1. INTRODUCTION
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1.1 Hyperlipidemia

Hyperlipidemia is one of the conditions in which excessive lipid contents in the blood plasma. Mixture of this lipid, calcium and other substances deposits plaque inside the artery and can significantly reduce the flow of blood over time (fig. 1.1). When plaques build up in coronary artery, patient would present clinically either angina or acute myocardial infarction (fig. 1.2), which is major coronary heart disease (CHD). More than 650,000 people die every year of coronary heart disease (CHD) in India alone.

![Plaque deposits in artery](image1)

**Figure 1.1: Plaque deposits in artery**

CHD patients have multiple risk factors (Non-Modifiable: age, sex, family and personal history of CHD; Modifiable: hyperlipidemia, hypertension, smoking, diabetes, obesity, lack of exercise). The third edition of the National Cholesterol Education Program (NCEP) Adult Treatment Panel guidelines (ATP III) recommends that lipid modification strategies should be matched to the patient’s risk for CHD.

![Progression of blood vessel blockage](image2)

**Figure 1.2: Progression of blood vessel blockage**
ATP recently updated LDL - C treatment target from less than 100 mg/dL to less than 70 mg/dL for patients at very high risk but it is a challenge to healthcare providers to keep levels as low as less than 70 mg/dL. A novel approach to achieving lipid goals statins are recommended as first-line therapy and other therapeutic modalities was classified as

**Classification of lipid lowering drugs (Anti-hyperlipidemic agents)**

The Anti-hyperlipidemic agents are broadly classified on the basis of their mechanism of action and the main groups are:

[I] Agents interfering with intestinal absorption of bile acids or cholesterol: Bile acid binding resins Cholestyramine, Colestipol, Divistramine

[II] Inhibiting synthesis or enhance degradation of LDL: Probucol

[III] Inhibiting production of VLDL and lipolysis in adipose tissue: Gemfibrozil, Nicotinic acid..

[IV] Enhancing lipoprotein lipase activity or promote degradation of lipoprotein: Clofibrate, Fenofibrate, Ciprofibrate, Bezafrate, Thyroid hormone analogues.

[V] Inhibitors of HMG-CoA reductase: Lovastatin, Simvastatin, Pravastatin, Atrovastatin, Fluvastatin, Cerivastatin, Rosuvastatin


Many patients at high risk for CHD fail to reach their ATP III target LDL – C levels with a single agent. To overcome these challenges, a statin is co-administered with a second agent with different mechanism of action that targets another aspect of lipid metabolism. Recent update of this approach is the co-administration of simvastatin with ezetimibe. In 1984 it was demonstrated for the first time that there exists a link between serum cholesterol levels and risk to CHD. A 1% drop in serum cholesterol reduces the risk for CHD by 2%. So the major cause of CHD is cholesterol.

![Cholesterol Structure](image_url)

**Figure 1.3: Structure of cholesterol.**
The structure in fig. 1.3 suggests cholesterol was a highly non-polar nature indicating that it should be reasonably insoluble in aqueous solution. Being non polar in nature, it should not soluble in plasma. Yet values are observed as high as 250 mg per deciliter which gives an amount of 2.5 g / L in plasma. This comes about because cholesterol does not occur alone in plasma. It is always associated with lipoproteins. Lipoproteins are proteins carrying lipids. Cholesterol is one of the lipids. Long chain fatty acids are also carried by these lipoproteins in the form of triglycerides (TG). Lipoproteins are classified as, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL), and high density lipoproteins (HDL), depending on the density of their packing or alternatively their size\(^1\). When there is unbalance in physiology of lipoprotein in plasma, five types of hyperlipidemia may occur as shown in Table 1.1.

<table>
<thead>
<tr>
<th>Type</th>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>N, &gt;</td>
<td>&gt;</td>
<td>&gt;</td>
<td>N, &gt;&gt;</td>
<td>N, &gt;</td>
<td>N, &gt;&gt;</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&gt;&gt;</td>
<td>N</td>
<td>&gt;</td>
<td>N, &gt;&gt;</td>
<td>&gt;</td>
<td>&gt;</td>
</tr>
<tr>
<td>Chylomicrons</td>
<td>&gt;&gt;</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>&gt;&gt;</td>
</tr>
<tr>
<td>VLDL</td>
<td>N, &gt;</td>
<td>N, &lt;&lt;</td>
<td>&lt;&lt;</td>
<td>N, &gt;</td>
<td>&gt;</td>
<td>&gt;</td>
</tr>
<tr>
<td>IDLD</td>
<td>&gt;</td>
<td>&gt;&gt;</td>
<td>&gt;&gt;</td>
<td>&gt;&gt;</td>
<td>N, &lt;</td>
<td>&lt;&lt;</td>
</tr>
<tr>
<td>LDL</td>
<td>&lt;&lt;</td>
<td>&gt;&gt;</td>
<td>&gt;&gt;</td>
<td>&gt;&gt;</td>
<td>N, &lt;</td>
<td>&lt;&lt;</td>
</tr>
<tr>
<td>HDL</td>
<td>&lt;&lt;</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N, &lt;</td>
<td>&lt;&lt;</td>
</tr>
</tbody>
</table>

'N' = Normal, '＞' = slight increase, '＞＞' = significant increase, '＜' = slight decrease, '＜＜' = significant decrease

Pathophysiology of Lipid Transport

Dietary fat including cholesterol and triglycerides are absorbed in the intestine and released in the blood stream as chylomicrons. These are least dense particles having very high proportion of triacylglycerides. Lipoprotein lipase acts on these particles to release some free fatty acids that deposit in adipose tissues. The remnants of chylomicrons are picked up by the liver which has a receptor specific to chylomicron remnants. After further clean up liver releases particles called the very low density lipoproteins in the blood. These have lower triacylglycerides than chylomicrons. Once again LDL works on these VLDL particles releasing more free fatty acids and changing the content of the particles to IDL and LDL. There are LDL receptors on the
cell membranes of the extrahepatic cells which can pick up the LDL particles. This is how cholesterol reaches the interior of normal cells. Within cells, LDL particles are repackaged. Excess cholesterol is esterified and stored. Excess cholesterol suppresses the biosynthesis of LDL-receptors so that intake of cholesterol decreases. It also suppresses cholesterol biosynthesis. Repackaged LDL particles called HDL particles are then released into the blood stream. These particles are sensed by the liver through the HDL-receptors. Thus the liver gets constant information as to how much LDL and HDL are present in the blood. Schematic diagram of pathophysiology of lipid transport given in fig. 1.4.

![Figure 1.4: Pathophysiology of lipid transport.](image)

1.2 Treatment of hypercholesterolemia.

Once hypercholesterolemia is established, dietary therapy is started to reduce consumption of cholesterol and fat containing foods.

**Dietary therapy:**

The obese patient generally has elevated levels of serum triglycerides, possibly a raised serum LDL level and a tendency to have a low HDL level. Weight reduction in such an individual will improve his or her hyperlipidemic profile.\(^\text{17}\) The body mass
index (BMI) in all but the most muscular individual gives a clinical measure of adiposity:

\[
\text{BMI} \ (Kg/m^2) = \frac{\text{weight (Kg)}}{\text{Height}^2 \ (m)}
\]

Where, \( \text{BMI} < 19.1 = \text{under weight} \), \( \text{BMI} = 20 \text{ to } 24.9 = \text{acceptable} \), \( \text{BMI} = 25 \text{ to } 29.9 = \text{low health risk} \), \( \text{BMI} = 30 \text{ to } 40 = \text{moderate health risk} \), \( \text{BMI} > 40 = \text{high health risk} \).

Diet modification alone may be successful in controlling hyperlipidemia associated with an inappropriate diet or obesity. The recommended diet should contain less total fat, saturated fat and cholesterol and more polyunsaturated and mono saturated fat. Protein intake should be kept constant and more of the total energy should be administered in the form of carbohydrates, particularly complex carbohydrates. The energy provided should be sufficient to achieve and maintain the desirable body weight. Drug therapy may be considered after a 3 month diet trial or even after 6 months after evaluating reduction in LDL cholesterol, when other risk factors are not present. If in a middle aged individual, after 3 months of low fat and cholesterol diet, the LDL cholesterol level are still greater than 190mg/dl and should be put on drug therapy, even if no risk factor is present.

**Drug therapy:** While a large number of drugs are available, HMG-CoA reductase inhibitors are being used as primary drug for adults of all ages. They are highly efficacious and may lower LDL levels by 25% - 45% with minimal side effects. For older patients with mild cholesterolemia, bile acid sequestrants are quite effective and can lower LDL levels by 15% - 30%. Similarly nicotinic acid is also beneficial and will reduce LDL by 10% - 20%. But both bile acid sequestrant and nicotinic acid cause side effects, limiting their use. For individuals with LDL cholesterol < 200mg there is a need to lower LDL levels by 50% or more. Single agent usually cause a lowering of about 20-30%. The patients with LDL cholesterol of 200 - 400 mg/dl, two or three hyperlipidemic drugs are usually given to lower the LDL cholesterol level to 400 mg/dl.\(^{15}\) Nicotinic acid plus a statin, by about 50% - 60% and triple drug therapy e.g. combination of bile acid resin, nicotinic acid and statin by about 70% or more.\(^{16}\) Hypercholesterolemic drug selection of single or combination drug as recommended by national cholesterol education program (NCEP) is given in Table 1.2.
Table 1.2. Single and combination drugs for hyperlipidemia

<table>
<thead>
<tr>
<th>HYPERLIPIDEMIA</th>
<th>SINGLE DRUGS</th>
<th>COMBINATION DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated LDL</td>
<td>Bile-acid Sequestrant</td>
<td>Bile acid seq.+ HMG CoA Reductase inhibitor.</td>
</tr>
<tr>
<td>Cholesterol and triglyceride</td>
<td>HMG CoA Red. Inhibitor</td>
<td>Bile acid seq. + nicotinic acid</td>
</tr>
<tr>
<td>&lt;200mg/dl</td>
<td>Nicotinic acid</td>
<td>HMG CoA red. inhibitor + nicotinic acid.</td>
</tr>
<tr>
<td>Elevated LDL</td>
<td>Nicotinic acid</td>
<td>Nicotinic acid + HMG CoA reductase</td>
</tr>
<tr>
<td>Cholesterol and triglyceride</td>
<td>HMG CoA Red. Inhibitor</td>
<td>HMG CoA red. + gemfibrozil</td>
</tr>
<tr>
<td>200-400mg/dl</td>
<td>Gemfibrozil</td>
<td>Nicotinic acid + bile acid seq.</td>
</tr>
</tbody>
</table>

The effects of AHA on controlling the hyperlipidemia is shown in scheme fig. 1.5.

Statins

Statins are most effective cholesterol lowering drugs. Statins lower total cholesterol and LDL particles. These are competitive inhibitors. The HMG-CoA has a conformation similar to the lactone moiety of statins resulting in binding at the same site without any productive effect. Similarity in conformation of the active moiety Orally administered drugs, once absorbed, are filtered through the liver through the portal vein. The drugs are extracted from the portal venous blood and concentrated in the hepatocyte to an extent that is related to their lipophilicity.

The more lipophilic statins[lovastatin > cerivastatin = simvastatin > fluvastatin > atorvastatin] exhibit facilitated passive diffusion through hepatocyte cell membranes, leading to selective accumulation in the liver. All statins are highly protein bound (95-98%) except for pravastatin (50%, due to carboxylate moiety). Most statins have a short half-life of about 1-3 hr except for atorvastatin which has an $t_{1/2}$ of about 14 h. A 15-30 point drop in LDL could be reasonably expected with most statins after a therapy of about 1 month. A combination therapy (with bile acid sequestering agents) is helpful for particularly difficult cases. The statins are divided into two groups: fermentation-derived (Lovastatin, Simvastatin, pravastatin and mevastatin(naturally occurring)) and synthetic (atorvastatin, cerivastatin, fluvastatin, pitavastatin). LDL-lowering potency varies between agents. Cerivastatin was the most potent, followed by (in order of decreasing potency) rosuvastatin, atorvastatin, simvastatin,
lovasatin, pravastatin, and fluvastatin. The relative potency of pitavastatin has not yet been fully established.

**Control of Hyperlipidemia**

**Figure 1.5: Control of hyperlipidemia**

**Fibrates**

Gemfibrozil was introduced in 1981 and remains the second most useful antilipidemic agent. It primarily decreases serum triglycerides. Newer drugs including beclofibrates, ciprofibrates and fenofibrates are more effective in lowering serum LDL cholesterol. However, the fibrates are almost never used alone. They are mostly used in combination with bile acid sequestering agents.

**Bile Acid Sequestering (BAS) Agents**

Colestipol and cholestyramine are anion exchange resins that are approved in 1970s for the reduction of elevated serum cholesterol in patients with hypercholesterolemia. These resins are water insoluble, inert to digestive enzymes in the intestinal tract and are not absorbed. Both resins are quaternized at stomach pH and exchange anions for bile acids dramatically reducing the reabsorption of bile acids. The liver senses that bile acid concentrations have gone down and hence turns on cholesterol metabolism. Serum HDL and TG levels remain unchanged but LDL levels are found to decrease. The fall in LDL concentration is apparent in 4 to 7 days. The decline in serum
cholesterol is usually evident by 1 month. When the resins are discontinued, the serum cholesterol usually returns to baseline within a month. When bile acid secretion is partially blocked, serum bile acid concentration rises.

**Nicotinic Acid**
Pharmacologic doses of nicotinic acid reduce serum cholesterol and TG levels in types II, III, IV, and V hyperlipoproteinemias. TG and VLDL are reduced by 20-40% in 1 to 4 days, LDL reduction may be seen in 5-7 days. The decrease in LDL is usually greater if niacin is used with a BAS resin. HDL is increased by 20%. The exact mechanism is unknown. It is known that niacin decreases lipolysis in adipose tissue, decreases TG esterification in the liver and increase LPL activity. Niacin is rapidly absorbed.

1.3 REFERENCES