Dyslipidaemia is a spectrum of lipid disorders which includes excessive levels of certain lipoproteins, such as low density lipoprotein cholesterol (LDL-C), or triglycerides; low levels of other lipoproteins, such as high density lipoprotein cholesterol (HDL-C); and abnormalities in the composition of the various lipoprotein particles.

By understanding dyslipidaemia and managing it appropriately clinicians can help to reduce cardiovascular events in patients with, or at risk of, cardiovascular disease. Dyslipidaemia can also predispose patients to other disorders, for example, pancreatitis in the case of hypertriglyceridaemia.

Lipids and lipid transport
Cholesterol and triglycerides are derived from dietary sources or manufactured by the liver. Meats and dairy products are sources of dietary cholesterol and triglycerides; after ingestion, lipids are absorbed and delivered to the liver, where they are processed. At times when dietary lipids are not available (eg, at night) the liver synthesises them.

Cholesterol is essential for a number of biological functions, especially for storing energy. It is also a key constituent of cellular membranes, co-factors for enzymes, signalling molecules, pigments, detergents, transporters, antioxidants and anchors for membrane proteins.

Excess lipids are converted to fats and stored by the body until needed for energy.

The liver distributes cholesterol and triglycerides by forming lipoproteins that deliver them to the rest of the body.

Chylomicrons Chylomicrons transport dietary cholesterol and triglycerides, after intestinal absorption, to different parts of the body. They are the largest of the lipoprotein particles and triglycerides normally constitute around 80% of their lipid core. Triglycerides are catalysed by lipoprotein lipase when chylomicrons pass through capillaries in adipose tissue and skeletal muscle. This forms free fatty acids and glycerol that can pass into the adipose tissue and skeletal muscle. Remnants of chylomicrons, rich in cholesterol, are cleared from the circulation by the liver.

Very low density lipoprotein cholesterol Very low density lipoprotein cholesterol (VLDL-C) is synthesised by the liver and is used to transport triglycerides to the peripheries. Lipoprotein lipase catalyses VLDL-C to release fatty acids and glycerol — leaving behind intermediate density lipoprotein cholesterol (IDL-C). Approximately half of this is cleared by the liver, but the rest is hydrolysed and modified to become LDL-C.
**Low density lipoprotein cholesterol** LDL-C, often referred to as “bad cholesterol” is the main cholesterol transporter lipoprotein. It is also primarily responsible for the development of atherosclerosis. Oxidised LDL-C and monocytes penetrate the endothelium and combine to form cholesterol-rich macrophages that drive the development of atherosclerotic plaques. Therefore, LDL-C is a primary target for cholesterol lowering strategies.

**High density lipoprotein cholesterol** HDL-C, often referred to as “good cholesterol”, mediates the return of lipoprotein and cholesterol to the liver for excretion as biliary cholesterol or bile acids — a process known as reverse cholesterol transport. HDL-C is formed from unesterified cholesterol and phospholipids that are removed from peripheral tissues and the surface of triglyceride-rich proteins. Because HDL-C removes cholesterol from the peripheral tissues and cholesterol-rich macrophages it is considered protective and higher levels are desirable.

**Measuring levels**

The ratio between total cholesterol and HDL-C correlates closely with cardiovascular risk: the greater the total cholesterol level in relation to the HDL-C level, the greater the risk of cardiovascular events. Ideally, the ratio should be less than four, and ratios greater than six are a concern. Measuring these levels only is enough to carry out a cardiovascular risk assessment. Total cholesterol and HDL-C are only marginally affected by food intake; therefore, fasting blood samples are not required for this purpose.

When a full lipid profile is required, ie, when treatment is being considered, a fasting blood sample is preferred. Because serum triglyceride levels increase after the ingestion of a meal, patients should fast for 12–15 hours before the sample is taken. Lipid levels (see Box 1) can be affected by excessive weight loss, recent myocardial infarction, serious illness or pregnancy — in these circumstances, measurements should be postponed for three months. Total cholesterol, HDL-C and triglycerides can be measured directly from a blood sample; however, LDL-C is calculated (in mmol/L) from these values using the Friedewald equation:

\[ LDL-C = (\text{total cholesterol} - \text{HDL-C}) - (0.45 \times \text{triglycerides}) \]

The Friedewald equation is less reliable for individuals with diabetes, is invalid if the serum triglyceride concentration is greater than 4mmol/L and should only be calculated using measurements taken from fasting blood samples.

**Hypertriglyceridaemia**

Hypertriglyceridaemia is often associated with low HDL-C levels, diabetes, hypertension, obesity and excess alcohol consumption. It remains unclear whether or not before the sample is taken. Lipid levels (see Box 1) can be affected by excessive weight loss, recent myocardial infarction, serious illness or pregnancy — in these circumstances, measurements should be postponed for three months. Total cholesterol, HDL-C and triglycerides can be measured directly from a blood sample; however, LDL-C is calculated (in mmol/L) from these values using the Friedewald equation:

\[ LDL-C = (\text{total cholesterol} - \text{HDL-C}) - (0.45 \times \text{triglycerides}) \]

The Friedewald equation is less reliable for individuals with diabetes, is invalid if the serum triglyceride concentration is greater than 4mmol/L and should only be calculated using measurements taken from fasting blood samples.
hypertriglyceridaemia is an independent risk factor for cardiovascular disease when adjusted for other cholesterol disorders, such as low HDL-C, and comorbidities. Although mixed dyslipidaemias, such as high LDL-C associated with high triglycerides, occur commonly in clinical practice, lowering LDL-C remains the aim of treatment. Excessively high triglyceride levels, above 10mmol/L, should be addressed because the risk of cardiovascular disease is thought to be greater at these levels. Furthermore, levels above 20mmol/L predispose patients to pancreatitis.

**Primary dyslipidaemia**

The most common inherited lipid metabolism disorder is heterozygous familial hypercholesterolaemia (FH), which affects one in 500 of the UK population. There are many potential gene mutations that can cause FH and those coding for the LDL-C receptor are among the most common. Patients with FH have high cholesterol levels from birth — rising to up to three times higher than average — and have a substantially higher risk of premature cardiovascular disease. Men with FH are more than 50% more likely to have coronary heart disease by the age of 50 years and women are up to 30% more likely by the age of 60 years, compared with the general population.

FH should be suspected in people who present with total cholesterol of greater than 7.5mmol/L, particularly if there is evidence of premature cardiovascular disease in the family. Patients with FH may also exhibit signs of cholesterol deposition including corneal arcus, tendon xanthoma and xanthelasma. Early identification and treatment of patients with FH is important. Once a patient is diagnosed with FH, cascade screening of his or her family needs to take place. Lipid modification in FH patients is approached differently from general lipid management and is best managed by specialists.

Homozygous FH is an extremely rare metabolic disorder, affecting one in a million of the world’s population. Individuals inherit gene mutations on both chromosomes, resulting in an inability to clear LDL-C particles from the circulation. This can result in very high cholesterol levels and the development of cardiovascular disease at a very young age. Myocardial infarction can occur in children aged as young as two years and patients, if left untreated, have much shorter lifespans — fatal cardiovascular events are common in the late teens and early 20s. Other primary disorders of lipid metabolism include:

- Familial combined hyperlipidaemia — resulting in excessive synthesis of VLDL-C and a predisposition to premature cardiovascular disease
- Familial type III hyperlipoproteinaemia — resulting in accumulation of chylomicrons and IDL, and a predisposition to premature cardiovascular disease
- Familial lipoprotein lipase deficiency — resulting in elevated triglycerides and chylomicron concentrations associated with acute pancreatitis
- Familial apolipoprotein C-II deficiency — resulting in hypertriglyceridaemia and predisposing patients to acute pancreatitis; premature atherosclerosis is unusual but has been reported

High levels of lipoprotein(a), a lipoprotein subclass, are associated with increased cardiovascular risk and appear to have a familial link. A parental history of early onset cardiovascular disease is associated with raised concentrations of lipoprotein(a) that appear to play a role in both atherogenesis and thrombosis. Concentrations over 0.3g/L occur in about 20% of Caucasians and increase the risk of coronary atherosclerosis and stroke. Across a wide range of clinical scenarios there are continuous, independent, and modest associations between lipoprotein(a) concentration and the risk of coronary heart disease and stroke.

**Secondary dyslipidaemia**

Dyslipidaemia can occur secondary to a range of conditions, as a result of poor diet or as a side effect of drug therapy (see Box 2, p194). In most cases, these dyslipidaemias will resolve when the underlying cause is addressed.

**Hypothyroidism** Hypothyroidism reduces LDL-C receptor activity, resulting in elevated LDL-C. Lipoprotein lipase activity is also reduced causing hypertriglyceridaemia and low HDL-C.

**Chronic kidney disease** Dyslipidaemia, usually hypertriglyceridaemia, commonly occurs in patients with chronic kidney disease before and during haemodialysis, or during ambulatory peritoneal dialysis.

**Nephrotic syndrome** Nephrotic syndrome is associated with an overproduction of VLDL-C and LDL-C, and a reduction in HDL-C. Nephrotic syndrome also often necessitates the use of corticosteroids, which may exacerbate the underlying lipoprotein abnormality.

**Obesity** Chronic and excessive intake of calories, as well as accompanying obesity, leads to high concentrations of triglycerides and low HDL-C.

**Alcohol** The high calorie content of many alcoholic drinks can cause obesity and can have an adverse effect on
Box 2: Drugs linked with dyslipidaemia

Medicines that can adversely affect serum lipid and lipoprotein concentrations and cause secondary dyslipidaemia include:

**Diuretics** Thiazide and loop diuretics increase very low density lipoprotein cholesterol (VLDL-C) and low density lipoprotein cholesterol (LDL-C) by mechanisms that are not completely understood. Taking a thiazide diuretic for less than one year has been reported to increase total cholesterol by up to 7%, with no change in high density lipoprotein cholesterol (HDL-C); however, longer-term studies have not shown this relationship. It is unclear whether any adverse effect on lipids negates the overall benefits of managing blood pressure with diuretics.

**Beta-blockers** Beta-blockers increase triglycerides and reduce HDL-C with little effect on LDL-C. The relevance of these effects is unclear.

**Oestrogen** Oestrogen-containing oral contraceptives and hormone replacement therapy can cause a slight increase in the hepatic production of VLDL-C and HDL-C, and reduce LDL-C levels. In contrast, progestogens increase LDL-C and reduce serum HDL-C and VLDL-C.

**Corticosteroids** Administration of corticosteroids, such as prednisolone, has been shown to increase total cholesterol and triglycerides by elevating LDL-C and, less consistently, VLDL-C. The changes are generally more pronounced in women. Alternate-day corticosteroid therapy has been suggested to reduce this adverse effect on lipoprotein levels.

**Ciclosporin** Ciclosporin has been associated with increased LDL-C levels that are often exacerbated by the concurrent administration of corticosteroids.

**Enzyme inducers** Medicines such as carbamazepine, phenytoin, phenobarbital, rifampicin and griseofulvin increase hepatic enzyme activity — causing a rise in serum HDL-C. Administration of these drugs may also slightly increase LDL-C and VLDL-C.

lipids. In addition, alcohol increases hepatic triglyceride synthesis, causing hypertriglyceridaemia.

**Cardiovascular risk**

Addressing cardiovascular risk is a primary concern when treating patients with dyslipidaemia. Some patients are managed aggressively, such as those with familial hyperlipidaemias, because these disorders are strongly linked to premature cardiovascular events. National Institute for Health and Care Excellence guidance for FH sets out strategies for managing such patients.

Patients with established cardiovascular disease or diabetes should also receive treatment to lower cholesterol once a diagnosis has been established.^

Primary prevention should be directed by a full cardiovascular risk assessment, which calculates a patient's 10-year risk of developing cardiovascular disease. Tools such as the modified Framingham risk score or the QRisk calculator assess the global risk of cardiovascular disease for an individual. These tools consider patients' blood pressure, age, gender, smoking status and other cardiovascular risk factors, including cholesterol levels. For patients with a 10-year cardiovascular risk of at least 20%, lipid lowering treatment is recommended.^

In England, the NHS Health Check programme offers a vascular risk assessment every five years to all people between 40 and 74 years to identify patients who have a high risk of developing cardiovascular disease.^

**References**


**How to undertake CPD**

**Reflect on your gaps in knowledge**
- How does the body transport lipids?
- What types of dyslipidaemia can occur and how are they characterised?
- How is dyslipidaemia treated?

**Act to enhance your practice**
- Read the CLINICAL FOCUS articles in this issue (pp189–99).
- Test your knowledge by completing the module at www.clinicalpharmacist.com

**Evaluate the activity**
- What have you learnt?
- How has it added value to your practice?
- What will you do now and how will this be achieved?