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# Hypercholesterolemia in Childhood

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Lorenzo Iughetti, Barbara Predieri and Patrizia Bruzzi

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## 1. Introduction

Hypercholesterolemia is a well-known risk factor for atherosclerosis in adulthood.

In the first years of life atherosclerosis is generally subclinical, but pathological studies demonstrate that, already in childhood, atherosclerotic vascular changes and their extent are associated with both the number of cardiovascular risk factors and their intensity [1, 2]. Fatty streaks and fibrous plaques at autopsy, presence of coronary artery calcium by electron-beam computed tomography, increased carotid-intima-media thickness, reduced arterial distensibility and compliance and endothelial dysfunction by ultrasound have been already associated with lipid abnormalities in youth [3]. Moreover, levels of cholesterol track strongly from childhood and adolescence over long follow-up period resulting in the progression of atherosclerosis process and increased cardiovascular disease (CVD) risk [4].

The mechanism by which hyperlipidemia contributes to atherogenesis includes several stages:

- Chronic hyperlipidemia, and especially hypercholesterolemia, might alter endothelial function, through the increased production of superoxide and other oxygen free radicals, which deactivate the nitric oxide, the main relaxing factor of the endothelium
- During chronic hyperlipidemia, lipoproteins are accumulated in intima increasing endothelial permeability
- Oxidative modification of lipids, induced by free radicals, leads to the formation of oxidized low-density-lipoproteins (oxLDL), which, in their turn, are easily phagocyted by macrophages and, consequently, form foam cells. OxLDL are chemotactic for circulating monocytes, they inhibit the mobility of macrophages already in the lesion, thus, promoting their recruitment and their persistence in the plaques. They also stimulate the release of growth factors and cytokines that, in their turn, induce the production of antibodies against oxidized lipoproteins and cause a chronic inflammation [5, 6]. Such state of chronic or not-resolving inflammation facilitates lipid accumulation in the atheroma [7].

In some conditions, characterized by altered lipid assessment or other evident disorders of risk factors, premature CVD could be manifest in the first decades of life. “Vascular age” is advanced in 73% of familial dyslipidemic children, independently from the presence of others atherosclerosis-promoting risk factors [8]. The American Heart Association (AHA), endorsed by the American Academy of Pediatrics (AAP), identified 8 high-risk pediatric diagnosis and developed practical recommendations for the management of cardiovascular risk [9]. The selected diseases comprise familial hypercholesterolemia (FH), together with diabetes mellitus (type 1 and 2), chronic kidney disease, heart transplantation, Kawasaki disease, congenital heart disease, chronic inflammatory disease and childhood cancer. Subclinical endothelial dysfunction, measured through non-invasive surrogate methods such as flow-mediated dilation (FMD), occurs early in FH children indicating an increased risk for premature CVD and reflecting the need for early initiation of anticholesterolemic treatment [10]. Moreover, increasing evidences indicate that, in high-risk conditions as well as in most children with a minor degree of vascular involvement, appropriate therapy could prevent and/or reverse the progression of these cardiovascular changes [11, 12]. Therefore, the identification and the management of hypercholesterolemia in children are of great consequence.

## 2. Lipid concentrations in childhood and adolescence

The thresholds for defining hypercholesterolemia and elevated low density lipoprotein cholesterol (LDL-C) in childhood and adolescence are not homogeneous. One set of values were derived from the National Cholesterol Education Program (NCEP) report (Table 1) [13]. An update, published in 2011, included values of apolipoprotein B (ApoB) and apolipoprotein A-1 (ApoA-1) coming from the National Health and Nutrition Examination Survey III. NCEP cutoffs seem to accurately estimate adult values of total cholesterol (TC), LDL-C and triglycerides (TG), while high lipoprotein cholesterol (HDL-C) levels are better predicted by National Health and Nutrition Examination Survey (NHANES) cutoff points [14].

Another set of values were derived from the Lipid Research Clinics Prevalence Study [15] and revised in 2008 by the AAP [16] (Table 2).

The lack of a consensus depends on: lipid variability during infancy, childhood and adolescence, the subsequent need of using percentiles instead of cut-off values (as used in adulthood) and the lack of studies that correlate lipid values in childhood with adult cardiovascular risk.

After birth, lipids and lipoproteins gradually increase up to 2 years of life, reaching values similar to adults: therefore, before the third year of life, the determination of the lipid profile is neither recommended nor useful. An increased stability with no significant differences between genders can be observed from 5 to 10 years: until pubertal activation, the use of reference values proposed by the AAP is recommended [16]. Taking into account the changes between genders occurring during puberty, the percentiles of reference proposed by Jolliffe and Janssen for males and females from 12 to 19 years could also be used: these percentiles are based on studies that correlate the values of lipid profile with the probability of subsequent clinical cardiovascular risk [17].

Category	Acceptable < 75° p	Borderline 75-90° p	High > 90°p
TC, mg/dl	< 170	170-199	≥ 200
LDL-C, mg/dl	< 110	110-129	≥ 130
ApoB, mg/dl	< 90	90-109	≥ 110
TG, mg/dl			
2-9 y	< 75	75-99	≥ 100
10-19 y	< 90	90-129	≥ 130
HDL-C, mg/dl	> 45* (≥25°p)	35-45 (5-25°p)	≤ 35 (≤ 5°p)
ApoA-1, mg/dl	>120	110-120	<110

\*desiderable: > 65 mg/dl, 75° p

**Table 1.** Plasma lipid concentration in children and adolescence modified from NCEP, 1992 [13, 14]. Legend: p, percentile

	Male			Female		
	5-9 ys	10-14 ys	15-19 ys	5-9 ys	10-14 ys	15-19 ys
TC, mg/dl						
50°p	153	161	152	164	159	157
75° p	168	173	168	177	171	176
90°p	183	191	183	189	191	198
95°p	186	201	191	197	205	208
TG, mg/dl						
50°p	48	58	68	57	68	64
75° p	58	74	88	74	85	85
90°p	70	94	125	103	104	112
95°p	85	111	143	120	120	126
LDL-C, mg/dl						
50°p	90	94	93	98	94	93
75° p	103	109	109	115	110	110
90°p	117	123	123	125	126	129
95°p	129	133	130	140	136	137
HDL-C, mg/dl						
5°p	38	37	30	36	37	35
10° p	43	40	34	38	40	38
25°p	49	46	39	48	45	43
50°p	55	55	46	52	52	51

**Table 2.** Lipid and Lipoprotein Distributions in Subjects Aged 5 to 19 Years [16]. Legend: p, percentile

Lipid concentrations vary also according to demographic variables (population specific): TC seems to be higher among Black children and adolescents than Caucasian ones [18]. Moreover, dietary habits together with current diseases and seasonality could transitionally influence cholesterol assessment.

Data from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2006 for participants 6 to 17 years of age documented that 5.2%-6.6% (depending on the cut points used) and 9.6%-10.7% of them presented an elevated concentration of LDL-C and TC, respectively [19].

3. Genetic Hypercholesterolemia

Lipid abnormalities can be classified as primary disorders that encompass all genetic (mono-genic) forms of dyslipidemia, as summarized in Table 3 [20], and secondary disorders.

Name	Genetic Defect	Trasmission	Clinical features
Classical Familial Hypercholesterolemia (FH)	LDLR, diminished LDL-C clearance	Autosomal dominant 1:300-1:1.000.000	Heterozygotes: TC 250-500 mg/dl (LDL-C > 135 mg/dl), xanthomas on the extensor tendons of the hands and feet, arcus cornea and premature CVD (40-60 y)
Other autosomal dominant hypercholesterolemia	PCSK9, diminished LDL-C clearance		Homozygotes: TC 500-1000 mg/dl, xanthomas and very premature CVD (< 10 y)
Autosomal recessive hypercholesterolemia (ARH)	ARH adaptor protein absent or unable to interact with the LDLR, diminished LDL-C clearance	Autosomal recessive 1:100.000 (Sardinia)	Variable, phenotype similar to homozygous FH, but generally less severe and more responsive to lipid-lowering therapy, large and bulky xanthomas from early childhood, TC > 500 mg/dl, in homozygotes: CVD < 30 y
Familial defective Apo B-100	Apo B, diminished LDL-C clearance	Autosomal dominant 1:700 (North-Centre Europe)	Heterozygotes: TC 250-500 mg/dl, xanthomas, arcus senilis and premature CVD (50-60 y) Homozygotes: TC > 500 mg/dl, premature CVD (< 30 y)
Familial combined hyperlipidemia	Polygenic		Premature CVD, Apo B elevated, TC 250-500 mg/dl, TG 250-750 mg/dl
Beta sitosterolemia	Carrier ABCG5/ABCG8	Autosomal recessive 1:1.000.000	High vegetables sterols and LDL-C

**Table 3.** Genetic Hypercholesterolemia [20]. Legend: LDLR, low density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9

## 4. Monogenic primary Hypercholesterolemia

Monogenic hypercholesterolemias are lifelong conditions that often present during childhood and adolescence with clinically and biochemically extreme phenotypes, due to a variety of gain-of-function or loss-of-function mutations in a range of candidate genes with important roles in lipid metabolism.

FH is an autosomal dominant monogenic condition. Homozygous familial hypercholesterolemia (HoFH) is rare, with an occurrence of 1:1.000.000 individuals, but the heterozygous state (HeFH) is present in the general population with an incidence ranging from 1:300 to 1:500. On this basis we can affirm that HeFH is the most common monogenic disorder in North America and Europe. Causative FH mutation alters the function of LDL-receptor (LDLR) resulting in a reduced clearance of LDL-C particles from the circulation and consequently in an elevation of their plasma levels. In addition to LDLR defects, a similar phenotype can be caused by a number of mutations in the ApoB gene (that disrupt the binding of the LDL-C particle to the LDLR) and by gain of function mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene (that increase LDLR degradation) [21]. So far, more than 1500 variants have been identified in the LDLR associated with FH, ranging from single-nucleotide substitutions to large deletions [22]. The clinical presentation of HeFH is characterized by two- to three-fold elevations in plasma LDL-C levels, by a family history positive for CVD, and, rarely in childhood, by the presence of physical symptoms of cholesterol deposits in tissues (tendon xanthomas, xanthelasma palpebrarum). Historically, left untreated, the cumulative risk of CVD in HeFH patient is greater than 50% in men by the age of 50 years and at least 30% in women by the age of 60 years. Homozygous and compound heterozygous FH subjects can experience serious cardiovascular events as early as in childhood: a six- to eight-fold increase in plasma LDL-C is found in these subjects and severe xanthomatosis and multiple types of xanthomas could occur.

Most people with FH are undiagnosed or only diagnosed after their first coronary event, but medical treatment seems to be effective and it could delay or prevent the onset of CVD. Therefore, early identification of affected individuals is crucial. Cholesterol levels alone are not sufficient to confirm a diagnosis of FH because of the extensive overlap in LDL-C levels existing between FH-causing mutation carriers and non-carriers (non-genetic polygenic hypercholesterolemia) and the high prevalence of modestly severe LDLR mutations that hampers the use of LDL-C cut-offs. Therefore, a diagnostic definition of FH, which supports cholesterol measurements with clinical signs and family history, has become widely used (Simon Broome Register Group definition of FH) [23]. According to this definition, a “definite” diagnosis of FH requires:

- a. TC level above 260 mg/dl in children under 16 years of age  
OR LDL-C levels above 160 mg/dl in children
- b. PLUS tendon xanthomas in patient or relative (parent, child, sibling, grandparent, aunt, uncle)
- c. OR DNA-based evidence of an LDLR mutation or familial defective Apo B.



A “possible” diagnosis of FH is suggested when (a) is present together with one of (d) or (e):

- d. family history of myocardial infarction before the age of 50 years in grandparent, aunt, uncle or before age 60 in parent or siblings
- e. family history of raised cholesterol in parents or siblings or levels above 290 mg/dl in grandparents, aunt or uncle.

A similar diagnostic tool has been developed by the Dutch Lipid Clinic Network. This includes similar features to the Simon Broome criteria, but adds the calculation of a numeric score [24]. These criteria differ in DNA testing and in their diagnostic effectiveness. In summary, a child with significant and isolated elevation of LDL-C ( $\geq 160$  mg/dl) should be considered to have FH, particularly if there is family history of early CVD.

After diagnosis of FH, cascade screening should occur in all first degree relatives after age 2 years. Cascade screening is a term used to describe searching for affected relatives of an inherited disorder once an affected person is known. In UK guidelines, DNA-based cascade testing is recommended in affected families; however, in about 60% of patients no mutations are found [25]. This finding leads to a great concern: assigning individuals to an “uncertain” category (when mutation is not identified) is unsatisfactory and provokes confusion and ambiguity both in children and adults.

After diagnosis, an appropriate treatment should be pursued, especially after CVD risk assessment, by a lipid specialist.

## 5. Polygenic forms of Hypercholesterolemia

Dyslipidemia may also result from interaction of synergic environmental and genetic factors developing the group of multifactorial or polygenic hypercholesterolemia. Because of this combination of causative factors, biochemical phenotype could be variable: LDL-C and TG may be high (rarely normal), HDL-C can be normal or reduced and there is significant production of small, dense LDL-C particles. Contrary to FH, it is less likely to be diagnosed in children because LDL-C elevation may occur frequently in adolescence, but strongly tracks into adulthood (70-75% of cases).

## 6. Secondary Hypercholesterolemia

The prevalence of lipid abnormalities in children is increasing because of the epidemic of obesity and subsequent metabolic syndrome (MS). Data from 1999-2004 NHANES demonstrated that approximately 10% of participants aged 8-19 years had high TC, 7% had low HDL-C, 9.7% had high TG and 7.6% had high LDL-C. In addition, prevalence of adverse lipid profile in youths with high adiposity was found significantly greater than participants without it [26]. Low HDL-C, high TG and small dense LDL-C, characterizing the so called “dyslipidemia of

insulin resistance”, are often associated with obesity and MS [27]. Promoting free-fatty acids release from visceral fat and altering the hepatic production of apolipoprotein, insulin resistance (IR) is the ethiological key of dyslipidemia in MS. Recently, the positive association demonstrated between PCSK9 activity and fasting glucose, insulin and homeostatic model assessment IR (in addition to lipid levels) suggests that PCSK9 could play a role in the development of dyslipidemia associated with the MS [28]. Moreover, the endocrine activity of adipose tissue produces inflammatory cytokines, such as adiponectin and tumor necrosis factor- $\alpha$ , influencing hepatic production of very low density lipoprotein (VLDL). All these findings highlight the importance to early counteract obesity to prevent the occurrence of dyslipidemia: the earlier the prevention begins, the better results are achieved.

Secondary dyslipidemia include also those caused by chronic disease, such as diabetes mellitus, chronic renal insufficiency, hypothyroidism, liver diseases and drugs (e.g. glucocorticoids, B-blockers, antiretroviral agents) (Table 4).

	Clinical features
Obesity	Increase TG, decreased HDL-C
Diabetes Mellitus	Increase TG and TC, decrease HDL-C
Chronic renal failure	Increase TG and TC, decrease HDL-C
HIV/AIDS wasting	Increase TG and TC, decrease HDL-C and LDL-C
HIV/AIDS (HAART)	Increase TG, TC and HDL-C
Hypothyroidism	Increase TG, TC and LDL-C
Nephrotic syndrome	Increase TC and LDL-C
Obstructive liver disease	Increase TC
Medications	Variable

Table 4. Secondary dyslipidemia.

## 7. Diagnosing Hypercholesterolemia in childhood

In 2011, the National Heart, Lung, and Blood Institute (NHLBI), backed by AAP, proposed an universal lipid screening to be performed with measurement of non fasting non-HDL-C (calculated by subtracting the HDL-C from the TC measurement) in all children between ages 9–11 and 17–21 years [14]. The normal variation in blood cholesterol levels within an individual over time is approximately 6%. Therefore, at least two elevated blood cholesterol measurements are required in a lapse of time between 15 days and 3 months, before a diagnosis of hypercholesterolemia can be made. In the remaining groups of age (2-8 and 12-16 years), NHLBI agrees with the use of selective screening, as proposed by the NCEP [13, 14]: lipid screening is recommended only in children with positive family history of premature CVD OR already known familial dyslipidemia OR unknown family history OR presence of multiple



risk factors such as hypertension, diabetes and obesity OR overweight/obesity alone. Cholesterol screening modalities in youth have been debated for decades. The primary goal of universal screening is to identify those with FH. It has been shown that family history is incomplete in young individuals, since parents and even grandparents may be too young to have demonstrated early CVD [29]. The second goal of universal screening is to use cholesterol assessment to identify children with components of MS in an effort to highlight and prevent progression of additional components. Nevertheless, there are several critiques that comprise: the definition of risk-to-benefit ratio, especially regarding moderate dyslipidemia, the potential risk to determine anxiety in patients and families and, lastly, the financial costs [30].

## 8. Treatment of Hypercholesterolemia in childhood

In 2010 the AHA, while developing the 2020 Impact Goals, defined the “cardiovascular health” concept and determined the metrics needed to monitor it over time [31]. In this way the first step proposed for management of children with identified lipid abnormalities is to assess their cardiovascular risk. It includes the collection of:

- anamnestic data about familial premature cardiovascular disease (premature means before 55 years of age in males and before 65 in females)
- individual anamnestic risk factors as smoking habit, drugs and the presence of current high or moderate risk conditions such as hypercholesterolemia, diabetes, Kawasaki disease, cancer treatment survivors...
- physical examination that include blood pressure and body mass index.

In children, the definition of ideal cardiovascular health includes several goals: avoid smoking, body mass index less than 85<sup>th</sup> percentile, more than 60 minutes of moderate- or vigorous-intensity physical activity every day, health diet, TC values less than 170 mg/dl (6-19 years of age), blood pressure less than 90<sup>th</sup> percentile (8-19 years of age) and fasting plasma glucose less than 100 mg/dl (12-19 years of age) [31].

### 8.1. Dietary treatment and lifestyle approach

The cornerstone of lipid-lowering therapy is a healthy lifestyle [32].

Dietary recommendations emphasize the following pattern of nutrient intake:

- adequate nutrition should be achieved by eating a wide variety of foods low in saturated fat and cholesterol
- total caloric intake should be sufficient to support normal growth and development and maintain desirable body weight
- saturated fatty acids should provide <10% of total calories
- total fat should provide an average of no more than 30% and no less than 20% of total calories

- polyunsaturated fatty acids should provide up to 10% of total calories
- less than 300 mg of cholesterol should be consumed per day
- children should consume 5 or more daily serving of vegetables and fruits and 6 to 11 daily servings of whole-grain or other grain foods
- children should eat adequate amounts of dietary fiber (Age + 5 g/day).

All children with LDL-C level >130 mg/dl should receive targeted intervention and follow-up. The NCEP suggests for hypercholesterolemic patients a two level cholesterol-lowering diet [13]. In the Step 1 diet (Table 5) approximately 30% of calories derive from fat (10% from saturated fat) and the total intake of cholesterol should be limited to 300 mg/day. If the lipid values remain elevated after 6 weeks, the Step 1 diet should be reviewed to increase the compliance. If the diet for at least 3 months fails to achieve LDL-C concentrations <130 mg/dl (the ideal goal is to lower it to <110 mg/dl), a more aggressive dietary approach is needed (Step 2 diet). The two main differences between the Step 1 and Step 2 diets are that in the latter, the amount of saturated fat is reduced to 7% of total calories and the intake of cholesterol is decreased to 200 mg/day (Table 5). In order to implement this more stringent diet, advice from a nutritionist trained in dealing with children and disorders of lipids is needed. No restriction of fat or cholesterol is recommended for infants <2 years of age, when rapid growth and development require high energy intakes. Dietetic guidelines called Therapeutic Lifestyle Changes (TLC) replaced Step 1 and 2 diets. For higher risk people they recommended an adequate caloric intake, including an increased consume of whole grains, low-fat dairy products, fruits, vegetables and fish and a reduction of soft drinks and salt (Table 5) [33].

	STEP 1	STEP 2	TLC diet
Total fats (% of total calories)	30	30	25-35+
Saturated fats (% of total calories)	No more than 10	Less than 7	Less than 7
Dietary Cholesterol (mg/day)	Limited to 300	Less than 200	Less than 200
Plants stanols/sterols (grams per day)	NA	NA	2
Increased viscous soluble fiber (grams per day)	NA	NA	10-25

Legend: +The 25-35% fat recommendation allows for increased intake of unsaturated fat in place of carbohydrates in people with metabolic syndrome or diabetes.

Table 5. Characteristics and Differences between STEP 1, STEP 2 and TLC diets [33].

The improvement of dietary habits seems to be effective when hyperlipidemia is secondary to other conditions, such as obesity [34], but it is not sufficient in primary hypercholesterolemia. Nevertheless, also in the latter dietary restrictions have to be requested, in order to reduce the

dose of medications and to avoid a further deterioration of the condition. No long-term (up to 10 years) adverse effects on growth and pubertal development have been documented [34-37].

In children with FH and polygenic hypercholesterolemia, additional benefit could derive from the introduction of soya protein [38] and/or plant stanols and sterol esters (2 g/day) in the diet [39]. Nevertheless, despite an improvement in TC and LDL-C levels, supplementation with stanols and sterols does not improve endothelial function, probably because they concomitantly reduce plasma carotenoids [39]. Recently, a significant reduction of small dense LDL-C has been demonstrated in 25 hypercholesterolemic children after the introduction in their diet of a yogurt-drink enriched with 2 gr/day plant sterols [40]. A large amount of sterol could also derive directly from fruits, vegetables and cereals (see table 6). Therefore, plant stanols and sterols have to be considered as beneficial, safe, tasteful, easy-accessible and low-cost lipid-lowering strategy, especially until children at risk become eligible for a more aggressive therapy.

Food	Sterol Content (mg/100 gr edible)
<b>Fruit and vegetables</b>	
Broccoli	44
Green peas	25
Orange	24
Apple	13
Cucumber	6
Tomato	5
<b>Cereals</b>	
Wheat bran	200
Swedish knackebrot	89
Wholemeal bread	53
Rolled oats	39
Wheat Bread	29
<b>Fats and Oils</b>	
Corn Oil	912
Rapeseed (canola) oil	668
Liquid margarine	522
Sunflower oil	213
Spreadable butter	153
Olive oil	154

**Table 6.** Sterol content in food.

The efficacy of a cholesterol-lowering diet, started in childhood, upon reduction of CVD later in life, has not been firmly established yet [41].

Soluble fibers, including those from psyllium husk, have been shown to increase the cholesterol-lowering effects of a low-fat diet. In 2011 guidelines, the water soluble fiber psyllium can be added to a low fat low-saturated fat diet as cereal enriched with psyllium at a dose of 6 g/d for children 2-12 of age and 12 g/day for those  $\geq 12$  y of age [14]. Accordingly, it has been shown that glucomannan, a hydrosoluble fiber, may decrease TC and LDL-C levels, without changing HDL-C levels, in hypercholesterolemic children [42]. A novel pioneering approach in reducing the serum cholesterolemia could be represented by the exploitation of probiotics exerting cholesterol-lowering properties. A recent Italian randomized, double-blind, placebo-control study evaluates the effects of a probiotic formulation containing three *Bifidobacterium* strains on lipid profiles in 39 children affected by primary dyslipidemia: compared to placebo, probiotics reduced TC by 3.9% and LDL-C by 3.8%. Moreover, this supporting therapy seems well tolerated [43].

Lifestyle change includes: regular physical activity, screen time less than 2 hours per day, attainment of ideal body weight (body mass index  $\leq 85^{\text{th}}$  centile for age and gender) and optimization of blood pressure. In adults the combination of intensive dietary restrictions and physical exercise improves lipid metabolism, IR and cardiorespiratory fitness, thereby diminishing cardiovascular risk factors [44]. Reported trials on benefits of physical activity on lipid-profile are scarce, rarely well-performed and their results are not optimistic. However, physical activity stimulates lipoprotein lipases and the function of some enzymes like the lecithin-cholesterol acyltransferase (LCAT), improving HDL-C formation and reducing their catabolism. Moreover, exercise reduced TG levels and is effective on size and density of LDL-C particles. Finally, exercise is safe and does not require any additional cost. Therefore, children should be encouraged to undertake 60 minutes or more of vigorous aerobic activity per day. The TLC diet itself recommends expending at least 200 kcal per day [33]. The abuse of tobacco and alcohol should be avoided. An early identification and correction of eating disorders should be recommended.

## 8.2. Pharmacological treatment

If cholesterol does not reach acceptable levels through diet, the recourse to a pharmacological treatment is allowed and advised [45]. The NCEP recommends the administration of medications only to children  $> 10$  years of age (better if either at pubertal Tanner stage II or higher or after onset of menses in girls) and only when an aggressive diet lasting at least 6-12 months fails [13]. A lipid specialist should be consulted. Traditionally, bile acid sequestrants (BAR) were considered the first-line therapy in hypercholesterolemic children. Since AHA statement, statins replaced BAR: their use is now recommended in children younger than 10 years of age (from 8 years of age). Surprisingly, AAP encouraged the application of this revised therapeutic approach [16] causing many controversies among experts: up to now, the efficacy of statins on adult-onset of CVD is not clearly defined and data about their long-term safety, particularly because they interfere with the production of steroid hormones and liver function, are still lacking. Nevertheless, in 2002-2005, the use of lipid-lowering drugs increased in children by

15% [46] and the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved pravastatin in children > 8 years, while simvastatin, lovastatin and atorvastatin were registered by the FDA for children > 10 years of age. Ezetimibe was also approved by the FDA and EMA for pediatric use from the age of 10 years.

### 8.3. 3-Hydroxy-3-MethylGlutaryl-CoA (HMG-CoA) reductase inhibitors

Statins inhibit HMG-CoA reductase, an enzyme fundamental in *de novo* cholesterol synthesis. Their action consequently provokes an increase in hepatic production of LDLR determining an additional decrease in LDL-C levels. Statins are commonly safe and well tolerated. However, because of the principal role of cholesterol in cellular structure and function, the use of statins is not allowed in prepubertal children. In HeFH children and adolescents, statins are effective in reducing levels of LDL-C by 20-40% and increasing HDL-C, but, because of the scarcity and the non-uniformity of trials shown by meta-analysis, no data about outcomes of different types, doses and length of therapy could be deduced [47,48]. In terms of safety, no differences in occurrence of adverse effects, alterations in sexual development and muscle or liver toxicity have been demonstrated in children treated with statins in comparison to placebo-treated ones [49]. Nevertheless, while adult guidelines do not recommend routine screening of liver and muscle enzymes during treatment, pediatric guidelines indicate to start statin at the lowest dose with baseline measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine kinase (CK). These levels plus a fasting lipid profile should be repeated four and eight weeks after initiation of therapy and then every 3–6 months. If liver enzymes are above 3 times the upper limit of normal and/or CK is above 10 times the upper limit of normal and/or patient complains any adverse effects, medication should be stopped to determine if there is an improvement. Some researchers have suggested hydrophilic statins, such as fluvastatin, rosuvastatin and pravastatin are less potentially toxic than lipophilic statins, such as atorvastatin, lovastatin, and simvastatin; the risk of myopathy was suggested to be lowest with pravastatin and fluvastatin, probably because they are more hydrophilic [50].

Up to now, few studies have examined vascular efficacy of statins in children, confirming an increase of impaired FMD before and a significant improvement after treatment [11, 51], long-term effects have been less studied [52]. Recently, secretory phospholipase A<sub>2</sub>-IIA (sPLA<sub>2</sub>-IIA) receives increased interest because of its role in the inflammatory process of atherosclerosis: it induce LDL-C modification, foam cell formation and activation of various immune mechanisms. Published data demonstrated no effects of 2-years-long pravastatin therapy in reducing sPLA<sub>2</sub>-IIA mass or sPLA<sub>2</sub> activity levels in 91 FH children compared to placebo [53].

Statins are contraindicated during pregnancy because of potential teratogenic risk. Because of this concern, statins should be used to treat adolescent FH females only if they are aware of the risk, under a close follow-up and on contraceptive therapy when indicated.

Target LDL-C is typically below 130 mg/dl, but ideally under 100 mg/dl in high risk populations such as FH. If target levels are not achieved within 3 months, the dose of statin can be gradually increased to maximum dose. Occasionally, a second agent such as a BAR may be useful. Multiple drug therapy should be guided by a lipid specialist.



#### 8.4. BAR

Even if FDA never approved BARs in children, they were used in the past as first-line therapy in hypercholesterolemia. Colestipol, cholestyramine and colestilan bind bile salts in the intestine preventing their re-absorption and increasing their excretion and discharge from cholesterol pool. Increased emission of bile acids causes a large conversion of cholesterol into bile salts; in liver, cholesterol pool decreases and a compensatory rise in LDLR synthesis takes place. In children with HeFH, BARs determine a decrease in TC of 10-20%. These drugs are not absorbed systematically, but local side-effects as abdominal pain and nausea could nullify compliance. Recently, a novel bile acid sequestrant, the colesevelam hydrochloride, with enhanced binding capacity for bile acids has been evaluated in HeFH children, alone or in combination with statin therapy: the therapeutical compliance has increased (about 85%) together with an effective LDL-C reduction [54].

#### 8.5. Niacin and fibrates

Niacin, a water-soluble B complex vitamin, increases HDL-C levels and significantly reduces hepatic production and release of VLDL but it is not commonly utilized in children because of lack of information about its safety. Adverse effects consist of flushing, hepatic insufficiency, myopathy, glucose intolerance and hyperuricemia. Therefore, niacin is limited both in HoFH children and in ones with stroke and increased lipoprotein A levels.

Fibrates (gemfibrazil, fenofibrate, bezafibrate and ciprofibrate) are mainly effective in lowering TG and in increasing HDL-C, while LDL-C levels seem only partially and variably influenced. They have a complex and poorly understood way of action and, due to the lack of data on safety, their use is restricted in HeFH children with high TG levels and an increased risk for pancreatitis.

#### 8.6. Ezetimibe

Ezetimibe is a new selective cholesterol absorption inhibitor acting at the brush border of the small intestine with no effects on the absorption of TG and fat-soluble vitamins. Target pathways may consist in the Niemann-Pick C1-like protein and the annexin-caveolin 1 complex. In 2002, FDA approved ezetimibe in FH children older than 10 years of age, but long-term effects have not been extensively evaluated yet. In HoFH, ezetimibe has a synergic effect in reducing LDL-C, if associated with statins, without increasing adverse effects. Satisfying data in term of efficacy and tolerance have also been documented in children with polygenic hypercholesterolemia, HeFH and familial combined hyperlipidemia treated with ezetimibe [55].

These positive data are partially dampened by an absolute lack of knowledge about the long-term effects of ezetimibe. In fact, the combination of statin and ezetimibe may not restore endothelial dysfunction [56]. Moreover, ezetimibe dose not influence HDL-C, an independent risk factor for CVD. Future data from the ongoing IMPROVED-IT study, enlisting 18.000 adults affected by acute coronary syndrome on simvastatin either with or without ezetimibe, may



clarify the role of ezetimibe in CVD prevention [57]. In addition, systemic effects of ezetimibe, in contrast to its minimal absorption have still to be clearly defined.

In the last years, new lipid-lowering drugs are coming out. Starting from the demonstration that PCSK9 loss-of-function mutations result in a significant drop in circulating LDL-C, subsequent studies demonstrated that PCSK9 binds the epidermal growth factor precursor homology domain-A on the surface LDLR and directs LDLR and PCSK9 for lysosomal degradation. A monoclonal antibody that binds circulating PCSK9 and blocks its interactions with surface LDLR and called Alirocumab has recently demonstrated a great potentiality in reducing LDL-C in adulthood. Nevertheless, there is no data in adolescence and no evidence on its capacity in improving CVD outcome yet [58].

## 9. HoFH: Treatment in childhood

HoFH has to be considered an almost exclusive pediatric disease. Because of the earlier risk of CVD, HoFH patients should started pharmacological therapy as soon as possible, as recommended by AHA [45]. LDL-C apheresis and/or liver transplant have been the historical treatment in this subset, although efficacy and success are variable [59]. LDL-C apheresis is an extracorporeal plasma-perfusion method that involves selective removal of LDL-C particles. The procedure takes three or more hours and is performed at 1- to 2-week intervals. Even if it results in the regression of coronary lesions and has been found to increase life expectancy, its use is limited by its availability, higher cost and difficulties in procedures [60]. As most of the LDLR are present in the liver, liver transplantation alone or in combination with pharmacotherapy is effective in normalizing the plasma cholesterol levels. Nevertheless, the associated risks include the need of a life-long immunosuppressive therapy [61]. HoFH may also benefit from lipid-lowering drugs. However, statins require some residual LDLR function, thus they are not effective in receptor-negative HoFH. Higher risk patients will benefit from combination therapy: ezetimibe, but also niacin, fibrates, and BAR. Therapeutic efficacy, safety, medication adherence, and compliance should be monitored closely. Novel medical therapies for adults with HoFH have recently been approved in the US. These include inhibitors of PCSK9, microsomal triglyceride transfer protein and cholesteryl ester transfer protein (CETP), as well as mipomersen, an apolipoprotein B synthesis inhibitor [62, 63].

## 10. Conclusions

The role of pediatrician in the prevention of chronic and disabling diseases in adulthood is reinforced by the extensive scientific evidence that proves the beginning of causative processes, such as atherosclerosis, in childhood. Therefore, the identification of patients at risk of premature CVD has become, today, one of the primary aims of pediatricians. The evaluation of hypercholesterolemic children should not be based exclusively on lipid assessment: it is essential to quantify the overall cardiovascular risk through the collection of a full medical history (including familial history), the performance of an accurate physical examination, the assessment of eating habits and the identification of concomitant risk factors. Moreover, in

hypercholesterolemic children, the monitoring over time of cardiovascular function through non-invasive methods can be useful.

Childhood could be considered as the best period of life to acquire a proper lifestyle and healthy eating habits, especially in patients at risk of premature CVD. The diet, low in saturated fat and cholesterol, should be the first therapeutic approach to be proposed in children with hypercholesterolemia. Early pharmacological treatment could be planned in cases of genetic hypercholesterolemia or when diet alone persistently fails. Several studies have demonstrated the short-term efficacy and safety of statins in childhood.

The definition of pediatric population-specific percentiles for lipid values, the achievement of a shared screening strategy and the demonstration of long-term safety and efficacy of statin therapy have to be considered the current priorities for improving the approach to childhood hypercholesterolemia.

## Nomenclature

AHA; American Heart Association

AIDS; Acquired Immune Deficiency Syndrome

ALT; Alanine aminotransferase

Apo; Apolipoprotein

AAP; American Academy of Pediatrics

AST; Aspartate aminotransferase

BAR; Bile acid sequestrants

CK; Creatine phosphokinase

CVD; Cardiovascular disease

EMA; European Medicines Agency

FDA; Food and Drugs Administration

FH; Familial Hypercholesterolemia

FMD; Flow-mediated dilation

HAART; Highly active antiretroviral therapy

HDL; High-density lipoprotein

HDL-C; High-density lipoprotein cholesterol

HeFH; Heterozygous familial hypercholesterolemia

HIV; Human immunodeficiency virus

HMG-CoA; 3-Hydroxy-3-MethylGlutaryl-CoA

HoFH; Homozygous familial hypercholesterolemia

IR; insulin resistance

LCAT; Lecithin-cholesterol acyltransferase

LDL; Low-density lipoprotein

LDL-C; Low-density lipoprotein cholesterol

LDLR; Low-density lipoprotein receptor

MS; Metabolic syndrome

NCEP; National Cholesterol Education Program

NHANES; National Health and Nutrition Examination Survey

NHLBI; National Heart, Lung, and Blood Institute

oxLDL; oxidized low-density lipoprotein

PCSK9; Proprotein convertase subtilisin/kexin type 9

sPLA<sub>2</sub>-AII; Secretory phospholipase A<sub>2</sub>-IIA

TC; Total cholesterol

TG; Triglycerides

TLC; Therapeutic lifestyle change

VLDL; Very low density lipoprotein

## Author details

Lorenzo Iughetti\*, Barbara Predieri and Patrizia Bruzzi

\*Address all correspondence to: [iughetti.lorenzo@unimore.it](mailto:iughetti.lorenzo@unimore.it)

Department of Medical and Surgical Sciences of Mothers, Children and Adults, University of Modena & Reggio Emilia, Pediatric Unit, Modena, Italy

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