP-1 receptor agonists or SGLT-2 inhibitors may be helpful options.
  - GLP-1 RA: increase satiety (reduce appetite) and slow gastric emptying time.
  - SGLT-2 inhibitors: increase glucose excretion.
- DPP-4 inhibitors: Sitagliptin (Januvia) and Linagliptin (Tradjenta) are "weight neutral" and may also be reasonable options for some patients.

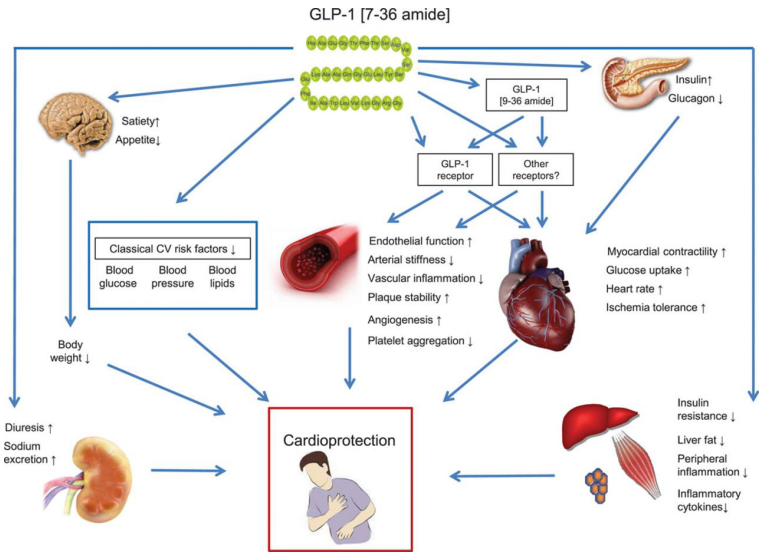


ASCVD (Atherosclerotic Cardiovascular Disease)

For patients with established ASCVD, use GLP-1 RAs, since they have demonstrated favorable cardiovascular outcomes, i.e., reduction of major adverse cardiovascular events (MACE).

- GLP-1 RA: Semaglutide (Ozempic, Wegovy), Dulaglutide (Trulicity), Liraglutide (Victoza), and Tirzepatide (Mounjauro).





Summary of Glucose-Lowering Pharmacologic Agents in Type II DM

Intervention	Expected decrease in A1C with monotherapy (%)	Advantages	Disadvantages
Initial therapy			
Lifestyle change to decrease weight and increase activity	1.0 to 2.0	Broad benefits	Insufficient for most within first year owing to inadequate weight loss and weight regain
Metformin	1.0 to 2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency (eGFR <30 mL/min/1.73 m^2)*
Additional therapy¶			
Insulin (usually with a single daily injection of intermediate- or long-acting insulin initially)	1.5 to 3.5	No dose limit, rapidly effective, improved lipid profile	1 to 4 injections daily, monitoring, weight gain, hypoglycemia, analogs are expensive
Sulfonylurea (shorter-acting agents preferred)	1.0 to 2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
GLP-1 receptor agonist (daily to weekly injections)	0.5 to 1.5	Weight loss, reduction in major adverse cardiovascular events (liraglutide, semaglutide, dulaglutide) in patients with established CVD and potentially for those at high risk for CVD	Requires injection, frequent GI side effects, expensive
Thiazolidinedione	0.5 to 1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, HF, weight gain, bone fractures, potential increase in MI (rosiglitazone) and bladder cancer (pioglitazone)
SGLT2 inhibitor	0.5 to 0.7	Weight loss, reduction in systolic blood pressure, reduced cardiovascular mortality in patients with established CVD, improved renal outcomes in patients with nephropathy	Vulvovaginal candidiasis, urinary tract infections, bone fractures, lower limb amputations, DKA
DPP-4 inhibitor	0.5 to 0.8	Weight neutral	Possible increased risk of HF with saxagliptin, expensive
Alpha-glucosidase inhibitor	0.5 to 0.8	Weight neutral	Frequent GI side effects, 3 times/day dosing


PHARMACY
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