Ministry of Defence

Synopsis of Causation

Hyperlipidaemia

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. Hyperlipidaemia is the term used to denote raised serum levels of one or more of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), or both TC and TG (combined hyperlipidaemia).[1]

1.2. Dyslipidaemia is a wider term that also includes low levels of high-density lipoprotein cholesterol (HDL-C).

1.3. Many types of hyperlipidaemia carry an increased risk of cardiovascular disease. HDL-C ("good cholesterol") however, confers protection.

1.4. Generally the risk of cardiovascular disease rises as the ratio of TC to HDL-C rises.[1]

2. Clinical Features

2.1. Dyslipidaemia is mostly asymptomatic. A high total serum cholesterol or low HDL-C may be identified on screening patients, especially those who have a family history of first degree relatives who have died at a young age with a heart attack or stroke.[2]

2.2. Patients who have dyslipidaemia usually present with established cardiovascular disease. This includes:

- Angina pectoris
- Myocardial infarction (heart attack)
- Stroke
- Peripheral vascular disease, including claudication and transient ischaemic attacks

2.3. A variety of systemic diseases may cause dyslipidaemia as a secondary feature. In such situations, the clinical features of the underlying disease will predominate, as follows:

- Diabetes: excessive thirst and urination, weight loss, cardiovascular disease, recurrent infections and visual disturbances
- Excess alcohol: signs of chronic liver disease
- Obesity
- Hypothyroidism: weakness, lethargy, cold intolerance, weight gain
- Liver disease: jaundice, gallstones
- Renal failure: anaemia, polyuria, electrolyte disturbances
- Nephrotic syndrome: proteinuria and oedema
- Medications: oral contraceptives, beta-blockers (used to treat hypertension), ciclosporin
- Anorexia nervosa/starvation
- Pregnancy

2.4. Very high triglyceride concentrations (> 11 mmol/L) can themselves increase the risk of developing acute pancreatitis,[3] which presents with acute onset of severe central abdominal pain often radiating to the back, shock, and abdominal skin discolouration. Even with treatment, acute pancreatitis is a potentially fatal condition.

2.5. Irrespective of the cause of the hyperlipidaemia, a small proportion of patients may exhibit xanthelasma or premature corneal arcus. However, the presence of tendon xanthomata is diagnostic of familial hypercholesterolaemia (FH).[4]

3. Aetiology

3.1. Conventionally, the causes of hyperlipidaemia are classified into primary and secondary.

3.2. **Primary dyslipidaemias.** These are inherited disorders of lipoprotein metabolism and are associated with abnormally high cholesterol and/or triglycerides, or low HDL cholesterol, or abnormal composition of lipoproteins.

3.3. The clinically important primary hyperlipidaemias are mentioned below:[2]

3.3.1. **Familial hypercholesterolaemia (FH).** This is the most severe of the hyperlipidaemias with respect to the propensity of affected individuals to develop atherosclerosis. Heterozygous FH has a frequency of about 1 in 500 of the population. It manifests as marked hypercholesterolaemia (raised LDL-C) and premature cardiovascular disease (often < 55 years of age). Tendon xanthomata in the Achilles tendon and the extensor tendons of the digits occur in approximately 70% of untreated patients and are pathognomonic of FH. Homozygous FH has a frequency of less than 1 in 1,000,000. It is associated with severe manifestations of hyperlipidaemia and the onset of cardiovascular disease in the first 2 decades of life.

3.3.2. **Common (polygenic) hypercholesterolaemia** is much more common in the UK. The frequency with which it is diagnosed will depend on what is taken as the upper cut off for a "normal" cholesterol. Thus, if a cut off of 5.2mmol/L is used, then nearly two-thirds of people will be classified as hypercholesterolaemic! In the overwhelming majority of patients, the Western lifestyle of a high-fat diet superimposed on a susceptible genotype appears to cause the hypercholesterolaemia.

3.3.3. **Familial hypertriglyceridaemia (FHTG)** has been demonstrated in certain large kindreds. The majority of the affected individuals have moderately raised triglyceride concentrations. Severe hypertriglyceridaemia usually results from a concomitant secondary cause superimposed on a primary inherited defect.

3.3.4. **Chylomicronaemia syndrome** manifests as eruptive xanthomata, lipaemia retinalis, recurrent bouts of abdominal pain including acute pancreatitis, and enlargement of the liver and spleen. A fasting blood sample shows lipid particles floating on top (especially after leaving the sample overnight).

3.3.5. **Familial combined hyperlipidaemia** is suggested by the finding of a raised cholesterol and/or triglycerides in 2 or more first degree relatives (provided other lipoprotein disorders have been excluded). It affects about 1% of the population.

3.4. **Secondary dyslipidaemias**. The commonest causes of this in clinical practice are obesity, diabetes and excess alcohol. The causes are summarised in Table 1 below. [4,5]

TABLE 1. Causes of secondary dyslipidaemias

Lipid abnormality	Cause
Hypercholesterolaemia	Diet Hypothyroidism Obstructive jaundice Anorexia nervosa Nephrotic syndrome Drugs: ciclosporin
Hypertriglyceridaemia	Obesity/diet Diabetes Alcohol abuse Hepatitis Pregnancy Renal failure Drugs: some oral contraceptives, beta-blockers (used to treat hypertension), isotretinoin (used to treat acne), protease inhibitors (used to treat AIDS)
Combined hypercholesterolaemia and hypertriglyceridaemia	Pregnancy Drugs: some oral contraceptives, corticosteroids, high doses of thiazides (used to treat hypertension) Multiple myeloma Some individuals with type 2 diabetes mellitus and obesity

3.5. **Diet and obesity**. Most elevations of cholesterol and/or triglyceride are modest and are due primarily to dietary excess. Hypertriglyceridaemia, glucose intolerance, hyperinsulinism and cardiovascular disease are all commonly associated with obesity. HDL-C is also low, being inversely correlated with body weight, and rises with weight reduction. Total cholesterol and LDL-C concentration may be normal but turnover studies show increased rate of synthesis.[6]

3.5.1. Subclinical genetic abnormalities may be brought to light by superimposed secondary causes. However, in day-to-day life, the commonest cause of dyslipidaemia is a diet high in saturated fats and refined sugars and lacking in complex carbohydrates (such as wholemeal breads, pasta and low-fat yogurts) and fresh fruits and vegetables. This is supported by Scottish observational data showing an association between low intake of fruit and vegetables and the prevalence of coronary heart disease (CHD).[7] For those who are able to make the necessary dietary changes, the benefits may be considerable.

3.6. **Diabetes mellitus**. Untreated/inadequately treated diabetes results in marked hypertriglyceridaemia. This is partly due to an absolute or relative deficiency of insulin and partly due to increased release of fatty acids from adipose tissue.

3.7. **Alcohol excess.** This is a common cause of raised triglycerides, especially in males. It is most marked in individuals with pre-existing inherited disorders and is enhanced by concomitant consumption of fat.

4. Prognosis

4.1. The UK population has one of the highest average serum cholesterol levels in the world. For men aged between 45 and 75 years, the median serum cholesterol is 6.2mmol/L. For women aged 45-55 years, it is 6.1mmol/L, and it is 6.8mmol/L for women aged over 55 years.[1]

4.2. Familial hypercholesterolaemia is the most important clinical syndrome leading to premature coronary heart disease. It results in a four-fold increased risk of coronary heart disease. Men are at greater risk than women are, and if untreated, 50-70% will have a myocardial infarction by the age of 60 years.

4.3. About 46% of deaths due to coronary heart disease may be attributable to raised serum cholesterol.[8]

4.4. A raised serum triglyceride level is an independent risk factor for coronary heart disease. People with both raised triglycerides and cholesterol are at greater risk than are people who just have raised cholesterol.

4.5. Decreased levels of serum HDL-C are also an independent risk factor for coronary heart disease.

4.6. Treatment for dyslipidaemia depends on the type and severity. For example, the objective of treating those with chylomicronaemia is to reduce triglyceride levels sufficiently to prevent the occurrence of acute pancreatitis. On the other hand, the main reason for treating high total cholesterol or low HDL-C is to minimise the risk of cardiovascular disease.[3]

4.7. Dietary modification is the cornerstone of any lipid-lowering regimen. Diet alone may be successful in controlling hyperlipidaemia. Ideally, dietary advice should be provided by a qualified dietician or nutritionist. Diet can reduce both cholesterol and triglyceride levels.

4.8. Other appropriate measures to reduce cardiovascular risk include weight reduction, regular physical exercise, and additional measures such as cessation of smoking, and blood pressure and blood glucose control.

4.9. Drug treatment focuses on the use of statins (which predominantly lower total cholesterol and LDL-C) and fibrates (which mainly lower the triglyceride levels and also help to raise HDL-C). Drug therapy should be medically supervised as it can rarely give rise to potentially fatal muscle inflammation and abnormalities of liver function.[9]

4.10. Newer drugs (for patients intolerant or unresponsive to statins) have been developed, which mainly inhibit the absorption of cholesterol from the gut.

4.11. Lipid-lowering therapy reduces the risk of CHD in high-risk individuals. Clinical trials have shown reductions of about 30% in relative risk of CHD events and 20% for relative risk of death.[4, 10-12]

5. Summary

5.1. Dyslipidaemia is a term used to denote raised serum levels of cholesterol or triglycerides or both, or reduced HDL cholesterol. Dyslipidaemia carries an increased risk of cardiovascular disease.

5.2 It may be classified into primary hyperlipidaemia (due to inherited disorders in the metabolism of lipoproteins) or secondary hyperlipidaemia (commonly due to obesity, diabetes mellitus or alcohol excess).

5.3 The UK population has one of the highest average serum cholesterol levels in the world. If a cut-off of 5.2mmol/L is used, then nearly two-thirds of people will be classified as hypercholesterolaemic!

5.4 Management of dyslipidaemia involves dietary modification, regular physical exercise, cessation of smoking, control of hypertension and blood glucose, and drug treatment to lower cholesterol and/or triglycerides.

5.5 Lipid-lowering therapy significantly reduces the risk of coronary heart disease in high-risk individuals.

6. Related Synopses

Atherosclerosis

Diabetes Mellitus

7. Glossary

angina pectoris	Retrosternal chest pain, which often radiates to the left arm and may be associated with shortness of breath. It is relieved by rest and treatment by nitrates and worsened by exertion.
anorexia nervosa	A serious eating disorder primarily of young women that is characterised especially by a pathological fear of weight gain leading to faulty eating patterns, malnutrition and, usually, excessive weight loss.
chylomicronaemia	The presence of an increased number of chylomicrons (a type of triglyceride-rich lipoprotein) in the bloodstream.
corneal arcus	A whitish ring-shaped or bow-shaped deposit in the cornea that frequently occurs in older age.
HDL-C	A lipoprotein of blood plasma that is composed of a high proportion of protein with lower levels of triglyceride and cholesterol.
hyperinsulinism	The presence of high serum concentrations of insulin.
hypothyroidism	Underfunctioning of the thyroid gland.
LDL-C	A lipoprotein of blood plasma that is composed of a moderate proportion of protein with little triglyceride and a high proportion of cholesterol.
multiple myeloma	A malignancy of B-cells found in bone marrow and usually associated with high serum immunoglobulin concentrations.
nephrotic syndrome	An inflammatory condition of the kidney, which results in abnormal losses of protein in the urine, low serum protein concentrations and oedema.
pancreatitis	Inflammation of the pancreas.
pathognomonic	A disease characteristic that indicates with certainty the presence of that disease.
peripheral vascular disease	Vascular disease affecting blood vessels outside of the heart and especially those vessels supplying the extremities.
polygenic	A disease with multifactorial causation.
renal	Pertaining to the kidney.

statins	A group of drugs that decrease synthesis of cholesterol by the liver.
triglycerides	Any of a group of lipids that are formed from glycerol and fatty acids. Triglycerides are widespread in adipose tissue and commonly circulate in the blood in the form of lipoproteins, particularly chylomicrons and very low density lipoprotein (VLDL), also called neutral fat.
xanthoma (*pl.* –mata)	A fatty irregular yellow patch or nodule containing lipid-filled cells that occurs on the skin (as of the eyelids, neck, or back) or in internal tissue. Xanthomata are associated especially with disturbances of lipid metabolism.
xanthelasma	A xanthoma of the eyelid.

8. References

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