Review Article

A Review: Atherosclerosis & its treatment

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ABSTRACT
Atherosclerosis is deposition of fatty substances into the inner wall of blood vessels. Due to deposition of lipid material into blood vessels there is restricted flow to blood to various organs like kidney, heart, lungs etc. To overcome this effect various drugs available in market like statins, fibrates etc. There is also way to clean lipid from inner lining of blood vessels through surgery which is last step of treatment. There are mainly two surgeries available that is bypass surgery of heart and angioplasty.

Keywords: Atherosclerosis, blood vessel, heart attack, lipoproteins

INTRODUCTION
Atherosclerosis: Atherosclerosis comes from the Greek words athero (meaning paste) and sclerosis (hardness). It is the process in which fatty substances, cholesterol, cellular waste products, calcium and other substances deposits in the inner lining of an artery. This buildup is called plaque. It usually affects large and medium-sized arteries. Hardening of arteries often occurs when people grow older. Plaques can grow large enough to significantly reduce the blood’s flow through an artery.

Plaques that rupture cause blood clots that can block blood flow or break off and travel to another part of the body. If either happens and blocks a blood vessel that feeds the heart, it causes a heart attack. If it blocks a blood vessel that feeds the brain, it causes a stroke. And if blood supply to the arms or legs is reduced, it can cause difficulty walking and eventually lead to gangrene.

Fig1: Atherosclerosis

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Aetiology: Atherosclerosis is a slow, complex disease that typically starts in childhood and often progresses when people grow older. In some people it progresses rapidly. Many scientists think it begins with damage to the innermost layer of the artery. This layer is called the endothelium.\(^1\)

Causes of damage to the arterial wall include:

1) **Elevated levels of cholesterol and triglyceride in the blood:** Due to elevated levels of cholesterol and triglyceride accumulation occurs into inner side of arteries.

2) **High blood pressure:** High pressure can damage the arteries making them more vulnerable to the narrowing and plaque build up associated with atherosclerosis.\(^7\)

3) **Tobacco smoke:** The nicotine and carbon monoxide in cigarette smoke damages the endothelium, which starts build-up of plaque.\(^6\)

4) **Diabetes:** High concentrations of glucose in the blood irritate the lining of the arteries that promotes the accumulation of "plaque." When the inside of an artery is blocked by plaque, the blood supply to that area of the body is reduced or completely blocked.\(^5\)

5) **Obesity:** It means accumulation of excess of lipids into abdomen area which is also responsible for atherosclerosis. Because of the damage to the endothelium fats, cholesterol, platelets, cellular waste products, calcium and other substances are deposited in the artery wall. These cells and surrounding material thicken the endothelium significantly. The artery's diameter shrinks and blood flow decreases, reducing the oxygen supply. Often a blood clot forms near this plaque and blocks the artery, stopping the blood flow.\(^4\)

Signs and Symptoms:
Complications It can cause serious health problems such as blood clots, heart attack, angina, and sudden death. A person's particular symptoms will depend on which part of the body is not receiving enough blood and oxygen due to the narrowing of arteries. These symptoms take some time to develop, as the disease must progress to the point where an artery is severely narrowed or completely locked. Common locations for narrowing and hardening of the arteries to occur include the:

- Heart
- Brain
- Legs, pelvis, or arms
- Kidneys.

Types of lipoproteins and atherosclerotic risk:
Atherosclerosis starts as a result of increasing levels of cholesterol and triglycerides. Lipids exist in blood as cholesterol and triglycerides. In addition there are smaller amount of phospholipids, fatty acids and fatty acid esters. Lipids are binding to proteins (albumin, globulin) General way of cholesterol synthesis is

\[
\text{Acetate} \rightarrow \text{Mevalonate} \rightarrow \text{Squalene} \rightarrow \text{Lanosterol} \rightarrow \text{Cholesterol}
\]

These lipoproteins differ in density and they are classified as

1) Chylomicrons
2) Very low density lipoprotein (VLDL)
3) Intermediate density lipoprotein (IDL)
4) Low density lipoprotein (LDL)
5) High density lipoprotein (HDL)
Table 1: Classification of hyperlipoproteinaemia with atherosclerosis risk +, increased concentration; βVLDL, a qualitatively abnormal form of VLDL identified by its pattern on electrophoresis.²

<table>
<thead>
<tr>
<th>Type</th>
<th>Lipoprotein elevated</th>
<th>Cholesterol</th>
<th>Triglycerides</th>
<th>Atherosclerosis risk</th>
<th>Drug treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>+</td>
<td>+++</td>
<td>NE</td>
<td>None</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>++</td>
<td>NE</td>
<td>High</td>
<td>Statin ± ezetimibe</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL + VLDL</td>
<td>++</td>
<td>++</td>
<td>High</td>
<td>Fibrates, statin, nicotinic acid</td>
</tr>
<tr>
<td>III</td>
<td>βVLDL</td>
<td>++</td>
<td>++</td>
<td>Moderate</td>
<td>Fibrates</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>+</td>
<td>++</td>
<td>Moderate</td>
<td>Fibrates</td>
</tr>
<tr>
<td>V</td>
<td>Chylomicrons + VLDL</td>
<td>+</td>
<td>++</td>
<td>NE</td>
<td>Fibrate, niacin, fish oil and statin combinations</td>
</tr>
</tbody>
</table>

Anti-atherosclerotic drugs and its classification:
These are the drugs essential for reduction of cholesterol and triglycerides. The main aim is to reduce LDL and increase HDL levels of serum.

**CLASSIFICATION**

1) **HMG-CoA Reductase Inhibitors (Statins)** e.g. Lovastatin, Atorvastatin, Fluvastatin, Pravastatin, Simvastatin etc
2) Bile acid binding resin e.g. Cholestyramine, Colestipol
3) Fibrates e.g. Clofibrate, Gemfibrozil, Fenofibrate, Bezafibrate etc
4) Other drugs e.g. Nicotinic acid, probucol, gugulipid etc

**1) HMG-CoA Reductase Inhibitors:**
HMG(3-hydroxy-3-methyl-glutaryl)CoA reductase is an enzyme required for the metabolic pathway that produces cholesterol. This enzyme is the target of the widely available cholesterol-lowering drugs known collectively as the statins.

**Mechanism of Action**
Drugs that inhibit **HMG-CoA reductase enzyme** which converts **HMG-CoA** to **mevalonic acid**. HMG-CoA reductase inhibitors (statins), are used to lower serum cholesterol as a means of reducing the risk for cardiovascular disease.

![Mevalonate pathway](Fig2)

These drugs include lovastatin (Mevacor), atorvastatin (Lipitor), pravastatin (Pravachol), fluvastatin (Lescol), and simvastatin (Zocor). Red yeast rice extract contains several naturally occurring cholesterol-lowering statins known as monacolins. The most active of these is monacolin K, or lovastatin (previously sold under the trade name Mevacor, and now available as generic lovastatin).

Vytorin is combination of simvastatin and ezetimibe, which blocks the formation and absorption of cholesterol. Simvastatin and pravastatin are specific, reversible, competitive inhibitor. Resulting decrease in hepatic
cholesterol synthesis leads to increased synthesis of LDL receptors and thus increased clearance of LDL and reducing its plasma concentration. Also causes reduction in small amount of triglyceride and increasing HDL cholesterol. All HMG-CoA reductase showing maximum activity at midnight all statins are administered at bed time as obtain maximum effectiveness. [4]

Pharmacokinetic: Absorbed orally. Metabolised in the liver.

Adverse Effects: Headache, GI disturbances, Insomnia, rash and blurred vision.

2) Bile acid binding resin Binding: 

Mechanism of Action 
Cholestyramine and Colestipol are anion exchange resins. These drugs bind to bile acid in intestine. Drug bile acid complex does not get absorbed and excreted as intact. This mechanism lowers serum cholesterol. This lowers the concentration of bile acids; the liver increases the conversion of cholesterol to bile acids with a resulting decrease in hepatocyte cholesterol levels. Decreased cholesterol levels in hepatocytes cause an increase in the uptake of LDL particles (and their cholesterol) through an increase in LDL receptors, so plasma LDL levels decrease. In some plasma HDL levels also increase.

Pharmacokinetics: Taken orally these agents are insoluble in water and are neither absorbed nor metabolically altered; they are totally excreted.

Adverse Effects: Since resins are not absorbed, systemic toxicity is low but Gastro Intestinal symptoms of nausea abdominal bloating, constipation or diarrhea are common. Impairs absorption of fat soluble vitamin. Colestipol is also an anion exchange resin has been introduced, which is similar in action to cholestyramine. It is given orally. [4]

3) Fibrates: Fenofibrate & gemfibrozil are derivatives of fibric acid that lower TGs and increase HDL levels. Fenofibrate is more effective at lowering LDL & TGs.

Mechanism of Action
• Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor super-gene family that regulates lipid metabolism. PPARs function as ligand-activated transcription factors.
• When activated they bind peroxisome proliferator response elements localized in numerous gene promoters for gene products involved in lipoprotein structure & function, including lipoprotein lipase. This increases catabolism of VLDLs & chylomicrons.
• It also reduces the hepatic metabolism of cholesterol.
• Fibrates increase the concentration of LPL.
• They increase HDL levels by increasing the production of Apo A I & II (components of HDL).

Pharmacokinetics Both are well absorbed orally and are widely distributed and bound to albumin.

Adverse Effects: GI effects: These are common & decrease with continued use. Lithiasis: Increased biliary cholesterol excretion increases the risk of gallstones.

4) Niacin (nicotinic acid) Niacin is able to reduce LDL levels while raising HDL levels. It can be used in combination with statins (see above).

Mechanism of Action
• Niacin strongly inhibits lipolysis in adipose tissue (the primary source of circulating fatty acids which are converted by the liver into TGs).
• Inhibits the synthesis & esterification of fatty acids in the liver.
• Decreased TG levels impair VLDL synthesis in the liver leading to a reduction in LDL. Niacin increases HDL levels.
• It also promotes the secretion of tissue-plasminogen activator (thrombolytic) and lowers fibrinogen levels (anti-thrombotic).
• Niacin is able to reduce LDL levels while raising HDL levels. It can be used in combination with statins.

Pharmacokinetics:
• Niacin is converted into the cofactor NAD, both niacin & NAD are excreted in the urine. NAD does not lower LDL.

Adverse Effects:
• The most common side effect is cutaneous flushing, feeling of warmth and pruritis following ingestion.

5) Ezetimibe selectively inhibits intestinal absorption of dietary & biliary cholesterol in the small intestine, leading to a decrease in the delivery of cholesterol to the liver. This lowers hepatic cholesterol stores resulting in extraction of cholesterol form the plasma. Ezetimibe lowers LDL cholesterol, TG and increases HDL cholesterol.

6) Gugulipid is a mixture of sterones obtained from gum guggul which has been used in ayurveda. Modest lowering of plasma CH and TGs occurs after continued use of gugulipid.

7) Probucol decreases elevated serum cholesterol level by reducing LDL concentration but does not reduce TGs. [3]

TREATMENT FOR ATHEROSCLEROSIS

1) Dietary intake: Dietary intake of cholesterol should be as low as possible.

2) Drug treatment: Following are the drugs used for atherosclerosis.

Cholesterol lowering drugs
- Angiotensin-converting enzyme inhibitors (ACE inhibitors)
- Anticoagulants
- Antiplatelets
- Beta blockers
- Calcium channel blockers
- Digitalis
- Diuretics
- Nitrates.

3) Surgical intervention

Angioplasty: Stents are inserted to physically expand narrowed arteries.

Bypass surgery: To create additional blood supply connections that go around the more severely narrowed areas.

CONCLUSION

Atherosclerosis is deposition of lipids into an artery's inner wall. Due to this blood supply to various organs decreases e.g. heart, brain, legs etc. There are various drugs available for atherosclerosis which reduces lipid level those are fibrates, statins, HMG CoA reductase inhibitors etc. There is need of new research because of several side effects of currently available drugs like headache, nausea, blurred vision etc. To overcome these difficulties there is need of new research.

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