Biochemistry

- Hyperlipidemia :- is abnormally elevated levels of any or all lipids (TAG & Cholesterol are the most important) in the blood.

- TAGs & Cholesterol are insoluble (lipids), so they need specific vehicles to move around the body which are the lipoproteins:-

- As you know, these lipoproteins consist of protein coat and core of lipids
- So let's revise their story, it is a cycle so you can start from any point, but I prefer to start from the liver :-

The liver forms the VLDLs and sends it to body organs via blood, in order for the liver to be able to manufacture these, the raw materials for VLDL must be available (which are TAG + cholesterol), there are 3 sources we will talk about :-

1- TAG-rich chylomicrons made by the SI from dietary lipids
2- The endogenous cholesterol which is synthesised by the liver itself
3- TAG from the adipose tissue

Let's talk about these points in detail :-

1

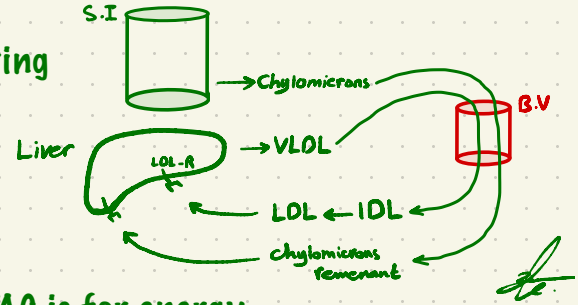
I. TAG-rich chylomicrons made by the SI from dietary lipids + VLDL from the liver, travel to the tissues via the bloodstream

عوجة ~ VLDL & Chylomicron الـ TAG ← كلسيريدز

II. While these two run in the blood stream, an enzyme called lipoprotein lipase degrades the TAG to FFAs - LPL is attached to the luminal surface of endothelia cells in capillaries It is most widely distributed in adipose ,skeletal ,cardiac tissues - which are used as a source of energy to produce ATP in the tissues or for storage

III. Over time, the TAG/Cholesterol ratio will decrease (Remember that LPL has nothing to do with cholesterol), hence
chylomicron >>> chylomicron remnant
VLDL >>> IDL >>> LDL

IV. chylomicron remnant & LDL consist mainly from cholesterol, they travel to the liver - the organ that can deal with cholesterol by consuming it to synthesise various materials, as bile acids which are released into the gut upon gallbladder emptying following meal ingestion , about 95% of them will be reabsorbed by the body



- Some notes :-

* Cholesterol is for synthesis, while TAG is for energy
* VLDL & LDL are related to each other, high VLDL means high LDL also
* LDL has specific receptors on many tissues in the body (hepatic & extrahepatic tissues) as well as receptors on the macrophages, so any error in returning it to liver or if its plasma level is high, that will stimulate phagocytes to engulf LDL, resulting in transforming macrophages to foam cells causing atherosclerosis
* HDL (good cholesterol, formed by liver), function: take up cholesterol from atherosclerotic plaques or foam cells

Doctor said : Don't memorize it

- But keep this in your mind :-
- Type IIa :- C ⏫
- Type IIb :- combined (TAG & C) ⏫
- Type IV & Type V :- TAG ⏫

Hyperlipoproteinemia		Labs description
Type I	Familial hyperchylomicronemia	Elevated **Chylomicrons and VLDL**
Type IIa	Familial hypercholesterolemia	Elevated LDL only
Type IIb	Combined hyperlipidemia ↳ means both TAG + C are elevated	Elevated LDL and VLDL and Triglycerides
Type III (RARE)	Familial Dysbetalipoproteinemia	Increased IDL
Type IV	Familial Hyperlipemia	Increased VLDL
Type V	Endogenous Hypertriglyceridemia	Increased VLDL and Chylomicrons

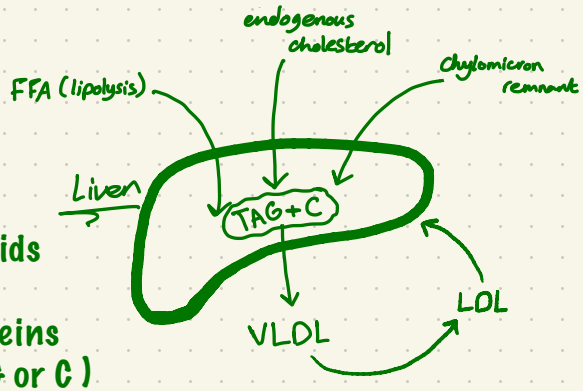
2

- Our body has also its own cholesterol machinery, which takes place in the liver, this process -as we remember from metabolism course- is complicated, Don't panic ! we won't go through it, we need just to remember the rate-limiting step, which is the production of mevalonic acid from HMG-CoA by HMG-CoA reductase

3

- Adipose tissue is the main producer of circulatory FFAs & it supplies the liver with TAG needed for VLDL synthesis

Summary



- Hyperlipoproteinemia means ↑lipoproteins, These lipoproteins consist of protein coat and a core of lipids
- Antihyperlipidemia drugs' moa is to decrease the production of the lipoproteins by decreasing the amount of lipids (TAG or C) So, no lipids no lipoproteins (VLDL/LDL)

Statins :- inhibit cholesterol synthesis
Fibrates :- increase TAG degradation
Niacin :- inhibits lipolysis (FA synthesis)
Bile acid-binding resins :- increase bile acids excretion
cholesterol absorption inhibitors :- 😄

- These agents may used singly or in combination.

Drugs

Statins

- These agents are classified according to their efficacy to :-
Intermediate statins :- Lovastatin, pravastatin, simvastatin, fluvastatin
Strong :- Atorvastatin, rosuvastatin (also called High intensity statins)
Very strong :- Cerivastatin
- Mostly used are Atorvastatin + Rosuvastatin (Strong against aggressive hyperlipidemia)
- Potency of these drugs is related to the side effects, and at the end of a day (with higher doses) they have similar efficacy

يعني بال strong statins بنقدر نرفع الجرعة بدون ما أخاف من زيادة الأعراض الجانبية

- Different drugs, different limits to start experiencing side effects
- Cerivastatin extremely potent "the most" , however it has aggressive rhabdomyolysis as a side effect, so it was withdrawn from market
- Lovastatin and fluvastatin are less likely to cause myopathy, so in cases which don't require high density statins you can use one of these

- They're used in hypercholesterolemia (high LDL) like in Types IIa & IIb

- **MOA :-** they are called "HMG CoA reductase inhibitors" , they inhibit cholesterol synthesis in the liver, the consequences of this inhibition are :-
1- decreased VLDL secretion, which will also reduce LDL concentration
2- stimulate the synthesis of LDL receptors which will promotes uptake of LDL from blood
3- stimulate HDL synthesis which will bring the cholesterol trapped in foam cells (from the circulation) to the liver

- **Side effects :-**
1- Myopathy :- Inhibition of Coenzyme Q10 of the ETC "electron transport chain" in muscles causing ATP depletion, related to pain and fatigue muscles, more common in females because they بشتغلو بالمطبخ . Its incidence is 7-8%. It has also a placebo effect, meaning that the incidence of side effects increase based on the drug's reputation (most common S.E)

Statins

2- rhabdomyolysis :- disintegration or dissolution of muscle, elevation in CK (creatinine kinase), its incidence is 0.6 out of 10000 people, causes secretion of muscle myoglobulin results in nephrotoxicity
3- nephrotoxicity (from rhabdomyolysis and high levels of CK)
4- Biochemical abnormalities in liver function "very little" , however they are contraindicated in liver cirrhosis, they also cause minor increases in AST,ALT (liver enzymes)

• some notes :-

1- evaluate muscles & liver function is needed by monitoring AST,ALT,CK levels
2- These agents are contraindicated during pregnancy and in nursing mothers. They also should not be used in children and teenagers.

• Statins interaction :-

* The catabolism of lovastatin, simvastatin, and atorvastatin proceeds chiefly through CYP3A4 (3A & 3 drugs) جماعة عسل ASL
* Whereas that of fluvastatin and rosuvastatin is mediated by CYP2C9.
*The exception is Pravastatin which is catabolized through other pathways, including sulfation
* Fibrates, especially gemfibrozil, are CYP450 inhibitors, so if you give your patient Fibrates with Statin you have to reduce the dose of Statin, so If you want to take statin with Fibrates the only one you can take is Pravastatin because it's metabolite by sulfate, So it's contraindicated with Fibrates (except for Pravastatin)
* Rifampin increases expression of CYP3A4 & CYP2C9, so you may need to increase the dose of the statin here
* Grapefruit juice inhibits CYP3A4, so plasma levels of lovastatin, simvastatin, and atorvastatin may be elevated

<u>The doctor didn't mention anything other than rifampin and grapefruit, but there are other interactions you can read from the slide</u>

Fibrates

- Fenofibrate and Gemfibrozil, Bezafibrate are derivatives of fibric acid

- These agents may used singly in the treatment of hypertriglyceridemia (high VLDL) like in Types IV & V, or in combination with statins in the treatment of combined hyperlipidemia

- **MOA :-** they bind to PPARs which are nuclear receptors that regulate lipid metabolism, resulting in reduction of TAG concentration by increasing the expression of lipoprotien lipase, the consequences are :-
1- rapid transport of free fatty acid from VLDL towards the adipose tissue which results in faster utilisation of VLDL towards LDL
2- The liver senses the increase in LDL so It absorbs it / Fibrates slightly decrease LDL
3- A part of peroxisome receptor effect is to increase HDL

- **Adverse effect :-**
a. The most common adverse effects are mild gastrointestinal disturbances
b. Lithiasis Because these drugs increase biliary cholesterol excretion, there is a predisposition to the formation of gallstones
c. Myositis (inflammation of a voluntary muscle) can occur (Rarely)

- **some notes :-**
* Fibrates compete with the coumarin anticoagulants (such as warfarin) for binding sites on plasma proteins.
* Not preferred to be used with statins because it inhibits CYP450 this will result in increased concentration of statin (especially gemfibrozil, it's contraindicated in combined hyperlipidemia), but in some cases like for Type IIb(combined hyperlipidemia) we may give them together (Fenofibrate not gemfibrozil) + one of the statins (Pravastatin is most preferred)
and here evaluation of muscles function is important

Niacin (vitamin B3)

- In the last decade, it was believed that the best treatment for hyperlipidemia is combination of Statin and Niacin, but It was withdrawn from market because of study which proved that increasing HDL has no value in treating hyperlipidemia
- Niacin is the most effective agent in increase the HDL (the good cholesterol carrier)

- It is used in type IIb and IV hyperlipoproteinemia, in which both VLDL and LDL are elevated .Also to treat other severe hypercholestrolemias

•MOA :-

1- strongly inhibits lipolysis in adipose tissue - the primary producer of circulating free fatty acids - so lowering plasma VLDL & LDL
2- It increases HDL level by inhibiting the catabolism of HDL through foam cells

•Adverse effects :-

1- hyperglycemia and hyperuricemia (as diuretics do)
2- Peptic ulcer activation happens because of the decreased platelet count which will result in increased bleeding.
3- Cutaneous flushing, burning and itching because niacin increases production of prostaglandins which are inflammatory mediators that cause dilation and increasing permeability of the vessels
Others :- elevation of liver enzymes, GI irritation, nausea and vomiting
* Niacin is contraindicated in peptic ulcer patients.
* When you give Niacin to your patient you have to scratching of the doses which means starting with low dose and increasing it gradually and monitoring the side effects, another solution is to give your patient aspirin pill or 200mg profen per day for first two weeks because they decrease prostaglandins synthesis, however tolerance may happen

Bile acid-binding resins

- Cholestyramine and colestipol have significant LDL cholesterol lowering effect, although the benefit is less than those observed with statins, however, we give them with statins in those patients who don't respond well to statins alone / for patients who have extremely high hyperlipidemia

- Also they are the drugs of choice (often in combination with diet or niacin) in treating Type IIa.

- Those drugs are taken with food as bile acids will be excreted more at this time (food intake), unlike statins that is preferred to be taken at night because they inhibit the cholesterol synthesis which happens during the fasting time of sleeping (the low metabolic time of sleeping)

- **MOA :-**
- These agents are resins that bind bile acid in the intestine, forming insoluble complexes that will be excreted in the feces.
Lowering bile acid levels will trigger the conversion of cholesterol into bile acid and the end result will be :-
1- Reduction of cholesterol concentration
2- increasing the expression of LDL receptors which eventually decreases LDL (same mechanism as statins)
- In addition, they slightly increase HDL

- **Adverse effects :-**
- The most common side effects are gastrointestinal disturbances such as constipation and nausea.
- At high doses they impair the absorption of fat soluble vitamins (AKED) أكيد
- These agents interact with the absorption of many drugs (fat soluble drugs),for example, Tetracycline,Digoxin, Warfarin, Aspirin. Therefore, those drugs should be taken at least 1 to 6 hr after resins intake

Cholesterol absorption inhibitors

- Ezetimibe selectively inhibit intestinal absorption of dietary and biliary cholesterol in the small intestine, resulting in an increase of cholesterol clearance from the blood
- Don't interact with bile acid
- Very good effect when given with statins

•MOA :-

- Very limiting activity when we use it alone, but if it's combined with statins we'll have synergistic activity toward the reduction of LDL, meaning that when you inhibit cholesterol synthesis within the liver , the body will compensate by many mechanisms, such as increasing the absorption of cholesterol by the portal vein, hence this drug will inhibit this compensatory mechanism which resists the statins' effect and that's what we mean by synergism

•Adverse effects :-

Common adverse effects are headache and/or diarrhea.

Summary

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS
HMG-CoA reducatase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

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اللهم انصر إخواننا المجاهدين في غزة و فلسطين و سائر بلاد المسلمين

اللهم ارحم شهداء المسلمين في غزة و إدلب و سائر بلاد المسلمين

Done by Zaid Alabsi