Familial hypercholesterolaemia

Part 2: Treatment options and screening approaches

Undetected and undertreated familial hypercholesterolaemia (FH) is a lethal medical condition. Effective treatments are available for patients with FH; most patients will require a combination of dietary modification and pharmacotherapy to achieve target LDL-cholesterol levels.

JOHN R. BURNETT
MB ChB, MD, PhD, FRCPA, FAHA

GERALD F. WATTS
DSc, MD, PhD, FRACP, FRCP

Dr Burnett is Consultant Medical Biochemist in the Lipid Disorders Clinic and Director of the Lipoprotein Research Laboratory, Department of Clinical Biochemistry, Royal Perth Hospital, and Clinical Associate Professor in the School of Medicine and Pharmacology, University of Western Australia, Perth, WA. Professor Watts is Director of the Lipid Disorders Clinic, Department of Internal Medicine, Royal Perth Hospital and Professor in the School of Medicine and Pharmacology, University of Western Australia, Perth, WA.

This is the second part of a two-part article on familial hypercholesterolaemia (FH), the most common and severe form of monogenic hypercholesterolaemia. Treatment options available for patients with this condition and approaches to screening are reviewed here. Part 1 of this article, published in last month's *Medicine Today*, discussed the aetiology and diagnosis of this condition.

Untreated, FH leads to premature coronary heart disease (CHD; Figure 1). Most people with FH are undiagnosed or diagnosed only after their first coronary event.

Treatment goals

Many patients who are diagnosed with FH do not subsequently achieve LDL-cholesterol target levels. A recent Dutch study of 745 patients with FH found that two years after screening, reduction of cholesterol levels still did not meet internationally accepted goals of treatment.[1] In addition, compliance with lipid-lowering therapies remains a problem, particularly in the younger age groups.

Although diet is the cornerstone of treatment of hypercholesterolaemia, it almost never suffices in achieving target LDL-cholesterol levels when

IN SUMMARY

- **The aim of lipid-regulating therapy is to achieve a target plasma LDL-cholesterol level of <2.6 mmol/L, as well as correction of any coexistent hypertriglyceridaemia and low HDL-cholesterol concentration.**
- **Although diet is the cornerstone of treatment of hypercholesterolaemia, it almost never suffices in achieving target LDL-cholesterol levels when used alone in patients with heterozygous FH.**
- **The three current drug treatment options for reducing LDL-cholesterol levels are bile acid binding resins, statins and ezetimibe.**
- **Other agents that could be added to statins to control dyslipidaemia, especially in patients with coexistent hypertriglyceridaemia and low HDL-cholesterol, include fibrates, nicotinic acid and fish oils.**
- **The present marked shortfall in the detection of FH highlights the need to develop a highly cost-effective screening and follow up program.**

used alone in patients with heterozygous FH. However, a fat-modified diet is an important adjunct to drug therapy. Statin therapy is effective in delaying or preventing the onset of CHD. However, effective primary prevention requires early diagnosis.

The aim of lipid regulating therapy is to achieve a target plasma LDL-cholesterol of less than 2.6 mmol/L as well as correction of any coexistent hypertriglyceridaemia and low HDL-cholesterol level. The latter is most often seen in patients who are obese or have the metabolic syndrome.

Dietary modification

The standard cholesterol lowering diet for patients with FH should be the US National Cholesterol Education Program (NCEP) Step 2 diet – that is, total fat intake less than 30% total calories, of which:

- less than 7% are saturated fatty acids
- up to 10% are polyunsaturated fatty acids
- 10 to 15% are monounsaturated fatty acids.

In this diet, dietary cholesterol should be limited to less than 200 mg/day. However, there is some debate as to the effectiveness of this in FH.

If patients are overweight, energy should be restricted to achieve a realistic desirable body weight over a given time period. Regular physical exercise should be encouraged in overweight patients with FH, acknowledging any limitations imposed by coexistent symptomatic coronary artery disease.

The precise role of employing a Mediterranean type diet high in α-linolenic acid and ω-3 fatty acids in patients with FH is unknown, although there is clinical trial evidence in secondary prevention that such a diet can influence cardiovascular outcomes in other patient groups. Dietary supplementation with plant sterols (up to 1.2 g/day) may assist with LDL-cholesterol reduction, especially if added to statin therapy.

Drug therapy

Since the principal abnormality in FH is an elevation in plasma LDL-cholesterol, drugs that target this lipoprotein are indicated. The three current options are:

- bile acid binding resins
- statins
- ezetimibe (Ezetrol).

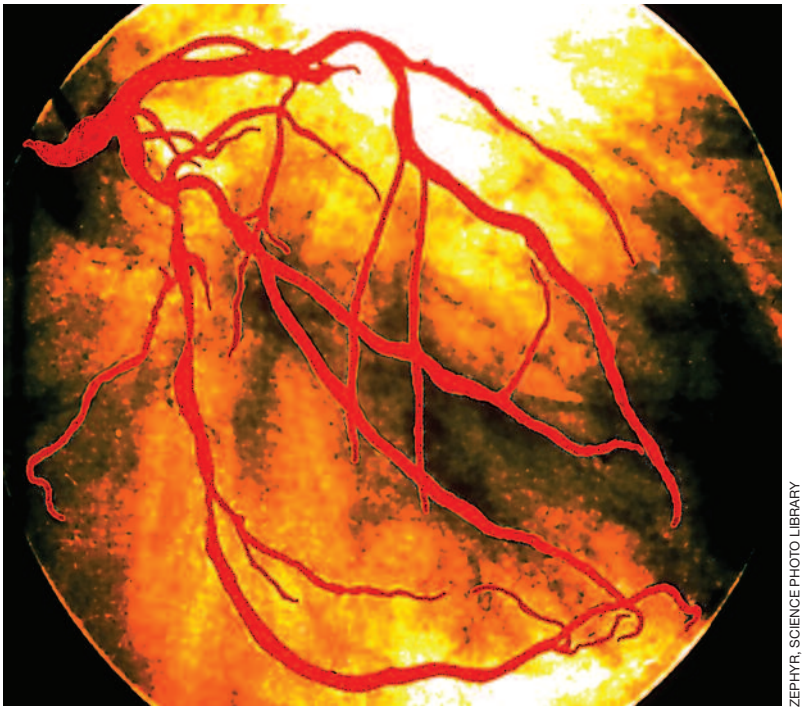

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Figure 1. Coloured angiogram showing coronary artery stenosis. Aggressive LDL-cholesterol lowering can retard progression of coronary atherosclerosis in heterozygous FH patients at high risk for cardiovascular disease.

Bile acid binding resins

Bile acid binding resins, such as cholestyramine (Questran Lite) and colestipol (Colestid Granules), reduce LDL-cholesterol by up to 15%, but their use in clinical practice is limited by gastrointestinal side effects, particularly dyspepsia, flatus and, occasionally, constipation. They can interfere with the absorption of various drugs, and there should be an interval of at least four hours between the intake of a resin and other agents, including statins and other cardiovascular drugs.

Statins

Statins are better tolerated than resins and can reduce LDL-cholesterol in certain patients by up to 60%, especially the more powerful agents such as atorvastatin (Lipitor) and simvastatin (Zocor, Lipex). Although statins are usually generally well tolerated, patients can occasionally report dyspepsia, headache and myalgia. They should be discontinued if muscle symptoms are present and/or serum creatine kinase concentration is three or more times the upper reference limit. The safety of statins before puberty is not established.

Both bile acid binding resins and statins have the net effect of increasing the number of hepatic LDL receptors, via different mechanisms, and when

used in combination they have a synergistic effect in lowering LDL-cholesterol.

Ezetimibe

Ezetimibe is the first of a new class of drugs that specifically inhibits cholesterol absorption across the brush border of the enterocyte. Taken as a single dose of 10 mg daily, it can decrease LDL-cholesterol by up to 15% and in combination with a statin incrementally achieve up to a further 25% reduction in LDL-cholesterol (see Figure 2 and Case study 1). This benefit results from the combination of reduced cholesterol supply to the liver and inhibition of cholesterol biosynthesis within the liver. The tolerability of ezetimibe in clinical trials to date has been excellent.

Other medications

Other agents that could be added to statins to control dyslipidaemia, especially in patients with coexistent hypertriglyceridaemia and low HDL-cholesterol, include fibrates, nicotinic acid and fish oils.

The combination of gemfibrozil and a statin is contraindicated because of risk of myositis. Fenofibrate (Lipidil) is not metabolised by cytochrome P450 3A4, and there are good safety data of its use in combination with other agents, such as statins.

The combination of a statin and fish oil supplements may be particularly useful in increasing the plasma concentration of HDL-cholesterol, especially in obese patients with FH.

Nicotinic acid (niacin) is popular in the USA, but our experience is that in its crystalline form, this drug is generally unacceptable to patients because of flushing and palpitations. A new slow-release form that is taken at night is available in other countries and is expected to be available soon in Australia. As with fibrates, certain caveats should be followed when using niacin with statins.

Clinical trials

Data from controlled clinical trials of the efficacy of aggressive LDL-cholesterol reduction with statin therapy in patients with FH are available only relating to surrogate cardiovascular endpoints. Such endpoints include carotid intima-medial thickness and brachial artery flow mediated dilatation in patients with heterozygous FH. Compared with simvastatin 40 mg/day, atorvastatin 80 mg/day achieved a greater LDL-cholesterol reduction and decrease in carotid intima-medial thickness over a period of two years. Similar results have been shown for high dose versus low dose statin in heterozygous FH in relation to improvement in endothelial dysfunction, as measured by post-ischaemic flow mediated dilatation of the brachial artery.

There are also angiographic data showing that LDL-cholesterol reduction with a combination of cholesterol lowering agents can retard progression of coronary artery disease in heterozygous FH.

For ethical reasons there have been no long term, placebo-controlled trials of lipid-lowering drugs on clinical endpoints in patients with FH. FH would have been an exclusion criterion for the statin trials. However, these trials collectively demonstrate that the greatest cardiovascular benefit from using statins derives from treating subjects at greatest risk, including those with higher LDL-cholesterol levels, and lowering LDL-cholesterol to below 2.6 mmol/L. A community cohort study in treated patients with FH has also shown that cardiovascular mortality decreased substantially after 1992, particularly in younger age groups, emphasising the value of treating all adults with FH with statins.

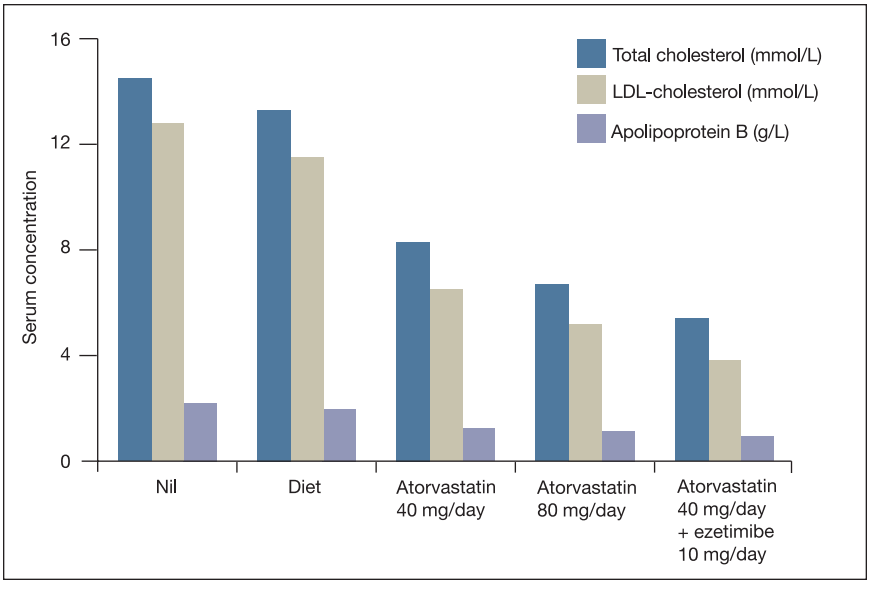

Figure 2. Example of a response to dietary and pharmacotherapeutic intervention in a patient with heterozygous FH.

Treating paediatric FH

The treatment of paediatric FH has been contentious. Some authorities have not recommended drug treatment until after the age of at least 18 years. This approach may be short-sighted, given that children with heterozygous FH are known to have endothelial dysfunction (the earliest phase of atherosclerosis) at an early age, and by 18 years coronary angiographic studies have shown clear evidence of stenotic lesions. The NCEP has recommended drug therapy for children:

- aged above 10 years whose LDL-cholesterol remains greater than

4.9 mmol/L after diet therapy
- whose LDL remains greater than 4.1 mmol/L in the presence of a positive family history of premature CVD, or when they have two or more other risk factors.

Resins are considered the first drug of choice in this age group, but their clinical efficacy is modest and long term compliance poor. Plant sterols are effective and safe, but cost, compliance, and the potential need for fat-soluble vitamin supplementation may limit this option.

There is clinical evidence that the statins can reduce LDL-cholesterol by 40% in children with FH and that this might also translate into an improvement in endothelial dysfunction, at least in the short term. Improvements in the lipid profile, including significant reduction in LDL-cholesterol, apolipoprotein B

Case study 1. Optimising LDL-cholesterol reduction with combination pharmacotherapy

Case history

A 40-year old woman presented to her GP requesting a cholesterol test. Her BMI was 24 kg/m^2 and blood pressure 110/80 mmHg. She was a cigarette smoker and was not on any medications. There was a strong history of premature CVD and death in the family. Her mother had ischaemic heart disease, severe carotid artery disease and marked hypercholesterolaemia requiring statin treatment. The patient's lipid profile was: total cholesterol, 14.5 mmol/L; HDL-cholesterol, 1.4 mmol/L; triglyceride, 1.2 mmol/L; and LDL-cholesterol, 12.8 mmol/L.

Discussion

The patient has hypercholesterolaemia due to a marked increase in LDL-cholesterol. Her glucose level, renal function, liver function and thyroid function should be measured to exclude several common secondary causes of hypercholesterolaemia.

Evidence of peripheral stigmata of lipid disorders – in particular, corneal arcus, xanthelasma, or Achilles and extensor tendon xanthomas – should be actively sought on examination.

Familial ligand-defective apoB-100 and any possible contribution of the *APOE* gene to the hypercholesterolaemia can be determined by genotyping.

A markedly increased LDL-cholesterol level, normal triglyceride level, family history of hypercholesterolaemia and premature CVD, along with the presence of tendon xanthomas would suggest the possibility of a genetic hypercholesterolaemia.

Case continued

Secondary causes of hypercholesterolaemia were excluded. By genotyping, the patient was negative for familial ligand-defective apoB-100 and was found to have normal apoE3/3.

Discussion continued

A thorough family history should be obtained and a pedigree constructed. Screening of first-degree relatives by measuring fasting lipid concentrations should be undertaken to identify other affected family members and establish the pattern of inheritance.

In the absence of CVD, this patient should initially be treated with lifestyle measures in the form of a lipid-lowering diet, increasing her physical activity and cessation of smoking. She should be investigated for latent atherosclerosis and coronary heart disease, with an exercise stress test, stress echocardiogram or myocardial perfusion scan, and also undergo carotid ultrasonography.

Even if there is no evidence of established coronary or carotid atherosclerosis, she should be treated with drugs in addition to lifestyle measures.

Case continued

A Duplex ultrasonographic study showed bilateral atherosclerotic plaque formation in the carotid arteries. An exercise stress test was negative. She was commenced on atorvastatin 40 mg/day and aspirin 100 mg/day. The statin was subsequently increased to the maximum 80 mg/day.

Discussion continued

The magnitude of this patient's hypercholesterolaemia made it likely that combination pharmacotherapy would be necessary to optimise LDL-cholesterol reduction.

Case continued

Unfortunately, the patient was unable to tolerate cholestyramine due to gastrointestinal side effects. She is currently on the combination of atorvastatin 40 mg/day and ezetimibe 10 mg/day. Her most recent lipid profile was: total cholesterol, 5.5 mmol/L; HDL-cholesterol, 1.4 mmol/L; triglyceride, 0.6 mmol/L; and LDL-cholesterol 3.8 mmol/L.

To facilitate family screening, a lipid disorders clinic nurse contacted the patient's GP. Screening of first-degree relatives confirmed an autosomal dominant pattern of inheritance, and subsequent biochemical genetic analyses confirmed that the patient, her mother, and two of her three children had FH. The children were found to have impaired flow-mediated dilatation and because of the adverse family history of premature CHD were treated with lipid-lowering therapy.

Table. Criteria for supporting FH population screening

- Familial hypercholesterolaemia represents an important health problem
- Its natural history is understood
- There is a detectable, early (preclinical) stage
- Early treatment is more effective than late treatment
- A suitable test for detecting people at an early stage exists
- The available test is acceptable
- The risks of screening, physical and psychological, are less than the benefits
- Balancing costs against benefits favours screening

(apoB) and triglyceride levels, have been shown in patients aged 10 to 17 years with FH, with no significant differences in adverse events over 26 weeks compared with placebo.

The safety and consequences for growth and development of statin use in young children is unclear. Hence, the decision to use these agents in this age group should be judiciously individualised to the family circumstances. It should also be based on good clinical judgement and a commitment to monitoring side effects and general health, while avoiding potential stigmatisation and psychological stress for children.

Treating homozygous FH

Homozygous FH is extremely rare. Even at high doses, statins and ezetimibe have only modest effects on decreasing plasma LDL-cholesterol and apoB levels in subjects with homozygous FH. The current treatment of choice for homozygous FH (and subjects with heterozygous FH whose plasma LDL-cholesterol remains

Case study 2. Hypercholesterolaemia in a patient with familial ligand-defective apoB-100

Case history

A 35-year-old man of Polish extraction presented to his GP and was found to be hypercholesterolaemic on biochemical testing. His lipid profile at this stage was: total cholesterol, 8.5 mmol/L; HDL-cholesterol, 1.2 mmol/L; triglyceride, 0.8 mmol/L; and LDL-cholesterol, 6.9 mmol/L.

Some years later, at age 44 years, the man was referred to the lipid disorders clinic. He reported no cardiovascular symptoms and was a nonsmoker. His physical activity was modest and his diet was in general healthy and balanced. A family history revealed that his father died 'suddenly' aged 55 years and that his sister has hypercholesterolaemia and is on statin treatment.

His BMI was 29 kg/m^2 and blood pressure 110/80 mmHg. He had no peripheral stigmata of lipid disorders. His lipid profile on simvastatin 40 mg/day was: total cholesterol, 5.7 mmol/L; HDL-cholesterol, 1.3 mmol/L; triglyceride, 0.7 mmol/L; and LDL-cholesterol, 4.1 mmol/L.

Discussion

An increased LDL-cholesterol, normal triglyceride, family history of hypercholesterolaemia and premature CVD despite the absence of tendon xanthomas would raise the possibility of a genetic hypercholesterolaemia.

Case continued

Secondary causes of hypercholesterolaemia were excluded. By genotyping, the patient was heterozygous for the mutation in the *APOB* gene that causes familial ligand-defective apoB-100.

Discussion continued

Although familial ligand-defective apoB-100 has a prevalence of one in 500 to 1000 in people of European descent, its prevalence is one in 250 in subjects of Polish descent. The defective apoB-100 leads to an accumulation of LDL particles, as in FH, and results in the similar clinical presentation. However, as shown in this case, patients with familial ligand-defective apoB-100 tend to have a less severe hypercholesterolaemia compared with FH and the typical peripheral stigmata of lipid disorders may be absent.

Case continued

The patient was treated with lifestyle measures in the form of a lipid-lowering weight reduction diet and advised to increase his physical activity. A Duplex ultrasonographic study showed increased carotid intima-medial thicknesses, but no evidence of atherosclerotic plaque.

On the combination of simvastatin 80 mg/day and ezetimibe 10 mg/day, the patient's most recent lipid profile was: total cholesterol, 4.3 mmol/L; HDL-cholesterol, 1.1 mmol/L; triglyceride, 0.5 mmol/L; and LDL-cholesterol 2.9 mmol/L.

Discussion continued

Screening of first-degree relatives confirmed an autosomal dominant pattern of inheritance, and subsequent genotyping confirmed that the patient, his son, his father (assumed), his sister, and one of her three children had familial ligand-defective apoB-100. His son is currently on high dose statin treatment.

elevated with drug therapy) is LDL apheresis. However, this procedure is time consuming, expensive and needs to be performed every one to two weeks.

For patients in whom LDL apheresis is not an option, portacaval shunting may be used, but while this may decrease LDL-cholesterol by up to 30%, there is measurable risk of hepatic encephalopathy. Another possibility is liver transplantation, but this requires major surgery and lifelong immunosuppression. Clearly, new therapies are required to treat these patients. Although attractive, liver-directed gene therapy, by transfer of the LDL-receptor, is not a viable option at present and will require major advances in vector technology.

Is screening justified?

In our opinion, FH satisfies the criteria for population screening (Table) and is ethically justified. Various screening strategies have been proposed to identify FH subjects, including:

- universal screening
- opportunistic screening in primary care
- screening all young people aged 16 years
- screening people admitted to hospital with premature myocardial infarction
- tracing family members of known affected patients (see Case study 2).

The latter, and so-called 'cascade screening', is the most cost-effective option for cases across the whole population. Children should not be screened at birth but after the age of 2 to 3 years, when dietary treatment could be started.

Screening for index patients with FH should centre on those with premature coronary artery disease who are attending departments of cardiology or cardiovascular medicine. Screening programs should also incorporate ethically acceptable protocols for approaching family members, and offer a genetic counselling service. The present marked shortfall in the detection of FH highlights the need to develop a highly cost-effective screening and follow up program.

MED-PED FH program

MED-PED (Make Early Diagnosis, Prevent Early Deaths) is an international program that promotes the identification and early diagnosis of patients with FH, thereby preventing premature death. Based in Utah, USA, and extending over 38 countries (including Australia, as part of MED-PED Asia-Pacific; www.medped-aust.com), its objectives are as follows:

- to prevent early deaths from heart disease by obtaining family histories of persons with inherited cholesterol disorders and tracing relatives who also may be affected
- to increase public, professional and government awareness of the importance of inherited high cholesterol in the community
- to improve the treatment of inherited high cholesterol through education, collaborative research and improved communication between the general public, health professionals and government.

Conclusion

Most people with FH are undiagnosed or diagnosed only after their first coronary event. Of those who are diagnosed, many are not achieving LDL-cholesterol targets and compliance with lipid-lowering therapies remains a problem, particularly in the younger age groups.

Cascade screening is the most cost-effective screening option for family members of index cases of FH across the whole population. Such screening programs should centre on those patients with premature coronary artery disease attending departments of cardiology or cardiovascular medicine.

Undetected and inadequately treated FH is a lethal medical condition that currently represents an unmet need in the management of lipid disorders. Health care systems require funding to establish cost-effective strategies for detecting these high-risk individuals at the earliest possible stage. MT

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