

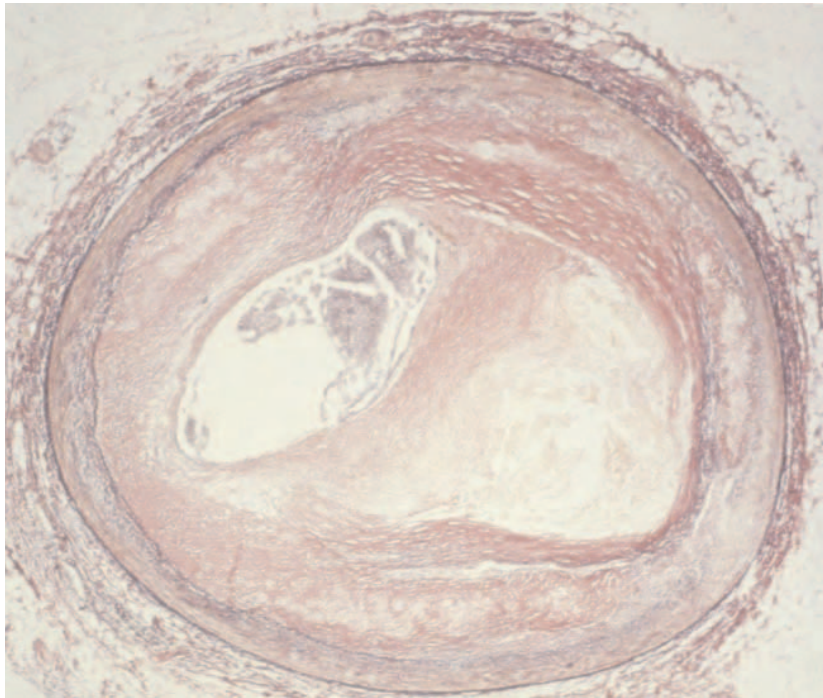
Fast Facts



Fast Facts: Hyperlipidemia

Allan Sniderman and Paul Durrington

Fifth edition





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Declaration of Independence

This book is as balanced and as practical as we can make it.
Ideas for improvement are always welcome: feedback@fastfacts.com

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Glossary

Android obesity: male-pattern obesity, characterized by increased accumulation of abdominal adipose tissue

ApoAI: apolipoprotein AI, the major apolipoprotein in HDL

ApoB₄₈: gut apolipoprotein B (its molecular weight is 48% of that of apoB₁₀₀)

ApoB₁₀₀: hepatic apolipoprotein B

Apolipoproteins: structural proteins, often containing receptor-binding sites

ARH: autosomal recessive hypercholesterolemia

ATPIII: Third Adult Treatment Panel of the NCEP (USA)

β-VLDL: chylomicron remnants and intermediate-density lipoprotein

CETP: cholesteryl ester transfer protein, which catalyzes transfer of cholesterol from HDL to circulating triglyceride-rich lipoproteins, and from LDL back to VLDL

CHD: coronary heart disease

Cholesteryl ester: esterified cholesterol, which is more hydrophobic than free cholesterol

CVD: cardiovascular disease

FCHL: familial combined hyperlipidemia

FDB: familial defective apoB

FH: familial hypercholesterolemia

Foam cell: a cell, usually a macrophage, the cytoplasm of which has become loaded with cholesterol

Gynoid obesity: female-pattern obesity, characterized by increased depots in the buttocks and other peripheral sites

HDL: high-density lipoprotein

HyperapoB: hyperapobetalipoproteinemia, raised apoB in the absence of a raised LDL cholesterol level

IDL: intermediate-density lipoprotein

LCAT: lecithin–cholesterol acyl transferase, which catalyzes the esterification of free cholesterol

LDL: low-density lipoprotein

Lipemia retinalis: pallor of the optic fundus and white appearance of the retinal veins and arteries caused by extremely high levels of circulating chylomicrons

Lp(a): lipoprotein (a), an LDL-like particle that contains apolipoprotein (a) in addition to apoB

LPL: lipoprotein lipase, an enzyme which breaks down triglycerides into fatty acids

LpX: lipoprotein X, an abnormal lipoprotein present in plasma in obstructive jaundice

LRP: LDL receptor-related protein

NASH: non-alcohol hepatic steatohepatitis (also known as non-alcoholic fatty liver disease)

NCEP: National Cholesterol Education Program (USA)

NEFA: non-esterified fatty acids

PCSK9: proprotein convertase subtilisin/kexin type 9

SCORE: Systematic Coronary Risk Evaluation

Small, dense LDL: cholesterol-depleted LDL

TSH: thyroid-stimulating hormone

VLDL: very-low-density lipoprotein

A note on conversion of units

So that values will accord more closely with those chosen by various consensus groups, we have sometimes used a factor of 40, rather than the more precise 38.6, to convert between mmol/L and mg/dL as units of cholesterol concentration. Similarly, a conversion factor of 90 has been used for triglycerides. Converted values are given to two significant figures.

Introduction

This edition, like earlier ones, is directed at a broad range of healthcare professionals, from primary care physicians to specialists. Our objective is to present a crisp and accurate summary of the field. In particular, we want to outline a coherent pathophysiological structure on which the physician can build a sound diagnostic and clinical approach.

Vascular disease is not beaten, but it is retreating, and it is therefore critical that we apply as rapidly as possible the major clinical and scientific advances that have occurred. Guidelines are one way to speed implementation – they are invaluable for guiding clinical practice – but they do not substitute for clear knowledge of the issues at stake.

That is why we have tried to provide a text that interprets clinical trial evidence in the context of pathogenesis and gives practical solutions to routine problems encountered in the clinical management of hyperlipidemias.

In this fifth edition, the importance of considering lipoprotein particles, not just their lipids, is addressed, with reference to the latest evidence. The emphasis on including apoB as a core clinical parameter distinguishes our presentation of the issues from most others. While we may be a bit ahead, we are not alone. The approach we advocate to assessment of the adequacy of low-density lipoprotein lowering therapy corresponds to that in the recent Consensus Statements issued by the American Diabetes Association, the American College of Cardiology and the American Association for Clinical Chemistry.

Lipoprotein particles are macromolecular complexes of lipids – cholesterol, cholesteryl ester, triglycerides and phospholipids – and proteins (Figure 1.1). The outer membrane of all lipoprotein particles is

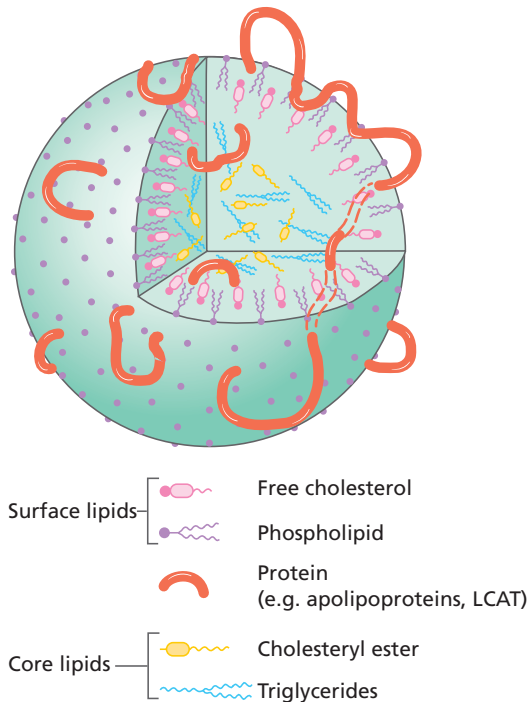
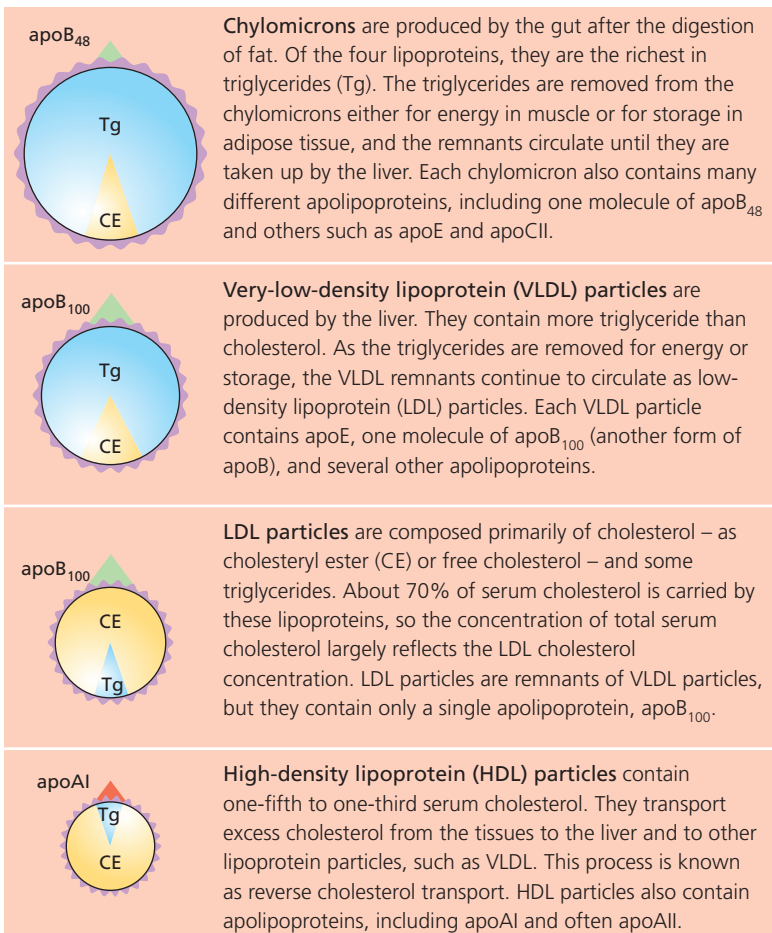


Figure 1.1 The structure of a lipoprotein. The most hydrophobic components (the triglycerides and cholesteryl esters) form a central droplet, which is surrounded by the more polar components (free cholesterol, proteins and phospholipids). Proteins are arranged with their hydrophobic sequences inside the particle and their hydrophilic regions oriented towards the aqueous environment. The polar groups of cholesterol and phospholipids also point outwards, away from the hydrophobic core. LCAT, lecithin–cholesterol acyl transferase.

a phospholipid monolayer. The apolipoproteins are the protein components – they differ in function and in whether or not they can leave one lipoprotein particle for another.

The four types of lipoprotein particle

Chylomicrons and very-low-density lipoproteins (VLDL) are the two triglyceride-rich lipoproteins, whereas low- and high-density lipoproteins (LDL and HDL, respectively) are the two cholesterol-rich lipoproteins. All four are illustrated in Figure 1.2.



8 **Figure 1.2** Four types of lipoprotein particle.

3 Familial (monogenic) hypercholesterolemia

Heterozygous familial hypercholesterolemia

Genetic basis. Familial hypercholesterolemia (FH) is the most common genetic disorder in Europe and the USA, affecting about 1 in 500 people in its heterozygous form. It is not the most common cause of hypercholesterolemia. Polygenic hypercholesterolemia and combined hyperlipidemia are more common (see Chapter 4). FH is dominantly inherited and has been recognized clinically for 80 years. Its genetic basis was revealed in 1974 when Goldstein and Brown discovered the low-density lipoprotein (LDL) receptor and found its expression to be diminished in fibroblasts from patients with FH. It is now known that the gene for the LDL receptor is located on chromosome 19.

The LDL receptor allows LDL in the tissue fluid to be taken up by cells. Newly synthesized receptors migrate to the cell surface where they can bind LDL. They move through the cell membrane to the region of the cell surface containing the coated pits. At these sites, active invagination of the cell membrane occurs, which internalizes a variety of receptors and their bound ligands. The LDL receptor–LDL particle complex dissociates within a lysosome. The LDL receptors are released back into the cytoplasm and travel back to the cell membrane so that the whole cycle can be repeated. The vesicles containing LDL fuse to form larger vesicles, called endosomes, into which enzymes are secreted that break down the apoB and esterified cholesterol to amino acids and free cholesterol, respectively. The cholesterol can then enter the cytoplasm and equilibrate with the sterol in the other cell organelles.

In FH, a mutation of the receptor prevents it from participating efficiently in LDL uptake because it cannot be transported to the cell surface, it cannot bind properly to LDL once it gets there, it cannot be internalized, or it is not released from the endosome. In FH heterozygotes, one of the LDL-receptor genes has a mutation; in homozygous FH, both do. Well before the discovery of the LDL-receptor defect, it was shown that the time LDL spent in the circulation before its removal was

increased from the normal 2.5 days to about 4.5 days in FH heterozygotes and even longer in FH homozygotes (Figure 3.1). Impaired LDL uptake is the explanation for this observation.

In large societies in which the overall frequency of FH is low, such as the UK and the USA, more than 1000 LDL receptor mutations have been found to cause the clinical syndrome of FH. By contrast, in other societies FH is caused by a small number of mutations, and the frequency may exceed 1 in 500. These societies tend to be ones that have arisen relatively recently from a small number of early settlers or migrants – for example, in South Africa, two of the three common mutations can be traced back to two of the early Dutch settlers and the other to a Huguenot migrant. A similar situation appears to exist among descendants of French Canadian settlers within a relatively remote region of Quebec. It has been suggested that a Crusader introduced the LDL-receptor mutation that now accounts for the high prevalence of FH in Lebanon.

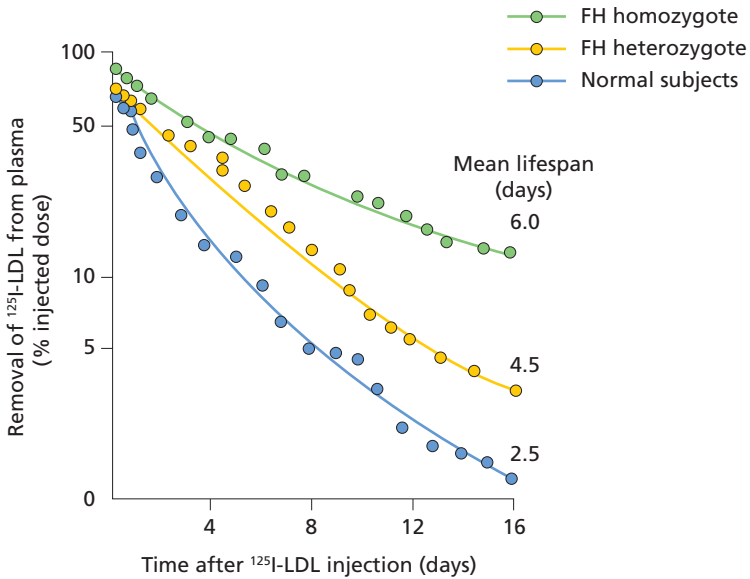


Figure 3.1 Radiolabeled low-density lipoprotein (LDL) disappears from the circulation more slowly in patients with familial hypercholesterolemia (FH) than in normal controls. Data from Bilheimer DW et al. *J Clin Invest* 1979;64:524–33.