MED441
KING SAUD UNIVERSITY

Revised & Reviewed by Abdulaziz Bahammam & Faye Wael Sendi

12&13. Drugs for hyper/lipid/emia

An excessive amount of

Blood stream

Fat, Adipo

Pharmacology
TEAM 441

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

HELPFUL VIDEO:

Drugs for Hyperlipidemia

Editing file

Color index:
Important
In male's slides only
In female's slides only
Extra information
Doctors notes

Introduction to Hyperlipidemia

- **Hyperlipidemia** is a major cause of atherosclerosis which may lead to Cardiovascular diseases and ischemic cerebrovascular disease.
- Denotes abnormally ↑ levels of any or all **Lipids** and/or **Lipoproteins** [LP] in blood.

Lipids originate from 2 sources

Endogenous

synthesized in the liver

Exogenous

ingested and processed in the intestine

Principle lipids in the blood

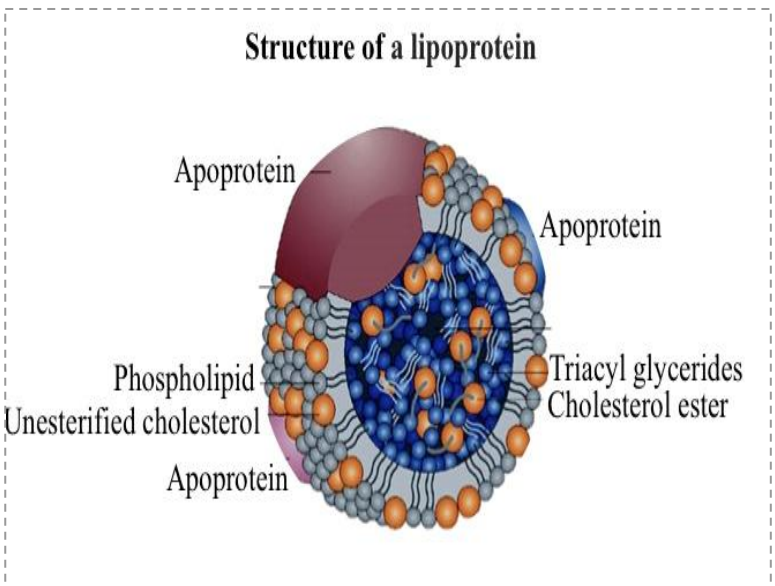
Cholesterol (C) | Phospholipids (PL) | Non-esterified fatty acids (NEFA) | Cholesterol esters (CE) | **Triglycerides (TG)**

Extra:

Lipoproteins:

- Endogenous molecules that contain both proteins and lipids in their structure
- transport (carry) lipids around the body in the blood
- *All are Atherogenic Particles except HDL

Types of lipoproteins:
Chylomicrons: Carry dietary TAG from intestinal mucosa to peripheral tissues
VLDL: Carry endogenous TAG from liver to peripheral tissue. (precursor of LDL)
LDL: " bad cholesterol" Synthesized in plasma from VLDL
HDL: "good cholesterol" Carry cholesterol from peripheral tissues to the liver



Introduction to Hyperlipidemia

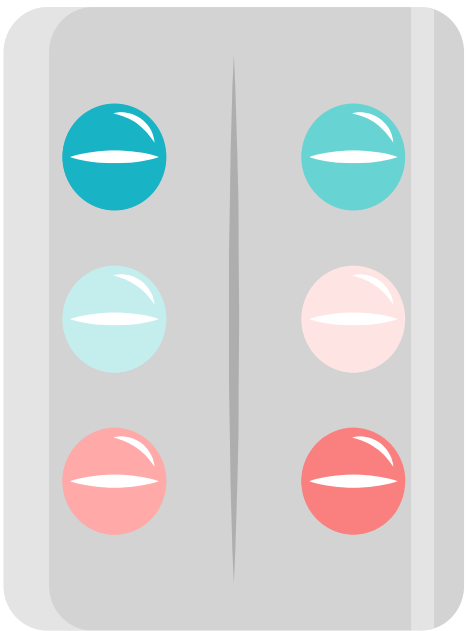
Familial Hyperlipoproteinemia			
L-Proteinemia	↑ LipoProtein	↑ Lipids	Risk
Type I	CM	TGs	-
Type IIa	LDL	C	↑
Type IIb	VLDL & LDL	TG & C	↑
Type III	IDL	TGs & C	↑
Type IV	VLDL	TGs	↑
Type V	VLDL & CM	TGs & C	-

EXTRA:

Normal lipid levels Lipid levels are detected in serum after a 12-hour fast	
C	<200 mg/dl
TGs	<220 mg/dl
LDL	<130 mg/dl (bad C)
HDL	>50 mg/dl (good C)

Therapeutic strategies for treatment of hyperlipidemia

Therapeutic lifestyle changes: (Non-pharmacological)



Regular exercise & Loss of weight

Cessation of hazardous habits; smoking, alcohol...

Eat food high in antioxidants vitamins

Avoid trans-fatty acids & acute increase in Cholesterol intake

Healthy Diet;Optimal quantitative & qualitative fat content
Diet has <30% of calories as fat, <7% as saturated fat and <200 mg cholesterol/day

Use vegetable oils rich in unsaturated fatty acids: oleic acid, linoleic acid & linolenic acids.Diet should also contain plant stanols (interfere with the formation of micellar cholesterol)

- Can achieve a fall in LDL/C of 8-15%, but long-term **compliance** is a problem

Antihyperlipidemic Drugs

Classified according to:

1- Site of action:

1- Agents targeting **exogenous** cholesterol:
-Resins : Colestipol,Colesevelam & cholestyramine
-Ezetimibe

2- Agents targeting **endogenous** cholesterol:
-Statins
-Fibrates
-Nicotinic acid

3- **Adjuvant** agents:
- Omega-3-Fatty Acids,
- Stanols

2- Mechanism of action:

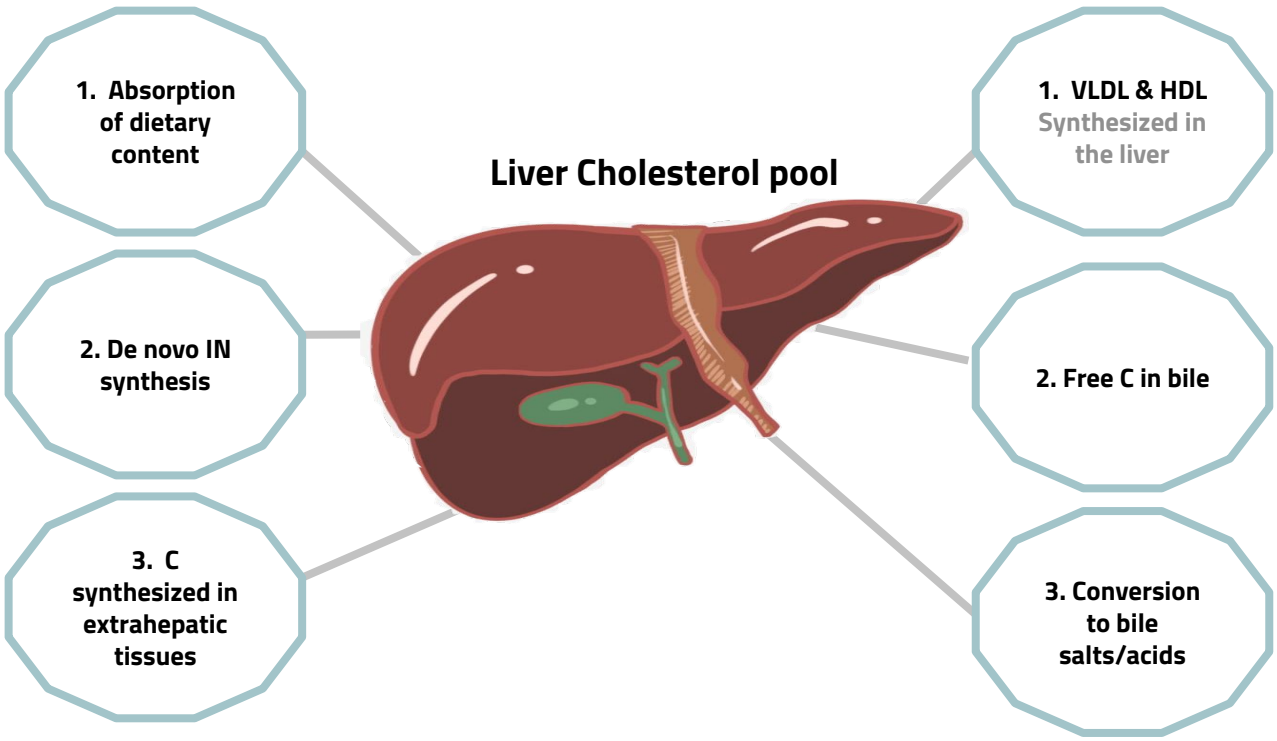
1- Inhibits cholesterol **absorption** in the intestine:
-Ezetimibe

2- **Sequester** bile acids in the intestine:
-Exchange resins

3- **Inhibits synthesis** of cholesterol: Inhibitors of HMG-CoA reductase
-Statins

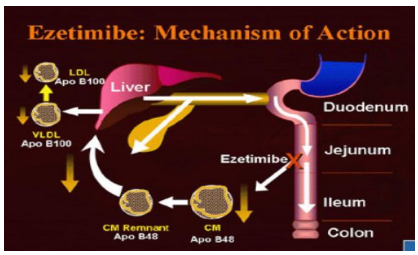
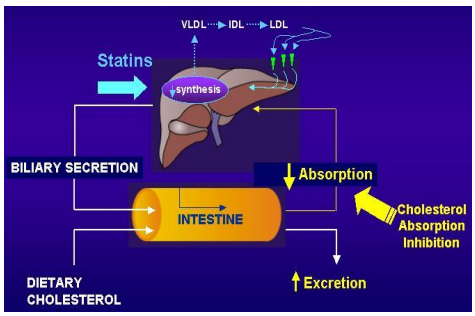
4- Alter relative levels & patterns of different plasma LPs:
-Fibrates, Nicotinic acids (Niacins)

Hepatic Cholesterol Metabolism EXTRA



Agents Targeting Exogenous Cholesterol

1-Cholesterol Absorption Inhibitors

Drug	**Ezetimibe**
M.O.A	Blocks C transporter located on brush border of small intestine→ ↓pool of C available to the liver→ upregulate LDL receptor, trapping more LDL particles from blood. It blocks **Niemann-Pick C1- Like transporter** 
Pharmaco-logical actions	↓LDL 20% ↓TG 8% **↑HDL 1-4%** No effect on steroids, lipid-soluble vitamins, bile acids
Pharmacokinetics	- Absorbed & conjugated in intestine to **active glucuronide** - Undergoes **enterohepatic** circulation - Its half-life is 22 hours , and Reaches peak blood level in 12–14 hours. - Most of the drug is **excreted in feces**
Clinical Uses	**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: **1. statins**; **synergistic** In **moderate/severe ↑ LDL** statins good combination because ezetimibe will work in exogenous while statins in endogenous cholesterols. 2. Or If must ↓ statin dose because of side effects 3. Or with other lipid lowering drugs As **fibrates**
ADRs	Not common ● GIT disturbance (the main symptoms for most of antihyperlipidemics) ● headache, fatigue, **arthralgia and myalgia**

Agents Targeting Exogenous Cholesterol

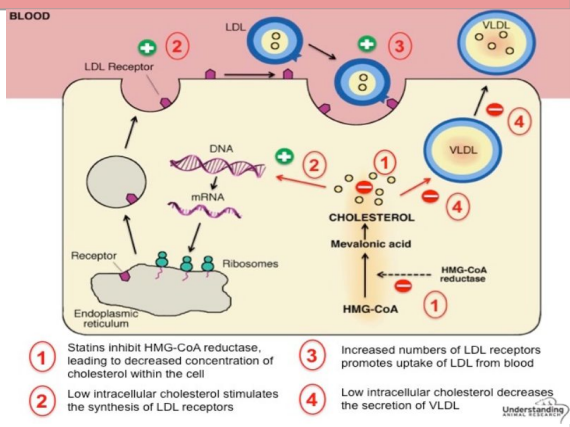
2-Exchange Resins or Bile acid sequestrants

Drug	**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 thus: -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**		
M.O.A	Bind to bile acids and bile salts in the small intestine. They form resin/bile acid (insoluble) complex which prevents their reabsorption from the intestine. They **disrupt the enterohepatic circulation of bile acids.**		
ADRS	• They are clinically **safe** as they are not systemically absorbed. • GIT upset: abdominal discomfort, bloating, constipation. • Decreased absorption of fat soluble vitamins (A, D, K). • The concentration of **HDL-C is unchanged.** (If a patient is taking multivitamins or needs to ↑ HDL, go for ezetimibe)		
Contraindications	• Complete Biliary obstruction (because bile is not secreted into the intestine). • Chronic **constipation**. • Severe hypertriglyceridemia (TG >400 mg/dL). -The bile acid binding resins can raise triglycerides modestly (about 5%) and cannot be used if the triglycerides are elevated.		
Interactions	• Interfere with the absorption of: Statins, Ezetimibe, Chlorothiazide, Digoxin, Warfarin. **IMPORTANT:** **Therefore, these drugs should be taken at least 1 hour before, or 4 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		

Agents Targeting Endogenous Cholesterol

- Hydroxy MethylGlutaryl-Coenzyme **(HMG-CoA) A reductase 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.**

1-HMG-CoA Reductase inhibitors

Drug	**Statins**
M.O.A	Statins are potent competitive inhibitors of (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 
P.K	▪ 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 anytime because of its long half-life (14 hours)
Preparations	▪ Rosuvastatin ▪ Atorvastatin long duration of action ▪ Simvastatin ▪ Pravastatin & Fluvastatin safe to use with drugs metabolized through CYP 3A4 ▪ Lovastatin **P**harmacists **R**ock **A**t **S**aving **L**ives and **F**lu prevention Thanks to Abdullah Alomran! ▪ Used alone or with other anti-hyperlipidemic drugs (ezetimibe) for treatment of drug-resistant dyslipidaemia
Pleiotropic (producing or having multiple effect from a single gene) **Anti/athero/genic Effects [> in vessels]**	1. Enhanced fibrinolysis 2. Improve endothelial function 3. Enhancing the stability of atherosclerotic plaques 4. Decreasing oxidative stress and inflammation (antioxidant) 5. Antithrombotic actions 6. Decrease vascular Inflammation 7. Decrease platelet aggregability 8. Extrahepatic effects on immune system, CNS and bone

Agents Targeting Endogenous Cholesterol

Drug	**Statins "continued":**
Indication	▪ **As monotherapy**; ▪ **Primary Prevention;** 1. Patients with hyperlipidemia and with other risks for ischemic insults. 2. Type IIa Hyperlipoproteinemia , If no control → combine (sequestrants ezetimibe, niacin) to decrease C. ▪ **2nd primary Prevention;** In all ischemic insults [stroke, AMI, ...etc.] So given from 1st day of ischemic attack they enhance endothelial function ▪ **As Combination therapy;** 1. Mixed dyslipidaemias; added to fibrates or niacin if necessary Fibrates are added with caution since they may cause statin induced myopathy 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	▪ **Common side effects:** Headache , myalgia, fatigue, GI intolerance, and flu-like symptoms ▪ **Hepatotoxicity**, raised concentrations of liver enzymes (serum aminotransferases) ▪ **Myopathy** (increased creatine kinase [CK] released from muscles) ▪ **Teratogenicity**, statins should be avoided during pregnancy Mnemonic: **HMG Reductase H**epatotoxicity, **M**yopathy, **G**I intolerance, **R**habdomyolysis Thanks to Abdullah Alomran!
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: ▪ Other antihyperlipidemics (fibrates) Why ? They each decrease the metabolism of the other. ▪ Drugs metabolized by **3A4 isoform of cytochrome P450:** erythromycin,verapamil, cyclosporin, ketoconazole ▪ **Pravastatin** and **fluvastatin** are the statins of choice in patients taking other drugs metabolized by cytochrome 3A4 system.

Statin induced myopathy

- 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**	**acute renal necrosis**

1.↑ serum transaminase: can progress to evident hepatotoxicity so lab investigations recommended every 6 month:

- **if levels ↑ up to 3 folds at any time, statin must be stopped then dose adjusted.**

2.↑ 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 fibrates**

Agents Targeting Endogenous Cholesterol

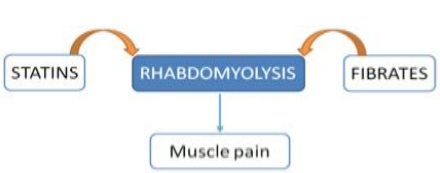
2-Niacin (Nicotinic Acid)

- Water soluble B-complex vitamin with multiple actions
- 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

M.O.A	**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 (FAs are the main precursors of TG) **In liver:** ● Niacin inhibits hepatocyte 2-diacylglycerol acyltransferase a key enzyme for TG synthesis. Thus it decreases VLDL production (decreased TG synthesis and esterification). **In plasma:** ● It increases Lipoprotein lipase (LPL) activity that increases clearance of VLDL & chylomicrons
Pharmacologic actions	**Effect on ↓VLDL by:** - ↓synthesis in liver. - increased clearance in plasma . - ↓mobilization of free fatty acids from adipose tissue. **Effect on↓ LDL:** logical - due to reduction of its precursor (VLDL). **Effects on ↑HDL by :** - Induces modest increase in HDL-C (The catabolism of HDL can be inhibited by nicotinic acid through a mechanism that is largely unknown). - Niacin also promotes hepatic **apoAI** production and slows hepatic clearance of apoA-I and HDL. → Q: How niacin increase HDL ?
Indications	**Monotherapy or in combination with fibrate, resin or statin** Type IIa hypercholesterolemia. Type IIa, IIb hypercholesterolemia & any combined hyperlipidemia. Patient with hypertriglyceridemia & low HDL-C.
Adverse Effects	**The most common side effect is** cutaneous flushing (which is prostaglandin-mediated, can be avoided by low dose Aspirin ½ hour before niacin). ● **GIT disturbances:** Dyspepsia, nausea, vomiting, reactivation of peptic ulcer (can be decreased if taken after ADRS meal) ● **High doses:** -Reversible ↑ in liver enzymes → hepatotoxicity. -Impairment of glucose tolerance → overt diabetes - ↑ uric acid → gout
Contraindications	• Gout. • Hepatotoxicity. • Peptic ulcer. • Diabetes mellitus.

Agents Targeting Endogenous Cholesterol

3.Fibric acid Derivatives (Fibrates)

	Clofibrate	**Gemfibrozil**	**Feno**fibrate
mnemonic	(Feno)(Clo)(Gem) (fi) (brazil) فينو **clo? In the gym** في **brazil** Thanks to Yara Almufleh!		
M.O.A	▪ Fibrates are agonists of **peroxisome proliferator activated receptors** (PPARα) which are a class of intracellular receptors that modulate fat metabolism ▪ They increase genes transcription for lipoprotein lipase (LPL) leading to increased catabolism of TG in VLDL and chylomicron		
Pharmacologic Actions	● ↑LPL activity which increases clearance of VLDL & chylomicron in plasma. ● A marked reduction in TG (due to stimulation of catabolism of VLDL). ● ↑FFA uptake by the liver actions ● ↑LDL-C uptake by the liver. ● ↑ 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.		
Indication	**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).		
ADRs	● GIT (indigestion, abdominal pain, diarrhea). GIT upset, headache, fatigue, weight gain, **myalgia** ● Rash, urticaria, hair loss. ● **Gallstones**: *Clofibrate* increases C content of bile, predisposes to gallstones and its use is therefore limited to patients who have cholecystectomy OR biliary tract disease ● **Myositis**: can occur resulting in weakness and tenderness of muscles (if left untreated may lead to Rhabdomyolysis → Acute renal failure), this occurs in: - If combined with statins (use of fibrates with statins if generally inadvisable) (each –ve metabolism of other) - In alcoholics - In impaired renal function.		
interactions	● Increased risk of myopathies when used with statins. ● They displace drugs from plasma proteins (oral anticoagulant like warfarin, oral hypoglycemic drugs). They displace warfarin from their protein binding sites which↑ bleeding tendency so anticoagulant dose must be adjusted.		
Contra-indications	▪ Patients with impaired renal functions ▪ Pregnant or nursing women ▪ Preexisting gallbladder disease		

Adjuvant Therapy in Hyperlipidemia:

Drug	Omega 3 FA	β-Sitosterol
Pharmacological actions	▪ ↓ **(TG) by:** - ↓ the enzymes involved in TG synthesis. - ↑ beta oxidation of FFA ▪ **provide some vascular protection by:** - ↓ platelet function. - Prolongation of bleeding time. - Anti-inflammatory effect.	Compete with dietary and logical biliary C absorption → actions ↓ LDL levels 10%
Indication	Approved as **adjunctive** for treatment of very high TGs	Given as food supplement before meal in hypercholesterolemia
Found in	Fish oil containing highly unsaturated Fatty acids	in plants with similar structure as Cholesterol (C).

Summary thanks to 439!

Drug class	Agents	Effects (% change)	Side Effects	Contraindications
Bile acid sequestrants (Resins)	**Cholestyramine Colestipol Colesevelam**	**↓LDL ↑triglycerides**	**-GI distress -constipation -decreased absorption of other drugs (except colesevelam) -Decreased absorption of fat soluble vitamins**	**1.Biliary obstruction 2.Chronic Constipation 3.Hypertriglyceridemia**
Cholesterol Absorption Inhibitors	**Ezetimibe**	**↓LDL(14-18) ↑HDL (1-3) ↓Triglyceride (2)**	**-Headache, fatigue, Arthralgia, & myalgia -GI distress**	
HMG-CoA Reductase Inhibitors (statins)	**Lovastatin Pravastatin Atorvastatin (long ½ life)**	**↓LDL (18-55) ↑HDL (5-15) ↓Triglycerides (7-30)**	**-Myopathy, -Increased liver enzymes (hepatotoxicity), -Potentiates anticoagulants & antidiabetic drugs**	**1.Pregnant women**
Niacin (Nicotinic Acid)		**↓LDL (15-30) ↑HDL (15-35) ↓Triglyceride (20-50)**	**-Flushing (most common) -Hyperglycemia, -Hyperuricemia, -GI distress -Reversible Hepatotoxicity**	**1.Diabetics 2.Gout 3.Peptic ulcers 4.Hepatotoxicity**
(Fibrates)	**Gemfibrozil Fenofibrate**	**↓LDL (5-20) ↑HDL (10-20) ↓Triglyceride (20-50)**	**-Dyspepsia, -gallstones - myositis & (myopathy if given with statins)**	**1.Impaired renal function 2.Pregnant or nursing women 3.Preexisting gallbladder disease**

These questions were given by the females' doctor

Q1. Which of the following drugs binds bile acids in the intestine,thus preventing their return to the liver via the enterohepatic circulation?

A. Ezetimibe
B. Resins

Q2: A 50 year old female with hyperlipidemia & hypothyroidism . Her current medications include cholestyramine & levothyroxine (thyroid hormone) What advice would you give to this patient to avoid drug interaction between her 2 medications?

A. Stop taking the levothyroxine as it can interact with cholestyramine
B. Take levothyroxine 1 Hour before cholestyramine on an empty stomach

Q3. What is the MOA of cholestyramine?

A. Inhibits Cholesterol absorption in the intestine
B. Sequester Bile acids in the intestine

Q4 True or false

A. The occurrence of coronary heart disease is positively associated with high total cholesterol & more strongly with elevated LDL-C (true / false)
B. High levels of HDL-C have been associated with an increased risk for heart disease
(true / false)

Q5. Which one of the following hyperlipidemias is characterized by elevated plasma levels of chylomicrons & has nor drug therapy available to lower the plasma lipoprotein levels?

A. Type 1
B. Type 2
C. Type 3
D. Type 4
E. Type 5

Q6. What is the main effect of niacin on lipid profile?
Answer: Increases HDL , Decreases LDL & VLDL

Q7. What is the first line therapy for lowering LDL ?
Answer: Statins (remember they are not safe for pregnant women)

Answers:
1B
2B OR Take levothyroxine 4 hours after cholestyramine OR Take colesevelam instead of cholestyramine
3B
4A True / 4B false
5A : Type 1 is not associated with risk of increased heart disease , it only characterized with elevated chylomicrons, this means that no drug is required only diet modifications.

SAQs:

1-A patient had LDL-C level of 250 and HDL 58, he took hypolipidemic drug after a month a test showed a decrease in his LDL-C level to 180 but he was complaining of muscle pain in both his legs. Which drug can produce this ADR?

2-A 42-year-old woman who has hyperlipoproteinemia type IIb uses an antihyperlipidemic drug for her condition. As a result, her cholesterol and LDL
levels have been reduced but her triglycerides and VLDL level have increased. Which drug is she using?

3-What is the mechanism of action of Atorvastatin ?

Click here!

Answers:

A1-Common side effect with : Statins Or Fibrates
*increased risk of rhabdomyolysis & myopathies if they were combined because they decrease the metabolism of each other.

A2-Resins: colestipol, colesevelam, & cholestyramine

A3-Statins are potent competitive inhibitors of (HMG-CoA) reductase which is an important enzyme of cholesterol synthesis in the liver.

Test yourself

From our amazing Qbank team

Good luck!

Pharmacology
TEAM 441

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