MUNI
PHARM

METABOLIC SYNDROME
DIABETES MELLITUS

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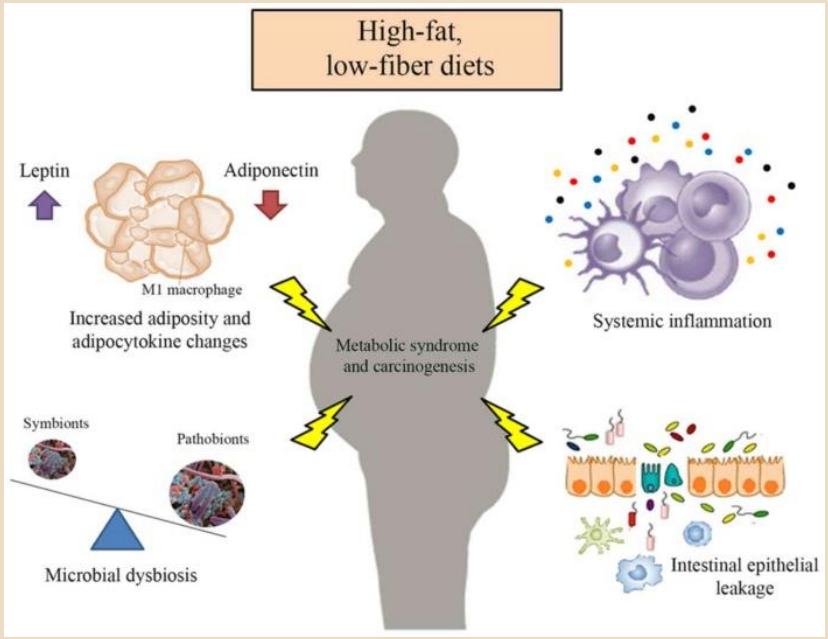
Lecture from Geriatric Pharmacotherapy 31.3. 2023

Metabolic syndrome

- **syndrome X**
- complex combination of
  - **abdominal obesity**
  - **dyslipidemia** (low HDL, high LDL and TAG)
  - **hypertension**
  - **insulin resistance** up to **diabetes mellitus**
  - **prothrombotic state**
  - **proinflammatory state**



Pathogenesis of metabolic syndrome

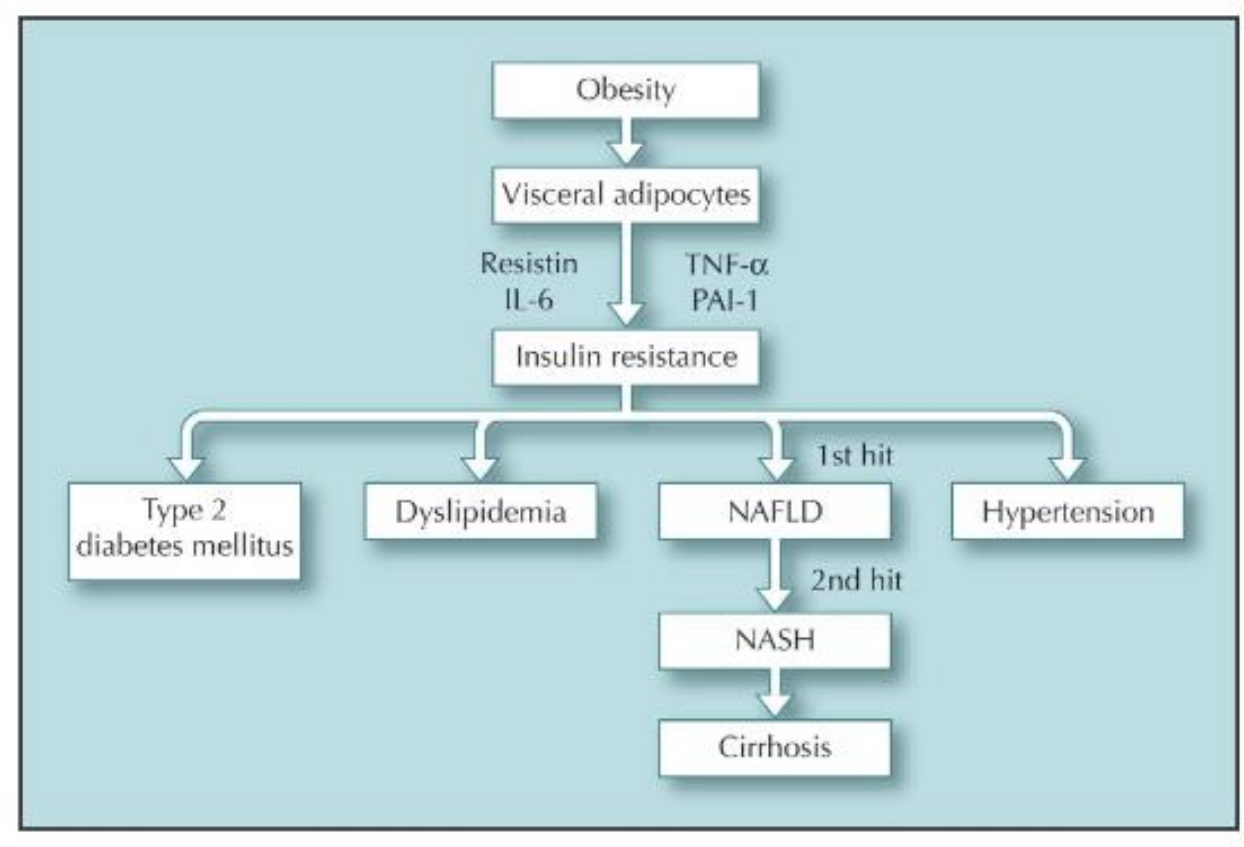


Figure 2. Pathogenesis of metabolic syndrome. IL-6—interleukin-6; NAFLD—nonalcoholic fatty liver disease; NASH—nonalcoholic steatohepatitis; PAI-1—plasminogen activator inhibitor-1; TNF- —tumor necrosis factor- .

Clinical signs of metabolic syndrome

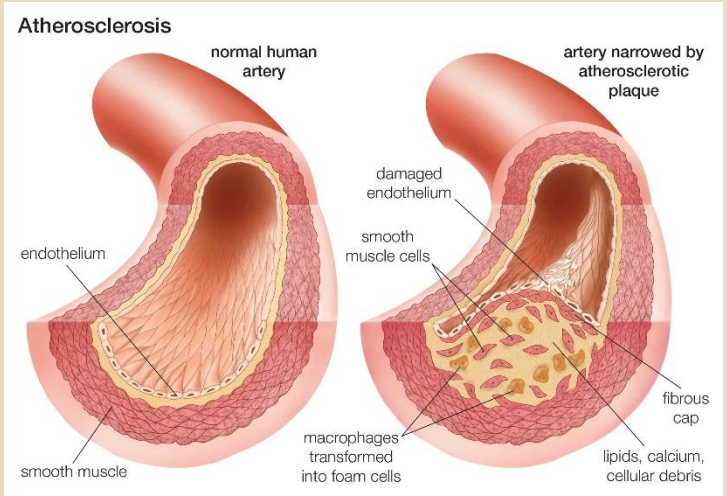
Component	Clinical Cutoff Values
Waist Circumference	≥102 cm in men ≥88 cm in women
Triglycerides	≥150 mg/dL
HDL Cholesterol	<40 mg/dL in men <50 mg/dL in women
Blood Pressure (BP)	≥130 mmHg Systolic BP or ≥85 mmHg Diastolic BP
Fasting Glucose	≥100 mg/dL
Diagnosis	Any 3 of the 5 features above

Obesity

- increasing prevalence because of raised caloric intake and decreased physical activity
- excess total body fat, specifically **central obesity**, is associated with cardiovascular disease risk factors
  - **insulin resistance**
  - **diabetes**
  - **hypertension**
  - **dyslipidemia**
- visceral adipocytes produce **resistin**, **interleukin-6** (IL-6), **plasminogen activator inhibitor-1** (PAI-1), **tumor necrosis factor-α** (TNF-α)
- management of obesity is multifactorial, consists of **exercise**, **diet modification**, **pharmacologic agents** and **surgery**

Dyslipidemia

- characterized by **decreased HDL cholesterol** and **elevated triglycerides (TAG) with LDL cholesterol**, partly as a result of visceral obesity
  - obesity increases fatty acid movements to the portal vein and liver and stimulates TAG production
- greater disposition to **myocardial infarction** and other **cardiovascular complications**



Dyslipidemia treatment

- **lifestyle and diet changes**
  - **omega-3 fatty acids**
- **3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors**
  - key enzyme in cholesterol synthesis
  - low-density lipoprotein (LDL) carriers of cholesterol play a key role in the development of atherosclerosis and coronary heart disease
  - side effects: **muscle pain and weakness**, **rhabdomyolysis**, **liver enzymes disturbances**, increased risk of DM
  - **pravastatin, simvastatin, atorvastatin, lovastatin**

Dyslipidemia treatment

- **fibrates**
  - stimulate **peroxisome proliferator-activated receptor (PPAR) alpha**, which controls the expression of gene products mediating the metabolism of TAG and HDL
  - synthesis of fatty acids, TG and VLDL is reduced
  - high-risk individuals with metabolic syndrome, low HDL cholesterol, or high TAG
  - usually in combination with statins
  - **fenofibrate, clofibrate, gemfibrozil**

- **ezetimibe**
  - **inhibition of cholesterol absorption**
  - combination with statins

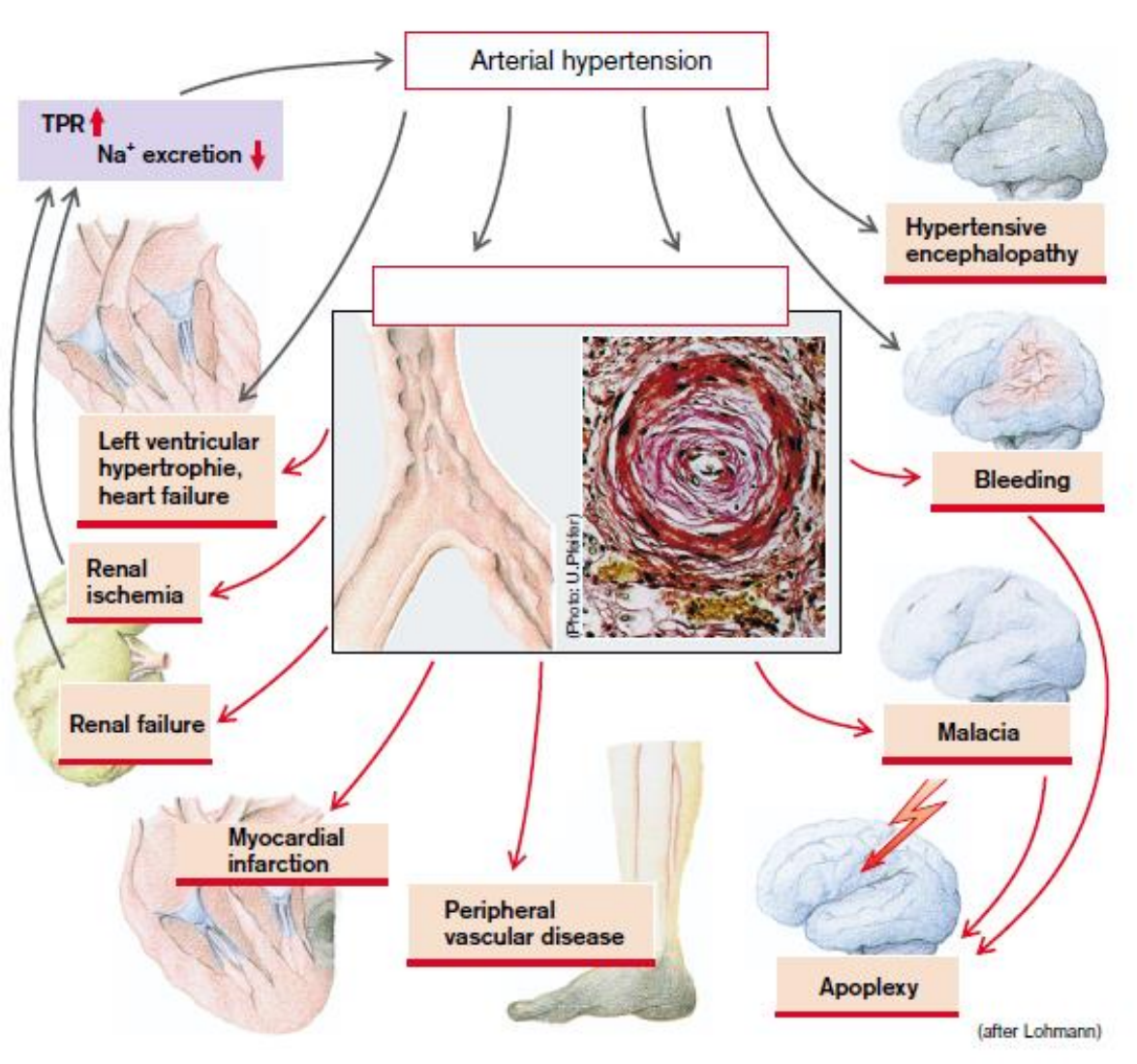
Dyslipidemia treatment

- **proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors**
  - monoclonal antibodies that bind and **inactivate PCSK9**
    - important regulator of the number of LDL receptors, promoting their intracellular degradation
  - marked increase of LDL uptake, thus LDL concentration lowering
  - administered as a subcutaneous injection every two or four weeks
  - **evolocumab, alirocumab**

Hypertension

- in the elderly, physiologic changes leading to stiffening the aorta and other arteries, resulting in the loss of compliance and **increase in peripheral vascular resistance**
- factors contributing to the development of hypertension
  - genetics
  - obesity
  - poor diet and alcohol consumption
- **risk of stroke, cardiovascular events, heart failure, dementia**

Hypertension consequences



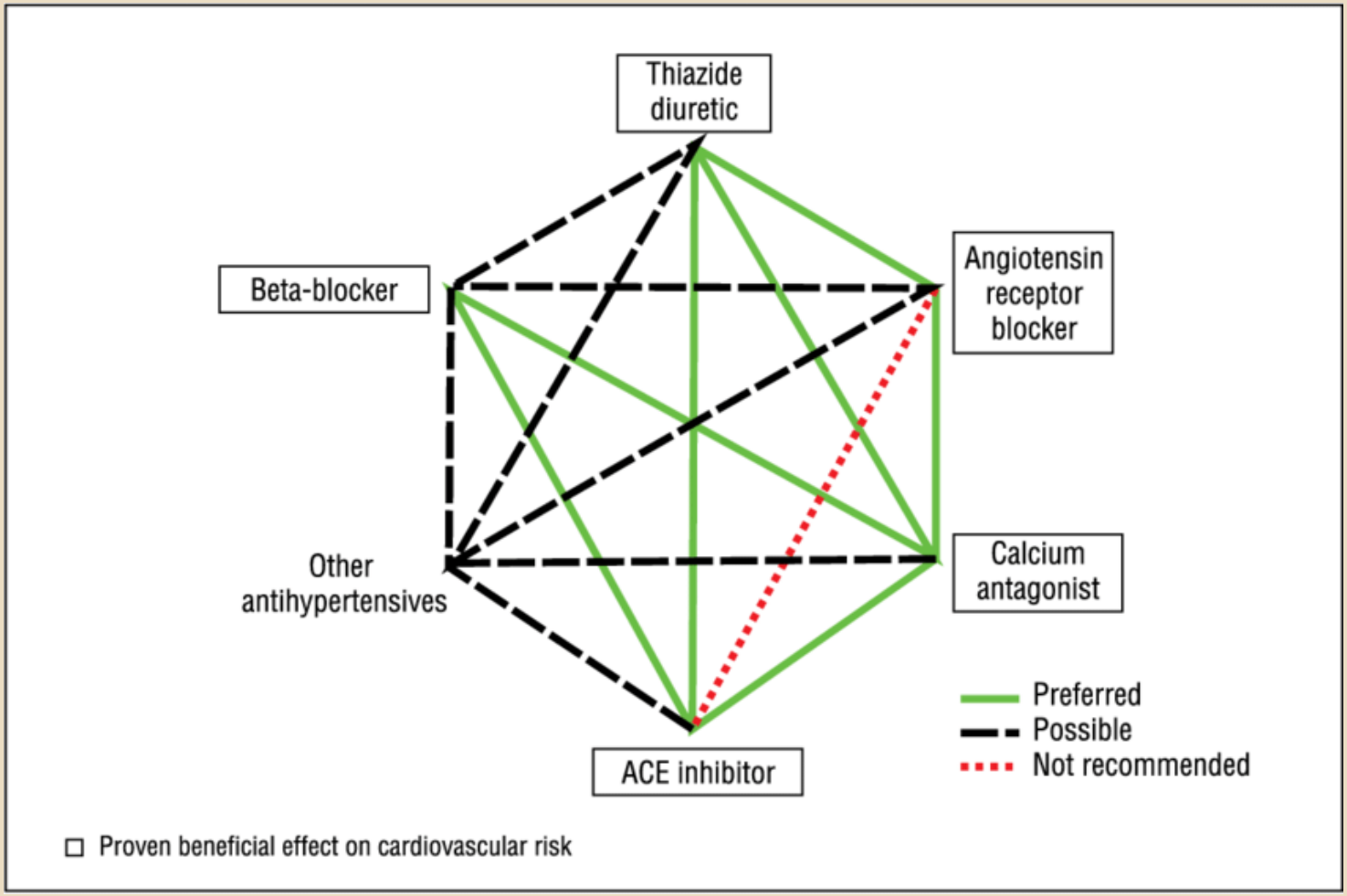
Hypertension treatment

- therapy should be aimed at reducing the blood pressure to a systolic of **less than 140 mmHg**/ diastolic **less than 90 mmHg**
- the choice of antihypertensives should be individually tailored depending on the individual's cardiovascular risk, presence of target organ damage, comorbidities and potential drug AEs
  - especially for postural hypotension
- **fixed-dose combination (FDC),** which is the combination of two antihypertensive drugs in a single tablet, has been shown to improve compliance

Hypertension treatment

- **lifestyle changes**
- **calcium channel blockers**
- **beta blockers**
- **diuretics**
- **angiotensin-converting enzyme inhibitors (ACEIs)**
- **angiotensin II receptor blockers (ARBs)**

Antihypertensive drugs combinations



Calcium channel blockers (CCBs)

- **bind to L-type calcium channels**
  - decrease the systemic vascular resistance
- preventing stroke in elderly patients
- **metabolically neutral**
- except for **peripheral edema**, relatively free of adverse effects
- the lack of adverse metabolic effects represent a major advantage of CCBs over diuretics for a population with metabolic syndrome/insulin resistance
- **nifedipine, lacidipine, isradipine, amlodipine**

Beta blockers (BBs)

- bind to **beta-adrenoceptors**, which **inhibit** normal sympathetic effects
  - decrease arterial blood pressure by reducing cardiac output
- should not be considered appropriate first-line therapy of uncomplicated hypertension in the elderly
- adjunctive hypertensive therapy in patients with other indications such as **heart failure, prior myocardial infarction, or symptomatic coronary disease** in an effort to better prevent cardiovascular disease
- **betaxolol, atenolol, bisoprolol, acebutolol**

Diuretics

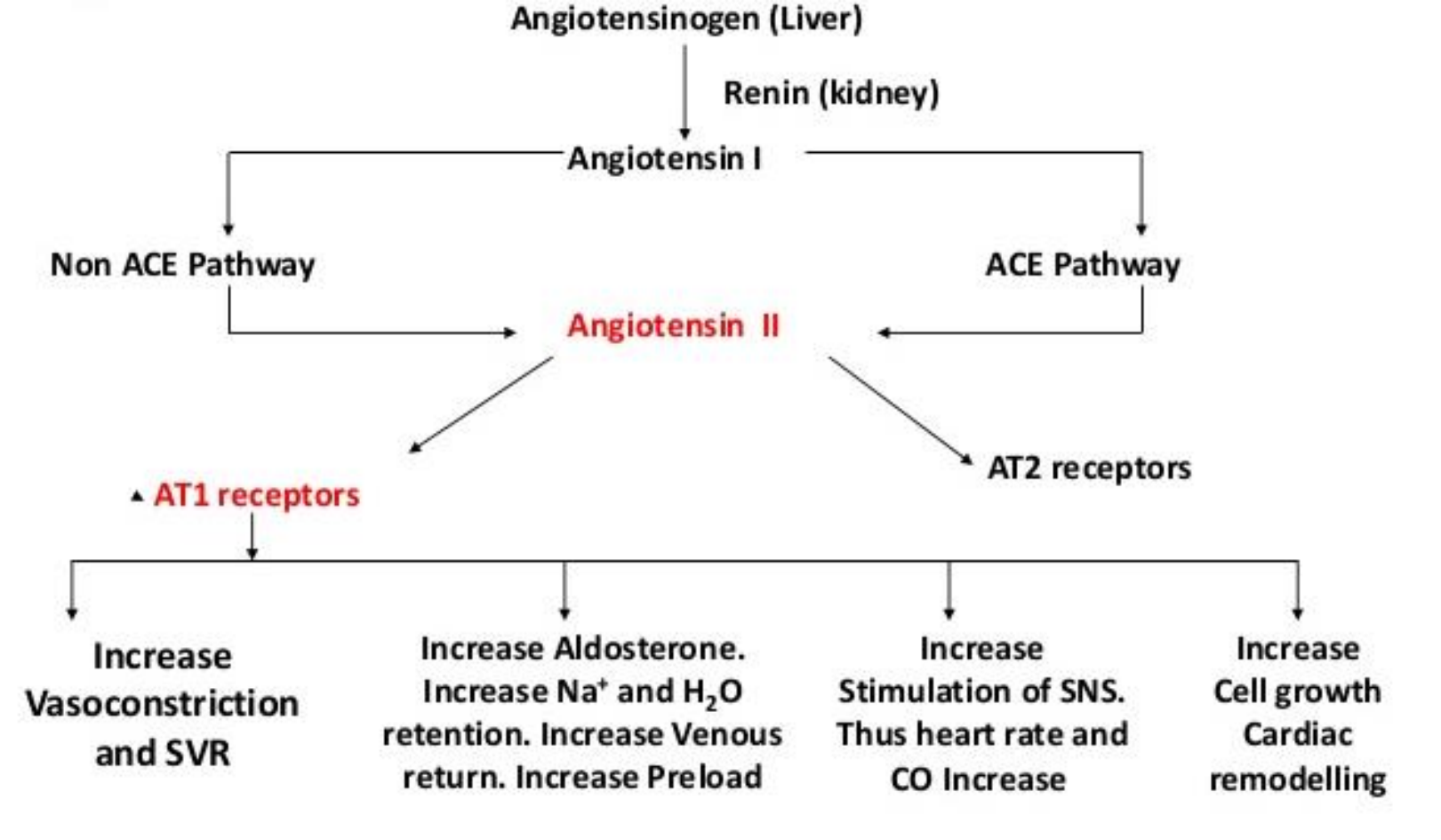
- decrease the peripheral resistance by a direct effect or a secondary effect due to decreased plasma volume

Thiazide-type diuretics

- **preventing stroke and cardiovascular events**
- **low cost**
- higher risk of metabolic disorders with **increase of insulin resistance**, and type 2 diabetes
- **hydrochlorothiazide, indapamide**

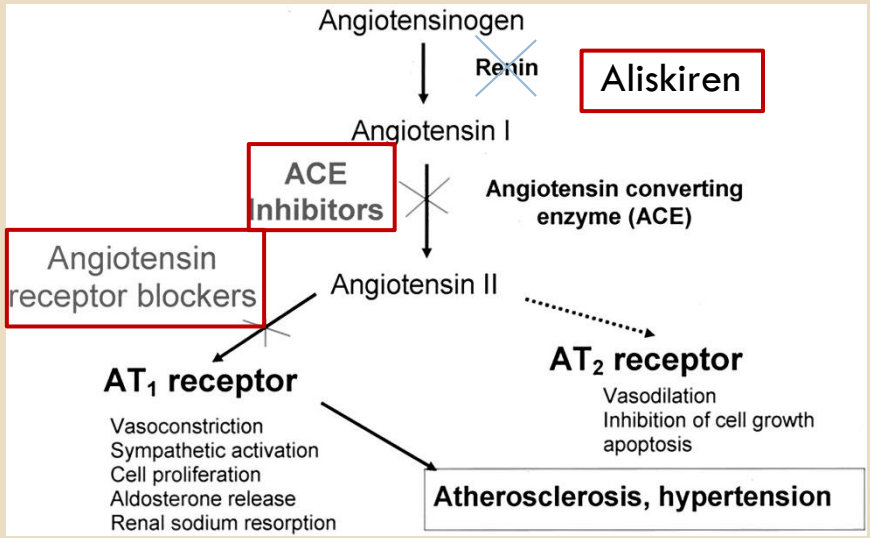
RAA system

- **renin angiotensin aldosterone system**



RAA system medications

- **direct renin inhibitors**
  - **aliskiren**
- **ACE inhibitors (ACEIs)**
  - **lisinopril, perindopril, ramipril, trandolapril**
- **angiotensin receptor blockers (ARBs)**
  - **candesartan, irbesartan, losartan**



Circulation, vol. 110, no. 8. Should Angiogtensin II Receptor Blockers and Statins Be Combined?

ACE Inhibitors and ARBs

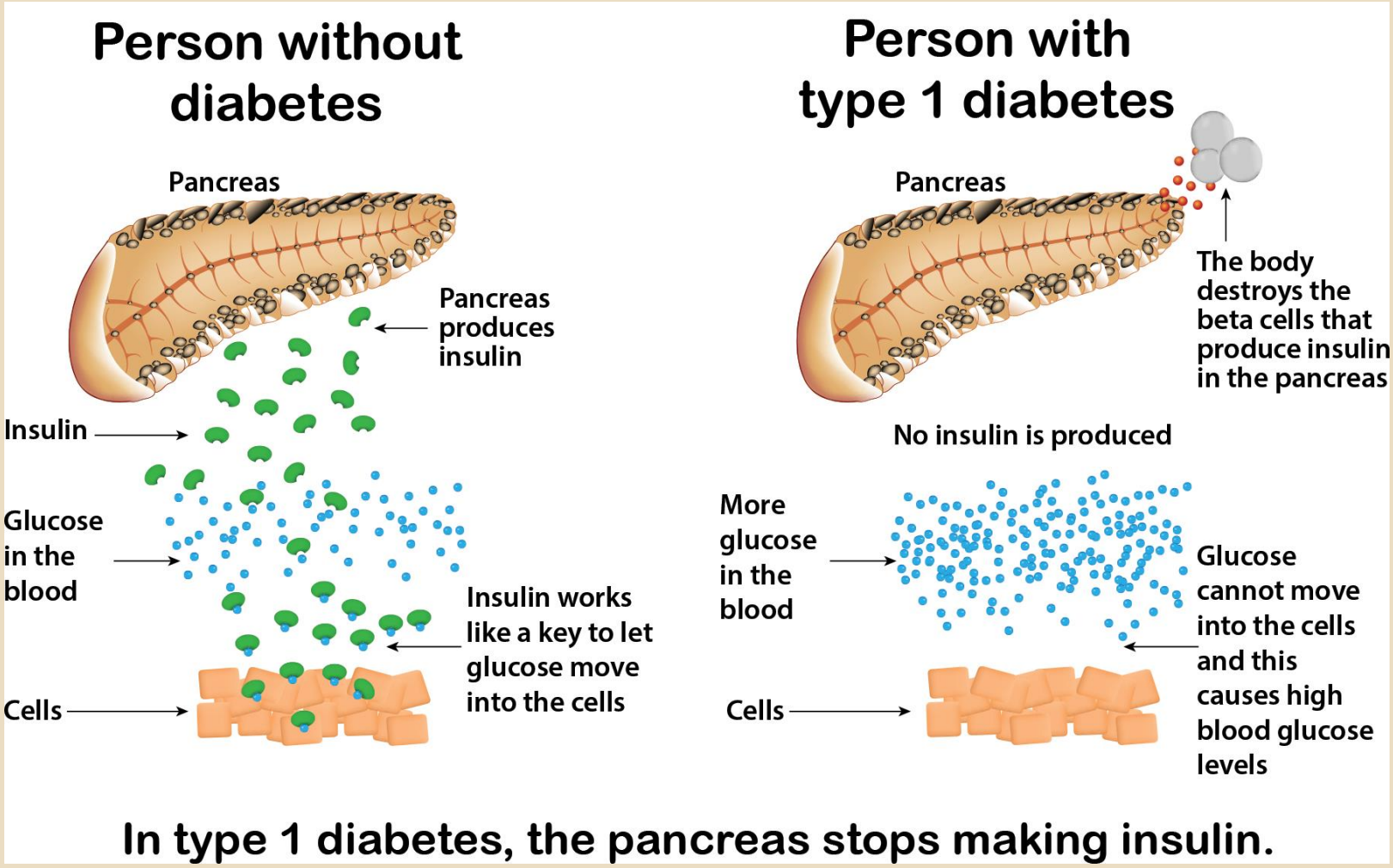
- advantages for patients with concomitant **cardiovascular diseases, diabetes with albuminuria,** or **chronic kidney disease**
- reduce the incidence of new-onset diabetes by about 25% compared with other active treatments
- except for **ACE inhibitor-induced cough**, they are better tolerated than other drug classes
- most useful in combination therapy with a diuretic or CCBs

Diabetes mellitus

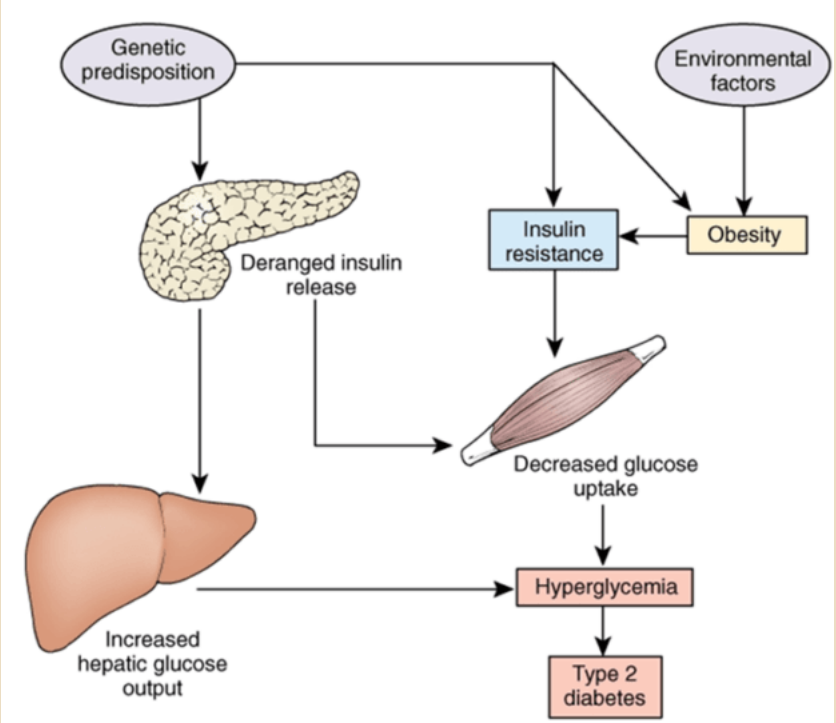
- **diabetes mellitus type 1**
  - exceptional in elderly as autoimmune disease
- **diabetes mellitus type 2**
  - most of the elderly patients due to insulin resistance
  - fasting glycemia **≥ 7 mmol/l**
  - **≥ 11,1 mmol/l** after glucose loading

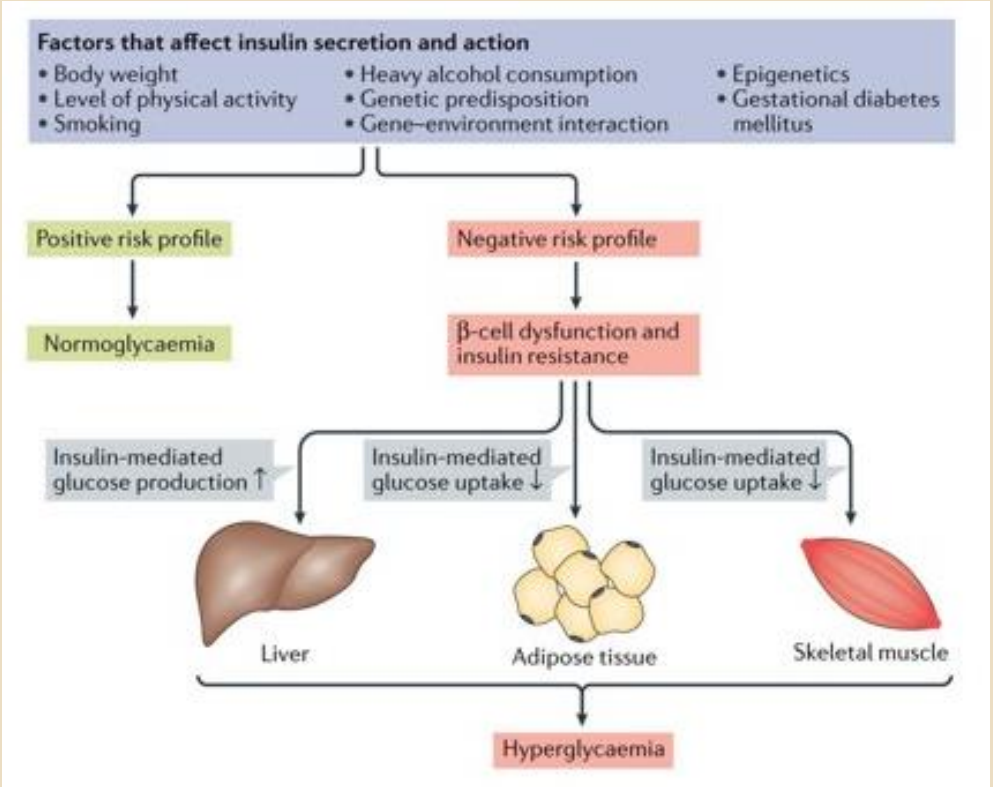
- **prediabetes (impaired glucose tolerance)**
  - fasting glycemia **≥ 5,6 mmol/l – < 7,0 mmol/l**
  - **≥ 7,8 – <11.1 mmol/l** after glucose loading

Diabetes mellitus type 1



Diabetes mellitus type 2





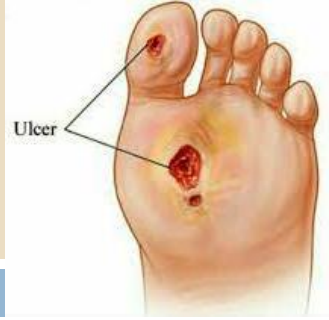
Diabetes mellitus (DM)

- prevalence of DM type 2 increases with aging
- proportion of lean body mass to body fat decreases and relative visceral fat increases
- **visceral adipocytes** produce substances promoting the development of DM
  - resistin, IL-6, TNF-α
- tight glycemic control is not necessary because of the **risk of hypoglycemia** enhanced by concomitant cognitive impairment, poor or irregular nutritional habits and reduced functions of autonomic system
- goal **glycated hemoglobin (HbA_{1c}) less than 53 mmol/mol (7%)**
- for comorbid patients goal should be aimed at **reducing effects of hyperglycemia** (polyuria, fatigue, weight loss)

Diabetes mellitus symptoms

- **typical symptoms** (polyuria and polydipsia) usually **lack**
- **fatigue, hypotension, incontinence, cognitive impairment, depression, dementia**
- **complications**
  - neuropathy
  - nephropathy
  - cardiovascular problems
  - recurrent urinary infections
  - skin problems (poor wound healing)

Diabetes mellitus complications

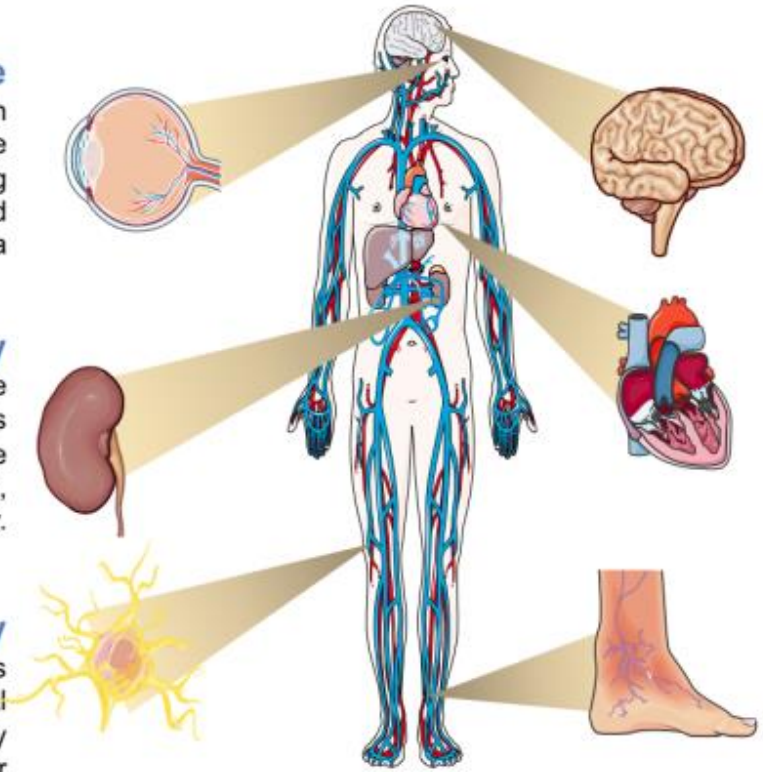


Microvascular

Eye
High blood glucose and high blood pressure can damage eye blood vessels, causing retinopathy, cataracts and glaucoma

Kidney
High blood pressure damages small blood vessels and excess blood glucose overworks the kidneys, resulting in nephropathy.

Neuropathy
Hyperglycemia damages nerves in the peripheral nervous system. This may result in pain and/or numbness. Feet wounds may go undetected, get infected and lead to gangrene.



Macrovascular

Brain
Increased risk of stroke and cerebrovascular disease, including transient ischemic attack, cognitive impairment, etc.

Heart
High blood pressure and insulin resistance increase risk of coronary heart disease

Extremities
Peripheral vascular disease results from narrowing of blood vessels increasing the risk for reduced or lack of blood flow in legs. Feet wounds are likely to heal slowly contributing to gangrene and other complications.

https://pdb101.rcsb.org/global-health/diabetes-mellitus/monitoring/complications

Diabetes mellitus therapy

Conservative

- lifestyle modification
- diet low in fat and carbohydrates combined with increased physical activity enhances insulin sensitivity

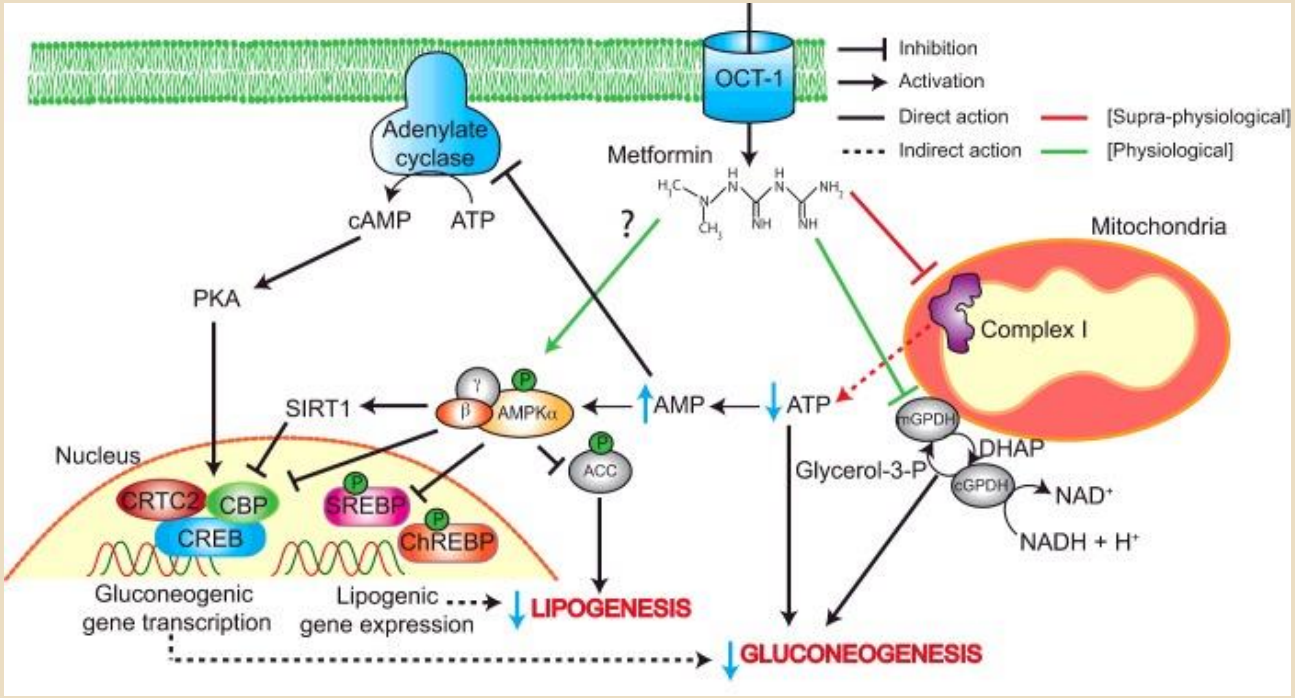
Pharmacotherapy

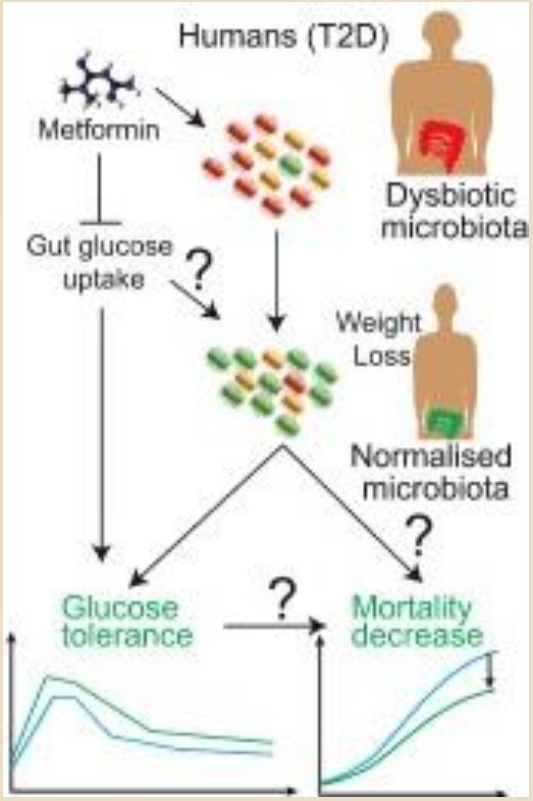
- oral hypoglycemic drugs and insulin are safe
- limitations due to hypoglycemic risk or comorbidities

Biguanides Metformin

- **first choice medication**
- **reduces glycemia** by
  - increase in insulin sensitivity
  - reduction of hepatic glucose release
  - increase in muscle glucose uptake
- **low risk of hypoglycemia**
- should be avoided in the patients with **risk of lactic acidosis** (stroke, pneumonia, myocardial infarction, heart failure, renal insufficiency), weight loss and GIT problems
- induces **vitamin B_{12} deficiency** leading to peripheral neuropathy

Metformin biohacking ??

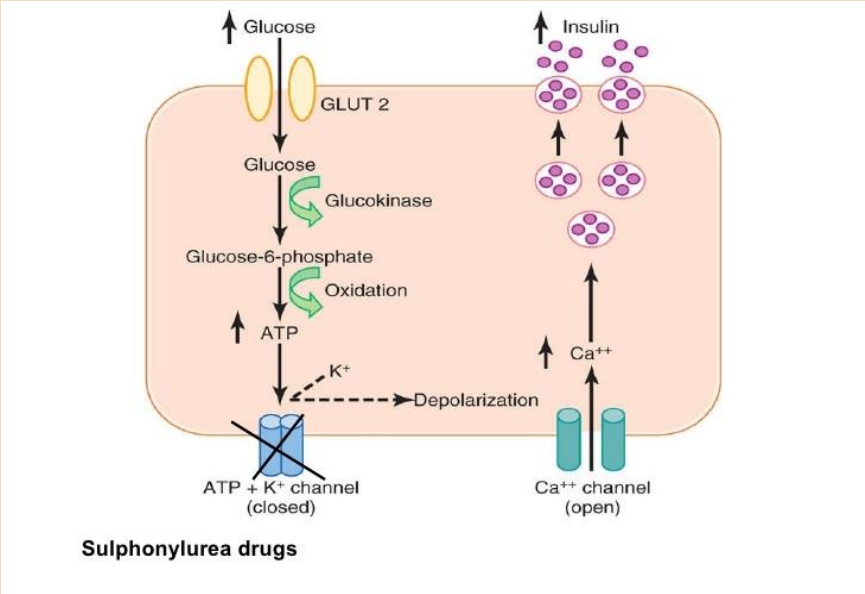




Biochem J. 2015 Nov 1; 471(Pt 3): 307–322

Insulin secretagogues Sulfonylureas

- bind to **ATP-sensitive K+ channels** on the pancreatic beta cells, which depolarizes the cell by preventing K from exiting
- depolarization opens voltage-gated Ca^{2+} channels
  - rise in intracellular calcium leads to increased secretion of insulin



Insulin secretagogues Sulfonylureas

- widely used because of efficacy, long experience use and low cost
- **hypoglycemia** is the most common and dangerous side effect
  - mostly in long-acting sulfonylurea drugs
- increase the risk for **weight gain**
- **glipizide, gliclazide, glimepiride**

Insulin secretagogues Glinides

- bind to an **ATP-sensitive K^+ (K_{ATP}) channel** on the pancreatic beta cells similarly to sulfonylureas but with weaker binding affinity and faster dissociation
  - secretion of insulin
- risk for **weight gain**
- **less risk of hypoglycemia**
- initial therapy in a patient with chronic kidney disease intolerant of metformin or sulfonylureas
- **repaglinide, nateglinide**

Thiazolidinediones (glitazones)

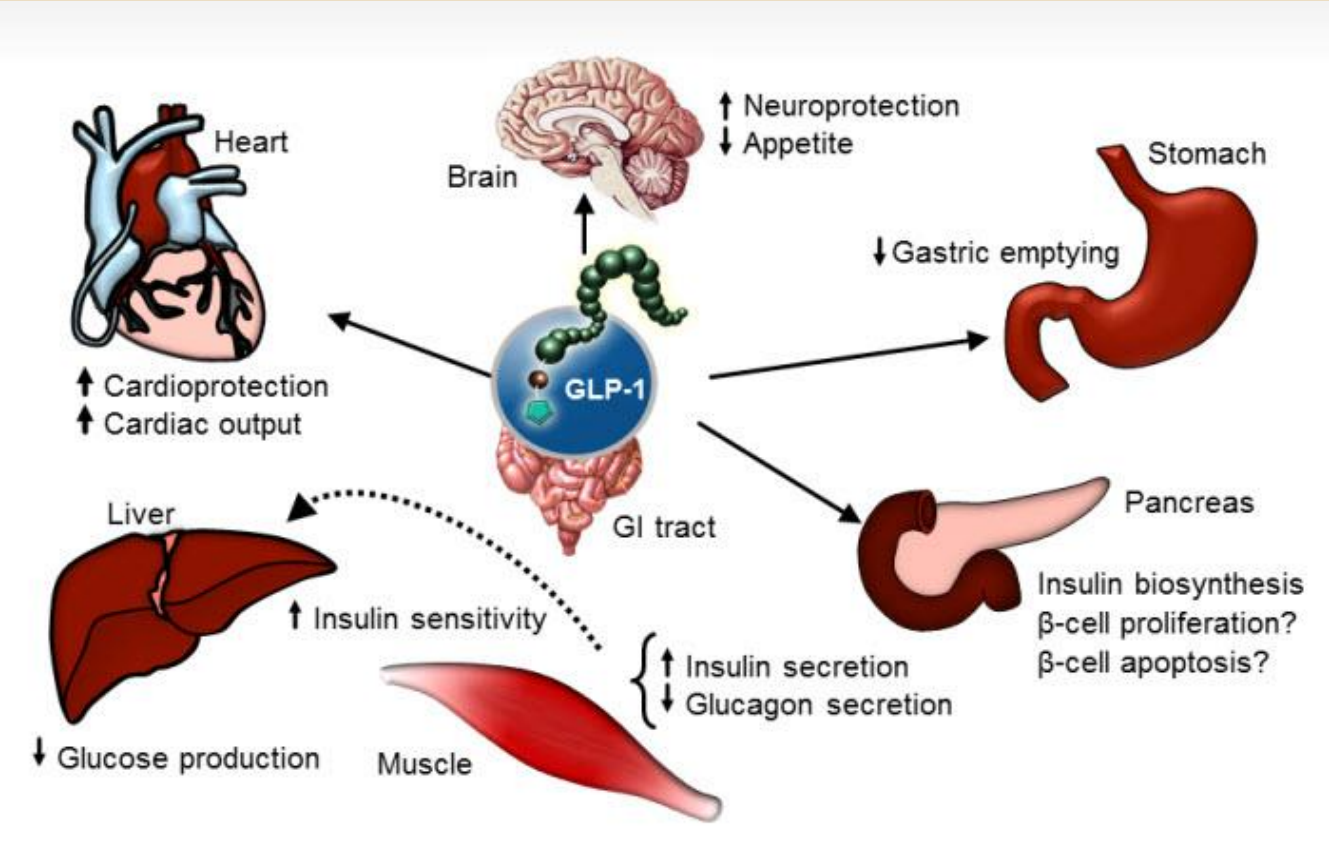
- act by activating **PPARs** (peroxisome proliferator-activated receptors)
- improve insulin resistance and insulin secretion in response to glucose
- require 2–4 weeks to exert their full effect
- well-tolerated in elderly patients, but risk of fluid retention, weight gain, osteoporotic fractures
- **pioglitazone**

Alpha-glucosidase inhibitors

- **inhibit** GIT enzyme **alpha-glucosidase**, that converts carbohydrates into monosaccharides
- reduce rise in postprandial blood glucose after meals
- used alone or combined with metformin, sulfonylureas or insulin
- main **adverse effects** are GIT troubles
  - flatulence, diarrhea
- **acarbose, miglitol**

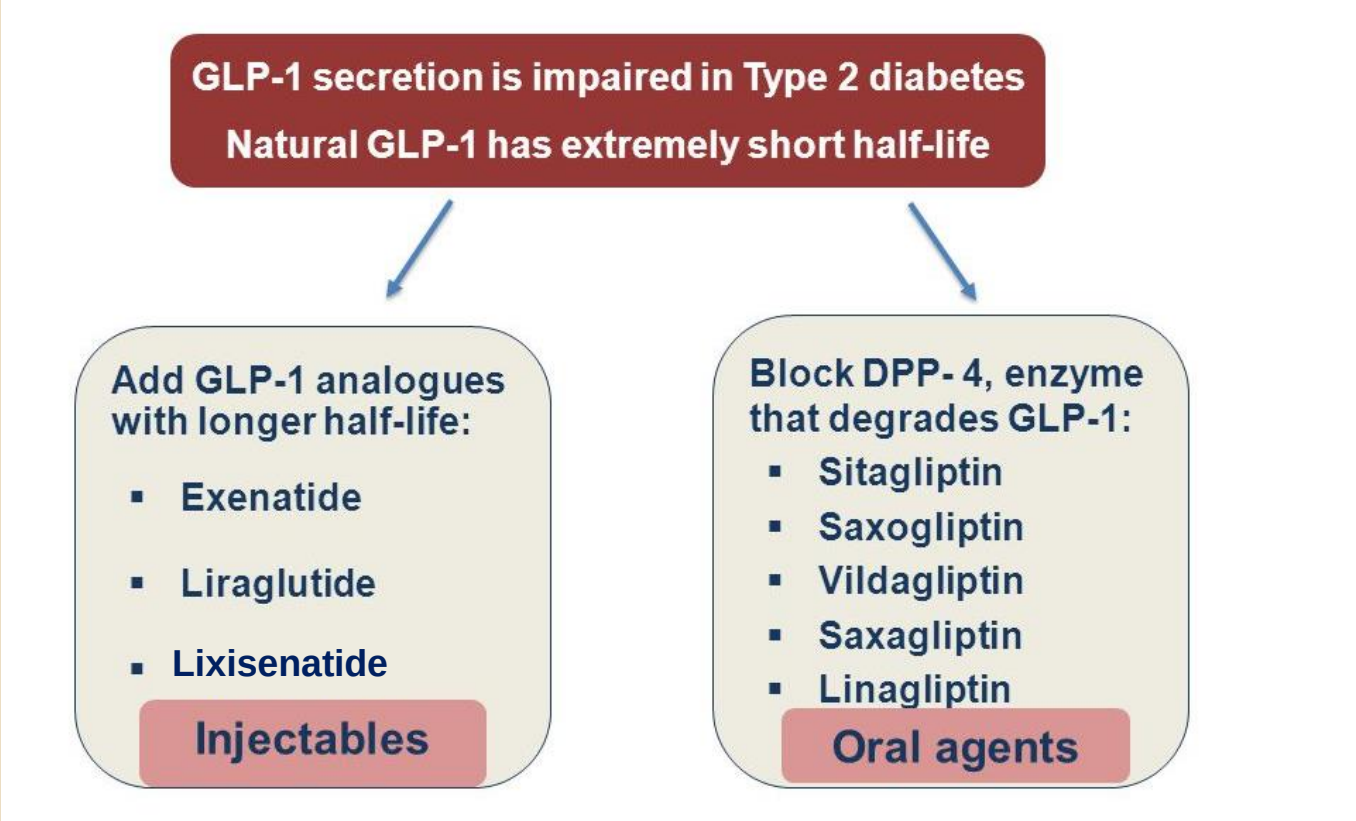
Incretin-based therapies

- **incretins** – GIT hormones released after eating and enhanced the insulin secretion



Incretin-based therapy

- **dipeptidylpeptidase-4 inhibitors(DPP-4)**
- **glucagon-like peptide-1 receptor agonists (GLP-1)**



Incretin-based therapy

DPP-4 inhibitors

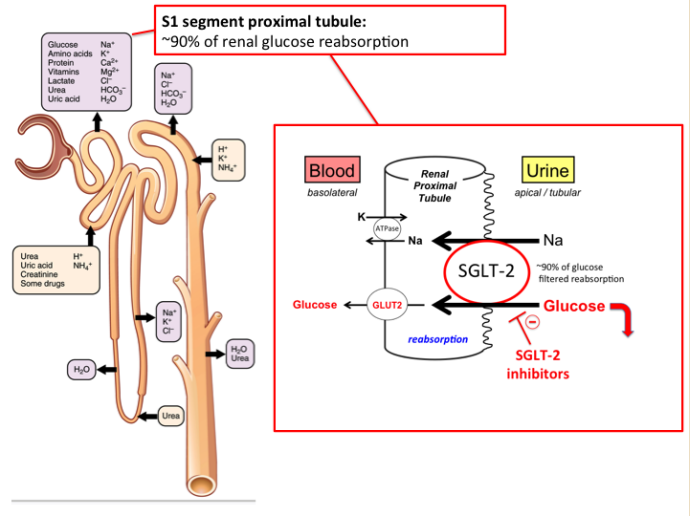
- **low hypoglycemic risk** when used alone or as add-on therapy to metformin
- weight-neutral
- dose should be adjusted in kidney insufficiency

GLP-1 agonists

- **low hypoglycemic risk**
- weight loss
- require a period of **2–4 weeks for dose titration**
- potential **neuroprotective properties** as advantage for old patients with neurodegenerative diseases

Sodium-glucose co-transporter type 2 inhibitors (SGLT2)

- act by inhibiting **sodium-glucose transport protein 2 (SGLT2)**
  - inhibit reabsorption of glucose in the kidney therefore lower glycemia
  - most often used as second- or third-line agents
  - should be used with caution in elderly people
- **frequent urinary and genital mycotic infections**
- hypotension, dizziness, renal functions worsening
- **canagliflozin, dapagliflozin**



Peroral antidiabetic drugs review

Oral antidiabetic drugs	Interesting because of	Limited use if	Contre - indications
Metformin	Low price, Efficient in insulin resistance Cancer prevention?	Gastro-intestinal troubles Creatinine clearance <30ml/mn Radiography with iodinated contrast agents	Lactic acidosis, heart insufficiency, kidney insufficiency, vascular accident, coronary insufficiency, heart infarction
Sulfonylureas			
Long action	Low price, efficient	Hypoglycemias To avoid if: Diarrhea, memory troubles, Alcoholism	Allergy Acute coronary syndrome
Short action (meglitinides)	low risk for hypoglycemias	Weight gain	
Thiazolinediones (pioglitazone*)	Low risk for hypoglycemias → used if Reduced glucose tolerance allergy to sulfonylureas	Fluid retention Increase in fracture risk High cost	Congestive heart failure
Alpha-glucosidase inhibitors (Acarbose. Miglitol)	Post prandial hyperglycemias	Flatulence and diarrhea Lack of long experience in elderly	
Incretin-based therapies			
DPP4 inhibitors	No hypoglycemias Weight neutral Can be associated to above mentionned treatments	High cost and no long experience in elderly	Dose ajustment in heart insufficiency (controversed)
GLP1 agonists	No hypoglycemias, weight loss Neuroprotective action	High cost, 2-4 weeks for titration	
Sodium-glucose co-transporter type 2 inhibitors (SGLT2)	Low risk for hypoglycemias	Genital and urinary infection risk, hypotension, increased risk or worsening of renal insufficiency	To avoid in elderly categories n°2 and 3 (nephrotoxicity)

Chentli F: Diabetes mellitus in elderly. Indian J Endocrinol Metab 2015;19(6):744-52.

Insulin

- sometimes underutilized because of hypoglycemia fear or way of application (s.c. by insulin pen)
- one or two daily insulin doses in many elderly diabetics will significantly improve the glycemia compensation
- peroral antidiabetics may be combined with insulin

Different regimens

- **basal analogues** (long-acting – /glargine,detemir,degludec/)
  - polymorbid patients, 1x daily, poorer compensation
- **basal or premixed analogues** (short- + long-acting)
  - 2x daily, better compensation
- **basal–bolus analogues** (long-acting – short-acting /aspart, glulisine, lispro/)
  - cooperating patient, flexibility of regimens, very good compensation, but a need for frequent glycemia control