Therapeutic areas – Part 3

Cardiovascular and Metabolic

Module 4 Topic 6_2

What is High Blood Pressure?

- Blood pressure is the force exerted on the arterial walls by flowing blood
- High blood pressure (hypertension) indicates that blood pressure - is consistently high.
- Blood pressure is recorded as two numbers:
- Systolic blood pressure (the upper number) - indicates how much pressure your blood is exerting against artery walls when the heart beats.
- Diastolic blood pressure (the lower number) - indicates how much pressure your blood is exerting against your artery walls while the heart is resting between beats

Blood Pressure Category	Systolic mm Hg (upper #)		Diastolic mm Hg (lower #)
Normal	less than 120	and	less than 80
Prehypertension	120 – 139	or	80 – 89
High Blood Pressure (Hypertension) Stage 1	140 – 159	or	90 – 99
High Blood Pressure (Hypertension) Stage 2	160 or higher	or	100 or higher
Hypertensive crisis (Emergency care needed)	Higher than 180	or	Higher than 110

Pathophysiology of hypertension

- Pathophysiology still uncertain
- A small number of patients (2% and 5%) have an underlying renal or adrenal disease (**Secondary HT**)
- In the remainder, no clear identifiable cause is found (**Essential HT**)
- Many interrelated factors contribute to the raised blood pressure in hypertensive patients, and their relative roles may differ between individuals

Hypertension Complications

The common complications are target organ diseases occurring in the

- Heart
  - Coronary artery disease
  - Left ventricular hypertrophy
  - Heart failure
- Brain
  - Stroke
- Kidneys
- Eyes
- Peripheral Vascular Disease

Hypertension Complications

- Cerebrovascular Disease
  - Stroke
  - Dementia

  "Treatment of hypertension reduces risk of stroke and dementia by 42%" Foex P. Anaesthesia, Critical Care & Pain | 2004;4:71
- Peripheral Vascular Disease
  - Erectile dysfunction
- Nephrosclerosis
- Retinal Damage

Lifestyle modification

- Weight loss
- Exercise
- Low salt diet
- Stress management and relaxation therapy
- Stop smoking
- Decreased alcohol intake

Pharmacotherapy of hypertension

Drug Class	Mode of action	Major side effects
Diuretics - Thiazides, Furosemide, K sparing	Increase Na and water excretion, reduce blood volume	Eletrolyte imbalance, hyperglycaemia, hyperuricemia
ACE inhibitors – Enalapril, Ramipril	Inhibit synthesis of Angiotensin II – decrease in peripheral resistance	Cough, angioedema, hypotensiondysgeusia
Angiotensin AT1 blockers – valsartan, telmisartan, Olmesartan	Blocks binding of Angiotensin II to its receptors	Low incidence of above side effects of ACE inhibitors
Beta blockers- Propranolol, Atenolol	Block beta receptors, reduced force and rate of contraction	Fatigue, lethargy, loss of libido

Pharmacotherapy of hypertension

Drug Class	Mode of action	Major side effects
Alpha blockers – Prazocin, Terazocin	Blocking of alpha receptors in smooth muscles – vasodilatation	Headache, dry mouth, postural hypotension
Ca channel blockers – Nifedipine, verapamil	Blocks influx of Ca++ in smooth muscle cells, vasodilation	Dizziness, fatigue, headache, itching
Vasodilators – Nitrates	Vasodilation	Palpitation, tachycardia, Na retention
K channel blockers - Minoxidil	Vasodilation	Hair growth
Centrally acting – Clonidine, methyldopa	Act on central α2A receptors to decrease sympathetic outflow – fall in BP	Cognitive impairment, postural hypotension, rebound hypertension

LIPIDS: Composition, Types and Function

What are lipids?

- Lipids are chemical compounds which are present in two forms in the body viz.
  - Triglycerides
  - Cholesterol

LIPIDS: Composition, Types and Function

Triglycerides

- They are a combination of glycerol and fatty acids
- They provide energy for different metabolic process
- Excess triglycerides are stored in adipose tissues

LIPIDS: Composition, Types and Function

Cholesterol

- It is chemically a sterol and is found widely in animal tissues
- It is present in egg yolk, various oils, liver, kidneys and adrenal glands
- Cholesterol is utilized by liver to synthesize various bile salts and bile acids which help in metabolism of nutrients as well as drugs.
- Cholesterol is useful in cell wall synthesis
- Cholesterol is used by liver for synthesis of steroids and sex hormones

What are lipoproteins?

- Lipoproteins are spherical particles which contains lipids (Cholesterol and Triglycerides) and proteins. (Lipoprotein = Lipid + Protein)
- Each lipoprotein also contains one or more apolipoprotein

The Physiology of Lipoprotein transport

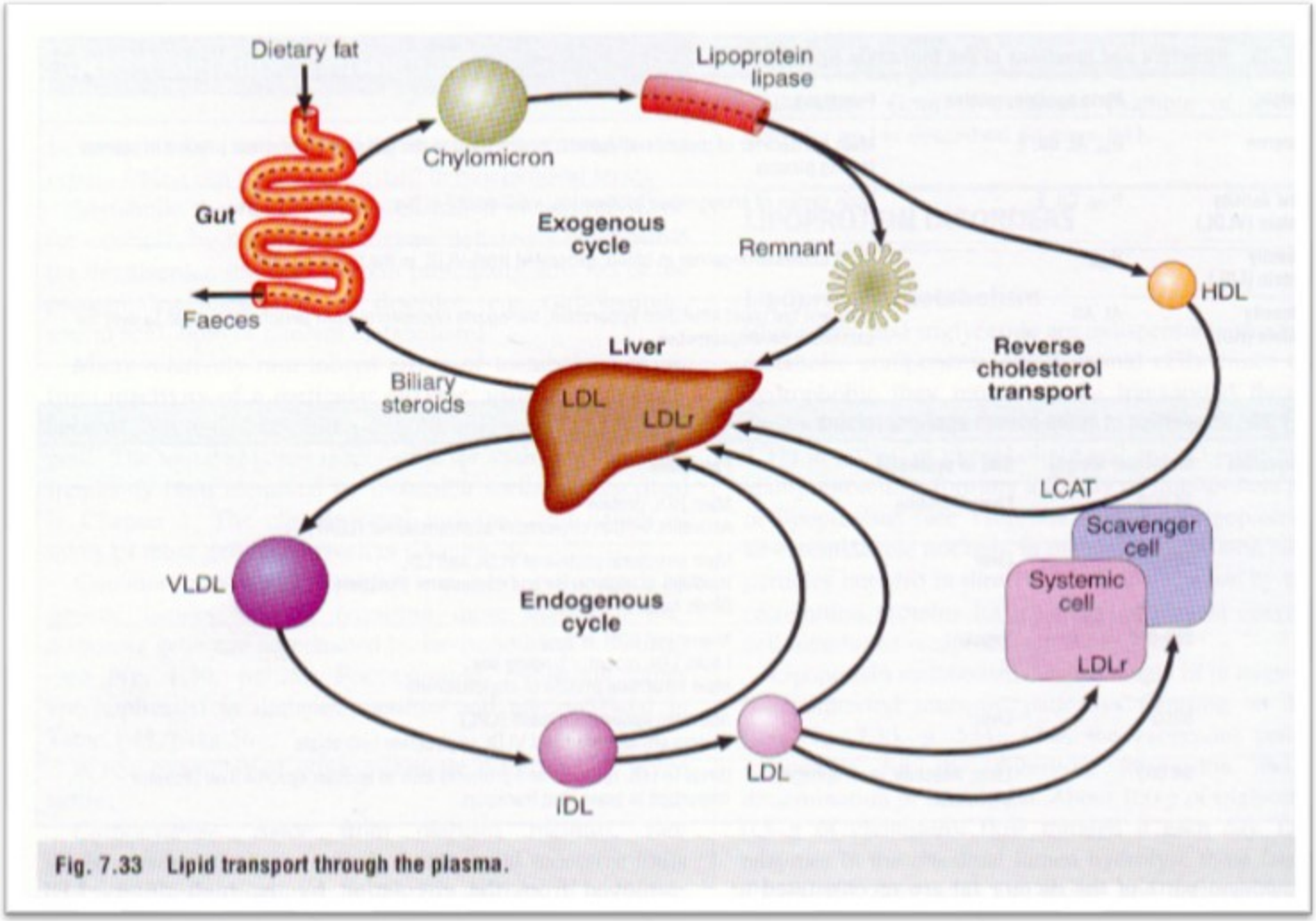


Fig. 7.33 Lipid transport through the plasma.

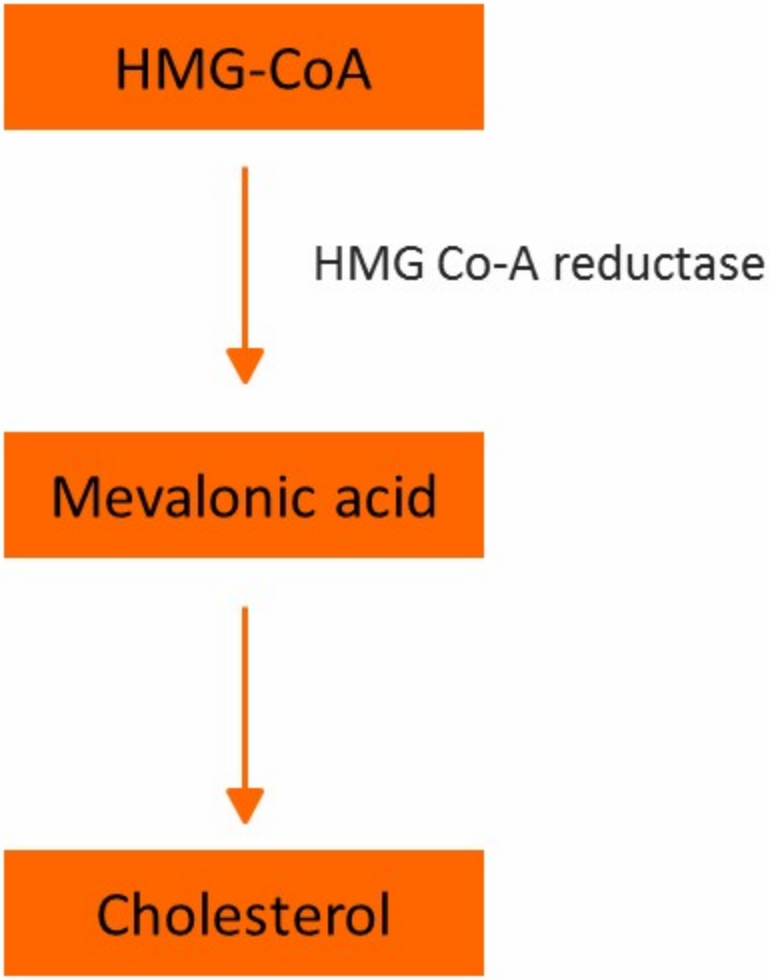
Endogenous system

- In the liver apolipoprotein apo-B-100 is combined with endogenously synthesized triglycerides, cholesterol and phospholipid to form VLDL
- This VLDL is acted upon by enzyme Lipoprotien lipase(LPL) which is present in adipose and muscle tissue
- As a result of which VLDL is converted to IDL and fatty acids. These fatty acids are stored as triglyerides in adipose tissues or muscles where they are oxidized for energy
- The intermediate density lipoproteins (IDL) either returns to the liver where it is removed by the LDL receptor (LDL r) or is metabolized to LDL

What do you mean by 'useful cholesterol' and 'harmful cholesterol'?

- Excess of LDL is dangerous as it leads to atherosclerosis. LDL is therefore harmful and LDL cholesterol is harmful cholesterol.
- On the contrary, function of HDL is to pick up excess cholesterol from the tissues and transport back to liver. HDL is therefore a good cholesterol.

How is cholesterol synthesized in liver



What are normal levels of lipids in the blood?

Normal levels of lipids are as follows:

Lipoproteins	Desired Concentrations In Blood
Total cholesterol	< 200mg/dl
LDL	< 130 mg/dl
HDL	> 60mg/dl
Triglycerides	< 200mg/dl

Lipid Disorders

Hyperlipidemia

- Hyper+ lipid + emia = excess of cholesterol/ triglycerides in the blood.

Hypercholesterolemia

- Higher than normal levels (> 200mg/dl) of cholesterol in the blood.

Hypertriglyceridemia

- Higher than normal levels (> 200mg/dl) of triglycerides in the blood

What are the consequences of lipid disorders?

Excess lipid levels may

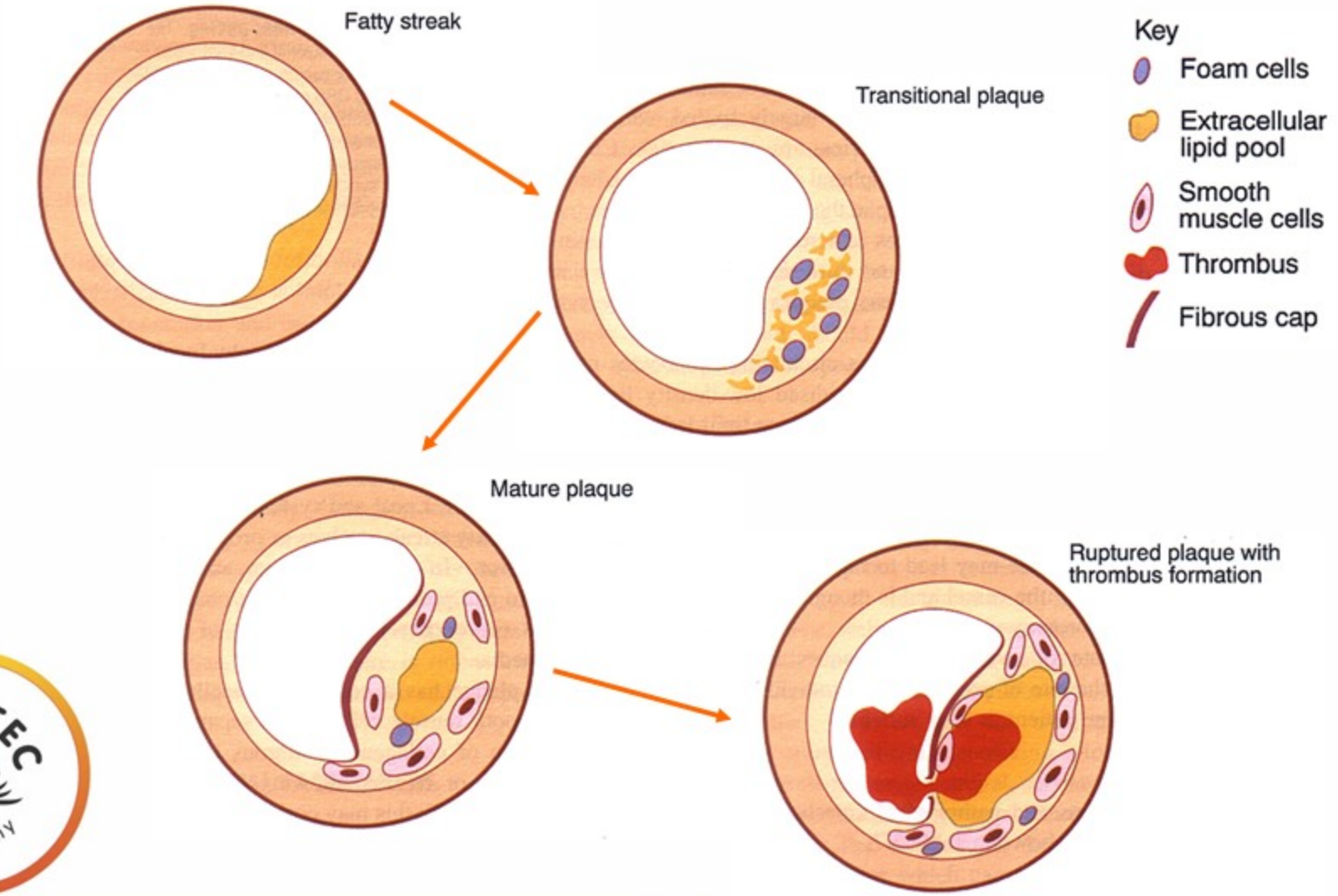
- Enhance atherosclerosis
- Lead to coronary artery disease
- Aggravate diabetic complications leading to accelerated atherosclerosis

Atherosclerosis

What is atherosclerosis?

- It is a disease of arteries which is characterized by thickening of the vessel and lipid accumulation in the innermost layer of the blood vessel
- The lipid deposits, ultimately results in the formation of a yellow patch called 'plaque' on the inner surface

Process of Atherosclerosis



Management of Hyperlipidemia

- Reduce saturated fat intake to provide about only 30% of total fat intake
- Reduce total fat intake to provide only about 30% of energy intake
- Reduce alcohol intake

Pharmacotherapy

Existing lipid lowering agents:

Lipid-Lowering drugs and their actions

Drug Group	Principal actions	Remarks
HMG CoA reductase inhibitors (e.g, simvastatin, pravastatin, atorvastatin) Atorvastatin is potent among all available statins.	• Inhibit cholesterol biosynthesis in the liver • Activate hepatic LDL receptor • Increase LDL statin catabolism • Lower plasma and LDL cholesterol	LDL reduction 25-45%

Pharmacotherapy

Existing lipid lowering agents:

Lipid-Lowering drugs and their actions

Drug Group	Principal actions	Remarks
Bile acid sequestrant resins (e.g cholestyramine, colestipol)	• Block intestinal reabsorption of bile acids • Divert hepatic cholesterol into bile acid production • Activate hepatic LDL receptors • Lower plasma and LDL cholesterol	LDL reductions by 10-35% HDL increased by 5%

Pharmacotherapy

Existing lipid lowering agents:

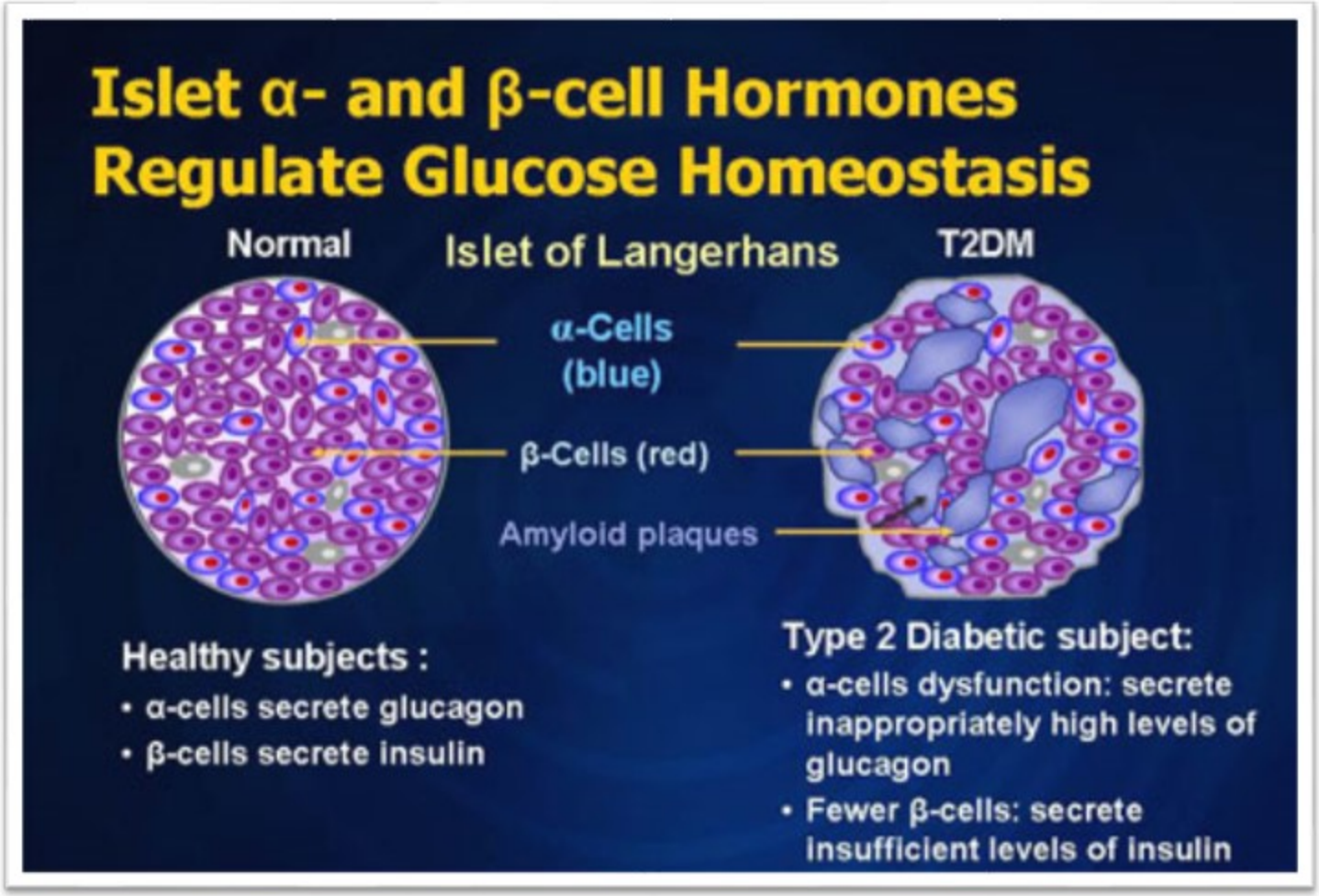
Lipid-Lowering drugs and their actions

Drug Group	Principal actions	Remarks
Nicotinic acid	• Activate LPL	TG reduced by 20- 80%
	• Lower triglyceride and increase HDL	LDL reduced by 10-15%

Diabetes mellitus - Overview

- Chronic systemic disease characterized by metabolic and vascular abnormalities
- Disorder of carbohydrate metabolism
- Results from inadequate production or underutilization of insulin

Diabetes mellitus - Overview



Diabetes mellitus - Overview

- Characterized by glucosuria and hyperglycemia
- Two forms
  - Type 1 - patient secretes no insulin. Cause is felt to be autoimmune.
  - Type 2 - patient secretes insufficient amounts of insulin and insulin receptors are resistant to circulating insulin

Diabetes mellitus - Overview

- Symptoms: polyuria, polydipsia, polyphagia, and possibly itching.
- Signs: hyperglycemia, glucosuria
- Fasting blood glucose higher than 120 mg%
- Manifested by: weight loss, weakness, increased frequency of infections

Diabetes mellitus - Overview

Complications:

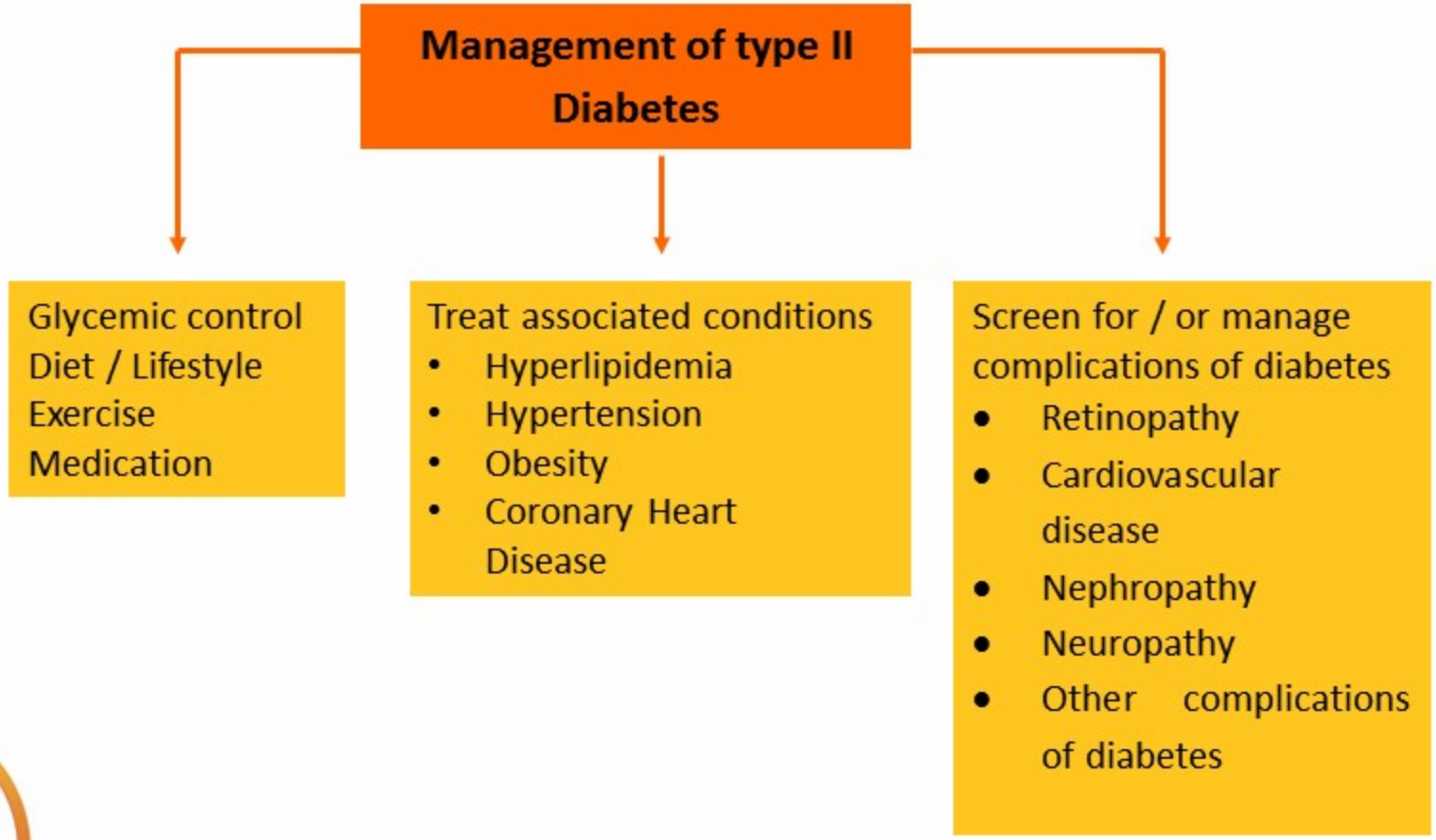
- **Diabetic Retinopathy**, macular oedema, cataract, retinal haemorrhage, retinal detachment and intravitreous haemorrhage
- **Diabetic neuropathy, Foot ulcers**, Impotence, delayed gastric emptying, & impaired bladder function

Diabetes mellitus - Overview

Complications:

- **Diabetic nephropathy**
- Peripheral vascular disease & gangrene
- Increased risk of infection of skin, oral and vaginal candidiasis

Diabetes mellitus - Overview



Diabetes mellitus - Overview

Diet recommendations:

- Weight reduction in obese patients & maintenance of appropriate weight
- Carbohydrates should provide 45 - 60 % of daily caloric intake depending on severity of diabetes
- Restriction of saturated fat to < 10 % of daily caloric intake
- Increased use of monounsaturated fats (e.g. olive oil, peanut oil)
- Decreased cholesterol intake to < 200 mg/d
- Sodium restriction in patients with / prone to hypertension

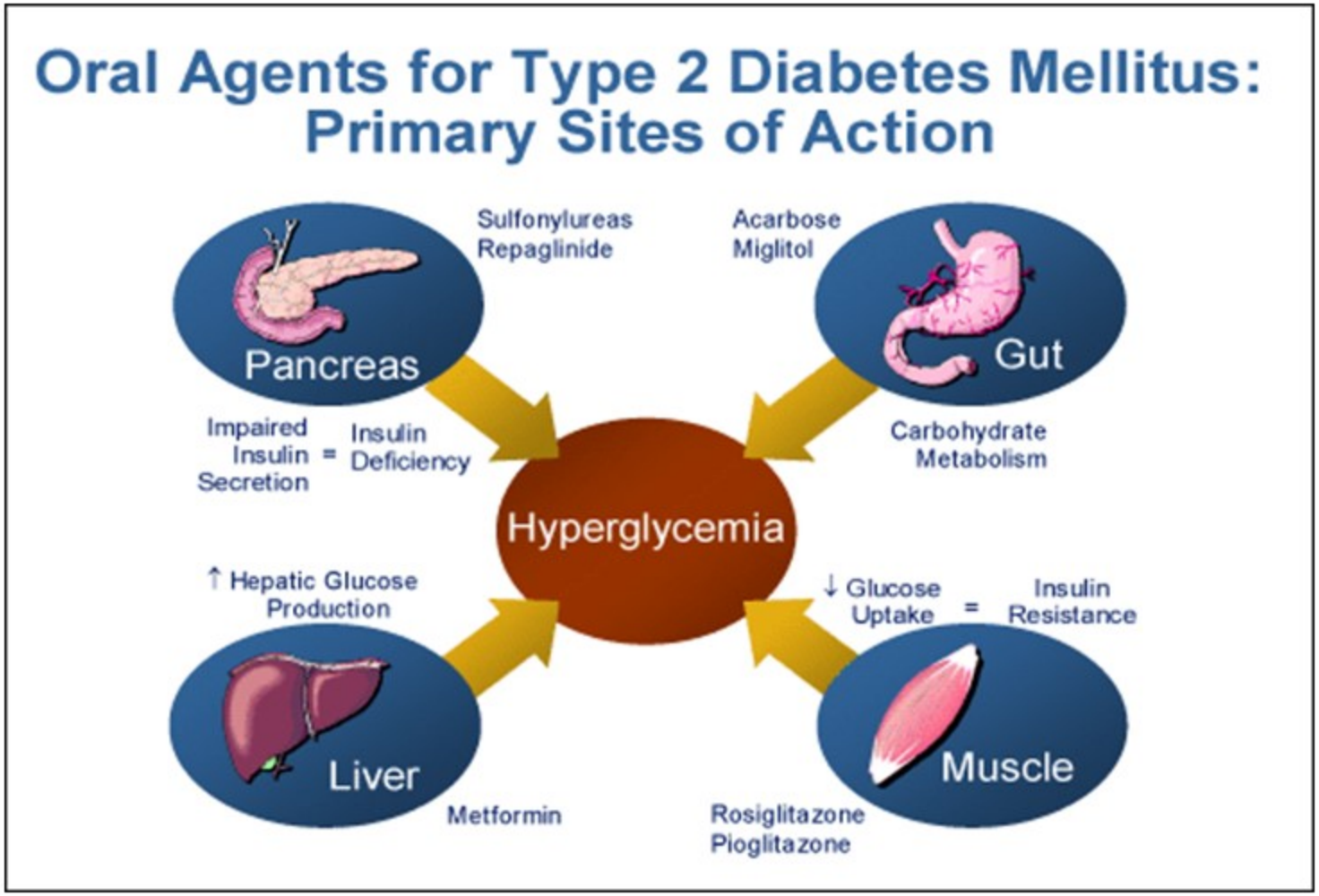
Diabetes mellitus - Overview

Oral hypoglycaemic agents

- **Sulfonylureas** e.g. glyburide, glipizide, glimperide
- **Biguanides** e.g. metformin
- **Meglitinides** e.g. repaglinide, nateglinide
- **Alpha-glucosidase Inhibitors** e.g. acarbose, miglitol
- **Thiazolidinediones** (peroxisome proliferator-activated receptor g i.e. ppr g inhibitors) e.g. pioglitazone, rosiglitazone
- **Dipeptidyl peptidase IV** (DPP-4 Inhibitors) e.g. sitagliptin, saxagliptin, linagliptin
- **GLP-1 receptor agonists** e.g. exenatide, liraglutide
- **SGLT2 inhibitors** e.g. canagliflozin, dapagliflozin
- **Amylin agonist** e.g. pramlintide
- **Combination Medicines**

SGLT2 = Sodium Glucose Cotransporter 2 (located in the kidneys)

Diabetes mellitus - Overview



Diabetes mellitus - Overview

Oral Anti-diabetic Agent	Mode of Action	Major Adverse Effect/s
Sulfonylureas	Enhance insulin secretion by binding with the receptors on the surface of beta cells in the pancreas	Hypoglycemia (more likely with 1st gen eg chlorpropamide, Less risk with 2nd gen esp glipizide), Skin rash, GI disturbances
Biguanides	Act mainly by reducing hepatic glucose production	Lactic acidosis (esp in those with renal failure), diarrhoea
Thiazolidinediones	Stimulation of peripheral glucose metabolism by reducing insulin resistance by activating peroxisome proliferator-activated receptor γ	Fluid retention, weight gain, heart failure, anemia

Diabetes mellitus - Overview

Oral Anti-diabetic Agent	Mode of Action	Major Adverse Effect/s
α - glucosidase inhibitors	Delay the absorption of glucose in the intestine	Flatulence, soft stools, mild abdominal pain
Meglitinides	Stimulate insulin secretion by binding with the receptors on the surface of beta cells in the pancreas	Hypoglycemia
Dipeptidyl peptidase IV (DPP-IV) enzyme inhibitors	Slowing inactivation of incretin hormones e.g. GLP-1 thereby enhancing glucose-dependent insulin secretion, inhibiting glucagon secretion and slowing gastric emptying	Abdominal pain, nausea, vomiting, loss of appetite Severe pancreatitis. Lactic acidosis