CHAPTER - 1

Hyperlipidaemia

Introduction to Hyperlipidaemia

Hyperlipidaemia is abnormally elevated levels of any or all lipids or lipoproteins in the blood. It is the most common form of dyslipidaemia. Hyperlipidaemia are divided into primary and secondary subtypes. Primary hyperlipidaemia is usually due to genetic causes while secondary hyperlipidaemia arises due to other underlying causes such as diabetes.

Lipids are biological molecules which are not dissolved in water but can be dissolved in organic solvents. In the body, lipoproteins/lipids are present in the intestines, liver and/or intestines and liver.

Lipoproteins: These are large globular particles that contain an oily core of nonpolar lipid (cholesteryl esters of triglycerides) surrounded by a polar coat of phospholipids free (i.e. unesterified) cholesterol and apoproteins. There are five classes of lipoproteins that differ from one another in size, density and properties of triglycerides and cholesterol.

Lipoproteins are of five types:

- Chylomicrons
- Very lowdensity lipoprotein (VLDL)
- Intermediate density lipoprotein (IDL)
- Low density lipoprotein (LDL)
- High density lipoprotein (HDL)

Chylomicrons

These are the largest particles both in size as well as in density, and its concentration is directly correlated with dietary triglyceride contents.

VLDL: Very low-density lipoproteins are smaller particles carrying lesser triglyceride contents than chylomicrons, and are secreted from the liver. VLDL carries cholesterol from the liver to organ and tissues in the body. They are formed from the combination of cholesterol and triglycerides.

IDL: VLDL particles after degradation by lipase enzyme in the capillaries of adipose tissue and muscle give rise to intermediate density lipoprotein.

LDL: Low-density lipoproteins are synthesised partly in intestinal cycle and partly after lipolysis of VLDL. It is directly correlated to Congestive Heart Disease (CHD).

HDL: HDL is commonly referred as good cholesterol. High-density lipoproteins are synthesised in the liver. It carries cholesterol and other lipids from tissues back to the liver for degradation. HDL plays an antiatherogenic role.

Lipoprotein Metabolism and Transport [1]

Dietary lipids are absorbed in the intestine with the help of bile acids. Chylomicrons (Chy) are formed and passed into lacteals—reach blood stream via thoracic duct. During their passage through capillaries, the endothelium bound lipoprotein lipase hydrolyses the TGs into fatty acids which pass into muscle cells to be utilized as energy source and in fat cells to be reconverted into TGs and stored. The remaining part—chylomicron remnant (Chy. rem.) containing mainly Cholesterol Esters (CHE) and little TG is engulfed by liver cells, which have receptors for the surface apoproteins of Chy. rem., and digested. Free Cholesterol (CH) that is liberated is either stored in liver cells after reesterification or incorporated into a different lipoprotein and released in blood or excreted in bile as CH/bile acids. Liver secretes very low density lipoproteins (VLDL) containing mainly TG and some CHE into blood. VLDL is acted upon by endothelial lipoprotein lipase in the same way as on Chy and the fatty acids pass into adipose tissue and muscle; the remnant called intermediate density lipoprotein (IDL) now contains more CHE than TG. About half of the IDL is taken back by the liver cells by attachment to another receptor (LDL receptor), while the rest loses the remaining TGs gradually and becomes low density lipoprotein (LDL) containing only CHE. The LDL circulates in plasma for a long time; its uptake into liver and other tissues is dependent on the need for CH. The rate of LDL uptake is regulated by the rate of LDL receptor synthesis in a particular tissue.

The CHE of LDL is deesterified and used mainly for cell membrane formation. The CH released into blood from degradation of membranes is rapidLy incorporated in high density lipoproteins (HDL), esterified with the help of an enzyme lecithin: cholesterol acyltransferase (LCAT) and transferred back to VLDL or IDL, completing the cycle. The excess lipoproteins in plasma are phagocytosed by macrophages for disposal. When too much of lipoproteins have to be degraded in this manner, CH is deposited in atheromas (in arterial walls) and xanthomas (in skin and tendons). Raised levels of VLDL, IDL and LDL (rarely Chy and Chy. rem. also) are atherogenic, while HDL may be protective, because HDL facilitates removal of CH from tissues

Epidemiology

In India, more than 10 Million people per year are suffering with hyperlipidaemia. The most prone people are diabetic and Coronary Artery Disease (CAD) patients. Hyperlipidemia disease has afflicted humankind since antiquity. In 2002, coronay heart Epidemiological evidence strongly supported the positive correlation between blood lipids, hyperlipidemia and its complications, mainly CHD. This relationship has been shown between and within cultures. While fats play a vital role in the body's metabolic processes, high blood levels of fats increase the risk of coronary heart disease (CHD). Cardiovascular diseases, especially coronary heart

disease (CHD), are epidemic in India. According to American Heart Association, the Centres for Disease Control and Prevention, the National Institutes of Health and other government sources, cardiovascular disease is the leading global cause of death, accounting for more than 17.3 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030.

Etiology

- Genetics
- **Diet and Obesity:** Food choices paly a role in high cholesterol. Obesity increases the amount of LDL cholestrol the liver makes. It also decreases clearance of LDL cholesterol form the blood. Inflammation throughout the body is a common complication of obesity. This constant inflammation decreases the body's response to changes in dietary fat intake. Insulin resistance is also common in obesity. It causes changes in the enzymes the body needs to hnadLe cholesterol normally.
- **Diabetes Mellitus:** The predominant abnormality of fat metabolism in diabetes is hypertriglyceridemia due to an increase of triglyceride-carrying lipoproteins, the chylomicrons and the very-low-density lipoproteins. VLDL and chylomicrons, which transport endogenous and exogenous triglycerides, are broken down by lipoprotein lipases. In insulin deficiency, the activity of the lipoprotein lipases is decreased, and this is one of the most common **causes of** hyperlipidemia in poorly controlled diabetes in type 1 and type 2. These patients also have decreased HDL cholesterol levels.
- **Smoking:** Hyperlipidemia and smoking are linked by an intricate network of multiple relations. The concentration of high-density lipoprotein (HDL) cholesterol is lower in heavy smokers, and the concentrations of triglycerides and cholesterol are higher. Due to this waxy plaques build up in the arteries.
- **Alcoholism:** Drinking alcohol raises the triglycerides and cholesterol in the blood. If triglyceride levels become too high, they can build up in the liver, causing fatty liver disease. The liver can't work as well as it should and can't remove cholesterol from blood, so cholesterol levels begin to rise.
- **Glucocorticoids:** Triglycerides are significantly increased in patient who took different time of glucocorticoids. Short term use is having less effect when compared to long term use.
- **Drugs like β-blockers:** Suppression of beta-adrenergic activity leads to unopposed alpha-adrenergic stimulation. In turn, alpha-adrenergic stimulation leads to a decrease in peripheral lipoprotein lipase activity and a subsequent reduction in catabolism of very low-density lipoprotein and triglycerides
- **Hypothyroid:** Body needs thyroid hormones to make cholesterol and to get rid of the cholesterol it does not need. When thyroid hormone levels are low, the body does not break down and remove LDL cholesterol as effficiently as usual. LDL cholesterol can then build up in the blood.
- **Lack of physical activity:** Lipoprotein metabolism is altered, so increased levels of LDL and decresased HDL cholesterol levels.

Types of Hyperlipidaemias based on causing factor:

1. **Primary Hyperlipidaemia** - Primary hyperlipidaemia is often genetic. It is a result of a defect or mutation in lipoproteins. These changes result in problems with accumulation of lipids in the body. It includes –
   (a) Familial combined hyperlipidaemia: It occurs as a history of familial hyperlipidaemia. It is mainly caused due to high levels of VLDL. When there is an increase in the synthesis of VLDL and LDL results in increase in triglycerides. This type is mainly seen in teenagers.
   People suffering with this type are more prone to get CAD which can lead to sudden heart attacks.
   (b) Familial hypercholesterolaemia: It occurs due to increase in the total cholesterol. The LDL is increased 2-3 times than the normal level. Signs of cholesterol deposition are seen in the form of
   - ✓ Corneal arcus: Deposition of lipids in cornea
   - ✓ Tendon xanthomas: yellowish papules in tendons

   (c) Familial hyperlipoproteinaemia: This type is mainly seen due to the accumulation of chylomicrons and VLDL. Due to the failure of clearance of Apo E in hepatic system, there is an increase in triglycerides and cholesterol.
   Signs and Symptoms:
   - ✓ Tubo eruptive xantomas: yellowish raised nodules on skin; mainly elbows and knees.
   - ✓ Palmar striae: yellowish raised streaks on palms

   (d) Familial lipoprotein lipase deficiency: Failure of lipolysis leads to accumulation of chylomicrons in plasma. Lipoprotein lipase deficiency will lead to hypertriglyceridaemia and chylomicronaemia. This type is mainly seen in children.
   Signs and Symptoms:
   - ✓ Abdominal pain
   - ✓ Spleenomegaly
   - ✓ Acute pancreatitis
   - ✓ Deposition of lipids in the eye

Table 1.1 Common forms of primary hyperlipidemia.

	Lipoprotein abnormality	Drug therapy
Familial hypercholesterolemia	↑↑LDL	Lovastatin
Familial defective apolipoprotein B	↑↑LDL	None
Polygenic hypercholesterolemia	↑LDL	Lovastatin
Familial lipoprotein lipase deficiency	↑Chylomicrons	Nicotinic acid
Familial hypertriglyceridemia	↑VLDL	Gemfibrozil
Familial combined hyperlipidemia	↑VLDL, ↑LDL, ↓HDL	Nicotinic acid, clofibrate
Familial dysbetalipoproteinemia	↑Chylomicrons, ↑LDL, ↓IDL, ↓HDL	Gemfibrozil

2. **Secondary hyperlipoproteinaemia:**

Acquired (Secondary) hyperlipidemia – Acquired hyperlipidemia (secondary dyslipoproteinemias) results from underlying disorders and lead to alterations in plasma lipid and lipoprotein metabolism. This type of hyperlipidemia may mimic primary forms of hyperlipidemia and can have similar consequences. They may result in increased risk of premature atherosclerosis, pancreatitis and other complications of the chylomicronemia syndrome. The most common causes of acquired hyperlipidemia are given below.

- Diabetes Mellitus
- Use of drugs such as diuretics, β-blockers and estrogens.
- Alcohol consumption.
- Some rare endocrine disorders and metabolic disorders.
- Hypothyroidism
- Renal failure
- Nephrotic syndrome

Table 1.2 Common forms of secondary hyperlipidemia.

	Lipid abnormalities	Lipoprotein abnormalities
Diabetes mellitus	↑TG	↑VLDL, ↓HDL
Nephrotic syndrome	↑Chol	↑LDL
Uremia	↑TG	↑VLDL, ↓HDL
Hypothyroidism	↑Chol	↑LDL
Obstructive liver disease	↑Chol	↑Lp(a)
Alcoholism	↑TG	↑VLDL
Oral contraceptive	↑TG	↑VLDL, ↓HDL
β-Adrenergic blocking agents	↑TG	↑VLDL, ↓HDL
Isotretinoin	↑TG	↑VLDL

Complications of Hyperlipidaemia

I. **Atherosclerosis:** It is a common disorder and occurs when fat, cholesterol and calcium deposits in the arterial linings. This deposition results in the formation of fibrous plaques. A plaque normally consists of three components: 1) atheroma which is a fatty, soft, yellowish nodular mass located in the centre of a larger plaque that consists of macrophages, which are cells that play a role in immunity; 2) a layer of cholesterol crystals; and, 3) calcified outer layer. Atherosclerosis is the leading cause of cardiovascular disease.

II. **Coronary Artery Disease (CAD):** Atherosclerosis is the major cause of CAD. It is characterised by the narrowing of the arteries that supply blood to the myocardium and

results in limiting blood flow and insufficient amounts of oxygen to meet the needs of the heart. The narrowing may progress to the extent that the heart muscle would sustain damage due to lack of blood supply. Elevated lipid profile is correlated to the development of coronary atherosclerosis.

III. **Myocardial Infarction (MI):** MI is a condition which occurs when blood and oxygen supplies to the cardiac arteries are partially or completely blocked, resulting in damage or death of heart cells. The blockage is usually due to the formation of a clot in an artery. This condition is commonly known as heart attack. The studies show that one-fourth of survivors of myocardial infarction were hyperlipidemic.

IV. **Angina Pectoris:** Angina is not a disease but a symptom of an underlying heart condition. It is characterised by chest pain, discomfort or a squeezing pressure. Angina occurs as a result of a reduction or a lack of blood supply to a part or the entire heart muscle. Poor blood circulation is usually due to CHD when partial or complete obstruction of the coronary arteries is present.

V. **Ischemic stroke or Cerebrovascular Accident (CVA):** It occurs when blood circulation in part of the brain is blocked or diminished. When blood supply, which carries oxygen, glucose, and other nutrients, is disrupted, brain cells die and become dysfunctional. Usually, strokes occur due to blockage of an artery by a blood clot or a piece of atherosclerotic plaque that breaks loose in a small vessel within the brain. Clinical trials revealed that lowering of LDL and total cholesterol by 15% significantly reduced the risk of first stroke.

Formation of Cholesterol

Fats and carbohydrates are digested and absorbed in the deodenum and opens in the small intestine. Small intestine has Na^+ and glucose transporters and glucose will be reabsorbed in the blood. Liver also receives glucose. With the help of glycolysis process, glucose in converted into pyruvate and enters into acetyl CoA. This acetyl CoA is converted into cholesterol.

Table 1.3 Normal levels for a lipid profile.

Lipids	Desirable value	Borderline	High risk
Cholesterol	Less than 200 mg/dL	200-239 mg/dL	240 mg/dL
Triglycerides	Less than 140 mg/dL	150-199 mg/dL	200-499 mg/dL
HDL cholesterol	60 mg/dL	40-50 mg/dL	Less than 40 mg/dL
LDL cholesterol	60-130 mg/dL	130-159 mg/dL	160-189 mg/dL
Cholesterol/HDL ratio	4.0	5.0	6.0

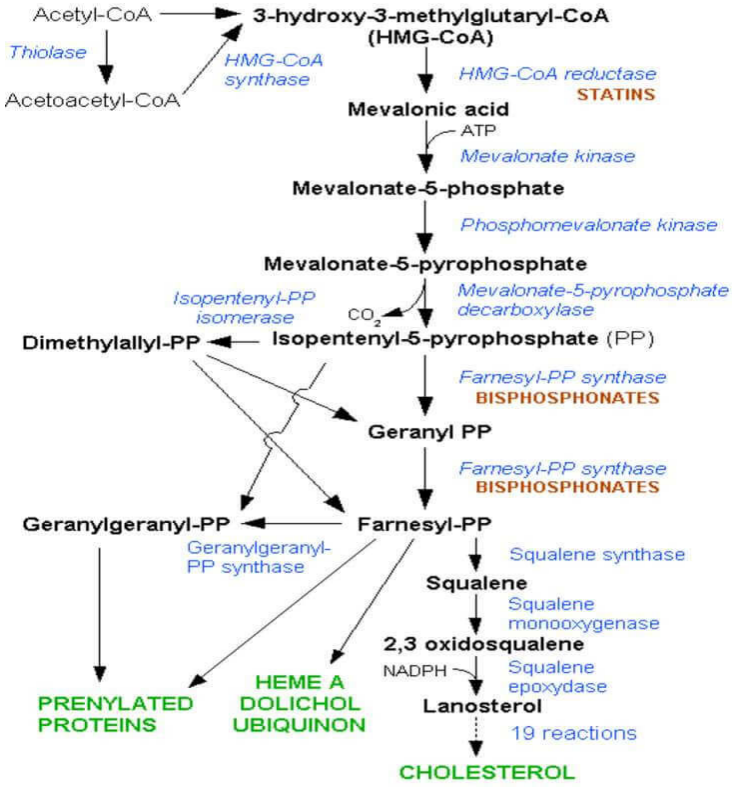

Fig. 1.1 Synthesis of Cholesterol.

Pathophysiology

Risk factors for hyperlipidaemia are HTN, DM, obesity, smoking, stress and genetic factors. Due to increase in cholesterol, accumulation of cholesterol from VLDL and LDL takes place. Free radicals oxidize the LDL. LDL is oxidized in the endothelial cells and released. Monocyte adhesion molecule (initial step for development of atherosclerotic plaque) attaches to oxidized LDL. Circulating monocytes attaches to endothelial surface. These trap the monocytes in endothelium and release chemoattractants (a substance which attracts motile cells). Monocytes are squeezed into the endothelium and converted to macrophages which contain LDL receptors. Ingestion of the excess VLDL and LDL particles, accumulatation in blood vessels by VLDL receptors. This process continues and forms foam cells. This leads to formation of raised lesions on blood vessels and forms fatty streaks. It further leads to atherosclerotic plaque, endothelium damage, vasoconstriction and initial Ischemic symptoms. Initially the plaque contains large lipids which were made from foam cells. During the plaque growth, macrophages, endothelial cells and smooth muscles get activated releases growth factor which leads to smooth muscle cell proliferation (plaque) and gets hardened by collagen coronary artery remodeling resulting in sudden MI and death.

Clinical Manifestation and Features

Signs and Symptoms

- ✓ Most patients are asymptomatic for many years.
- ✓ Symptomatic patients may complain of chest pain, pain, palpitations, sweating, anxiety, shortness of breath, abdominal pain, loss of consiousness or difficulty with speech or movement.
- ✓ Depending on the lipoprotein abnormality, signs on physical examination may include cutaneous xantomas, peripheral polyneuropathy, high blood pressure and increased body mass index or waist size.

Diagnosis Algorithm [2]

Check the fasting lipid profile (FLP) (atleast 2 times)

1. If LDL-C ≥ 250mg/dL: Request a specialist.
2. If 130 ≤ LDL ≤ 250 mg/dL: Secondary cause exclusion; risk evaluation and CHILD (Cardiovascular Health Integrated Lifestyle Diet) for 6 months + Lifestyle modification should be followed. After the followup of 6 months if LDL-C is less than 130 mg/dL-continue CHILD and FLP should be done every 1 year.
3. If LDL-C 130-189 mg/dL; the patient has no family history and no risk factors-follow CHILD and FLP testing should be repeated every 6 months.
4. (i) If LDL-C ≥ 190 mg/dLl
   (ii) If LDL-C 160-189 mg/dL; the patient has family history, > 1 high risk factor or ≥ moderate risk factors
   (iii) If the patient has a) LDL-C 130-159 mg/dL b) ≥ 2 high risk factors c) 1 high risk factor or ≥ 2 moderate risk factors or clinical cardiovascular disease
      - ➢ Statin treatment should be initiated.
5. If TG ≥ 500mg/dL: Request a specialist.
6. If 130 ≤ TG < 500 mg/dL: CHILD for 6 months + lifestyle modification with weight loss.
7. (i) If TG < 130 mg/dL: Continue CHILD –TG. Check FLP every 1 Year.
   (ii) If TG 130-199 mg/dL: Follow CHILD-TG and reinforce weight loss. Increase fish intake. FLP after 6 months
   (iii) If TG ≥ 200-499 mg/dL: If non-HDL-C ≥ 145mg/dL –consider omega-3 fatty acids.

1. Know the complete history of the patient.
2. Check if there are any cardiovascular risks.
3. Serum lipid tests to check - total cholesterol, VLDL, LDL, HDL
4. According to NCEP ATP –III guidelines
   - ✓ Total cholesterol < 200mg/dL → desirable
     200-239mg/dL → boderline high
     ≥240mg/dL → high risk

- ✓ LDL cholesterol
  - < 100mg/dL → optimal
  - 100-129mg/dL → normal or above optimal
  - 130-159mg/dL → boderline high
  - 160-189mg/dL → high
  - ≥190mg/dL → very high
- ✓ HDL cholesterol
  - <40mg/dL → low
  - ≥60mg/dL → high
- ✓ Triglycerides
  - <150mg/dL → normal
  - 150-199mg/dL → borderline high
  - 200-499mg/dL → high
  - ≥ 500mg/dL → very high

REVISED NCEP ATP III VS ACC/AHA ATP IV GUIDELINES

National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) Guidelines

NCEP ATP III

1. Risk categories: 3 main risk catgories- CHD/CHD risk equivalent (DM, clinical CHD, symptomatic CAD, PAD)
2. + risk factors & 10-yr risk ≤ 20%
   0-1risk factors & 10-yr risk < 10%
3. Treatment targets: LDL-C primary target <100mg/dL
   < 130mg/dL (< 100 if risk 10-20%)
   <160mg/dL
4. Treatment recommendations: statin (or bile acid sequesterants or nicotinic acid) to achieve LDL-C goal
5. Risk factor counting
6. Treat to LDL goal
7. Address NON-HDL target

NCEP ATP IV

1. **Risk categories:** 4 statin benefit groups: clinical ASCVD; primary LDL-C elevations ≥190mg/dL; DM without clinical ASCVD; No DM/CVD with 10-yr ASCVD risk ≥7.5%
2. **Treatment targets:** Intensity of statin therapy; High intensity statin therapy (LDL-C reduction ≥ 50%) is recommended for most patients in 4 statin benefit groups
3. **Treatment recommendations:** Maximally tolerated statin first-line to reduce risk of ASCVD events
4. There is no target
5. The intensity of statin therapy is the focus of treatment

Summary

Although there are similarities between ATP III and American College of Cardiology (ACC/AHA) guidelines, the two are fundamentally different. In contrast, the ATP III panel made use of all types of relevant science. It emphasized Randomised Control Trials (RCTs), but where appropriate, used epidemiological data, genetic and metabolic studies, and various in vivo and in vitro investigations to flesh out the guidelines. Evidence statements based on various types of scientific data were developed to stand behind recommendations. ATP III is the summation of several decades of research on the relation of atherogenic lipoproteins to ASCVD. It is based on the concept that lowering atherogenic lipoproteins will prevent ASCVD. ACC/AHA guidelines under the influence of an Institute of Medicine (IOM) paradigm are transformed into statin treatment instructions. They give lip service to lifestyle intervention but are embarrassed by a lack of RCTs to underpin lifestyle recommendations. They further can be questioned because they make risk assessment based on older data that may not be suitable for the current US population. Since the ACC/AHA guidelines depend entirely on RCTs, they should not be considered to be comprehensive cholesterol guidelines. Therefore, if using these guidelines, the physician must rely on a heavy dose of clinical judgment. ATP III is still useful for guiding the physician's clinical judgment.

Pharmacological Therapy

Classification of Drugs

1. **HMG Co-A reduactase inhibitors:** Lovastatin 20-8-mg/Provastatin 20-40mg/ Simvastatin 20-80mg
   Fluvastatin 20-80 mg/Atorvastatin 10-80 mg
2. Bile acid sequestrants: Cholestyramine 4-16g/colestipol 5-20g/Colesevelam 2.6-3.8g
3. Nicotinic acid: Immediate release (Crystalline) nicotinic acid 1-5-3g
4. **Fibric acids:** Gemfibrozil 600mg bid/Fenofibrate 200 mg
   Clofibrate 1000mg bid

Management

Non-Pharmacological Treatment

- ✓ Change lifestyle modification and sedentary lifestyle.
- ✓ Dietary modifications like reduce salt intake and salt rich food.
- ✓ Weight reduction by physical activities, yoga etc.,
- ✓ Alcohol and smoking cessation.

Pharmacological Treatment

HMG CoA Reductase Inhibitors

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, inturrupting conversion of HMG-CoA to mevalonate, the rate limiting step in cholesterol biosynthesis. When used as monotherapy, statins are the most potent cholesterol and LDL lowering agents. Constipation occurs in fewer than 10% of patients taking statins. Other adverse effects include elevated serum aminotransferase levels (primarily alanine aminotransferase), elevated creatine kinase levels, myopathy, and rarely rhabdomyolysis.

E.g.,: Atorvastatin 10-80mg
Rosuvastatin 5-40mg
Simvastatin 10-20mg

Fibric Acids

Fibrate monotherapy is effective in reducing VLDL. Plasma HDL levels may rise 10-15% or more by fibrates. GI complaints occur in 3% to 5% of patients, rash in 2%, dizziness in 2.4%, and transient elevations in transaminase levels and alkaline phosphatase in 4.5% and 1.3%, respectively.

E.g.,: Gemfibrozil 600mg-1.5gm, fenofibrate 200mg, clofibrate 1000mg bid

Ezetimibe

Ezetimibe interferes with the absorption of cholesterol from the brush border of the intestines. It is approved for monotherapy and for use with statins. The dose is 10 mg once daily, given with or without food. When given alone, it results in 18% reduction in LDL cholesterol. When given with a statin, it lowers LDL by an additional 12% to 20%.

Bile Acid Resins (BARs)

The primary action of BARs is to bind bile acids in the intestinal lumen, with a concurrent interruption of enterohepatic circulation of bile acids, which decreases the bile acid pool size and stimulates hepatic synthesis of bile acids from cholesterol. It helps in depletion of hepatic pool of cholesterol which results in an increase in cholesterol biosynthesis and an increase in the LDL on liver which increases the HDL levels.

Side effects may include Gastro Intestinal (GI) irritation, epigastric fullness, nausea.

E.g.,: Cholestyramine 8gm TID Cholestepin hydrochloride 10gm BD

Niacin

It decreases the synthesis of VLDL which inturn leads to decrease in the synthesis of LDL and increase in the HDL. Niacin also increases HDL by reducing its catabolism. The principal use of niacin is for mixed hyperlipidemia or as a second-line agent in combination therapy for

hypercholesterolemia. It is a first-line agent or alternative for the treatment of hypertriglyceridemia and diabetic dyslipidemia.

Side effects: pruritis (itching), Elevated liver function tests, hyperuricemia, and hyperglycemia, hepatitis is more common with sustained-release preparations.

Contraindications: Liver disease, gout and diabetes.

Dose – 0.5mg to 1gm TID

E.g., Niaspan 1-2gm OD

Fish Oil Supplements

Diets high in omega-3-polyunsaturated fatty acids, reduces the cholesterol, triglycerides, LDL and VLDL and may elevate HDL cholesterol. It may be most useful in patients with hypertriglyceridemia. E.g., Lovaza 4gm/day as 4 times [1gm,1gm,1gm,1gm]. This product lowers triglycerides by 14-30% and raises HDL by 10%.

Algorithm [3, 4, 5]

Primary prevention: Assess the ASCVD (Atherosclerotic cardiovascular disease) risk in each age group and emphasize adherence to healthy Lifestyle

1. **Based on age**
   (a) If age group is 0-19 yrs-then lifestyle modifications are advised to prevent or reduce ASCVD risk. Diagnosis of Familial hypercholesterolemia is to be done based on that a statin is advised.
   (b) If age group is 20-39 yrs: Estimate lifetime risk and encourage lifestyle modifications to reduce ASCVD risk. Statin therapy can be considered if family history is present.
   (c) If age group is 40-75 yrs and LDL-C>70-190 mg/dL without diabetes mellitus, then 10-year risk has to be estimated.
      (i) If risk is <5%-considered as "Low risk": emphasize on lifestyle modification to reduce risk.
      (ii) If risk is 5% --< 7.5%, considered as "Borderline risk": moderate-intensity statin therapy to be initiated.
      (iii) If risk is ≥ 7.5%-<20%, considered as "Intermediate risk": if risk estimate + risk enhancers favor statin, initiate moderate –intensity statin to reduce LDL-C by 30%- 49%.
      (iv) If risk is ≥ 20%: considered as "High risk": Initiate statin to reduce LDL-C ≥50%.
2. (a) If LDL-C ≥ 190mg/dL: Directly high-intensity statin has to be initiated
   (b) If the patient has diabetes mellitus and age between 40-75 yrs: Moderate –intensity statin has to be initiated
   (c) If age >75yrs: clinical assessment to be done and risk discussion is encouraged.

3. **Adults with chronic kidney disease:** Starting moderate-intensity statin alone or in combination with ezetimibe can be useful
4. **Adults with chronic inflammatory disorders and HIV:** In adults age 40–75 with LDL-C 70–189 mg/dL with a 10-year ASCVD risk of over 5%, discuss moderate- or high-intensity statin therapy
5. **Women:** History of premature menopause (before age 40) or history of pregnancy-related disorders (hypertension, pre-eclampsia, gestational diabetes, small-for-gestational-age infants, and preterm deliveries) are risk-enhancing factors and should influence lifestyle and pharmacologic therapy decisions

ASCVD Risk enhancers:

1. Family history of premature ASCVD
2. Persistently elevated LDL-C ≥ 160mg/ dL
3. Chronic kidney disease
4. Metabolic syndrome
5. Pre-eclampsia
6. Inflammatory diseases (esp-R. Arthritis, psoriasis, HIV)

Secondary Prevention: Atherosclerotic Disease [6, 7]

High-intensity statin therapy is recommended for all patients with atherosclerotic cardiovascular disease, including acute coronary syndromes, myocardial infarction, stable or unstable angina, or with a history of coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease including aortic aneurysm, all of atherosclerotic origin.

(a) If the patient subgroup is at very high risk: If low-density lipoprotein cholesterol (LDL- C) levels are ≥ 70 mg/dL with the maximal tolerated statin therapy, it is reasonable to add ezetimibe

If LDL-C level is ≥ 70 mg/dL on maximal tolerated statin and ezetimibe, it is reasonable to add a PCSK9 inhibitor

(b) If the patient subgroup is not at very high risk

Age ≤ 75: Goal is LDL-C reduction by 50%

Use moderate-intensity statins if high- intensity statins are not tolerated

If LDL-C ≥ 70 mg/dL on high-intensity statins, it is reasonable to add ezetimibe

Age > 75: Starting or continuing either moderate- or high-intensity statins is reasonable

NCEP ATP III Major Risk Factors That Modify LDL-C Goals

Positive Risk Factors (↑Risk)

Age: Male ≥45 yr

Female: ≥55 yr

Family history of a premature CHD (definite MI or sudden death before 55 yr in father or other male first-degree relative or before 65 yr in mother or other female first-degree relative)

Current cigarette smoking

Hypertension (≥140/90 mm Hg or on antihypertensive drugs)

Low HDL-C (<40mg/dL)

Negative Risk Factor (↓Risk, protective)

Intensity of statin therapy:

1. High intensity and target reduction in LDL by ≥ 50%
   Atorvastatin 40-80mg
   Rosuvastatin 20-40mg
2. Moderate intensity and target reduction in LDL by 30-50%
   Atorvastatin 10-20mg Rosuvastatin 5-10mg Simvastatin 20-40mg
   Pravastatin 40-80mg Fluvastatin XL 80mg Pitavastatin 2-4 mg
3. Low intensity and target reduction in LDL by < 30%
   Simvastatin 10mg Pravastatin 10-20mg Lovastatin 20mg
   Fluvastatin 20-40mg Pitavastatin 1 mg

Statin-Associated Side Effects (SASE)

1. **Statin-associated muscle symptoms (SAMS):**
   (a) Myalgias (CK normal)-infrequent
   (b) Myositis/myopathy (CK > ULN) with concerning symptoms or objective weakness-Rare
   (c) Rhabdomyolysis (CK >10× ULN + renal injury) Rare HMG CoA Reductase
   (d) Statin-associated autoimmune myopathy (HMGCR antibodies, incomplete resolution) Rare
2. **Liver:** Transaminase elevation 3× ULN- infrequent
3. **Central nervous system:** Memory/cognition-rare

NCEP ATP III and AHA/ACC LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy

1. If the Risk Category is CHD or CHD risk equivalents (10-year risk >20%), then the
   (a) LDL- C reduction target goal is to achieve < 100 mg/dL of LDL-C (reasonable goal is <70mg/dL)
   (b) If LDL-C is >100mg/dL therapeutic lifestyle changes to be initiated
   (c) If LDL-C is >100mg/dL drug therapy has to be initiated.
2. If the Risk Category is: 2+ risk factors and 10-year risk is 10% to 20% then,
   (a) LDL-C reduction target goal is <130mg/dL (reasonable goal is <100mg/dL)
   (b) If LDL-C is >130mg/dL Therapeutic Lifestyle Changes to be initiated
   (c) If LDL-C is >130mg/dL (100-129mg/dL) drug therapy has to be initiated.

3. If the Risk Category is: 2+ risk factors and 10-year risk is <10% then,
   (a) LDL-C reduction target goal is <130mg/dL
   (b) If LDL-C is >130mg/dL Therapeutic Lifestyle Changes to be initiated
   (c) If LDL-C is >160mg/dL drug therapy has to be initiated.
4. If the Risk Category is: <2 risk factors
   (a) LDL-C reduction target goal is <160mg/dL
   (b) If LDL-C is >160mg/dL Therapeutic Lifestyle Changes to be initiated
   (C) If LDL-C is 190mg/dL (160-189mg/dL) LDL-C lowering drug therapy is optional.

Treatment Algorithm/Therapy for Hypertriglyceridemia

1. Borderline high triglyceride level (150-199mg per dL) or
2. High triglyceride level (200 to 499mg per dL) or
3. Very high triglyceride level (500mg per dL)

Then initiate therapeutic lifestyle changes, optimize glycemic control in patients with diabetes, screen for metabolic syndrome, and search for secondary or acquired causes.

(i) If the patient is at or near LDL-C goal- consider adding a fibrate, niacin, or fish oil to achieve the non-HDL-C goal. Consider statins for moderate to high risk patients for myopathy.

- If the patient is not near LDL-C goal-then add a statin, increase or switch statins until patient is at or near the LDL-C goal.

ii) If the triglyceride level is higher than 1000mg per dL—Initiate a very low-fat diet (15% or less of calorie intake) and aggressive body weight redction.

- Observe and follow up. If now the triglyceride level is 500mg per dL or lower- then work on reaching LDL-C goal.
- If triglyceride level is not below 500mg per dL –then add a fibrate or niacin. Consider adding a fish oil to reach LDL-C goal.

Drug Induced Hyperlipidemia [8, 9, 10]

Table 1.4 Drugs That May Cause Dyslipidemias.

	LDL Cholesterol	Triglycerides	HDL Cholesterol
Cardiovascular /Endocrine			
Amiodarone	↑Variable	↔	↔
β-Blockers***	↔	↑10-40%	↓5-20%
Loop diuretics	↑5-10%	↑5-10%	↔
	LDL Cholesterol	**Triglycerides**	**HDL Cholesterol**
Thiazide diuretics . (high dose)	↑5-10%	↑5-15%	↔
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	↑3-8%	↔↓	↑Variable

Contd…

	LDL Cholesterol	Triglycerides	HDL Cholesterol
Steroid Hormones/Anabolic Steroids			
Estrogen	↓7-20%	↑40%	↑5-20%
Select progestins	↑Variable	↓Variable	↓15-40%
Selective Estrogen Receptor Modulators	↓10-20%	↑0-30*	↔
Danazol	↑10-40%	↔	↓50%
Anabolic steroids	↑20%	↔	↓20-70%
Corticosteroids	↑Variable	↑Variable	↔
Antiviral Therapy			
Protease inhibitors	↑15-30%	↑15-200%	↔
Direct Acting Antivirals	↑12-27%	↔	↑14-20%
Immunosuppressants			
Cyclosporine and tacrolimus	↑0-50%	↑0-70%	↑0-90%
Corticosteroids	↑Variable	↑Variable	↔
Centrally Acting Medications			
First Generation antipsychotics	↔	↑22%	↓20%
Second Generation antipsychotics	↔	↑20-50%	↔
Anticonvulsants	↑Variable	↔	↑Variable
Other Medications			
Retinoids	↑15%	↑35-100%	↔**
Growth Hormone	↑10-25%	↔	↔↑7%
ABBREVIATIONS: LDL, low-density lipoprotein; HDL, high-density lipoprotein. *Raloxifene has not been shown to increase Triglyceride levels, while reported increases of up to 30% have been reported with use of tamoxifen**Data remains conflicting and some evidence shows a decrease, no effect, or increase***Varies based on individual drug			

Several medications and medication classes have been reported to affect the lipid profile. Risk factors include elevated lipid levels at baseline and high cardiovascular (CV) risk patients. This should be considered when evaluating patients with elevated levels of total cholesterol (TC), low-density lipoproteins cholesterol (LDL-C), non-high-density lipoprotein cholesterol (Non-HDL-C), triglycerides (TG) and reductions in high-density lipoprotein cholesterol (HDL-C). Cardiovascular medications, antipsychotics, anticonvulsants, hormones and certain immunosuppressives are just some of the more commonly known medications to have a negative impact on lipid levels. In some cases, this is a class effect and in others it might depend on dose and specific drug.

Case Study of Hyperlipidemia

Summary

A 46 years old male patient was admitted in hospital with the chief complaints of positive Tread Mill Test (TMT), for cardiac risk assessment. Past medical history includes hypertension and DM. Past medication history include T.telma-H 40mg OD, T.AZULIX – MF 2mg MF OD. Weight: 95.3kg, Height: 175cm. Blood pressure:140/80 mmHG; Pulse rate: 84/min; CVS:S1 S2 normal.

Lab Reports:

Hb:15.8 g/dL; PCV:45.8; RBC:4.98millions; WBC: 6800thousands; PLATELETS:2.43lakhs

Serum creatinine:0.9 mg/dL, Blood sugar:201 mg/dL; Total cholestral:240 mg/dL

LDL cholesterol :155 mg/dL; Triglycerides:180 mg/dL; HDL:32 mg/dL

Coronary angiogram: mild CAD

Final diagnosis: Based on subjective and objective data, patient was diagnosed with **hyperlipidemia, mild CAD**, type 2 diabetes mellitus , HTN.

Treatment:

Start medication:

INJ. Hydrocortisone 100mg IV STAT

INJ. Fentanyl 50mg IV STAT

INJ. Heparin 5000IU IV STAT

Drug Chart:

T.ROZALET	10/75 mg	OD
T.TELMA	40mg	OD
T.AZULIX	2mg	BBF OD

Drug Indications:

Drug name	Generic name	Indication
ROZALET	Rosuvastatin+clopidogrel	Lower the cholesterol levels and reduce the risk of narrowing arteries.
TELMA – H	Telmisartan+hydrochlorthiazide	Treatment of HTN
AZULIX-MF	Glimipiride+metformin hydrochloride	Lowers blood glucose levels.

Discharge Medication

Cap.roseday-CV (Rosuvastatin+Clopidogrel) 10mg/75mg OD {after dinner}

T. Telma – H (Telmisartan+hydrochlorthiazide) 40mg OD

T. Azulix (Glimepiride) 2mg OD BBF

T. Taxim – O (Cefixime) 200mg BD 3 days.

Drug Drug Interactions

Hydrochlorthiazide +glimepiride	Minor interaction	Hydrochlorothiazide decreases the effect of glimepiride by phrmacodynamic antagonism
Hydrochlothiazide +metformin	Minor interaction	Hydrochlothiazide will increase the level or effect of metformin by basic drug competition for renal tubular clearance

Assignment

1. **What are the laboratory test values indicating hyperlipidemia:**
   Total cholestral: 240 mg/dL.(normal: <200 mg/dL)
   LDL Cholesteral: 155 mg/dL(normal <100 mg)
   HDL: 32 mg/dL (normal -40-60 mg/dL)
   Triglycerides: 180 mg/dL (normal<150 mg/dL)

   Severity:

   Total cholesterol: high
   LDL cholesterol: borderline high
   HDL: low, major risk factor for heart disease.
2. **What are the risk factors for cardiovascular disease:**
   Modified risk factors: Type 2 diabetes, High blood pressure, High cholesterol, Obesity, Over weight
   Non modified risk factors: age; -male gender: men have greater risk of cardiovascular disease, -heredity.
3. **What is the CAD risk categorisation and target LDL goal**

Risk category	Risk factors	LDL
High risk	>2 factors (DM,HTN,obesity)	<100 mg/dL

4. **Write the pharmacological goals of treatment**:
   - reduction of cardiovascular events, relief of symptoms of Cardiovascular Artery Disease (CAD)
   - reduction of cholesterol levels, controlling blood glucose levels
   - in case of HTN, lower the blood pressure

5. **Write the non pharmacological treatment goals:**
   - controlling the amount of salt in the diet, -Lose excess weight
   - reduce stress, -procedures: coronary artery bypass surgery, angioplasty.
6. **Write the non pharmacological therapy to maintain total cholesterol level:**
   - reduce the amount of saturated fat in diet, losing weight, -eating plenty of fruits and vegetables, garlic and fish oil, exercise, smoking cessation.
7. **What are the pharmacotherapeutic options for hyperlipidemia and Cardiovascular Disease (CAD)**

   Antiplatelet therapy: clopidogrel 75 mg PO/Day
   Beta blockers: Atenolol: 25-50 mg/day
   Statins: rosuvastatin: 10-20 mg OD
   ACE inhibitors: captopril: initial 25 mg PO
   Calcium channel blockers: amlodipine: 5mg/day PO initially
8. **What are the Life Style Modifications**
   - The goal of life style change is to prevent further build up of plaque and decrease damage to blood vessels.

   Dietary Changes: Avoid saturated fat, full fat dairy products, low salt diet.
   - exercise regularly, reduce excess weight, decrease or discontinue alcohol consumption.
   - control blood glucose levels, Maintain normal blood pressure, stress management
   - cardiac rehabilitation, use medication regularly, adhere to treatment plan.
9. **What drug monitoring parameters are necessary for evaluating the efficacy and safety of the patient?**
   - Rosuvastatin- cretinine, liver enzyme abnormalities, creatine kinase are monitored periodically.
   - Clopidogrel-monitor platelet function
   - Telmisartan-monitor BP, electrolytes.
   - Glimepiride- monitors blood glucose levels.
   - Metformin- monitors hemoglobin and renal function.
10. **Write the patient counselling measures:**
    - **High blood pressure:** Makes heart work harder, damages blood vessels and also cause greater plaque buildup, To control blood pressure, Maintain a healthy body weight
    - Take mediation as prescribed, Follow health nutrition plan, Practice stress management
    - **High blood cholesterol:** High levels of LDL can damage artery walls. HDL cholesterol is good, Healthy body weight, Take medication
    - **Diabetes:** It can lead to changes in the circulatory system these changes may cause damage to heart. Eat regular meals; -eat breakfast; -limit sugars, regular soft drinks.

Nutrition Plan

Include vegetables and fruits at each meal, Choose healthy oil, Eat fresh food, Choose low fat dairy products, Use garlic in food, Consult doctor if any complications are seen, Patients are often concerned about anti platelet agents due to potential for bleeding and may discontinue these agents.

Garlic: Garlic showed a significant reduction in total cholesterol level in some studies. Raw garlic is more beneficial than the cooked form in reducing blood lipid and glucose levels. Garlic has a beneficial effect on blood lipid and glucose.

Fish Oil: Oily fish such as salmon, sardines contain two important fatty acids called docosahexaenoic acid and eicosapentanoic acid. Eating a diet that include one or two serving of oily fish per week can lower triglycerides and reduce the risk of CAD.

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