12.6 Lipid disorders 2055

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ESSENTIALS High blood cholesterol and high blood triglycerides are causal risk factors for atherosclerotic cardiovascular disease, which remains the leading cause of death in the developed world. Lipid and lipoprotein metabolism Cholesterol, triglycerides, and fat-soluble vitamins are transported with specific proteins in the blood as multimeric complexes called lipoproteins. Lipid and lipoprotein metabolism are effected by three principal physiological processes: (1) intestinal absorption of dietary lipid and transport in the blood of dietary lipid and lipids, principally derived from the liver (as triglyceride-rich lipoproteins) to peripheral tissues for catabolism by skeletal and cardiac muscle or storage in adipose tissue; (2) return of triglyceride-rich lipoprotein remnants to the liver, hepatic synthesis of low-density lipoprotein (LDL), and the transport of cholesterol between peripheral tissues and the liver; and (3) reverse cholesterol transport by high-density lipoprotein (HDL) between peripheral tissues and the liver. Dyslipidaemias are disorders of lipoprotein metabolism in which there is elevation of total cholesterol and/or triglycerides, often ac- companied by reduced levels of HDL cholesterol. They are caused by a combination of genetic (primary) and acquired (secondary) factors (lifestyle, metabolic conditions, and drugs). Causes of dyslipidaemia Particular lipid disorders—(1) polygenic hypercholesterolaemia—in people with predominantly hypercholesterolaemia who do not show Mendelian inheritance, and do not have the clinical features of primary hypercholesterolaemia syndromes, polygenic hyperchol- esterolaemia is likely. (2) Familial hypercholesterolaemia (FH)—an autosomal codominant disorder most commonly caused by dele- terious mutation of the LDLR gene which encodes the LDL receptor. Premature atherosclerotic cardiovascular disease is very common. (3) Combined hypercholesterolaemia and hypertriglyceridaemia— mixed (combined) dyslipidaemia is common and caused by a combination of genetic (primary) and acquired (secondary) fac- tors. Elevated fasting triglycerides, increased total cholesterol and low HDL concentration are commonly associated with athero- sclerotic vascular disease. (4) Familial combined hyperlipidaemia— polygenic and non-Mendelian. (5) Familial dysbetalipoproteinaemia (also called type 3 hyperlipoproteinaemia)—a Mendelian reces- sive disorder, which becomes manifest when an acquired cause of dyslipidaemia also occurs. (6) Severe hypertriglyceridaemia—can be due to overproduction of very LDL, defective peripheral lipolysis, and/or reduced triglyceride uptake. Can be associated with recurrent pancreatitis. Secondary or aggravating factors—these include excess alcohol, diabetes mellitus, obesity and insulin resistance, hypothyroidism, chronic kidney disease, nephrotic syndrome, Cushing’s syndrome, certain drugs (such as β-adrenergic blocking agents or thiazide diur- etics), and liver disease. Management of dyslipidaemia The key questions are: (1) what classes of lipoproteins and lipids are increased or decreased in the patient’s plasma? (2) Does the pa- tient has a primary (genetic) or

secondary (acquired) dyslipidaemia (often contributions from both influences)? (3) Is the patient at risk of atherosclerotic cardiovascular disease or acute pancrea- titis? (4) What other risk factors (e.g. hypertension or diabetes) are present? (5) What treatments might be used to address these abnormalities? Hypercholesterolaemia In those with a 10% or greater risk of a cardiovascular event in the next 10 years, according to United Kingdom guidelines, it is usually recommended that cholesterol should be reduced. In the United States of America, a threshold of 7.5% for treatment is used, with the option for treatment at 5% risk. The National Institute for Health and Care Excellence in the United Kingdom currently recommends target reductions greater than 40% of non- HDL cholesterol (an accurate predictor of cardiovascular risk), but such targets are no longer recommended in the United States of America. The principal objectives of treatment are primary and secondary prevention of atherosclerotic cardiovascular disease and its complications. Lifestyle—an atheroprotective lifestyle should be instituted, with encouragement of weight loss in overweight and obese individuals. Statins—HMG-CoA reductase inhibitors are the first-line drugs for the treatment of hypercholesterolaemia, with much evidence sup- porting their use in reducing the risk of atherosclerotic cardiovascular disease. 12.6 Lipid disorders Jaimini Cegla and James Scott

 Other drugs—these include ezetimibe (blocks the action of the NPC1L1 protein and intestinal cholesterol absorption, bile acid sequestrants (resins), nicotinic acid, and PCSK9 inhibitors (fully humananized monoclonal antibodies that block the protease, PCSK9, at the surface of hepatocytes thereby reducing the physio- logical degradation of the LDL receptor). LDL apheresis—generally restricted to homozygous FH patients and heterozygotes with rapidly progressive cardiovascular disease. Raised lipoprotein(a)—associated with seriously increased risk of atherosclerotic cardiovascular disease. Specific treatment is chal- lenging as treatment of acquired factors does not affect concentra- tions of lipoprotein(a). Nicotinic acid (no longer readily available in Europe and the United Kingdom) and PCSK9 inhibitors have some effect. An antisense lipoprotein(a) mRNA inhibitor has proved re- markably efficacious in early clinical trials and is in late-phase clinical development. Hypertriglyceridaemia Triglyceride concentrations greater than 10 mmol/litre (900 mg/dl) cause an increased risk of acute pancreatitis and require prompt treatment. A secondary treatment goal is to reduce the risk of ath- erosclerotic cardiovascular disease. In addition to diabetes mellitus, other causes including dietary in- discretion with high fructose intake, obesity, insulin resistance, excess alcohol consumption, reproductive hormone deficiency, or medical use of steroid hormones should be considered. Lifestyle changes—these often reduce plasma triglyceride concen- trations markedly. A reasonable dietary goal is to restrict total fat in- take to around 20–30 g daily and avoid refined carbohydrate. Drug treatment—includes fibrates (the drugs of first choice), omega- 3 fatty acids, and statins (can reduce modest hypertriglyceridaemia but have no value in severe hypertriglyceridaemia). Introduction Despite a more than 50% reduced prevalence over the past 50 years (Fig. 12.6.1), atherosclerotic cardiovascular disease remains the leading cause of death in the developed world. Atherosclerotic car- diovascular disease accounts for about a third of all deaths, and 60% of people will suffer major life-threatening cardiovascular events. By contrast with the developed world, the occurrence of atherosclerotic cardiovascular disease is increasing in the developing world where it is becoming a leading course of mortality. Atherosclerotic cardiovascular disease is a disease of large- and medium-sized arteries. It develops slowly over many years as a direct consequence of several major risks factors. Evidence from epidemiology, meta-analyses of cholesterol-lowering end-point clinical trials, human and animal genetics, and pathology over- whelmingly demonstrate the prominence of elevated levels of high blood cholesterol as a causal risk factor for atherosclerotic

cardio- vascular disease. Cholesterol is termed the ‘agent provocateur’ of atherosclerosis, because its accumulation as oxidized low-density lipoprotein (LDL) cholesterol within macrophages in the artery wall has a direct patho- genetic role in atherosclerosis. Cholesterol-laden macrophages have a characteristic foamy appearance. ‘Foam cells’ are a hallmark feature of atherosclerosis (Fig. 12.6.2) (see Chapter 16.13.1). High blood triglycerides (TGs) are also causally linked to atherosclerotic cardiovascular disease. Unhealthy diet, lack of exercise, hyperten- sion, diabetes, and smoking are other major risk factors associated with atherosclerotic cardiovascular disease. Improvements in lifestyle and pharmaceutical treatment to re- duce blood cholesterol and other risk factors for atherosclerotic car- diovascular disease in part account (Fig. 12.6.1) for the decrease in disease prevalence in the developed world. In the countries of the developing world, the risk factors for atherosclerotic cardiovascular disease are becoming more prevalent as their populations espouse a Western lifestyle, and this is likely to be the cause for the increase in disease. Cholesterol, TGs, and fat-soluble vitamins are transported with specific proteins in the blood as multimeric complexes called lipoproteins. Here the normal physiology of lipoproteins will be described, together with their pathophysiology in relation to ath- erosclerotic cardiovascular disease and other diseases, particularly acute pancreatitis. The importance of genetic, dietary, and acquired factors which influence lipoprotein metabolism, together with diagnostic and treatment approaches to disease prevention will be discussed. Lipoproteins, lipids, and apolipoproteins Lipoproteins Lipoproteins are large, multimeric complexes of lipid and specific proteins called apolipoproteins (see ‘Apolipoproteins’). They trans- port lipid in plasma and other bodily fluids (lymph, interstitial fluid) between metabolically active tissues (Table 12.6.1, Fig. 12.6.3) (see ‘Lipid and lipoprotein metabolism’). The outer shell of lipoproteins consists of amphipathic (having hydrophilic and hydrophobic parts) lipids (phospholipid and free cholesterol) and apolipoproteins surrounding a core of water- insoluble, hydrophobic lipids (TG and cholesteryl ester). Lipoproteins are grouped into five classes (Table 12.6.1, Fig. 12.6.3) according to their density (assessed by ultracentrifugation), which determines their size (assessed by MRI and nondenaturing electro- phoresis). The amount of lipid in a lipoprotein determines its density, because lipids are not as dense as water. The lipid and apolipoprotein composition of lipoproteins differs (Table 12.6.1, Fig. 12.6.4). Chylomicrons contain the most lipid and are the least dense; they are amongst the largest entities se- creted from eukaryotic cells. Chylomicron remnants, the product of peripheral lipolysis of chylomicron TG, remain very large. Very low-density lipoproteins (VLDLs), VLDL remnant intermediate- density lipoproteins (IDLs), LDLs, and high-density lipoproteins (HDLs) are increasingly dense and less buoyant and have lower lipid content. LDL and HDL also vary in size and lipid compos- itions and this affects their atherogenicity (see ‘Lipid and lipopro- tein metabolism’). Lipoprotein(a) Lipoprotein(a) (Lp(a)) is a LDL particle with a single molecule of apolipoprotein(a) (apo(a)) linked to apoB100 by a disulphide bridge (Fig. 12.6.5). Its physiological function is uncertain. Lp(a) is not

 fully formed until the apo(a) protein is for the main part conju- gated with LDL in the extrahepatic space, though some assembly may occur with intracellular LDL-sized particles. Apo(a) is similar to plasminogen; the genes reside together in the genome, but apo(a) has no catalytic activity. In addition to the plasminogen domain, it contains repeated domains called kringles, after a Belgian cake, which is similar in shape to apo(a). Apo(a) proteins vary due to a size polymorphism, and a variable number of kringle IV repeats (each of 114 amino acids) in the gene. This results in apo(a) proteins with 10 to 50 or more kringle IV re- peats. There is an inverse correlation between the size of the apo(a) isoform and the Lp(a) plasma concentration. The larger

the isoform, the slower the rate of production, which limits the plasma concen- tration. Particle number is the now favoured measure as this reflects atherogenicity (Fig. 12.6.6). Lp(a) is cleared mainly by the liver but the receptor has not been determined. Some may be cleared by the kidney because Lp(a) plasma levels increase in chronic renal failure. 1600 (a) 1200 800 400 0 Age-standardized cardiovascular disease death rate per 100,000 Men Women Year 1950 1960 1970 1980 1990 2000 2010 1950 1960 1970 1980 1990 2000 2010 Hungary Japan USA France Greece Australia Finland Norway Congenital abnormalities 73 deaths Suicide 952 males 249 females Coronary heart disease 7,987 males Breast cancer 3,665 females Coronary heart disease 15,466 males 7,394 females Coronary heart disease 17,894 males 21,405 females 25000 (b) 15000 20000 1000 5000 0 Number of deaths 1–4 5–34 35–64 Age (years) 65–79 80+ Men Women Fig. 12.6.1 Cardiovascular death rates in the developed world. (a) Trends in death rates from cardiovascular diseases in adults over 30 years of age in selected countries with vital registration and medical certification of the underlying cause of death. Death rates are age-standardized to the World Health Organization standard population and smoothed using a 5-year moving average. (b) Death rates in the United Kingdom by age. Source data from (Panel (a)) Ezzati M and Riboli E. (2012). Can noncommunicable diseases be prevented? Lessons from studies of populations and individuals. Science, 21, 337(6101), 1482–7. Copyright © 2012, American Association for the Advancement of Science. (Panel (b)) Government data, Office for National Statistics, UK 20 October 2011.

section 12 Metabolic disorders 2058 Lipids The major lipoprotein lipids are TG, phospholipid, free cholesterol, cholesteryl ester, and fat-soluble vitamins (Fig. 12.6.7). Triglycerides TGs are the essential energy transfer and storage lipids. They com- prise three fatty acids, which can be either saturated or unsaturated fatty acids, esterified to a glycerol backbone, and are water-insoluble. The main dietary sources of TGs are fatty red meat, poultry skin, lard, high-fat dairy products, shellfish, and shrimps. Vegetable oils contain TGs. TGs are also the product of endogenous synthesis in the liver from excess dietary carbohydrate. Excess carbohydrate in the liver signals the activation of a carbohydrate responsive tran- scription factor MLXIPL/CHREBP, and of LXR alpha and sterol regulatory element-binding protein (SREBP), which together acti- vate the genes encoding the enzymes required for the biosynthesis of fatty acids and, in turn, TGs (Fig. 12.6.8). Hepatic TG is normally secreted as VLDL (see ‘Hepatic lipid transport’). Excess bodily TG is stored as fat depots in adipose tissue, and in liver and other tissues in times of gross nutritional excess— overweight and obesity; or burned as a source of energy by skeletal and cardiac muscle. Phospholipids Phospholipids are a major structural component of most bio- logical membranes. They also have an important role in cell sig- nalling through acetyl choline and prostaglandin synthesis, and phosphatidylinositol signalling pathways. They are amphipathic: the head is hydrophilic and the tail hydrophobic. This property enables them to form the lipid bilayer of biological membranes, and the monolayer outer shell of lipoproteins. Like TGs, they comprise a hydrophobic glycerol backbone, but with only two fatty acids bonded to the glycerol (usually one satur- ated and one unsaturated). The third side-group of glycerol is occu- pied by a hydrophilic phosphate group. Fig. 12.6.2 Foam cells, a hallmark feature of atherosclerotic plaque. Atherosclerotic plaque (AHA stage 4, i.e. with lipid necrotic core and fibrous cap). Brown, immunoperoxidase/di-aminobenzidine for CD68 (a macrophage lysosome protein). Blue, haematoxylin counterstain. A series of macrophages are shown, including foam cells in increasing stages of lipid accumulation and foam cell formation. The brown- staining extracellular matrix is not background or nonspecific staining but represents residual epitopes on cellular debris derived from dead macrophages. For reference, typically, a

leucocyte would be expected to be approximately 10 mm in diameter. The foam cell shown is therefore in the region of 10-fold the diameter of a typical leucocyte. Photo courtesy of Joseph Boyle, Imperial College London. Table 12.6.1 Major types of lipoproteins in circulating blood HDL LDL VLDL Chylomicrons Physical property Particle size (nm) 4.5–12 18–25 30–75

> 75 Density (g/litre) 1064–1210 1019–1063 1006 <950 Components Triglycerides 3% 10% 59% 80–95% Cholesterol (free and esters) 2% 45% 15% 3–7% Phospholipids 27% 22% 5% 3–6% Proteins 48% 20–25% 10% 1–2% Apolipoproteins A1/2, C1/2/3, E B100,C2/3, E, (a) B100, C2/3, E B48, C2/3, E Other components LCAT, CETP paroxonase Vitamin E Vitamin E Retinyl ester Vitamin E 0.95 1.006 Particle density (g/mL) Particle size, diameter (nm) 1.02 1.06 1.10 1.2 5 VLDL remnants VLDL Chylomicron remnants Chylomicron IDL HDL3 HDL2 sdLDL Lp(a) 18–25 Buoyant LDL 10 20 40 60 80 1000 Fig. 12.6.3 Lipoprotein subclasses classed by particle size and density.

12.6 Lipid disorders 2059 The phosphate groups can be modified with simple organic mol- ecules such as choline to form lecithin or phosphatidylcholine, or serine, ethanolamine, or inositol to form phosphatidylserine, phosphatidylethanolamine, or phosphatidylinositol respectively. Plasmalogens and sphingomyelin are also phospholipids, and constitute more than 20% of total phospholipids in cell membranes. Eggs, organ and lean meats, fish, shellfish, cereal grains, and oil- seeds are the main sources of phospholipids. Their synthesis in ani- mals occurs in the cytosol through endoplasmic reticulum (ER) membrane-located enzymes. Cholesterol Free cholesterol is an essential structural component of all animal plasma membranes. It is required to maintain membrane structural integrity and fluidity by reason of its packing with phospholipids. The properties of cholesterol are conferred by a single hydroxyl (OH) group, which renders cholesterol polar, but only slightly sol- uble in water. These properties enable cholesterol to function in intracellular transport by caveolae and clathrin-coated pits and cell signalling through receptor clustering in lipid rafts. Cholesterol serves as a precursor for the biosynthesis of steroid hormones, bile acids, and vitamin D. LDL receptor binding Cysteine rich Lipoprotein assembly Triglyceride cholesteryl-ester Fat-soluble vitamins Other apolipoproteins ApoC5, ApoE Phospholipid Free cholesterol COOH ApoB100 75–1000 nM ApoB100, B48 LDL receptor binding Cysteine rich Triglyceride rich lipoprotein LDL Phospholipid Free cholesterol COOH 20–30 nM ApoB100 NH2 NH2 Fig. 12.6.4 Comparison of a triglyceride rich lipoprotein (e.g. VLDL and chylomicron) and low-density lipoprotein. LDL receptor binding Cysteine rich Phospholipid Free cholesterol S–S (ApoB100–Lp(a)) COOH 200–300A ApoB100 KIV-3 to 10 Kringle IV type 2 repeats (variable number) (KIV-2) KV Protease (plasminogen homology) NH 2 Fig. 12.6.5 The structure of Lp(a). Lp(a) is an LDL particle with a single molecule of apo(a) linked to apoB100 by a disulfide bridge. Apo(a) contains an inactive protease domain, one kringle V, and kringle IV which is composed of 10 different types based on their amino acid sequences, referred to as KIV types 1 to 10. KIV types 1 and 3 to 10 are present as single copies, whereas KIV type 2 (KIV-2) is present as multiple copies, varying in number from 3 to more than 40 copies, explaining the isoform size heterogeneity between patients. Lp(a)-P(nmol/L) Lp(a)-Mass(mg/dL) 50 0 100 150 200 250 900 800 700 600 500 400 300 200 100 0 MW = 700–800 MW = 600–700 MW = 300–600 Fig. 12.6.6 Discordance between Lp(a) mass and particle number assays. Comparison of Lp(a) particle number in nmol/litre (Lp(a)-P)

with Lp(a) mass in mg/dl for samples of large (blue, n = 51), intermediate (green, n = 25), and small (red, n = 38) Lp(a) isoform sizes. Isoform sizes determined by Western blot analysis. The difference in slopes observed here indicates that the mass assay is influenced by apo(a) isoform size. Source data from Guadagno PA, et al. (2015). Validation of a lipoprotein(a) particle concentration assay by quantitative lipoprotein immunofixation electrophoresis. Clinica Chimica Acta, 439, 219–24.

section 12 Metabolic disorders 2060 Fig. 12.6.7 The chemical structure of key lipids molecules. Glucose Triglycerides MLXIPL L-PK Citrate Acetyl-CoA Malonyl-CoA FFA FAS LCE SCD ACC ACL Pyruvate Glycolysis Lipogenesis Mitochondria Krebs cycle ApoB100 ApoC2/3/A5 VLDL FFA LPL Adipose tissue Fig. 12.6.8 De novo biosynthesis of fatty acids from carbohydrate. Excess carbohydrate in the liver signals the activation of a carbohydrate responsive transcription factor, MLX-interacting protein-like (MLXIPL) (also known as carbohydrate-responsive element-binding protein (CHREBP)), which activates the genes encoding the enzymes required for the biosynthesis of fatty acids and in turn triglycerides. ACC, acetyl- CoA carboxylase; ACL, ATP-citrate lyase; FAS, fatty acid synthase; FFA, free fatty acids; LCE, long-chain fatty acyl elongase; L-PK, liver pyruvate kinase; LPL, lipoprotein lipase; SCD, stearoyl-CoA desaturase.

12.6 Lipid disorders 2061 The main dietary sources of cholesterol are the same as TGs. Egg yolks are also rich in cholesterol. Plants make cholesterol in very small amounts. Rather, plants make phytosterols, which are chem- ically similar to cholesterol and can compete with cholesterol for absorption in the intestinal tract, thus potentially reducing cholesterol absorption (see ‘Plant sterols’). Cholesterol is essential for animal life therefore most cells synthe- size cholesterol from acetyl-coenzyme A (CoA) through a complex multistep pathway. Humans synthesize about 1 g of cholesterol daily, and compensate for any excess absorption by reducing cholesterol synthesis. Thus 12 h after ingestion, cholesterol will show little effect on total body cholesterol content or concentrations of cholesterol in the blood. In the 7 h after ingestion of cholesterol, however, the levels in plasma increase, and this is moderated by genetic factors (see ‘Lipid and lipoprotein metabolism’). Cholesterol is susceptible to oxidation and easily forms oxygen- ated derivatives known as oxysterols. Oxysterols exert inhibitory actions on cholesterol biosynthesis. Oxidized LDL is associated with the pathogenesis of atherosclerotic cardiovascular disease (see ‘Introduction’). Cholesterol is also oxidized by the liver into bile acids, which may be conjugated with glycine, taurine, glucuronic acid, or sulphate (Fig. 12.6.9). A mixture of conjugated and nonconjugated bile acids (c.80% of biliary constituents), with free cholesterol and phospho- lipids (c.20% of bile constituents), is excreted from the liver into the bile, and stored in the gallbladder. The gallbladder empties in response to food in the intestine. In the intestine, bile salts form miscelles, which solubilize lipids and facilitate their absorption. Approximately 95% of the bile acids are reabsorbed from the ileum and the remainder are lost in the faeces. The excretion and reabsorption of bile acids forms the basis of the enterohepatic circulation, which is essential for the digestion and absorption of dietary lipids. The liver also excretes free cholesterol in bile into the duodenum. Typically, about 50% of the excreted choles- terol along with dietary cholesterol is reabsorbed by the small bowel, but this varies between people. The biosynthesis of cholesterol is directly regulated by the choles- terol levels in the cell (Fig. 12.6.10). Thus high dietary intake reduces endogenous production, whereas lower intake does the reverse. The principal regulatory mechanism is the sensing of intracellular chol- esterol in the ER by the proteins SREBP1 and SREBP2. In the pres- ence of cholesterol, SREBP is bound to two other proteins: SREBP cleavage-

activating protein (SCAP) and insulin-induced gene 1 (INSIG1). At low cholesterol levels, INSIG1 dissociates from the SREBP– SCAP complex, which then moves to the Golgi apparatus. In the Golgi apparatus, SREBP is cleaved by site-1 protease and site-2 protease (S1P and S2P), two enzymes that are activated by SCAP at low cholesterol levels. After cleavage SREBP migrates to the nu- cleus, where it binds to the sterol regulatory element (SRE), and pro- motes transcription of multiple genes that control lipid formation, HO 7 HO H HO Cholesterol Chenodeoxycholic acid 7α-hydroxylase (CYP7A1) ‘Classic pathway’ HO 7 HO HO H HO HO 7-hydroxycholesterol Cholic acid Several steps Sterol 12α-hydroxylase (CYP8B1) HSDB37 HSDB37 Fig. 12.6.9 Bile acid synthesis. Cholesterol is oxidized by the liver into bile acids. A hydroxyl optionally added in the liver determines the formation of chenodeoxycholic acid versus cholic acid. In the liver, bile acids may be conjugated with glycine, taurine, glucuronic acid, or sulphate. A mixture of conjugated and nonconjugated bile acids, with free cholesterol and phospholipids, is excreted from the liver into the bile, and stored in the gallbladder. In the gut, a hydroxyl group may be removed by gut bacteria to create deoxycholic acid and lithocholic acids from cholic acid and chenodeoxycholic acid respectively.

section 12 Metabolic disorders 2062 metabolism and energy supply, including the LDL receptor (LDLR) and 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCoAR). The LDLR removes LDL from plasma. HMGCoAR is the rate- limiting enzyme of cholesterol biosynthesis. The turnover of HMGCoAR by protein degradation is sensitive to cholesterol levels in the cell (Fig. 12.6.11). The activity of the LDLR is also regulated by protein convertase subtilisin/kexin type 9 (PCSK9), an extracellular protein which binds to the epidermal growth factor-like repeat A (EGF-A) domain of the LDLR, inducing its degradation. After internalization, the LDLR usually disassociates in the acid environment of the endosome and recycles to the cell surface. With PCSK9 bound, the LDLR is targeted to the lysosome and degraded rather than recycled. Cholesteryl esters are formed between the carboxylate group of a fatty acid and the hydroxyl group of cholesterol. Cholesteryl esters have a lower solubility in water due to their increased hydrophobicity. They are the intracellular storage form and intravascular transport form of cholesterol. Plant sterols Phytosterols derived from plants account for 25% of dietary sterols. The most commonly occurring phytosterols in the human diet are β-sitosterol, campesterol and stigmasterol, which account for about 65%, 30%, and 3% of diet contents, respectively, but are not normally well absorbed by humans. Stanols are saturated sterols, having no double bonds in the sterol ring structure, and normally form only a tiny component of the diet, but are synthesized as a gut microbial byproduct of cholesterol metabolism. Absorbed plant sterols are re-excreted in bile or by the enterocyte. Plant sources are vegetable oils, nuts, peanuts, and avocados. Plant sterols compete with cholesterol for absorption, with potential beneficial effect on plasma cholesterol levels. SCAP SCAP WD SREBP HLH WD SREBP HLH SREBP HLH INSIG SRE – ACS – FAS – GPAT – Squalene synthase – HMGCoAR – LDLR – etc. High cholesterol Low cholesterol ER membrane Cytoplasm Lumen Cytoplasm Lumen Nucleus S2P S1P Golgi apparatus SREBP HLH Fig. 12.6.10 Regulation of cholesterol biosynthesis. The principal regulatory mechanism is the sensing of intracellular cholesterol in the ER by the proteins, sterol regulatory element-binding protein (SREBP) 1 and 2. Starting out wrapped in the ER membrane, their activation as transcription factors requires a maturation process tightly controlled by the levels of cholesterol present in the membrane. In the presence of cholesterol, SREBP is bound to two other proteins: SREBP cleavage-activating protein (SCAP) and insulin-induced gene 1 (INSIG1). SCAP acts as a sensor of the content of cholesterol in the ER membrane. In the presence of high levels of cholesterol, SCAP remains anchored in the ER membrane due to its interaction with the

INSIG proteins. At low cholesterol levels, INSIG1 dissociates from the SREBP–SCAP complex, which then moves to the Golgi apparatus. SREBP is then cleaved by site-1 protease and site-2 protease (S1P and S2P), two enzymes that are activated by SCAP at low cholesterol levels. This fragment contains a basic helix–loop–helix (HLH) leucine zipper domain, which functions as a transcription factor. After cleavage, SREBP migrates to the nucleus, where it binds to the sterol regulatory element (SRE), and promotes transcription of multiple genes that control lipid formation, metabolism, and energy supply, including the LDL receptor (LDLR) and 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCoAR). WD, WD40 domain. Source data from Desvergne B, et al. (2006). Transcriptional regulation of metabolism. Physiological Reviews, 86(2), 465–514.

12.6 Lipid disorders 2063 Trans fatty acids Artificial trans fats are created in an industrial process that adds hydrogen to liquid vegetable oils to make them more solid. The primary dietary source for trans fats in processed food is ‘partially hydrogenated oils’. They are used by food manufacturers because they have a long shelf life and are able to withstand repeated heating without breaking down. Doughnuts, biscuits, crackers, muffins, pies, and cakes are examples of foods that may contain trans fat. Trans fats may also be produced when ordinary vegetable oils are heated to fry foods at very high temperatures and this is one reason why take- away foods can sometimes be high in trans fats. While many old- fashioned margarines contain a high proportion of trans fats, newer brands should contain low amounts. Fat-soluble vitamins Vitamin E is one of the most abundant lipid-soluble antioxidants found in the plasma and somatic cells of higher mammals. It comes mainly from plant rather than animal sources. The main dietary forms of preformed vitamin A are carotenoids in fruits and veget- ables and long-chain fatty acids esters of retinol in foods of animal origin. Apolipoproteins Apolipoproteins function as structural components of lipopro- tein particles (Table 12.6.2). They also act as cofactors for en- zymes of lipid metabolism and as ligands for cell surface receptors. There are two types of apolipoproteins. The first are the huge LDL receptors LDL Protein ER Lysosome Cholesteryl linoleate 1. HMG CoA reductase 2. ACAT 3. LDL receptors Cholesterol Cholesteryl oleate Amino acids Regulatory actions Lysosomal hydrolysis Internalization LDL binding Fig. 12.6.11 Intracellular uptake of LDL by the LDL receptor. LDL is internalized through receptor-mediated endocytosis. The cholesterol derived from lysosomal hydrolysis exerts feedback to protect the cell from overaccumulation of cholesterol by (1) suppressing activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), the rate-controlling enzyme of cholesterol biosynthesis; (2) activating acyl-CoA:cholesterol acyltransferase (ACAT), a cholesterol-esterifying enzyme so that excess cholesterol can be stored as cholesteryl ester droplets; and (3) suppressing synthesis of new LDL receptors thus preventing further cholesterol intake into the cell. Source data from Goldstein J and Brown M (2009). The LDL receptor. Arterioscler Thromb Vasc Biol, 29, 431–8. Table 12.6.2 Major apolipoproteins and their function Apolipoprotein Primary source Lipoprotein association Function ApoA1 Intestine, liver HDL, chylomicrons Structural protein HDL Activates LCAT ApoA2 Liver HDL, chylomicrons Structural protein HDL ApoA4 Intestine, liver HDL, chylomicrons Unknown ApoA5 Liver VLDL, chylomicrons Promotes LPL-mediated TG lipolysis Apo(a) Liver Lp(a) Unknown ApoB48 Intestine Chylomicrons, chylomicron remnants Structural protein for chylomicrons ApoB100 Liver VLDL, IDL, LDL, Lp(a) Structural protein for VLDL, LDL, IDL, Lp(a) Ligand for binding LDL receptor ApoC1 Liver Chylomicrons, VLDL, HDL Unknown ApoC2 Liver Chylomicrons, VLDL, HDL Cofactor for LPL ApoC3 Liver, intestine Chylomicrons, VLDL, HDL Inhibits LPL activity and lipoprotein binding to receptors ApoE Liver Chylomicron remnants, IDL, HDL Ligand for binding to LDL receptor and other receptors

section 12 Metabolic disorders 2064 apoB-containing lipoproteins, which associate with lipid droplets irreversibly (they do not exchange between lipoprotein particles) from the time of assembly of lipoproteins within the ER and se- cretion from the cell, until they are cleared from the circulation by the LDLR. Lipid binding through apoB is mainly by amphipathic β strands, with less of the amphipathic α helices that characterize other apolipoproteins. The two forms of apoB, apoB100 (514 kDa) and apoB48 (247 kDa), are the products of the same gene, and in humans are synthesized in the liver and intestine respectively. ApoB48 is generated by editing of the APOB100 mRNA by a site-specific RNA editing cytosine deaminase designated apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1 (apoBEC1), which terminates the transla- tional reading frame, to create the smaller apoB48. ApoB48 is required for TG-rich chylomicron assembly and se- cretion from the intestine, and for the delivery of TG to peripheral tissues. ApoB48 lacks the C-terminal LDLR binding domain found in apoB100. The clearance from the circulation of chylomicron remnants after depletion of TGs is mediated by apoE through the LDLR. ApoB100 is required for TG-rich VLDL assembly and secretion from the liver. After secretion, VLDL goes on to form remnants or IDL and subsequently LDL, which is cleared from the circulation by direct interaction of apoB100 with the LDLR. All other apolipoproteins are very much smaller and make im- portant exchanges between lipoprotein particles in the course of lipoprotein metabolism and remodelling in the circulation. The smaller exchangeable apolipoproteins, the apoAs, apoCs, and apoE form a multigene family, and have similar intron/exon organiza- tion in their genes. They bind lipid through repeated amphipathic α helices in their structure. They are the products of duplication of an ancestral gene. ApoA1 and apoA2 are the core structural proteins of HDL. ApoA4 is thought to act primarily in intestinal lipid absorption. ApoA5 pos- sibly acts by increasing VLDL production in the liver, stimulation of proteoglycan-bound lipoprotein lipase (LPL) at the endothelium of capillaries in peripheral organs, or enhancing the clearance of TG- rich lipoproteins via lipoprotein receptors in the liver. The function of apoC1 and apoC4 is uncertain. ApoA1 and apoC2 are cofactors for lecithin–cholesterol acyltransferase (LCAT) and LPL respectively. ApoC3 is an inhibitor of LPL. ApoE is a ligand for the LDLR and mediates the clearance of chylomicron and VLDL remnants or IDLs by the liver LDLRs. Lipid and lipoprotein metabolism Lipid and lipoprotein metabolism can be grouped into a variety of physiological processes: (1) the intestinal absorption of dietary lipid (long-chain fatty acids, cholesterol, fat-soluble vitamins) and transport in the blood of dietary lipid and hepatically derived lipids, principally TGs as TG-rich lipoproteins, to peripheral tis- sues for catabolism by skeletal and cardiac muscle or storage in adipose tissue; (2) the transfer of the TG-rich lipoproteins rem- nants back to the liver, and the formation of LDL and the transport of cholesterol between peripheral tissues and the liver; and (3) re- verse cholesterol transport by HDL between peripheral tissues and the liver. Intestinal lipid absorption and transport as chylomicrons Intestinal lipid sources TG is the main lipid in the diet, contributing 90 to 95% of the lipid- derived energy. Dietary lipids also include phospholipids, cholesterol and plant sterols, and fat-soluble vitamins. The main phospholipid in the small intestinal lumen is phosphatidylcholine, mostly derived endogenously from bile, 10 to 20 g per day in humans, with 1 to 2 g contributed by the diet. The predominant dietary sterols are choles- terol, of animal origin, and sitosterol, the major plant sterol. The Western diet provides 300 to 500 mg of cholesterol daily. Bile contributes 800 to 1200 mg daily and intestinal mucosal turnover provides around 300 mg. Approximately 50% of the cholesterol in the intestine is absorbed, but this varies between individuals; the re- mainder is excreted in faeces. In high absorbers, there is more likely to be an increase in plasma cholesterol levels, and better response to a low-cholesterol diet. The essential fat-soluble vitamins, vitamins E and A, are derived mainly from plants, or secondary animal

sources. Emulsification, digestion, and micelle formation Lipid digestion begins in the mouth and stomach through the action of lingual lipase and gastric enzymes. Gastric peristalsis breaks up dietary fat globules into much smaller emulsion droplets (emulsifi- cation). Fine emulsion droplets enter the duodenum and mix with amphipathic biliary phospholipid, free cholesterol, bile acids, pan- creatic enzymes, and colipase (an amphipathic protein that anchors lipase at the surface of the emulsion droplet). Emulsification greatly increases the surface area where water-soluble enzymes act to digest water-insoluble lipids. In the jejunum, TG is digested primarily by pancreatic lipase to yield free fatty acids and glycerol; phospholipid digestion is car- ried out by pancreatic phospholipase A2 and lysophospholipase; and cholesteryl ester. About 10 to 15% of dietary cholesterol is hydrolysed by cholesterol esterase to release free cholesterol. After digestion, monoglycerides, free fatty acids, free cholesterol, and fat- soluble vitamins associate with bile salts and phospholipids to form micelles. Micelles are about 200 times smaller than emulsion drop- lets, and are small enough to enter between the microvilli and be absorbed (Fig. 12.6.12). Absorption Free fatty acids are taken up from the intestinal lumen into the entero- cytes and used for the biosynthesis of neutral fats (TG, cholesteryl ester) (Fig. 12.6.12). Fatty acid transport proteins (FATPs) such as FATP4 and FAT/CD36 facilitate the uptake of fatty acids by the enterocytes. Cholesterol and plant sterol absorption is controlled by Niemann– Pick C1-like 1 (NPC1L1) and ATP-binding cassette (ABC) proteins ABCG5 and ABCG8, which act as cholesterol uptake transporters and as plant sterol efflux transporters respectively. ABCA1 transfers enterocyte cholesterol to apoA1 for intestinal HDL formation and secretion into lymph, and accounts for 30% of all HDL. Vitamin E absorption requires micelle formation, and scav- enger receptor class B member 1 (SRB1) for absorption. Dietary vitamin A is in the form of carotenoids and fatty acid esters of ret-inol. Carotenoids are cleaved to generate retinol or absorbed intact.

12.6 Lipid disorders 2065 Retinyl esters must be hydrolysed by lipase to release free retinol before it can be taken up by enterocytes from micelles. Chylomicrons Nascent chylomicrons are huge, spherical, TG-rich lipoproteins. ApoB48 is the principal structural component of chylomicrons. It is very large, hydrophobic, and nonexchangeable. The lipoprotein core contains TGs (85% of chylomicron lipid), cholesteryl esters, and fat- soluble vitamins. The surface contains a monolayer of phospholipids (mainly phosphatidylcholine) and free cholesterol. The surface is populated by apoA1, apoA4, and the apoCs. Free fatty acids (>12 carbons), monoglycerides, and vitamin E are transferred from the enterocyte microvillus membrane to the ER for re-esterification and lipoprotein assembly by fatty acid binding Efflux Micelles MTP CM Golgi ER ApoA1 Nascent HDL CM Blood Lymph NPC1L1 ABCG5/8 ApoB-independent ApoB48-dependent CD36 MAG Retinol SR-B1 C C FA FA FA RE 2 3 4 5 6 1 ACAT FABP FATP ABCA1 DGAT LRAT CRBP A4 HDL B48 R VitE CE
Fig. 12.6.12 Lipid absorption. Hydrolysed lipids are solubilized in micelles and presented to the apical membranes of enterocytes. Here, transport proteins facilitate the uptake of various lipid entities: Niemann–Pick C1-like 1 (NPC1L1) is involved in cholesterol uptake, CD36 and fatty acid (FA) transport protein (FATP) facilitates FA transport and scavenger receptor class B type I (SR-BI) is involved in vitamin E (Vit E) uptake. In the cytosol, FA-binding protein (FABP) and cellular retinol-binding protein (CRBP) transport FAs and retinol (R) respectively. In the endoplasmic reticulum (ER) membrane, acyl-CoA:cholesterol acyltransferase (ACAT), diacylglycerol acyltransferase (DGAT), and lecithin:retinol acyltransferase (LRAT) facilitate the esterification of cholesterol, monoacylglycerols (MAG), and retinol respectively. These esterified products are then incorporated into apoB48- containing chylomicrons; this process is mediated by microsomal triglyceride (TG) transport protein (MTP). The newly synthesized prechylomicrons are transported in specialized

vesicles to the Golgi apparatus for further processing and secretion. Enterocytes also express ATP-binding cassette (ABC) transporter A1 on the basolateral membrane to promote the efflux of cholesterol. A3, apoA3A4, apoA4; C, free cholesterol; CE, cholesteryl ester; RE, retinyl ester. Source data from Iqbal J, et al. (2009). Intestinal lipid absorption. Am J Physiol Endocrinol Metab, 296, 1183–94.

section 12 Metabolic disorders 2066 proteins (FABPs). Re-esterification of free fatty acids and cholesterol is mediated by diacylglycerol acyltransferase (DGAT1) and acetyl- CoA acetyltransferase (ACAT2). Retinol is transferred to the ER by cellular retinol-binding proteins (CRBP). Chylomicrons nucleate in the ER around a single molecule of apoB48. TGs, phospholipids, free cholesterol, and cholesteryl esters along with fat-soluble vitamins are loaded onto apoB48 during chylo- micron assembly in the ER by a microsomal triglyceride transfer protein (MTTP). Chylomicrons are further lipidated in the secretary pathways, before secretion from the enterocyte basolateral mem- brane into the lymphatic system, and delivery by the thoracic duct to the systemic circulation. In the circulation, chylomicrons undergo extensive modification (Fig. 12.6.13). They transfer phospholipid and cholesteryl ester to HDL, which in turn donates apoC2 and apoE to the nascent chylo- micron, converting it to a mature chylomicron. In the peripheral capillaries of adipose tissue, skeletal muscle and heart chylomicrons associate with LPL, which is anchored to glycosylphosphatidylinositol-anchored protein (GPIHBP1). Lipase maturation factor 1 (LMF1) resides in the ER, and is involved in the maturation and transport of LPL, hepatic lipase (HL), and pancre- atic lipase through the secretory pathway. ApoC2 is the cofactor for LPL activity. Chylomicron TG is hydrolysed by LPL releasing free fatty acids, which are stored in fat as TG or burnt to create energy in muscle. Some free fatty acids associate with albumin and are transported to other tissues, mainly the liver. The chylomicron progressively de- creases in size as TG is hydrolysed. Once TG is depleted, the chylomicron remnant returns apoC2 to the HDL but retains apoE. The remnant of this metabolism is rapidly cleared from the circulation by the interaction of apoE with hepatic LDLRs. In the normal postprandial state, few or no chylomicrons or chylomicron remnants are present in blood after a prolonged fast, except in those with dyslipidaemia, in whom they may persist. Hepatic lipid transport as VLDL, IDL, and LDL VLDL Lipids from the liver are transported to the periphery on VLDLs (Fig. 12.6.13). VLDLs, like chylomicrons, are TG-rich lipoproteins. They also carry free cholesterol and cholesteryl ester, with a TG-to- cholesterol ratio of approximately 5:1, and vitamin E. VLDLs, like chylomicrons, nucleate in the ER around a single molecule of apoB, in this case apoB100 rather than apoB48. ApoB100 is twice the size of the apoB48 on the centile system. VLDL TGs are derived predominantly from the esterification of the long-chain fatty acids in the liver. These come from chylomicron remnants and through de novo synthesis from excess dietary carbo- hydrate. As with chylomicrons, TG is loaded on to apoB100 in the ER through the agency of MTTP. After secretion into the blood, VLDL acquires several molecules of apoE and of the apoC apolipoproteins from HDL. As with chylo- microns, the VLDL TGs are hydrolysed by LPL in peripheral adi- pose tissue, muscle, and heart blood capillaries. IDL and LDL The remnants of peripheral lipolysis, IDLs, disassociate from LPL. After TG hydrolysis, IDLs contain approximately the same amount of cholesterol and TG. About half of IDLs are removed by liver LDL receptors through interaction with its ligand apoE. The remaining IDL is refashioned by HL with removal of further TG and phospho- lipid to form the cholesterol-rich LDL. In the process of LDL formation, apoE and the apoCs are trans- ferred to other lipoprotein particles. LDL comprises one molecule of apoB100, a shell of phospholipid and free cholesterol, and a core of cholesteryl ester. LDL can vary in size according to its neural lipid content; particles with more TG and less cholesteryl ester are smaller

and denser (sdLDL). The size of LDL has implications for its atherogenicity (Table 12.6.1, Fig. 12.6.4). Most LDL is removed ApoB100 Adipose tissue, muscle, heart LPL, ApoA5, C2,C3 Adipose tissue, muscle, heart LPL, ApoA5, C2,3 ApoE LDL VLDL ApoC IDL LDLR Exogenous Endogenous Chylomicron ApoB48 ApoC ApoE Gut Liver Other sites Remnant Fig. 12.6.13 The exogenous and endogenous lipid metabolism pathways. Chylomicrons from the gut transport dietary triglycerides to tissue where they are removed by lipoprotein lipase (LPL). The remnants are taken up by the liver via remnant and LDL receptors and catabolized. VLDL is synthesized in the liver and transports endogenous triglycerides to tissue where they are removed by LPL, resulting in IDL. Some IDL is taken up directly by hepatocytes but for the majority of IDL, further triglyceride is removed by hepatic lipase and thereby IDL is converted to LDL. LDL is removed by the liver via the LDL receptor (LDLR).

12.6 Lipid disorders 2067 from the blood by the liver through the binding to the LDLR by a C-terminal LDL receptor binding domain in apoB100. Reverse cholesterol transport by HDL While most cells make cholesterol, it cannot be degraded and only the liver and intestine excrete it, either by secretion into bile or into the intestinal lumen by the enterocyte. Biliary cholesterol is either in the form of free cholesterol or bile acids, after the conversion of liver cholesterol to bile acids. HDL mediates the ‘reverse cholesterol trans- port’ of cholesterol derived from peripheral cell plasma membranes back to the liver and gut for recycling or excretion (Fig. 12.6.14). Freshly secreted apoA1 acquires phospholipids and free choles- terol from liver and intestinal cell plasma membranes, where their efflux is mediated by ABCA1. The nascent HDL gains additional free cholesterol from peripheral cells or circulating lipoproteins. The free cholesterol in HDL is esterified by the enzyme LCAT, which is as- sociated with HDL, and the cholesteryl ester transferred to the core of the lipoprotein particle. ApoA1 is a necessary cofactor for LCAT. The acquisition of further cholesteryl ester, phospholipid, and add- itional apoCs and apoE transferred from chylomicrons and VLDL during lipolysis creates the mature HDL particle. HDL particles are extensively modified in the blood. Cholesteryl ester and phospholipid are transferred by cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) to HDL from other lipoproteins or between various ‘classes’ of HDL lipo- proteins (Table 12.6.1, Fig. 12.6.14). CETP and PLTP generate a TG-rich HDL, which is substrate for HL. HL hydrolyses TG and phospholipid to generate small HDL particles. Another lipase, endo- thelial lipase, hydrolyses HDL phospholipid and generates even smaller HDL, which is rapidly catabolized. HDL cholesterol (HDL-C) is cleared by the liver. Cholesterol from HDL can also be taken up by hepatic SRB1 cell surface receptors that mediate the selective uptake of lipids into cells. Cholesteryl ester from HDL is also transferred to apoB-containing IDL and LDL lipoproteins in exchange for TGs by CETP. These apoB-containing particles are then removed by LDLR-mediated endocytosis. Some apoA1 is catabolized by the kidneys. Dyslipidaemia affecting cholesterol and triglyceride plasma levels The term dyslipidaemia is used to describe disorders of lipoprotein metabolism in which there is elevation of TC and/or TGs, often ac- companied by reduced levels of HDL-C. It is very common. Dyslipidaemia is also used here to encompass high levels of apoB and LDL particle number without elevation of LDL chol- esterol (LDL-C), which indicates the presence of sdLDL; high levels of Lp(a); low levels of apoB-containing lipoproteins; low HDL-C; and high levels of HDL-C. The terms hyperlipidaemia or hyperlipoproteinaemia refer to raised lipids, and do not encompass HDL. The term dyslipidaemia is used preferentially in this chapter. Cholesterol Cholesteryl ester CETP and PLTP, transfer of cholesteryl ester and phospholipids SR-B1 Bile Excretion Intestine Liver Macrophage Peripheral cell Circulation Tissue CM VLDL Mature HDL ApoA1 ABCG1 ABCA1 ABCG1 ABCA1 Nascent discoid HDL HDL

Fig. 12.6.14 Reverse cholesterol transport. Nascent HDL acquires free cholesterol from extrahepatic cells. The free cholesterol in HDL is esterified by lecithin cholesterol acyltransferase (LCAT). ApoA1 is a necessary co-factor for LCAT. Further cholesteryl esters (CE), phospholipids, and apoC and apoE are transferred during lipolysis from chylomicrons and VLDL to create mature HDL particle. Cholesteryl ester and phospholipid are transferred by cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) respectively. CETP and PLTP generate a TG-rich HDL, which is then hydrolysed by hepatic lipase to generate small HDL particles. HDL-C is cleared by the liver. Additionally, cholesterol from HDL can be taken up by hepatic SRB1 cell surface receptors.

section 12 Metabolic disorders 2068 The units used here are in mmol/litre with mg/dl in brackets. The conversion factor for cholesterol from mmol/litre to mg/dl is times 38.7, and for TGs is times 88.6. In clinical practice, the lipid profile of total cholesterol (TC), TG, and HDL levels is routinely measured, and LDL-C and/or non-HDL cholesterol (NHDL-C) usually calculated. The use of calculated LDL-C versus NHDL-C is discussed later in this chapter. The measurement of lipid and lipoprotein levels in clinical prac- tice is important because the presence of raised plasma levels of cholesterol is causally associated with atherosclerotic cardiovascular disease, and intervention to lower cholesterol levels will decrease the risk of atherosclerotic cardiovascular disease events. Raised plasma TG is also causally associated with increased atherosclerotic cardio- vascular disease risk, and lowering TGs decreases atherosclerotic cardiovascular disease events. By contrast, low plasma HDL levels are a marker of increased atherosclerotic cardiovascular disease risk, but this relationship is not causal. Less commonly there can be severe hypertriglyceridaemia, which should be recognized as it can cause potentially fatal, acute pancreatitis, the risk of which can be reduced by treatment of hypertriglyceridaemia. Dyslipidaemia is caused by a combination of genetic (primary) and acquired (secondary) factors (lifestyle, medical or metabolic conditions, and drugs). The genetic architecture of dyslipidaemia is made up of both common and low-frequency polymorphic variants, which affect lipid and lipoprotein metabolism and other metabolic traits such as obesity, insulin resistance, and hypertension. Rare al- leles make a small population, but large individual contribution to genetic risk. Genetic variation confers around 50% to the total vari- ation in LDL-C, TG, and HDL-C levels. Traditionally, familial hyperlipidaemias have been typed ac- cording to the Fredrickson (World Health Organization) classifica- tion (Table 12.6.3), which is based on the pattern of lipoproteins on electrophoresis or ultracentrifugation. This is a descriptive typing of apoB-containing lipoproteins, and does not include HDL. The Fredrickson classification does not distinguish among the gene defects that are wholly or partially responsible for the dyslipidaemia. Here, reflecting advances in mechanistic cell biology and molecular genetics, a classification-based mechanism is pre- ferred, and where the genetic basis is known this is used, rather than the Fredrickson classification. The Fredrickson classification is of value in severe hypertriglyceridaemia (see the ‘fridge test’, described in ‘Familial chylomicronaemia (syndrome)). The evidence base The evidence concerning the relationship the between plasma lipid and lipoprotein levels and atherosclerotic cardiovascular disease comes from epidemiology, genetics, and the meta-analysis of clin- ical trials to treat dyslipidaemia. This data is supported by experi- mental medicine and pathology. Epidemiology demonstrates a very strong relationship between blood cholesterol at all blood cholesterol levels and atherosclerotic cardiovascular disease events; TG levels throughout the normal range and with mild to moderate elevations are similarly associated (Figs. 12.6.15 and 12.6.16). Genome-wide association studies and Mendelian randomization (Fig. 12.6.17) studies show that this relationship between LDL-C and TG levels and

atherosclerotic cardiovascular disease is causal. Mendelian causes of severe hypercholesterolaemia are strongly linked to premature atherosclerotic cardiovascular disease. Severe hypertriglyceridaemia also possibly increases the risk of atheroscler- otic cardiovascular disease. An important distinction between TGs and cholesterol is that TGs can be broken down by most cells, but cholesterol can be de- graded by none. This property of cholesterol and the small size of LDL, which enables it to enter the vascular intima, account for the direct atherogenicity of LDL. In the intima it is oxidized to form oxidized LDL, which along with native LDL, is taken up by activated macrophages leading to a cascade of events that cause atheroscler- otic cardiovascular disease. The role of TGs in atherogenesis is less clear. TG-rich lipoproteins and remnants both appear to be involved. TG-rich chylomicron and VLDL are, however, too large to enter the vascular intima, where they could have a direct pathogenetic role in atherosclerotic car- diovascular disease. Rather, free fatty acids and monoacylglycerol released by TG lipolysis from TG-rich lipoproteins can produce low-grade intimal inflammation. Remnants are small enough to pass into the vascular intima, where remnant cholesterol is the likely agent provocateur of atherosclerotic cardiovascular disease. Foam cells accumulate cholesterol not TGs. The meta-analyses of large clinical trials with statins overwhelm- ingly and conclusively demonstrate that LDL-C lowering at all Table 12.6.3 Fredrickson/World Health Organization classification of primary hyperlipidaemias Type Overnight serum High lipoprotein particles Clinical disorders Serum TC Serum TG 1 Creamy top layer Chylomicrons Lipoprotein lipase deficiency, apoC2, apoA5, GPIHBPI, LMF1, GDP1 deficiency N ++ 2a Clear LDL Familial hypercholesterolaemia, polygenic hypercholesterolaemia, nephrotic syndrome, hypothyroidism, familial combined hyperlipidaemia ++ N 2b Clear LDL, VLDL Familial combined hyperlipidaemia ++ + 3 Turbid IDL Dysbetalipoproteinaemia +/++ +/++ 4 Turbid VLDL Familial hypertriglyceridaemia, familial combined hyperlipidaemia, sporadic hypertriglyceridemia, diabetes N+ ++ 5 Creamy top,
turbid bottom Chylomicrons, VLDL Diabetes, lipoprotein lipase deficiency, apoC2, apoA5, GPIHBP1, LMF1, GPD1 deficiency + ++ +, increased; ++, greatly increased; N, normal; N+, normal or increased; TC, total cholesterol.

 plasma concentrations reduces atherosclerotic cardiovascular dis- ease events. This is the case for LDL-C levels to as low as 1.3 mmol/ litre (50 mg/dl). The remarkable success of statins is without harm, apart from a modest increase in the risk of diabetes. Even this low level of LDL-C is double the true physiological con- centration seen in animals in the wild and human neonates, so that the level to which LDL-C can be reduced to prevent atherosclerosis remains to ascertained. No increase in the risk of haemorrhagic stroke has been observed at very low cholesterol levels. While large clinical trials have not formally evaluated the effect of TG reduction on atherosclerotic cardiovascular disease events, sec- ondary analysis of trials of fibrates and nicotinic acid on TG reduc- tion indicate a comparable effect to that achieved with statins. This needs to be validated in appropriately designed clinical trials. Contrary to previously held views, low HDL levels are not as- sociated with increased atherosclerotic cardiovascular disease risk in genome-wide association studies and Mendelian randomiza- tion studies, and the meta-analysis of large clinical trials show no benefit from increasing HDL levels. Rather, HDL levels appear to be a biomarker of risk conferred by associated factors such as obesity, insulin resistance, and diabetes. Whether improvement in the functionality of HDL, as, for example, in reverse cholesterol trans- port improves atherosclerotic cardiovascular disease risk is not at present known. Intestinal lipid absorption and dyslipidaemia Intestinal cholesterol absorption varies between 30 and 80% in indi- viduals, and on average is around 50%. These differences are partly genetic and likely to be

conferred by common and low-frequency variants for the main part, but strongly influenced by secondary (acquired) factors. 40 30 20 10 5 4 3 2 1 0 4.0 5.0 6.0 7.0 8.0 Total cholesterol (mmol/L) Shanghai study CVD mortality (MRFIT) Bulk of CVD Total mortality (MRFIT) Age-adjusted 6-year death rate per 1,000 men (n=361,662) Fig. 12.6.15 Population cholesterol levels and cardiovascular risk. MRFIT study: this prospective study of 356 222 American men, aged 35 to 57 years in 1973 to 1975, demonstrated that the relationship between serum cholesterol and risk of cardiovascular disease death was continuous, graded (dose related), and strong over the entire range of the distribution of cholesterol levels. The Shanghai Study: Chen et al. followed 9021 men and women aged 35 to 64 from urban Shanghai, China, for 8–13 years and found that even for cholesterol levels significantly lower than those in the MRFIT study, there was a significant correlation between cholesterol levels and atherosclerotic cardiovascular disease death, with the risk increasing 4.5 times from the lower values to the higher and no apparent threshold. MRFIT study figure source data from: Stamler J, et al. (1986). Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA, 256(20), 2823–8. Shanghai Study figure source data from: Chen Z, et al. (1991). Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. BMJ, 303(6797), 276–82. Non-fasting triglycerides (mmol/L) Mainly fasting triglycerides (mmol/L) 0 1 2 3 4 5 Hazard ratio (95% CIs) for ASCVH N = 93410 (cardiac events = 7183) Median follow-up 6 years N = 302430 (cardiac events = 12785) Median follow-up 8 years Copenhagen City Heart Study and Copenhagen General Population Study Emerging Risk Factors Collaboration 0 1 1 2 3 1 2 3 4 5 6 7 2 3 4 5 Hazard ratio (95% CIs) for ASCVD 4 Fig. 12.6.16 Population triglyceride levels and cardiovascular disease risk. Observational associations between raised concentrations of triglycerides and cardiovascular disease in the Copenhagen City Heart Study and Copenhagen General Population Study combined (left) and in the Emerging Risk Factors Collaboration (right). Hazard ratios were estimated by Cox proportional hazard regression models, and were adjusted for age, sex, and trial group. From Nordestgaard BG and Varbo A (2014) Triglycerides and cardiovascular disease. Lancet, 384 (9943):626–35.

section 12 Metabolic disorders 2070 Primary factors affecting intestinal lipid absorption Polymorphic genetic variation at the APOE locus accounts for about a quarter of variability in the absorption of cholesterol. APOE2 car- riers have the lowest absorption and APOE4 carriers the highest absorption. Those with an APOE4 allele also show a greater eleva- tion in plasma cholesterol levels in response to dietary cholesterol. Common variants of the cholesterol 7 α-hydroxylase gene (CYP7A1) also affect intestinal bile acids and cholesterol absorption. Rare mutations of the NPC1L1 gene decrease cholesterol absorption and are associated with a decreased risk of atherosclerotic cardiovascular disease. Sitosterolaemia Sitosterolaemia also known as ‘phytosterolaemia’ is a rare autosomal recessive disease. LDL-C levels can be normal to severely elevated in the familial hypercholesterolaemia (FH) range (see ‘Familial hyper- cholesterolaemia’). It results from a deleterious mutation in either of two related ABC half-transporter genes, ABCG5 and ABCG8, which are expressed in enterocytes and liver cells. ABCG5 and ABCG8 proteins heterodimerize to form a transporter for plant sterols such as sitosterol and campesterol, and cholesterol from the liver into bile and from the enterocytes into the gut. Normally approximately 5% of plant sterols are absorbed by the jejunum, and these are disposed of by secretion into bile after cycling through the liver. Consequently, systemic levels of plant sterols remain very low. Patients with sitosterolaemia have high jejunal absorption of plant sterols and cholesterol, but

biliary and faecal excretion is decreased causing high blood and tissue con- centrations of plant sterols and cholesterols. In the liver, the high level of sterols suppresses the expression of the LDLR gene, with low LDL-C clearance and high plasma cholesterol levels. In con- sequence, there is a failure to respond well to statins as the LDLR is not induced. Patients can have prominent tendon xanthomas, and these may be disproportionate to the cholesterol levels, and occurrence of prema- ture atherosclerotic cardiovascular disease. They also have abnormal haematological and liver function test results due to the presence of plant sterols in cell membranes. They can get attacks of haemolysis, and may have splenomegaly. These distinct clinical characteristics suggest the diagnosis: tendon xanthomas, perhaps in disproportion to the cholesterol levels, and high cholesterol in the absence of a family history of atherosclerotic cardiovascular disease. A further clue to the clinical diagnosis is a poor response to statins. The diagnosis is made by the laboratory finding of high blood levels of sitosterol and campesterol, and gene sequencing. The diagnosis is important because a low plant sterol diet, cholesterol absorption inhibitors, and bile acid sequestrants are highly effective treatments, while statins are less so. LDL and sitosterol blood levels require monitoring as elevated plant sterols are themselves atherogenic. Acquired (secondary) factors affecting intestinal lipid absorption Secondary factors such as dietary fibre and plant sterol consump- tion affect cholesterol absorption. The microbiome is increasingly recognized as important. Intestinal bacteria dehydroxylate and deconjugate bile acids, and this affects cholesterol absorption. They also break down nonabsorbable dietary constituents rendering them absorbable and a source of nutrients. Stanols are synthesized as a gut microbial byproduct of cholesterol metabolism. Despite the primary and secondary factors affecting cholesterol absorption, a 1-g per day difference in dietary intake of cholesterol on average only results in a 5% change in plasma cholesterol. This is the main reason why restriction in dietary cholesterol intake is no longer recommended in the United States of America (see ‘Treatment of dyslipidaemia’ and ‘Lifestyle’). HDL-C allele score Restricted (19 SNPs) 16 (11826,53514) LogTG allele score Restricted (27 SNPs) .. .. .. LDL-C allele score Restricted (19 SNPs) .. .. .. 0.91 (0.42, 1.98) 0.817 1.61 (1.00, 2.59) 0.05 1.92 (1.68, 2.19) 4.6x10–22 0.5 1 2 3 Odds ratio Allele score Studies (cases, total) Odds ratio per 1 unit increase in lipid (95% CI) P-value Fig. 12.6.17 Mendelian randomization of HDL, TG, and LDL for atherosclerotic cardiovascular disease risk. This meta-analysis demonstrates the effect of a 1-unit increase in blood lipid traits on atherosclerotic cardiovascular disease risk. The genetic findings support a causal effect of triglycerides and LDL on atherosclerotic cardiovascular disease risk, but a causal role for HDL-C is not clear. Estimates were derived incorporating data on the association between the allele scores and blood lipid traits from prospective cohorts (in which most individuals were free from disease when lipid traits were measured) and applying this estimate to all studies with data on the association between the scores and coronary heart disease. Adapted from: Holmes MV, et al. (2015) Mendelian randomization of blood lipids for coronary heart disease. Eur Heart J. 36(9):539–50.

 Interindividual variation in cholesterol absorption and response in plasma cholesterol levels does, however, have therapeutic impli- cations. High absorbers respond well to dietary restriction of choles- terol and in turn to ezetimibe treatment, and low absorbers respond poorly. The measurement of noncholesterol sterols and stanol concen- trations provides a measure of cholesterol absorption status—high absorbers have high plant sterol plasma levels—but these tests are not generally available, nor are they fully validated. ApoE4 carriers also have higher levels of cholesterol absorption, and tend to show a poor response to statins, perhaps partly due to the effect of apoE4 on cholesterol absorption. Empirical use of a low-cholesterol diet in those with

hyperchol- esterolaemia is well worthwhile as high absorbers may show a dra- matic effect. Patients with a poor response to ezetimibe are likely to be low absorbers. Chronic kidney disease (CKD) patients respond well to ezetimibe with reduction in atherosclerotic cardiovascular disease events, when used with statins, potentially implicating increased cholesterol absorption in chronic renal disease. Reduced production of chylomicrons and VLDL by the intestine and liver Primary factors affecting production of chylomicrons and VLDL Abetalipoproteinaemia The production of apoB48-containing chylomicrons and apoB100- containing VLDL in the gut and liver respectively requires MTTP to load the nascent lipoproteins with TGs, phospholipids, and fat- soluble vitamins (as discussed previously). Abetalipoproteinaemia is a rare Mendelian recessive disorder caused by deleterious mutations of the MTTP gene. Blood levels of cholesterol and TG are exceptionally low, and chylomicrons, VLDL, LDLs, and apoB are absent from blood. Parents display normal lipid and apoB-containing lipoprotein levels. Affected infants may ap- pear normal at birth, but by the first month of life fail to thrive; they develop steatorrhea, abdominal distention, and growth retardation due to fat and fat-soluble vitamin malabsorption. Neurological and retinal abnormalities occur due to fat-soluble vitamin deficiency, particularly of vitamins E and A, which are nor- mally carried to the liver by chylomicrons and chylomicron rem- nants. Vitamin E is then transported on VLDL out of the liver to other tissues. Infants develop neurological abnormalities with loss of reflexes and decreased vibration and joint position sense. Later in life, in the third and fourth decade, ataxia and a spastic gait develop. A pigmented ret- inopathy is also characteristic, with reduced night-time and colour vision and later eventually blindness. This constellation of clinical fea- tures is similar to Friedreich’s ataxia, and can lead to incorrect diag- nosis. In addition, patients have acanthocytosis of red blood cells. The diagnosis is made by intestinal biopsy and special fat staining as with oil red O, which shows fat accumulation in enterocytes, and confirmed by DNA sequencing of the MTTP gene. Diagnosis and management is best achieved in specialized centres. Abetalipoproteinaemia patients are treated with a low-fat, high- calorie diet, and large parenteral fat-soluble vitamin supplements especially of vitamin E. Early treatment is essential to prevent neurological complications, which can still develop even with ap- propriate parenteral vitamin supplements. Medium-chain TGs can be helpful, with the caveat that their long-term use may be hepato- toxic. Without treatment death is usually by the third decade. In later life, due to failure to export lipid there is chronic fatty liver, often with raised transaminases, and there is increased fibrosis, pro-gressing sometimes to cirrhosis. Hypobetalipoproteinaemia Hypobetalipoproteinaemia is an autosomal codominant disorder caused by mutation of the APOB gene, with low TC, LDL-C, and apoB levels. Often mutations lead to the formation of truncated apoB, with defective chylomicron and VLDL and the formation of small lipoproteins that are rapidly removed from the blood. The diagnosis is based on the lipid levels and inheritance pattern. DNA sequencing will confirm the diagnosis, but is not usually done as the gene is large. Heterozygotes often have TCs of approximately 2.5 mmol/litre (100 mg/dl), TGs of approximately 0.5 mmol/litre (45 mg/dl), and LDL-C levels below 1.25 mmol/litre (50 mg/dl). ApoB levels are approximately 20 mmol/litre (60–140 mg/dl, 5th to 95th percentile). Vitamin E levels tend to be mildly reduced or low normal. Fatty liver with raised transaminases is common, though not as marked as in abetalipoproteinaemia. Inflammation with pro- gression to fibrosis and cirrhosis is not frequent. Hypobetalipoproteinaemia patients tend to be long-lived, pre- sumably due to the low levels of LDL-C and reduced atherosclerotic cardiovascular disease. Hypobetalipoproteinaemia homozygotes are very rare. They resemble abetalipoproteinaemia, but the parents are typical hypobetalipoproteinaemia heterozygotes, and the fat-soluble vitamin deficiency and neurological sequelae less problematic,

because of the ability to transport some fat. Again, diagnosis can be made by intestinal biopsy showing fat accumulation in the enterocytes. PCSK9 deficiency PCSK9 deficiency also causes very low remnant and LDL plasma levels, and is discussed further later in this chapter. Acquired (secondary) factors affecting production of chylomicrons and VLDL Very low levels of apoB-containing lipoproteins with LDL-C below 1.5 mmol/litre (60 mg/dl) can be a feature of serious chronic illness such as cirrhosis, cancer cachexia, malnutrition, or malabsorption. In the generally well person, however, it may reflect genetic defi- ciency of apoB-containing lipoproteins (see 'Abetalipoproteinaemia' and 'Hypobetalipoproteinaemia'). Overproduction of VLDL by the liver and dyslipidaemia Mixed (combined) dyslipidaemia with elevated fasting levels of TGs, increased TC, and low levels of HDL is often seen in clinical practice. Excess production of the VLDL by the liver is a common cause of mixed dyslipidaemia. It is usually caused by a combination of gen- etic (primary) and acquired (secondary) factors. Mixed dyslipidaemia is often associated with the metabolic syn- drome, which includes obesity, insulin resistance, hypertension, diabetes, renal disease, and pre-eclampsia (Table 12.6.4). Often there is sdLDL. Hypertriglyceridaemia and excess sdLDL with low

 levels of HDL is called 'atherogenic dyslipidaemia', because of its as- sociation with atherosclerotic cardiovascular disease (Table 12.6.1, Fig. 12.6.17). SdLDL is produced by vascular remodelling of lipoproteins as a result of metabolic disturbance. The key predisposing factor is hypertriglyceridaemia with large VLDL, which leads to the forma- tion of slowly metabolized LDL particles that are subject to exchange processes with removal of cholesteryl ester from the particle core and replacement with TG. This altered LDL is a substrate for HL, and lipolysis generates sdLDL. SdLDL shows defective clearance by the LDLR, increased vascular proteoglycan binding, and suscepti- bility to oxidation, rendering it more atherogenic. The metabolic factors associated with the formation of sdLDL also probably con- tribute to atherosclerotic cardiovascular disease. Mixed dyslipidaemia is also associated with a carbohydrate-rich diet, excessive alcohol consumption, and drugs such as oestrogen (Table 12.6.4). Primary causes of VLDL overproduction Common and low-frequency variants of a number of genes that increase the risk of atherosclerotic cardiovascular disease are asso- ciated with VLDL overproduction. Mendelian causes are listed in Table 12.6.5. Familial combined hyperlipidaemia (FCHL) FCHL features increased levels of apoB-containing lipoprotein pro- duction from the liver giving rise to elevated levels of fasting VLDL TG, LDL-C, and often low levels of HDL. TG levels vary between 3 and 7 mmol/litre (265 and 620 mg/dl), TC levels between 5 and 10 mmol/litre (200 and 400 mg/dl), and HDL-C below 1 mmol/ litre (40 mg/dl) in males and 1.25 mmol/litre (50 mg/dl) in females. Patients tend to have sdLDL and plasma apoB levels are increased. Sometimes LDL-C levels can be normal, but LDL particle number and apoB levels are increased, indicative of sdLDL. This condition has been called hyperapoB. FCHL affects about 1% of people. About a quarter of patients with FCHL develop premature atherosclerotic cardiovascular dis- ease (men <55 years and women <65 years). The lipid phenotype (high TC or TG or both) in an individual can vary from time to time depending on metabolic factors such as diet, exercise, overweight, insulin resistance, and diabetes. FCHL often does not emerge until early or even middle adult life probably due to the accumulation of the metabolic factors, which contribute to the phenotype. It is rarely seen in children. Although the FCHL clusters in families, the lipid phenotype varies between individuals. While inheritance studies have suggested major gene effects, the mode of inheritance is non-Mendelian, and no single gene defect has been identified to cause this disorder. Rather, it is likely to be polygenic due to the clustering of several genes with significant

gen- etic variation. The diagnosis is indicated by family history, and the finding of mixed dyslipidaemia, or isolated raised TC or TGs in family mem- bers, in whom the lipid phenotype varies, and low HDL. ApoB levels are always high. Early treatment should be vigorous because of the high risk of premature atherosclerotic cardiovascular disease. Dietary interven- tion should include decreased intake of sugar and starch, which are turned into TG by the liver and secreted as VLDL (Table 12.6.6), in conjunction with weight reduction and physical exercise. Insulin resistance should be recognized and treated. Diabetes should be aggressively managed. High-intensity lipid lowering with statins is indicated, often with omega-3 fatty acids derived from fish. Fibrates are indicated if the TGs are not reduced by statin and omega-3 fatty acid treat- ment (Tables 12.6.7 and 12.6.8), and the benefits outweigh the risk Table 12.6.4 Secondary causes of dyslipidaemia VLDL elevated LDL elevated LDL reduced Obesity Type 2 diabetes Glycogen storage disease Nephrotic syndrome Hepatitis Alcohol Renal failure Sepsis Cushing's syndrome Pregnancy Acromegaly Lipodystrophy Drugs: oestrogen, β-blockers, glucocorticoids, bile acid binding resins, retinoic acid Hypothyroidism Nephrotic syndrome Cholestasis Acute intermittent porphyria Anorexia nervosa Hepatoma Drugs: thiazides, ciclosporin, carbamazepine Severe liver disease Malabsorption Malnutrition Gaucher's disease Chronic infectious disease Hyperthyroidism Drugs: nicotinic acid IDL elevated Chylomicrons elevated HDL elevated HDL reduced Lp(a) elevated Multiple myeloma Monoclonal gammopathy Autoimmune disease Hypothyroidism Autoimmune disease Type 2 diabetes Alcohol Exercise Exposure to chlorinated hydrocarbons Drugs: oestrogen Obesity Type 2 diabetes Smoking Gaucher's disease Acute glomerular nephritis Chronic kidney disease Nephrotic syndrome Inflammation Menopause Orchidectomy Hypothyroidism Acromegaly Drugs: growth hormone, isotretinoin

12.6 Lipid disorders 2073 of rhabdomyolysis with combined statin and fibrate use (see 'Drug treatment of hypertriglyceridaemia'). Lipodystrophy In lipodystrophy, there is a marked reduction in adipose tissue, which may affect all or just some adipose depots (partial lipodystrophy). There is dyslipidaemia with raised TGs, TC, and low HDL. VLDL is overproduced and there is decreased lip- olysis of TG-rich chylomicrons and VLDL. Complete absence of fat is sometimes congenital. It is associated with absence of leptin. A variety of causal gene defects have been described. It is very rare. Table 12.6.5 Genetic defects affecting apoB-containing lipoprotein metabolism Genetic disorder Gene defect Lipoproteins elevated Clinical findings Hypercholesterolaemia Familial hypercholesterolaemia (AD) LDL receptor (LDLR) LDL Tendon xanthomas, CHD Familial defective apoB100 (AD) ApoB100 (APOB) LDL Tendon xanthomas, CHD Autosomal dominant hypercholesterolaemia, type 3 (AD) PCSK9 (PCSK9) LDL Tendon xanthomas, CHD Autosomal recessive hypercholesterolaemia (AR) ARH (LDLRAP) LDL Tendon xanthomas, CHD Sitosterolaemia (AR) ABCG5 or ABCG8 LDL Tendon xanthomas, CHD Hypertriglyceridaemia Lipoprotein lipase deficiency (AR) LPL (LPL) CM, VLDL Eruptive xanthomas, hepatosplenomegaly, pancreatitis Familial apoC2 deficiency (AR) ApoC2 (APOC2) CM, VLDL Eruptive xanthomas, hepatosplenomegaly, pancreatitis ApoA5 deficiency (AR) ApoA5 (APOA5) CM, VLDL Eruptive xanthomas, hepatosplenomegaly, pancreatitis GPIHBPI deficiency (AR) GPIHBP1 CM Eruptive xanthomas, pancreatitis LMFI deficiency Eruptive xanthomas, pancreatitis Combined hyperlipidaemia Familial hepatic lipase deficiency (AR) Hepatic lipase (LIPC) VLDL remnants, HDL Pancreatitis, CHD Familial dysbetalipoproteinaemia (AR) ApoE (APOE) CM remnants VLDL remnants Palmer and tuberoeruptive xanthomas AD, autosomal dominant; AR, autosomal recessive; CHD, coronary heart disease; CM, chylomicron. Table 12.6.6 Cardioprotective lifestyle measures Diet • Total fat intake 30% or less of total energy intake, with saturated fat 7% or less of energy, and minimal trans fat.

Saturated fat should be replaced by mono-unsaturated and poly-unsaturated fats (in moderation). Cholesterol intake should be limited to 300 mg daily • Replace fat from animal sources with mono-unsaturated fat from olive oil or rape seed oil, or spreads made from these oils • Try to eat red meat no more than 3–4 times weekly • Instead of frying foods—which adds unnecessary fats and calories—use cooking methods that add little or no fat, like stir-frying, grilling, baking, poaching, and steaming • Avoid overheating cooking oils to their smoke-point as this causes oils to lose their beneficial nutrients and forms trans fats • Avoid prolonged storage of oils, especially in the light, as this causes oils to become rancid through the formation of compounds like butyrate which, though not harmful, taste unpleasant • Choose wholegrain varieties of starchy food • Reduce sugar intake from food and drink, and this will reduce both glucose and fructose • Eat at least five portions of fruit and vegetable daily, but beware starchy vegetables, and very sweet fruit in excess, raw is better than cooked • Eat two portions of fish per week, including one of oily fish • Eat at least four to five portions of unsalted nuts, seeds, and legumes per week Exercise • 3000–4000 metabolic equivalent of tasks (MET) minutes a week.a This can be a combination of many different activities • For example, to reach the total number, one could do all of these every day: • Climbing stairs for 10 min • Vacuuming for 15 min • Gardening for 20 min • Running for 20 min • Walking or cycling for 25 min • Or do all of these every day: • Biking for an hour • Walking the dog for 30 min at a leisurely stroll • Cooking and washing dishes for 30 min • Or do this every day: • Running at a vigorous pace for an hour • Weight loss, avoidance of excessive alcohol consumption, and smoking cessation are to be strongly encouraged Notes: recent guidelines from the United States of America no longer restrict cholesterol consumption as, on average, this does not greatly impact plasma cholesterol levels. Cholesterol consumption is best limited in those with hypercholesterolaemia, as individuals vary greatly in the amount they absorb and the effect of this on plasma levels of cholesterol. Two large meta-analyses have suggested that reduction in saturated fat consumption and increased unsaturated fat consumption does not decrease atherosclerotic cardiovascular disease risk. The interpretation of these conclusions is unclear as other studies indicate benefit from reduced saturated fat consumption. a Kyu H, Bachman V, Alexander L, et al. (2016) Physical activity and risks of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ, 354, i3857.

section 12 Metabolic disorders 2074 Primary partial lipodystrophy is a codominant disorder associated with defects of lamin A and other genes. Acquired partial lipodystrophy is described in membranoproliferative glom- erulonephritis and autoimmune diseases such as systemic lupus erythematosus, often with complement C3 consumption and the presence of C3 nephritic factor. Partial lipodystrophy is associated with decreased fat on the torso and limbs, though there may also be increased fat in other areas such as the face. Insulin resistance is very common, and this may be profound. There is usually hepatic steatosis, and this can be exacerbated by cer- tain drugs that block VLDL secretion such as nicotinic acid. Diabetes may develop. Acute pancreatitis can be precipitated by various drugs (Table 12.6.4). Patients with partial lipodystrophy are at increased risk of athero- sclerotic cardiovascular disease. Treatment can be difficult, especially in complete lipodystrophy. The treatment of the dyslipidaemia is similar to that in FCHL, focusing on the insulin resistance and diabetes. GPD1 deficiency This is a very rare autosomal disorder caused by mutations in the GPD1 (glycerol-3-phosphate dehydrogenase) protein, which cata- lyses the reversible redox reaction of dihydroxyacetone phosphate and NADH to glycerol-3-phosphate and NAD. Presentation is with massive hepatomegaly, steatosis, and marked, albeit transient,

hypertriglyceridemia in infancy. VLDL production is increased. The hypertriglyceridaemia corrects with age. Acquired (secondary) causes of increased VLDL production. Acquired causes of VLDL overproduction often accompany primary causes, particularly as this condition is polygenic in origin. The sec- ondary causes of dyslipidaemia are listed in Table 12.6.4. Diet and alcohol Excess dietary sugar and starch are rapidly turned into fatty acids and then TGs by the liver leading to increased VLDL production. Dietary carbohydrate excess is very common in Western society. Table 12.6.7 Statin characteristics Drug Reduction in TC (%) Reduction in LDL-C (%) Reduction in TG (%) Increase in HDL-C (%) Metabolism Half-life (h) Hydrophilic Pravastatin 16–25 22–34 15–24 2–12 Sulphation 2–3 Hydrophilic Fluvastatin 16–27 22–36 12–25 3–11 CYP2C9 0.5–3.0 Lipophilic Simvastatin 19-36 26–47 12–34 8–16 CYP3A4 1–3 Lipophilic Atorvastatin 25–45 26–60 17–53 5–13 CYP3A4 13–30 Lipophilic Rosuvastatin 33–46 45–63 10–35 8–14 CYP2C9 19 Hydrophilic Pitavastatin 20–45 20–48 6–24 14–25 CYP2C9 11 Lipophilic Table 12.6.8 Nonstatin lipid-lowering drugs Major indications Starting dose Maximal dose Mechanism of action Common side effects Cholesterol absorption blockers Ezetimibe Elevated LDL-C 10 mg daily 10 mg daily ↓Cholesterol absorption, ↑LDL receptors Headache, dyspepsia Bile acid sequestrants Colesevelam Cholestyramine Colestipol Elevated LDL-C 3.75 g daily 4 g daily 5 g daily 4.375 g daily 32 g daily 40 g daily ↑Bile acid excretion and ↑LDL receptors Constipation, worsening hypertriglyceridaemia MTP inhibitor Lomitapide HoFH 5 mg daily 60 mg daily ↓VLDL production Nausea, steatorrhoea, increased hepatic fat ApoB inhibitor Mipomersen HoFH 200 mg SC weekly 200 mg SC weekly ↓VLDL production Injection site reactions, flu-like symptoms, increased hepatic fat Fibric acid derivativesa Gemfibrozil Fenofibrate Bezofibrate Elevated TG 300 mg twice daily 67 mg once daily 400 mg once daily 600 mg twice daily 267 mg once daily 400 mg once daily ↑LPL ↓VLDL production Dyspepsia, myalgia, gallstones, elevated transaminases Omega-3 fatty acids Omega-3 fatty acid ethyl esters Elevated TG 2 g daily 4 g daily ↓VLDL synthesis ↑TG catabolism Dyspepsia HoFH, homozygous FH. a With concomitant statin, there is an increased risk of myopathy and rhabdomyolysis; use reduced dose. Risk highest with gemfibrozil.

12.6 Lipid disorders 2075 Too much, frequent alcohol consumption impairs fatty acid β- oxidation leading to increased TGs and VLDL production, often in the presence of raised HDL-C caused by an increased transport rate of apoA1 and apoA2. Elevated TGs and HDL-C found together sug- gests excessive alcohol consumption. Obesity, insulin resistance, and type 2 diabetes (See Chapters 11.5, 11.6, and 13.9.1.) Dyslipidaemia is a common finding in obesity, insulin resistance with hyperinsulinaemia, and diabetes. The dyslipidaemia features raised TGs and low HDL-C; often with raised LDL-C and sdLDL—atherogenic dyslipidaemia. Overweight and obesity are associated with inflammation in fat tissue leading to insulin resistance, hyperinsulinaemia, and per- turbed lipid metabolism—the metabolic syndrome. A prominent characteristic is VLDL overproduction from the liver, which is driven by free fatty acids released from fat tissue and transported to the liver principally on albumin. In the liver, free fatty acid is converted to TG and phospholipid and assembled into VLDL for discharge into the blood, and this is favoured by hyperinsulinaemia. Accompanying reduction in LPL function, with impaired lipolysis of chylomicrons and VLDL TG, worsens the ele- vation of TGs. The metabolic syndrome is associated with a serious excess risk of atherosclerotic cardiovascular disease. The treatment is weight loss and good diabetes control. Lipid lowering medication may be required, and should be considered in diabetes. Cushing’s syndrome (See Chapter 13.5.1.) Glucocorticosteroid excess due to Cushing’s syndrome or glucocorticoid treatment causes increased fatty acid and TG biosynthesis, VLDL overproduction, and elevated blood TGs. Cushing’s syndrome sufferers often have raised TGs and low HDL-C, and

sometimes high LDL-C. Glucocorticoid-induced in- sulin resistance may contribute to VLDL overproduction. The management is that of Cushing's syndrome, or modulation of the therapeutic doses of glucocorticoids. Nephrotic syndrome (See Chapters 21.3 and 21.6.) Increased VLDL secretion is common in the nephrotic syndrome. This is considered to be caused by the low oncotic pressure in blood due to hypoalbuminaemia leading to increased biosynthesis of liver protein, but the mechanism for this is not understood. Treatment of the kidney disease is im- portant to decrease the loss of albumin in the urine and correct the hypoalbuminaemia. Unrelieved nephrotic syndrome is likely to need lipid-lowering drug treatment. Liver disease The liver affects lipoprotein metabolism through several pro- cesses because it is both a major organ of lipoprotein synthesis and of clearance. VLDL production is increased with modest hypertriglyceridaemia in hepatitis caused by viruses, alcohol, and medications. Failure of VLDL synthesis with marked reduction in plasma chol- esterol and TGs occurs in severe hepatitis and hepatic failure. Bile is an important channel for excretion of cholesterol, either after conversion to bile acids or directly as cholesterol. Markedly raised plasma cholesterol levels can occur in cholestatic disease, which impairs biliary cholesterol excretion. Free cholesterol and phospholipids are secreted into the blood as a lamellar particle des- ignated lipoprotein-X (LP-X). LP-X can form xanthomas in skin folds similar to those found in FDBL (xanthomata striata palmaris), as well as planar and eruptive xanthomas. Statins appear to be safe and effective in severe chronic cholestasis such as in primary biliary cirrhosis. Increased liver transaminases and statin treatment are dis- cussed later in this chapter (see 'Drug treatment of hypercholester- olaemia' and 'Statins'). Defective peripheral lipolysis and dyslipidaemia The main goal in severe hypertriglyceridaemia is to prevent acute pancreatitis (see 'Drug treatment of hypertriglyceridaemia'). Raised plasma TGs are also associated with an increased risk of atheroscler- otic cardiovascular disease. Decreased lipolysis of TG-rich lipoproteins is commonly associ- ated with dyslipidaemia. LPL is the principal enzyme responsible for the peripheral lipolysis of chylomicron and VLDL TGs. Decreased LPL activity gives rise to fasting hypertriglyceridaemia with low levels of HDL-C, mostly in the absence of raised LDL-C or apoB. LPL is synthesized by and secreted from adipocytes, and skeletal and heart muscle cells, where it becomes bound to vascular endothelial cells through GPIHBP1. ApoC2 is a necessary cofactor for activation of LPL. ApoA5 and LMF1 activate and mature LPL respectively. LPL may be reduced for genetic or acquired reasons. Primary causes of defective lipolysis of triglyceride-rich lipoproteins Fifty per cent of the variance of TG levels has a genetic basis, and is likely to be caused by a combination of common and low-frequency genetic variants, and rare alleles. Variants are described in multiple genes that cause increased plasma TG levels, and several of these affect lipolysis. Numerous variants are also described in LPL and genes directly associated with LPL activity, and some of these are associated with Mendelian recessive forms of hypertriglyceridaemia (Table 12.6.5). Familial chylomicronaemia (syndrome) Primary deficiency of LPL or of its cofactor apoC2 causes marked hypertriglyceridaemia (type 1 and 5 hyperlipoproteinaemia) (Table 12.6.3). Fasting TG levels are invariably greater than 10 mmol/litre (900 mg/dl), and can be 20 to 40 times normal with levels of 30 to 65 mmol/litre (2500–5700 mg/dl). In the nonfasting state, particularly when there are intercurrent factors such as poorly controlled diabetes, plasma TG levels can reach 100 times the normal value with levels of 170 mmol/litre (15 000 mg/dl). In type 5 hyperlipidaemia, where increased VLDL production is prominent, fasting cholesterol levels can be five times normal. Primary LPL deficiency is an autosomal recessive disorder with a frequency of around 1 per million people. It is best characterized for mutations of the LPL and APOC2 genes, but mutants of APOA5, GPIHBP1, and LMF1 (see 'Chylomicronaemia due to other gene de- fects') can all cause chylomicronaemia with a type 1 or 5 'hyperlipid- aemia pattern'. Many causal mutations of LPL and

APOC2 have been described. LPL heterozygotes often have mild to moderate eleva- tions of TG. APOC2 defective heterozygotes do not. Type 1 ‘hyper- lipidaemia’ is more likely to be caused by null alleles, and type 5 by less deleterious alleles.

section 12 Metabolic disorders 2076 Nearly all patients have recurrent episodes of severe abdom- inal pain, with or without overt acute pancreatitis, that interfere with normal life and result in frequent hospitalizations. These episodes can result in chronic pancreatitis and symptoms of exo- crine or endocrine pancreatic insufficiency, including diabetes and even fatal events. Other symptoms include arthralgia and neuro- logical symptoms such as loss of feeling in the feet or legs, and memory loss. On physical examination, patients may display small yellowish papules (eruptive xanthomas), which are often grouped on the ex- tensor surfaces of the arms and legs, back, and buttocks. They are painless, but may itch. Visualization of the fundus reveals milky- white discoloration of retinal blood vessels—lipaemia retinalis. Hepatosplenomegaly may be caused by chylomicron uptake by the mononuclear phagocyte system. Not all patients develop acute pan- creatitis or the cutaneous features. There is an increased risk of ath- erosclerotic cardiovascular disease, but premature atherosclerotic cardiovascular disease is not a major manifestation. A simple diagnostic test is to place a fasting plasma sample in the refrigerator at 4°C overnight. Colloquially this is called the ‘fridge test’ or refrigerator test. Chylomicrons are of low density and float to the top, where they form a narrow, creamy band with a clear or mildly cloudy infranatant (type 1), or the infranatant may be more markedly turbid (type 5); this infranatant is VLDL and remnants. The diagnosis is best confirmed by showing absence of lipase ac- tivity for TGs in postheparin plasma, which releases endothelium- bound LPL. LPL activity is very low in LPL and apoC2 defective patients. In apoC2- or apoA5-deficient patients, however, it is cor- rected by supplementing apoC2 or apoA5 from normal plasma. DNA sequencing of the LPL, APOC2, APOA5, GPIHBP1, and LMF1, and possibly other hypertriglyceridaemic genes, will help es- tablish the diagnosis. In the short term, the management of very severe hyper triglyceridaemia to prevent acute pancreatitis is as described in ‘Drug treatment of hypertriglyceridaemia’. For the long-term treat- ment of chylomicronaemia, dietary fat restriction to less than 20 to 30 g daily with fat-soluble vitamin supplementation is neces- sary. Calories can be supplemented with medium-chain TGs which provide energy, as they are absorbed directly into the portal vein, though there is a possibility of liver damage with long-term treat- ment. Exercise can reduce TG levels. Secondary factors, commonly diabetes, should be vigorously treated, and those drugs that increase TGs avoided or substituted. Factors that increase VLDL production will overwhelm residual LPL function and greatly worsen hypertriglyceridaemia. Fibrates are the drugs of first choice in the management of severe hypertriglyceridaemia (Table 12.6.8). Omega-3 fatty acids (fish oils) act by decreasing VLDL secretion so that they are not useful in pure LPL deficiency, where they can increase hypertriglyceridaemia (see ‘Omega-3 fatty acids’). In type 5 ‘hyperlipoproteinaemia’, they are an important treatment and can be used at doses well in excess of doses normally used in patients with mild forms of hypertriglyceridaemia, particularly for short periods. Gene therapy with LPL has also been trialled using an adeno- associated viral vector containing the LPL gain-of-function variant (Alipogene Tiparvovec) given by intramuscular injection leading to myocyte expression of LPL. A second-generation modified anti- sense APOC3 mRNA inhibitor (2′-O-(2-methoxyethyl)- modified antisense oligonucleotide) has also proved remarkably efficacious as a treatment, confirming the role of apoC3 in the LPL-mediated metabolism of TG-rich lipoproteins. Small- molecule inhibitors or DGAT1 and MTTP are efficacious in reducing TG absorption, but are not licensed for this use. The management of primary hypertriglyceridaemia is particu- larly

troublesome in acute hypertriglyceridaemic pancreatitis and during pregnancy, which are discussed in ‘Drug treatment of hypertriglyceridaemia’. Chylomicronaemia due to other gene defects Deleterious mutations of APOA5, GPIHBP1, and LMF1 can all cause chylomicronaemia syndrome with a type 1 or 5 ‘hyperlipidaemia pattern’. Affected patients can be homozygotes or even be heterozy- gous for defects of two of these genes acting together to reduce LPL activity, and produce the type 1 or 5 ‘hyperlipidaemia pattern’, par- ticularly type 5. LMF1 mutations cause combined lipase deficiency. DNA sequencing of these genes will disclose mutations in more than 80% of cases of type 1 and 60% of type 5 ‘hyperlipidaemia’. Others genes, which have yet to be characterized and secondary factors con- tribute to this phenotype. The treatment is as previously described. Familial hypertriglyceridaemia (FHTG) FHTG features raised fasting TGs, in the range 2.3 to 10 mmol/litre (200 to 900 mg/dl) without another primary or secondary reason, often low levels of HDL-C, and familial clustering. LDL-C levels may be normal or low due to reduced formation from TG-rich lipo- proteins in the blood. ApoB levels unlike in FCHL are normal, and the risk of atherosclerotic cardiovascular disease is not usually very high. There is generally reduced lipolysis of TG-rich lipoproteins, often with overproduction of VLDL by the liver. The blood is likely to display a type 4 ‘hyperlipoproteinaemia picture’ without chylomicrons rather than type 1 or 5. Acquired factors can worsen the hypertriglyceridaemia and give risk to chylomicronaemia and acute pancreatitis (see ‘Secondary causes of impaired lipolysis’). No single gene has been identified, rather the condition appears to be caused by a combination of gene variants leading to polygenic hypertriglyceridaemia. It is important to identify and treat associ- ated acquired causes. Diet and exercise are valuable. Lipid-lowering medication, with statins (if plasma TGs are <5 mmol/litre (450 mg/ dl)), fibrates, and fish oils may be required to treat higher TG levels. The risks of the combined use of statins and fibrates are shown in Table 12.6.8. Acquired (secondary) causes of impaired lipolysis of triglyceride-rich lipoproteins The secondary causes of dyslipidaemia are listed in Table 12.6.4. Obesity, insulin resistance, and type 2 diabetes (See Chapters 11.5, 11.6, and 13.9.1.) Obesity, insulin resistance, and type 2 diabetes are associated with increased VLDL secretion, but can also decrease LPL activity. There may be decreased expres- sion of the LPL gene in peripheral tissues, and increased expres- sion of the gene for the LPL inhibitor apoC3 in the liver leading to hypertriglyceridaemia. Clinical management is by weight loss and good diabetes control. Lipid-lowering medication may be required.

 Alcohol As well as increasing VLDL secretion, excessive alcohol significantly decreases LPL activity. Defective hepatic clearance of remnants and LDL as a cause of dyslipidaemia Defective clearance of LDL and chylomicron and VLDL lipoprotein remnants by the hepatic LDLR is a frequent cause of dyslipidaemia. It is caused by genetic and acquired factors. Variation in a number of genes interferes with lipoprotein clearance by the LDLR and these may give rise to polygenic disorders with elevated cholesterol. Mendelian disorders, which give rise to defective hepatic clear- ance of apoB-containing lipoproteins, can cause marked elevation of LDL-C with premature atherosclerotic cardiovascular disease (Table 12.6.5). The clinical features of polygenic and Mendelian hypercholesterolaemia overlap. A diet high in saturated and trans fats decreases LDLR activity and increases plasma cholesterol levels, which can worsen genetic causes of hypercholesterolaemia. Hypothyroidism, CKD, and oes- trogen deficiency after the menopause are associated with reduced LDLR activity. Primary (genetic) causes of impaired liver uptake of lipoproteins Multiple common gene variants have been identified that affect clearance of LDL and remnant lipoproteins by the LDLR. Indeed, more than 50% of the variation in LDL-C levels is determined by genetic factors. In people with predominantly hypercholesterolaemia (type 2a and b

‘hyperlipidaemia’; Table 12.6.3) who do not show Mendelian inheritance, and do not have the features of one of the very rare primary hypercholesterolaemia syndromes de- scribed in the following subsections, in whom a DNA diagnosis is not made, polygenic hypercholesterolaemia is likely. Plasma cholesterol levels often overlap with those found in FH, but the inheritance is not dominant, perhaps affecting around 10% of first-degree relatives. Inheritance of the number of variants to- gether with elevated cholesterol coupled with diet is generally the cause of this condition. In the evaluation of hypercholesterolaemia, however, single-gene Mendelian disorders are relatively common and should be con- sidered in the differential diagnosis (Table 12.6.5). Common genetic variants also exacerbate FH. Familial hypercholesterolaemia FH is an autosomal codominant disorder caused by deleterious mu- tation of the LDLR gene. Patients have asymptomatic high TC, due to elevation of remnants and LDL-C, without raised TGs, usually in the range of 7.5 to 10 mmol/litre (290–390 mg/dl). Premature ath- erosclerotic cardiovascular disease is very common. The frequency of heterozygous FH is as high as 1 in 200 of the population according to recent estimates. In certain populations, the frequency can be even higher due to a founder effect. These include Afrikaners in South Africa, French Canadians, Christian Lebanese, and the Finns. It is important to recognize and treat FH early so as to prevent ath- erosclerotic cardiovascular disease in middle life. Secondary causes of marked hypercholesterolaemia, including hypothyroidism, neph- rotic syndrome, and obstructive hepatic disease, must be excluded in the differential diagnosis. Numerous LDLR gene mutations have identified by DNA sequen- cing (Fig. 12.6.18). Some are recurrent due to small founder effects Class I: LDLR is not synthesized at all Class II: LDLR is not properly transported from the endoplasmic reticulum (receptor negative) to the Golgi apparatus for expression on the cell surface. Class III: LDLR does not properly bind LDL on the cell surface because of a defect in either apolipoprotein B100 (R3500Q) or in LDL-R. Class IV: LDLR bound to LDL does not properly cluster in clathrin-coated pits for receptor-mediated endocytosis. Class V: LDLR is not recycled back to the cell surface. Extent of LDLR deficiency will depend on deleteriousness of amino acid change. 1 Signal sequence 21 a.a. Ligand binding 292 a.a. EGF precursor homology 400 a.a. O-linked sugars 58 a.a. Membrane-spanning 22 a.a. Cytoplasmic 50 a.a. mRNA Binding Transport Recycling Transport PCSK9 binding No effect Secreted Internalization ARH binding Exon number 15 18 mRNA = 5.3 kb 3’ 5’ 45 kb 17 16 14 13 12 11 10 9 8 7 6 5 4 3 2 Fig. 12.6.18 LDL receptor gene (LDLR) structure and familial hypercholesterolaemia mutations.

 or possibly recurrent mutation at susceptible sites such as CpG dinucleotides. Mutations causing complete loss of LDLR activity (receptor nega- tive) compared to those with low activity (receptor defective) lead to higher levels of cholesterol. LDLR defects decrease hepatic clearance of LDL from the blood; removal of IDL is also decreased with in- creased production of LDL from IDL. Individuals with two mutated receptor alleles (FH homozygotes) with the same or different mu- tations (compound heterozygotes) have very much higher levels of LDL-C than those with one mutant allele (FH heterozygotes). Hypercholesterolaemia in FH patients is present from birth or be- fore. The early lesions of atherosclerosis, fatty streaks, can be seen in the fetus. Hypercholesterolaemia can be detected in the neonate if family history indicates the need for cholesterol measurement. Detection of FH is either due to finding hypercholesterolaemia on health assessment screening, suspicion due to adverse family history, the appearance of tendon xanthomas (Achilles tendon, dorsum of the hand or feet), cutaneous xanthelasmas, often with corneal arcus, or development of premature atherosclerotic cardiovascular disease. Clinical stigmata are present in many but not all patients

with het- erozygous FH, and this may depend on the level of cholesterol. Dominant inheritance causes an affected parent to transmit the disease to half of all children, so that usually there is a strong family history of premature atherosclerotic cardiovascular disease from the one half of the family harbouring the mutant LDLR gene. Polygenic factors from both sides of the family may confound this pattern. Untreated FH heterozygotes have a very high risk of premature atherosclerotic cardiovascular disease. Males have an approximately 50% likelihood of myocardial infarction before the age of 60 and females have an approximately 30% chance. The manifestations of atherosclerotic cardiovascular disease vary greatly in their age of ap- pearance. This may depend on the level of cholesterol determined by whether the LDLR mutation causes deficient (10% of mutations) or defective LDLR protein function (Fig. 12.6.18), and the presence of other atherosclerotic cardiovascular disease risk factors such as hypertension, smoking, obesity, diabetes, and elevation of Lp(a). DNA sequencing is the only definitive diagnostic test, and with advances in this technology, this becomes increasingly available in routine practice through specialized medical centres. Four genes are routinely analysed: LDLR, PCSK9, and LDLRAP by exon sequen- cing, and APOB by typing the glutamine for arginine at amino acid 3500 mutation (see ‘Familial defective apoB100 (FDB)’). A DNA diagnosis will be found in about 70% of patients with ‘definite’ FH (see ‘Simon Broome criteria’, Table 12.6.9). In those with possible FH on Simon Broome criteria, a DNA diagnosis will be found in about 30% because many of these patients have polygenic hypercholester- olaemia. DNA diagnosis facilitates family cascade screening. No other laboratory test is available for diagnosis, though in re- search laboratories LDLR binding studies for LDL in cultured cells has been valuable in characterizing the function of different dele- terious mutations. Clinical criteria have therefore been established for diagnosis. In the United Kingdom, these are the Simon Broome criteria (Table 12.6.9), and in other parts of Europe such as the Netherlands, similar criteria are used. FH heterozygotes should be very vigorously treated to reduce LDL-C levels, and other risk factors minimized, preferably starting in childhood. In children, a low-cholesterol diet with low saturated and trans fat is valuable. Bile acid sequestrants can be used before puberty, with other lipid-lowering drugs being introduced after puberty. The rationale for this delay is the importance of cholesterol for growth and sex hormone biosynthesis, but this is not evidence based. Increasingly, some centres are commencing statin therapy in the first decade of life, depending on the child’s LDL levels and the family history of premature atherosclerotic cardiovascular disease. The powerful, long-acting statins are the most efficacious drugs and should be used at high intensity in adults (Tables 12.6.7 and 12.6.10). It is reasonable to supplement statins with cholesterol absorption inhibitors or bile acid sequestrants, and often these drugs are used in conjunction to achieve greater than 50% LDL- C lowering. Other newer drugs, known as PCSK9 inhibitors, have recently become available for treatment of conditions such as FH, but their use is currently highly restricted (see ‘Drug treatment of hypercholesterolaemia’). In those planning pregnancy, statins should be stopped, as animal data suggests that statins are teratogenic although there is no human data to support this. When stopping statins prior to conception, a 3-month washout period is often recommended, but this is not evi- dence based, and shorter periods are probably acceptable. Targets for LDL-C/NHDL-C lowering should be to greater than 50% of the starting highest level. Greater reduction to the levels ad- vised for secondary prevention is reasonable, LDL-C to less than 2 mmol/litre (80 mg/dl), to minimize the risk of atherosclerotic car- diovascular disease, and this is mandatory in established disease. The role of imaging by carotid ultrasonography of CT coronary cal- cium scoring in detecting premature atherosclerotic cardiovascular disease is discussed in ‘Diagnosis of dyslipidaemia’. Some FH heterozygotes will not achieve greater than 50% LDL-C lowering with available medication. These

patients are candidates for use of PCSK9 inhibitors (see ‘Drug treatment of Table 12.6.9 Simon Broome criteria for the diagnosis of familial hypercholesterolaemia Definite familial hypercholesterolaemia • Total cholesterol >6.7 mmol/litre or LDL cholesterol >4.0 mmol/litre in a child <16 years • Total cholesterol >7.5 mmol/litre or LDL cholesterol >4.9 mmol/litre in an adult. (Levels either pretreatment or highest on treatment) • Plus tendon xanthomas in patient, or in first-degree relative (parent, sibling, child), or in second-degree relative (grandparent, uncle, aunt) • Or DNA-based evidence of an LDL receptor mutation or familial defective apoB100 Possible familial hypercholesterolaemia • Total cholesterol >6.7 mmol/litre or LDL cholesterol >4.0 mmol/litre in a child <16 years • Total cholesterol >7.5 mmol/litre or LDL cholesterol >4.9 mmol/litre in an adult • Plus a family history of myocardial infarction: below age of 50 in second-degree relative or below age 60 in first-degree relative • Or a family history of raised total cholesterol >7.5 mmol/litre in adult first- or second-degree relative or >6.7 mmol/litre in child or sibling <16 years

12.6 Lipid disorders 2079 hypercholesterolaemia’ and ‘PCSK9 inhibitors’). FH patients whose LDL-C remains markedly elevated, greater than 5 mmol/litre (200 mg/dl) with cardiovascular disease or 7.5 mmol/litre (300 mg/dl) without cardiovascular disease, despite maximum tolerated drug treatment, especially those with high Lp(a) levels, can be probably be improved with LDL apheresis (see ‘Drug treatment of hyperchol- esterolaemia’ and ‘LDL apheresis’). Homozygous FH is caused by mutations of the LDLR gene passed on from each parent. The frequency is around 1 in a million people. Those with complete absence of LDLR activity (re- ceptor negative) compared to those with low, but present activity (receptor defective) have higher LDL-C levels. LDL-C levels in homozygous FH patients range from about 12 (480) to in excess of 25 mmol/litre (1000 mg/dl). Those with higher LDL-C levels develop tendon xanthomas on the hands, wrists, elbows, knees, Achilles tendons, or buttocks. Homozygotes develop atherosclerotic cardiovascular disease in childhood or adolescence. Lesions are common in the aortic root and aortic valve with subvalvular stenosis, often reaching into the coronary ostia, which become narrowed. The carotids and peripheral blood vessels become narrowed and can be problematic. Sudden cardiac death is relatively common. Symptoms reflect decreased car- diac output and cardiac ischaemia. Without treatment, death is in the second to third decade, reflecting disease severity. Apheresis is the mainstay for treating homozygous FH. With apheresis and lipid- lowering drugs, this grim prognosis is much improved. Homozygous FH is suggested by the very high TC (>12 mmol/ L, 480 mg/dl) and LDL-C levels (>10 mmol/L, 400 mg/dl) in the absence of an acquired reason. Skin xanthomas are virtually pathog- nomonic. Atherosclerotic cardiovascular disease in a young patient and TC greater than 7.5 mmol/litre (300 mg/dl) in both parents are both highly suggestive of homozygous FH. DNA sequencing will generally identify LDLR mutations. Receptor-negative homozygotes are most commonly due to consanguinity, but are fortunately rare. Homozygous FH patients should be treated early and most vigor- ously to retard the relentless onset and progression of atherosclerosis. While maximal drug treatment may be adequate to treat some LDLR patients most will require apheresis as well. High-intensity statin treatment, ezetimibe, and sequestrants are reasonably given together. Receptor-negative patients do not respond to these drugs. Liver transplantation has been used to treat homozygous FH, because the liver is the main site of LDL clearance, but its use is limited by problems associated with immunosuppression and graft rejection. Three new drugs have potential value. PCSK9 inhibitors which increase LDLR activity apparently have value in receptor-defective patients and are now licensed for use. A MTTP inhibitor, which prevents chylomicron and VLDL synthesis and subsequent conver- sion into remnants and LDL is effective in lowering LDL. Antisense oligonucleotide treatment to block apoB

synthesis is used in the United States of America, but not in Europe. These drugs are dis- cussed in later subsections. Familial defective apoB100 (FDB) FDB is an autosomal dominant hypercholesterolaemia, which is clinically like heterozygous FH. Mutations of the APOB gene cause FDB, and these usually affect the region of apoB100 that contains the LDLR-binding domain, which is lacking in apoB48. It is mostly usually caused by a predominant mutation of glutamine for arginine at amino acid 3500, which reduces the binding and clearance of LDL by the LDLR. It is seen in patients of central European origin and in derived populations in the United States of America, where the frequency is 1 in 500 to 1 in 1000, and this reflects a founder effect mutation. It is common in the Pennsylvania Amish but is found worldwide. Recurrent mutation occurs as Arg3500 is encoded by a CpG di- nucleotide, which is a hotspot for mutation. Mutations elsewhere in the gene have also been described. FDB is less common than FH, likely because the target for muta- tion is mainly restricted to the LDLR binding domain of apoB100. Homozygotes are extremely rare. Individuals with both LDLR and FDB mutations have been described, and they behave as homozygotes. In FDB there is elevated plasma LDL-C, but not of remnants be- cause clearance through the interaction of apoE with the LDLR is normal. Thus TC levels tend to be lower than in FH. TGs are normal. Tendon xanthomas are less prominent than in FH. Premature ath- erosclerotic cardiovascular disease is common. FDB cannot be distinguished clinically from FH. Homozygotes tend to be less severely afflicted than FH homozygotes due to the lower cholesterol levels, because remnants are cleared normally through the interaction of apoE with the LDLR. The definitive diag- nosis is by DNA genotyping, which is usually focused on the amino acid 3500 mutation, or by DNA sequencing. The treatment is similar Table 12.6.10 High-, moderate-, and low-intensity statin therapy High intensity Moderate intensity Low intensity Daily dose lowers LDL-C on average by 50% Daily dose lowers LDL-C on average by 30% to <50% Daily dose lowers LDL-C on average by <30% Atorvastatin 40–80 mg Rosuvastatin 20 (40) mga Atorvastatin 10–20 mg Rosuvastatin 10 mg Simvastatin 20 mgb Pravastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 20 mg twice daily Pitavastatin 2 mg Simvastatin 10 mg Pravastatin 10–20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg Mechanism of action is by lowering cholesterol synthesis and increasing liver LDLR activity. Common side effects are myalgia, myopathy, elevated transaminase, and dyspepsia. Specific statins and doses are noted in bold that were evaluated in randomized clinical trials, which showed a reduction in major cardiovascular events. Statins and doses not tested in clinical trials are in italics. Individual responses to statin therapy vary and there might be a biological basis for a poor response. a Starting dose 5 mg if hypothyroid, >65 years, Asian. The 40-mg dose is contraindicated in Asians. b Simvastatin 80 mg is not recommended due to the increased risk of myopathy, including rhabdomyolysis.

 to FH for heterozygotes. The very rare homozygotes may require apheresis as well as drugs. Autosomal dominant hypercholesterolaemia due to gain-of-function mutations in PCSK9 PCSK9 gene gain-of-function mutations are a very rare autosomal dominant form of FH. The function of PCSK9 was described earlier in this chapter. These mutations are much more frequent in individ- uals of African descent. Loss-of-function mutations in PCSK9 can cause low levels of LDL-C (see ‘Enhanced hepatic clearance of rem- nants and LDL as a cause of low cholesterol levels’). Gain-of-function missense mutations that increase the activity of PCSK9 cause hypercholesterolaemia because the number of LDLRs is reduced. Clinically, patients are similar to those with FH, but they are highly responsive to PCSK9 inhibitors (see ‘Drug treatment in hypercholesterolaemia’ and ‘PCSK9 inhibitors’). Autosomal recessive hypercholesterolaemia (ARH) ARH is a very rare Mendelian recessive disorder. Clinically, pa- tients

have plasma LDL-C levels between those of heterozygous and homozygous FH, and the TC levels are more variable. ARH results from mutation of the gene encoding the LDLR- adapter protein, (LDLRAP), which is needed for LDLR-mediated endocytosis particularly in the liver. LDLRAP binds to the in- ternal domain of the LDLR, linking it to the endocytic machinery (Fig. 12.6.11). With ARH, LDL binds the LDLR, but is not endocytosed, and accumulates at the liver cell surface. Individuals are mostly of Middle Eastern, Turkish, or Sardinian origin, but cases of ARH occur worldwide. Tendon xanthomas are found. Atherosclerotic cardiovascular disease develops by the third decade. ARH is more responsive to lipid-lowering therapy than homozygous FH and may not require apheresis. Cholesteryl ester storage disease Cholesteryl ester storage disease is a rare Mendelian recessive dis- order. It features raised TC and LDL-C, often with increased TGs and low HDL-C. Its worst manifestation, Wolman's disease, is fatal in infancy. Cholesteryl ester storage disease and Wolman's disease are caused by deleterious mutation of the gene encoding lysosomal acid lipase (LAL). Patients with no enzyme activity are likely to have the childhood severe presentation and those with partial deficiency the adult presentation. LAL hydrolyses TGs and cholesteryl esters from remnants and LDL taken up by the liver by the LDLR. This leads to the accumulation of large amounts of neutral lipid in liver cells and hepatosplenomegaly, with steatosis, fibrosis, and ultimately cirrhosis. The high LDL may be the result of both increased produc- tion of apoB-containing lipoproteins and decreased clearance. The diagnosis is suggested in patients with elevated LDL-C, low HDL-C, and fatty liver without the metabolic syndrome. Diagnosis is made by measuring LAL activity on a dried blood spot, and veri- fied by DNA sequencing. It is important to establish the diagnosis and evaluate the liver as cirrhosis may occur. Heterozygotes may have mild to moderately disturbed lipids. In 2015, the Food and Drug Administration in the United States of America and European Medicines Agency recommended granting a marketing authorization for Kanuma (sebelipase alfa), recom- binant acid lipase, for the treatment of LAL deficiency. The recom- mendation was based on four studies which provided evidence on the safety and efficacy in infants (<6 months of age), children, and adults. A total of 106 patients (including 14 infants) with LAL defi- ciency received treatment with sebelipase alfa. Significant improve- ments were observed for a number of disease parameters, including improvement in survival of infants with LAL deficiency for which no treatment was available up until now. The long-term efficacy of this treatment is continuing through an ongoing study in infants with LAL deficiency. Sitosterolaemia This rare autosomal recessive cause of increased absorption of chol- esterol and suppressed LDLR expression has already been described in the Sitosterolaemia' subsection in 'Primary factors affecting intes- tinal lipid absorption'. Familial dysbetalipoproteinaemia (FDBL) FDBL is also called type 3 hyperlipoproteinaemia (Table 12.6.3). It is a Mendelian recessive disorder, which becomes manifest when an acquired cause of dyslipidaemia also occurs. It features combined dyslipidaemia with similarly raised levels of both cholesterol and TGs due to accumulation of remnant particles (chylomicron and VLDL remnants). Remnant clearance by the LDLR is mediated by apoE on these lipoproteins. ApoE has three common alleles. ApoE3 is most fre- quent; apoE2 and apoE4 each differ from apoE3 by one amino acid. Homozygosity for the apoE2 allele (frequency of about 1/200) underlies FDLB. Overall the APOE gene locus confers approximately 1.5 to polygenic dyslipidaemia and to risk of atherosclerotic cardio- vascular disease. The apoE4 allele causes a modestly higher LDL-C level and increases cholesterol absorption (see 'Primary factors af- fecting intestinal lipid absorption'), with increased atherosclerotic cardiovascular disease risk, but does not cause FDBL. The presence of one or two APOE4 gene copies does, however, increase the risk of Alzheimer's disease. ApoE2 has much reduced binding affinity to the LDLR, so that it slows the rate of remnant clearance; homozygosity for apoE2 is present in most patients with FDBL; heterozygotes are at

moderate increased risk of dyslipidaemia. Very rare dominant mu- tants of apoE can cause FDBL. The acquired (Table 12.6.4) precipitating factors for FDBL in- clude high fat and carbohydrate diets, obesity, insulin resistance and diabetes, hypothyroidism, kidney disease, HIV, alcohol, and some drugs. In women, it is rare prior to the menopause, after which oes- trogen deficiency plays a role. FDBL patients present as adults with mixed dyslipidaemia, with similarly raised TC and TGs carried in IDL, and normal HDL-C. Typically, the TC is 8 to 12 mmol/litre (320–480 mg/dl) and TGs 5 to 20 mmol/litre (420–1800 mg/dl). LDL-C is low due to reduced formation from VLDL and normal clearance by the LDLR. There may be premature atherosclerotic cardiovascular disease, affecting the peripheral blood vessels as well as the coronaries. There are dis- tinctive, pathognomonic xanthomas; tuberoeruptive xanthomas form small groups of small papules on the elbows, knees, or but- tocks, but can expand to be thumb nail-sized; palmar xanthomas (called xanthoma striae palmaris) are orangey, yellow discolorations in the palmar and wrist creases. The diagnosis is best made by demonstrating apoE2 homozygosity in conjunction with high levels of remnant lipoproteins. Methods of phenotyping apoE include ultracentrifugation (β-quantification),

 lipoprotein electrophoresis (broad β-band), and MRI, but these are not routinely available. Polymerase chain reaction can be used to type the common alleles, but will miss rare disease-causing variants. As a rule, cases of FDBL have a TC/apoB ratio greater than 6.0 and a TG/apoB ratio of less than 10.0, which are highly predictive, whereas in type 4 hyperlipidaemia, the TC/apoB ratio is below 5.0 and in type 5 hyperlipidaemia, the TG/apoB ratio is much greater than 10.0. FDBL needs to be vigorously treated because of the high risk of premature atherosclerotic cardiovascular disease. The acquired metabolic factors that have precipitated FDBL need to be managed. FDBL patients improve with weight reduction, atheroprotective life- style (Table 12.6.6), and reduction of alcohol consumption. Fibrates are the drug of first choice as they have a spectacular ef- fect in lowering TGs and cholesterol in FDBL through VLDL and IDL reduction. Often both LDL-C and HDL-C increase. A statin may also be required, with the caveat concerning the safety of the combined use of these drugs. Fish oils can reasonably be used if TGs remain raised. Hepatic lipase deficiency HL hydrolyses TGs and phospholipids in remnants and HDL, which favours liver uptake by apoE, and conversion of remnants into LDL. HL deficiency is a very rare autosomal recessive disease caused by mutations of the HL gene, a relative of LPL. Deficiency features mixed dyslipidaemia due to remnant accumulation and raised HDL-C, and in this respect resembles alcohol overconsumption. To make the diagnosis, HL activity is measured in postheparin plasma or the DNA of the gene sequenced. Statin therapy is appropriate to reduce potential atherosclerotic cardiovascular disease risk from remnant accumulation. Acquired (secondary) causes of impaired liver uptake of lipoproteins The secondary causes of dyslipidaemia are listed in Table 12.6.4. Diet Diet plays a major role in determining LDL-C levels. Western na- tions such as the United States of America and European nations have overall higher cholesterol levels than nations such as China and Japan. Even subjects with FH in China have much lower chol- esterol levels than their Western counterparts. Animals in the wild and human neonates have very low cholesterol levels (LDL-Cs of 0.65 mmol/litre (25 mg/dl)), consistent with the view that the human diet plays a major role in determining plasma cholesterol levels. Saturated fat raises LDL-C more than most other dietary compo- nents. Saturated fat is found in red meats, dairy products, chocolate, baked goods, deep-fried food, and processed food—all common in the Western diet. Among saturated fatty acids, lauric, myristic, and palmitic acids are considered to be more hypercholesterolaemic than stearic acids. Lauric and myristic acids are found in coconut. Trans fatty acids (trans fats) also raise LDL-C and lower HDL- C. Trans fats are made when hydrogen is

added to vegetable oil to harden it. They are used in processed food to prolong its shelf life. Trans fats are also generated by high-temperature frying. Saturated and trans fats increase plasma LDL-C by increasing the formation of LDL in the plasma compartment by decreasing LDL turnover and by decreasing the activity of the LDLR through the activity of SREBP. Because dietary cholesterol intake is not found to correlate well with serum cholesterol levels, dietary restriction is not now recom- mended in the United States of America, but reduction of saturated fat intake will perforce decrease cholesterol consumption. Recent meta-analyses have not found an association between saturated fat consumption and atherosclerotic cardiovascular disease, while other meta-analyses have suggested increased risk (Table 12.6.6). Saturated fat should be replaced by unsaturated fat to lower LDL- C levels (Table 12.6.6). Low-fat diets which replace saturated fat with carbohydrates lower LDL-C, but also lower HDL levels. Hypothyroidism Hypercholesterolaemia is common and often severe in hypothy- roidism. It is due to reduction of liver LDLR levels and reduced LDL and remnant clearance. The expression of the LDLR gene is decreased in hypothyroidism. Mild hypertriglyceridaemia may coexist. Screening of all patients with high LDL-C for hypothy- roidism is mandatory as hypothyroidism is easy to overlook. Hormone replacement corrects the hypercholesterolaemia, un- less there is another underlying dyslipidaemia. Statin treatment in hypothyroidism can be dangerous because of the risk of severe muscle toxicity. Oestrogen and progesterone Endogenous oestrogens are important regulators of lipid metab- olism and inhibit atherosclerotic cardiovascular disease develop- ment in premenopausal women. Oestrogen reduces LDL-C levels and increases HDL levels by increasing LDLR activity and decreasing LDL production and apoA1 and ABCA1 protein expression. It also potently reduces the oxidation of LDL. Administration of oestrogen to postmenopausal women in clinical trials using ‘conjugated’ (horse) oestrogens and synthetic progestins (medroxyprogesterone acetate) as hormone therapy have shown in- creased atherosclerotic cardiovascular disease risk despite beneficial effects on the lipid profile. More recent trials using natural oestrogen or the selective oestrogen receptor modulators such as lasofoxifene suggest therapeutic potential for the prevention of atherosclerotic cardiovascular disease, warranting further clinical trials. But this is mitigated by increase breast and ovarian cancer risk. Oral contraceptives and oral oestrogens (as hormone re- placement therapy) are contraindicated in patients with severe hypertriglyceridaemia (type 1, 3, 4, and 5 hyperlipidaemias) as they are reported to precipitate acute pancreatitis. Oestrogen decreases activity of HL, the actions of which include hydrolysis of VLDL, pos- sibly decreased LPL activity, and increased synthesis of TGs in the liver and secretion of VLDL. Oestrogen patches do not affect TG levels. Progesterone-only pills reduce HDL. Enhanced hepatic clearance of remnants and LDL as a cause of low cholesterol levels PCSK9 deficiency Inherited deleterious alleles of PCSK9 cause increased LDLR ac- tivity and decreased plasma LDL-C levels. Deleterious mutations of PCSK9 are best described in people of African origin, but are also described in Europeans. Heterozygotes have a 30 to 40% decrease in plasma levels of LDL-C with much reduced occurrence of ath- erosclerotic cardiovascular disease most likely as a consequence of the low LDL-C. Homozygotes for such mutations have LDL-C levels

 below 0.5 mmol/litre and are well, indicating that lifelong low chol- esterol levels are not deleterious to human health. HDL cholesterol and dyslipidaemia In clinical practice, TC, TGs, HDL-C, LDL-C, and/or NHDL-C plasma levels (the standard lipid profile) are routinely determined and the ratio of TC to HDL-C calculated. The TC-to-HDL-C ratio is one of the best predictors of atherosclerotic cardiovascular disease risk, and it is the plasma lipid metric used in standardized athero- sclerotic cardiovascular disease risk calculators (see ‘Screening of

plasma lipid and lipoprotein levels'). Low levels of blood HDL-C are very common in atherosclerotic cardiovascular disease sufferers. Yet low HDL-C is a not causal factor in atherosclerotic cardiovascular disease, rather than a marker of association with other risk factors. Low HDL- C is not independent despite its important role in reverse chol- esterol transport, and may reflect the clustering of primary and secondary atherosclerotic cardiovascular disease risk factors, which lead to the strong inverse correlation of low HDL-C with atherosclerotic cardiovascular disease risk. HDL-C levels are much affected by other atherosclerotic cardiovascular disease risk fac- tors including Toll-like receptors, obesity, insulin resistance, and systemic inflammation. Primary causes of low HDL-C (hypoalphalipoproteinaemia). As with the other components of the standard lipid profile, HDL-C levels are determined by genetic and acquired factors. Genetic fac- tors determine approximately 50% of the total phenotypic variance of HDL-C, and these are accounted for by the clustering of multiple common polymorphisms, low frequency, and rare variants (as pre- viously described). Increased risk of atherosclerotic cardiovascular disease in people with low HDL may occur due to the presence of other genes affecting pathways of lipid metabolism that increase risk. Common genetic variants that affect the components of meta- bolic syndrome also affect HDL levels. A number of the key genes involved in HDL metabolism have been found to have deleterious mutations, which affect HDL biosynthesis and catabolism and can result in dramatic reductions in plasma levels of HDL-C (Table 12.6.11). Quite unlike the genes that confer high levels of LDL-C, which greatly increase the risk of atherosclerotic cardiovascular disease, these genetic forms of hypoalphalipoproteinaemia are not defini- tively linked to increased risk of atherosclerotic cardiovascular disease. APOA1 gene cluster deletions The genes encoding apoA1, apoA5, apoC3, and apoA4 are grouped together on chromosome 11. Patients with deletion of the entire APOA1 gene, or of the whole gene cluster, have almost no HDL. In these patients, the absence of LCAT activation leads to increased free cholesterol levels in the blood and tissues such as the eyes and skin, which can form substantial deposits in the cornea and skin re- sulting in corneal opacities and palmar xanthomas. Despite having very low levels of apoA1, deficient patients are not at increased risk of atherosclerotic cardiovascular disease. APOA1 gene mutations Deleterious mutations of the APOA1 gene are a rare cause of low HDL-C (often <0.5 mmol/litre (20 mg/dl)). A number of variants have been described and these are usually named after the place in which they were identified, such as apoA1 Milano and Marburg. They do not apparently cause premature atherosclerotic cardiovas- cular disease. This lack of association with atherosclerotic cardio- vascular disease is despite the finding that many apoA1 variants produce very low levels of plasma HDL-C levels due to defective LCAT activation by apoA1 and enhanced removal of the abnormal HDL lipoprotein. ApoA1 Milano, which leads to dimerization of apoA1 with itself or apoA2, appears to decrease the risk of atherosclerotic cardiovas- cular disease, and has been used as a potential therapeutic agent, and this has led to development of infusible HDL mimetics that rapidly remove cholesterol from arteries and stabilize unstable plaque. In addition some coding sequence variants of APOA1 and APOA2 can aggregate and cause systemic amyloidosis. Table 12.6.11 Genetic defects affecting HDL metabolism Variant Molecular defect Inheritance Metabolic defect Lipoprotein abnormality Clinical features Premature atherosclerosis Familial apoA1 deficiency ApoA1,3,4,5 gene cluster Autosomal codominant Absent apoA1 biosynthesis HDL <0.5 mmol/L, TGs increased when cluster is deleted Planar xanthomas, corneal opacities No Familial apoA1 structural mutations Abnormal apoA1 Autosomal dominant Rapid apoA1 catabolism and abnormal HDL HDL 0.4–0.8 mmol/L, TGs normal Often none, sometimes corneal opacities No Familial LCAT LCAT deficiency (complete) Autosomal recessive Rapid HDL catabolism HDL <0.5 mmol/L, TGs increased Corneal opacities, anaemia, proteinuria, renal insufficiency No Fish-eye disease LCAT deficiency (partial) Autosomal

recessive Rapid HDL catabolism HDL <0.5 mmol/L, TGs increased Corneal opacities No Tangier disease ABCA1 deficiency Autosomal codominant Very rapid HDL catabolism HDL <0.5 mmol/L, TGs usually increased Corneal opacities, enlarged orange tonsils, hepatosplenomegaly, peripheral neuropathy No to yes Familial hypoalphalipoproteinaemia Unknown Autosomal dominant Usually rapid HDL catabolism HDL <1.0 mmol/L, TGs normal Often none, sometimes corneal opacities No to yes

12.6 Lipid disorders 2083 Tangier disease (ABCA1 deficiency) Tangier disease is caused by rare Mendelian codominant defects of the ABCA1 gene. ABCA1 mediates the cellular efflux of unesterified cholesterol and phospholipids for capture by apoA1 from the liver, small intestine, and peripheral tissues. Without ABCA1, the poorly lipidated apoA1 is rapidly removed from the blood. Tangier disease patients have very low blood HDL-C and apoA1 levels. Heterozygotes have low HDL-C levels of approximately 0.5 mmol/ litre (20 mg/dl). Cholesterol collects in the mononuclear phagocyte system causing hepatosplenomegaly and pathognomonic enlarged greyish, yellow, or orange tonsils. Patchy peripheral neuropathy and rarely a syringomyelia-like condition can occur. Nearly all children affected by Tangier disease are identified on the basis of large, yellow-orange tonsils, but it can be undetectable or overlooked in adults because tonsils have often been removed. Foam cell formation from lipid storage in cells can be detected by endoscopic examination of the rectal mucosa. In many patients, proctoscopy reveals a pale mucosa studded with 1- to 2-mm dis- crete orange-brown spots. Other signs of Tangier disease are thrombocytopenia, anaemia, gastrointestinal disorders, and cor- neal opacities. The diagnosis can be confirmed by DNA sequencing. There is no clear evidence whether Tangier disease patients have an increased risk of atherosclerotic cardiovascular disease. LCAT deficiency Deleterious mutations of the LCAT gene cause a rare Mendelian recessive disease. LCAT secretion from the liver is decreased, and LCAT is reduced or absent from circulating lipoproteins. LCAT es- terifies free cholesterol in lipoproteins to form cholesteryl esters. LCAT deficiency greatly increases the proportion of free cholesterol in lipoproteins (from 25 to 70% of total plasma cholesterol). HDL maturation is defective and there is rapid clearance of apoA1— LCAT’s activating cofactor. Complete LCAT deficiency with complete absence of protein ac- tivity contrasts with partial deficiency of enzyme activity. In com- plete deficiency and partial deficiency (called fish-eye disease), there is progressive corneal opacification caused by accumulation of free cholesterol in the cornea. Very low circulating HDL-C and often hypertriglyceridaemia are features of both disorders. Complete LCAT deficiency is also associated with haemolytic an- aemia and progressive renal failure. In partial deficiency, there are no such clinical features. Premature atherosclerotic cardiovascular disease has been described, but is not a usual accompaniment to ei- ther form of the disease. The diagnosis is suggested by the corneal opacification and the combination of haematological abnormality, renal dysfunction with proteinuria, very low HDL-C, and high TG levels. The LDL is cholesteryl ester poor and small and sometimes apoB is raised; these later features may be atherogenic. The diagnosis is made by measuring LCAT activity in plasma, and confirmed by DNA sequencing. Lipid-lowering treatment should be considered. Familial hypoalphalipoproteinaemia (isolated low HDL) The familial clustering of low plasma HDL-C, well below 1.0 mmol/ litre (40 mg/dl), with normal TGs and LDL particle size, with Mendelian (possibly codominant) transmission, without secondary causes, is called familial or primary hypoalphalipoproteinaemia. Some patients can have heterozygous defects of ABCA1 and strictly speaking have Tangier disease. LCAT deficiency can usu- ally be excluded clinically, but some patients may have APOA1 gene defects. Polygenic clustering of low HDL gene variants is the likely

cause as no major gene has been discovered. The diagnosis is made in patients with no known genetic or sec- ondary causation. Mechanistically, there is often rapid catabolism of HDL, and of apoA1 and apoA2. It can be associated with athero- sclerotic cardiovascular disease, but the extent to which this is the case may depend on the underlying gene defects. Acquired (secondary) causes of low HDL-C The secondary causes of dyslipidaemia are listed in Table 12.6.4. Obesity, insulin resistance, and diabetes By far the most significant among the acquired factors associated with low HDL-C is the tide of obesity afflicting modern society, which leads to the metabolic syndrome of insulin resistance and type 2 diabetes. This clustering of metabolic abnormalities markedly increases the risk of atherosclerotic cardiovascular disease. HDL levels are decreased through complex effects on lipid and lipoprotein metabolism. There is increased lipolysis in adipose tissue; particularly intra-abdominal fat, which is metabolically very active. Free fatty acids are released into the portal circulation. The liver converts free fatty acids into TGs. This and an increased supply of glucose, which leads to fatty acid and further TG biosynthesis and overproduction of VLDL, raises the concentration of circulating TG-rich lipoproteins. There is reciprocal exchange of lipids between lipoprotein par- ticles. Cholesteryl esters are transferred to VLDL and chylomicron remnants, while TGs are transferred to LDL and HDL particles to form highly atherogenic, cholesterol-poor sdLDL, and HDL (Table 12.6.1, Fig. 12.6.13). There is also rapid catabolism of HDL-C and its core protein apoA1 with further reduction of HDL-C. Atherogenic dyslipidaemia—the simultaneous presence of raised TGs and apoB concentration, and an increased proportion of sdLDL with low HDL is associated with a considerable increase in the risk for atherosclerotic cardiovascular disease. The management of these lifestyle and metabolic factors and the treatment of raised cholesterol are the most efficacious approaches to manage low HDL (Table 12.6.6). Lipid lowering is reasonable. Renal disease Very rarely, patients with glomerulonephritis with massive protein- uria can develop very low levels of HDL-C, which is self-limiting with the resolution of the proteinuria. Urinary loss of apoA1 con- tributes to the low HDL-C. Inherited causes of very high levels of HDL-C Very high levels of HDL-C with large, fluffy HDL-C, and reduced particle number appear to be atherogenic.
CETP deficiency Deleterious mutation of both copies of the CETP gene lead to a marked increase in HDL-C levels (>4 mmol/litre (160 mg/dl)) and produce large, fluffy HDL without increased particle number, due to

 the high cholesteryl ester content. Heterozygotes have only modestly raised HDL-C levels. Normally, CETP transfers cholesteryl esters from HDL to apoB-containing lipoproteins and TG in reciprocity (Fig. 12.6.14). In its absence, there is increased cholesteryl ester in HDL; plasma levels of LDL-C are reduced. The large cholesterol-rich HDL particles are cleared slowly. CETP deficiency is rare outside Japan, where it was first diagnosed. It is uncertain whether CETP deficiency causes or prevents atherosclerotic cardiovascular dis- ease, but low CETP activity is not associated with increased lon- gevity. Clinical trials do not yet support the use of CETP inhibitors to reduce the risk of atherosclerotic cardiovascular disease by raising HDL. Importantly, the finding of unduly advanced disease on vas- cular imaging should indicate the need for lipid lowering. Lipoprotein(a) production by the liver Lipoprotein(a) Lp(a) is synthesized exclusively in the liver. Its plasma levels differ greatly among people, and 75% of this reflects genetic variation in the LPA gene. Secondary factors such as renal disease, oestrogen de- pletion, and severe hypothyroidism can increase Lp(a) to a modest extent. As described earlier and in Fig. 12.6.5, a common copy-number variation within the LPA gene determines the number of kringle IV repeats and hence the isoform size of apo(a). An inverse relation- ship exists between the number of repeats and Lp(a) plasma levels. A small number of common variant alleles account for much of

the genetic variance conferred by the LPA gene locus. Variants particu- larly associated with increased atherosclerotic cardiovascular dis- ease tend to be small and be associated with an increased particle number. As a consequence of genetic variation, Lp(a) plasma levels can vary 100-fold, where borderline risk is defined as greater than 30 mg/dl (75 nmol/litre), high risk is 50 mg/dl (125 nmol/litre), and very high risk is greater than 50 mg/dl (>125 nmol/litre), rarely up to a massive 300 mg/dl (750 nmol/litre). Lp(a) levels should be checked in any patient with premature car- diovascular disease, FH, family history of premature cardiovascular disease, family history of elevated Lp(a), recurrent cardiovascular disease despite statin treatment, and at least a 3% 10-year risk of fatal cardiovascular disease according to the European guidelines. An increased level of Lp(a) is associated with a seriously increased risk of atherosclerotic cardiovascular disease, including both cor- onary disease and stroke. It also increases the risk of calcific aortic stenosis. The risk of atherosclerotic cardiovascular disease is greater with very high LDL-C, particularly in FH. The mechanism by which an increased level of Lp(a) lipoprotein increases the risk of disease is not well understood. This may involve LDL-C and atherogenesis, inhibition of conversion of plasminogen to plasmin, activation of tissue factor and thrombogenesis, or the carriage of proinflammatory oxidized phospholipids. Treatment is problematical (see ‘Drug treatment of hypercholes- terolaemia’ and ‘Lipoprotein(a)’). The treatment of acquired factors does not impact Lp(a) levels. Nicotinic acid and the new PCSK9 in- hibitors can each reduce Lp(a) by approximately 30%. Nicotinic acid is not available in the United Kingdom. CETP inhibitors also po- tentially lower Lp(a). An antisense Lp(a) mRNA inhibitor has also proved remarkably efficacious as a treatment in early clinical trials, and is in development. In one large clinical trial (AIM-HIGH), however, after LDL-C lowering to 1 to 2 mmol/litre (40 to 80 mg/dl) with statins no further benefit was accrued from the addition of nico- tinic acid to lower the Lp(a), suggesting that dramatic lipid lowering alone is a reasonable treatment. Aspirin or another antiplatelet drug should be given to suppress the thrombogenicity of Lp(a). Other secondary causes of dyslipidaemia Chronic kidney disease Modest elevation of TGs is frequently seen in CKD due to impaired lipolysis through alteration in the composition of circulating TGs, which become enriched with the LPL inhibitor apoC3. There is reduced LPL and HL activity. Lp(a) is increased due to decreased clearance. Atherosclerotic cardiovascular disease is common in se- vere CKD so that dyslipidaemia needs vigorous treatment with the combination of statins and cholesterol absorption inhibitors as this will decrease cardiovascular events, and mitigates the need for high- dose statins and potential toxicity. The reduction of LDL-C/NHDL- C is reasonable at all levels to reduce cardiovascular events. Transplant patients, due to the immunosuppressive drugs they re- quire, often have dyslipidaemia, which again needs careful, but vig- orous treatment with statins and cholesterol absorption inhibitors and sequestrants to help avoid muscle side effects from statins and possible nephrotoxicity. Anorexia nervosa Anorexia affects mainly teenagers and young adults, and is the third most common long-term illness among teenagers. Fifty per cent of suffers develop dyslipidaemia, often with high total, LDL, and HDL cholesterol. TGs are not raised. The pathogenesis is not clear, and is certainly not simply due to malnutrition, which reduces plasma cholesterol levels. It is argued that lipid lowering is not necessary be- cause HDL is raised as well as LDL. TC levels can, however, be over 9 mmol/litre (360 mg/dl), so that careful review on a case-by-case basis is required. Alcohol and other substance abuse need to be con- sidered as exacerbating factors. Effective treatment of the primary disorder is the best way forward. Drugs Numerous medicinal drugs affect lipid and lipoprotein metabolism through various mechanisms and cause dyslipidaemia. Many drugs also interact with lipid-lowering drugs, so that coadministration should be approached with caution (Tables 12.6.4 and 12.6.8). See also Table 12.6.4 for other secondary causes of dyslipidaemia. The

patient with dyslipidaemia Cholesterol reduction with statins is highly effective in decreasing vascular events. TG reduction appears to be similarly effective, but the data are less robust than for cholesterol. Increasing HDL-C is not effective in reducing events—rather, HDL is a biomarker for other risk factors. The diagnosis of dyslipidaemia and its effective treat- ment is thus of major clinical importance. This section is based on the up-to-date evidence-based guide- lines on lipids from the United States of America and Europe, with key differences highlighted (Table 12.6.12). It is supported by the latest thinking in the field. A particular focus of these guidelines is

12.6 Lipid disorders 2085 a patient-centred approach to treatment options and lifestyle with emphasis on individual global risk factor assessment through the use of risk calculator tools. Screening of plasma lipid and lipoprotein levels The measurement of standard lipid and lipoprotein levels should be a routine part of clinical practice. Screening is best done by the general practitioner or as part of a health screen. According to guidelines from the United States of America, all adults above 21 years of age should have TC, TGs, HDL-C, LDL-C, and/or NHDL-C screened, and screening should be repeated approximately every 5 years. In the United Kingdom, screening is recommended in those over 40 years (Box 12.6.1). Screening is particularly strongly indicated in patients with established atherosclerotic cardiovascular disease (secondary prevention) with a view to establishing or maintaining treatment goals. It is also strongly recommended in those with a family history of atherosclerotic cardiovascular disease, particularly if premature, those with other atherosclerotic cardiovascular disease risk factors, all those with acute pancreatitis, and to monitor those on lipid-lowering medication. Most clinical chemistry laboratories measure TC and TG enzymatically. The HDL-C is usually measured after precipitation of apoB-containing lipoproteins. The LDL-C is then most commonly estimated using the Friedewald formula: [LDL-C] = [TC] minus [TG divided by 2.2] minus [HDL-C] (where all concentrations are given in mmol/litre). For this, the VLDL cholesterol is estimated by dividing the plasma TG by 2.2, the usual TG to cholesterol in VLDL particles. Table 12.6.12 Comparison of international lipid guidelines: NICE (2014), ESC/EAS (2011), and ACC/AHA (2013) NICE guidelines ESC/EAS guidelines ACC/AHA guidelines Year of publication 2014 2011 2013 Use of evidence Comprehensive literature review Comprehensive literature review Randomized controlled trials Risk assessment tool QRISK2 SCORE Pooled cohort equations End points CHD death, CHD (MI or angina), stroke and transient ischaemic attack CHD death or fatal stroke CHD death, nonfatal MI, fatal or nonfatal stroke Derivation sample British population, updated annually 12 European countries (pooled data) 4 cohort studies (pooled data) Risk factors selected in the multivariable model Age, sex, total cholesterol, HDL-C, systolic blood pressure, hypertension treatment status, diabetes mellitus, smoking status, ethnicity, family history of CHD, body mass index, socioeconomic deprivation, rheumatoid arthritis, CKD, and atrial fibrillation Age, sex, total cholesterol, systolic blood pressure, and smoking status (NB: separate models for high- and low- risk countries) Age, sex, total cholesterol, HDL-C, systolic blood pressure, antihypertensive treatment status, diabetes mellitus, and smoking status (NB: separate models created for white patients and black patients) Cholesterol treatment targets endorsed 40% reduction in non-HDL from pretreatment level LDL-C (see below) Consider apoB or non- HDL-C as alternative target No Statin therapy for primary prevention in those without diabetes mellitus 10-year risk ≥10% or CKD LDL-C ≥4.9 mmol/litre (190 mg/dl) LDL-C <4.9 mmol/litre (190 mg/dl), and: • 10-year risk ≥10% • Moderate to severe CKD LDL-C ≥2.5 mmol/litre (100 mg/dl) and • 10-year risk 5–9.9% • Severe risk factors: LDL-C ≥3.0 mmol/ litre (115 mg/dl) and • 10-year risk 1–4.9% LDL-C ≥4.9 mmol/litre (190 mg/dl) LDL-C 1.8–4.8 mmol/litre

(70–189 mg/dl) and: • 10-year risk ≥7.5% • 10-year risk <7.5% after consideration of other factors Statin therapy for primary prevention in those with diabetes mellitus Type 2 diabetes mellitus and 10-year risk ≥10% Type 1 diabetes mellitus and age

> 40 years, duration of disease 10 years, nephropathy, or CVD risk factors Type 2 diabetes mellitus and LDL-C ≥2.5 mmol/litre (100 mg/dl) High-risk type 2 diabetes mellitusa and LDL-C ≥1.8 mmol/litre (70 mg/dl) Type 1 diabetes mellitus and target organ damage LDL-C ≥70 mg/dl CKD considered a high-risk feature Yes Yes No Recommendations for the elderly QRISK2 is validated to age ≤84 years SCORE validated for ages 40–65 years Clinician judgement in elderly Pooled cohort risk equations not validated for age >79 years Consider lower-intensity statin Additional considerations for risk assessment Non-LDL-C targets Non-LDL-C targets Lifetime risk ACC/AHA American College of Cardiology/American Heart Association; apoB, apolipoprotein B; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction. NICE, National Institute for Health and Care Excellence; SCORE, Systemic Coronary Risk Evaluation. a High-risk type 2 diabetes mellitus is defined as diabetes mellitus plus one of the following risk factors: established atherosclerotic cardiovascular disease, CKD, age over 40 years, and one or more cardiovascular risk factor or target organ damage. Source data from with permission from Brown MS, Goldstein JL. Receptor-mediated endocytosis: Insights from the lipoprotein receptor system. Proc Natl Acad Sci U S A. 1979;76: 3330–3337.

section 12 Metabolic disorders 2086 While the Friedewald equation is an adequate method, it has shortcomings. Calculated LDL-C is not accurate in patients who are nonfasting, have TGs greater than 5.0 mmol/litre (450 mg/dl), or have type 3 hyperlipoproteinaemia. The equation is particularly inaccurate when LDL-C is below 1.8 mmol/litre (70 mg/dl). For ex- ample, calculated LDL-C underperforms in obese diabetics, and de- viates significantly from LDL-C directly measured at concentrations below 1.8 mmol/litre (70 mg/dl). LDL-C can be measured directly by a variety of methods. As with calculated LDL-C, directly measured LDL-C has shortcom- ings. Directly measured LDL-C can be discordant with other LDL- related measures and may not reflect atherosclerotic cardiovascular disease risk. Recent guidelines endorse the use of NHDL-C (i.e. TC minus HDL-C). NHDL-C accurately predicts atherosclerotic cardiovas- cular disease risk. It does not suffer from the discrepancies with LDL-C measurement. A fasting sample is not generally needed, which is more convenient for patients. NHDL-C is on average 1.0 mmol/litre (40 mg/dl) higher than LDL-C. Nonfasting TGs are also better predictors than fasting TGs of atherosclerotic cardiovas- cular disease events. The main disadvantage of moving to NHDL-C is that national guidelines have previously used (and in the United States of America still do use) LDL-C. Furthermore, clinical trials and other clinical studies have often been performed using LDL-C. It will take effort, but should improve patient care. The use of risk assessment tools such as QRISK2 (Box 12.6.2), Joint British Societies' consensus recommendations for the pre- vention of cardiovascular disease (JBS2/3), or

the American heart risk calculator is recommended to assess absolute atherosclerotic cardiovascular disease risk for the primary prevention in people up an age between 75 to 84 years. Risk assessment using calcu- lators is based on large amounts of observational data from the general population in whom the risk predictions are valid. The lipid metric most calculators use is the TC-to-HDL ratio, which is the best predictive lipid parameter that we have. In addition, these tools evaluate the contribution of ethnicity, deprivation, dia- betes, kidney disease, and rheumatic conditions such as systemic lupus erythematosus to the risk of atherosclerotic cardiovascular disease. Global risk, however, has never been used as a selection criterion for statin trials. While risk is driven largely by older age, in the ab- sence of vascular risk factors, it merits treating by cholesterol reduc- tion as evidence suggests this will reduce risk. There is little data on HIV-positive and solid organ transplant patients, but lipid lowering may be considered. Risk assessment tools that aid clinical decisions about lifestyle modification, and whether to use lipid- and blood pressure-lowering medication are valuable, but should not replace clinical judgement. Statin treatment is recommended in those with a 10-year risk above 7.5% in the United States of America and it is suggested that treatment be considered above 5% risk at 10 years. In the United Kingdom, the recommended threshold is 10%. Caveats to the use of risk calculators are given in Box 12.6.2. Risk calculators should not be used in those people with suspected genetic dyslipidaemia. Guides for the treatment of dyslipidaemia are given in Tables 12.6.7, 12.6.8, and 12.6.10 and Fig. 12.6.19. In a nonfasting individual, a NHDL-C concentration greater than 5.5 mmol/litre (220 mg/dl) may indicate genetic hypercholester- olaemia that requires further investigation. If nonfasting TGs are greater than 5.0 mmol/litre (450 mg/dl), a fasting lipid panel should be performed; persistent elevation will suggest a genetic cause. Box 12.6.1 United Kingdom criteria for screening lipids 1 People with diagnosed coronary heart disease (CHD) or other oc- clusive arterial disease (cerebrovascular accident, peripheral vas- cular disease) not yet on cholesterol-lowering therapy for secondary prevention. 2 People with diagnosed CHD or other occlusive arterial disease taking cholesterol-lowering therapy for secondary prevention—to check that target lipid concentrations are being achieved. 3 People without diagnosed CHD or other occlusive arterial disease not on cholesterol-lowering therapy—when CHD risk is to be estimated (e.g. in people known to have CHD risk factors, especially those with a family history of premature CHD1). (Risk assessment tool: http://www. qrisk.org/.) 4 People without diagnosed cardiovascular or other occlusive arterial disease taking cholesterol-lowering therapy for primary prevention— to check that target lipid concentrations are being achieved. 5 People with CVD risk equivalents—patients with diabetes mellitus, hypertension, or familial hypercholesterolaemia. 6 Patients admitted with acute pancreatitis. Box 12.6.2 QRISK risk assessment tool for atherosclerotic cardiovascular disease and its exclusion criteria • The QRISK2 risk assessment tool can be used to assess atherosclerotic cardiovascular disease (ASCVD) risk for primary prevention in people up to 84 years. • Do not use QRISK2 in people with an estimated GFR of less than 60 ml/min per 1.73 m2 and/or albuminuria as these people are at in- creased risk of ASCVD. • Do not use QRISK2 in people with type 1 diabetes as these people are at increased risk of ASCVD • Do not use QRISK2 for people with pre-existing ASCVD • Do not use QRISK2 for people who are at high risk of developing CVD because of familial hypercholesterolaemia or other inherited disorders of lipid metabolism. • Use QRISK2 to assess CVD risk in people with type 2 diabetes. • Note that standard ASCVD risk scores will underestimate risk in people who have additional risk because of underlying medical conditions or treatments including:

— people treated for HIV

— people with serious mental health problems

— people taking medicines that can cause dyslipidaemia (e.g. anti- psychotic medication, corticosteroids, or immunosuppressant drugs)

— people with autoimmune disorders, e.g. systemic lupus erythematosus. • Note that ASCVD risk will be underestimated in people who are al- ready taking antihypertensive or lipid modification therapy, or who have recently stopped smoking. Use clinical judgement to decide on further treatment of risk factors in people who are below the ASCVD risk threshold for treatment. • Note that severe obesity (body mass index >40 kg/m2) increases ASCVD risk. • Consider people aged 85 or older to be at increased risk of ASCVD because of age alone, particularly people who smoke or have raised blood pressure.

12.6 Lipid disorders 2087 Referral to a specialist lipid clinic is indicated in patients with (1) possible familial dyslipidaemia, (2) those who fail to respond adequately to diet and first-line drug therapy, (3) those with severe hypertriglyceridaemia who are at risk of acute pancreatitis, (4) those in whom statin intolerance is severe, and (5) those for whom there is any uncertainty about diagnosis. In the lipid specialist clinic, estimate of lipids are still gener- ally done on a fasting blood specimen, taken 12–14 h after an overnight fast with complete dietary restriction (with the excep- tion of water and medication). This is of value because postpran- dial TGs remain elevated for several hours, particularly in those with certain forms of dyslipidaemia, and to make an accurate Statin Benefit Groups Cardioprotective life-style is the basis of ASCVD prevention. In those not receiving statin, recalculate estimated 10-y ASCVD risk every 4–6 y in individuals aged 40–84 y without clinical ASCVD or diabetes and with LDL–C 1.8–4.74 mmol/L (70–189 mg/dL) Clinical ASCVD LDL–C ≥4.75 mmol/L (190 mg/dL) Age <84 y High-intensity statin (Moderate-intensity statin if not suitable for high-intensity statin) Age >84 y OR if not candidate for high-intensity statin Moderate-intensity statin High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin) Moderate-intensity statin Estimated 10-y ASCVD risk ≥10%* High-intensity statin Moderate-to-high intensity statin Adults age >21 y and a candidate for statin therapy No No No No Yes Yes Yes Yes Yes Yes Yes Yes Definitions of high- and moderate-intensity statin therapy High Daily dose lowers LDL–C by appox. ≥50% Moderate Daily dose lowers LDL–C by appox. 30% to <50% Diabetes* Type 1 or 2 Age 40–84 y Estimate 10-y ASCVD risk with risk calculation tools ≥10% estimated 10-y ASCVD risk and age 40–84 y Benefit of statin in ASCVD prevention may be less clear in others Consider additional factors influencing ASCVD risk and potential ASCVD risk benefits and adverse effects, drug interactions, and patient attitude to statin treatment *In diabetes less than 40 years statins are optional and depend on clinical judgement Fig. 12.6.19 Statin therapy for atherosclerotic cardiovascular disease (ASCVD): primary and secondary prevention. Incorporating aspects of both the 2013 American College of Cardiology/American Heart Association Blood Cholesterol Guideline for statin initiation and the National Institute for Health and Care Excellence guideline (CG181) ‘Cardiovascular disease: risk assessment and reduction, including lipid modification’. Note: the American guidance considers statin initiation at a 10-year atherosclerotic cardiovascular disease risk of 5%/7.5% whereas the United Kingdom threshold is 10%. The Americans also consider atherosclerotic cardiovascular disease risk at age 21 years in comparison to the United Kingdom where atherosclerotic cardiovascular disease risk is assessed at age 40. Reproduced from Stone NJ, et al. (2013). ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of

Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 24; 129 (25 Suppl 2):S1–45 with permission from Wolters Kluwer and Rabar S, et al. (2014). Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. BMJ, 349, g4356 with permission from BMJ Group.

section 12 Metabolic disorders 2088 diagnosis of the nature of the dyslipidaemia, fasting TGs are preferable. Diagnosis of dyslipidaemia Once screening has established that a patient has a dyslipidaemia a full clinical, diagnostic evaluation is needed. The key questions are: (1) what classes of lipoproteins and lipids are increased or de- creased in the patient's plasma? (2) Does the patient has a primary (genetic) or secondary (acquired) dyslipidaemia, or as is often the case contributions from both? (3) Is the patient at risk of atheroscler- otic cardiovascular disease or acute pancreatitis? (4) What other atherosclerotic cardiovascular disease or pancreatitis risk factors are present? (5) What are the treatment options? The evaluation should include a full medical, family, social, and lifestyle history, and physical examination. The physical exam- ination should be thorough, but specifically focus on cutaneous, tendon and ocular manifestations of dyslipidaemia, and evaluation of the cardiovascular system. Blood tests should include standard lipids, urea and electrolytes with estimated GFR, liver function tests, fasting blood glucose, thyroid function tests including thyroid-stimulating hormone and Lp(a) measurement (Figs. 12.6.5 and 12.6.6), and apoB and apoA1 as measures of apoB-containing lipoproteins and HDL particles. ApoE phenotyping is indicated if TC and TGs are both elevated. In statin-intolerant patients, SLCO1B1 genotyping may be indicated (see 'Muscle'). Urine analysis should assess the presence of protein- uria. A resting ECG should be performed to alert to overt CVD. The clinical evaluation and tests described just described will de- termine the presence of secondary causes of dyslipidaemia including CKD and nephrotic syndrome, hepatitis and cholestasis, the meta- bolic syndrome and diabetes, and hypothyroidism. In the absence, or with only a minor contribution from a sec- ondary cause of dyslipidaemia, then a primary (genetic) cause is likely. However, patients will often display components of both. In primary dyslipidaemia, a full family history often with lipid studies in the family and occasionally specific tests will indicate the diagnosis. Imaging of the arteries by carotid ultrasonography or CT cor- onary artery calcium can be of value, as risk factors do not accur- ately predict the extent of atherosclerotic cardiovascular disease. The carotid ultrasonographic and coronary artery calcium scans are ap- proximately 70% correlated, and both detect the presence of athero- sclerotic plaque. The age at which coronary calcium can be detected is 40 years in men and 50 in women. A coronary artery calcium score greater than the 75th percentile is indicative of an increased risk of myocardial infarction or stroke. In younger patients with suspected FH, due to more 'cholesterol- exposure years' the finding of carotid plaques or coronary artery cal- cium will support the diagnosis as longstanding dyslipidaemia in FH leads to plaques at an earlier age. In polygenic hypercholesterolaemia in which the dyslipidaemia is considered to develop later than in FH, due to less 'cholesterol- exposure years' the coronary artery calcium is likely to be less advanced, and imaging may help the differential diagnosis from FH, if clinical criteria or a DNA diagnosis have not already established this. Risk assessment tools have recently been combined with coronary artery calcium scores and appear to be better predictors of risk than risk assessment tools alone, but require better validation, and may not help in younger people aged less than 40 years. More esoteric lipoprotein biomarkers are sometimes measured and these include LDL and HDL particle number, sdLDL measures, and HDL fractions, as well as markers of general inflammation such as high-sensitivity C-reactive protein and fibrinogen, and markers of arterial inflammation such as MPO and LpPLA2. Increased LDL particle number and the presence of sdLDL

are directly pro-atherogenic; low HDL particle number is a predictor of risk. Inflammatory markers indicate active disease. The rela- tionship of inflammatory markers to the incidence of vascular events is uncertain. However, for monitoring treatment, per- sistent inflammation may indicate the need for more aggressive treatment. Hypercholesterolaemia In the United Kingdom, the mean TC is approximately 5.2 mmol/ litre (210 mg/dl) for men and women. Recommended levels are TC 5 mmol/litre (200 mg/dl), NHDL-C 4 mmol/litre (160 mg/ dl), and LDL-C 3 mmol/litre (120 mg/dl) or less in healthy adults. Nonetheless, approximately 40% of myocardial infarctions occur in apparently healthy people with levels TC below these levels. After measuring lipid levels global risk assessment is, therefore, recommended. In those with a 10% or greater risk of an event in the next 10 years, cholesterol levels should be reduced according to United Kingdom guidelines. In the United States of America, a threshold of 7.5% for treatment is used, with the option for treat- ment at 5% risk. In younger people, in whom the likelihood of an event in the next 10 years is low, a lifetime assessment is reasonable, though not well validated by population data. TC levels in adults above 6 mmol/litre (240 mg/dl), that is, the 95th percentile, are high and abnormal and suggest the presence of genetic factors. In those with suspected primary hypercholesterol- aemia, risk calculation should not be used as the tools grossly under- estimate risk. Secondary causes also need to be identified. Often primary and secondary causes coexist. The differential diagnosis of primary from secondary factors is greatly helped by an accurate family history. A TC level above 7.5 mmol/litre (300 mg/dl) and a dominant pat- tern of inheritance (50% of siblings and children) with premature atherosclerotic cardiovascular disease will suggest the diagnosis of FH, and is diagnostic if accompanied by xanthomas (see ‘Familial hypercholesterolaemia’; Table 12.6.9). Severe hypercholesterolaemia without a family history is rare, but might suggest a recessive disorder and diagnosis of ARH, sitosterolaemia, or cholesteryl ester storage disease (see ‘Cholesteryl ester storage disease’). In suspected FH patients, DNA sequencing is likely to reveal a causal mutation in the LDLR or one of the other three genes asso- ciated with FH in 70% of patients with ‘definite’ FH (Table 12.6.9, Fig. 12.6.18). In patients with TC levels below or approximately 7.5 mmol/litre (300 mg/dl), with ‘possible’ FH, or in whom there is a family history, but not clearly dominant, perhaps coming from both sides of the family, a clear DNA diagnosis is less likely. It is likely to be achieved in approximately 30% of individuals. In patients, who do not receive a DNA diagnosis by sequencing, the clustering of polymorphic hypercholesterolaemia alleles and a

 polygenic mode of inheritance is likely, and may affect about 10% of family members. There is often overlap between FH and poly- genic hypercholesterolaemia, and polygenic factors can worsen the FH phenotype. Hypertriglyceridaemia Clinically, hypertriglyceridaemia can be classified as mild to mod- erate (fasting plasma levels >1.7–2.3 mmol/litre (150–200 mg/dl) and <5.0 mmol/litre (450 mg/dl)), severe (fasting 5–10 mmol/L, 450–900 mg/dl)), and very severe (fasting >10 mmol/litre (900 mg/dl). A fasting TG level elevated above 5 mmol/litre (450 mg/dl) sug- gests a primary cause, but secondary factors are often also present, of which undiagnosed or poorly controlled diabetes is common (Table 12.6.4). If a nonfasting level is above 5 mmol/litre (450 mg/dl), a fasting level should be obtained. Critically, those patients with TG levels above 10 mmol/litre (900 mg/dl) have an increased risk of acute pancreatitis and this becomes more likely with levels between 15 and 20 mmol/litre (1350 and 1800 mg/dl). These patients should be treated to lower their TG levels and the risk of pancreatitis. The ‘fridge test’ may help in making the initial diagnosis. If chylomicrons are observed (type 1 and 5 hyperlipidaemia), then familial chylomicronaemia or a related disorder must be considered. The measurement of LPL activity or DNA sequencing can help in making the diagnosis. The finding of

chylomicrons is an indicator of an increased risk of acute pancreatitis. Many people with chylomicronaemia also have raised plasma VLDL (type 5). These people may not have a Mendelian problem, but a genetic predisposition plus acquired factors. Excessive VLDL secretion can swamp residual LPL function and grossly worsen hypertriglyceridaemia. In addition to diabetes, other secondary causes such as dietary indiscretion, obesity, insulin resistance, ex- cess alcohol consumption, and reproductive hormone deficiency or treatment should be considered (Tables 12.6.4 and 12.6.6). Mixed (combined) dyslipidaemia The diagnosis of patients with combined hyperlipidaemia may be tricky as a variety of genetic and acquired factors can be involved. High plasma levels of TC and TGs are seen in patients with in- creased plasma levels of VLDL, remnants lipoproteins, and LDL-C. Measurement of plasma apoB levels should be performed. A careful family history helps make the diagnosis. If the TC is greater than 7.0 mmol/litre (280 mg/dl), FH must be considered, as approximately 30% of people have FH particularly if there is a Mendelian autosomal dominant family history. A DNA diagnosis can be ascertained by sequencing. In such patients, other polygenic factors or a secondary cause is likely to be responsible for the high TGs. If the TC and TGs are raised to around the same level, this sug- gests a defect of remnant clearance (remnants contain equimolar amounts to TG and cholesterol), and FDBL or type 3 hyperlipid- aemia must be considered (see ‘Familial dysbetalipoproteinaemia’) (Table 12.6.3). In cases of FDBL a TC/ApoB ratio greater than 6.0 and a TG/ApoB ratio of less than 10.0 are highly predictive, whereas in type 4 hyperlipidaemia, the TC/apoB ratio is below 5.0 and in type 5 the TG/apoB ratio is much greater than 10.0. In all such patients, apoE typing should be performed as the presence of apoE2 homo- zygosity will confirm the diagnosis. The family history of FDBL is of an autosomal recessive disorder. The secondary trigger factor should be discovered. An assay of plasma apoB levels also helps diagnose patients with FCHL. In FCHL, a family history is to be expected, but this is likely to be polygenic (see ‘Primary causes of VLDL production’). Those with increased apoB are at high risk of atherosclerotic cardiovas- cular disease. In FHTG, the apoB levels are not generally raised. HL deficiency is a very rare cause of mixed dyslipidaemia. Obesity, the metabolic syndrome of insulin resistance, and dia- betes are common secondary causes of mixed dyslipidaemia, often with atherogenic dyslipidaemia. There is frequent exacerbation by genetic factors. In mixed dyslipidaemia, ascertainment of the nature of the lipo- protein abnormality will greatly affect treatment options and efficacy. Treatment of dyslipidaemia The major treatment objectives are primary and secondary preven- tion of atherosclerotic cardiovascular disease and its complications, and prevention of hypertriglyceridaemic, acute pancreatitis. Cholesterol reduction to prevent atherosclerotic cardiovascular disease There is overwhelmingly robust data that the reduction in LDL-C with statins at all ages less than 75 years, at all cholesterol levels, with and without other risk factors such as diabetes and smoking, greatly decreases the risk of atherosclerotic cardiovascular disease, and its complications such as angina, heart attack, heart failure, stroke, and overall mortality. Even at older ages evidence is reasonable that treatment reduces risk. Patients with high cholesterol must, there- fore, be assessed for atherosclerotic cardiovascular disease risk and appropriate treatment. This is particularly the case at the higher TC levels as seen in FH. All patients with atherosclerotic cardiovascular disease should be treated irrespective of initial cholesterol values. The treatment pathway for the patient with hypercholesterolaemia is illustrated in Fig. 12.6.19 and Table 12.6.12. In the United States of America, particular emphasis is given to patients with (1) clinical atherosclerotic cardiovascular disease; (2) primary TC levels above 4.75 mmol/litre (190 mg/dl); (3) diabetics above 40 years of age, with LDL-C levels between 1.8 and 4.75 mmol/litre (70 to 190 mg/dl); and (4) estimated 10-year risk greater than 7.5%. The recommended target reduction to be achieved by the treat- ment of dyslipidaemia is a greater than

40% reduction in NHDL- C by the National Institute for Health and Care Excellence in the United Kingdom; targets are no longer recommended in the United States of America. Previously, LDL-C targets were used, but these have not been tested in clinical trials. Rather, now a high-, moderate-, and low- intensity statin treatment approach based on risk is adopted (Fig. 12.6.19). The ‘lower is better’ approach to achieve values of at least less than 2.5 mmol/litre for NHDL-C (equivalent to <1.8 mmol/ litre for LDL-C) is adopted by the JBS3, but not by guidelines from the United Kingdom or United States of America as it has not been tested (Fig. 12.6.20). In patients with other serious risk factors such as diabetes, CKD, and high Lp(a), it is reasonable to reduce LDL-C levels to 1 mmol/ litre (40 mg/dl). The association between atherosclerotic cardiovascular disease and LDL-C levels will probably bottom out at levels of 0.65 mmol/

section 12 Metabolic disorders 2090 litre (25 mg/dl), the ‘physiological level’ in animals and human neo- nates, so that potentially there is much scope for further risk reduc- tion, and no indication so far that we are overtreating to hazardously low LDL-C levels. In addition, the concept that more ‘cholesterol-exposure years’ as in FH, compared to polygenic and secondary hypercholesterolaemia patients and healthy people, is associated with increased risk sug- gests that reduction of cholesterol in early life could result in long- term benefit. Evidence to better support these important concepts is still to be established. Lifestyle Modification of lifestyle is important in the management of ath- erosclerotic cardiovascular disease risk. An atheroprotective life- style should be instituted (Table 12.6.6). In overweight and obese individuals, weight loss should be encouraged in line with re- cent guidelines (http://www.nhs.uk/livewell/loseweight/Pages/ Loseweighthome.aspx in the United Kingdom and http://www. cdc.gov/healthyweight/losing_weight in the United States of America). This is particularly the case in patients with the meta- bolic syndrome or diabetes, where the risk of atherosclerotic cardiovascular disease is high. The patient should have expert nu- tritional counselling. They should expect on average a 5 to 10% reduction in chol- esterol levels, and this is coloured by genetic factors so that this can vary considerably. Aerobic exercise has only a small effect in lowering cholesterol levels, but it has general health and circula- tory health benefits in addition to improving lipids. Exercise can be dramatic in reducing TG levels. Other risk factors should be minimized. Drug treatment of hypercholesterolaemia The decision to implement cholesterol-lowering drug treatment is determined by the level of LDL-C/NHDL-C, the presence of other atherosclerotic cardiovascular disease risk factors, and overall ath- erosclerotic cardiovascular disease risk. A risk assessment tool should be used to assess the 10-year risk in patients more than 40 years of age. Exclusions to the use of risk assessment tools are shown in Box 12.6.2. This should aid clinical decisions about lifestyle and whether to use lipid and blood pressure-lowering medication, but should not replace clinical judgement. National guidelines are of great help in making this decision (https://www.nice.org.uk/guidance/cg181 for the United Kingdom and https://www.guideline.gov/summaries/ summary/48337 for the United States of America). Present guide- lines suggest a 10-year risk of atherosclerotic cardiovascular dis- ease of more than 7.5% and more than 10% should be considered for statin treatment in the United States of America and United Kingdom respectively. FH or other genetic disorders of lipid metabolism are important exclusions to the use of risk assessment tools as they grossly under- estimate risk. In younger people, in whom the likelihood of an event in the next 10 years is low, a lifetime assessment is reasonable. The treatment of FH in children is discussed in previous sections. Statins Statins are the first-line drug for the treatment of hypercholester- olaemia. The evidence base for their use to prevent atherosclerotic cardiovascular disease is very strong. Statins are orally active inhibitors of the cholesterol biosynthesis enzyme HMG-CoA reductase. HMG-CoA reductase is rate limiting in the

multistep cholesterol biosynthesis pathway. Inhibition of chol- esterol biosynthesis reduces intrahepatic cholesterol levels, leading to activation of the LDLR gene and increased hepatic LDLR activity (see ‘Lipids’ and ‘Cholesterol’). The resultant increased uptake of LDL by the liver reduces plasma according to statin dose. Apart from lipid lowering, evidence does not support other mechanisms to re- duce atherosclerotic cardiovascular disease. Statins vary considerably in their structure, hydrophobicity and hydrophilicity, potency, and duration of action (Table 12.6.7). The efficacy of statins in reducing LDL-C/NHDL-C is patient de- pendent, but beyond the initial lowest dose, doubling the statin dose incrementally reduces the LDL-C by approximately 6%, that is, ap- proximately 20% overall. With high-intensity treatment, reductions of LDL-C/NHDL-C are routinely greater than 50%, and even with low-intensity statin treatment, a 30% reduction can be anticipated. If TGs are raised, but to less than approximately 5.0 mmol/litre (450 mg/dl), statins also reduce TGs in the same proportion as LDL- C, and this is not statin-type dependent. Statins are administered once daily orally and without adverse re- actions in most people. With the longer-acting statins this can be at any time of day, but with the shorter-acting statins, administration is best in the evening (Table 12.6.7). The guidelines for statin use are summarized in Fig. 12.6.19 and Table 12.6.12. Statin side effects One in ten people will experience mild to moderate side effects, which are fully reversible on drug withdrawal. The most common Fig. 12.6.20 Results of clinical trials and effect of LDL lowering on atheroma volume. The relationship between low-density lipoprotein cholesterol levels and change in per cent atheroma volume for several intravascular ultrasonography trials. There is a close correlation between these two variables ($r2 = 0.97$). Note that in the Asteroid trial, treatment to LDL levels below currently accepted guidelines can actually regress atherosclerosis in coronary disease patients. A-Plus, Asteroid, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; Avasimibe and Progression of Lesions on Ultrasound; Camelot, Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; Reversal, Reversal of Atherosclerosis With Aggressive Lipid-Lowering. Source data from Nissen SE, et al. (2006). Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA, 295(13), 1556–65.

 side effect is muscle pain, due to interference with muscle mitochon- drial electron transport function. Indigestion, headache, fatigue, and joint pain also occur. Muscle The risk of statin-induced myopathy is increased by age, renal im- pairment, concomitant administration of drugs, and dietary com- ponents (grapefruit juice in large quantities increases statin side effects by increasing blood levels) that interfere with the oxidation of statins, mainly through using the same cytochrome P450 (CYP) pathway (Table 12.6.7), and those with a previous history of statin- associated muscle pain. The risk of statin myalgia and myopathy is statin and dose related. It depends in part on a pharmacogenetic variation of SLCO1B1 (OATP2), which transports statins into the liver, and the CYPs that metabolize statins. Polymorphic variants of the SLCO1B1 gene are present in 15% of the population, with a homozygous frequency of 1 in 200. SLCO1B1 variants increase blood statin levels, and are associated with myalgia, and myopathy with raised creatine kinase (CK) levels, as well as the other side effects. A single copy of one of the SLCO1B1 variants increases the risk of muscle problems from high-dose simvastatin treatment ap- proximately fivefold, and two copies by approximately 20-fold. By contrast, rosuvastatin treatment is less associated with muscle com- plaints, and this is regardless of SLCO1B1 genotype, and despite the greater potency of rosuvastatin. Atorvastatin appears to be less likely to cause muscle and other toxicities than simvastatin. It is possible that the increased circulating levels of the more hydro- philic statins (pravastatin and rosuvastatin) produced by SLCO1B1 variants are less toxic to

muscle than the more hydrophobic statins such as simvastatin, even though the more hydrophilic statins such as rosuvastatin are more dependent on the SLCO1B1 protein for transport into the liver. In consequence of its greater toxicity, simvastatin is less favoured for use. The differences between statins are in part due to alternative pathways of statin metabolism, as well as genetic variation of the CYP450s. Myopathic complaints are apparently more likely with statins oxidized by CYP3A4, simvastatin, and atorvastatin rather than those not oxidized by CYP3A4, pravastatin, and rosuvastatin. Although there are insufficient data to come to firm conclu- sions about the value of SLCO1B1 genotyping in predicting statin side effects, available data do suggest that those with the decreased transport variants are at increased risk of statin side effects. These genotyping assays are available and may be of value in those patients in whom high-intensity statin therapy is indicated, particularly if their history indicates previous side effects on statins. In patients in whom muscle problems or other side effects are serious, genotyping of SLCO1B1 variants is now common practice as this may inform the choice of statin and dose. SLCO1B1 homozygotes are at greater risk of serious myopathy and the fortunately rare rhabdomyolysis. Serious myopathy is best avoided by starting statins, particularly in those at risk, at modest doses rather than straightaway at the top dose. The exception to this ‘slowly, slowly’ approach is in patients with acute coronary syndromes, when the top dose of the more powerful statins is given. Patients who start statins should visit their doctor at once if they get unexpected muscle pain. In patients who get muscle pain, the plasma CK should be measured to differentiate myalgia from my- opathy. In the event of raised CK greater than five times the upper limit of the reference range, the statin should be stopped as there is a risk of rhabdomyolysis. This is a serious condition likely to require hospitalization, as it can cause acute tubular necrosis in the kidneys. CK levels in patients on statins are not routinely measured as ele- vated CK without muscle pain is not a feature of myopathy, and does not mean the statin needs to be stopped. Low vitamin D levels can exacerbate symptoms, so that vitamin D should be measured, and replenished if low. There are no arguments for the use of CoQ10 to reduce statin muscle side effects. Raised CK levels have other causes, the most common of which is physical training. Primary muscle disease is also potentially a problem and may militate against statin use and needs specialist as- sessment. MacroCK, a CK-IgG antibody complex often associated with an underlying autoimmune myositis, or oligomeric mitochon- drial CK often seen in patients with malignancy or hepatic disease are not uncommon, and are diagnosed by simple laboratory tests. A benign inherited hyperCKaemia due to defective caveolae, can also confound interpretation. The management of statin muscle problems is to (1) reduce dose and increase incrementally until the threshold for side ef- fects is reached or (2) change the statin or resort to nonstatin lipid-lowering medications. Atorvastatin or rosuvastatin given on a weekly, biweekly, or alternate-day basis are efficacious because of their long half-life and potency (Table 12.6.7). Referral to a spe- cialist centre is advised for severe problems. CK levels should be monitored. Liver Liver enzymes should be measured prior to starting statin therapy, at 3 and 12 months according to United Kingdom guidelines. Measurement is no longer recommended in the United States of America unless there are signs or symptoms of liver disease— fatigue, weakness, loss of appetite, abdominal pain, or icterus. Statins can be started with safely in patients with abnormal liver enzymes, even over three times normal, but if after starting statins liver transaminases (alanine transaminase and aspartate aminotransferase) become further raised, the statin should be stopped while the situation is assessed. Although data are not available on the toxicity of hydrophilic (Table 12.6.7; actively transported by SLCO1B1) versus hydro- phobic (passive diffusion and high first-pass uptake) statins, a dif- ferent statin or a lower dose can be introduced to determine the effect on liver function. Abnormal transaminases are also common in

the fatty liver that commonly accompanies obesity, insulin resistance and diabetes, and excess alcohol consumption, and can be confused as being due to statins. The statin-associated increase in transaminases resolves upon discontinuation of the medication, whereas that due to other causes does not. Serious statin-induced hepatitis is very rare, so that there is a reduced tendency to monitor liver function as indicated by guidelines from the United States of America. Too many physicians stop statin medication unnecessarily and forget the benefits of statins in reducing cardiovascular morbidity and mortality by approximately 50% because they think a small rise in the liver function tests means that there is ongoing damage to the liver.

section 12 Metabolic disorders 2092 Statins can be used safely in patients with chronic liver disease and well-treated cirrhosis, but the physician may need to follow the pa- tient more closely than would occur in a normal healthy patient on a statin, and the same applies to approximately threefold increases in transaminases. Increased transaminases must first be established to be due to statins. If so, the dose can be reduced or the statin changed. Persistently raised transaminases can be tolerated but requires careful monitoring for risk of fibrosis or cirrhosis. Brain Hydrophobic statins enter the brain, whereas hydrophilic statins do not (Table 12.6.7). Not infrequently hydrophobic statins cause cerebral symptoms including sleep disturbance, vivid dreams, anx- iety, and memory disturbance. These side effects are fully reversible on stopping the hydrophobic statin and substituting a hydrophilic statin. There is no evidence that the statin memory disturbance con- tributes to dementia. Other causes of these symptoms such as other medications, neuropsychiatric conditions, or organic brain disease must be excluded. Diabetes and other side effects A serious consequence of statin therapy is an increased risk of dia- betes with an estimated risk in excess of 10%, particularly with higher doses of the potent statins. In most people with high ath- erosclerotic cardiovascular disease risk, the reduced risk outweighs the risk of diabetes. Statins are also the main treatment to prevent macrovascular disease in diabetics. If the glycated haemoglobin or fasting glucose levels increase or indeed diabetes develops, changing statin therapy is not recommended. Lifestyle modification may miti- gate the risk or the diabetes. Very rarely, neuropathy, autoimmune myopathy—distinct from toxic myopathy, an autoimmune lupus-like syndrome, autoimmune hepatitis, and pancreatitis are ascribed to statin use. Haemorrhagic stroke has not been a problem even when the LDL-C is very low. The value of statin in the treatment of those with advanced heart failure or on haemodialysis is uncertain. Otherwise, in very large meta-analyses, statins have been shown to be effective and safe at all cholesterol levels and at all adult ages. There is no propensity to develop cancer. They are the most used lipid-lowering drug. Ezetimibe Ezetimibe is a small-molecule drug that specifically blocks NPC1L1 and intestinal cholesterol absorption (see ‘Intestinal lipid absorption and transport as chylomicrons’). Intestinal cholesterol is two-thirds derived from bile and about one-third dietary. A single ezetimibe 10 mg dose reduces cholesterol absorption by more than 50% so that that there is signification reduction of delivery of intestinal choles- terol to the liver and consequent induction of LDLR activity. Plasma LDL-C is reduced by about 20%, and this adds to the ef- fect of statins when the two drugs are used together. Occasionally a larger dose of 20 mg has been used safely, but this is not gener- ally efficacious. Ezetimibe has no effect on TGs or HDL. It is only used alone in those intolerant of statins. For sitosterolaemia, it is the drug of choice. It has been shown to be efficacious in redu- cing atherosclerotic cardiovascular disease events in clinical trials when used with statins. Deficiency of the NPC1L1 gene is associated with reduced atherosclerotic cardiovascular disease risk, again sup- porting its therapeutic role. Ezetimibe is safe and well tolerated. The main side effects are headache and gastrointestinal in about 1% of people; infrequent side effects are

myalgia, abnormal liver function tests, and rarely hyper- sensitivity reactions (rash, angio-oedema) or myopathy may occur. Cases of rhabdomyolysis have been reported, as has pancreatitis. Ezetimibe is used as an adjunct to maximum statin dosing and when statin side effects occur. Bile acid sequestrants (resins) These time-tested drugs bind bile acids (Table 12.6.8) in the intes- tine, and promote their excretion instead of their normal reabsorp- tion by the ileum. In turn, the liver synthesizes more bile acids from cholesterol, which reduces the liver cholesterol pool and induces the LDLR with increased LDL-C clearance. Bile acid sequestrants are traditionally available in resin form as cholestyramine and colestipol, which must be suspended in water; colesevelam is a tablet. Sequestrants need to be taken twice a day with the higher dose in the morning with breakfast and some- what less in the afternoon. Colesevelam is taken as up to four tab- lets with breakfast and up to three tablets in the afternoon. Taking sequestrants with breakfast is desirable as it coincides with emptying of the gallbladder, which fills overnight, and facilitates maximum bile acid binding. The effect of sequestrants is dose dependent. At maximum dosing with colesevelam, around a 30% reduction in LDL-C levels can be achieved. Resins should be given with caution in patients with hyper triglyceridaemia as they can worsen this. Interruption of the entero- hepatic recirculation of bile acids has important effects on hepatic lipoprotein metabolism. Activation of phosphatidic acid phos- phatase promotes hepatic TG synthesis and induces VLDL secre- tion, and consequently, increases plasma TG levels. Sequestrants are not systemically absorbed so that other side ef- fects are restricted to intestinal bloating and constipation. In conse- quence, they are very safe and can be used in pregnancy and during lactation. They are efficacious when given with statins or ezetimibe, but need to be taken several hours apart from other drugs and vitamins, which they bind to and prevent their absorption. They can be taken with statins and ezetimibe for the management of severe hyperchol- esterolaemia. In statin intolerance, they can be used alone or with ezetimibe. Resins have not been tested in clinical trials. Their use needs to be determined by clinical experience. Recalcitrant heterozygous FH, and homozygous FH, including those with high Lp(a), are indica- tions, particularly with symptomatic atherosclerotic cardiovascular disease. They are also indicated in those with serious statin side ef- fects, and in pregnancy and lactation. Nicotinic acid Nicotinic acid, also called niacin or vitamin B3, has been used to lower lipids over many years, particularly in the United States of America, but is no longer recommend for use in Europe (see next paragraph). In adipocytes, it decreases lipolysis by activation of the nicotinic acid receptor (NIACR1, a high-affinity G protein-coupled receptor) which reduces the levels of intracellular cAMP thereby inhibiting lipolysis. In the liver, nicotinic acid suppresses APOC3

 gene expression, thereby enhancing LPL activity. It suppresses VLDL and LDL-C by about 30% at optimum doses and raises HDL- C comparably. Clinical trial data do not support its use to raise HDL for prevention of atherosclerotic cardiovascular disease. Clinical trials, however, have shown that combination use of statins with drugs containing nicotinic acid did not lead to add- itional benefits in reducing the risk of major vascular events such as heart attack and stroke, but did result in a higher frequency of non- fatal but serious gastrointestinal events and infection. As a result, nicotinic acid is not available for use in Europe. It is also, with PCSK9 and possibly CETP inhibitors, one of the few drugs that reduce Lp(a). A 30% reduction in Lp(a) can be anticipated at optimum doses of these drugs, but this is of uncertain value (see ‘Lipoprotein(a)’). Cutaneous flushing is a troubling side effect of nicotinic acid. It is mediated through NIACR1 and prostaglandin in the skin. Nicotinic acid therapy is therefore usually started at a low dose and slowly increased to higher doses, under the cover of aspirin to re- duce prostaglandin activity and flushing. Nicotinic acid can cause dyspepsia, mild increases in transaminases, and plasma uric acid.

It can precipitate gout in susceptible people. Acanthosis nigricans and maculopathy are rare side effects. There are no strong arguments for the use of nicotinic acid in lipid lowering.
PCSK9 inhibitors Inhibitors of PCSK9 are fully human monoclonal antibodies that block PCSK9 at the liver surface and reduce LDLR degradation. This concept emerged from the discovery that loss-of-function muta- tions in the PCSK9 gene reduce plasma LDL-C, along with the risk of atherosclerotic cardiovascular disease. They have proved highly efficacious in meta-analysis of clinical trials in reducing LDL-C and TGs by approximately 50% and increasing HDL, but end-point trials have not been reported as yet. They also reduce Lp(a) by 30%. These new and exciting drugs have recently received regulatory approval by the FDA and European Medicines Agency, but the criteria for general use are restricted to severe genetic hypercholesterolaemia with progressive atherosclerotic cardiovascular disease and failure of adequate response to other lipid-lowering agents. Their initial target is genetic hypercholesterolaemia, where cholesterol lowering is not adequate, or when there are severe statin side effects. With very very low LDL-C levels, the risk of haemorrhagic stroke has not materialized. Dietary supplements Supplements to the diet with plant sterols or stanols (such as FloraProActive or Benecol respectively) which compete for chol- esterol absorption thus reducing plasma cholesterol levels can be used as an adjunct to lifestyle measures. A daily intake of 1.5 to 2.4 g sterols or stanol ester can lower the plasma cholesterol by 7 to 10% in 2 to 3 weeks as part of a healthy diet and lifestyle. Drugs for homozygous FH Two orphan drugs are available to treat homozygous FH. Lomitapide is an inhibitor of MTTP, which mimics abetalipoproteinaemia in its mechanism of action, and suppresses VLDL secretion. It is approved for use in homozygous FH. It can achieve a greater than 30% reduc- tion of LDL-C when used alone or in conjunction with apheresis. It is effective in receptor-negative patients, because its action is inde- pendent of LDLR activity. Its side effects are mechanism of action based, with intestinal upsets due to fat malabsorption and fatty liver. Progressive hepatic fibrosis has not been problematic thus far. Another drug is mipomersen a second-generation 2′-O- methoxyethyl chimeric antisense oligonucleotide, which inhibits the synthesis of apoB. It is approved in the United States of America for treatment of homozygous FH. It achieves a similar LDL-C reduc- tion to lomitapide. As with lomitapide, mipomersen causes intes- tinal upsets due to fat malabsorption and fatty liver. It has not been approved in Europe due to a 50 to 70% rate of side effects, mainly injection site reactions, flu-like symptoms, liver enzyme elevations, and proteinuria. PCSK9 inhibitors also reduce LDL-C by greater than 30% in homozygous FH patients, who are receptor deficient, but have no effect in receptor-negative patients. LDL apheresis Apheresis (ἀφαίρεσις ‘a taking away’) is a physical approach to re- moving LDL from the blood, analogous to haemodialysis. The blood of the patient is passed through a separator, which removes LDL by specific binding to columns and spares other lipoprotein fractions including HDL and returns the blood to the patient. Most homozygous FH patients do not achieve satisfactory reduc- tion of LDL-C levels on maximum drug treatment alone and disease will progress. Those with atherosclerotic cardiovascular disease and LDL-C levels above 5 mmol//litre (200 mg/dl), or without athero- sclerotic cardiovascular disease and LDL-C levels above 7 mmol/ litre (280 mg/dl) are candidates for apheresis. Apheresis is performed weekly or twice-monthly depending on the degree of lipid lowering achieved. It is well tolerated and achieves a good reduction in LDL-C levels, though there is rebound at the end of the treatment cycle to high levels of LDL-C, due to increased synthesis and defective LDLR function. Atherosclerotic cardiovas- cular disease still progresses, but at a reduced rate. The main disadvantage is long-term access to the circulation, which is best achieved by an arteriovenous fistula, but venous access or a central line can be used. The advent of effective apheresis and effective drug treatment with conventional drugs has greatly improved the prognosis for homozy-

gous FH. Further improvement is hoped for and anticipated with the drugs described previously described. Lipoprotein(a) The treatment of elevated Lp(a) is a problem. It is a serious atherosclerotic cardiovascular disease risk factor and a risk factor for calcific aortic stenosis. There is no truly effective treatment. Both nicotinic acid and PCSK9 inhibitors reduce Lp(a) by approximately 30%, but the efficacy of this is uncertain compared to dramatic lipid lowering. Nicotinic acid is not available in the United Kingdom. The role of CETP inhibitors in lowering Lp(a) has still to be established. A second-generation antisense Lp(a) mRNA inhibitor has also proved remarkably efficacious as a treatment in early clinical trials, and is in development. In the large AIM-HIGH clinical trial, after LDL-C lowering to 1 to 2 mmol/litre (40 to 80 mg/dl) with statins no further benefit was accrued from the addition of nicotinic acid to lower the Lp(a). Profound lipid lowering should be aimed at and this may be

section 12 Metabolic disorders 2094 sufficient. Whether this applies with very high Lp(a) levels (>100 mg/dl (250 nmol/litre) is not known. Aspirin or another antiplatelet drug should be given to suppress the thrombogenicity of Lp(a). In patients with high Lp(a) and symptomatic atherosclerotic car- diovascular disease, apheresis is effective in reducing Lp(a) levels and has potential to reduce disease progression, but its use is un- likely to be commonplace. Triglyceride reduction to prevent acute pancreatitis and atherosclerotic cardiovascular disease The primary treatment goal in severe hypertriglyceridaemia is to lower TGs rapidly to reduce the risk of acute pancreatitis. Elevated plasma TGs are also a risk factor for atherosclerotic cardiovascular disease, as previously discussed. A secondary goal is therefore to re- duce the risk of atherosclerotic cardiovascular disease. TG levels in patients are best measured on fasting samples, be- cause in the nonfasting state diet can have a profound effect on TG levels. Nonfasting TGs are better predictors of atherosclerotic car- diovascular disease risk than fasting TG, probably because they better reflect our usual status. Patients with fasting TGs levels above 10 mmol/litre (900 mg/dl) are at increased risk of acute pancreatitis. Although in practice acute pancreatitis is rare with levels below 15 mmol/litre (1300 mg/dl), fat consumption can readily achieve this level in the predisposed. Those patients that display chylomicronaemia (type 1 and 5 hyper- lipidaemia) as ascertained by the ‘fridge test’ are at particular risk of acute pancreatitis. TGs can vary markedly and rapidly and a patient with only mod- erately elevated TGs may develop acute pancreatitis following a short period of dietary indiscretion, which leads to much higher TG levels. There are also patients, however, with persistent marked hypertriglyceridaemia who never develop pancreatitis. Pancreatitis is therefore an unpredictable complication of hypertriglyceridaemia and usually strikes unexpectedly. It is thus generally accepted that patients with very high TG levels should be treated to reduce TGs and the risk of acute pancreatitis. No clinical trial has been per- formed to validate this view. Lifestyle Moderately severe hypertriglyceridaemia (<15 mmol/litre (1300 mg/dl)) in the absence of chylomicrons (type 4 hyperlipidaemia) can be managed in the outpatient setting. Lifestyle changes will usually significantly reduce plasma TG levels. A reasonable dietary goal is to restrict total fat intake to around 20 to 30 g daily. This is not always easy to achieve, because normal consumption is approximately 70 g daily, and requires dedication from the patient in understanding their dietary fat consumption. Excessive intake of starch and sugar should be discouraged because they drive TG production in the liver. A formal dietary consultation and regular review with a dietitian with specific experience in the management of severe hypertriglyceridaemia is desirable. Dietary fat restriction needs constant reinforcement. Spiking TG values on follow-up are often related to dietary indiscretions. Alcohol con- sumption should be limited or stopped. Regular physical activity, particularly strenuous activity, is valu- able to reduce

TG levels, and may have dramatic results. Weight reduction by diet and exercise should help decrease TG. In obese and overweight individuals, weight loss should be encouraged. ‘The rescue diet’ In more severe hypertriglyceridaemia (>15 mmol/litre (1300 mg/ dl)), especially with chylomicronaemia, and out-of-control diabetes, the patient is often best managed in the hospital setting to achieve rapid control. An extremely low-fat diet, less than 10 g of fat daily, for about 3 days is necessary (Table 12.6.13). This diet is called the ‘rescue diet’ as it rapidly lowers TGs. This strict low-fat diet is not easy to maintain and not nutritionally adequate in the long term. Secondary factors Other factors contributing to hypertriglyceridaemia need to be ac- tively sought and treated. In clinical practice, the most common problem is either undiagnosed or uncontrolled diabetes. In suscep- tible individuals, certain drugs, such as oestrogen, steroids, retin- oids, and protease inhibitors, can also trigger hypertriglyceridaemia (Table 12.6.4). If drugs are contributing significantly to hyper triglyceridaemia, treatment should be switched or discontinued if the patient’s clinical condition allows and there are effective alterna- tive treatment options. Further information on the secondary causes of hypertriglyceridaemia is found in Table 12.6.4. Drug treatment of hypertriglyceridaemia Severe hypertriglyceridaemia with TGs above 5 mmol/litre (450 mg/dl) despite adequate lifestyle management is likely to need drug treatment. Fibrates and omega-3 fatty acids derived from fish are the only drugs available to treat hypertriglyceridaemia in the United Kingdom. Nicotinic acid is not used in Europe, but is in the United States of America (see ‘Nicotinic acid’). Statins can reduce TG, when levels are below 5 mmol/litre (450 mg/dl), but have no value in severe hypertriglyceridaemia. Statins may be necessary with fibrates if LDL-C/NHDL-C remains high after TGs have been controlled (Table 12.6.8, with caveats for the combined use of statins and fibrates). Ezetimibe does not lower TGs significantly but can be combined with fibrates if additional LDL-C lowering is required and statins are not tolerated. Cholestyramine can raise TGs and should be avoided in moderate to severe hypertriglyceridaemia. Fibrates Fibrates are central to the management of severe hypertrigly ceridaemia (TGs >5 mmol/litre (450 mg/dl)) and are the drugs of first choice. They lower TGs, increase HDL-C, and may either lower or in some cases increase LDL-C. Fibrates are particularly effica- cious in FDBL. They do not very much decrease atherosclerotic cardiovascular disease events due to hypercholesterolaemia, but are efficacious in hypertriglyceridaemia. Fibrates regulate lipid metabolism by their agonist effect on the nuclear receptor PPARα. PPARα stimulates LPL and apoA5 expres- sion and inhibits apoC3 expression. The increase in plasma HDL- C depends partly on an overexpression of apoA1 and apoA2. They also increase fatty acid β-oxidation by mitochondria. An increase in LDL-C arises in hypertriglyceridaemic subjects when more efficient lipolytic processing brought about by fibrates results in increased LDL-C production.

 They are safe and have few side effects, but can increase the likeli- hood of gallstones. In the presence of existing gallstones they should be used with caution. Fibrates (particularly gemfibrozil) are associ- ated with toxic myopathy especially when combined with statins or nicotinic acid (Table 12.6.8). Care and appropriate monitoring is needed in patients on anti- coagulants and some diabetic blood glucose-reducing drugs as fibrates interact with these classes of drug. Fibrates are excreted renally and doses need to be adjusted to renal function. They raise creatinine by about 10%, but this is not due to a lowered GFR and reverses on discontinuation. In the light of recent reanalysis of clinical trials of fibrates, their use in treating mild to moderate hypertriglyceridaemia and preventing atherosclerotic cardiovascular disease needs reconsideration. Omega-3 fatty acids Omega-3 polyunsaturated fatty acids or fish oils are present in high concentration in oily fish. They come from a variety of plants sources, but omega-3

fatty acids of plant origin are less well studied, and are not a recommended substitute for fish oils. Eicosapentaenoic acid and docosahexaenoic acid are the main active ingredients in fish oil. Fish oils are given in capsules as 4 g daily in divided doses, and effect- ively reduce TG levels in moderately severe hypertriglyceridaemia, and may lower TGs by up to 40% in some patients. They work in part mechanistically by increasing the turnover of MLXIPL mRNA (see ‘Lipids’ and ‘Triglycerides’), which inhibits the de novo biosynthesis of fatty acids from carbohydrate. Fish oils are effective for the treatment of moderate hyper triglyceridaemia with levels of approximately 5 mmol/litre (450 mg/dl). With more severe hypertriglyceridaemia, they are good in com- bination with fibrates. Higher doses of up to 12 g have been used with apparent safety and efficacy in very severe hypertriglyceridaemia, but should not be used in pure type 1 hyperlipidaemia, where they may exacerbate the phenotype. High doses can also be used with ap- parent safety in hypertriglyceridaemia during pregnancy. They can cause a modest increase in LDL-C. The main side effect is dyspepsia. They may increase the bleeding time. It is important that the fish oil is purified to remove mercury, dioxins, polychlorinated biphenyls, and other toxins that contam- inate fish, particularly if prolonged use is anticipated or in pregnancy. There are active clinical trials to see if they reduce atherosclerotic cardiovascular disease risk due to high TGs. Table 12.6.13 Hypertriglyceridaemia rescue diet Daily menu Grams of fat Grams of fat Breakfast (1.7 g) 125 ml orange juice 0.3 1 banana 0.4 3/4 cup Rice Krispies 0.0 250 ml skimmed milk 0.5 1 slice white bread 0.5 15 ml honey 0.0 Lunch (1.6 or 2.4 g) 2 medium potatoes (2 slices bread) 0.2 (1.0) 60 g fat-free cottage Salad (lettuce, cucumber, tomato ...) 0.5 cheese 0.9 Supper (2.4 or 3.4) 375 ml white rice 0.6 (1.6) 125 ml tomato/onion mix 0.4 125 ml lentils 0.4 Vegetables (carrot, broccoli) 0.4 Fruit (3 slices of pineapple) 0.6 Snacks (1.3 g) Apple, morning 0.6 Pear, afternoon, morning 0.7 Other supplements No diabetes Diabetes Beverages Carbonated drinks including colas Lucozade Fruit juice, including orange, apricot, apple, grape Dietetic cold drinks Low-calorie Lecol, Oros Sweets Boiled sweets Jelly babies, wine gums, marshmallows Peppermints, vitamin C sweets Artificially sweetened Spreads Sugar, syrup, honey, molasses Jam, marmalade Dietetic jams Desserts Jelly, canned fruit, custard made with skimmed milk (0.4 g fat/250 ml) Meringues without cream Dried fruit Artificially sweetened jelly Low-calorie canned fruit Source data from Blom DJ, et al. (2010). Hypertriglyceridaemia: Aetiology, Complications and Management. JEMDSA, 15(1), 11–17.

section 12 Metabolic disorders 2096 Acute pancreatitis Severe hypertriglyceridaemia is a well-established trigger for acute pancreatitis. The pathogenesis of hypertriglyceridaemic acute pancreatitis remains ill-understood. A likely precipitating factor is sludging of the very large chylomicron particles in the microvasculature of the pancreas leading to leakage of pancre- atic enzymes into the circulation. This may lead to intravascular TG hydrolysis by lipase with subsequent bulk release of ‘toxic’ proinflammatory free fatty acids into the circulation; and activation of the proteolytic enzyme trypsin in the circulation may lead to pan- creatic autodigestion. Accurate measurement of serum amylase is challenging in the presence of lipidaemia and pancreatitis may be falsely ruled out when the amylase is not apparently elevated. In many patients, TGs are only measured several days after the onset of pancrea- titis and a prolonged period of nil per mouth. In such situations, hypertriglyceridaemia may have improved markedly and may then be erroneously excluded as a possible cause of pancreatitis. The treatment of hypertriglyceridaemic pancreatitis does not differ greatly from that of pancreatitis of any other cause. Metabolic disturbances should be sought and controlled. Should total paren- teral nutrition be necessary, it is important to avoid excess fat supply (e.g. Intralipid or Lipovenoes). Other

therapeutic measures in order to correct the hypertriglyceridemia include the use of low molecular weight heparin and insulin. Apheresis or plasma exchange will rapidly, but transiently, lower plasma TGs, and may have a role if the high TGs are intransigent to other treatment approaches. In the early stages of recurrent acute pancreatitis and in pregnancy it may have value. There is, however, no evidence that patients treated with apheresis recover more rap- idly or have fewer pancreatitis-associated complications, or have reduced mortality. Subsequently, severe restriction of dietary fat in- take is necessary. Pregnancy Hypertriglyceridaemia can be particularly troublesome in preg- nancy. It is usually worse in the third term, when physiological hormonal changes normally increase VLDL production. This will potentially markedly exacerbate an underlying genetic defect in peripheral lipolysis (see 'Primary causes of defective lipolysis of triglyceride-rich lipoproteins'). Gestational diabetes may exacerbate this, and needs appropriate control if necessary with metformin and insulin. A low-fat diet needs careful monitoring to avoid reduced nutrition. Omega-3 fatty acids are highly efficacious as they lower VLDL secretion. Doses of fish oils well above the usually recommended daily maximum of 4 g can be given with apparent efficacy and safety; up to 12 g appears efficacious. Fibrates are also helpful in the third term, when teratogenicity is not a problem, and they are apparently safe and effective. In patients at risk of or with acute pancreatitis, apheresis may be indicated. An additional risk of severe hypertriglyceridaemia in pregnancy is still birth. Bariatric surgery Weight loss surgery is highly efficacious in the treatment of severe obesity, and is effective in the management of type 2 diabetes. If obesity and diabetes are present in a patient with hypertriglyceridaemia then it can be highly effective in reducing TG levels. In the decision as to whether to offer a patient bariatric surgery, the presence of dia- betes and hypertriglyceridaemia are important considerations. Treatment protocols and new drugs Treatment protocols, existing drugs, and new drugs for the treat- ment of dyslipidaemia are given in Tables 12.6.7, 12.6.8, 12.6.10, and 12.6.12 and Fig. 12.6.19. FURTHER READING Abifadel M, et al. (2012). Identification and characterization of new gain-of-function mutations in the PCSK9 gene responsible for autosomal dominant hypercholesterolemia. Atherosclerosis, 223, 394–400. Adhyaru BB, et al. (2015). New cholesterol guidelines for the manage- ment of atherosclerotic cardiovascular disease risk: a comparison of the 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines with the 2014 National Lipid Association recommendations for patient-centered management of dyslipidemia. Cardiol Clin, 33, 181–96. Alphonse PAS, et al. (2016). Revisiting human cholesterol synthesis and absorption: the reciprocity paradigm and its key regulators. Lipids, 51, 519–36. Blom DJ, et al. (2010). Hypertriglyceridaemia: aetiology, complica- tions and management. JEMDSA, 15, 11–17. Brunham LR, et al. (2006). Intestinal ABCA1 directly contributes to HDL biogenesis in vivo. J Clin Invest, 116, 1052–62. Chowdhury R, et al. (2014). Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med, 160, 398–406. Clarke R, et al. (2009). Genetic variants associated with Lp(a) lipopro- tein level and coronary disease. N Engl J Med, 361, 2518–28. Cohen J, et al. (2005). Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet, 37, 161–5. Cuchel M, et al. (2013). Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet, 381, 40–6. Danik JS, et al. (2013). Lack of association between SLCO1B1 polymorphisms and clinical myalgia following rosuvastatin therapy. Am Heart J, 165, 1008–14. Dayspring TD, et al. (2015). Biomarkers of cholesterol homeostasis in a clinical laboratory database sample comprising 667,718 patients. J Clin Lipidol, 9, 807–16. De Oliveira e Silva ER, et al. (2000). Alcohol consumption raises HDL cholesterol levels by increasing the transport rate of

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