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**Hyperlipidemia** is abnormally elevated levels of any or all lipids and/or lipoproteins in the blood. It is the most common form of dyslipidemia (which includes any abnormal lipid levels.

 Cholesterol, triglycerides, and phospholipids are the major lipids in the body, and they are transported as complexes of lipid and proteins known as lipoproteins.

 Plasma lipoproteins are spherical particles with surfaces that consist largely of phospholipid, free cholesterol, and protein and cores that consist mostly of triglyceride and cholesterol ester.

 The are four classes of lipoproteins:

1. Chylomicrons transport triglycerides and cholesterol from the GIT to the tissues, where they are split by lipase, releasing free fatty acids. There are taken up in muscle and adipose tissue. Chylomicron remnants are taken up in the liver

2. Very low density lipoproteins (VLDL), which transport cholesterol and newly synthetized TG to the tissues, where TGS are split by lipase, leaving low density lipoproteins

3. Low density lipoproteins (LDL) with a large component of cholesterol, some of which is taken up by the tissues and some by the liver, by endocytosis via specific LDL receptors

4. High density lipoproteins (HDL),Which absorb cholesterol derived from cell breakdown in tissues and transfer it to VLDL and LDL

 Each type of lipoprotein has its specific proteins called apolipoproteins embedded on its surface for example apolipoproteins A present on the surface of HDL whereas apolipoproteins B present on the surface of LDL and apolipoproteins C on the surface of Chylomicrons &VLDL.

 These apolipoproteins serve four main purposes:

1. Required for assembly and secretion of lipoproteins.

2. Serve as major structural components of lipoproteins.

3. Act as ligands (apolipoprotein B and apolipoprotein E) for binding to receptors on cell surfaces (LDL receptors).

4. Can be co-factors (such as apolipoprotein C-II) for activation of enzymes (such as lipoprotein lipase) involved in the breakdown of triglycerides from chylomicrons and VLDL.

 Abnormalities of plasma lipoproteins can result in a predisposition to coronary, cerebrovascular, and peripheral vascular arterial disease.

 Apolipoprotein A production is increased by estrogens, leading to higher HDL levels in women and in individuals receiving estrogen.



**Etiology of hyperlipidemias**

1- Primary (genetic origin): hereditary.

2- Secondary to:

 Diseases e.g. hypothyroidism.

 Drugs: β blockers, alcohol, thiazides.

**Drug therapy in hyperlipidemia**

1. Competitive inhibitors of HMG-CoA : statins (fluvastatin, lovastatin, pravastatin, simvastatin, **atorvastatin, rosuvastatin**)

2. Specific cholesterol absorption inhibitors: ezetimibe

3. Bile acid binding (resins): cholestyramine and colestipol, colesevelam.

4. Fibrates: clofibrate, gemfibrozil, bezafibrate, and fenofibrate

5. Nicotinic acid (niacin), acipimox

6. Others: CETP inhibitors (torcetrapib), prubucol, orlistat, omega-3-faty acid

**Competitive inhibitors of HMG-CoA**

It is the most important class since it is the most effective in reducing LDL. It decreases oxidative stress and vascular inflammation with increased stability of atherosclerotic lesions. Therefore, they are initiated immediately after acute coronary syndromes, irrespective of lipid levels.

**Mechanism of action**

 They are structural analogues of HMG-CoA intermediate required for the synthesis of mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. These analogues inhibit cholesterol synthesis by competitive inhibition of HMG-CoA reductase.

Statins use will result in up-regulation of LDL receptors. This effect will increase the liver’s extraction of LDL and its clearance from the blood, thus reducing serum LDL further. They also cause modest decrease in triglycerides and small ↑ in HDL-Ch.

 **Other cardio-protective effects of statins (pleiotropic effects)**

 **Blood vessels:**

 Improve endothelial function (increase NO)

 Decrease Arterial muscle proliferation and migration

 Decrease Progression of hypertrophy of the vessel wall

 Increase Neo-vascularization of ischemic tissues

 **Plaque:**

 Stabilize the athermatos plaque

 Have antioxidant properties ( decrease LDL.C oxidation).

 Have anti-inflammatory effects (decrease macrophages)

 Have antithrombotic effects (dec. Fibrinogen, dec.platelat aggregation, increase fibrinolysis)

**Blood:**

 Dec. Blood viscosity, increase blood Flow

**Pharmacokinetic**

Administered orally, with variable absorption (40-75%). Fluvastatin is completely absorbed. Simvastatin and lovastatin are prodrugs and need to be activated. However, atorvastatin, fluvastatin and rosuvastatin are active as such. All have high first pass extraction rate by the liver except pravastatin. 5-20% is excreted in the urine. Half life (1-3hr), except atorvastatin (14 hr) and rosuvastatin (19hr).

**Uses**

The statins are the most powerful drugs for lowering LDL-cholesterol (LDL-C), with reductions in the range of 30 to 63 % .They are used as mono- or combination therapy to ↓ LDL and they are administered at night. They are contraindicated in pregnant and lactating women.

**Adverse effects**

**1)** Deranged liver function tests; transaminases may rise with statins (up to 3 times normal) in some patients intermittently. Levels above 3 times normal or underlying liver disease needs discontinuation. LFT should be measured at baseline, at 1-2 months, and then every 6-12 months.

Myopathy; minor rise in creatine kinase (CK) may happen. Higher levels, associated with muscle pain, tenderness or weakness are suggestive of myopathy that needs discontinuation of the drug before development of rhabdomyolysis and myoglobinuria (renal impairment). CK should be measured at baseline.

“Cerivastatin” was withdrawn from the market worldwide in 2001 due to the reports of fatal rhabdomyolysis.

**3)** Drug interaction; (simvastatin, lovastatin and atorvastatin) are metabolized by CYP3A4 and accordingly, subject to enzyme induction/inhibition reactions. Pravastatin appears to be the drug of choice if concomitant use of other drugs is expected to cause problems since, it can be metabolized through other pathways.

**4)** Hypersensitivity syndromes; lupus-like disorder and peripheral neuropathy.

Statins should be discontinued temporarily during serious illness, trauma or major surgery.

**Specific cholesterol absorption inhibitors: ezetimibe**

Ezetimibe inhibit intestinal absorption of cholesterol. Its primary clinical effect is reduction of LDL levels.

**Mechanism of action**

It is a selective inhibitor of intestinal absorption of cholesterol through acting on transport protein. It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in the bile.

**Pharmacokinetic**

Administered orally, metabolized by glucuronide conjugation in liver and small intestine. With active glucuronide metabolite.

**Uses**

In primary hypercholesterolemia, it reduces LDL by 18% only. Therefore used in combination therapy with statins.

**Adverse effects**

Rarely; allergic reaction, deranged LFT and myositis

**Bile acid-binding resins**

Colestipol and cholestyramine are large catinonic exchange resins that are insoluble in water (bile acids sequestrants).

**Mechanism of action**

They increase removal of bile acids from body by forming insoluble complexes in intestine, which are then excreted in feces. When bile acids are excreted, plasma cholesterol is converted (in the liver) to bile acid to normalize bile acid levels. The conversion of cholesterol lowers plasma cholesterol concentrations. Bile acid sequestrants are primarily used to treat hypercholesterolemia, (isolated increase in LDL). Increased uptake of LDL and IDL from plasma results from up-regulation of LDL receptos, particularly in the liver. Thus they are not effective in patients with receptor defect.

**Pharmacokinetic**

They are taken orally with meals, available as tablets/granules. They are not absorbed from GI.

Other medications should be taken 1 hr before or 2 hours after the resins

**Uses**

In combination therapy for primary hypercholesterolemia, (20% reduction in LDL).

They can also be used to treat the pruritus, or itching in patients who have cholestasis and bile salt accumulation.

**Adverse effects**

**1)** Constipation and bloating

**2)** Heartburn and diarrhea

**3)** Malabsorption of vitamin K and folic acid

**4)** Reduced absorption of other drugs

**New Bile Acid Sequestrant: Colesevelam**

 Lower dose for effect

 Fewer GI complaints than with other bile acid sequestrants

 **Limitations of Current bile Acid Sequestrant**

 Noncompliance

 GI tolerability

 Reduced absorption of lipid-soluble vitamins

**Fibric acid derivatives (Fibrates): clofibrate, gemfibrozil, bezafibrate, and fenofibrate**

**Mechanism of action**

Increases activity of peroxisome proliferator-activated receptor-alpha (PPAR-α), a receptor which is involved in metabolism of carbohydrates and fats, as well as adipose tissue differentiation. This increases synthesis of lipoprotein lipase therefore increasing clearance of triglycerides.

They reduce triglycerides and VLDL levels along with moderate reduction in LDL and moderate rise in HDL.

**Other effects;**

 Dec. blood fibrinogen and uric acid

 Improve glucose tolerance.

 Dec.Platelet adhesion, C-reactive protein & SM inflammation.

**Pharmacokinetic**

Gemfibrozil is absorbed after oral administration, bound to plasma proteins. Half-life is 1.5 hr and 70% excreted unchanged by the kidneys.

**Uses**

Useful in hypertriglyceridemias (predominant VLDL) and dysbetalipoproteinemia.

**Adverse effects**

**1)** Skin rash and GI disturbance

**2)** Myopathy (specially with combination with statins)

**3)** LFT derangements

**4)** Reduction in white cell count and hematocrit.

**5)** Increase the risk of cholelithiasis

**Niacin (nicotinic acid)**

Niacin, nicotinic acid or vitamin B3, a water-soluble vitamin whose derivatives such as NADH, NAD, NAD+, and NADP play essential roles in energy metabolism and DNA repair.

**Mechanism of action**

**1.** Blocks the breakdown of fats in adipose tissue (lipolysis), thus altering blood lipid levels.

**2.** It reduces VLDL synthesis and secretion by the liver possibly by decreasing the flux of free fatty acids to the liver.

**3.** Because it inhibits VLDL secretion, in turn decreases LDL.

**4.** It also increases the clearance of VLDL via lipoprotein lipase (LPL) pathway.

**5.** It also decreases the catabolism of HDL.

**Uses**

In combination therapy for all hyperlipidemia (↓TG and CH). It is the most effective agent for increasing HDL and therefore it is sometimes prescribed for patients with low HDL, who are also at high risk of a heart attack.

**Adverse effects**

**1)** Cutaneous vasodilatation and flushing (prevented with aspirin and ibuprofen).

**2)** Skin: pruritis, rashes, dry skin or mucous membranes and acanthosis nigricans

**3)** GIT: nausea and abdominal discomfort, avoided in severe peptic disease

**4)** Liver and LFTs: deranged LFT, rarely hepatotoxicity

**5)** Hyperurecimia and precipitation of gout (allopurinol can be given)

**6)** Others: impaired carbohydrate tolerance, arrhythmias and toxic amblyopia

**Note:**

* Statins inhibit the other processes of this enzyme, such as CoQ10 production, and CoQ10 production is important for muscle cells and in blood sugar regulation.
* Cognitive decline and memory loss with statins
* hydrophilic statins, such as fluvastatin, rosuvastatin, and pravastatin, are less toxic for muscle than lipophilic statins, such as atorvastatin, lovastatin, and simvastatin, but other studies have not found a connection; the risk of myopathy was suggested to be lowest with pravastatin and fluvastatin, probably because they are more hydrophilic and as a result have less muscle penetration Lovastatin induces the expression of gene *atrogin-1*, which is believed to be responsible in promoting muscle fiber damage.
* Statins are associated with a slightly increased risk of diabetes
* Statins may reduce the risk of esophageal cancer, colorectal cancer, gastric cancer, hepatocellular carcinoma, and possibly prostate cancer.
* High doses of niacin may elevate blood sugar, thereby worsening diabetes mellitus
* Niacin produces marked anti-inflammatory effects in a variety of tissues – including the brain, gastrointestinal tract, skin, and vascular tissue. Niacin has been shown to attenuate neuroinflammation and may have efficacy in treating neuroimmune disorders such as multiple sclerosis and Parkinson's disease

**أَحْبِبْ حَبِيبَكَ هَوْناً مَا عَسَى أَنْ يَكُونَ بَغِيضَكَ يَوْماً مَا وَ أَبْغِضْ بَغِيضَكَ هَوْناً مَا عَسَى أَنْ يَكُونَ حَبِيبَكَ يَوْماً مَا**