

Treatment of Dyslipidaemia in Children

Subjects: Pediatrics

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Definition

Childhood dyslipidaemia is one of the main traditional cardiovascular risk factors that initiate and exacerbate the atherosclerotic process. Current guidelines recommend healthy behaviours as the first-line treatment for childhood dyslipidaemia. The therapeutic lifestyle changes should focus on dietary modifications, daily physical activity, reduction in body weight and tobacco smoking cessation. Parents play a key role in promoting their children's healthy habits. In children with more severe forms of lipid abnormalities and in those who do not benefit from healthy behaviours, pharmacological therapy should be considered. Safe and effective medications are already available for children and adolescents. Statins represent the first-line pharmacological option, while ezetimibe and bile acid sequestrants are usually used as second-line drugs. Despite their limited use in children, other lipid-lowering agents (already approved for adults) are currently available or under study for certain categories of paediatric patients (e.g., familial hypercholesterolemia).

1. Pathophysiology

Dyslipidaemia is a clinical condition that is characterised by disorders of lipid metabolism. Although lipids are essential for maintaining health, abnormal lipid and lipoprotein concentrations in the blood may be dangerous. Depending on the underlying cause, childhood dyslipidaemia may be classified into primary and secondary dyslipidaemia ^[1]. Primary dyslipidaemia is usually caused by inherited disorders in lipid metabolism: single or multiple gene mutations (e.g., gene mutations in low-density lipoprotein receptors) may alter both lipid production and removal. Among the forms of primary dyslipidaemia, familial combined hyperlipidaemia and familial hypercholesterolemia are the most common genetic causes of dyslipidaemia. It is important to note that genetic causes are often responsible for the most severe lipid abnormalities ^[2]. In contrast, secondary dyslipidaemia typically occurs as the result of specific conditions, diseases or drugs that may interfere with lipid concentrations over time. The causes of secondary dyslipidaemia include obesity, diabetes, renal and chronic inflammatory diseases and corticosteroids. Secondary causes of dyslipidaemia should always be evaluated and treated; in fact, the correct management of the causative disease may often result in lipid abnormalities resolution ^[3].

2. Paediatric Guidelines

Clinical practice guidelines are designed to provide a synthesis of evidence and to translate the evidence into graded recommendations; these recommendations may be helpful in improving clinical decision making ^[4]. Paediatric guidelines for dyslipidaemia have undergone several modifications in recent years. The first paediatric guidelines for dyslipidaemia were published in 1992 by the National Cholesterol Education Program (NCEP) following guidelines for adults that were developed by the same NCEP ^[5]. Although many of the recommendations were mainly based on expert opinion rather than on systematic evidence review, these guidelines were adopted by several paediatric scientific societies. Undoubtedly, these initial guidelines engendered some controversy; however, they were important for increasing the awareness of childhood dyslipidaemia and for stimulating the research on this important topic. Moreover, the cut-off points for acceptable, borderline and high plasma lipid concentrations based on percentiles from the Lipid Research Clinical Prevalence Study were the first to be presented ^[6]. As new data and new evidence became available, organisations such as the American Heart Association (AHA) and the American Academy of Pediatrics (AAP) updated the original guidelines. In 1998, the AAP Committee on Nutrition produced a statement on cholesterol in childhood ^[7], which was followed by an additional clinical report in 2008 ^[8]. Furthermore, the AHA first published a consensus statement on dietary recommendations for children and then a scientific statement on drug therapy for high-risk lipid

abnormalities in children and adolescents [9][10]. The most up-to-date guidelines for the management of childhood dyslipidaemia were published in 2011 by the National Heart Lung and Blood Institute (NHLBI) after performing a systematic review and grading the best available evidence [1]. The 2011 Guidelines constitute a part of an integrated approach with a focus on all cardiovascular risk factors in children and adolescents; they represent a cornerstone for cardio-metabolic risk reduction and cardiovascular health in youth. As regards lipid abnormalities, the NHLBI Guidelines outlined the currently used reference values for plasma lipid, lipoprotein and apolipoprotein concentrations in children and adolescents (**Table 1**); moreover, they give recommendations concerning both lipid assessments in youth and the management of paediatric lipid disorders.

Table 1. Lipid and lipoprotein reference values and corresponding centile in children and adolescents.

	ACCEPTABLE		BORDERLINE		HIGH		
	mg/dL	Percentile	mg/dL	Percentile	mg/dL	Percentile	
Children and Adolescents	TC	<170	<75th	170-199	75-95th	>200	>95th
	LDL-C	<110	<75th	110-129	75-95th	>130	>95th
	TG						
	0-9 years	<75	<75th	75-99	75-95th	>100	>95th
	10-19 years	<90	<75th	90-129	75-95th	>130	>95th
	HDL-C	>45	>10th	40-45		<40	<10th
	Non-HDL-C	<120	<75th	120-144	75-95th	>145	>95th

Adapted from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.

In accordance with previous guidelines, the non-pharmacological approach (including dietary and lifestyle modifications) remained an integral part of the treatment for dyslipidaemia in children and adolescents; on the other hand, the recommendations for pharmacotherapy substantially changed in comparison with previous guidelines [11]. Due to the increasing data on efficacy and safety, along with the Food and Drug Administration (FDA) approval for the use of several lipids lowering drugs in children, the therapeutic options for children with dyslipidaemia have expanded and, nowadays, statins are the preferred drugs in paediatrics [1][12].

3. Management of Dyslipidaemia in Children

3.1. Non-Pharmacological Approaches

Although several pharmacological treatments are available or under development, current guidelines recommend healthy behaviours as the first-line treatment for childhood dyslipidaemia. It is important that healthy behaviours should be recommended for all children and adolescents; however, they should be strongly encouraged in those children with borderline or high plasma lipid and lipoprotein concentrations.

For children with an altered lipid profile, the initial management should consist of therapeutic lifestyle changes that focus on dietary modifications, daily physical activity, improving body weight and tobacco smoking cessation [13]. Moreover, in order to prevent obesity in children, they should be encouraged to sleep for a decent amount of hours per day and to limit screen time (including television, cell phone, computer use, videogames, handheld electronics) to less than 2 h per day. In 2016, The AAP consensus groups recommended adequate daily hours of sleep (including naps) for children and adolescents, depending on their age [14]. As regards sedentary activities, in a recent study, it was observed that every additional hour of watching television was correlated with increased triglycerides (TG) and decreased

high-density lipoprotein (HDL-C) levels [15]. Several possible reasons were proposed: among them, the lower energy expenditure and the increased intake of energy-dense foods (e.g., soft drinks, fast food) while watching television.

Although dietary treatment remains under debate, a modified diet can improve abnormal lipid profiles by inducing a lipid-lowering effect, mainly on triglycerides (TG) levels, but it also has a modest impact on total cholesterol (TC) and low-density lipoprotein (LDL-C). In adults, the PREDIMED study (the largest dietary prevention trial) demonstrated that the Mediterranean diet is beneficial in reducing the incidence of major cardiovascular events. Similarly, adherence to the Mediterranean diet in children may improve the carotid intima-media thickness test (CIMT), which is an early marker of atherosclerosis [16][17]. In view of these observations, it is likely that dietary modifications are relevant for the prevention of atherosclerotic cardiovascular disease in both children and adults. The specific dietary changes should emphasise decreasing total, trans and saturated fats; decreasing cholesterol amounts; and increasing the intake of fibre. The NCEP suggests two approaches for proposing a modified diet: the population approach is a group of recommendations for all youths in order to prevent an abnormal lipid profile and the atherosclerotic process. In contrast, the individual approach consists of suggestions for children with confirmed dyslipidaemia and an increased risk for cardiovascular disease. It is important to note that this latter approach uses a two-step nutritional change (CHILD-1 and CHILD-2) and that CHILD-1 recommendations coincide with those of the population approach [18]. The recommended population diet, as well as the diet Cardiovascular Health Integrated Lifestyle Diet-1 (CHILD-1), should limit the total fat consumption to 20–30% of total calories, saturated fat intake to less than 10% of total calories and average cholesterol ingestion to less than 300 mg/day. Children should also avoid trans-fatty acids (<1%), preferring polyunsaturated fatty acids and monounsaturated fatty acids, which should be up to 10% and between 10 and 15% of total daily calories, respectively. It is also recommended to increase the intake of dietary fibre through whole grains, vegetables and fruit (five or more a day). For children at an increased cardiovascular risk and for children with confirmed dyslipidaemia who have failed to achieve the lipid goals after 3 months of the CHILD-1 diet, more intensive restrictions are needed. The Cardiovascular Health Integrated Lifestyle Diet-2 (CHILD-2) requires limiting saturated fat intake to less than 7% and cholesterol average ingestion to less than 200 mg/day [1][19]. The other step 1 recommendations should not be interrupted through the step 2 diet.

It is noteworthy that the NCEP recommends dietary modifications in children from 2 years of age: the first two years of life are critical for the development and the growth of children and it is important to provide them with an adequate amount of calories and nutrients [20]. This also applies to children older than 2 years old and both CHILD-1 and CHILD-2 should ensure adequate daily caloric intake for normal growth and development: as a consequence, these diets should consist of 50–60% of total daily calories from carbohydrates and 10–20% from proteins [19]. It is never suggested to limit protein consumption, while in children with elevated TG, it is recommended to decrease simple sugar consumption (including fruit juices and sugar drinks) and replace them with complex carbohydrates [20].

For children with hypertriglyceridemia, an increase in omega-3 fatty acid dietary intake should also be encouraged by increasing the consumption of fish. Long-chain omega-3 fatty acids are also available in the form of unregulated fish oil products and prescription drugs; although it is not clear the exact mechanisms by which they reduce TG concentrations and limited data exist in children and adolescents, prescription products seem to lower TG levels and have been safely used in children [12][21][22]. However, they lack the approval for use in children and should be used in consultation with a lipid specialist. For patients with increased LDL-C values, the CHILD-2 diet also recommends dietary adjuncts, such as plant stanol and sterol esters and water-soluble fibre psyllium. Plant sterol and stanol, when taken up to 2 g per day, were shown to inhibit intestinal cholesterol absorption, leading to a reduction in LDL-C levels by approximately 9% [23].

Although the effectiveness of dietary changes is variable, it is important to remember that the above-mentioned dietary modifications are safe and well tolerated over time. Several studies, such as the

Special Turku Coronary Risk Factor Intervention Project (STRIP) and the Dietary Intervention Study in Children (DISC) showed that reducing fat intake (total fat, saturated fat and cholesterol) was not significantly associated with changes in somatic growth, pubertal development, mean body mass index, nutritional sufficiency and psychological/social features [24][25]. Moreover, a recent study concluded that beneficial nutritional interventions can be safely introduced in youth and sustained over 20 years [26].

Consultation with a registered nutritionist may help with promoting long-term adherence to a diet; a study of 1062 children (540 children in the intervention group and 522 controls) showed that repeated dietary counselling was helpful in reducing both saturated fat consumption and LDL-C concentrations [27]. In addition, a paediatric dietitian plays a key role in setting goals, tracking progress, making dietary adjustments and educating parents about nutritional plans inside and outside of the home [13]. It is important to set realistic short-term dietary goals and to consider social, parental and cultural factors in order to ensure the effective implementation of nutritional changes [28]. It is also important that dietary modifications should never be portrayed as punitive, but rather in terms of the child's education, and that adequate non-food-based rewards should be given when accomplishing the goals. Improving the quantity and the quality of nutrition is equally important: children with obesity often consume exaggerated portions and large quantities of non-nutritive but calorie-dense food. Common sources of non-nutritive foods include ultra-processed products, soft and energy drinks, snacks and fast food [19]. The elimination of these foods and limitation of portion sizes should be strongly encouraged to improve the nutritional status. Furthermore, it is crucial that children and adolescents avoid skipping meals (in particular breakfast); in accordance with a retrospective, observational study, children who consumed fewer than two meals per day had higher levels of TC and LDL-C compared with those eating three times or more per day [29].

In addition to nutritional changes, physical activity and weight reduction are the cornerstones of preventing and treating lipid abnormalities in children. Physical activity is associated with a variety of health benefits, both in healthy children and in youths with chronic disease [30]. The benefits of physical activity were widely documented and include improved musculoskeletal, mental, behavioural and cardiovascular health. In particular, being physically active has a positive effect on cardiorespiratory fitness, serum glucose concentrations and insulin sensitivity, blood pressure, bone density and lipid profile [31]. As a consequence, regular physical activity should always be encouraged in children with dyslipidaemia; it may be useful in lowering TC, TG and LDL-C levels, increasing HDL-C and, more importantly, it may assist with body fat and body mass index (BMI) reduction. Therefore, it is critical that all children and adolescents should engage in at least 1 h of moderate-to-vigorous physical activity every day [1]. Interestingly, a study of 1235 adolescents showed a dose-response relationship between an increased number of minutes of physical activity and improved lipid concentrations (HDL-C and TG values) [32]. It is important that physical activity is age appropriate, various (including unstructured and structured activities) and enjoyable to the child. Further recommendations are available in the 2018 Physical Activity Guidelines; these guidelines, released by the US Department of Health and Human Services, provide important guidance on the amounts and types of physical activity for multiple paediatric populations groups [33].

Weight management is another important recommendation for children with an altered lipid profile and represents the primary treatment goal for obese or overweight children with dyslipidaemia. The excess adiposity adversely affects not only the lipid profiles but the entire cardio-metabolic health of young people [34]; it is, therefore, necessary to maintain a healthy BMI. A 5 to 10% reduction in body weight through dietary modifications and increased physical activity is beneficial for reducing cardiovascular risk and improving lipid abnormalities. Via different mechanisms (improved insulin sensitivity, enhanced activity of lipoprotein lipase, reduced free fatty acids release from adipose tissues), weight loss is expected to increase the TG catabolism and removal by approximately 20% [35][36]. Only when obesity-related comorbidities (such as dyslipidaemia) are not sufficiently reduced with adequate weight reduction, they should be treated independently [2].

3.2. Family-Based Approach

Parents play a key role in promoting healthier eating habits and adequate activity levels in their children and several authors consider parents one of the main focuses of childhood dyslipidaemia prevention and treatment [37]. This is a critical point, although it is often overlooked. Therapeutic lifestyle changes should be adopted by the entire family: if the whole family does not change their habits, dyslipidaemia is unlikely to improve [20]. First, parents are responsible for the portions served to the child and for food and beverages that enter the home. It is important to note that the food available in the home is often the food that children learn to consume and that children's consumption of fruit and vegetables is predicted by their availability [38]. Second, parents play a role in creating a healthy home environment (e.g., a smoke-free environment) and promoting healthy habits (e.g., a healthy sleep routine); important factors that may affect children's lipid profile are the sources of food (prepackaged or homemade meals), TV watching during the meal and the frequency of family meals [39]; the promotion of regular family meals is protective for obesity and its related consequences, such as dyslipidaemia [40]. Third, considering that children often mimic their close family members, parents serve as models for healthy behaviours and are very important for children's education in terms of the amount of physical activity and eating habits [41]. In view of this, and considering that the introduction of healthy behaviours at a young age may be carried throughout adult life, families must promote a healthy lifestyle.

3.3. Pharmacological Treatment

Although secondary dyslipidaemia (e.g., obesity-related dyslipidaemia) is usually successfully treated with the management of the underlying disorder and therapeutic lifestyle changes, the adoption of healthy habits and long-term adherence to lifestyle modifications may be challenging. Moreover, children with primary dyslipidaemia (e.g., FH) do not equally benefit from healthy behaviours: in children with FH, a low-fat diet was shown to have only modest effects, leading to an LDL-C reduction by approximately 10% [42][43]. In such cases, as well as in children with more severe forms of lipid abnormalities, the use of pharmacological therapy should be considered. This could be possible thanks to the approval in children of safe and efficient pharmacological options. According to the NHLBI Guidelines, decisions regarding the need for drug treatment should take account of the baseline lipid levels, the child's age, the presence of moderate-to-high cardiovascular risk factors or condition and the familial history of premature cardiovascular disease [1]. In particular, the NHLBI Guidelines state that children with LDL-C > 250 mg/dL or TG > 500 mg/dL should consult a lipid specialist in order to promptly start the pharmacological treatment. In children with less severe lipid abnormalities, medication therapy should be recommended after at least 6 months of therapeutic lifestyle changes if LDL-C > 130–190 mg/dL; the LDL-C threshold at which statin therapy should be initiated may depend on the number of cardiovascular risk factors or condition and the familial history of premature cardiovascular disease. Basically, the goal of pharmacological therapy in children is to obtain acceptable values of LDL-C (<130 mg/dL); however, children with high-risk cardiovascular conditions (e.g., FH), may require stricter LDL-C targets (<100 mg/dL) [1][2]. It is important that healthy behaviours should be implemented even though medications are initiated: therapeutic lifestyle changes may be useful as a synergic mechanism to improve the lipid profile and for the lowering dosages of lipid-lowering drugs [44].

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Keywords

children;dyslipidaemia;management;non-pharmacological approach;pharmacotherapy