Hyperlipidaemia in paediatric practice

Peter Dale
Graham J Shortland
Dev Datta
Duncan Cole

Abstract

Assessment of hyperlipidaemia in children is important to prevent cardiovascular disease later in life. Secondary causes of hyperlipidaemia should always be considered during clinical assessment. There are several primary causes of primary hyperlipidaemia, of which familial hypercholesterolaemia (FH) is the most important. It is believed that up to 85% of the 120,000 individuals with FH are currently not identified but the process of cascade testing is likely to identify more children with this important condition in the near future. This process has begun in Wales in 2010 and is due to begin shortly in other areas of the UK.

Recent NICE guidelines for the treatment of FH have been produced. These include clear guidance for the diagnosis, management and treatment of children and young people who are diagnosed with this condition. Several classes of drugs are used to treat hyperlipidaemia in children, but the statins are most commonly used. They are effective and safe to use in older children.

Keywords child; genetic testing; hydroxymethylglutaryl-CoA reductase inhibitors; hyperlipidaemias; hyperlipoproteinaemia type II

Introduction

Cardiovascular disease remains the commonest cause of mortality and morbidity in the United Kingdom (UK). Treatment of lipid disorders in adults has had a significant impact in reducing the overall burden of cardiovascular disease, particularly in individuals who have sustained a cardiovascular event such as myocardial infarction or stroke (secondary prevention). It is increasingly recognised that assessment and treatment of hyperlipidaemia in children is important to decrease the risks of cardiovascular disease in adulthood.

Peter Dale *MBBS FRCPCH is a Consultant Paediatrician at Royal Gwent Hospital, Newport, UK. Conflict of interest statement: there are no conflicts of interest to declare.*

Graham J Shortland *BM DCH FRCPCH is a Consultant Paediatrician at the University Hospital of Wales, Cardiff, UK. Conflict of interest statement: there are no conflicts of interest to declare.*

Dev Datta *MB BCh MD MRCP FRCPath is a Consultant in Metabolic Medicine at University Hospital Llandough, Penarth, UK. Conflict of interest statement: there are no conflicts of interest to declare.*

Duncan Cole *BSc MB BCh PhD MRCP FRCPath is a Consultant and Senior Lecturer in Metabolic Medicine at the University Hospital of Wales, Cardiff, UK. Conflict of interest statement: there are no conflicts of interest to declare.*

There has been much progress in the diagnosis, screening and management of FH. Throughout the United Kingdom genetic diagnosis of FH and cascade testing is leading to an increasing number of children and young people being diagnosed with this condition. There have been concerns about starting treatment but medication, together with lifestyle changes remains safe and effective treatment for hyperlipidaemia.

Secondary causes of hyperlipidaemia are of increasing relevance in childhood due to the burgeoning obesity epidemic and its association with type 2 diabetes mellitus. In this review we provide an overview of lipid metabolism and discuss both secondary and primary causes of dyslipidaemia in childhood, with a particular focus upon FH. Current treatment options will also be appraised.

Overview of lipid metabolism

There are two main pathways of lipid metabolism: the exogenous and endogenous pathways (see Figure 1). The exogenous pathway distributes triglycerides and cholesterol absorbed from the diet to peripheral tissues for use or storage. It is characterised by the formation of the largest lipoproteins, chylomicrons that are triglyceride-rich. Once deplete of triglycerides the particle is known as the chylomicron remnant, which is cleared by the liver.

The endogenous pathway functions in the fasted state to deliver lipids to peripheral tissues. This is achieved by the formation of very low density lipoprotein (VLDL) in the liver, a triglyceride-rich lipoprotein which also contains cholesterol. Triglycerides are delivered peripherally and the particle reduces in size and increases in density; these are sequentially known as intermediate density lipoprotein (IDL) and finally low density lipoprotein (LDL). These contain proportionally more cholesterol, and LDL in particular functions to deliver cholesterol to tissues. Any that remains is cleared by the liver via the LDL-receptor (LDL-R); this is the defective step in familial hypercholesterolaemia.

High density lipoprotein (HDL) is produced by the liver and the metabolism is complex. One role of HDL is to obtain cholesterol and other lipoproteins from peripheral tissues and transport it to other cells and the liver. Low levels of high-density lipoproteins (HDL) are associated with increased cardiovascular risk.

Cholesterol concentrations also vary with age. In children they show a slight rise until age 10–11, and then dip during puberty before rising to adult levels. A steady rise then occurs throughout adulthood.

Cardiovascular risk in children

The assessment of cardiovascular risk is well established in adults. Calculation of cardiovascular risk is commonly used to target therapies for primary prevention. Several tools may be used, but the concept of 'lifetime cardiovascular risk' is now recognised. This acknowledges the important role of multiple cardiovascular risk factors in the development of atherosclerosis from a young age. Risk factors and risk behaviours that accelerate the development of atherosclerosis begin in childhood, and there is increasing evidence that risk reduction delays progression toward clinical disease, although long term data are still required.

Increased weight is associated with raised risk of an abnormal blood pressure and lipid profile, and could contribute to early

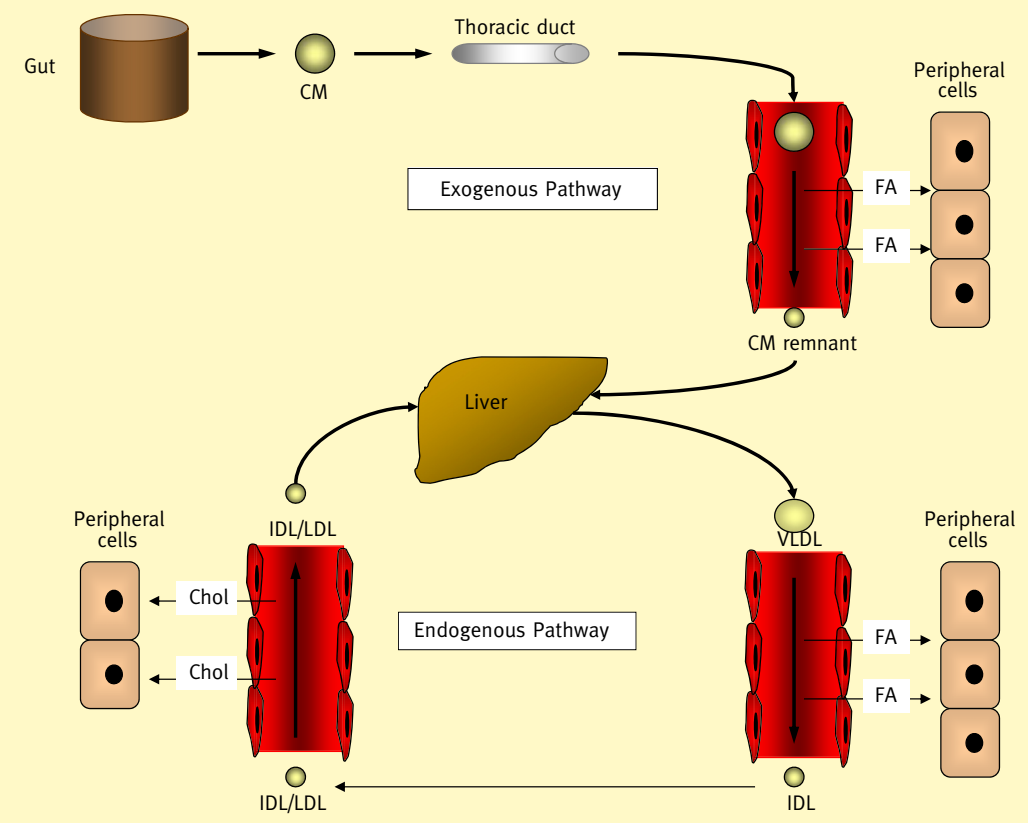

Figure 1 Exogenous and endogenous cholesterol pathways. Triglyceride (TG) -rich particles from the gut (chylomicrons, CM) and liver (very low density lipoproteins (VLDL) release fatty acids (FA) via the action of lipoprotein lipase on TGs. Cholesterol is released to peripheral tissues from LDL particles.

changes in risk parameters for cardiovascular disease in children. The American Academy of Paediatrics recommends assessment of lipid status in overweight and obese children, and in those with diabetes mellitus or hypertension as well as smokers and those with a family history of dyslipidaemia or premature cardiovascular disease.

Secondary causes of hyperlipidaemia

When interpreting a lipid profile it is important to recall that a number of conditions can be associated with dyslipidaemia. Treatment of the underlying disease will often completely correct this. Several biochemical tests should therefore be requested as part of the assessment of a lipid disorder (see Table 1).

Diabetes mellitus

Type 1 and type 2 diabetes mellitus are both associated with an increased lifetime risk of cardiovascular disease. However, well controlled type 1 diabetes mellitus is not typically associated with significant dyslipidaemia. The obesity epidemic has driven the rate of development of type 2 diabetes mellitus, with increasing numbers of cases diagnosed in childhood. Type 2 diabetes mellitus is often associated with characteristic lipid abnormalities, typically an increase in total cholesterol and triglycerides and a reduction in HDL-C. There is currently no evidence to support lipid lowering therapy for the vast majority of children with diabetes mellitus. However, given that the increased lifetime cardiovascular risk attributable to the disease, treatment should be considered particularly when there are multiple risk factors present, such as obesity, smoking and hypertension.

Thyroid disease

Untreated hypothyroidism may be associated with increased total and LDL cholesterol. Treatment of the hypothyroidism almost invariably results in resolution of hypercholesterolaemia. Use of statins in untreated hypothyroidism is associated with an increased risk of myopathy.

Laboratory investigations for the assessment of hyperlipidaemia

Investigation
Total cholesterol, LDL-C, HDL-C, triglycerides
Renal function and urine dipstick
Bilirubin, albumin, ALP, ALT or AST
Fasting plasma glucose
Thyroid function test

LDL-C = low density lipoprotein cholesterol.
HDL-C = high density lipoprotein cholesterol.
ALP = Alkaline phosphatase.
ALT = Alanine aminotransferase.
AST = Aspartate aminotransferase.

Table 1