An overview of childhood dyslipidaemia

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Abstract
Dyslipidaemia poses a significant challenge in the paediatric population, mostly due to the fact that serum lipid abnormalities in children are often missed. It has been shown that the lack of routine screening in children and adolescents may account for as many as half of this population, with either inherited or acquired cholesterol abnormalities, being missed during childhood. This article provides a high-level overview of dyslipidaemia in children and adolescents, including the screening and management of lipid abnormalities in the paediatric population.

Introduction and background
Dyslipidaemia poses a significant challenge in the paediatric population, mostly due to the fact that serum lipid abnormalities in children are often missed. It has been shown that the lack of routine screening in children and adolescents may account for as many as half of this population, with either inherited or acquired cholesterol abnormalities, being missed during childhood.

Dyslipidaemia is known to be a risk factor for atherosclerosis and coronary artery disease (CAD), contributing to a high cardiovascular death rate. The development and progression of these atherosclerotic lesions are directly related to the number of risk factors that are present in any given patient, as well as the severity of each one.

Dyslipidaemias are lipid and/or lipoprotein disorders, usually occurring without any signs or symptoms during the childhood years. Such disorders include hydrophobic fat molecules such as fatty acids and cholesterol, as well as aggregate molecules consisting of lipids and apolipoproteins that bind to lipids.

Dyslipidaemia refers to the combination of elevated levels of total and LDL-cholesterol (as well as the triglycerides), combined with decreased levels of HDL-cholesterol, and is considered to be a disorder of lipoprotein metabolism. There is an undisputed association between elevated levels of total and LDL-cholesterol, as a major modifiable risk factor, and coronary heart disease. LDL-cholesterol transports around two-thirds of all the circulating cholesterol in the human body. Elevated levels of LDL, in particular, are considered to constitute a primary risk factor for the occurrence of atherosclerosis and associated ischaemic coronary events.

Atherosclerotic cardiovascular disease has the highest mortality rate globally, with ischaemic heart disease being the leading cause of death worldwide. Atherosclerotic cardiovascular disease represents 28.2% of the global all-cause mortality. Estimates predict that, by the year 2020, cardiovascular diseases, and more notably atherosclerosis, will become the leading cause of the world’s total disease burden.

Risk factors for cardiovascular disease (CVD) were introduced in 1961 by the Framingham Heart Study, which linked the presence of specific antecedent conditions (e.g. elevated cholesterol levels, arterial hypertension, diabetes mellitus and tobacco use) to future cardiovascular disease. These risk factors may be classified as being either traditional or non-traditional. The traditional risk factors include:

- Constitutional factors, like a family history of atherosclerosis, age and gender;
- Behavioural or lifestyle factors. This group of risk factors include aspects like nutrition, physical activity and tobacco exposure;
- Physiological factors, such as blood pressure, lipids and obesity, as well as glucose metabolism (including diabetes mellitus);
- In addition, medical diagnoses, such as diabetes mellitus and chronic kidney disease, are included.

Conversely, the non-traditional risk factors—or novel biomarkers—that may be of value in predicting CVD include adipocyte dysfunction, mitochondrial dysfunction and oxidative stress, inflammation, haemostasis and thrombosis, as well as insulin resistance. The clinical utility of the non-traditional risk factors remains limited because of inconsistent associations with CVD, especially in children. The role of these biomarkers, especially in
identifying childhood risk factors, is increasingly being studied.16

The pathogenesis of CHD remains largely unknown, but it is
generally accepted to be a polygenetic disease, resulting from
several gene interactions, in addition to environmental and
psychosocial factors. Two of the risk factors, which are consistently
being recognised as contributors towards the development of
CHD, are circulating blood lipid levels and atherosclerosis.17

These abnormal amounts of circulating blood lipids and lipoproteins
may be described in one of two ways, namely1,4,5,8:

- Primary dyslipidaemia, when it includes genetic disorders
responsible for defects in the metabolic pathways; or

- Secondary dyslipidaemia, being caused by lifestyle and
environment, metabolic or endocrine disorders, concomitant
diseases or medication.

Primary disorders of cholesterol metabolism include familial
hypercholesterolaemia (FH), familial combined hyperlipidaemia
(FCHL) and the less common hypertriglyceridaemia, where
patients are likely to have a defect in their lipoprotein lipase
(LPL).1,4,5,8

Atherosclerosis as a risk factor

Atherosclerosis is an inflammatory disease that is associated with
lipid and metabolic abnormalities. This causes alterations in the
arteries, and is considered to be the major cause of cardiovascular
disease.14 Atherosclerotic plaques are initiated by the so-called
fatty streak or initial lesion. These initial lesions arise from localised
increases in the lipid content of lipoproteins and, in particular, of the
fraction that pertains to the low-density lipoprotein, or LDL. These
lipoproteins bind to constituents of the extracellular matrix in the
intima of arteries, and therefore increasing the lipid-rich particles
within the arterial wall. Lipoprotein particles in the extracellular
space of the intima may undergo oxidative modifications,
forming oxidised lipoproteins that support a pathogenic role
in atherogenesis.15 Oxidative stress plays an important role in
cholesterol metabolism. Oxidised low-density lipoprotein is toxic
to the vascular network, whereas high-density lipoprotein (HDL)
acts as an antioxidant. Oxidative stress is believed to be a major
cause of plaque rupture and resultant thrombosis, both being late
events in the progression of atherosclerosis.16

Reduced levels of HDL-cholesterol is an important risk factor for
CVD as well, because the so-called reverse cholesterol transport
that is mediated by this high-density lipoprotein, provides for
an independent pathway for lipid removal, away from atheroma
formation.13,15

Familial hypercholesterolaemia

The most common genetic dyslipidaemia syndrome in children is
familial hypercholesterolaemia (FH). FH is an autosomal dominant
trait, constituting a mutation of the LDL-receptor gene on
chromosome 19, which can often be identified by elevated levels of
umbilical cord blood cholesterol.18 FH is therefore characterised
by defects of the LDL-receptors, and some individuals produce
non-functional and kinetically impaired receptors.19

FH may either be present as homozygous familial
hypercholesterolaemia (HoFH), or as heterozygous familial
hypercholesterolaemia (HeFH). The latter has a 1-in-500
prevalence in most populations, with higher incidences described
in the Afrikaner (from South Africa) and in French Canadians. The
underlying genetic disorder seems to be attributable to a loss-of-
function mutation in the LDL-receptor alleles, with more than
1 in 600 mutations having been identified. Other causes that occur
less frequently include defects in apolipoprotein B-100 (ApoB) and
the gain-of-function mutation in proprotein convertase subtilisin/
kevin type 9 (PCSK9) serine protease.20

In the case of the HoFH form, affected children would inherit
the abnormal gene from both their parents (i.e. both alleles would be
pathogenic) and therefore suffer from the most severe form of
this disease. Refer to Figure 1. The clinical manifestations of HeFH
versus HoFH are listed and compared in Table I.

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Heterozygous (HeFH)</th>
<th>Homozygous (HoFH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendon xanthoma</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Cutaneous xanthoma</td>
<td>-</td>
<td>Present</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>Older than 25 years of age</td>
<td>Younger than 25 years of age</td>
</tr>
<tr>
<td>LDL-cholesterol levels</td>
<td>&gt; 5 mmol/l, &lt; 12 mmol/l</td>
<td>&gt; 12 mmol/l</td>
</tr>
</tbody>
</table>

Figure 1: The mode of inheritance of familial hypercholesterolaemia, showing both the heterozygous and homozygous forms of the disease
The extremely elevated LDL-C levels in HoFH contribute to atherosclerosis, which in turn affects the aortic valve and increases the risk for CAD. HeFH, which rarely presents with xanthomas, will however manifest with an increased thickening of the carotid’s inner wall and decreased brachial endothelial reactivity, often leading to cardiovascular (CV) events like stroke or myocardial infarction before the age of 50 years.1,2,4

Most hypertriglyceridaemia in children will be due to VLDL overproduction and can include disorders such as LPL deficiency, hepatic lipase deficiency and apolipoprotein C-II (ApoC-II) defects (the co-factor for LPL). Identification of hypertriglyceridaemia is common, although secondary causes of increased TG levels should also be assessed.2,4

Pathophysiology

Significant pathophysiological events centre on adipocyte dysfunction, and the transport and metabolism of lipoproteins:

Adipocyte dysfunction

Pathophysiological and metabolic consequences of excess adiposity appear as central phenomena in the pathway to CVD. Excessive levels of circulating glucose and triglycerides cause energy imbalances, which lead to adipocyte hypertrophy and hyperplasia. The subsequent result is an inflammatory process within adipose tissue.15 Excesses of circulating nutrients can then not be absorbed and the capacity of the adipocyte to store triglycerides and glucose is overwhelmed, causing adipocyte dysfunction. This dysfunction is characterised by infiltration of inflammatory cells and elevated pro-inflammatory cytokines that activate additional inflammatory pathways.16

Transport and metabolism of lipoproteins

The most important lipids in the body are phospholipids, cholesterol and the triglycerides, with the latter two also constituting the major plasma lipids. These lipids are transported in the bloodstream as lipoprotein complexes. The liver is the primary organ responsible for the metabolism of lipoproteins. The latter complexes mostly may fall into one of three categories, namely HDL, LDL and VLDL (refer to Table II). The category of intermediate-density lipoprotein (IDL) is typically grouped with LDL in the clinical practice setting (IDL is also referred to as LDLs, with the more characteristic connotation with LDL actually referring to LDL3).9,10

Secondary dyslipidaemia and risk factors

The most prevalent secondary cause for dyslipidaemia in children is obesity.1,4,8 If a child does not have any underlying genetic disorders, the lipid levels will normalise when correcting these causes.3 A low HDL concentration, moderate to severe elevation of TG and normal to mildly increased LDL is regularly seen in overweight and obese children.5,8

Risk factors critical to CVD risk include blood pressure requiring drug therapy, a body mass index (BMI) equal to, or greater than the 95th percentile, inactivity, cigarette smoking (including secondary smoking) and the presence of high risk conditions, such as diabetes mellitus and chronic kidney disease. A BMI equal to, or greater than the 97th percentile, is considered to be a high-level risk factor.1,5,7

It has been shown that risk factors in children predict CVD later in life; as the number of risk factors in children increase, the severity of asymptomatic coronary and aortic atherosclerosis also increases.1,7 However, by controlling such risk factors in childhood, adult CVD risk can be decreased and even eliminated.5,6,21

The aforementioned factors form the basis of paediatric cholesterol screening, as recognition of children at enhanced risk for atherosclerosis and treatment of the contributing risk factors, like obesity, can lead to their modification and reduce CVD morbidity.3,5

Dyslipidaemia screening in children

Optimal detection of dyslipidaemia in children includes two major approaches, namely selective screening of a defined target population, and the universal screening of the population at large. Targeted screening for high-risk children is recommended when they have a family history of premature CVD, or multiple CVD risk factors, such as the presence of hypercholesterolaemia (elevated total cholesterol (TC)), obesity and metabolic syndrome. Whenever

### Table II: Important terminology pertaining to the density of commonly-occurring lipoprotein complexes9,10

<table>
<thead>
<tr>
<th>Term/Acronym</th>
<th>Definition/Description</th>
</tr>
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<tbody>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein. LDL is sub-divided into LDL1 (or intermediate-density lipoprotein) and LDL2 (the typical LDL that constitutes the major component of low-density lipoprotein)</td>
</tr>
<tr>
<td>VLDL</td>
<td>Very-low-density lipoprotein</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein (sub-fractions of HDL also exist, namely HDL2 and HDL3)</td>
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</table>
risk factors are present, or where the family history of the child is unobtainable, fasting lipid profile screening should commence from the age of two years. The lipid profile should include the TC, HDL-C, LDL-C and TGs.1,7

The recommendation for universal screening has taken the following aspects into consideration7:

- Cholesterol levels begin to stabilise in children from the age of two years onwards. It is not routine practice to measure blood cholesterol levels on children younger than the age of two years.
- Additionally, cholesterol levels may be expected to decrease by 10–20% during adolescence.

Therefore, the proposition is for global screening to take place prior to the onset of adolescence, but after the age of two years. The proposed range is between the ages of two and ten years. A normal cholesterol level in a high-risk child during puberty should be re-assessed towards the end of puberty (i.e. at the age of 16 years for girls, and around 18 years for boys). The ideal age for the routine universal screening of children for the presence of dyslipidaemia is probably around 10 years of age (with a range from 9–11 years), to be repeated between the ages of 17–21 years. Universal screening may be conducted in the non-fasting state.1,7

In conclusion, the presence of specific CV risk factors determines the frequency and type of lipid screening.1

Managing dyslipidaemia in children

The management of dyslipidaemia in children, as for adults, usually requires a two-pronged approach, namely a combination of lifestyle changes (including dietary modifications) and pharmacotherapy (if and when indicated).

Lifestyle modifications

In terms of lifestyle changes, the mainstay of non-drug treatment involves appropriate dietary modifications and a proper level of physical activity (exercise).5,7
- Limit the so-called sedentary or screen time (i.e. the time that children and teenagers spend in front of the television, computer, smart phone, gaming device, or any other form of electronic apparatus), to less than two hours per day.5,7
- An increased level of physical activity (especially a suitable exercise regimen), for one hour per day, is associated with decreases in arterial blood pressure and insulin resistance, an increase in HDL-C levels, as well as decreased body fat and BMI, and lowered levels of TC, TG and LDL-C.7

In addition, children that are at risk should be maintaining optimal blood pressure levels, as well as an ideal body weight (which may be defined as a BMI equal to, or below the 85th percentile for age and gender).5

Dietary modifications may be considered from the age of two years and older. The main emphasis falls on a reduction in the dietary intake of cholesterol and total fat, as well as saturated and trans-fats. There should be a limitation on the intake of simple sugars, and complex carbohydrates should be favoured as a source of energy. The intake of omega-3 fatty acids should also be encouraged. However, the daily caloric intake should still be adequate for normal growth and development to take place. A dietetic or paediatric nutritional consultation is highly recommended.5,7

Lifestyle modifications should be applied for at least six to twelve months, and those children who fail to respond adequately, should subsequently be considered candidates for the initiation of drug therapy, once they are older than ten years of age.5,7

Pharmacotherapy

The main classes of lipid-lowering agents that could be used in children and adolescents are:

- The bile acid sequestrants (or bile acid-binding resins): Cholestyramine, for example, is not absorbed from the intestinal tract, where it facilitates the excretion of bile acids by effectively preventing their reabsorption. This lowers the LDL-cholesterol levels in patients with primary hypercholesterolaemia.7,22
- Niacin (nicotinic acid): This vitamin (B3) reduces the levels of free fatty acids in the bloodstream through the inhibition of lipolysis. This leads to a reduction in VLDL levels in particular, a rise in HDL-cholesterol levels due to a decrease in its catabolic rate, and a less-pronounced decrease in LDL-cholesterol levels.7,21
- The statins: The drugs in this group, which includes examples such as simvastatin, lovastatin and pravastatin, block the synthesis of cholesterol through their inhibition of the enzyme HMG-CoA-reductase (the rate-limiting enzyme in the biosynthesis of cholesterol). They effectively decrease the total serum cholesterol levels, the LDL levels and the VLDL levels, and also increase HDL-cholesterol levels to some extent. Other examples are atorvastatin, fluvastatin and rosuvastatin. Some of the more commonly reported adverse effects associated with statins include gastrointestinal disturbances, raised plasma transaminase levels and myalgia (muscle pain), albeit to a limited extent. These agents do not affect normal growth or pubertal maturation. Statins should be taken at bedtime, to optimise their effects on cholesterol synthesis, which mostly takes place at night.22

The statins are generally regarded as safe and well-tolerated in the paediatric population; however, a more conservative approach to their use in children is probably warranted. It is recommended that treatment be commenced at the lowest possible dosage, with judicious monitoring of muscle and liver enzymes.5

- The fibrates (or fibric acid derivatives): These drugs decrease LDL levels to a lesser or variable degree, and also triglyceride levels (by decreasing the VLDL levels) in the bloodstream. They may also increase HDL-cholesterol levels to some extent. Their main indication, however, is to manage hypertriglyceridaemia. Examples are gemfibrozil, fenofibrate and bezafibrate.2,22
• **Ezetimibe:** This drug inhibits the absorption of cholesterol from the intestinal tract. Ezetimibe may be used on its own, or in combination with a statin to reduce LDL- and total serum cholesterol levels.²,²²

**Conclusion**

The detection and management of dyslipidemia in children is a challenging issue in clinical practice. Without proper screening, half of the paediatric population with lipid abnormalities may be missed. Screening is being recommended on a universal level for all pre-pubescent children, and to be repeated in late adolescence. In addition, children with known risk factors, a positive family history, or no family history at all, should undergo targeted screening as well. Wherever risk factors do exist, and elevated levels of TC, TGs and LDL-C (as well as deficient levels of HDL-C) have been detected, suitable lifestyle modifications need to be employed. From the age of ten years, lipid-lowering treatment may also be instituted. It is of vital importance that dyslipidaemia in children be recognised early on and managed appropriately.

**References**


