

## **Dyslipidaemias.**

### **Learning Objectives:**

- 1. To understand the link between cardiovascular disease and elevated blood lipid levels.**
- 2. To recognise the common clinical signs of dyslipidaemias.**
- 3. To understand the differences between primary and secondary hyperlipidaemias.**
- 4. To appreciate the principles of medical management in these conditions.**

The two main circulating lipids are triglycerides and cholesterol. They are bound to phospholipid and lipoproteins to make them water soluble for transportation. The surface apoproteins ( apolipoproteins) of these soluble masses facilitate the recognition of the different transport complexes.

**Chylomicrons** - Chylomicrons contain 85% triglycerides and 4% cholesterol. They are produced in the mucosa of the small intestine and broken down in the liver and peripheral tissues by lipoprotein lipase. They initially contain apoprotein B-48 (apo B-48) and acquire apo E and apo C-II from circulating HDL. Following metabolism by lipoprotein lipase in capillary endothelial cells, chylomicron remnants are removed by the liver.

**Very low density lipoproteins (VLDL)** - VLDL contain 50% triglyceride, 15% cholesterol and 18% phospholipids. They are produced with triglycerides that have been synthesized in the liver. VLDL also contains apoB-100 and apo E. They are broken down by lipoprotein lipase in peripheral tissue to give IDL and other remnants that are removed by the liver.

**Intermediate density lipoproteins (IDL)** - IDL are VLDL remnants that contain mainly cholesterol and phospholipid. They are removed by the liver or metabolized to LDL.

Low density lipoproteins (LDL) - LDLs contain 45% cholesterol, 10% triglyceride and 20% phospholipid. LDLs have apo B-100 on their surface and transport most of the cholesterol in circulation. The liver has specific LDL receptors to extract it from the circulation. Half of the body's circulating LDL is removed from the plasma each day, mainly by the liver. Smaller, denser or oxidised LDLs (15% of the LDL pool) are removed by a scavenger pathway in macrophages and liver sinusoidal endothelial cells. Accumulation of oxidised LDL in macrophages produces the foam cells that are seen in atheromatous plaques.

High density lipoproteins (HDL) - HDLs are produced by the liver and gut. They contain 17% cholesterol, 4% triglyceride and 24% phospholipid. HDLs transport 20-50% of circulating cholesterol.

### **Primary and secondary hyperlipidaemia**

Elevated blood lipid levels are a modifiable risk factor for the development of atherosclerosis, a major cause of death from coronary heart disease, peripheral vascular disease and stroke. Hyperlipidaemia occurs due to a combination of genetic factors and dietary intake. Primary hyperlipidaemias are usually genetically determined while secondary hyperlipidaemias occur due to a combination of disease, drugs and diet.

### **Hyperlipidaemia**

Hyperlipidaemia and hypercholesterolaemia are extremely common, and their main effect is the development of atherosclerosis. Sub-intimal plaques start in medium-sized blood vessel walls when LDL cholesterol accumulates. A cholesterol-rich necrotic core develops and is surrounded by smooth muscle cells and fibrous tissue. Plaques can result from a combination of diffusion of elevated LDL cholesterol, qualitative abnormalities of LDL cholesterol or endothelial cell damage. This can frequently be caused by physical trauma such as with hypertension, toxins such as tobacco and alcohol, low-grade infection, inflammation, immune complex damage, or any combination of these. Plaque ulceration is associated with thrombosis, which can obliterate the lumen of a blood vessel, and distal embolism.

There is a direct relationship between hypercholesterolaemia and coronary heart disease. Reductions in total and LDL cholesterol reduce coronary events, cerebrovascular events and mortality. The converse is true of HDL cholesterol, which has an inverse relationship with coronary heart disease such that higher levels are beneficial. The association between isolated hypertriglyceridaemia and vascular disease is still debated, but mixed hyperlipidaemia is clearly associated with coronary heart disease. The Helsinki Heart study showed a 4-fold greater risk of cardiac events if the LDL : HDL ratio was  $>5.0$  and the triglycerides  $>2.3$  mmol/l compared to those with lower levels of triglycerides.

The main presenting features are complications associated with atherosclerosis (coronary heart disease, peripheral vascular disease and stroke). Clinical features directly associated with hyperlipidaemia include xanthomas, xanthelasma and a corneal arcus.

### **Xanthomas and xanthelasma**

Xanthomas are lesions characterised by accumulations of lipid-laden macrophages. Cutaneous xanthomas associated with hyperlipidaemia can be clinically subdivided into xanthelasma palpebrum, tuberous xanthoma, tendinous xanthoma, eruptive xanthoma, plane xanthoma, and generalized plane xanthoma. Xanthelasma palpebrum is the most common of the xanthomas. The lesions are asymptomatic and usually bilateral and symmetric. They are soft, velvety, yellow, flat, polygonal papules around the eyelids, most common in the upper eyelid near the inner canthus. Usually, the lesions have evolved for several months and enlarged slowly from a small papule.



Tuberous xanthomas are firm, painless, red-yellow nodules, frequently coalescing to form multilobated tumours. They usually develop in pressure areas, such as the extensor surfaces of the knees, the elbows, and the buttocks.



Tendinous xanthomas appear as slowly enlarging subcutaneous nodules related to the tendons or the ligaments. The most common locations are the extensor tendons of the hands, the feet, and the Achilles tendons. These lesions are often related to trauma, and are associated with severe hypercholesterolemia and elevated LDL levels.



Eruptive xanthomas most commonly arise over the buttocks, the shoulders, and the extensor surfaces of the extremities. Rarely, the oral mucosa or the face may be affected. The lesions typically erupt as crops of small, red-yellow papules on an erythematous base, often spontaneously resolving over weeks. Pruritus is common, and the lesions may be tender. Eruptive xanthomas are associated with hypertriglyceridaemia, and may also appear in secondary hyperlipidaemias, particularly in diabetes.



Plane xanthomas are mostly macular and rarely form elevated lesions. They can occur in any site. Involvement of the palmar creases is characteristic, and they can also be associated with secondary hyperlipidaemias, especially in cholestasis. Generalized plane xanthomas can cover large areas of the face, the neck, and the thorax, and the flexures can also be involved.



## Corneal Arcus

Corneal arcus is a lipid-rich and predominantly extracellular deposit that forms at the corneoscleral limbus (margin). It is the most common peripheral corneal opacity and is associated with the deposition of lipids. It appears as a greyish-white ring (or part of a ring), most frequently in middle and old age, due to a lipid infiltration of the corneal stroma. With age the condition progresses to form a complete ring (arcus senilis), separated from the limbus by a zone of clear cornea.

The condition can also appear in early or middle life and is referred to as arcus juvenilis. This appears as a much whiter ring, and is frequently associated with heart disease in men.



A. senilis



A. juvenilis

The deposition of cholesterol in the peripheral cornea follows a similar pattern to that in arterial walls in that both are accelerated by elevated serum levels of atherogenic lipoproteins, such as low-density lipoproteins (LDL). It has been associated with hypercholesterolemia, xanthelasmas, alcohol intake, increased blood pressure, cigarette smoking, diabetes, increasing age, and coronary heart disease. However, it is still unclear whether or not corneal arcus is an independent risk factor for coronary heart disease.

## Key Learning Points :



1. Elevated blood lipid levels are a modifiable risk factor for the development of atherosclerosis.
2. Hyperlipidaemia and hypercholesterolaemia are extremely common, and their main effect is the development of atherosclerosis.
3. Clinical features directly associated with hyperlipidaemia include xanthomas, xanthelasma and a corneal arcus.

## General Management

In practice, patient management is via their levels of cholesterol (total cholesterol, LDL, HDL) and triglycerides. A lipid profile needs to be a fasting sample taken after a 12-hour overnight fast. In non-fasting samples, only total and HDL cholesterol measurements are accurate. Triglyceride levels rise post-prandially therefore fasting is required to gain an accurate value.

Measurements should not be taken during an acute illness or during periods of rapid weight loss as these lead to artificially low results. This is particularly important from 24 hours after a myocardial infarction for up to 6 weeks (less if thrombolysis was undertaken). During this time, the levels of total and LDL cholesterol may be artificially reduced. Pregnancy or recent weight gain is associated with increased lipid levels. After rapid weight gain or weight loss, at least 1 month should elapse once the patient is stable before lipid levels are reassessed.

Hypercholesterolaemia is defined as elevated total or LDL cholesterol with normal triglyceride levels. Hypertriglyceridaemia is an isolated elevation of triglyceride

levels. An elevation of both cholesterol and triglycerides is termed mixed hyperlipidaemia.

Total cholesterol measurements alone can be misleading as isolated HDL elevations will elevate the total serum cholesterol level. Use of total cholesterol to HDL ratio or a LDL:HDL ratio is preferred, especially in women and in diabetic patients.

The emphasis of management will depend on the cause of the hyperlipidaemia and is aimed at reducing cardiovascular and cerebrovascular risk. There are now recommended target values when treating patients.

	<b>Total cholesterol</b>	<b>LDL cholesterol</b>	<b>HDL cholesterol</b>	<b>Triglycerides</b>
Patients without complications of atherosclerosis	Less than 5.2 mmol/l	Less than 4.0 mmol/l	More than 1.0 mmol/l	N/A
Patients with coronary heart disease	Less than 4.0 mmol/l	Less than 2.5 mmol/l	N/A	Less than 1.5 mmol/l

If these optimal levels are not achievable, at least a 30% fall from pre-treatment serum cholesterol concentration is acceptable

Dietary advice - In general, fat should constitute less than 30% of consumed calories, and saturated fats must be less than 30% of the total fat content. The total dietary cholesterol ideally should not exceed 300mg per day. Three to four months should be allowed to elapse to see if dietary manipulation works. It is unusual to see more than a 25% fall in cholesterol from dietary measures. A 10 kg weight loss in an obese subject reduces LDL cholesterol by 7% and increases HDL cholesterol by 13%.

Physical activity - Acute exercise transiently changes lipoprotein levels and increases lipoprotein lipase activity. These effects are more lasting with regular exercise. Triglyceride levels fall, HDL cholesterol levels rise (especially the HDL2 subfraction) with more vigorous exercise, and LDL cholesterol is less dense and less atherogenic. The alteration seen is dose dependent with increasing exercise, and a 20% alteration in each variable is achievable after 6 weeks. Other risk factors such as hypertension, smoking and blood glucose control should be addressed.

## **Medical management**

### **HMG CoA reductase inhibitors (statins)**

Statins lower cholesterol by 25-40% and triglycerides by 10-20%. Complications include hepatitis and myositis (rare), therefore liver function tests and creatine kinase should be measured before they are prescribed. Statins should be discontinued if the levels of liver enzymes aspartate (AST) and alanine (ALT) aminotransferase increase by more than 2-3 times above the normal limit. In general, statin therapy for hypercholesterolaemia reduces major coronary events by 27%, stroke by 18%, and all-cause mortality by 15%.

### **Fibrates**

These medications are less effective than the statins at lowering cholesterol but better at increasing HDL cholesterol and more effective in lowering triglycerides. They should not be prescribed to patients with severe liver disease or renal dysfunction. Fibrates reduce triglyceride levels by about 50% and increase HDL cholesterol by 15-20%.

### **Anion exchange resins (bile acid sequestrants)**

Colestyramine and colestipol are effective in lowering cholesterol, but compliance can be poor due to gastrointestinal side effects. These medications can exacerbate hypertriglyceridaemia. Under optimum conditions, LDL cholesterol can be reduced by 20-30%. HDL cholesterol is slightly increased. Bile acid binding resins can affect uptake of other medications, which need to be taken at least an hour before or 4-6 hours after the resins.

### **Nicotinic acid and acipimox**

Nicotinic acid is the most effective medication to increase HDL cholesterol. It can lower triglycerides as well as total and LDL cholesterol. However, it is severely limited by its side effects, especially vasodilatation (facial flushing). Nicotinic acid can adversely affect glucose control in diabetes mellitus.

### **Omega 3 fatty acids**

These fish oils are useful in reducing hypertriglyceridaemia but are ineffective in lowering cholesterol.

## **Primary hyperlipidaemias**

### **Familial hypercholesterolaemia (FH)**

Familial hypercholesterolaemia is an autosomal dominant disorder, with a frequency of 1 in 500 in Western Europe and North America. The genetic defects are mutations in the LDL receptor gene, the apolipoprotein B-100 gene and the recently identified proprotein convertase subtilisin/kexin type 9 gene (*PCSK9*). The result is high serum LDL levels due to prolonged LDL clearance, from 2.5 to 4.5 days.

Patients with familial hypercholesterolaemia have early-onset coronary disease and a standardised mortality ratio nine times greater than normal population. Homozygotes typically present in childhood. Heterozygotes usually present after 30 years of age. Lipid deposits occur around the eyes (xanthelasma) and tendons (xanthomas of the fingers, hands, elbow, knee and Achilles tendon). Achilles tendinitis may be the first clue to the presence of this condition in childhood, and the corneal arcus occurs early in life (30-40 years old).

Biochemically, familial hypercholesterolaemia (FH) is characterised by high total cholesterol (>7.8 mmol/L heterozygotes, >15 mmol/L homozygotes) and high LDL (from birth).

Heterozygote - an individual who has inherited two different forms of a particular gene, one from each parent. Such individuals are often known as 'carriers'.

Homozygote - an individual who has inherited two identical forms of a particular gene, one from each parent.

### **Familial hypertriglyceridaemia**

Familial hypertriglyceridaemia affects 1 in 300 people, often as an autosomal dominant disorder. The biochemical disorder is elevated VLDL levels and frequently hypercholesterolaemia. It is characterised by eruptive xanthomata, which are red and painful, and lipaemia retinalis. Exacerbating factors include alcohol and medications (thiazide diuretics, glucocorticoids, oral contraceptive pill). Adherence to a low-fat, alcohol-free diet with weight reduction usually helps.

Two rare but important familial causes of gross hypertriglyceridaemia are lipoprotein lipase deficiency and apolipoprotein C-II deficiency. Both are autosomal recessive conditions that present in childhood. Lipoprotein lipase is required to metabolise chylomicrons, and a defect or absence of this enzyme results in hyperchylomicronaemia. Apo C-II is required for the activation of lipoprotein lipase, and deficiency gives the same clinical picture. Patients do not have premature coronary disease but can develop recurrent abdominal pain from pancreatitis.

### **Polygenic hypercholesterolaemia**

Polygenic hypercholesterolaemia is the most common cause of hypercholesterolaemia. It arises due to a combination of genetic and environmental factors, more commonly diet-related. LDL clearance appears to be reduced by a variety of mechanisms and hepatic VLDL production is increased. This disease is often linked with a high fat intake and obesity. Patients do not have xanthelasmata or extensor tendon deposits as seen in familial hyperlipidaemia. It is often diagnosed during primary cholesterol screening programmes or when investigating manifestations of atherosclerosis.

### **Familial combined hyperlipidaemia**

Familial combined hyperlipidaemia occurs in 1 in 250 individuals. It is the most common type of inherited dyslipidaemia and associated with 10% of patients with premature coronary disease. The aetiology is not yet known, and the condition has no unique clinical manifestations that distinguish it from the other inherited

hyperlipidaemic syndromes. The diagnosis is based on raised lipids (greater than 95th centile for age) and a family history of premature coronary disease in first-degree relatives.

### **Familial defective apolipoprotein B-100**

Familial defective apolipoprotein B-100 affects 1 in 500 individuals. All lipids originating from the liver are bound to Apo B-100. The genetic defect of Apo B-100 results in the delayed clearance of cholesterol due to the production of an oxidation-prone LDL that overloads the scavenger pathways.

### **Familial dysbetalipoproteinaemia**

Familial dysbetalipoproteinaemia is also known as Type III hyperlipidaemia or broad beta disease. It is an uncommon disorder affecting 0.04% of people with elevated IDL and chylomicron remnants. This condition is characterised by accumulation of IDL. A characteristic clinical feature is the presence of palmar striae and tuberous xanthomata over the tuberosities of the elbows and knees. The xanthomata can also be found on pressure areas such as the heels

### **Rare familial mixed dyslipidaemias**

*Familial lecithin cholesterol acyltransferase (LCAT) deficiency* - LCAT is the enzyme required for intravascular lipoprotein metabolism. The deficiency is a recessively inherited disorder that results in elevated serum cholesterol and triglyceride levels. Clinically, corneal lipid deposits result in visual disturbances, and renal deposits result in glomerular damage, proteinuria and renal failure.

*Tangier disease* - also known as alpha lipoproteinaemia, or familial alpha lipoprotein deficiency. It is an autosomal recessive condition that results in the deficiency of Apo A-I. The result is low levels of HDL and cholesterol with normal to high levels of triglycerides. Cholesterol accumulation results in enlarged orange-coloured tonsils, hepatosplenomegaly, polyneuropathy and corneal opacities. It is not associated with premature coronary disease.

*Fish eye disease* - Fish eye disease is a rare disorder from northern Sweden characterised by high VLDL, low HDL levels and triglyceride-rich LDL. Hypertriglyceridaemia and dense corneal opacities can occur, giving rise to visual impairment

*Abetalipoproteinaemia* - a rare condition that results in fat accumulation in the intestine due to failure of Apo B-100 production. It results in neurological abnormalities, retinitis pigmentosa and acanthocytosis. Vitamin E injections may prevent the onset of some of the neurological abnormalities.

## Secondary hyperlipidaemias

Secondary dyslipidaemias are relatively common, accounting for up to 20% of patients with hyperlipidaemia. Biochemically, there can be a mixed hyperlipidaemia, or a simple increase in serum cholesterol or triglyceride levels. A number of conditions can result in a secondary hyperlipidaemia (listed below), and management is based upon identifying and treating the underlying disease before treatment of the raised lipid levels. Often, more than one cause is apparent.

Elevated LDL cholesterol	Elevated triglycerides	Reduced HDL cholesterol
Diet (high saturated fats, high calories, anorexia)	Diet (weight gain plus excess alcohol)	Diet (some low fat diets)
Drugs (glucocorticoids, thiazide and loop diuretics, ciclosporin)	Drugs (glucocorticoids, beta-blockers, oestrogen, isotretinoin)	Drugs (anabolic steroids, tobacco, beta-blockers)
Hypothyroidism	Hypothyroidism	Type 2 diabetes
Nephrotic syndrome	Type 2 diabetes	Insulin resistance, obesity
Chronic liver disease	Insulin resistance	Chronic renal failure
Cholestasis plus biliary obstruction	Cushing's syndrome	
Pregnancy	Chronic renal failure	
	Peritoneal dialysis	
	Pregnancy	

## Key Learning Points :



1. The emphasis of management will depend on the cause of the hyperlipidaemia and is aimed at reducing cardiovascular and cerebrovascular risk.
2. Hypercholesterolaemia is defined as elevated total or LDL cholesterol with normal triglyceride levels. Hypertriglyceridaemia is an isolated elevation of triglyceride levels. An elevation of both cholesterol and triglycerides is termed mixed hyperlipidaemia.
3. General management aims to look at diet and activity levels.
4. Medical management involves the use of a range of medications, such as statins and fibrates.
5. Familial hypercholesterolaemia is one of the more common primary hyperlipidaemic disorders, with a frequency of 1 in 500 in Western Europe and North America. The genetic defects are commonly mutations in the LDL receptor gene, resulting high serum LDL levels due to prolonged LDL clearance, from 2.5 to 4.5 days.
6. Patients with familial hypercholesterolaemia have early-onset coronary disease and a standardised mortality ratio 9 times greater than normal population.
7. Secondary dyslipidaemias are relatively common, accounting for up to 20% of patients with hyperlipidaemia. They are related to an underlying physical or pathological condition.