The diagnosis and management of familial hypercholesterolaemia

A.D. MARAIS, J.C. FIRTH

Lipidology Division of Internal Medicine & MRC Cape Heart Group
Groote Schuur Hospital and University of Cape Town Health Science Faculty –
Cape Town (South Africa)

Abstract. – Familial hypercholesterolaemia is a clinical entity comprising high concentrations of low density lipoproteins, tendinous deposition of cholesterol in a large proportion of affected subjects, and a propensity for the development of atherosclerosis and its complications in the coronary arteries. The aim of this review is to integrate publications with clinical experience into a concise profile of the disorder and its management. In less than a century this disease has been recognised, its lipoprotein derangement identified and numerous causal mutations have been detected. Although the phenotype is most commonly due to the occurrence of mutations in the low density lipoprotein receptor, defects in the apolipoprotein B100 may result in a similar phenotype. The same phenotype has also been linked to a gene and its product, PCSK9 and NARC1, that may be involved in the regulation of cholesterol in the cell. In the past few decades statins, by inhibiting cholesterol synthesis at the rate-limiting enzyme (hydroxymethylglutaryl coenzyme A reductase) have been developed and proven safe and effective in reducing the low density lipoprotein cholesterol, promoting regression and reducing mortality and morbidity. Additionally, advances in imaging techniques are allowing non-invasive insights into the impact of the disease on atherosclerosis. For these reasons there should be a high index of suspicion for this treatable condition in which genetic therapy and further modulation of atherosclerosis can be expected in the future.

Key Words:

Familial hypercholesterolaemia, Dyslipidaemia, Diagnosis.

Abbreviation list

ACAT acylcoA: Cholesterol Acyltransferase;
Apo = Apolipoprotein;
CE = Cholesterol ester;
CETP = Cholesterol Ester Transfer Protein;
CM = Chylomicron;
EGF = Epidermal Growth Factor;
FCH = Familial Combined Hyperlipidaemia;
FDB = Familial Defective Apolipoprotein B;
FH = Familial Hypercholesterolaemia;
HL = Hepatic Lipase;
HDL = High Density Lipoprotein;
HMGCoA = Hydroxymethylglutaryl Coenzyme A;
LCAT = Lecithin Cholesterol Acyltransferase;
LDL = Low Density Lipoprotein;
LDLR = Low Density Lipoprotein Receptor;
LPL = Lipoprotein Lipase;
MTP = Microsomal Triacylglycerol Transfer Protein;
NARC1 = Neural Apoptosis Regulated Convertase 1;
PCR = Polymerase Chain Reaction;
PCSK9 = Proprotein Convertase Subtilisin/kexin 9;
SREBP = Sterol Regulatory Element Binding Protein;
TC = Total Cholesterol;
TG = Triacylglycerol (Triglyceride);
VLDL = Very Low Density Lipoprotein.

Introduction

Medical practice over the past century has witnessed exciting developments in the understanding of disorders and their management. Familial hypercholesterolaemia (FH) is an excellent example of how clinical observation of a physical sign was linked not only to a high risk of heart disease but also to a high plasma total cholesterol (TC) concentration. With the advent of ultracentrifugation that could separate various lipoproteins that transport the plasma cholesterol, it was shown that the high TC was accounted for by an increase in low density lipoproteins

(LDL). This lead to studies demonstrating defective uptake of LDL into cells through dysfunctional LDL receptors (LDLR), in which an abundance of genetic mutations has been reported. The summary of the work of Brown and Goldstein[1], who were awarded the Nobel Prize in 1985, seemed to contain all the explanations for cholesterol balance in cells and in the body, the regulation of blood LDL cholesterol by the liver in response to diet, the impact of heterozygous and homozygous states of LDLR defects and how inhibitors of the rate determining enzyme in cholesterol biosynthesis, hydroxymethylglutaryl co-enzyme A (HMGCoA) reductase, could ameliorate the biochemical derangements. Over the subsequent 2 decades additional clinical observations and scientific investigation have revealed greater complexity and new disorders giving rise to identical phenotypes. These developments have recently been reviewed[2].

The aims of this review are to provide an understanding of familial hypercholesterolaemia as a clinical phenotype, to differentiate it from similar clinical presentations, and to provide strategies for the treatment of this disorder. A simplified and limited discussion of lipid and lipoprotein metabolism is provided to understand the pathophysiology of the disorder.

Pathophysiology of Familial Hypercholesterolaemia

It is generally appreciated that cholesterol, a crucial component of cell membranes, can be synthesised by all cells when they require cholesterol. Additionally, LDLR can be expressed to import lipoproteins containing the ligands apolipoprotein E (apoE) or apolipoprotein B100 (apoB). The LDLR is a transmembrane protein comprising a ligand binding domain, an epidermal growth factor (EGF) precursor homologous domain and a carbohydrate-rich domain extracellularly as well as an intracellular cytoplasmic tail. The LDLR accumulate in clathrin-coated pits on the plasma membrane. Together with the bound ligand the LDLR is internalised, by virtue of an interaction of the cytoplasmic tail. This requires a specific sequence that interacts with adaptor proteins. In the endosomal compartment of the cell, the EGF precursor homologous domain is involved in the release of the ligand and the LDLR returns to the cell surface many times before being degraded.

The synthesis and importation of cholesterol are regulated by the sterol regulatory element binding protein (SREBP), which is adjacent to sterol cleavage activating protein in the smooth endoplasmic reticulum. When cholesterol is depleted, this complex migrates to the Golgi apparatus where two proteases cleave SREBP. One of its fragments migrates to the nucleus to activate the genes for the de novo synthesis of cholesterol, as well as the expression of LDLR, and some additional genes involved in lipid metabolism. The regulatory process is incompletely understood and there is still much to learn about intracellular cholesterol trafficking and cellular cholesterol homeostasis. Under conditions of intracellular cholesterol excess, the provision of cholesterol is halted by turning off the two processes above. The conversion of cholesterol to cholesterol ester (CE) by acylcoA:cholesterol acyltransferase (ACAT) as well as the export of cholesterol due to transfer onto extracellular high density lipoprotein (HDL) will maintain intracellular cholesterol at an appropriate level. Macrophages actively take up cholesterol by scavenger receptors that import oxidised lipoproteins and cell debris. Macrophages can accumulate vast stores of CE as foam cells in atherosclerotic plaque.

Hepatocytes and enterocytes produce lipoproteins, complexes of lipids and proteins that are rich in triglyceride (TG) and have different fates according to their apoprotein complements. The apolipoproteins include apoAi, Aii, Aiv, Ci, Cii, Ciii and E. These apoproteins can transfer between lipoproteins and are synthesised in the liver, gut and some other cells. Since the metabolism of chylomicrons secreted by enterocytes appears essentially normal in FH, the focus of this review will be on the apoB100-containing plasma lipoproteins that the liver makes (Figure 1). In the hepatocyte, apoB100 appears to be constitutively expressed and will avoid degradation by receiving neutral lipid by a transfer process mediated by microsomal triacylglycerol transfer protein (MTP). The sources of triacylglycerol are the diet (by chylomicron remnants from the circulation), fatty acids coming from adipose tissue and de novo syn-
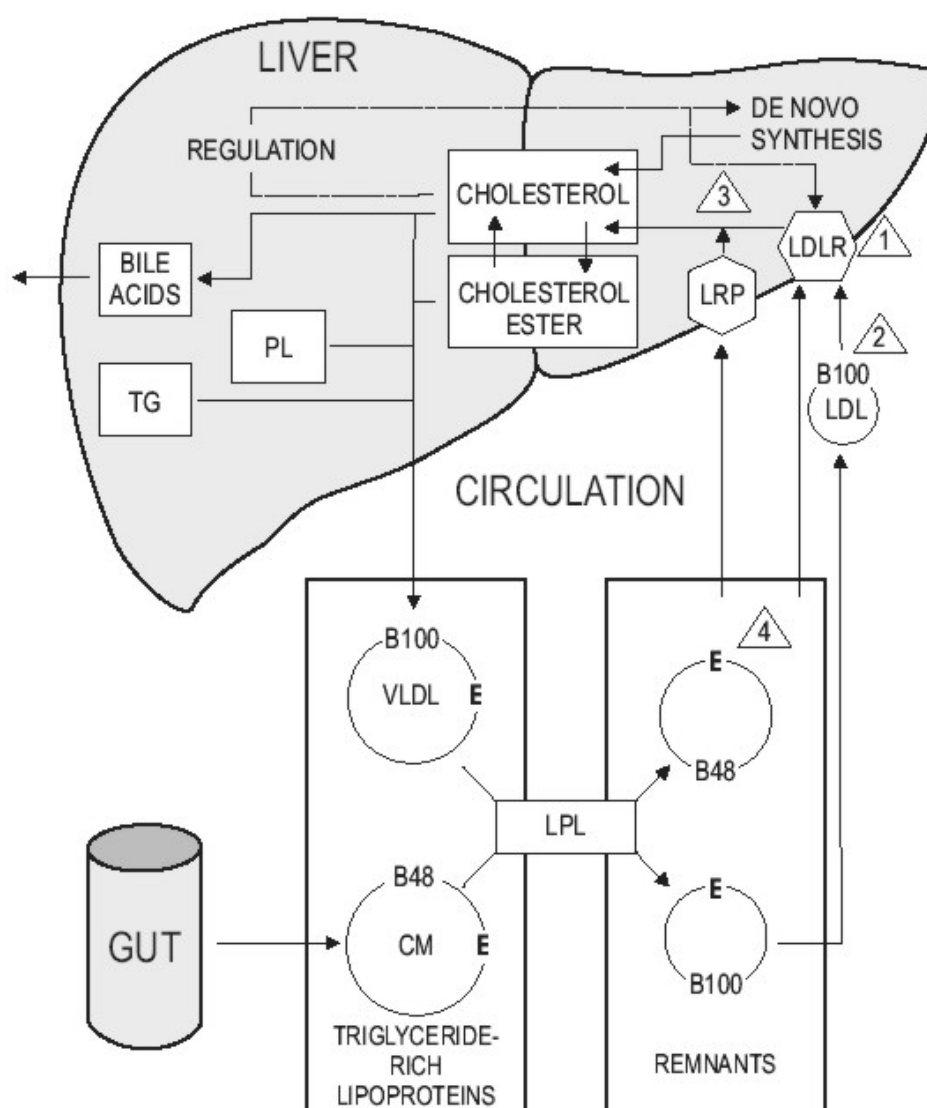
Figure 1. Lipoprotein metabolism and the metabolic errors in the commoner severe monogenic dyslipidaemias. Abbreviations are PL phospholipids, TG triacylglycerol, VLDL very low density lipoprotein, CM chylomicrons, LPL lipoprotein lipase, LDL low density lipoprotein, LDLR low density lipoprotein receptor, LRP low density lipoprotein receptor related protein. B100, B48 and E are apolipoproteins. The FH phenotype is caused by mutations in the LDLR (1), apoB100 (2), putative regulatory problems for LDLR (3); all leading to higher LDL concentrations. Defects in apoE (4) retard the clearance of remnants to cause dysbetalipoproteinaemia. The defect in familial combined hyperlipidaemia is thought to be due to an overproduction of lipoproteins.

thesis of fatty acids. The CE content of hepatocytes depends on the cholesterol balance of the cell. Additionally the activity of ACAT2 provides CE at the lumenal aspect of the endoplasmic reticulum where lipoprotein assembly takes place. A range of very low density lipoproteins (VLDL) is secreted. These TG-rich lipoproteins are substrates for lipoprotein lipase (LPL) in capillaries, chiefly in muscle and adipose tissue. This process is activated by apolipoprotein Cii (and inhibited by apolipoprotein Ciii). The lipoproteins, now depleted in TG are termed remnants. The remnants contain apolipoprotein E (apoE) that will bind the LDLR as well as the low density lipoprotein receptor related protein. Although all the chylomicron (CM) remnants are cleared by this route, a proportion of VLDL remnants will be further metabolised by hepatic triglyceride lipase

(HL) to LDL. ApoB100 now achieves the appropriate conformation to be a ligand for the LDLR. The liver, having a continuous requirement of cholesterol to produce bile acids, biliary cholesterol and lipoproteins, is responsible for the removal of the bulk of plasma LDL. The half-life of LDL being about 2.5 days, means the response to any intervention is complete by 4 weeks.

Lipid and lipoprotein metabolism is complex and the monogenic diseases present variably, depending on whether the affected gene is in a unique or rate-limiting step or whether there is a metabolic stress on the system to expose the affected gene. Additionally, the atherosclerosis associated with the hyperlipidaemia is influenced by environmental and other genetic factors. The severe monogenic disorders may be overlooked because are not always known to the medical practitioner, the index of suspicion may not be high, a specific diagnosis is not always sought and the disease phenotypes may be variable.

According to current understanding, mutations disrupting the function of 3 different genes impair the removal of LDL from the circulation (Figure 1). These clearance defects result in a clinical phenotype recognised as (heterozygous) FH: dominantly transmitted LDL hypercholesterolaemia of > 5 mmol/L, deposition of cholesterol in tendons to form xanthomata (not invariable) and premature coronary artery disease (not invariable). Since patients are identified as having FH by this phenotype, it is best to retain FH as a broader entity than only being due to LDLR mutations. The mutations in the LDLR are numerous, disrupting function partially or completely, and mostly relate to the apoB binding domain of the LDLR. There are a few mutations in apoB100 that render it a poor ligand for the LDLR. The most recently discovered gene associated with the familial hypercholesterolaemia phenotype is proprotein convertase subtilisin/kexin 9 (PCSK9)[3] which codes for neural apoptosis regulated convertase 1 (NARC1) but the exact mechanism by which LDLR activity becomes limited in this disorder is unknown. The homozygous FH phenotype involves the occurrence of cutaneous and tendinous xanthomata, typically already in early childhood, with LDL hypercholesterolaemia that is commonly > 15 mmol/L and coronary

disease typically sets in by the 3rd decade if the condition is not treated. This phenotype is usually due to LDLR defects but an autosomal recessive disorder due to adaptor protein defect has been described[4].

Other causes of severe monogenic dyslipoproteinaemia are familial combined hyperlipidaemia (FCH) and dysbetalipoproteinaemia. FCH has eluded the identification of a causal gene[5]. An overproduction of lipoproteins may be the mechanism of disease and, depending on other genes, could result in a variable pattern of hypercholesterolaemia, hypertriglyceridaemia or mixed hyperlipidaemia in the family. In dysbetalipoproteinaemia mutations disrupting the ligand-binding domain of apoE will decrease the clearance of remnants of both CM and VLDL. This leads to hypertriglyceridaemia together with hypercholesterolaemia from the cholesterol-enriched VLDL (dysbetalipoprotein). Lower LDL concentrations are generally found in this disorder, due to upregulation of hepatic LDLR and probably also to reduced production of LDL. It appears that only in adulthood, and possibly due to additional metabolic stress(es) such as diabetes, the production of VLDL exceeds the clearance of the remnants to the extent that there is severe hyperlipidaemia, tendon and/or cutaneous xanthomata and premature atherosclerosis.

All of these monogenic disorders indicate the powerful role of high concentrations of lipoproteins in the promotion of atherosclerosis. A discussion on atherogenesis by these lipoproteins is beyond the scope of this article.

A Clinical Approach to Familial Hypercholesterolaemia

About 1% of the population display the degree of hypercholesterolaemia in which the disorders mentioned above need to be considered. While the commonest disorder is FCH, there are regions in the world where FH occurs at a higher frequency than the generally accepted 1/500, as a result of founder effects. The founder effects for LDLR mutations in the Afrikaner and French Canadian are well-known. There appears to be a founder effect for FDB in central Europe[6].

These disorders may be identified by premature coronary artery disease in the patient

or the family, by the presence of physical signs (Figure 2) or the incidental discovery of hyperlipidaemia. Secondary dyslipidaemias must be excluded by clinical evaluation and tests for diabetes, proteinuria and hypothyroidism. The family pedigree may reveal the occurrence of premature heart disease or dyslipidaemia. It may also reveal information that could guide genetic testing, especially if there is a link to a founder population for FH or FDB. The physical examination may well reveal xanthelasma on the eyelids but this sign is not specific to severe hyperlipidaemias. The eyelid should be lifted to expose the whole cornea for inspection for arcus cornealis, which may lose its significance for dyslipidaemia in older people. Careful inspection of the extensor tendons of the fingers may reveal nodules, which will move with the tendons: these are tendon xanthomata that confirm a severe monogenic dyslipidaemia. Palmar crease deposition of lipid is a rare physical sign that is found in dysbetalipoproteinaemia. The elbows may have eruptive or tubo-eruptive xanthomata, which are rarely seen in heterozygous familial hypercholesterolaemia but are more commonly seen in dysbetalipoproteinaemia. The most important physical sign is a xanthoma of the Achilles tendon. Some experience is required to detect lesser deviations from normal. The examination is best done with the foot at 90 degrees and by palpating the edges of the tendon from the calcaneus to the junction with the muscle. A normal tendon has a smooth surface and parallel edges and conveys an impression of being less than 12 mm wide and thinner in the anteroposterior dimension. In FH the tendon may become rounded and wider, remaining smooth and parallel on palpation. Nodules may form on such a tendon or even on a tendon which is otherwise normal. Achilles tendons are also amenable to ultrasound examination[7] but this is not a requirement for clinical diagnosis and management. The clinical evaluation should also focus on the cardiovascular system and other risk factors for vascular disease. The high risk of atherosclerosis and the occurrence of silent ischaemia have lead to the suggestion that exercise stress tests are indicated in the management of FH[8].

It is often possible to make a reasonably confident diagnosis of FH and dysbetal-ipoproteinaemia by a thorough clinical consultation (see Table I), but the diagnosis of FCH depends not only on the dyslipidaemia of the individual but also requires an investigation for dyslipidaemia in the pedigree. A system has been suggested for making a diagnosis of FH[9]. Lipid clinics may provide valuable assistance with diagnosis and management, especially when the patient does not conform to the expected patterns or response to treatment. Specialised laboratories may also provide additional investigations for the diagnosis of the monogenic disorders. Plasma TG, TC, HDL cholesterol and LDL cholesterol are the minimum lipid investigations to make a diagnosis. Such a lipid profile is influenced by the acute phase response (after a myocardial infarction) that may render low values for HDLC and LDLC by 24 hours after the event. The apolipoprotein B concentration reflects LDL cholesterol very well but the LDL cholesterol derived by the Friedewald calculation is invalid in dysbetalipoproteinaemia. Lipoprotein electrophoresis on agarose typically reveals a Fredrickson type IIa pattern in the FH phenotypes, a type IIb pattern in FCH and a type III pattern in dysbetalipoproteinaemia. Acrylamide gradient gel electrophoresis typically describes small dense LDL in FCH whilst it may also reveal dysbetalipoproteinaemia[10]. Ultracentrifugation can also confirm dysbetalipoproteinaemia and small dense LDL. Whilst the genetic diagnosis is specific and appealing to make, it is not always practical. Most laboratories use the polymerase chain reaction (PCR) that is specific to a mutation or at best can reveal only a few mutations by heteroduplex formation or single strand conformational polymorphisms. In regions with founder effects, it is more cost-effective to make a genetic diagnosis than in regions where there are numerous mutations. Advancing technology may make comprehensive tests available to simplify the genetic diagnosis of FH and related disorders.

Management of Familial Hypercholesterolaemia

Making a specific diagnosis of a monogenic dyslipidaemia is useful because the monogenic dyslipidaemias outlined in this review all have severe implications for vascular disease. These dyslipidaemias require a compre-

Figure 2. Physical signs of dyslipidaemia. Panel A demonstrates xanthelasma, an unreliable sign and arcus cornealis. Arcus cornealis is a more specific sign of familial hypercholesterolaemia and can be situated inferiorly, superiorly or circumferentially. Panel B demonstrates xanthomata of the extensor fingers of the hands. Panel C demonstrates typical Achilles tendon xanthomata.

hensive management strategy to reduce their risk of vascular disease. The establishment of the diagnosis of a severe monogenic dyslipidaemia creates an opportunity for identifying family members for primary prevention of coronary disease.

The risk calculations for coronary disease complications based on general population data underestimate the risk of these severe dyslipidaemias. The average age of ischaemic heart disease reported for FH[11] is 43 years for men in Britain and 54 years for men in Japan[12], suggesting that lifestyle can make a significant impact on the prognosis. This is further supported by a genealogic study within one country where the high risk of complications became evident only in the beginning of the 20th century[13]. Studies of carotid intima media thickness have revealed thickening already in adolescence[14]. Regression of carotid intima-media thickness was demonstrated with aggressive treatment with statins in FH[15]. Treatment appeared to improve the

life-expectancy of FH subjects in a few years[16], but studies evaluating the impact of a range of risk factors from the same register indicated that coronary artery disease was only associated with age, gender, HDLC and smoking[17].

The patient with a monogenic dyslipidaemia should cease smoking, modify the diet, participate in regular exercise and attain ideal body mass. The failure to stress these factors repeatedly can create the perception in the patient that they are unimportant. The low cholesterol and low saturated fat diet lowers the LDL cholesterol. It is likely that favouring fish (n-3 fatty acids) will modulate eicosanoid products in a beneficial way in coagulation and inflammation. There are few dietary studies in FH, and none with a clinical outcome. Unpublished findings from our clinic indicated that enthusiastic counselling can reduce LDL cholesterol by approximately 1.5 mmol/L. (18% reduction compared to presentation).

While the lifestyle changes can be applied from early childhood, pharmacological treatment is generally started in adults. Men are generally treated from early adulthood. Women are often only treated after the family is complete since the onset of coronary disease is later and because drugs are not advisable during pregnancy. The demonstration of the safety and efficacy of statins in children and adolescents with FH[18,19] does not necessarily advocate drug treatment at a younger age. Young subjects with higher risk than average should be considered for treatment, especially if there is very premature heart disease in the parent or if multiple other risk factors are adverse.

The drugs of choice for FH are the statins as they are powerful and safe. In the majority of cases the statins do not suffice to lower LDLC to < 3 mmol/L. By inhibiting HMG-CoA reductase, the statins force the upregulation of LDLR when cellular cholesterol is depleted. More LDL is taken up by the increased expression of the (normal) LDLR in the liver[1]. Statins may also impair the production of lipoproteins in the liver[20]. A comparison of atorvastatin and rosuvastatin at 80 mg/d revealed the achievement of target by 24% and 47% respectively[21]. The average responses to the statins are known[22] and could be used to plan treatment to target LDL cholesterol concentrations. We still prefer titrations from low to high doses of statins to establish efficacy, tolerability and safety and to limit expense. If the target LDL concentration is not achieved, or if statins are not tolerated or only tolerated at a low dose, the addition of a bile acid sequestrant such as cholestyramine or cholesterol absorption inhibitors such as phytosterols or ezetimibe may have an additional impact by depleting the hepatocyte of cholesterol.

Previous strategies of combination treatment for FH, utilising a bile acid sequestrant

Table I. The differential diagnosis of monogenic hypercholesterolaemias. The FH phenotype is represented by defects in the low density lipoprotein receptor, apolipoprotein B and neural apoptosis regulated convertase 1 coded by the proprotein convertase subtilisin/kexin 9 gene. Alternatives are given in brackets.

	LDLR	**FDB**	**NARC1**	**FCH**	**Dysbetalipo-proteinaemia**
Gene	LDLR	ApoB100	PCSK9	Unknown	ApoE
Inheritance	Dominant	Dominant	Dominant	Dominant	Recessive (dominant)
Prevalence	1/500-1/75	Rare to 1/75	Very rare	1/100	1/2000
Founder Effects	Afrikaners, French-Canadians, Lebanese	Swiss-German	Unknown	Unknown	Autosomal dominant forms in Netherlands, South Africa
Dyslipid- aemia	LDL from birth	LDL from birth	LDL from birth	LDL ± VLDL worsens in adulthood	Remnants Phenotype in adults
Arcus	Common	Common	Common	Uncommon	Uncommon
Xanthoma	Tendons	Tendons	Tendons	None	Tendons and/or skin
Vascular disease	Coronary	Coronary	Coronary	Coronary	Coronary peripheral vessels
Diagnosis	PCR Numerous mutations	PCR Few mutations	PCR Few mutations	Clinical	PCR Electro- phoresis
Drug choice	Statins (plus ezetimibe or resins)	Statins (plus ezetimibe or resins)	Statins (plus ezetimibe or resins)	Statins (fibrates)	Statins and/or fibrates

and niacin, established that treatment could bring about regression at the advent of the statin era[23]. Other approaches to lowering LDL in FH include ileal bypass, plasmapheresis and portocaval shunting. Plasmapheresis was compared with statin treatment[24] but was not found to be significantly better and may not be necessary as combination treatment has become highly effective. The POSCH study[25], after long-term follow-up of ileal bypass surgery, showed a definite beneficial effect on cardiovascular outcome by achieving similar reductions in LDL cholesterol to that of the statins. Inhibitors of MTP could impair lipoprotein production powerfully but concerns about fatty liver have retarded their development. Inhibition of CETP raises HDL cholesterol. This strategy together with a statin is under investigation in FH to combat atherosclerosis. While some reverse cholesterol transport happens as a result of the transfer of cholesterol to the apoB-containing lipoproteins by CETP, it is possible that lesser transfer to these lipoproteins or other properties of HDL could confer protection against atherosclerosis and its complications.

In conclusion, familial hypercholesterolaemia is one of the commoner severe monogenic dyslipidaemias. Its diagnosis and treatment are important owing to the very high risk of coronary artery disease. An high index of suspicion and a thorough clinical evaluation with conventional measurements of plasma lipids and lipoproteins may be adequate for a clinical diagnosis. Management should encompass the whole family and should address all risk factors but drug treatment is still required to lower the plasma cholesterol concentration to ideal values. Statins are the drugs of choice but generally need to be used at high doses to achieve control. Combination treatment with statins and cholestyramine or ezetimibe or niacin may be necessary to achieve LDL cholesterol targets. Confirmatory laboratory tests for the diagnosis of FH or the other monogenic disorders are not essential for control of the hyperlipidaemia. These tests are still of interest because they enhance family screening, assist in borderline cases and may provide clues to new disorders. Research in the future will reveal more insight into the pathogenesis of atherosclerosis which will hopefully be a remediable complication of FH.

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