Chapter-15 Hyperlipidemias and Cardiovascular Diseases

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CHAPTER 15

Hyperlipidemias and Cardiovascular Diseases

ChapterataGlance

The learner will be able to answer questions on the following topics:

- Hyperlipidemias
- Atherosclerosis and coronary artery disease
- Risk factors for coronary artery disease
- Prevention of atherosclerosis
- Hypolipoproteinemias

Clinical Significance of Cholesterol

Students should be familiar with cholesterol and lipoproteins described in detail in Chapter 14. A summary of lipoproteins is given in Table 15.1 and their metabolic relationships are shown in Figure 15.1. LDL is said to be "bad" cholesterol and HDL is "good" cholesterol (Fig. 15.2). The level of cholesterol in blood is related to the development of atherosclerosis. Abnormality of cholesterol metabolism may lead to cardiovascular accidents and heart attacks.

ATHEROSCLEROSIS

Greek word, sclerosis means hardening. Coronary artery obstruction and myocardial infarction top the list of killer diseases in the world. In India 20% deaths are due to coronary artery disease (CAD). It is estimated that by the year 2020, it will account for 33% of all deaths.

Atherosclerosis and LDL

Stage I: Formation of foam cells:

TABLE 1-5.1: Characteristics of different classes of lipoproteins

	Chylomicron	*VLDL*	*LDL*	*HDL*
Density g/L	<0.95	0.95–1.006	1.019–1.063	1.063–1.121
Diameter (nm)	500	70	25	15
Electrophoretic mobility	origin	pre-beta	beta	alpha
Apoproteins	A, B-48, C-II, E	B-100, C-II, E	B-100	A-I, C, E
Transport function	TAG from gut to muscle and adipose tissue	TAG from liver to muscle	Cholesterol liver to peripheral tissues	Cholesterol from peripheral tissues to liver

Increased levels of cholesterol for prolonged periods will favour deposits in the **subintimal region** of arteries. Aorta, coronary arteries and cerebral vessels are predominantly affected by the atherosclerotic process. The LDL cholesterol, especially **oxidized** LDL particles are deposited in the walls of arteries. Plasma LDL is mainly catabolized via apo-B-LDL receptor pathway. But a small part of LDL particles are degraded by nonspecific uptake by macrophages. Free radical induced **oxidative damage** of LDL will accelerate this process. Later, the macrophages become overloaded with cholesterol, and these are then called **"foam cells"**. These form the hallmark of atherosclerotic plaques.

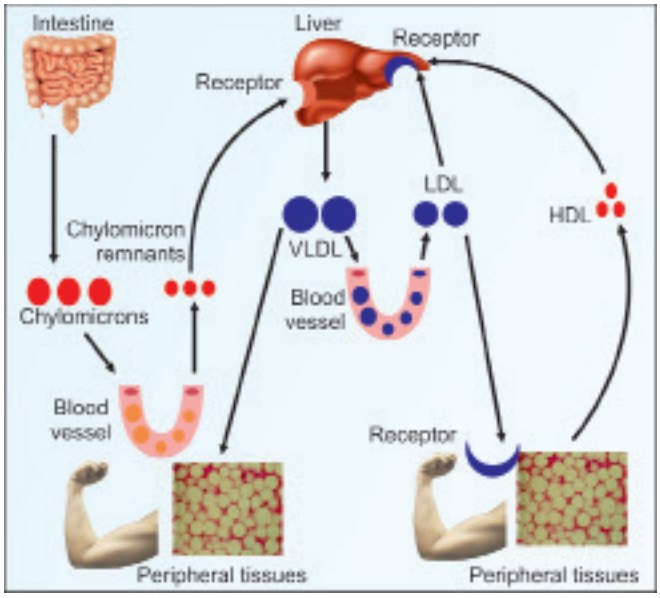


Fig. 15.1: Summary of lipoprotein metabolism

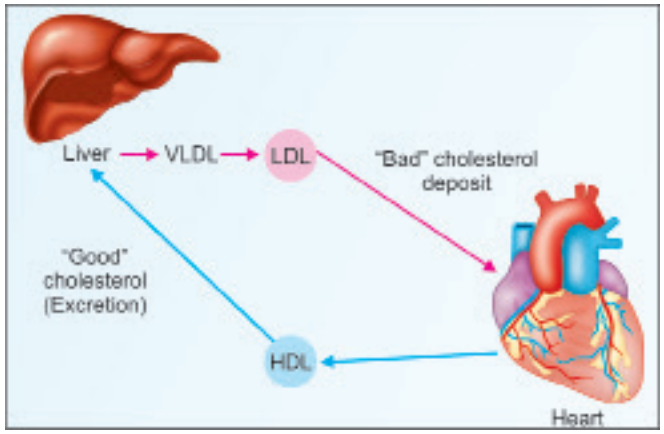


Fig. 15.2: Forward and reverse transport of cholesterol

Stage II: Progression of atherosclerosis: Smooth muscle cells containing lipid droplets are seen in the lesion. During early stages of atherosclerosis, the condition is reversible if plasma lipid levels, especially LDL-cholesterol levels are lowered. But when lipid accumulates, the lesion progresses unchecked and the arterial changes become irreversible.

Stage III: Fibrous proliferation: Due to liberation of various **growth factors** by macrophages and platelets collagen is accumulated. Thus there is a definite component of inflammation in atherosclerosis. This chronic infection leads to increased plasma high sensitive **C-reactive protein** (hs-CRP) (see Chapter 26).

Stage IV: Advancing fibrous plaque: This leads to narrowing of vessel wall when proliferative changes occur (Fig. 15.3). The blood flow through the narrow lumen is more turbulent and there is tendency for clot formation.

Myocardial Infarction (MI)

Finally, a clot is formed which occludes one of the major vessels. **Thrombosis** in coronary artery leads to ischemia of the tissue supplied, due to hindrance to oxygen supply (Fig. 15.3). Ultimately **infarction** (death of tissue) occurs (Fig. 15.4). Result is inefficient contraction of heart muscle, and if allowed to progress further, death of the muscle cells in the affected region. Usually the diagnosis can be made from the clinical history, the electrocardiogram and cardiac markers (troponin T, CK-MB, etc, described in Chapter 6). Size of the infarct may be reduced by immediate administration of **Tissue plasminogen activator** (t-PA).

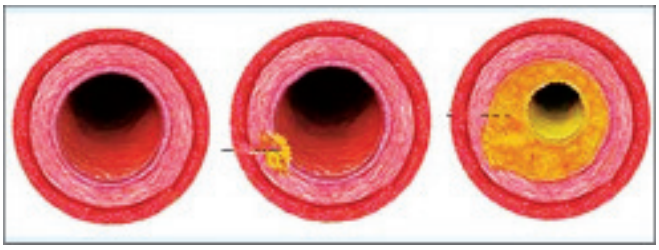


Fig. 15.3: Left, cut section of normal artery; middle, early plaque formation; right, advanced plaque formation

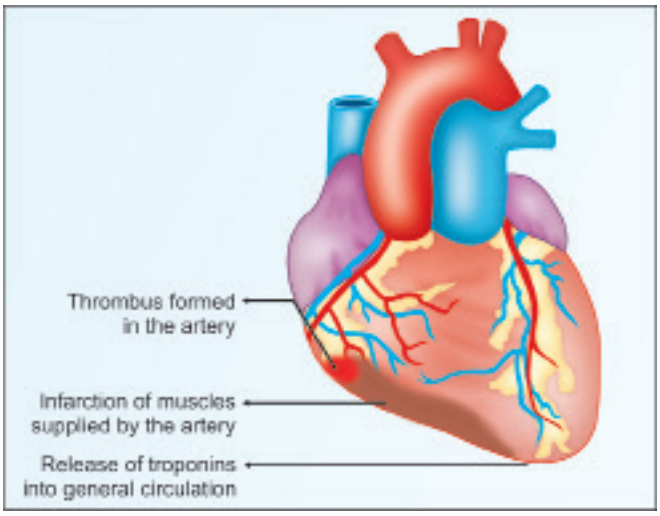


Fig. 15.4: Thrombosis in the artery leads to infarction of the area supplied by the artery

PLASMA LIPID PROFILE

The sample of serum should be taken after 12–14 hours of **fasting**. A complete lipid profile is assessed by estimating the following parameters in plasma/serum.

1. Total cholesterol
2. HDL-cholesterol
3. LDL-cholesterol
4. Triglycerides
5. Apo-B level
6. Apo-A-I level
7. Lp(a) level

In routine clinical practice only the first four parameters are measured in a fasting sample.

Box 15.1 shows the conditions in which abnormal levels of serum cholesterol are seen. Box 15.2 gives the indications for checking the lipid profile.

RISK FACTORS FOR ATHEROSCLEROSIS

Risk factors for atherosclerosis and future myocardial infarction (MI) are shown Box 15.3. Out of these, the total cholesterol, HDL and LDL levels are the most important indices (Box 15.4, item A). Cardiac markers, which indicate the presence of acute myocardial infarction are listed in Box 15.4, item B.

Box 15.1: Clinical conditions in which serum cholesterol level is increased

1. *Diabetes mellitus:* Acetyl CoA pool is increased and more molecules are channeled to cholesterol.
2. *Obstructive jaundice:* The excretion of cholesterol through bile is blocked.
3. *Hypothyroidism:* The receptors for HDL on liver cells are decreased, and so excretion is not effective.
4. *Nephrotic syndrome:* Albumin is lost through urine, globulins (including lipoproteins) are increased as a compensatory mechanism.

Box 15.2: When should check lipid profile?

1. Suspected cardiovascular disease, coronary artery disease and peripheral vascular disease
2. All patients with diabetes mellitus, atleast once in 6 months.
3. Thyroid, liver and renal diseases, where lipid metabolism may be altered.
4. All persons above 40, should be checked once in a year.

Box 15.3: Risk factors for cardiovascular disease

Class 1: Modifiable risk factors; Interventions have been proved to lower CAD risk

1. Cigarette smoking
2. High total cholesterol
3. High LDL cholesterol
4. Low HDL cholesterol
5. High fat/cholesterol diet
6. Left ventricular hypertrophy (LVH)
7. Thrombogenic factors

Class 2: Modifiable risk factors; Interventions are likely to lower CAD risk

8. Lipoprotein (a) or Lp(a)
9. Diabetes mellitus
10. Hypertension
11. Physical inactivity
12. Obesity
13. High triglycerides
14. High homocysteine
15. Increased high-sensitivity-CRP (hs-CRP)
16. Stress

Class 3: Non-modifiable risk factors

17. Age
18. Male gender
19. Family history of CAD

Serum Cholesterol Level

Framingham epidemiological study demonstrated that increase in serum cholesterol level is associated with

and increased risk of death from CHD. For every 10% lowering of cholesterol, CHD mortality was reduced by 13%. In healthy persons, cholesterol level varies from 150 to 200 mg/dL (Table 15.2). If other risk factors are present, cholesterol level should be kept preferably **below 180 mg/dL.** Values around 220 mg/dL will have moderate risk and values above 240 mg/dL will need active treatment. Females have a lower level of cholesterol which affords protection against atherosclerosis. Plasma cholesterol levels would tend to slowly rise after the 4th decade of life in men and postmenopausal women.

LDL-Cholesterol Level

National Cholesterol Education Program (NCEP) identified elevated LDL-C as a primary risk factor for CHD. Blood levels **under 130 mg/dL** are desirable (Table 15.2). Levels between 130 and 159 are borderline; while above 160 mg/dL carry definite risk. Hence LDL is **"bad"** cholesterol (Fig. 15.2). Oxidized LDL initiates fatty streaks, which is the starting point of atheroma formation.

Box 15.4: Cardiac markers

A. Risk markers of cardiac disease (prediction) (see Chapter 15)
   1. Total cholesterol level in serum
   2. LDL cholesterol and Apo B100 level
   3. HDL cholesterol and Apo A1 level
   4. Plasma hsCRP
   5. Lp(a) level
   6. Serum triglycerides
   7. Blood HbA1c
   8. Serum homocysteine level

B. Cardiac markers of acute coronary syndrome (see Chapter 6)
   1. Creatinine kinase (CK-MB)
   2. Cardiac troponins (cTnT and cTnI)
   3. High sensitivity troponin
   4. BNP and NTproBNP

TABLE 15.2: CHD risk and lipid parameters

	Low risk (desirable level)	*Borderline risk*	*High risk*
Total cholesterol (mg/dL)	<200	200–240	>240
LDL cholesterol (mg/dL)	<130	130–160	>160
HDL cholesterol (mg/dL)	>60	35–60	<35
Triglyceride (mg/dL)	<200	200–400	>400

HDL-Cholesterol Level

The HDL level **above 60 mg/dL** protects against heart disease. (Table 15.2). Hence, HDL is **"good"** cholesterol. A level below 40 mg/dL increases the risk of CAD. For every 1 mg/dL drop in HDL, the risk of heart disease rises 3%. If the ratio of total cholesterol/HDL is more than 3.5, it is dangerous. Similarly, LDL:HDL ratio more than 2.5 is also detrimental.

Apoprotein Levels and Ratios

Apo A-I is a measure of HDL-cholesterol (good) and apo B measures LDL-cholesterol (bad). Ratio of **Apo B : A-I** is the most reliable index. The ratio of 0.4 is very good; the ratio 1.4 has the highest risk of cardiovascular accidents.

Lp(a)

Lp(a) inhibits fibrinolysis. Levels more than 30 mg/dL increase the risk 3 times; and when increased Lp(a) is associated with increased LDL, the risk is increased 6 times. (See Lp(a) in Chapter 14). Nicotinic acid will reduce serum Lp(a) level.

Non-HDL Cholesterol

A value of more than 160 mg/dL carries high risk (Box 15.5).

High Sensitive C Reactive Protein (hsCRP)

It is also called ultra sensitive CRP. It measures low levels of CRP (1–10 ng/dL). It is a marker for risk for atherosclerosis and is used as a predictor for future myocardial infarction within the next 12 months. The hs-CRP test clearly adds to the predictive value.

Less than 1 mg/L (0.1 mg/dL) is considered as low risk and single measurement is sufficient. Levels between 1–3 mg/L are border line, indicating some risk, and will need assessment of serial samples at 1 week intervals. Levels more than 3 mg /L is having high risk for future MI, and will need active medical

intervention. If the hsCRP value is more than 10 mg/L, it indicates significant acute phase reaction, and is not indicative of any cardiac pathology. Thus, hsCRP is tested only when other inflammatory conditions are ruled out. Atherosclerosis has an inflammatory component, which causes production of CRP in small quantities. This CRP binds selectively to LDL, activates complement, resulting in plaque formation.

Serum Triglyceride

Normal level is 50–150 mg/dL. Blood level **more than 150 mg/dL** is injurious to health.

Homocysteine Level

Plasma homocysteine above 15 m/L will increase the risk of coronary artery disease and stroke at a **younger age**. Administration of pyridoxine, vitamin B_{12} and folic acid may lower the homocysteine level.

Diabetes Mellitus

Cardiovascular disease is responsible for 80% of total mortality in diabetes. It is associated with an increase in LDL, high TAG and low HDL levels. In the absence of insulin, hormone sensitive lipase is activated, more free fatty acids are formed, which are catabolized to produce acetyl CoA. These cannot be readily utilized, as the availability of oxaloacetate is reduced and citric acid cycle is sluggish. So acetyl CoA pool is increased, and it is channelled to cholesterol synthesis.

In diabetes, atherogenic LDL is increased while atheroprotective HDL is decreased. The glycation and oxidation of LDL will promote the uptake by macrophages. At the same time, the level of HDL in diabetic patients and those with metabolic syndrome is low. Glycation of Apo-A1 decreases its ability to stimulate LCAT, and thereby the esterification and efflux of cholesterol from the cells.

Box 15.5: Non-HDL Cholesterol and evaluation of cardiovascular risk

Non HDL cholesterol or Atherogenic cholesterol = (LDL+ VLDL+ IDL+ Lpa). As per NCEP guidelines, the value of non-HDLC is important for the risk evaluation.

<130	(100–130) mg/dL	= Very little risk
<160	(130–160) mg/dL	= Border line high
<190	(160–190) mg/dL	= High risk
>190	mg/dl	= Very high risk

Another way of expressing the risk is as follows:

	LDL-C	Non HDL-C
Risk grade 1	<160mg/dL	<190mg/dL
Risk grade 2	<130	<160
Risk grade 3	< 100	<130

Smoking

Cigarette smoking is the most important modifiable risk factor for CAD (Box 15.3). Risk from smoking is dose dependant; depends on the age at which the person started smoking and the number of cigarettes smoked per day. Smoking enhances oxidation of LDL, reduces HDL, increases CRP and augments aggregation and adhesion of platelets. Nicotine of cigarette will cause lipolysis and thereby increase acetyl CoA and cholesterol synthesis. Nicotine also causes transient constriction of coronary and carotid arteries.

Hypertension

Systolic blood pressure more than 160 further increases the risk of CAD. An increase in 10 mm of BP will reduce life expectancy by 10 years. Increase of 5 mm Hg of diastolic pressure is associated with 34% increase in stroke risk.

Obesity and Sedentary Lifestyle

The classical description of Pickwick (in Pickwick papers) by Charles Dickens reminds of a person with high risk for CAD. People with “apple type” of obesity or truncal obesity are more prone to get myocardial infarction. A person is obese when BMI exceeds 27.8 kg/m^2 in men and 27.3 kg/m^2 in women. Obesity causes glucose intolerance, insulin resistance, hypertension and dyslipidemia.

Adipose tissue releases a large number of bioactive mediators that influence insulin resistance leading to endothelial dysfunction and atherosclerosis. A summary of adipose tissue function is given in Chapter 35.

PREVENTION OF ATHEROSCLEROSIS

Almost 90% of CAD is predictable, preventable and curable. Lifestyle changes are required, which include regular exercise, balanced diet, cessation

of smoking, maintaining proper weight, control of hypertension, diabetes and dyslipidemia. The aim is to reduce total cholesterol below 180 mg/dL; to decrease LDL-cholesterol below 130 mg/dl and to keep HDL-cholesterol above 35 mg/dL (Box 15.6).

Reduce Dietary Cholesterol

Cholesterol in the diet should be kept less than 200 mg per day. Eggs and meat contain high cholesterol. One egg yolk contains about 500 mg of cholesterol (Fig. 15.5A). One double omelet increases the blood cholesterol, 15 mg more than the original level.

Vegetable Oils and PUFA

Vegetable oils (e.g. sunflower oil) and fish oils contain polyunsaturated fatty acids (PUFA). They are required for the esterification and final excretion of cholesterol. So PUFA is helpful to reduce cholesterol level in blood (Fig. 15.5B). **Omega-3 fatty acids** from fish oils reduce LDL and decrease the risk of CAD. Recommended intake of omega-3 fatty acid (fish oils) is 1 g/day (EPA and DHA combined).

Moderation in Fat Intake

The accepted standard is that about 20% of total calories may be obtained from fat, out of which about one-third from saturated, another one-third from monounsaturated and the rest one-third from polyunsaturated fatty acids. The recommended daily allowance will be about **20–25 g of oils** and about 2–3 g of PUFA per day for a normal adult.

Green Leafy Vegetables

Due to their **high fiber content,** leafy vegetables will increase the motility of bowels and reduce reabsorption of bile salts (Fig. 15.6). Vegetables also contain plant sterols (**sitosterol**) which decrease the absorption of cholesterol. About 400 g/day of fruit and vegetables are desirable. Clinical studies have suggested that DHA, (docosa hexenoic acid) and EPA, (eicosapentaenoic acid) lower triglycerides; slow the buildup of atherosclerotic plaques; as well as reduce the risk of heart attack.

Avoid Sucrose and Cigarette

Cigarette smoking (Fig. 15.7) is the single most important modifiable risk factor for CAD (Box 15.3). Sucrose will raise plasma TAGs. High carbohydrate diet, especially sucrose, should be avoided by patients with hypercholesterolemia.

Exercise

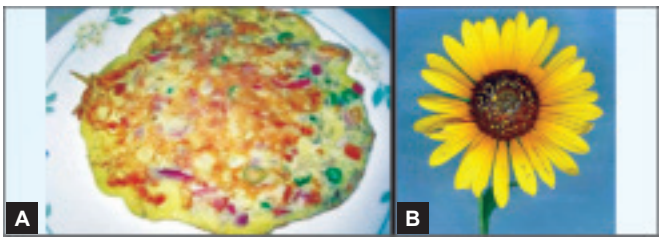
Regular moderate exercise (30 min per day) will lower LDL (bad cholesterol) and raise HDL (good cholesterol) levels in blood. It will also reduce obesity. Individuals spending more than 2000 kcal/week in exercise are at a lower risk.

Hypolipidemic Drugs

i. **HMGCoA reductase inhibitors** ("statins"): Atarvostatin and Simvostatin are popular drugs in this group. They are effective in reducing the cholesterol level and decreasing the incidence of CAD.
ii. **Bile acid binding resins** (Cholestyramine and Cholestipol) decrease the reabsorption of bile acids.
iii. **Probucol** increases LDL catabolism and prevents accumulation of LDL in arterial walls. So more holesterol will be converted to bile acids, thus reducing the cholesterol level.
iv. **Aspirin** is widely used to prevent thrombus formation, because of its anti-platelet activity (see Chapter 16).

Box 15.6: Treatment policy in high risk patients; Targets to be achieved

1. Reduce total cholesterol below 180 mg/dL
2. Decrease LDL-cholesterol below 130 mg/dL; In persons with documented CHD, the goal of therapy is to reduce LDL to below 100 mg/dL. In general, lowering of LDL cholesterol by 1 mg/dl (1 mmol/L) reduces the risk of cardiovascular disease by 25%
3. Keep HDL-cholesterol above 40 mg/dl.



Figs 15.5A and B: (A) Reduce dietary cholesterol by avoiding egg omelet; (B) Sunflower oil and other vegetable oils contain

v. Anti-oxidants such as **vitamin E** will minimize oxidation of LDL and so, atherosclerosis may be reduced.
vi. Plant derived products having cholesterol-lowering action are enumerated in Box 15.7. The guggul (resins) from the Mukul myrrh tree (*Commiphora Mukul*) has cholesterol lowering action.

Avoid Trans Fatty Acids (TFA)

Trans fatty acids (with double bonds having trans configuration) are formed during the partial hydrogenation of vegetable oils. They are widely used in food industry because of their long shelf-life. Trans fatty acids (TFA) are found to be more atherogenic than saturated fatty acids. It alters secretion and composition of apo-B100 containing lipoproteins (LDL and VLDL). It increases catabolism of apo-A-I, decreases HDL and increases LDL levels. Reducing the intake of TFA to 2–7 g/day is now strongly advised.

PUFA, in Excess, may be Harmful

PUFA can definitely reduce cholesterol level. But there should be moderation. It is known that the diet should contain correct type and quantity; the optimum ratio of omega-6 to omega-3 fatty acids is 4:1. Very high intake of omega-6 oils will cause lowering of HDL, elevation of plasma triglycerides, and will promote platelet aggregation. Vegetable oils (sunflower oil) containing PUFA are rich in omega-6 variety; while ghee and butter are low in omega-6. Omega-3 group is present in fish oils. Normal Indian diet consisting of cereals, pulses and vegetables provides **"invisible oils"**, which contains about 10 g of PUFA/ day (out of which about 2 g is omega-3 and the rest 8 g is omega-6). Further intake of omega-6 oils is unnecessary and may be harmful.

Fig. 15.6: Green leafy vegetables are very good

Fig. 25.7: Avoid cigarettes

The optimal **ratio for omega-6 to omega-3** in diet is 4:1. In an average Indian diet, this is about 30:1. In sunflower oil, this value is 160:1, and therefore, unnecessary addition of such vegetable oils will further deteriorate the condition. Although contains saturated fatty acids, coconut oil has the omega ratio 3:1, and therefore is superior to sunflower oil in this respect.
The general advice against the use of ghee and coconut oil needs re-evaluation. This mis-information arose, when long chain saturated fatty acids (LCSFA) were shown to increase cholesterol level. Since butter and coconut oil also contain saturated fatty acids, people equated them with LCSFA. Now it is known that ghee and coconut oil contain small chain (SCFA) and medium chain fatty acids. The drastic differences in metabolisms of LCFA and SCFA are given in Chapter 16. In summary, ghee and coconut oil, within normal limits, neither decrease nor increase cholesterol levels. But it is to be noted that consumption of ghee (any oil in general), increases the total fat intake as well as calorie intake. That is harmful. Again, moderation is the key.

HYPOLIPOPROTEINEMIAS

Abetalipoproteinemia

All apo-B containing lipoproteins are reduced since microsomal triglyceride transfer protein is defective. Hence TAG is not incorporated into VLDL and chylomicrons. (Table 15.3). Beta lipoprotein (LDL) is absent. Fat-soluble vitamins are not absorbed, causing mental and physical retardation. Serum levels of triglycerides, cholesterol and phospholipids are extremely low. Blindness may occur as a result of degenerative changes in retina. Erythrocytes have spiny projections (**acanthocytes**).

Box 15.7: Plant derived products having cholesterol-lowering action

Plant derived fiber: Reduces serum cholesterol
Legumes: Reduces cholesterol even on high fat diet
Onion and garlic: Reduces serum cholesterol and TG
Embelia Ribes (Vidanga): Dried berries alone or along with amla has hypolipidemic effect
Commiphora Mukul (Guggulu): Hypolipidemic and cardioprotective
Cyperus Rotundus (Musta): Hypolipidemic; improves metabolic activity
Spices, flavinoids, red wine: Natural antioxidants prevent oxidative modification of LDL

Hypo-alpha-lipoproteinemia

This is inherited as an autosomal dominant trait. Serum HDL is decreased. There is increased risk for coronary artery diseases (Table 15.3).

Tangier Disease

It was first described in patients from Tangier island in North-West Africa. It is a relatively benign, autosomal dominant condition. It is characterized by a defect in the efflux (flowing out) of cholesterol from cells, and reduction of HDL levels in the blood. The biochemical defect is the absence of **"ATP-Binding Cassette Transporter-1**" (ABC-1), which is involved in transferring cellular cholesterol to HDL. So, plasma HDL is low and alpha band is nost seen in electrophoresis. Cholesterol esters are accumulated in tissues. Manifestations are large orange yellow tonsils, muscle atrophy, recurrent peripheral neuropathies and atherosclerosis.

HYPERLIPIDEMIAS

The most widely accepted **Frederickson's** classification is shown in Table 15.4. In all cases of hyperlipidemias,

TABLE 15.3: Classification of hypolipoproteinemias

Disease	*Lipoproteins*	*Cholesterol*	*Triacylglycerols*	*Clinical findings*
Familial hypo beta lipoproteinemia	LDL decreased B-100 decreased	Decreased	Normal disease	Decreased risk of coronary artery
Abeta lipoproteinemia	VLDL↓; LDL↓↓ B-48↓; B-100↓↓	Markedly decreased	Decreased	Malabsorption; mental and physical retardation; acanthocytosis
Hypo alpha lipoproteinemia	HDL↓ A-I↓	Normal	Normal	Increased risk of coronary artery disease
Familial alpha Lp-deficiency	HDL↓↓ A-I↓↓	Normal	Normal	Increased risk of CAD

TABLE 15.4: Frederickson's classification of hyperlipoproteinemias (N = Normal; ↑ = Increased)

Type	*Lipoprotein fraction elevated*	*Cholesterol level*	*TAG level*	*Appearance of plasma after 24 hr*	*Metabolic defect*	*Features*	*Management*
Type I	Chylomicrons	N	↑↑	Creamy layer over clear plasma	Lipoprotein lipase deficiency	Eruptive xanthoma; hepatomegaly; Pain abdomen.	Restriction of fat intake. Supplementation with MCT
Type II A	LDL	↑↑	N	Clear	LDL Receptor defect; Apo B ↑	Atherosclerosis, coronary artery disease, Tuberous xanthoma	Low cholesterol diet. Decreased intake of saturated fat. Give PUFA and drugs like statins.
Type II B	LDL and VLDL	↑↑	↑	Slightly cloudy	Apo B ↑ Apo CII	Corneal arcus	Do
Type III	Broad beta-VLDL and Chylomicrons	↑↑	↑	Cloudy	Abnormal apo-E; Apo CII ↑	Palmar xanthoma. High incidence of vascular disease	Reduction of weight, restriction of fat and chol. Give PUFA and drugs
Type IV	VLDL	↑	↑↑	Cloudy or milky	Over produc tion of VLDL; Apo CII ↑	Associated with diabetes, heart disease, obesity.	Reduction of body weight. Restrict carbo hydrate and cholesterol
Type V	VLDL Chylomicrons	N	↑↑	Creamy layer over milky plasma	Secondary to other causes	Chronic pancreatitis	High PUFA intake, hypocholipidemic drug

the elevated lipid fraction is either cholesterol or TAG or both.

The elevation of lipids in plasma leads to the deposition of cholesterol on the arterial walls, leading to **atherosclerosis.** (See under coronary artery diseases). The coronary and cerebral vessels are more commonly affected. Thrombo-embolic episodes in these vessels lead to **ischemic heart disease** and cerebrovascular accidents.

The deposition of lipids in subcutaneous tissue leads to **xanthomas**. The type of xanthoma depends on the nature of lipid deposited. **Eruptive xanthomata** are small yellow nodules associated with deposition of triglycerides. They disappear when the lipid level falls. Deposits of lipids in cornea lead to **corneal arcus***;* indicating hyper cholesterolemia.

Hyperlipidemias, in the order of highest to lowest incidence are Type IIA, IIB, IV, I, III and V.

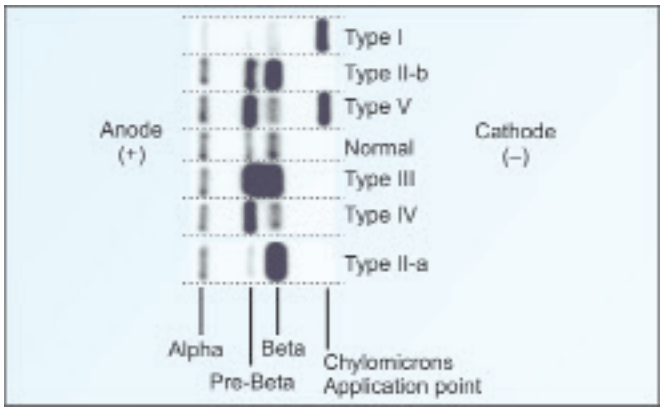


Fig. 15.8: Electrophoretic pattern of hyperlipidemias

TABLE 15.5: Secondary hyperlipidemias

	Serum cholesterol	*Serum triglyceride*
Diabetes	Increased	Increased
Nephrotic syndrome	Increased	Increased
Hypothyroidism	Increased	Increased
Biliary obstruction	Increased	Normal
Pregnancy	Normal	Increased
Alcoholism	Normal	Increased
Oral contraceptives	Normal	Increased

Type II A (Primary Familial Hypercholesterolemia)

There is elevation of LDL. Patients seldom survive the second decade of life due to ischemic heart disease (Table 15.4 and Fig. 15.8). The cause is **LDL receptor** defect. Receptor deficiency in liver and peripheral tissues will result in the elevation of LDL levels in plasma, leading to hypercholesterolemia. The LDL receptor defect may be due to the following reasons.

1. **LDL receptor deficiency.**
2. **Defective binding** of B-100 to the LDL receptors. This defect is known as B-3500 or **familial defective apo B.**
3. Receptor-LDL complex is not internalized.

Secondary type II hyperlipoproteinemia is seen in hypothyroidism, diabetes mellitus, nephrotic syn drome and cholestasis (Table 15.5).

Salient features of other types of hyperlipoproteinemias are shown in Table 15.4.

Clinical Case Study 15.1

A 48-year-old male presents to the clinic because of concerns about heart disease. He reports that his father died from a heart attack at age 46, and his older brother has also had a heart attack at age 46 but survived and is on medications for elevated cholesterol. The patient reports chest pain occasionally with ambulation around his house and is not able to climb stairs without significant chest pain and shortness of breath. The physical examination is normal, and the physician orders an electrocardiogram (ECG), exercise stress test, and blood work. The patient's cholesterol result comes back as 350 mg/dL (normal 200). The physician prescribes medication, which he states is directed at the rate limiting step of cholesterol biosynthesis.

What is the rate-limiting step of cholesterol metabolism? What is the class of medication prescribed?

Clinical Case Study 15.2

A 51-year-old male presents to the emergency center with chest pain. He states that he has had chest discomfort or pressure intermittently over the last year especially with increased activity. He describes the

chest pain as a pressure behind his breastbone that spreads to the left side of his neck. Unlike previous episodes, he was lying down, watching television. The chest pain lasted approximately 15 minutes then subsided on its own. He also noticed that he was nauseated and sweating during the pain episode. He has no medical problems that he is aware of and has not been to a physician for several years. On examination, he is in no acute distress with normal vital signs. His lungs were clear to auscultation bilaterally, and his heart had a regular rate and rhythm with no murmurs. An electrocardiogram (ECG) revealed ST segment elevation and peaked T waves in leads II, III, and aVF. Serum troponin I and T levels are elevated. What is the most likely diagnosis? What biochemical shuttle may be active to produce more adenosine triphosphate (ATP) per glucose molecule?

Clinical Case Study 15.3

A 48-year-old male presented to OP with chest pain. Family history shows that his father died of a heart attack at the age of 46, and his elder brother also had a heart attack at the same age. The patient reports that he gets chest pain occasionally with ambulation and is not able to climb stairs without significant chest pain and shortness of breath. His plasma cholesterol level was 450 mg%. What is the possible diagnosis?

Clinical Case Study 15.1 Answer

Diagnosis; Hypercholesterolemia.
Rate-limiting step: The enzyme hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase) catalyzes an early rate-limiting step in cholesterol biosynthesis.
Likely medication: HMG-CoA reductase inhibitor, otherwise known as "statin" medications.

Clinical correlation: Hyperlipidemia is one of the most treatable risk factors of atherosclerotic vascular disease. In particular, the level of the low-density lipoprotein (LDL) correlates with the pathogenesis of atherosclerosis. Exercise, dietary adjustments, and weight loss are the initial therapy of hyperlipidemia. If these are not sufficient, then pharmacologic therapy is required. The exact LDL targets depend on the patient's risk of cardiovascular disease. For example, if an individual has had a cardiovascular event previously (heart attack or stroke), the LDL target is 100 mg/dL; 1 to 2 risk factors without prior events =130 mg/dL; and no risk factors =160 mg/dL.

Clinical Case Study 15.2 Answer

Likely diagnosis: Acute myocardial infarction.

Clinical correlation: Patient's symptoms in this case are very typical of myocardial infarction, that is, chest pressure or chest pain, often radiating to the neck or to the left arm. The pain is usually described as deep and "squeezing chest pain." Cardiac muscle is perfused by coronary arteries with very little redundant or shared circulation; thus, occlusion of one coronary artery usually leads to ischemia or necrosis of the corresponding cardiac muscle. Laboratory confirmation of myocardial infarction (death of cardiac muscle) includes ECG showing elevation of the ST segment and/or increase of the cardiac enzymes. When there is insufficient oxygen available for the cardiac muscle, then the glycolytic pathway must be used, which leads to a very small amount of ATP per glucose molecule.

Clinical Case Study 15.3 Answer

The patient might be suffering from familial hypercholesterolemia (FH). An LDL-C higher than 200 mg% in a patient less than 20 years is suggestive of heterozygous FH. It is an autosomal dominant condition where total cholesterol and LDL-C show severe elevation. Sometimes, it is also a moderate elevation. It carries a risk premature CAD and hence early detection and treatment are important. Exercise, dietary adjustments and weight loss are the initial steps, but if they fail drugs may be needed.

FH is due to a defect in LDL receptor. LDL receptor activity may be completely absent or up to 25% activity may be present. There are 3 types; in the first type LDL receptor is absent, in the second type there is mutation in the terminal region so that binding is affected and in the third type, there is mutation in the C terminal region so that endocytosis is affected. Cholesterol synthesis continues even when plasma cholesterol is very high in these patients.

In children with FH, typically cholesterol levels may be above 600 mg%, and LDL-C may be 200 – 400 mg%. Foam cell formation, plaque cell formation and premature CAD are typical features. Cholesterol may accumulate in other areas, leading to xanthelasma and variety of xanthomas. Corneal arcus and valvular abnormalities are seen secondary to cholesterol deposition.

The condition may be homozygous (which is a rare condition, with an incidence of 1 in 1 million) or heterozygous (which is much more common, with an incidence of 1 in 500 persons). Men are more prone to develop CAD than women. Symptoms appear later in heterozygotes.

LEARNING POINTS, CHAPTER 15

1. LDL carry cholesterol from the liver to the heart, while HDL carries cholesterol from the heart to the liver.
2. LDL is 'bad' cholesterol and HDL is 'good' cholesterol.
3. Higher concentration of Lipoprotein (a) or Lp(a) increases risk of a myocardial infarction.
4. Tangier's disease is caused by the deficiency of alpha lipoprotein. It is an example of hypolipoproteinemia.
5. Hypercholesterolemia is seen in diabetes mellitus, hypothyroidism and nephrotic syndrome.
6. Serum cholesterol above 200 mg %, cigarette smoking, hypertension, diabetes mellitus and high Lp(a) levels are risk factors for atherosclerosis.
7. Hypolipidemic drugs such as Clofibrate and Nicotinic acid lower serum cholesterol and are used in the treatment of hypercholesterolemia.
8. The ideal ratio of omega-6 to omega-3 in the diet is 4:1.