Hyperlipidaemia

Hyperlipidaemia is the term used to denote raised serum levels of one or more of total cholesterol (TChol), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), or both TChol and TG (combined hyperlipidaemia).

Dyslipidaemia is a wider term that also includes low levels of high-density lipoprotein cholesterol (HDL-C)\(^1,2\). Many types of hyperlipidaemia carry an increased risk of cardiovascular disease (CVD). HDL-C confers protection. It is important as one of the three main modifiable risk factors for CVD (the others being smoking and hypertension).

**Epidemiology\(^1\)**

- The UK population has one of the highest average serum cholesterol levels in the world.
- Two thirds of the UK population have a serum cholesterol level greater than 5.2 mmol/L.
- Low levels of HDL-C are often associated with raised TG levels (eg, in familial combined hyperlipidaemia and in dyslipidaemia in type 2 diabetes).
- Heterozygous familial hypercholesterolaemia is one of the most common familial conditions, with a prevalence of about 1 in 500. Homozygous familial hypercholesterolaemia is rare\(^3\).
- Of the theoretical estimated prevalence of 1/500 for heterozygous familial hypercholesterolaemia, less than 1% are diagnosed in most countries\(^4\).

**Aetiology\(^{[3,5]}\)**

See the separate article on **Prevention of Cardiovascular Disease**.

**Inherited disorders**

- Familial dyslipidaemias.
- Familial hypercholesterolaemia
- Familial combined hyperlipidaemia.
- Apoprotein disorders - see the separate article on **Apolipoproteins** for further details.

**Editor's Note**

**Nov 2017** - Dr Hayley Willacy recommends the recently updated NICE guidelines on familial hypercholesterolaemia\(^6\). They advise suspecting familial hypercholesterolaemia (FH) as a possible diagnosis in adults with a total cholesterol level greater than 7.5 mmol/L and/or a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative). Primary care records should be systematically searched for people younger than 30 years, with a total cholesterol concentration greater than 7.5 mmol/L and those 30 years or older, with a total cholesterol concentration greater than 9.0 mmol/L. These are the people who are at highest risk of FH. People with a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative), whose total cholesterol is unknown, should be offered a total cholesterol measurement.

**Secondary causes**

- Medical conditions - eg, hypothyroidism, obstructive jaundice, Cushing's syndrome, anorexia nervosa, nephrotic syndrome, diabetes mellitus, and chronic kidney disease.
- Drugs - eg, thiazide diuretics, glucocorticoids, ciclosporin, antiretroviral therapy, beta-blockers, combined oral contraceptive pill, atypical antipsychotics, and retinoic acid derivatives.
- Pregnancy.
- Obesity.
- Alcohol abuse.

**Assessment\(^{[5]}\)**

See also the separate article on **Cardiovascular Risk Assessment**.

- Measure both TChol and HDL-C to achieve the best estimate of CVD risk.
- Before starting lipid modification therapy for the primary prevention of CVD, take at least one lipid sample to measure a full lipid profile. This should include measurement of TChol, HDL-C, non-HDL-C and TG concentrations. A fasting sample is not needed.
- Use the clinical findings, lipid profile and family history to judge the likelihood of a familial lipid disorder rather than the use of strict lipid cut-off values alone.
Exclude possible common secondary causes of dyslipidaemia (eg, excess alcohol, uncontrolled diabetes, hypothyroidism, liver disease and nephrotic syndrome) before referring for specialist review.

Consider the possibility of familial hypercholesterolaemia if:
- TChol concentration is more than 7.5 mmol/L; and
- There is a family history of premature coronary heart disease (CHD).

Arrange for specialist assessment of people with a TChol concentration of more than 9.0 mmol/L or a non-HDL-C concentration of more than 7.5 mmol/L even in the absence of a first-degree family history of premature CHD.

Refer for urgent specialist review if a person has a TG concentration of more than 20 mmol/L that is not a result of excess alcohol or poor glycaemic control.

In people with a TG concentration between 10 and 20 mmol/L:
- Repeat the TG measurement with a fasting test (after an interval of five days, but within two weeks); and
- Review for potential secondary causes of hyperlipidaemia; and
- Seek specialist advice if the TG concentration remains above 10 mmol/L.

In people with a TG concentration between 4.5 and 9.9 mmol/L:
- Be aware that the CVD risk may be underestimated by risk assessment tools; and
- Optimise the management of other CVD risk factors present; and
- Seek specialist advice if non-HDL-C concentration is more than 7.5 mmol/L.

Presentation\textsuperscript{[1, 3, 5]}

The condition is often diagnosed during routine screening, as part of a risk assessment associated with comorbidities or other risk factors (eg, obesity, smoking), or the patient may present as a relative of an index case with premature CVD. Rarely, there may be a genetic cause. Most familial dyslipidaemias go undiagnosed but, if identified, can enable more effective prevention and treatment in individuals and their families - where suspected, refer to secondary care.

Although the diagnosis is primarily biochemical, two physical signs may be evident in patients with familial hypercholesterolaemia:
- Premature arcus senilis - a white or gray opaque ring in the corneal margin\textsuperscript{[7]}
- Tendon xanthomata - these are hard, non-tender nodular enlargement of tendons. They are most commonly found on the knuckles and the Achilles tendons.

**Familial hypercholesterolaemia\textsuperscript{[3]}**

Suspect familial hypercholesterolaemia where:
- Adults have a raised TChol concentration (typically >7.5 mmol/L) and there is a personal or family history of premature CHD.
- Rule out secondary causes of hypercholesterolaemia.
- Do not rule out familial hypercholesterolaemia simply because physical signs such as tendon xanthomata are not present.
- Make a diagnosis using the Simon Broome criteria (see below).
- Check two fasting LDL-C measurements to confirm the diagnosis.

**The Simon Broom diagnostic criteria\textsuperscript{[3]}**

**Definite** familial hypercholesterolaemia is diagnosed if an individual has:
- A TChol level in an adult of >7.5 mmol/L (>6.7 mmol/L in a child) and an LDL-C of >4.9 mmol/L (>4.0 mmol/L in a child); PLUS
- Tendon xanthomata or evidence of these signs in a first-degree or second-degree relative; OR
- DNA evidence of an LDL receptor mutation, familial defective apo-B-100 or a PCSK9 mutation.

**Possible** familial hypercholesterolaemia should be diagnosed if the cholesterol concentrations fit these criteria and the individual has at least one of the following:
- A family history of myocardial infarction in a second-degree relative aged 50 years or younger, or in a first-degree relative aged 60 years or younger.
- A family history of raised TChol greater than 7.5 mmol/L in adult first-degree or second-degree relatives or greater than 6.7 mmol/L in a child, brother or sister aged younger than 16 years.

**Familial combined hyperlipidaemia**

This is the most common genetic dyslipidaemia, occurring in about 1 in 100 people but is usually polygenic in origin.

Lipid phenotypes in familial combined hyperlipidaemia vary considerably but suspect where:
- There is family history of hyperlipidaemia or premature CHD not due to familial hypercholesterolaemia.
- Moderate-to-severe mixed hyperlipidaemia (typically TChol 6.5-8.0 mmol/L and TG 2.3-5.0 mmol/L).

Before considering pharmacological treatment of dyslipidaemias, always try to identify and correct/optimise any secondary or contributory causes.
Investigations

- Lipid profile: includes TChol, LDL-C (or non-HDL-C), HDL-C and TGs. Triglycerides rise dramatically after a meal so a fasting sample is required.
- Fasting blood glucose: this should be done to exclude hyperlipidaemia secondary to diabetes mellitus.
- Renal function: this should be done to exclude chronic kidney disease.
- LFTs (transaminases): to rule out liver disease in the event of a statin having to be initiated (raised transaminases should not preclude the use of a statin if levels are less than three times the upper limit of normal).
- TSH: this should be done if dyslipidaemia is present, to exclude myxoedema.

Further investigations may be required if an underlying cause of hyperlipidaemia is suspected.

DNA testing[^3]

People with a clinical diagnosis of familial hypercholesterolaemia should be offered a DNA test to increase the certainty of their diagnosis and to aid diagnosis among their relatives.

Children[^3]

In children at risk of familial hypercholesterolaemia because of one affected parent, the following diagnostic tests should be carried out by the age of 10 years or at the earliest opportunity.

- A DNA test if the family mutation is known.
- LDL-C concentration measurement if the family mutation is not known. When excluding a diagnosis of familial hypercholesterolaemia, a further LDL-C measurement should be repeated after puberty because LDL-C concentrations change during puberty.

Management[^5]

The aim of treating hyperlipidaemia is to prevent or reduce the risk and complications of CVD. Such risk reduction includes non-drug measures (such as addressing lifestyle factors) and drug treatment using lipid-lowering therapy.

It should be noted that cardiovascular risks exceeding the 5-10% level may be found in elderly gentlemen based on age (and gender) only, even when other cardiovascular risk factor levels are relatively low. This could lead to excessive usage of drugs in the elderly and should be evaluated carefully by the clinician.

See the separate article on Prevention of Cardiovascular Disease and the Lipid-regulating Drugs article, which includes using fibrates in primary care.

Plasmapheresis, generally in combination with additional pharmacological treatment, is a proven option in the management of homozygous hyperlipidaemia[^8].

Complications

- The INTERHEART study suggested that 45% of heart attacks in Western Europe are due to abnormal blood lipids[^9].
- People with heterozygous familial hypercholesterolaemia have a four-fold increased risk of CHD[^10].
- People with familial combined hyperlipidaemia also have an increased risk of CHD, but CHD usually only presents after the age of 60 years[^3].
- Very severe hypertriglyceridaemia (more than 10 mmol/L) is a risk factor for pancreatitis.
- Decreased levels of serum HDL-C are also an independent risk factor for CHD[^11].
Indications for referral [3, 5]

- Suspected familial hypercholesterolaemia:
  - Offer referral to a lipid specialist if:
    - Confirmation of diagnosis is needed or cascade testing (a method of identifying whether a person is at risk of a genetic condition, by a process of family contact tracing).
    - A child or young person needing investigation for familial hypercholesterolaemia or who has been diagnosed with familial hypercholesterolaemia.
    - An adult with familial hypercholesterolaemia is at very high risk of a coronary event because they have established CHD, a family history of premature CHD or two or more other cardiovascular risk factors (eg, male gender, smoking, obesity, diabetes).

- Offer referral to a cardiologist if:
  - A person has been diagnosed with homozygous familial hypercholesterolaemia (suspect adults with an LDL-C concentration greater than 13 mmol/L, children/young people with an LDL-C concentration greater than 11 mmol/L).
  - A person with familial hypercholesterolaemia has symptoms or signs of possible CHD (refer urgently unless immediately life-threatening, in which case refer as an emergency).

- Asymptomatic children or young people with heterozygous familial hypercholesterolaemia do not routinely need to be referred.

  - Suspected familial combined hyperlipidaemia, ie mixed hyperlipidaemia and a family history of hyperlipidaemia or premature CHD.
  - Failure of therapy: failure to meet target lipid reduction despite maximally tolerated therapy.
  - Severe hypercholesterolaemia: initial TChol greater than 10 mmol/L.
  - Very severe hypertriglyceridaemia: TGs greater than 10 mmol/L.

Further reading & references

- 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias; European Society of Cardiology (2016)
- Familial hypercholesterolaemia; NICE Quality standards (Aug 2013)
- Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia; NICE Technology Appraisal Guidance, June 2016
- Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia; NICE Technology Appraisal Guidance, June 2016

2. European guidelines on cardiovascular disease prevention in clinical practice; European Society of Cardiology (2012)
3. Identification and management of familial hypercholesterolaemia; NICE Clinical Guideline (August 2008 - last updated July 2016)
5. Lipid modification - cardiovascular risk assessment and the modification of blood lipids for the prevention of primary and secondary cardiovascular disease; NICE Clinical Guideline (July 2014)

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