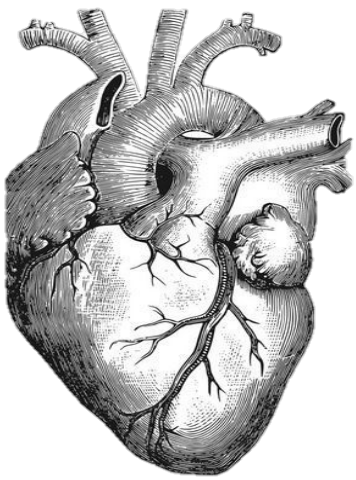
Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY



Drugs for Hyperlipidemia

Objectives:

- Define hyperlipidemia vs normal lipid levels
- Discuss the non-pharmacological treatment of
- hyperlipidemia
- Classify lipid lowering agents targeting exogenous &
- endogenous pathways
- Expand on the pharmacology of drugs related to each
- group
- Hint on adjuvant drugs that can help in lipid lowering

Important Notes Extra

Hyperlipidemia

Hyperlipidemia is a major cause of atherosclerosis which may lead to coronary artery disease (CAD) and ischemic cerebrovascular disease.
hyperlipidemia means abnormal ↑ levels of any/or all Lipids and/or Lipoproteins [LP] in blood

Lipids originate from two sources:

a-endogenous : lipids synthesized in liver.

b-exogenous: lipids that comes from food which is processed in intestine.

Types of lipids in blood are:
cholesterol(C).
triglycerides(TG).
Phospholipids(PL).
Non-esterified fatty acid(NEFA)
Cholesterol esters(CE).

Classification of Hyperlipidemia

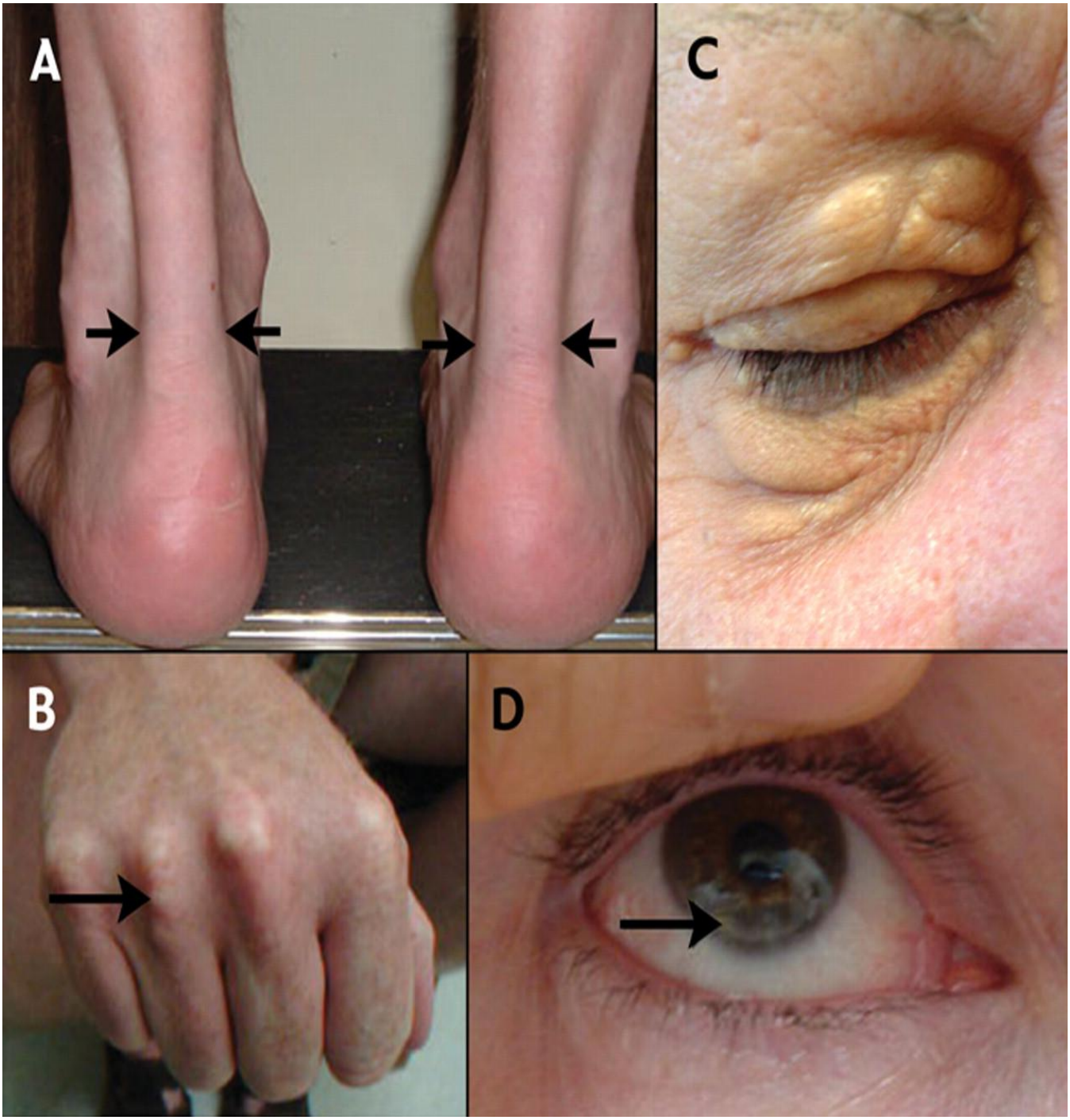
1-Primary (familial; hereditary) hyperlipidemia: is genetically determined.

Class	Increased Lipoprotein	Synonym	Risk
Type I	↑Chylomicron	Familial Chylomicronemia	-
Type IIa IIb	↑LDL ↑LDL and VLDL	Familial hypercholesterolemia Familial combined hyperlipidemia	← ←
Type III	↑IDL	Familial dysbetalipoproteinemia	↑
Type IV	↑VLDL	Familial hypertriglyceridemia	↑
Type V	↑VLDL and Chylomicron	Familial mixed hyperlipidemia	-

2-Secondary (acquired) hyperlipidemia:

- Hypercholesterolemia: hypothyroidism, nephrotic syndrome, and drugs.
- hypertriglyceridemia: DM, alcohol, gout, chronic renal failure.

Clinical Signs (Extra)



A-xanthoma along achilles. c-xanthoma around eyes

b-fat deposition in knuckle d-cholesterol ring in eyes

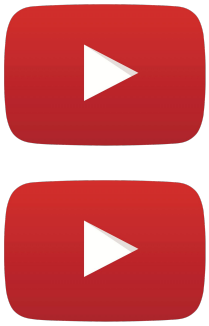
note: the patient doesn't have to be presented with these signs so blood test is required

Therapeutic strategies for treatment of hyperlipidemia

Lifestyle changes

- healthy diet & optimal fat content.
- eating adequate amount of antioxidant vitamins and unsaturated fatty acids.
- Losing weight.
- regular exercise.
- stopping bad habits:
- alcohol , smoking,fast food.

will reduce LDL-C by 8 to 15% but the long term compliance is a problem.



Antihyperlipidemic Drugs

According to Mechanism of Action:

1-Inhibiting cholesterol absorption
eg.Ezetimibe

2-Sequester bile acids in intestine
eg.Exchange resins

3-Inhibiting cholesterol synthesis
eg.Inhibitors of hydroxymethylglutaryl coenzyme A reductase(Statins)

4-Alter relative levels and patterns of different plasma LPs
eg.Fibrates, Niacins (Nicotinic Acids)

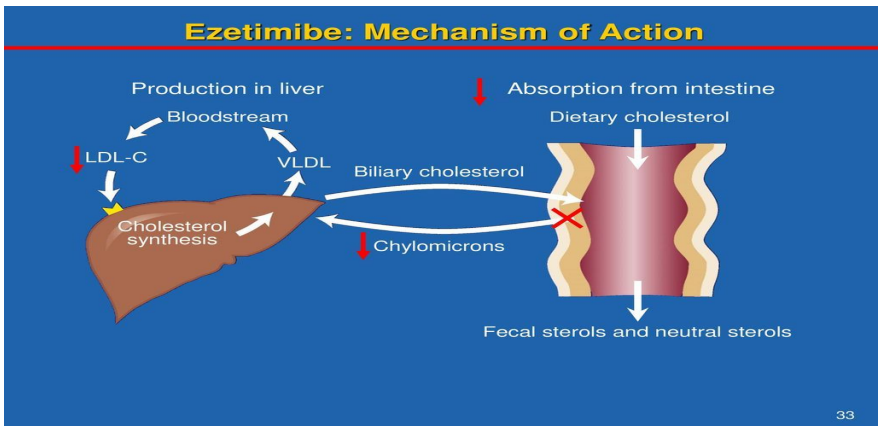
According to Site of Action:

I-Agents targeting exogenous cholesterol
Ezetimibe, Colestipol & cholestyramine

II-Agents targeting endogenous cholesterol
eg.Statins, Fibrates
Nicotinic acid very informative and easy vid .

III-Adjuvant agents
Omega-3-Fatty Acids(fish oil), Stanols(nuts)

Cholesterol Absorption Inhibitors (Targeting Exogenous Cholesterol)

drug	Ezetimibe
Mechanism of action	Selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and lowers LDL by reducing its precursor (VLDL) 
Pharmacological action	↓LDL 20% ↓TG 8% , ↑HDL 1-4% (does not raise HDL by much) No effect on steroids, lipid-soluble vitamins, bile acids.
Pharmacokinetics	-Absorbed & conjugated in intestine to active glucuronide -Reaches peak blood level in 12–14 hours -Undergoes enterohepatic circulation -Its half-life is 22 hours -Most of the drug is excreted in feces
Indications	-As Monotherapy: Primary prevention of low risk of CHD which needs modest LDL. (if LDL is very high, statins should be used. Ezetimibe isn't used alone except in modest of LDL) -As Combination Therapy; it's safe With: (statins; synergistic In moderate/severe LDL) Or (If must ↓ statin dose because of side effects) Or (With other lipid lowering drugs As fibrates).
ADRs	• GIT disturbance (the main symptoms for most of antihyperlipidemics) • headache, fatigue, arthralgia and myalgia (muscle pain) .

Exchange resins Bile Acid Sequestrants (Targeting Exogenous Cholesterol)

Drugs	Cholestyramine	Colestipol	Colesevelam
Overview	• Moderately effective with excellent safety record. • Large MW polymers which bind to bile acids and the acid-resin complex is excreted so their fecal excretion ↑ 10 folds – prevents enterohepatic cycling of bile acids – obligates the liver to synthesize replacement bile acids from cholesterol • The liver increases the number of LDL receptors to obtain more cholesterol • The levels of LDL-C in the serum are reduced as more cholesterol is delivered to the liver • Excellent choice for people that cannot tolerate other types of drugs		
Mechanism of action	- Bind to bile acids and bile salts in the small intestine - They form resin/bile acid (insoluble) complex which is prevent their reabsorption from the intestine .		
Adverse Effects	• They are clinically safe as they are not systemically absorbed • GIT upset: abdominal discomfort, bloating, constipation • Decreased absorption of fat soluble vitamins (A, D, E, K) • The concentration of HDL-C is unchanged		
Contra-indications	• Complete Biliary obstruction (because bile is not secreted into the intestine) • Chronic constipation • Severe hypertriglyceridemia (TG >400 mg/dL), because the bile acid binding resins can raise triglycerides modestly (about 5%) and thus cannot be used if the triglycerides are elevated		
Interactions	- decrease absorption of some drugs : Statins, Ezetimibe, Chlorothiazides, Digoxin, Warfarin. Therefore, these drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after taking resins. - Colesevelam has not been shown to interfere with the absorption of co-administered medications and is a better choice for patients on multiple drug regimens		

HMG-CoA Reductase Inhibitors (Statins)

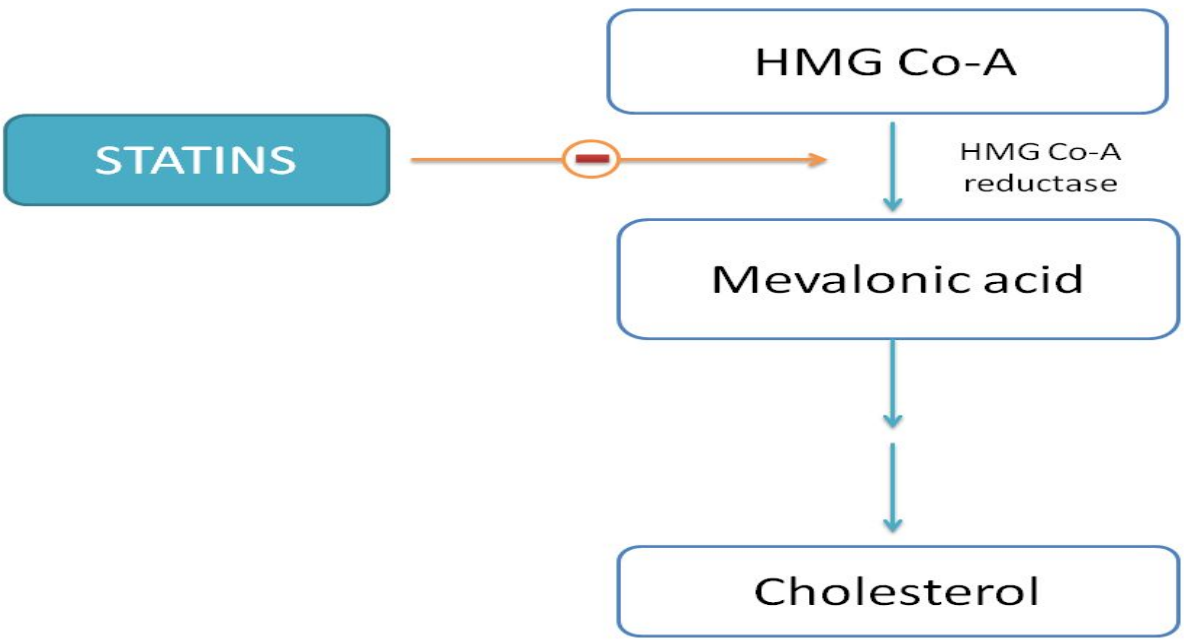
Hydroxy MethylGlutaryl-Coenzyme A reductase (HMG-CoA) inhibitors or **statins** are the **most effective** and **best-tolerated** agents for treating hyperlipidemia.

Statins are considered as first-line drugs when **LDL-lowering drugs are indicated**.
Statins are the best LDL lowering drugs with raising HDL effect.

Preparations

1-Rosuvastatin.
2-Atorvastatin.
3-Simvastatin.
4-Pravastatin.
5-Lovastatin.
these can be used alone or with other anti-hyperlipidemic drugs (ezetimibe) for **treatment of drug resistant dyslipidemia**.

PLEIOTROPIC EFFECTS OF STATINS:**
1-improvement of endothelial function.
2- Decrease vascular inflammation.
3-stabilization of atherosclerotic plaques.
4-Decrease platelet aggregability.
5-Antithrombotic actions
6-Enhanced fibrinolysis



Statins

Mechanism of Action	Statins are potent competitive inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, which catalyzes an early, rate limiting step in do-novo hepatic C synthesis. Thus, HMG-CoA is not converted to mevalonic acid. liver compensates by the ↑ LDL receptors on the surface of hepatocytes (upregulation of LDL- R). This results in removal of LDL from blood and ↓ serum LDL- C levels. Because C is required for the synthesis of the precursor of LDL-C, production of VLDL ↓. Statins cause modest ↓ plasma TG and slight ↑ HDL-C
Pharmacokinetics	•Most statins have a high first-pass clearance by the **liver**. • Greater than 95% of most of these drugs are bound to plasma proteins with short half-life. • Drug-drug interactions involve specific interactions with the cytochrome P-450 drug metabolizing system, especially **CYP3A4**. • All statins are taken **orally at bedtime** because of hepatic C synthesis is maximal between midnight and 2:00 a.m. , **except atorvastatin** taken at any time because of its long half-life (14 hours).
Indications	As **monotherapy**: • **Secondary Prevention**; In all ischemic insults [stroke, AMI, …..etc.] So given from 1st day of ischemic attack. • **Primary Prevention**; 1-Patients with hyperlipidemia and with other risks for ischemic insults. 2-Type IIa Hyperlipoprotinemia. **If** no control , combine (sequestrants / ezatimibe, niacin,..) to decrease C. • As **Combination therapy:** 1. Mixed dyslipidaemias; added to fibrates or niacin if necessary. 2. In diabetics and patients with insulin resistance [metabolic syndrome] because these patients will possess small dense LDL (severely atherogenic) + evident endothelial dysfunction + increased thrombotic profile.
ADRS	1-Common side effects: Headache , myalgia, fatigue, GI intolerance, and flu-like symptoms. 2-Hepatotoxicity, raised concentrations of liver enzymes (serum aminotransferases) 3-Myopathy (increased creatine kinase [CK] released from muscles) 4-**Teratogenicity**, statins should be avoided during pregnancy check next slide
Drug Interactions	Statins potentiate the action of oral anticoagulant and anti-diabetic drugs (by displacement from plasma protein binding sites). ❖Drugs that increase the risk of statin-induced myopathy include: 1-Other antihyperlipidemics (fibrates). 2-Drugs metabolized by **3A4 isoform of cytochrome P450**: erythromycin, verapamil so hypertensive patients are liable to get myalgia with statin use, cyclosporin, ketoconazole. **Pravastatin and fluvastatin** are the statins of choice in patients taking other drugs metabolized by cytochrome 3A4 system.

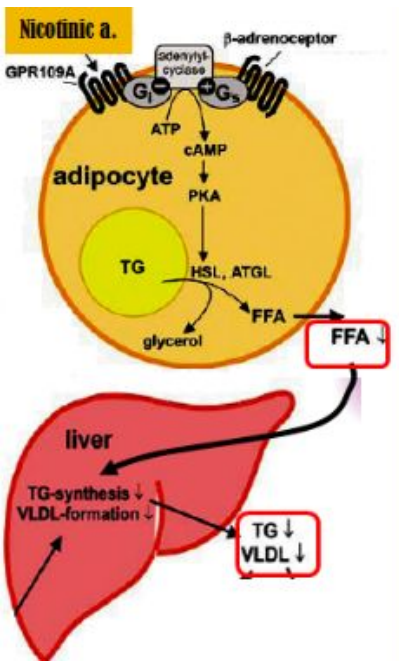
Statin Induced Myopathies

muscle aches, soreness, or weakness associated with an elevation of creatine kinase (CK) , are the best indicator of statin-induced myopathy.

- Failure to recognize myopathy and to discontinue drug therapy can lead to **rhabdomyolysis**, myoglobinuria, and acute renal necrosis.
- Elevation of serum transaminase can progress to evident hepatotoxicity. So lab investigations are recommended every 6 months. If levels increase up to 3 folds at any time, statin must be **stopped** then the dose is adjusted.
- Elevation of creatine kinase activity (index of muscle injury) measured only if myalgia or myositis develops. **If** it is up to 3-5 folds we decrease statin doses / omit combination with fibrate.

Niacin (Nicotinic Acid)

- Water soluble B-complex vitamin with multiple actions
- Niacin is the most effective medication for increasing HDL cholesterol levels and it has positive effects on the complete lipid profile
- It is useful for patients with mixed dyslipidemias Niacin exerts greatest beneficial effects on wide range of lipoprotein abnormalities So if we have a patient with very high LDL the drug of choice would be Statins, but high LDL and low HDL Niacin will be the drug of choice



Niacin (Nicotinic Acid) Vitamin B3

mech-anism of action	1-In adipose tissue: it binds to adipocytes nicotinic acid receptors, this will lead to decrease in free fatty acids mobilization from adipocytes to the liver ---resulting in ↓ TG and thus VLDL synthesis (reduce mobilization of free fatty acid from adipocytes to liver) 2-In liver: niacin inhibits hepatocyte 2-diacylglycerol acyltransferase, a key enzyme for TG synthesis Thus, it decreases VLDL production (decreased TG synthesis and esterification) 3-In plasma: it increases LPL activity that increases clearance of VLDL & chylomicron
Pharmacological Actions	**VLDL**↓ by decreasing its synthesis in liver, increasing its clearance in plasma, and decreasing mobilization of free fatty acids from adipose tissue. **LDL**↓ due to reduction of its precursor (VLDL) **HDL**↑ (decrease its catabolism) Niacin also promotes hepatic apoA-I production and slows hepatic clearance of apoA-I and HDL
Indications	As monotherapy or in combination with fibrate, resin, or statin 1-Type IIa hypercholesterolemia 2-Type IIa, IIb hypercholesterolemia & any combined hyperlipidemia 3-Patient with hypertriglyceridemia & low HDL-C (like in diabetes) (it disturbs glucose levels but not fully contraindicated)
ADRS	• The most common side effect is cutaneous flushing (which is prostaglandin-mediated, can be avoided by aspirin ½ hour before niacin) • GIT disturbances: Dyspepsia , nausea , vomiting , reactivation of peptic ulcer (can be decreased if taken after meal) (increase acid production) • High doses: 1-Reversible increase in liver enzymes leading to hepatotoxicity. 2-Impairment of glucose tolerance (if prediabetic → overt diabetes) 3- ↑ uric acid = gout
Contraindications	Gout Peptic ulcer Hepatotoxicity Diabetes mellitus should be avoided during pregnancy

Fibrates

Drugs	Clofibrate** & Gemfibrozil & Fenofibrate
mech. of action	1-agonist of peroxidase proliferator* activated receptors (PPAR-α) 2-increase gene transcription of lipoprotein lipase(LPL) leading to catabolism of TG in VLDL and chylomicrons *receptors that modulates fat metabolism , three types, **PPAR**-γ agonists for diabetes **1st drug discovered, causes gall bladder stone and its carcinogenic Feno Clo (fibrate)? Gem fi brozil Thank you Ghada Al-Qarni!
pharmacological effects	↑**LPL activity**, which increases clearance of **VLDL & chylomicron** in plasma -A marked reduction in TG (due to stimulation of catabolism of VLDL) - Increase FFA* uptake by the liver –**LDL-C** uptake by the liver –Increase in HDL-C(by increasing the production of the apoprotein components of HDL) -↑ excretion of hepatic C in bile , thus endogenous hepatic C synthesis may be decreased (*free fatty acids)
Indications	1st-line defense for: **-mixed dyslipidemia** (i.e. raised serum TG and C) -Patients with **low HDL** and high risk of atheromatous disease (often **type 2 diabetic patients**) -Patients with severe treatment - **resistant dyslipidemia** (combination with other lipid-lowering drugs).
interactions	-Increased risk of myopathies when used with statins use of fibrates with statins is generally inadvisable -they displace drugs from plasma proteins (oral anticoagulant like warfarin, oral hypoglycemic drugs) - They ↓ metabolism of statins = toxicity myalgia, myositis..so we Give lower doses
ADRs	**-GIT** (indigestion, abdominal pain, diarrhea) **-Myositis**(main adve): can occur resulting in weakness and tenderness of muscles,(if left untreated may lead to Rhabdomyolysis→Acute renal failure occurs -In alcoholics, -If combined with statins (each –ve metabolism of other) -In impaired renal function **-Gallstones**: **Clofibrate** increases C content of bile, predisposes to gallstones, and its use is therefore limited to patients who have **cholecystectomy** (removal of gallbladder) -Rash, urticaria, hair loss
contra-indi-cation	Impaired renal function Pregnant or nursing women Preexisting gallbladder disease

you have to know how it affects each lipid and in comparison to the other drugs

Drug Class	Agents	Effects (% change)	Side Effects
HMG CoA reductase inhibitors all Statins4	Lovastatin durations Pravastatin	↓**LDL (18-55),** ↑ HDL (5-15) ↓ Triglycerides (7-30)	Myopathy, increased liver enzymes
Cholesterol absorption inhibitor	Ezetimibe	↓ LDL(14-18), ↓ ↑ HDL (1-3) ↓Triglyceride (2)	Headache, GI distress Can give with statin preferred
Nicotinic Acid		↓**LDL (15-30),** ↑ **HDL (15-35)** ↓ **Triglyceride (20-50)**	Flushing, Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity
Fibric Acids	Gemfibrozil Fenofibrate	↓LDL (5-20), ↑HDL (10-20) ↓**Triglyceride (20-50)**	Dyspepsia, gallstones myopathy
Bile Acid sequestrants	Cholestyramine	↓ LDL ↑ HDL ↑ **triglycerides**	GI distress, constipation decreased absorption of other drugs

Adjuvant Therapy in Hyperlipidemia

They are not used alone, rather they are used to help other drugs.
examples: omega-3-FA.B-Sitosterol.

NAME OF DRUG	Omega-3- FA	B-Sitosterol
Mechanism	it will decrease (TG) by decreasing the enzymes involved in TG synthesis. and by increasing beta-oxidation of free fatty acid. It will also provide some vascular protection because it will decrease platelet function and it will have some anti inflammatory effect.	compete with dietary and biliary cholesterol absorption by decreasing LDL levels
indication	as adjunctive in high TG	hypercholesterolemia
found in	fish oil	in plants with same structure as Cholesterol (C)

Questions

MCQs:

1.Which one of the following is the most common side effect of antihyperlipidemic drug therapy?

A. Elevated blood pressure.
B. Gastrointestinal disturbance.
C. Neurologic problems.
D. Heart palpitations.
E. Migraine headaches.

2. Which one of the following hyperlipidemias is characterized by elevated plasma levels of chylomicrons and has no drug therapy available to lower the plasma lipoprotein levels?

A. Type I.
B. Type II.
C. Type III.
D. Type IV.
E. Type V.

3.Which one of the following drugs decreases cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3- methylglutaryl coenzyme A reductase?

A. Feno brate.
B. Niacin.
C. Cholestyramine.
D. Lovastatin.
E. Gembrozil.

4.Which one of the following drugs causes a decrease in liver triglyceride synthesis by limiting available free fatty acids needed as building blocks for this pathway?

A. Niacin.
B. Feno brate.
C. Cholestyramine.
D. Gembrozil.
E. Lovastatin.

Questions

MCQs:

5.Which one of the following drugs binds bile acids in the intestine, thus preventing their return to the liver via the enterohepatic circulation?

A. Niacin.
B. Feno brate.
C. Cholestyramine.
D. Fluvastatin.
E. Lovastatin.

6.JS is a 65-year-old man who presents to his physician for management of hyperlipidemia. His most recent lipid panel reveals an LDL cholesterol level of 165 mg/ dL. His physician wishes to begin treatment to lower his LDL cholesterol levels. Which of the following therapies is the best option to lower JS's LDL cholesterol levels?

A. Feno brate.
B. Colesevelam.
C. Niacin.
D. Simvastatin.
E. Ezetimibe.

1-B 2-A 3-D 4-A 5-C 6-D

Questions

SAQ:

1. 46-year-old woman with a history of hyperlipidemia was treated with a drug. The chart below shows the results of the patient's fasting lipid panel before treatment and 6 mo after initiating drug therapy. Normal values are also shown.

Time of Lipid Measurement	Triglyceride	Total Cholesterol	LDL Cholesterol	VLDL Cholesterol	HDL Cholesterol
Before treatment	1000	640	120	500	20
Six months after starting treatment	300	275	90	150	40
Normal values	<150	<200	<130	<30	>35

A-What is the most likely drug to be the one that this patient received?

Niacin

B- 4 ADRS for this drug.

1-Headache

2-Hepatotoxicity

3-Teratogenicity

4-myalgia

Questions

SAQ:

2. A 35-year-old woman appears to have familial combined hyperlipidemia. Her serum concentrations of total cholesterol, LDL cholesterol, and triglyceride are elevated. Her serum concentration of HDL cholesterol is somewhat reduced.

A- Which drug is most likely to increase this patient's triglyceride and VLDL cholesterol concentrations when used as monotherapy?

Cholestyramine

B- If this patient is pregnant, which drug should be avoided because of a risk of harming the fetus?

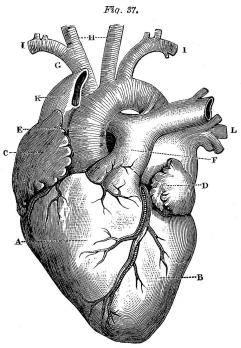
Pravastatin

C- The patient is started on gemfibrozil. What is the major mechanism of gemfibrozil's action?

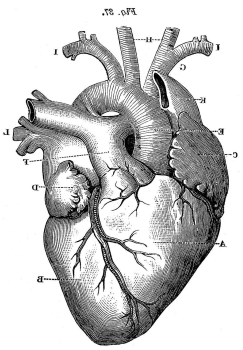
Increased triglyceride hydrolysis by lipoprotein lipase

D- Which of the following is a major toxicity associated with gemfibrozil therapy?

Cholelithiasis



"It is not hard, you just made it to the end!"



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✓ Doctors' notes and slides

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