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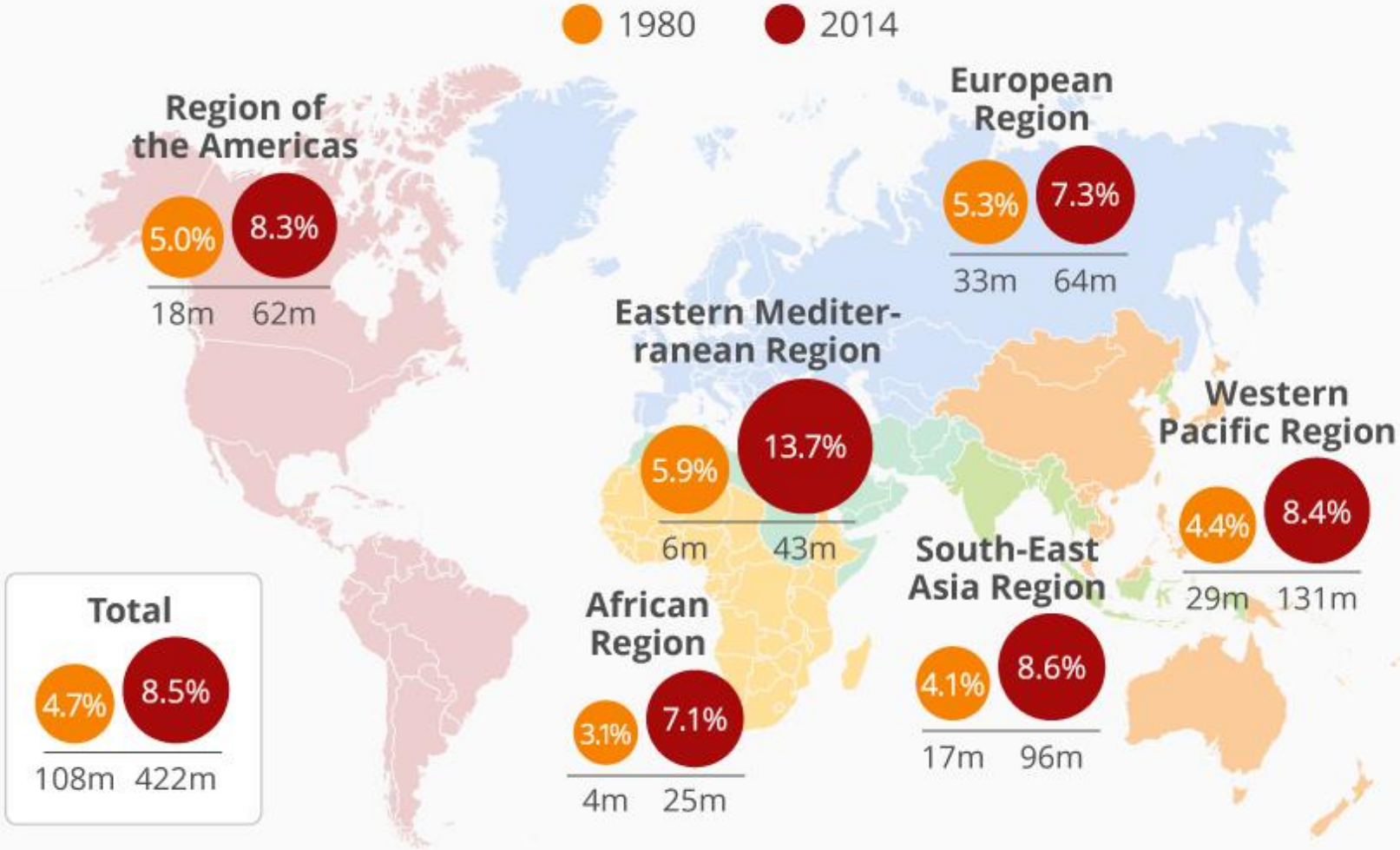
Outline

- ✓ Introduction
- ✓ Pathogenesis
- ✓ Diagnostic criteria
- ✓ Screening
- ✓ Diabetic complication
- ✓ Medical treatment

- Type 2 diabetes mellitus (T2DM) is one of the most common health problems facing mankind and is a major public health problem.
- The International Diabetes Federation (IDF) estimated in 2014 that 387 million people have diabetes worldwide and that by 2035 this number will rise to 592 million.

The Unrelenting March Of Diabetes

% prevalence and number of adults with diabetes by WHO region in 1980 and 2014*



* Millions of people and % of total regional population

Source: World Health Organization

- Globally in 2013, it is estimated that almost 382 million people suffer from diabetes with a prevalence of 8.3%.
- Top 10 countries with higher prevalence of diabetes are Tokelau (37.5%), Federated States of Micronesia (35%), Marshall Islands (34.9%), Kiribati (28.8%), Cook Islands (25.7%), Vanuatu (24%), Saudi Arabia (23.9%), Nauru (23.3%), Kuwait (23.1%) and Qatar (22.9%).
- Saudi Arabia is among top ten countries of the world with highest prevalence

IDF Diabetes Atlas : sixth edition, 6th ed., International Diabetes Federation, Basel, Switzerland.

Diabetes in Middle-East and North Africa

Top 5 countries

Top 5 countries for age-adjusted prevalence of people with diabetes (20–79 years)	2011	2021
Pakistan	8.0%	30.8%
Egypt	21.1%	20.9%
Iran (Islamic Republic of)	16.9%	9.1%
Saudi Arabia	20.2%	18.7%
Sudan	8.7%	18.9%

Top 5 countries for number of people with diabetes (20–79 years) in millions	2011	2021
Pakistan	6.3m	33.0m
Egypt	7.3m	10.9m
Iran (Islamic Republic of)	4.7m	5.5m
Saudi Arabia	2.8m	4.3m
Sudan	1.7m	3.5m

IDF Diabetes Atlas : Tenth edition, 10th ed., International Diabetes Federation,

Criteria for the Diagnosis of Diabetes

Increased Risk					
Test	Normoglycemia	mpaired Fasting Glucose	Impaired Glucose Tolerance	High Risk	Diabetes
PG, fasting (mg/dL)	<100	100-125			≥126
PG, 2-hour (mg/dL)	<140		140-199		≥200 plus classical symptoms of diabetes or hyperglycemic crisis
Hemoglobin A1c (%)				5.7-6.4	≥6.5
PG, casual (mg/dL)					

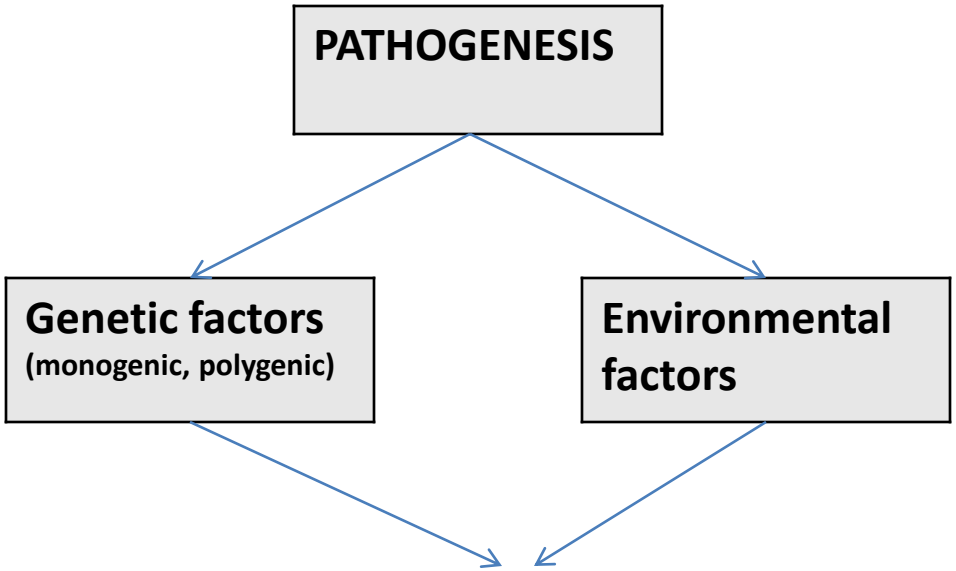
Modified from American Diabetes Association. Standards of medical care in diabetes—2010. Diabetes Care. 2010;29:s11-s61

Classification

- **I. Type 1 diabetes (beta-cell destruction, usually leading to absolute insulin deficiency)**
- Immune mediated, including LADA
- Idiopathic
- **II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)**
- **III. Gestational Diabetes mellitus (GDM)**
- **IV. Monogenic / MODY**
- **V. Others**

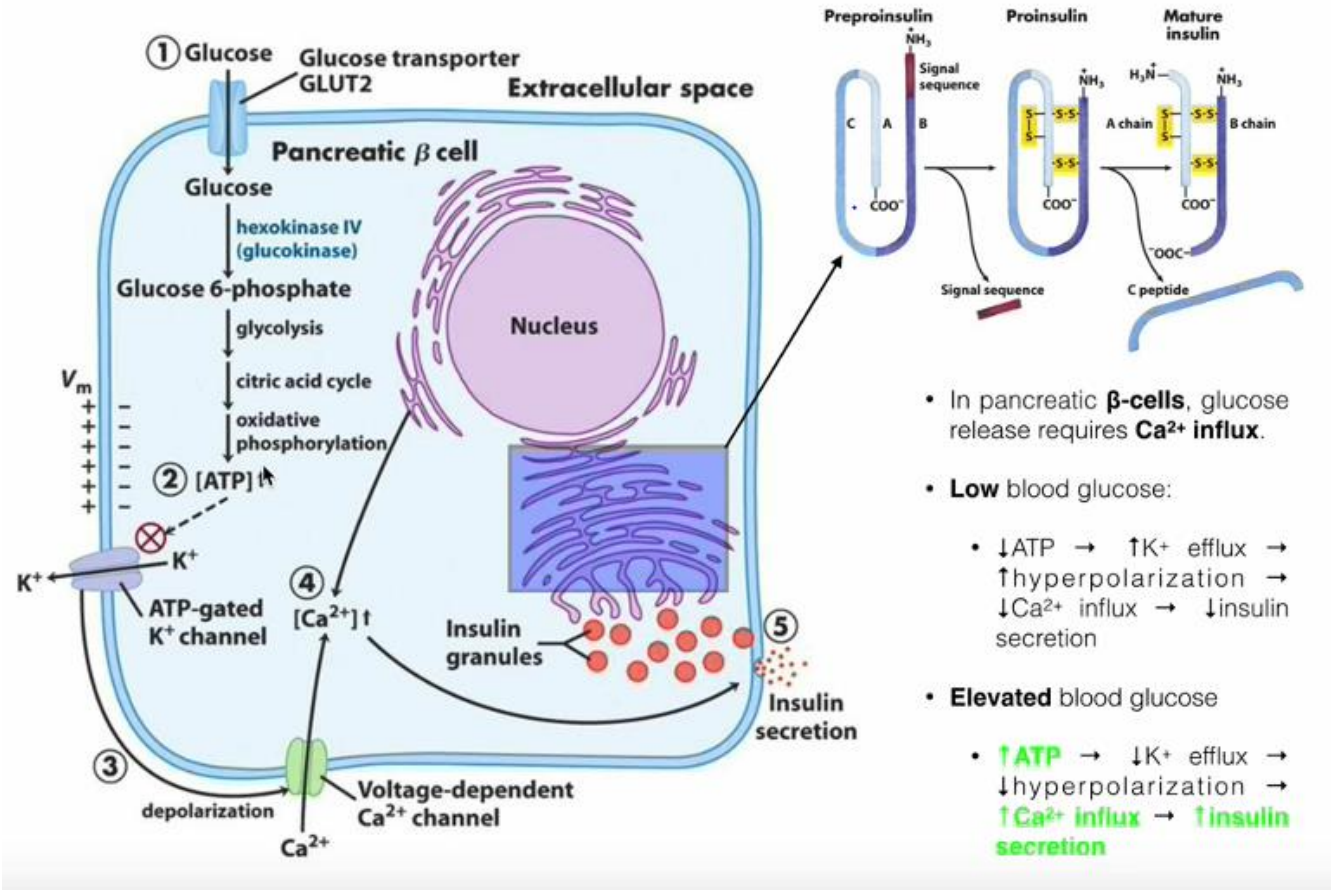
Major Risk Factors for Type 2 Diabetes

- Overweight (BMI ≥25 kg/m2 or ≥23 kg/m2 in Asian Americans)
- Physical inactivity
- First-degree relative with diabetes
- Member of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Female with a history of delivering a baby weighing >4 kg or prior diagnosis of GDM
- Hypertension (≥140/90 mm Hg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dL (0.90 mmol/L) or triglyceride level >250 mg/dL (2.82 mmol/L) or both
- Female with polycystic ovary syndrome
- Hemoglobin A1c ≥5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- History of cardiovascular disease
- Age over 45 years

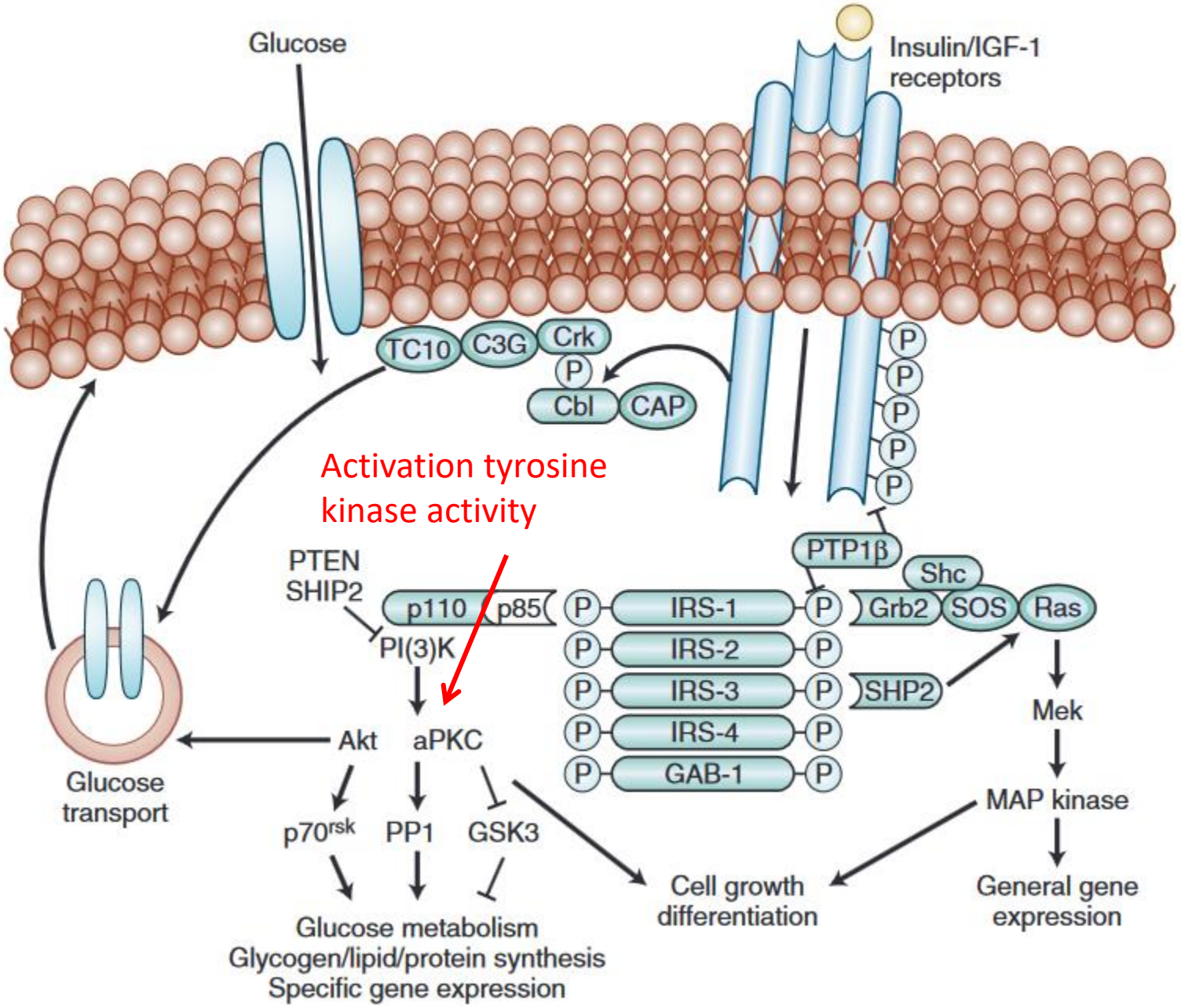


- **Resistance to the action of insulin in peripheral tissues,**
particularly muscle and fat but also liver
- **Defective insulin secretion, particularly in response to a glucose stimulus**
- **Increased glucose production by the liver**

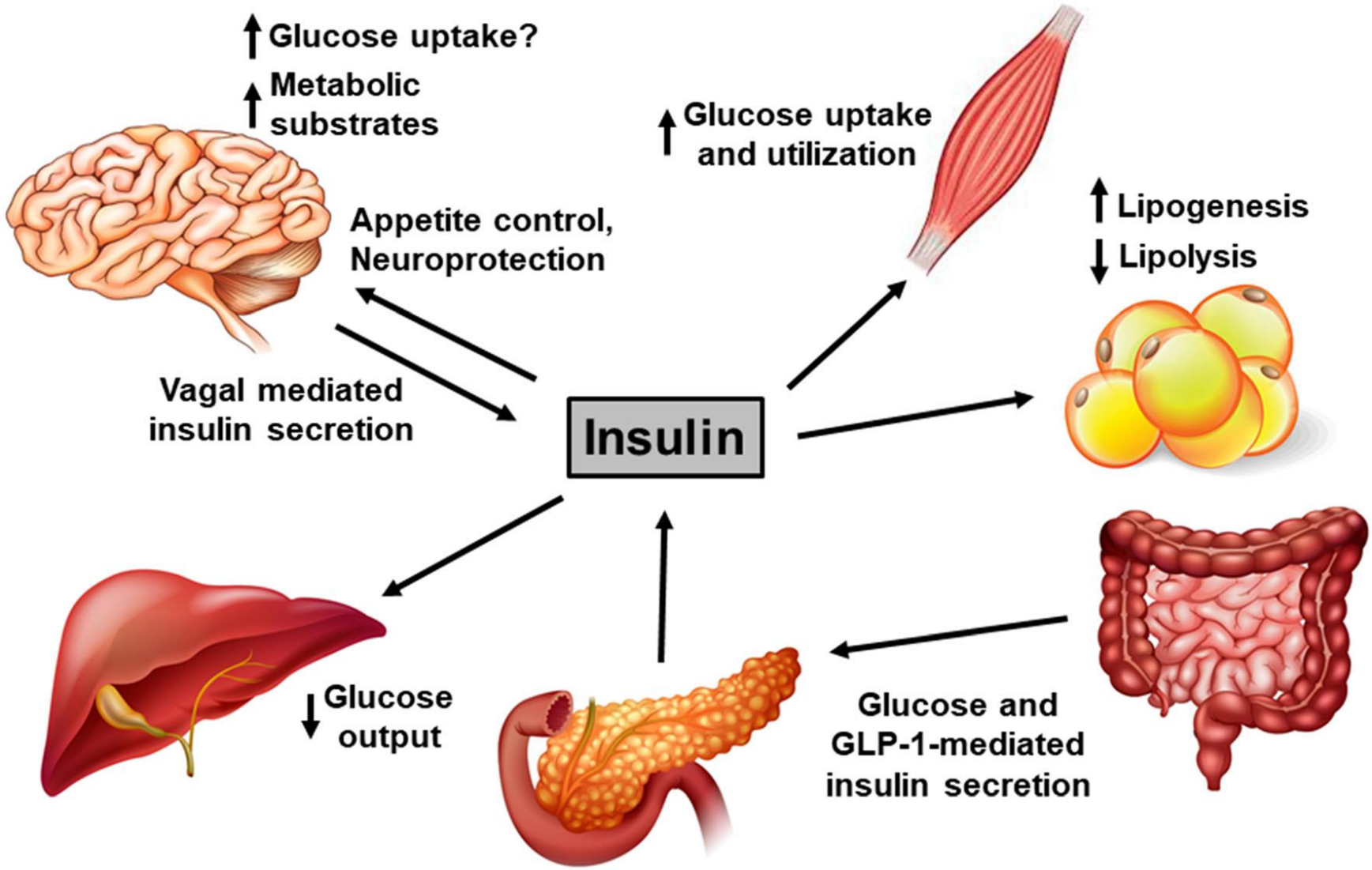
Pancreatic β-cell Glucose Detection & Insulin Release

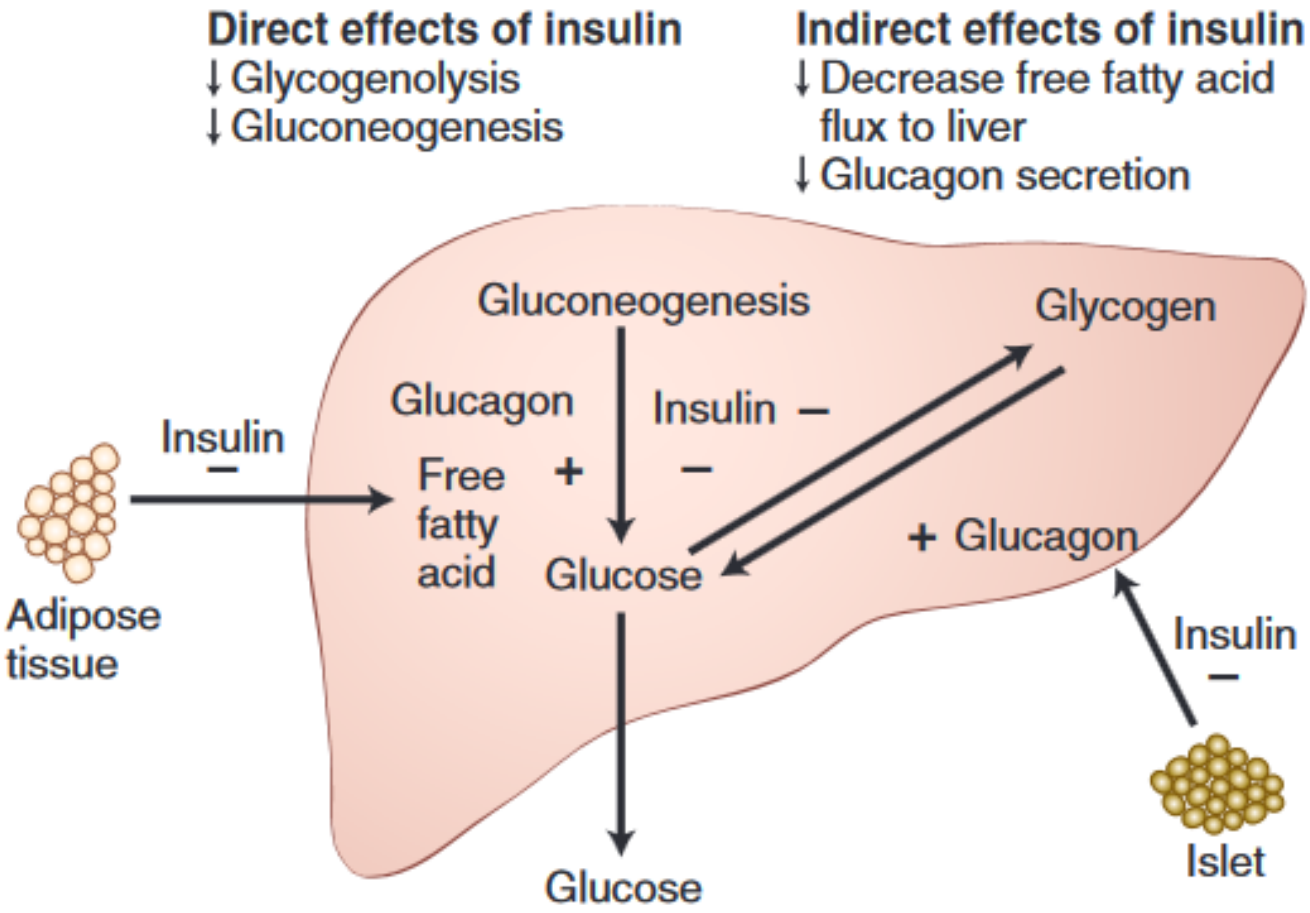


- In pancreatic **β-cells**, glucose release requires **Ca^{2+} influx**.
- **Low** blood glucose:
  - ↓ATP → ↑K^+ efflux → ↑hyperpolarization → ↓Ca^{2+} influx → ↓insulin secretion
- **Elevated** blood glucose
  - ↑ATP → ↓K^+ efflux → ↓hyperpolarization → ↑Ca^{2+} influx → ↑insulin secretion


Glucose
Insulin/IGF-1
receptors
TC10
C3G
Crk
P
Cbl
CAP
P
P
P
P
P
Activation tyrosine
kinase activity
PTP1β
PTEN
SHIP2
Shc
p110
p85
P
IRS-1
P
Grb2
SOS
Ras
PI(3)K
P
IRS-2
P
P
IRS-3
P
SHP2
Mek
P
IRS-4
P
Akt
aPKC
P
GAB-1
P
Glucose
transport
MAP kinase
p70rsk
PP1
GSK3
Cell growth
differentiation
General gene
expression
Glucose metabolism
Glycogen/lipid/protein synthesis
Specific gene expression

Insulin action on multiple tissues




Direct effects of insulin
↓ Glycogenolysis
↓ Gluconeogenesis
Indirect effects of insulin
↓ Decrease free fatty acid flux to liver
↓ Glucagon secretion
Gluconeogenesis
Glycogen
Glucagon
Insulin –
Insulin
–
Free fatty acid
+
Glucose
+ Glucagon
Adipose tissue
Insulin
–
Glucose
Insulin
–
Islet

Insulin Resistance(Diminished insulin sensitivity)

- presence of an impaired biologic response to either exogenously administered or endogenously secreted insulin.
- Insulin resistance is primarily manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and impaired insulin suppression of adipocyte lipolysis and hepatic glucose output.

  (affects the muscle, liver, and adipose tissues).

Insulin Resistance(Diminished insulin sensitivity)

- Insulin resistance → increases gluconeogenesis in the liver and impairs glucose uptake and utilization in muscle →lipolysis → large amounts of non-esterified fatty acids (NEFAs) → inhibit insulin secretion, by enhancing the accumulation of triglycerides within the β cells.
- adipose tissue produces cytokines, such as TNF-α, resistin and IL-6, all of which have been shown to interfere with insulin action.
- TNF-α inhibit tyrosine kinase activity at the insulin receptor and decrease expression of the glucose transporter GLUT-4.
- Resistin is an adipocyte-secreted hormone that increases insulin resistance

Insulin Resistance(Diminished insulin sensitivity)

- Adiponectin is a hormone with anti-inflammatory and insulin-sensitising properties that is secreted solely by fat cells.
- It suppresses hepatic gluconeogenesis and stimulates fatty acid oxidation in the liver and skeletal muscles, as well as increasing muscle glucose uptake and insulin release from the β cells.
- Circulating adiponectin is reduced in obesity.

MODY

Monogenic Forms of Diabetes
Forms Associated With Insulin Resistance
Mutations in the insulin receptor gene
Type A insulin resistance
Leprechaunism
Rabson-Mendenhall syndrome
Lipoatrophic diabetes
Mutations in the PPARγ gene
Forms Associated With Defective Insulin Secretion
Mutations in insulin or proinsulin genes
Mitochondrial gene mutations
Maturity-onset diabetes of the young (MODY)
HNF-4α (MODY 1)
Glucokinase (MODY 2)
HNF-1α (MODY 3)
IPF1 (MODY 4)
HNF-1β (MODY 5)
NeuroD1/BETA2 (MODY 6)

HNF, hepatocyte nuclear factor; IPF, insulin promoter factor; NeuroD1/BETA2, neurogenic differentiation 1/beta cell E-box *trans*-activator 2; PPAR, peroxisome proliferator-activated receptor.

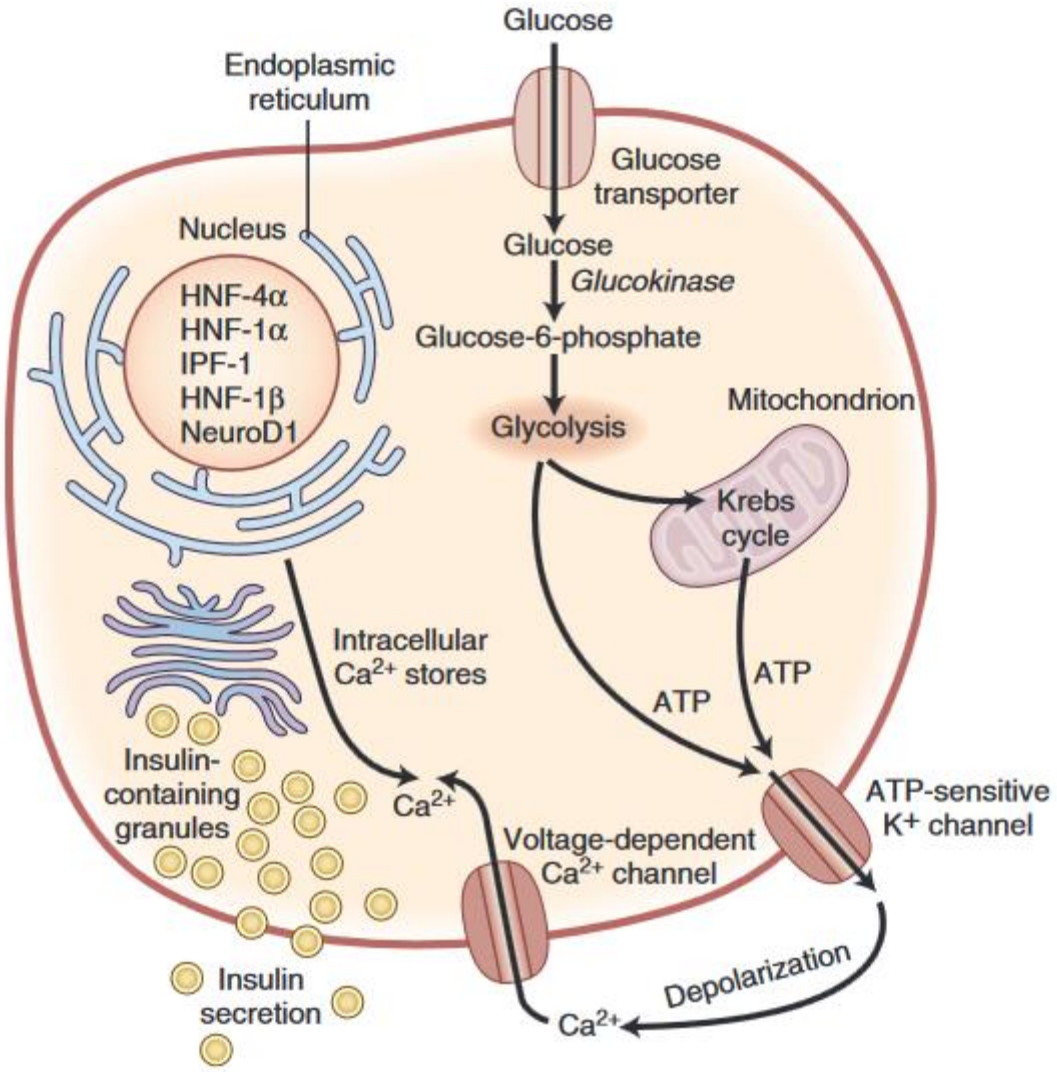


Figure 31-2 Model of a pancreatic beta cell and the proteins implicated in maturity-onset diabetes of the young. ATP, adenosine triphosphate; HNF, hepatocyte nuclear factor, IPF, insulin promoter factor; NeuroD1, neurogenic differentiation 1. (From Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med.* 2001;345:971.)

Diabetic Complications

- Chronic hyperglycemia → complications
  - Cardiac disease
  - Renal failure
  - Neuropathy
  - Blindness
- **Two key underlying mechanisms**
  - Non-enzymatic glycation
  - Sorbitol accumulation

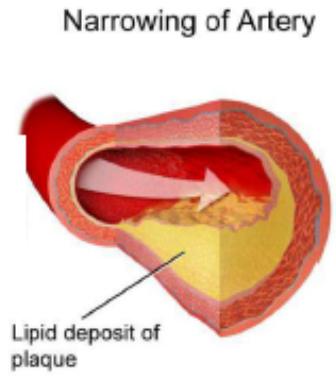
Non-enzymatic Glycation

- Glucose added to amino groups on proteins
- No enzyme required
- Driven by high glucose levels
- Leads to crosslinked proteins
- "Advanced glycosylation end products" (AGEs)

Atherosclerosis

Diabetic Macroangiopathy

- AGEs trap LDL in large vessels → atherosclerosis
- **Coronary artery disease**
  - Angina, myocardial infarction
- **Stroke/TIA**
- **Peripheral vascular disease**
  - Claudication
  - Arterial ulcers
  - Poor wound healing
  - Gangrene



BruceBlaus/Wikipedia

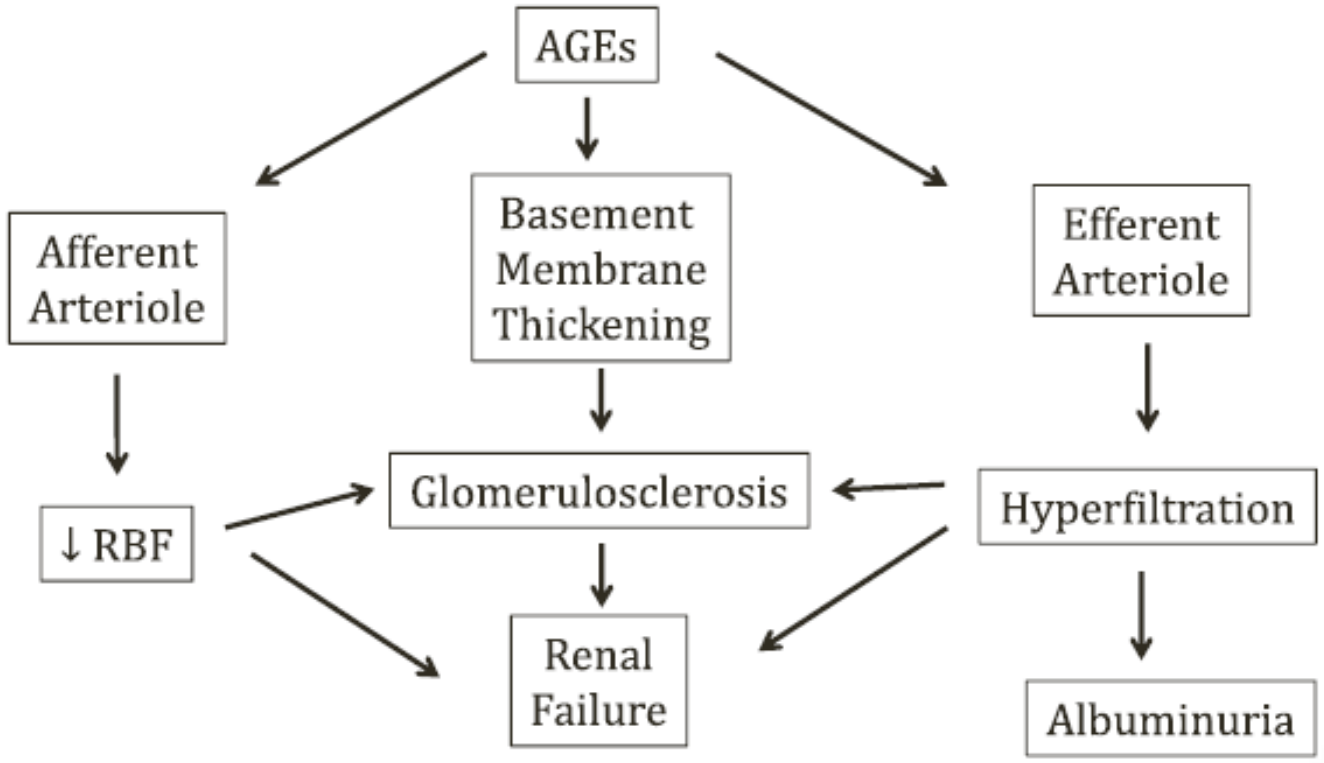
Diabetic Kidney Disease

Diabetic Microangiopathy

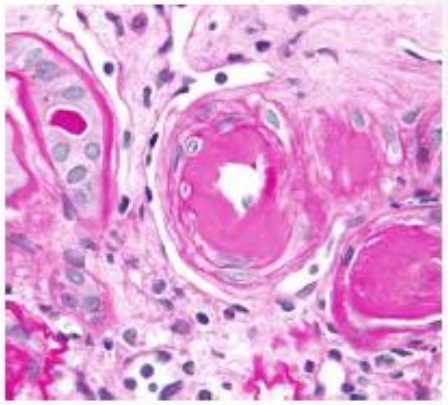
- AGEs → damage to **glomerulus** and **arterioles**
- Leads to **end stage kidney disease** in many diabetics

Diabetic Kidney Disease

Diabetic Microangiopathy



Renal Arterioles



Nephron/Wikipedia

- Hyaline arteriosclerosis
  - Thickening of arterioles
  - Also seen in HTN
- Can result from AGEs
  - Crosslinking of collagen
- Commonly occurs in **kidneys** of diabetics
  - Can involve afferent **AND efferent** arteriole
  - Afferent arteriole: Ischemia
  - Efferent arteriole: Hyperfiltration
  - Efferent arteriosclerosis rarely seen except in diabetes

Proteinuria in Diabetics

- Annual screening for albumin in urine
- Evidence of protein is indication for **ACE-inhibitor**
- ACEi shown to reduce progression to ESRD
  - Potential mechanism is dilation of efferent arteriole
  - Reduction in hyperfiltration

Glomerular Basement Membranes

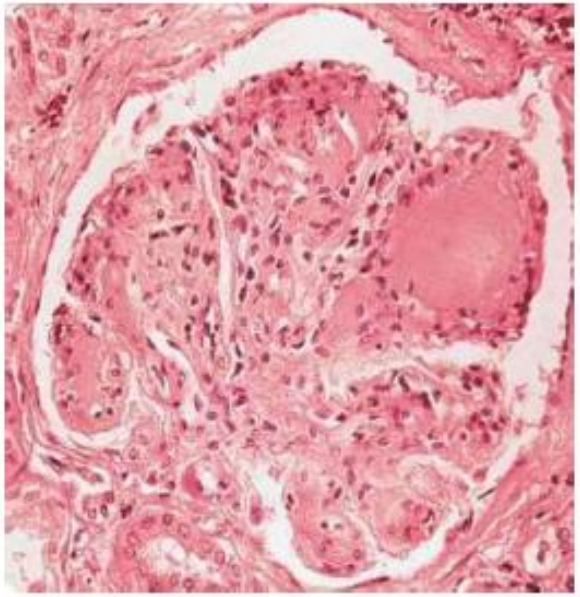
- AGEs → diffuse **basement membrane thickening**
- Visible on electron microscopy
- Can lead to mesangial proliferation in glomeruli
- End result is glomerulosclerosis

Glomerulosclerosis

- Diffuse glomerulosclerosis
  - Deposits of proteins (collagen IV)
  - Diffusely on basement membranes of glomeruli capillary loops
  - Mesangial cell proliferation
  - Also occurs with aging and hypertension
  - If severe → **nephrotic syndrome**
- **Nodular** glomerulosclerosis
  - Nodules form in periphery of glomerulus in mesangium
  - Rarely occurs except in diabetes
- Can lead to fibrosis/scarring of entire kidney

Kimmelstiel-Wilson Nodules

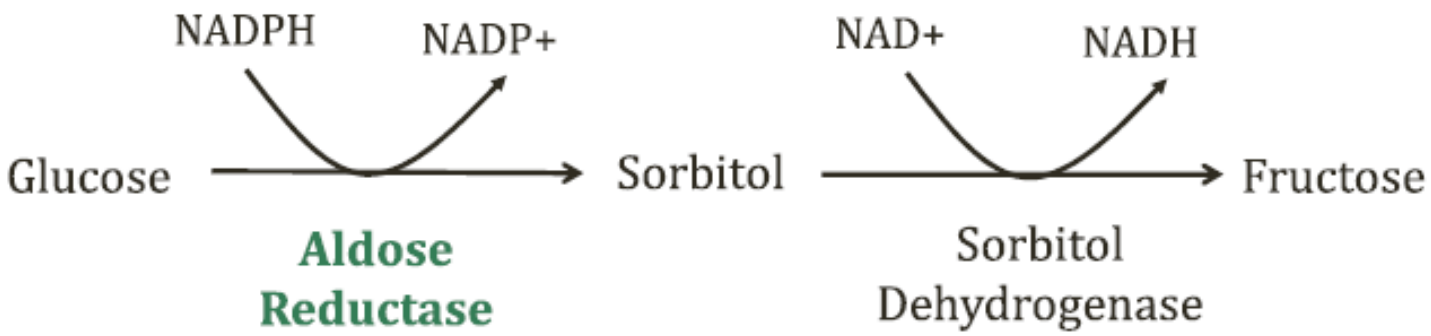
- Hallmark of nodular sclerosis of diabetes
- Pathognomonic of diabetic kidney disease



bilalbanday

Sorbitol Accumulation

Polyol Pathway

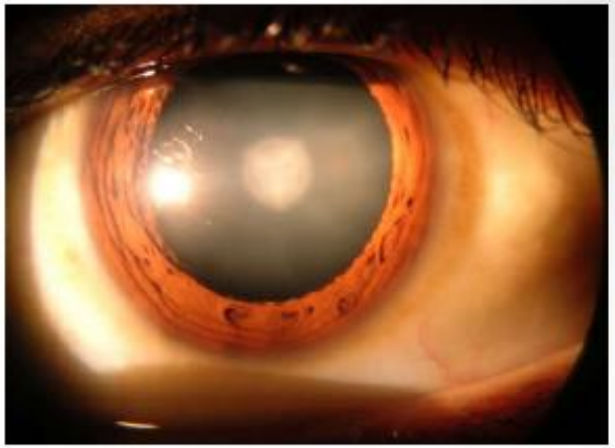


Polyol Pathway

- Little activity at physiologic glucose levels
- Chronic hyperglycemia can lead to ↑sorbitol
- Sorbitol is osmotic agent
- Draws in fluid → **osmotic damage**
- Likely involved in many diabetic complications
  - Cataracts
  - Neuropathy

Cataracts

- Sorbitol accumulates in **lens**
- ↑ osmolarity
- Fluid into lens
- Opacification over time



Rakesh Ahuja, MD/Wikipedia

Neuropathy

- **Sorbitol** can accumulate in **Schwann cells**
  - Myelinating cells of peripheral nerves
  - Osmotic damage → neuropathy

Lifestyle Intervention

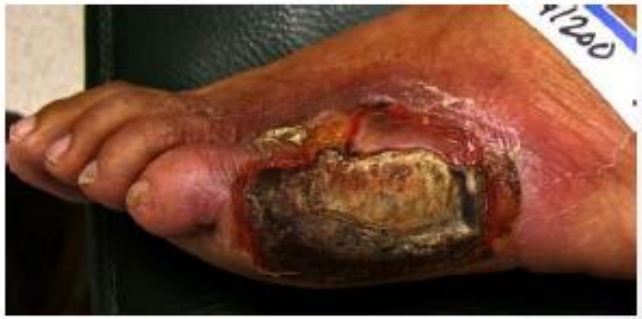
- The components of lifestyle intervention include medical nutrition counseling, exercise recommendations, and comprehensive diabetes education.

Neuropathy

- Classically causes "stocking-glove" sensory loss
  - Longest axons affected most
  - Often feet/legs
  - Worse distally; better proximally
- Loss of **vibration sense**, **proprioception**
- Impairment of pain, light touch, temperature
- **Autonomic neuropathy**
  - Postural hypotension
  - Delayed gastric emptying

Diabetic Foot Disease

- Neuropathy + ischemia can lead to:
  - Ulcers
  - Infection
  - **Amputation**
- Made worse by poor wound healing from PVD
- Prevention: **Regular foot exams**
- Ulcer treatment:
  - Wound management
  - Sometimes antibiotics
  - Hyperbaric oxygen chamber



DrGnu/Wikipedia

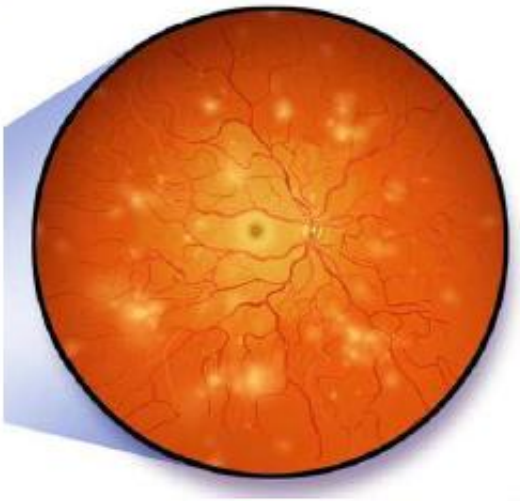
Diabetic Retinopathy

- Can cause blindness among diabetics
- Multiple factors likely involved:
  - Capillary basement membrane thickening (AGEs)
  - Hyaline arteriosclerosis
- **Pericyte degeneration**
  - Cells that wrap capillaries
  - Evidence of sorbitol accumulation
  - **Microaneurysms**
  - Rupture → **hemorrhage**
- Annual screening for prevention

Diabetic Retinopathy

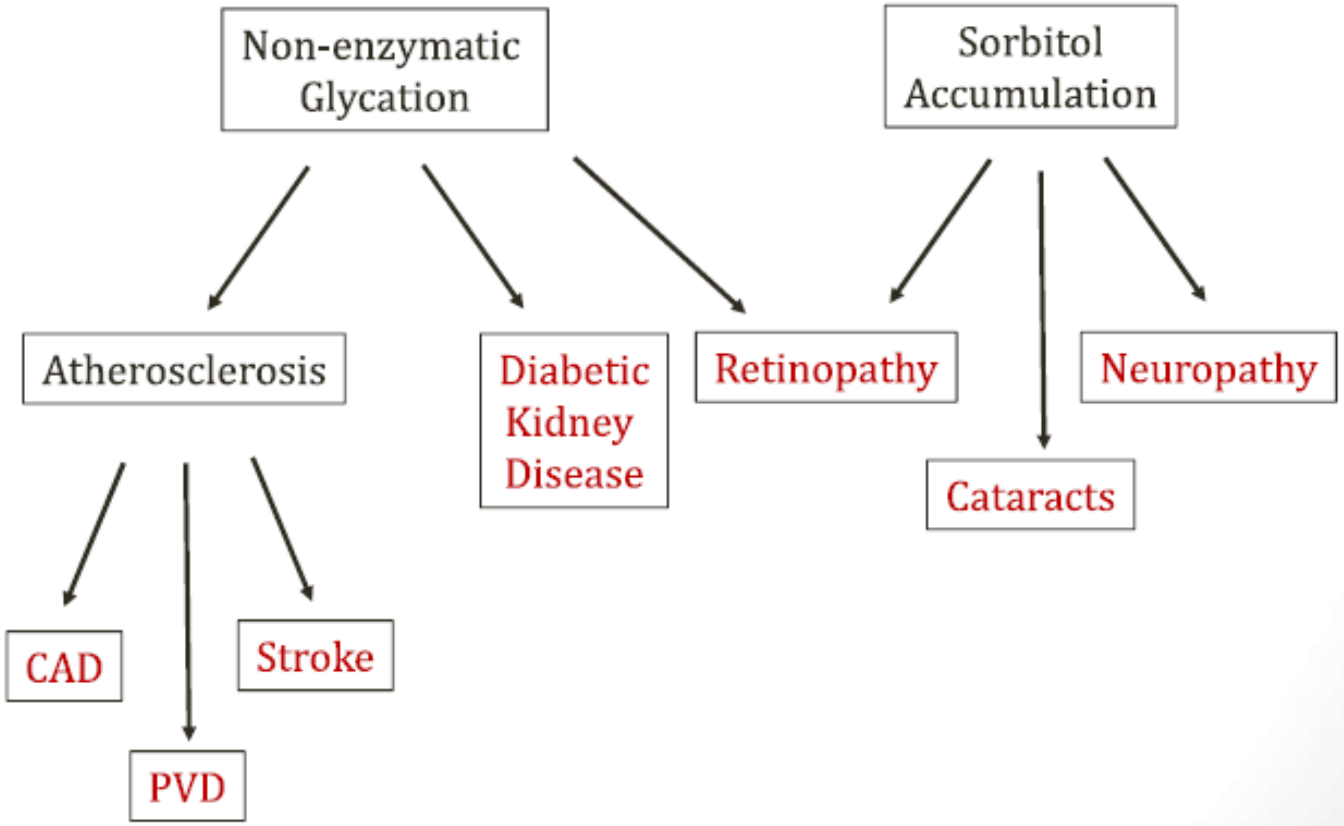
Findings

- Microaneurysms, Hemorrhages
  - Loss of pericytes
- Exudates
  - Leakage proteins, lipids
- Cotton-wool spots
  - Nerve infarctions
  - Occlusion of precapillary arterioles
- Vessel proliferation ("proliferative retinopathy")
  - Retinal ischemia → new vessel growth
  - "Neovascularization"



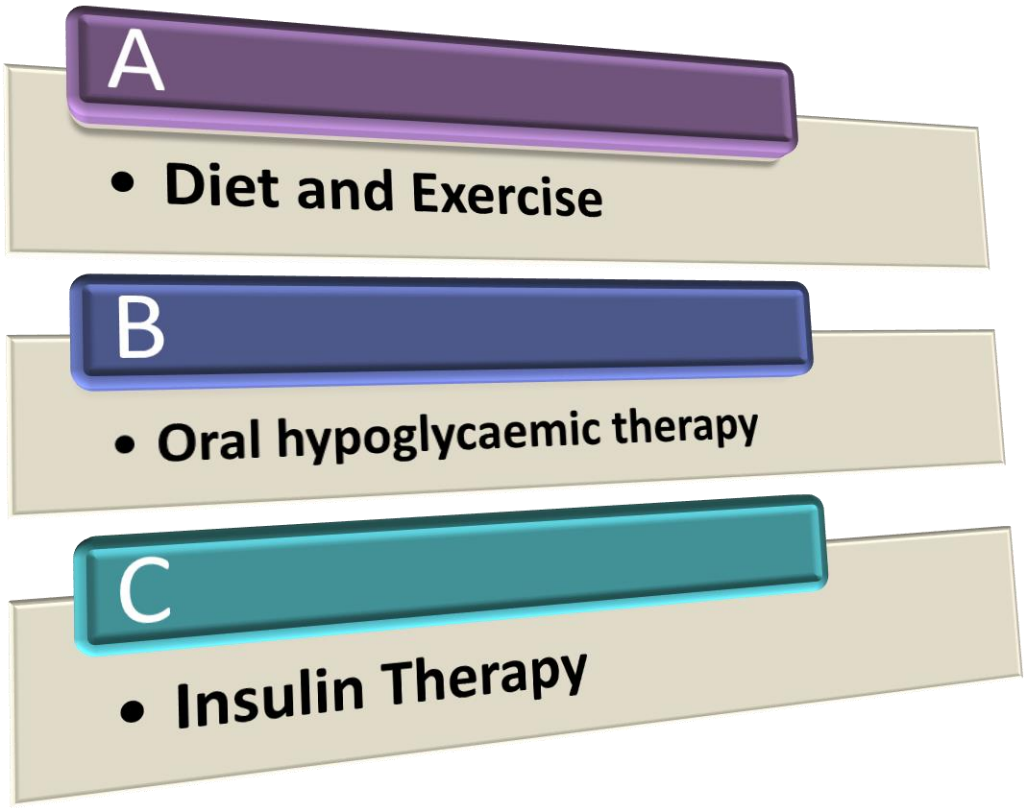
"Blausen gallery 2014"
Wikiversity Journal of Medicine.

Diabetes Complications



Management of DM

- The major components of the treatment of diabetes are:



Exercise

- Physical activity promotes weight reduction and improves insulin sensitivity, thus lowering blood glucose levels.

- Together with dietary treatment, a programme of regular physical activity and exercise should be considered for each person. Such a programme must be tailored to the individual's health status and fitness.

- People should, however, be educated about the potential risk of hypoglycaemia and how to avoid it.

A. Diet

- Diet is a basic part of management in every case. Treatment cannot be effective unless adequate attention is given to ensuring appropriate nutrition.

- **Dietary treatment should aim at:**
  - ensuring weight control
  - providing nutritional requirements
  - allowing good glycaemic control with blood glucose levels as close to normal as possible
  - correcting any associated blood lipid abnormalities

A. Diet (cont.)

The following principles are recommended as dietary guidelines for people with diabetes:

- Dietary fat should provide *25-35% of total intake of calories but saturated fat intake* should not exceed 10% of total energy. Cholesterol consumption should be restricted and limited to 300 mg or less daily.

- Protein intake can range between 10-15% total energy (0.8-1 g/kg of desirable body weight). Requirements increase for children and during pregnancy. Protein should be derived from both animal and vegetable sources.

- Carbohydrates provide *50-60% of total caloric content of the diet.* Carbohydrates should be complex and high in fibre.

- Excessive salt intake is to be avoided. It should be particularly restricted in people with hypertension and those with nephropathy.

Pharmacotherapy for Type 2 Diabetes Mellitus

I. Insulin Sensitizers With Predominant Action in the Liver (biguanide)

- **Metformine** – stimulate skeletal muscle glucose uptake and inhibition of hepatic gluconeogenesis.

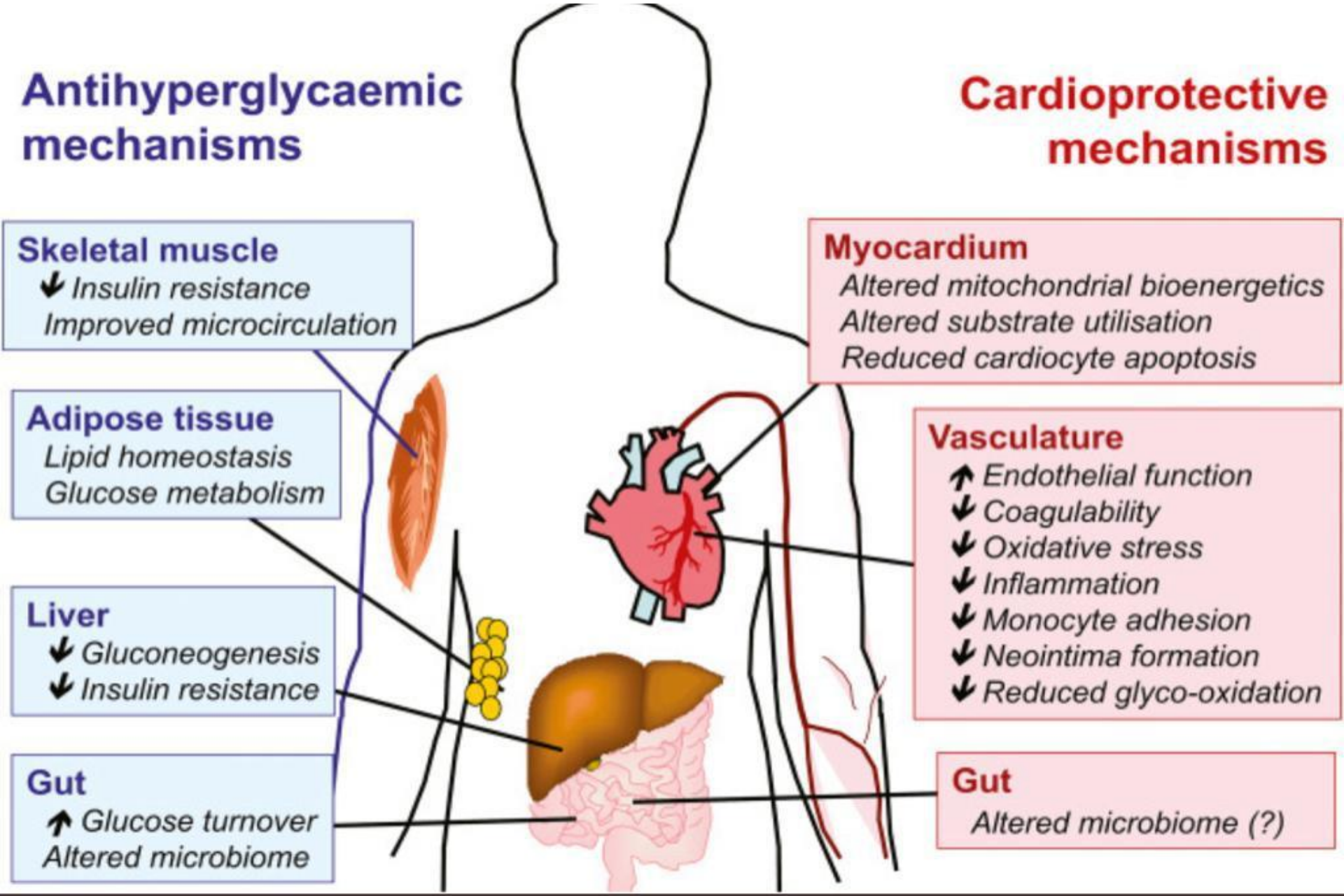
The major clinical activity of metformin is to reduce hepatic gluconeogenesis and glucose production, and improves insulin sensitivity in peripheral tissues.

- Adverse events are gastrointestinal : nausea, diarrhea, crampy abdominal pain, and dyspepsia , very rare can cause lactic acidosis.
- Not associated with a significant risk of hypoglycemia.
- Does not cause weight gain.
- contraindicated in patients with :-

(1)renal insufficiency estimated glomerular filtration rate (eGFR) less than 35 mL/minute per 1.73 m2.

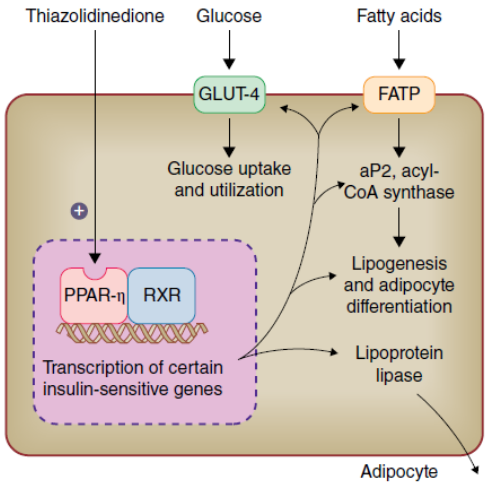
(2)hepatic insufficiency and in the setting of alcohol abuse.

Biguanide mechanism of action



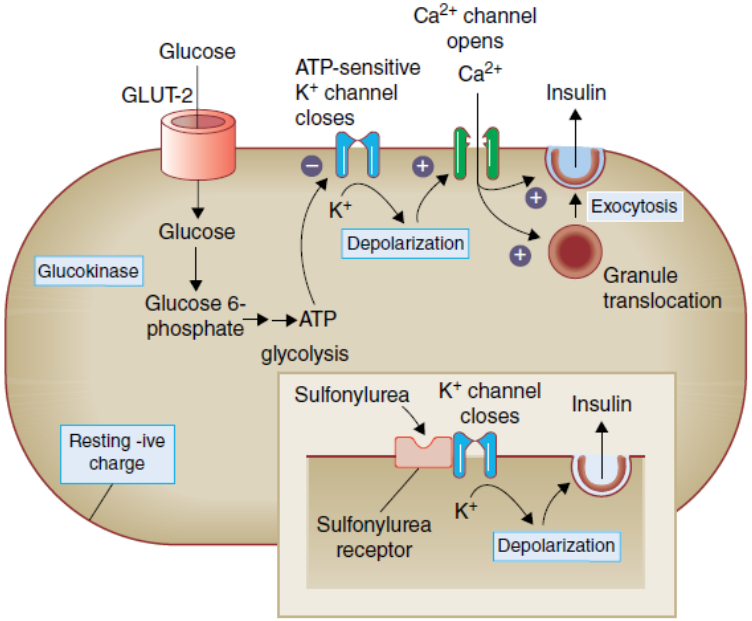
II. Insulin Sensitizers With Predominant Action in Peripheral Insulin-Sensitive Tissues - thiazolidinedione class (TZDs, or glitazones).

- **pioglitazone and rosiglitazone**
- These agents work through binding and modulation of the activity of peroxisome proliferator-activated receptors (PPARs), leads to improvement in glycemic control over weeks to months in parallel with an improvement in insulin sensitivity and a reduction in FFA levels.
- Adverse effects are weight gain and fluid retention (and associated edema formation and hemodilution), and increased risk of bone fractures.
- contraindicated in patients with active hepatocellular disease and in patients with unexplained serum alanine aminotransferase (ALT) levels greater than 2.5 times the upper limit of normal.



Insulin Secretagogues

- insulin secretagogues bind to the SUR1, a subunit of the K ATP potassium channel on the plasma membrane of pancreatic beta cells, leads to closing of the channel, as do increases in intracellular ATP and decreases in ADP resulting in membrane depolarization that causes opening of voltage-dependent calcium channels and calcium influx results in an increase in intracellular calcium, which leads to insulin secretion.
- **Sulfonylurea group , and Glinides**



Insulin Secretagogues

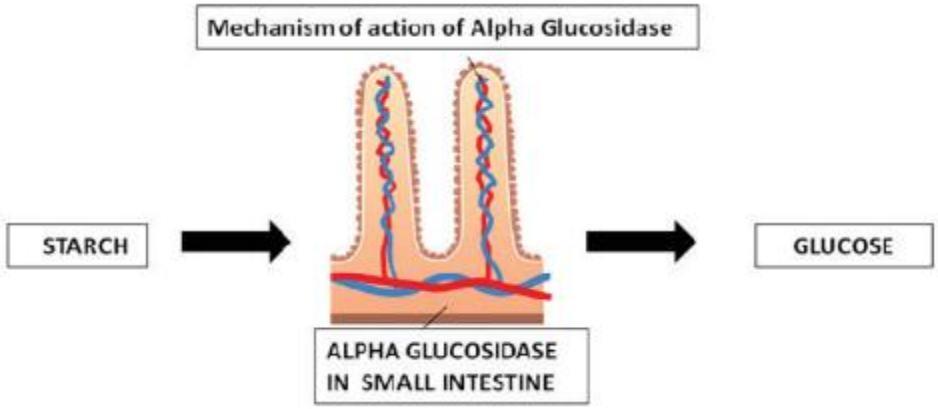
- **Sulfonylurea** (Chlorpropamide, Tolazamide, Tolbutamide, Glipizide, Glimepiride, Gliclazide)
- Adverse effects are weight gain and hypoglycemia.
- Has a long half-life, has an effect on both pre-pandial and post-prandial.
- Contraindicated in renal failure, and hepatic failure.

Insulin Secretagogues

- **Glinides**
- Repaglinide and Nateglinide are members of the meglitinide family of insulin secretagogues, distinct from the sulfonylureas.
- It has a short half-life and a distinct SUR1 binding site.
- it is typically taken with each meal and provides better **postprandial** control and generally less hypoglycemia and weight gain than Sulfonylurea
- Suitable for use in diabetic patients with IRF or with renal failure undergoing dialysis.

Carbohydrate Absorption Inhibitors:

- **α-Glucosidase Inhibitors**
  - inhibit the terminal step of carbohydrate digestion at the brush border of the intestinal epithelium, as a result, carbohydrate absorption is shifted more distally in the intestine and is delayed.
  - Available agents are **acarbose** and **miglitol.**
  - Adverse effects flatulence and gastrointestinal upset.
  - Doesn't cause hypoglycemia .
  - Weight neutral.



Incretin-Related Therapies

- **GLP-1 Receptor Agonists and DPP4 Inhibitors.**
- GLP-1(glucagon like peptide) is produced in intestinal L cells and is secreted in response to nutrients.
- GLP-1 stimulates insulin secretion in a glucose-dependent fashion, inhibits inappropriate hyper-glucagonemia, slows gastric emptying, reduces appetite and improves satiety.
- GLP-1 has a very short half-life in plasma (1 to 2 minutes) due to aminoterminal degradation by the enzyme dipeptidyl peptidase 4 (DPP4).

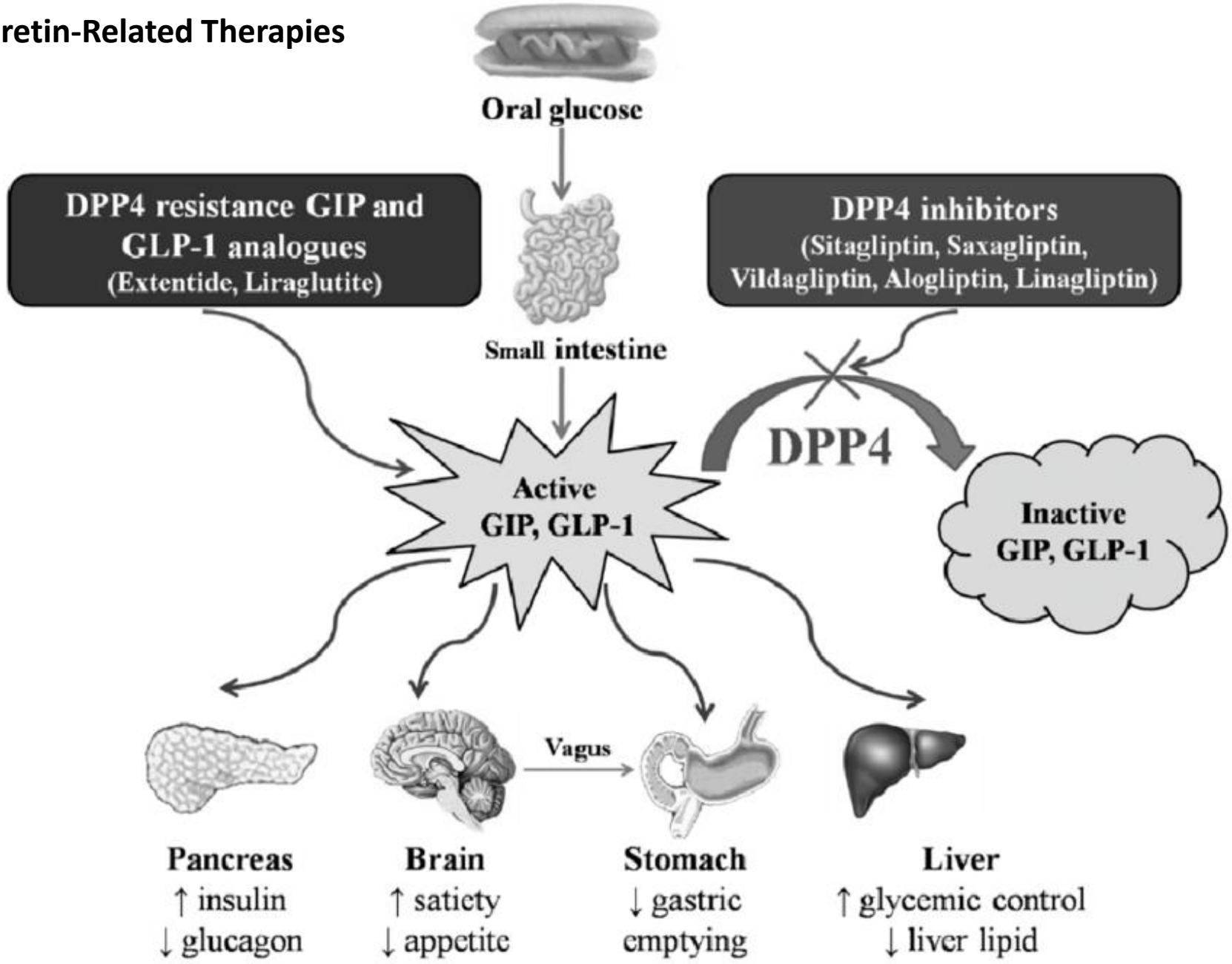
Incretin-Related Therapies

- **DPP4 Inhibitors** (sitagliptin, saxagliptin, linagliptin, and alogliptin)
- they are not associated with nausea because of the lesser increase in GLP-1 activity.
- Weight effect neutral
- Contraindication : history of pancreatitis, and advanced kidney disease (eGFR <30 mL/minute per 1.73 m2), except linagliptin which can be used
- Saxagliptin: increased risk for heart failure hospitalization.

Incretin-Related Therapies

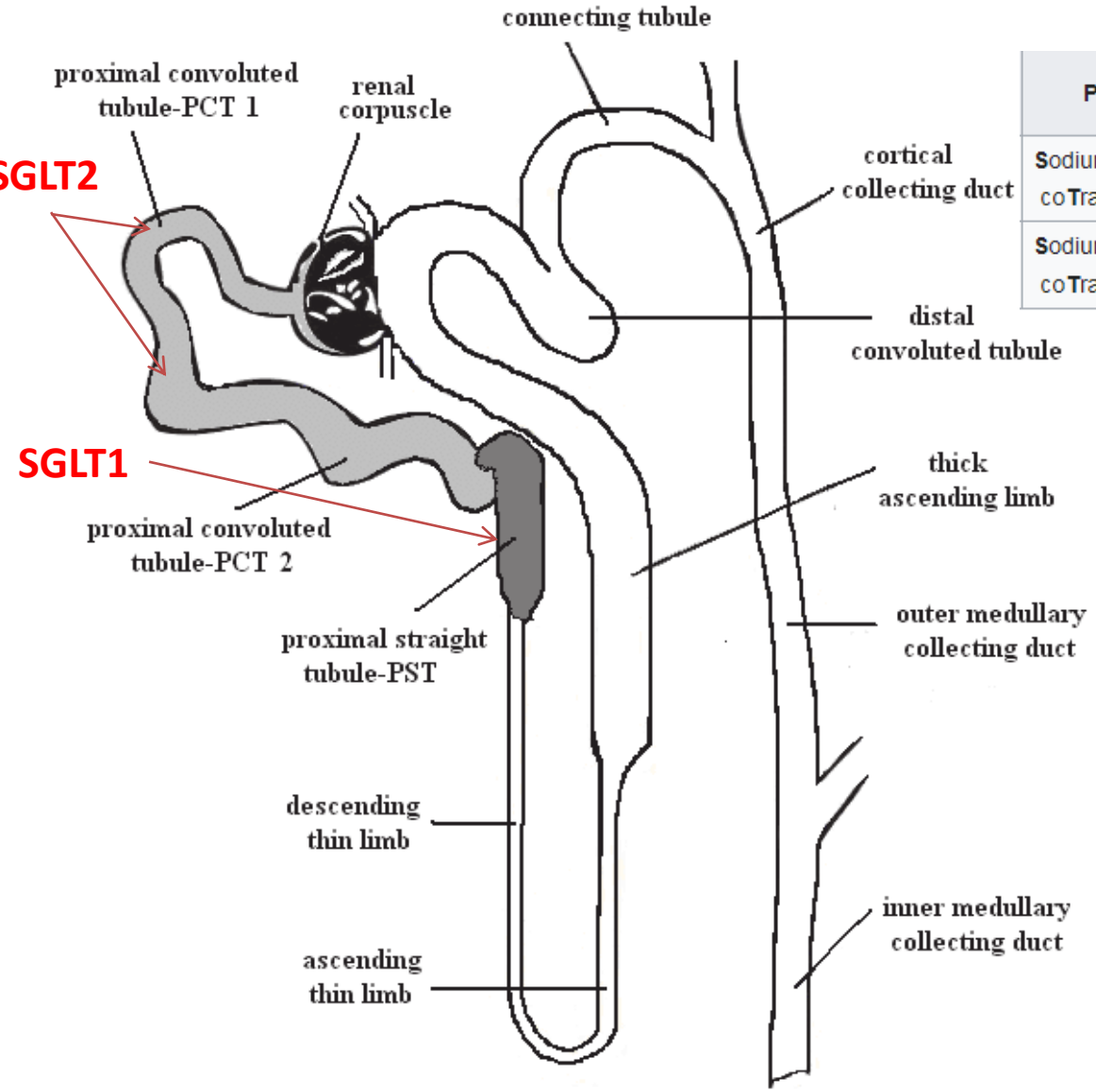
- **GLP-1 Receptor Agonists :** Exenatide, Liraglutide, Dulaglutide, semaglutide, etc.
- Effect :Weight loss and reduction in HbA1c.
- Does not cause hypoglycemia.
- Associated with gastrointestinal adverse effects
- Beneficial effect include weight reduction, and positive cardiovascular outcome (all cause mortality, nonfatal stroke , and nonfatal MI).
- Contraindication : history of pancreatitis, family or personal history of medullary thyroid carcinoma (there is a clear increase in the incidence of these tumors in rodents), and advanced kidney disease (eGFR <30 mL/minute per 1.73 m2).

Incretin-Related Therapies



Sodium-Glucose Transporter-2 Inhibitors. SGLT2i

- Sodium-glucose cotransporters (SGLTs) are important mediators of glucose uptake across apical cell membranes.
- SGLT1 mediates almost all sodium-dependent glucose uptake in the small intestine and kidney's proximal straight tubule.
- SGLT2 mediates almost all sodium-dependent glucose uptake in kidney's proximal convoluted tubule.



Protein	Acronym	Tissue distribution in proximal tubule[2]	Na^+:Glucose Co-transport ratio
Sodium/**GL**ucose co**T**ransporter **1**	SGLT1	S3 segment	2:1
Sodium/**GL**ucose co**T**ransporter **2**	SGLT2	predominantly in the S1 and S2 segments	1:1

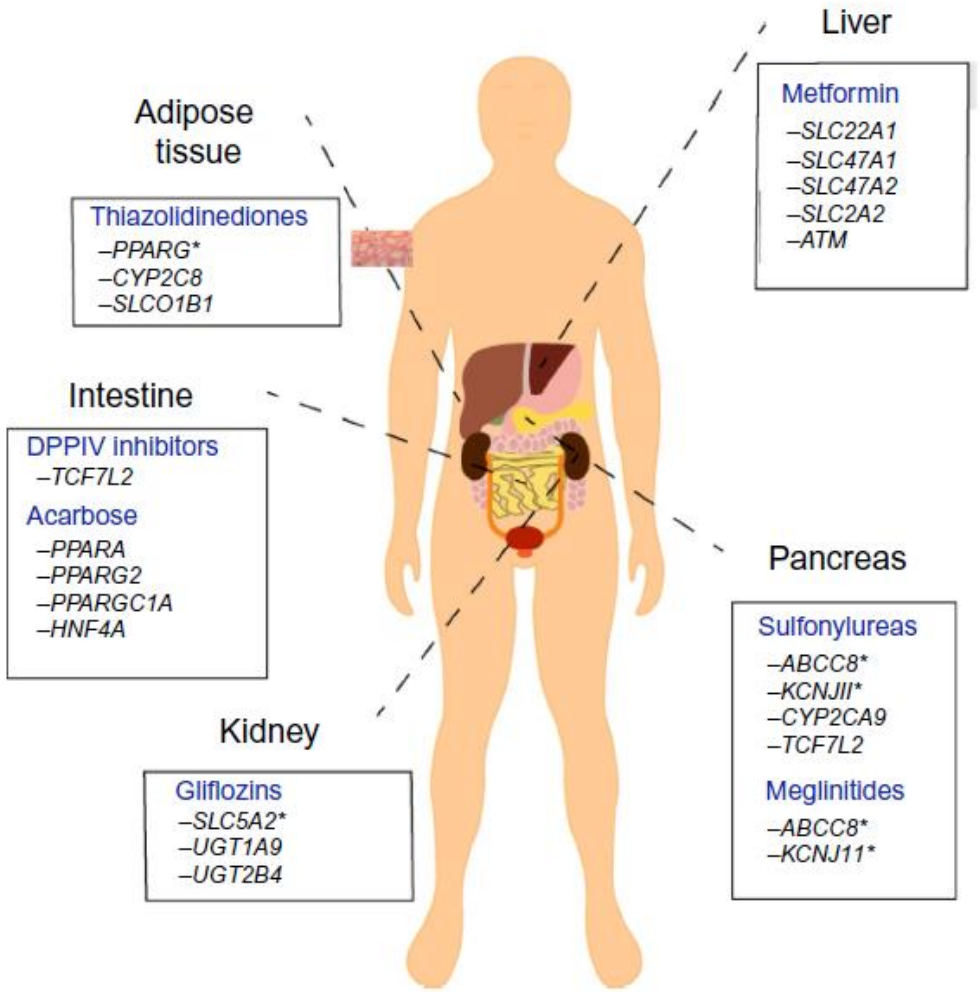
Sodium-Glucose Transporter-2 Inhibitors. SGLT2i

- SGLT2, and to a lesser extent SGLT1, account 90% and nearly 10%,respectively, of glucose reabsorption from the glomerular ultrafiltrate.
- If the plasma glucose concentration is too high (hyperglycemia), glucose passes into the urine (glucosuria) because SGLT are saturated with the filtered glucose.

Sodium-Glucose Transporter-2 Inhibitors. SGLT2i

- **Sodium-Glucose Transporter-2 Inhibitors**(Empagliflozin, Canagliflozin, Dapagliflozin, etc).
- They work by blocking the SGLT2 protein located in the proximal convoluted tubule of the nephron resulting in glycosuria and thereby lowering plasma glucose concentration.
- Beneficial effect include weight reduction, positive cardiovascular outcome (all cause mortality, nonfatal stroke , and nonfatal MI),and lower hospitalization for heart failure.
- Associated with risk of diabetic ketoacidosis, dehydration, increased incidence of genitourinary tract infection “fungal”.
- Canagliflozin :- increased risk of fracture and toe amputation.

Major sites of action of antidiabetic drugs and genes associated with pharmacokinetics or clinical response



BIGUANIDES

Agents: Metformin

Side Effects: GI symptoms
Vitamin B12 deficiency
Rare cases of lactic acidosis

*AWP = 84-108.

GLP-1 RECEPTOR AGONISTS

Agents: Exenatide, Dulaglutide, Liraglutide, Semaglutide, Lixisenatide

Side Effects: FDA black box on risk of thyroid C-cell tumors
GI side effects common
Injection site reactions
Acute pancreatitis risk

†Weight loss varies across the class.
*AWP = 774-1106.

SGLT2 INHIBITORS

Agents: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

Side Effects: ↑ Amputations (FDA black box canagliflozin)
↑ Genital infections
↑ Risk of DKA
↑ Risk of Fournier's gangrene
↑ Risk of fractures (canagliflozin)
↑ Risk of volume depletion

†Efficacy depends on renal function.
*AWP = 338-593.

DPP-4 INHIBITORS

Agents: Sitagliptin, Saxagliptin, Linagliptin, Alogliptin

Side Effects: Rare urticaria/angioedema
↑ HF (saxagliptin)
Potential acute pancreatitis risk
Arthralgia

†Costs will vary by region.
*AWP = 234-475.

SULFONYLUREAS

Agents: Glibenclamide, Glipizide, Glimepiride

Side Effects: FDA black box on increased risk of cardiovascular mortality based on studies of the older sulfonylurea tolbutamide
↑ Risk of hypoglycemia

*AWP = 48-93.

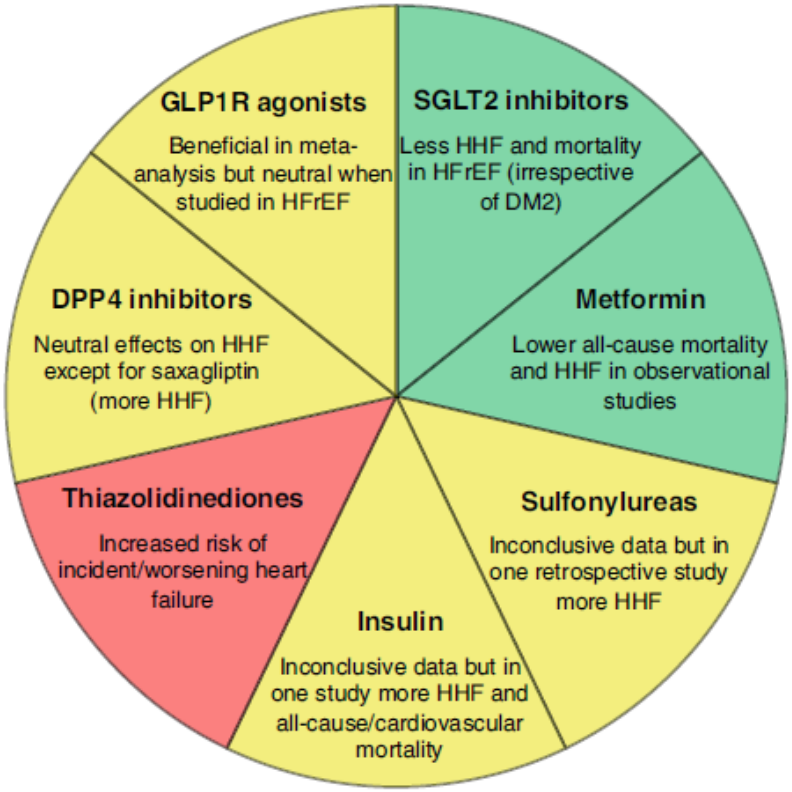
THIAZOLIDINEDIONES

Agents: Pioglitazone, Rosiglitazone

Side Effects: ↑ FDA black box for congestive heart failure
↑ Bone fractures
↑ Bladder cancer (pioglitazone)
↑ Fluid retention (edema)

†Costs will vary by region.
*AWP = 348-407.

Antidiabetic medication and cardiovascular safety



Summary of the effects of antidiabetic agents on heart failure. *ADHF* acute decompensated heart failure, *DM2* diabetes mellitus type 2, *DPP4* dipeptidyl peptidase-4, *GLP1R* glucagon-like peptide-1 receptor, *HHF* heart failure hospitalisation, *HFrEF* heart failure with reduced ejection fraction, *SGLT2* sodium-glucose cotransporter-2