Hyperlipidaemia

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Abstract

Hyperlipidaemia includes hypercholesterolaemia, hypertriglyceridaemia and mixed hyperlipidaemia. It is a common biochemical disorder with primary (inherited) and secondary causes. All patients should be investigated for possible secondary causes. Hypercholesterolaemia is commonly polygenetically inherited, whereas familial hypercholesterolaemia is monogenic and has a high risk of cardiovascular disease (CVD). Evidence of CVD risk in hypertriglyceridaemia is weaker than in hypercholesterolaemia, but concentrations >10.0 mmol/litre are associated with a high risk of acute pancreatitis. The primary screening test is serum fasting full lipid profile. Serum apolipoproteins (Apo-A1, Apo-B), lipoprotein (a) and highly sensitive C-reactive protein can be useful in patients with unusual or borderline CVD risk. Management includes treating secondary causes and optimizing modifiable risk factors including lifestyle. Assessing 10-year CVD risk is always recommended before starting treatment in primary prevention, whereas treatment is always indicated in patients with established CVD risk. Statins are the first-line treatment in hypercholesterolaemia; the treatment target depends on the individual's CVD risk. In hypertriglyceridaemia, statins are first-line therapy for a concentration <6.0 mmol/litre, but fibrates and/or high-dose fish oils should be considered for concentrations >6.0 mmol/litre. Hypertriglyceridaemia >10.0 mmol/litre indicates fibrates and a very low-fat diet. A statin–fibrate combination can be used in mixed hyperlipidaemia.

Keywords Cardiovascular disease; hypercholesterolaemia; hyperlipidaemia; hypertriglyceridaemia; MRCP; statins

Key points

- In all patients with hyperlipidaemia, potential secondary causes should be checked and treated appropriately
- The decision to treat in primary prevention (i.e. patients with no past history of cardiovascular disease (CVD)) should be based on formal CVD risk assessment using recommended risk equations
- Risk assessment tools should not be used in patients who have a high CVD risk and need lipid-lowering treatment
- Statins are first-line treatment for hypercholesterolaemia; muscle symptoms are a recognized adverse effect
- Raised triglycerides can cause acute pancreatitis; the risk is significantly high when concentrations are >10 mmol/litre

Definition

Hyperlipidaemia is a condition in which serum cholesterol (hypercholesterolaemia), triglycerides (TGs or triacylglycerols; hypertriglyceridaemia) or both (mixed hyperlipidaemia) are abnormally elevated. The curvilinear association between cardiovascular disease (CVD) and high cholesterol, especially low-density lipoprotein cholesterol (LDL-C), is well established and independent of other risk factors.

Pathogenesis

Lipid is transported in the circulation by different lipoproteins. These contain specific apolipoproteins that bind enzymes, or receptors to facilitate lipid transfer to body tissues. Dietary TGs are transported by chylomicrons from the gut to the liver. The liver secretes very low-density lipoproteins (VLDLs) containing apolipoprotein B100 (Apo-B100). As TGs are removed from VLDL to muscle and adipose tissues, these become denser, ultimately becoming pro-atherogenic low-density lipoproteins (LDLs). Apo-B100 is the main apolipoprotein needed for LDL uptake by the liver. When LDL concentrations are high, non-receptor uptake of LDL by scavenger cells becomes significant and results in the formation of atherosclerotic plaques, leading to CVD.

High-density lipoprotein (HDL) contains Apo-A1, which aids the removal of unesterified cholesterol from the circulation; HDL concentrations are inversely associated with development of CVD.[1] Causes of low HDL include metabolic syndrome, obesity, sedentary lifestyle, smoking, drugs such as β-adrenoceptor blockers, thiazides, androgens and genetic causes. HDL concentrations can be increased by physical activity, cessation of smoking, oestrogen and alcohol intake.

The causes of hyperlipidaemia (Table 1) can be divided broadly into primary (familial) and secondary. Hypercholesterolaemia is frequently polygenetically inherited, whereas familial hypercholesterolaemia (FH) is monogenic and inherited in an autosomal dominant pattern; it is most commonly caused by an LDL-receptor mutation (heterozygote frequency approximately 1 in 500).[2] Individuals with FH have a significantly higher risk of premature CVD.

Severe hypertriglyceridaemia (>10 mmol/litre) can be seen in poorly controlled diabetes mellitus and alcohol abuse, and carries a risk for acute pancreatitis.

Diagnosis

Patients frequently present with an abnormal lipid profile detected on screening and no symptoms. The medical history should include:

- personal history of CVD
- relevant medical history (e.g. hypertension, diabetes mellitus, HIV infection, vasculitides)

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Primary and secondary causes of hyperlipidaemia

Primary hyperlipidaemia	Lipid abnormalities	Secondary hyperlipidaemia	Lipid abnormalities
Lipoprotein lipase deficiency	Chylomicrons ↑ Triglycerides ↑	Chronic renal failure	LDL-C normal or ↑ Triglycerides ↑
FH[a]	LDL-C ↑	Nephrotic syndrome	LDL-C ↑
Familial defective Apo-B100	LDL-C ↑	Liver disease[a] Intrahepatic cholestasis	LDL-C ↑
Polygenic hypercholesterolaemia	LDL-C ↑	Anorexia nervosa	
Remnant hyperlipoproteinaemia	LDL-C ↑ Triglycerides ↑	Diabetes mellitus	VLDL ↑ Triglycerides ↑
Familial combined hyperlipidaemia	LDL-C ↑ VLDL ↑ Triglycerides ↑	Hypothyroidism	VLDL ↑ Triglycerides ↑
Familial hypertriglyceridaemia	Chylomicrons ↑ VLDL ↑ Triglycerides ↑	Obesity	VLDL ↑ Triglycerides↑
		Excessive alcohol ingestion	VLDL ↑ Triglycerides ↑
		Storage disease (Gaucher's disease, glycogen storage disease, Niemann–Pick disease)	
		Medications: glucocorticoids, anabolic steroids, progestins, protease inhibitors,[a] thiazide diuretics, retinoids, tamoxifen, β-adrenoceptor blockers, non-nucleoside reverse transcriptase inhibitors,[a] nucleoside reverse transcriptase inhibitors,[a] immunoglobulins, olanzapine	Triglycerides ↑
		Medications: (sirolimus[a], ciclosporin, anti-epileptics)	LDL-C ↑

[a] Patients should be referred to specialist lipid clinics if there is suspected FH (including in children) and other genetic hyperlipidaemias, significant abnormal pre-treatment liver enzymes and secondary dyslipidaemia related to transplantation or HIV disease.

Table 1

- family history of premature CVD and hyperlipidaemias
- history of lipid-lowering therapy and other medications
- lifestyle (exercise/physical activity, diet, smoking, alcohol ingestion).

A full cardiovascular assessment should be carried out and clinical signs of hyperlipidaemia sought. Tendon xanthomas (hands, elbows, knees, Achilles tendons), xanthelasmas and corneal arcus can be associated with hypercholesterolaemia, whereas xanthomas over the buttocks, elbows and trunk can be seen with severe hypertriglyceridaemia.

Investigations

- **Fasting full lipid profile** – this comprises serum total cholesterol (TC), TG, LDL-C and HDL-cholesterol (HDL-C). TC, TG and HDL-C are measured directly, but LDL-C is calculated using the Friedewald equation: TC – (HDL + (TG/2.2)), with all values in mmol/litre. Estimated LDL-C becomes inaccurate with serum TG >4.5 mmol/litre. However, the newest recommendation is to use calculated non-HDL-cholesterol (TC minus HDL-C) in preference to LDL-C as a treatment target because the former has shown to have a better predictive value for CVD and fasting is not needed.[3]
- **Exclude potential causes of secondary hyperlipidaemia** (Table 1) – test renal, thyroid and liver function, glycated haemoglobin, fasting glucose and urine for proteinuria.
- **Apolipoproteins** – Apo-B concentration represents total atherogenic particles including LDL. It is considered to be helpful in assessing CVD risk in patients with a borderline or unusual risk of CVD or with raised TGs. In these patients, LDL-C alone could underestimate the true atherogenic burden. Apo-B is less subject to laboratory errors than LDL-C. Although these measurements are currently not widely available in clinical laboratories, where measured, an Apo-B concentration <0.9 g/litre should be the target for treatment of patients with a high risk of CVD.[4] Serum Apo-A1 can identify the actual number of HDL particles in patients with low HDL-C.
- **Serum creatine kinase** – this is useful when assessing statin-induced muscle symptoms. Baseline measurement before starting statin treatment is generally not needed in patients with no muscle symptoms.[3]