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REVIEW ARTICLE

Dyslipidemia in childhood: A literature review

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Abstract

Objective: To describe the state of the art in the assessment and management of pediatric patients with dyslipidemia. **Methods:** The review was carried out using the PubMed database, taking into account articles published between 2005 and 2021. The publications were selected based on the keywords: "dyslipidemia AND (treatment OR screening OR diagnosis) NOT adult" and those articles that strayed from the topic were excluded. **Results:** Dyslipidemia is a growing concern in pediatrics, characterized by changes in lipid metabolism, leading to an increased cardiovascular risk. It can be classified as primary or secondary according to its etiology. Among the primary etiologies, familial hypercholesterolemia (FH) is highlighted due to its severity, leading to early cardiovascular outcomes. Universal screening for dyslipidemia should be performed in children aged 9-11 years and 17-21 years, and selective screening in children aged 2-8 years and 12-16 years. In addition to lifestyle changes, such as diet and physical exercise, the first-line drug treatment is based on the prescription of statins, with a more aggressive treatment being required in cases of FH, which needs the association of ezetimibe and an earlier prescription of LDL-apheresis. The most critical cases should be referred to a specialist. Periodic follow-up should be performed with lipid profile and laboratory and imaging tests to rule out possible side effects of medications. **Conclusions:** The approach to dyslipidemias is still a very controversial topic. Longer cohort studies are needed to assess the long-term effect of drug therapies on cardiovascular risk in adulthood.

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INTRODUCTION

Dyslipidemia, a condition characterized by alterations in lipid metabolism that lead to increased cardiovascular risk, is a growing concern in pediatrics. These alterations can manifest in the form of increased total cholesterol (TC), LDL-cholesterol (LDL-c), and triglycerides (TG) levels or decreases in HDL-cholesterol (HDL-c) [1, 2].

According to the National Survey on Health and Nutrition Examination carried out in 2011 and 2012, one in every five children have abnormal levels of TC, HDL-c, or non-HDL-c. The causes of dyslipidemia have changed over the years. Previously, dyslipidemia of a genetic origin was more prevalent in children. In recent decades, however, dyslipidemia of secondary etiologies has increased in prevalence, especially the number of cases associated with obesity [3]. In Brazil, 32.8% of the children aged 12-19 years have elevated levels of TC, with females preferentially affected [2].

Many countries have seen increases in the prevalence of hypercholesterolemia, mainly due to changes in eating habits and increased time spent in sedentary occupational and recreational activities [4]. It is extremely important to prevent, identify, and, if needed, treat pediatric dyslipidemia to prevent the development of atherosclerosis and cardiovascular disease (CVD) in adults [5]. This study describes the state of the art in the evaluation and management of pediatric dyslipidemia.

METHODS

Search Strategy

We searched PubMed for articles published between 2005 and 2021. The publications were selected using the following keywords: "dyslipidemia AND (treatment OR screening OR diagnosis) NOT adult". A total of 41,083 references were found.

The articles were filtered by publication period, language (Spanish, English, or Portuguese), and patient age (0 to 18 years). A total of 1,839 articles were found. The steps for article selection are shown in Figure 1.

Inclusion and exclusion criteria

Original articles, meta-analyses, book chapters and documents, clinical trials, multicenter studies, reviews, guidelines, observational studies, systematic reviews, and classic articles on the subject were considered. Articles such as editorials, animal trials, and clinical cases were not included.

Selection Strategy

Articles unrelated to the subject of the study were excluded. We read the abstracts of the remaining articles, and the ones discussing a substantially different subject were excluded. The remaining articles were read in full and the ones deemed relevant for the subject of interest were selected.

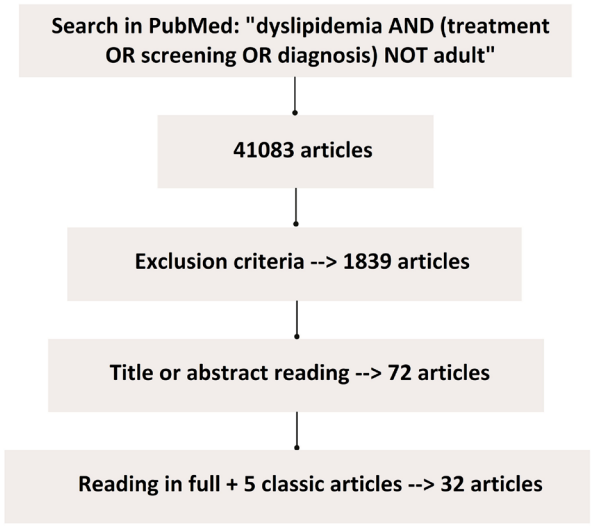


Figure 1. Search strategy flowchart.

ETIOLOGY

Dyslipidemia can have primary or secondary causes, as shown in table 1. Primary causes include genetic conditions such as familial hypercholesterolemia (FH), as the main example, along with dysbetalipoproteinemia; familial combined hyperlipidemia; familial hyperchylomicronemia syndrome; familial hypertriglyceridemia; familial hypoalphalipoproteinemia; familial hypobetalipoproteinemia; abetalipoproteinemia; chylomicron retention disease; mutations inactivating proprotein convertase subtilisin/kexin type 9 (PCSK9); lecithin-cholesterol acyltransferase (LCAT) deficiency; Tangier disease. And the main secondary causes: obesity, diabetes mellitus, nephrotic syndrome, metabolic syndrome, and polycystic ovary syndrome (PCOS). Dyslipidemia associated with obesity, as mentioned above, has increased in recent decades [3, 6, 7].

RISK FACTORS

The following risk factors have been associated with dyslipidemia: smoking; sedentary lifestyle; a diet high in fats and sugars; hypertension; diabetes mellitus; obesity; chronic kidney disease; HIV infection; chronic inflammatory disease; kidney transplantation; nephrotic syndrome; Kawasaki disease with or without aneurysm; family history of early cardiovascular disease (CVD); and first-degree relatives with dyslipidemia and obesity [4, 6, 8, 9].

Cultural factors and family lifestyle may affect the diet offered to children, with some showing a preference for easy-to-cook, prepared meals, and foods that are more readily available. Family habits such as eating at the table, watching television during meals, and eating at home or in restaurants can also affect children's lipid levels [8].

Table 1. Causes of Dyslipidemia.

Primary Causes	
Homozygous and heterozygous familial hypercholesterolemia	Familial hypobetalipoproteinemia
Dysbetalipoproteinemia	Abetalipoproteinemia
Familial combined hyperlipidemia	Chylomicron retention disease
Familial hyperchylomicronemia syndrome	Mutations inactivating PCSK9
Familial hypertriglyceridemia	LCAT deficiency
Familial hypoalphalipoproteinemia	Tangier disease
Secondary Causes	
Smoking, drinking, and a diet high in carbohydrates and saturated fat	
Diabetes mellitus, decompensated hypothyroidism, hypopituitarism, hypercortisolism, GH deficiency, metabolic syndrome, obesity, PCOS	
Nephrotic syndrome, chronic kidney disease, hemolytic uremic syndrome	
Cholestasis, biliary atresia, Alagille syndrome, biliary cholangitis, sclerosing cholangitis	
Kawasaki disease, heart transplantation	
Glycogenosis, Gaucher, Niemann-Pick disease, and Tay-Sachs disease	
SLE, rheumatoid arthritis	
Anorexia nervosa, acute intermittent porphyria, Klinefelter syndrome, Werner syndrome, AIDS	

GH: growth hormone, PCOS: polycystic ovary syndrome, SLE: systemic lupus erythematosus. Source: Adapted[3,6,7].

Breastfeeding for more than six months; eating a Mediterranean diet [8]; performing moderate to vigorous physical activity (brisk walking; cycling; working out; dancing; playing basketball, soccer or tennis; running; swimming; jumping; outdoor games) for 45 minutes a day and eating five meals a day [10] are considered protective factors against dyslipidemia.

FAMILIAL HYPERCHOLESTEROLEMIA

FH is an autosomal dominant disease that causes elevated serum cholesterol levels, especially LDL-c, and predisposes patients to early-onset atherosclerosis [5, 6, 9, 11, 12, 13, 14]. FH may occur in homozygosity or heterozygosity, with heterozygosity being more prevalent [6, 9]. The heterozygous form of the disease affects approximately 1 in 200 to 300 people worldwide [5, 9, 13, 15, 16, 17, 18]. Although rare, the homozygous form (prevalence 1 in 250,000 to 1,000,000 people) presents greater concerns, since it may cause early-onset CVD and decrease life expectancy [5, 6, 9, 14, 16, 17, 18].

The main mutation, seen in 90% of the cases of FH, affects the LDL-c receptor (LDLR), which results in absent or decreased LDLR activity on the surface of hepatocytes, elevating serum LDL-c and total cholesterol. Ten percent of the patients with the disease have a mutation in the gene encoding apolipoprotein B. In less than 1% of the cases, mutation occurs in the gene encoding PCSK9, causing LDLR degradation [6, 9, 13, 14, 15, 19]. LDL-c accumulates in tissues, especially in arterial walls, predisposing patients to early atherosclerosis and increased cardiovascular risk [5, 12, 14, 15, 16, 19].

FH is usually asymptomatic, [9, 17] but potential clinical manifestations include xanthomas and xanthelasma, mainly in the Achilles tendon; corneal arcus; endothelial dysfunction; and thickening of the carotid mid-intimal layer [6, 15, 20, 21]. Most signs and symptoms appear after decades, except in homozygous FH, in which they appear within the first years of life. FH must be considered particularly in patients with symptoms, especially xanthomas. Phenotype severity depends on underlying mutation and residual LDLR activity [9, 21].

Atherosclerosis progresses quickly, starting at 10 years after birth, and causes early signs and symptoms including angina pectoris in children and early cardiovascular events in adolescents. Prompt introduction of lipid-lowering drugs may slow progression [9, 13, 14, 21].

DYSLIPIDEMIA SCREENING

Dyslipidemia screening can be performed with tests for TC, LDL-c, very-low-density lipoprotein-linked cholesterol (VLDL-c), HDL-c, and non-HDL-c; and genetic analysis, in cases suspected with FH; or both [20, 22]. Four types of screening can be used to detect cases of dyslipidemia, as shown below and summarized in figure 2:

1. Universal screening: known for its high sensitivity, it consists of routinely determining TC levels in children at a predetermined age. [13, 14].
2. Selective screening: consists of determining the TC levels in children with a family history of dyslipidemia. About 30-60% of the children with dyslipidemia may be missed [13, 14, 18].
3. Direct cascade screening: when one of the parents has a mutation associated with FH, genetic tests of first-degree relatives, including children, are performed. This is the most sensitive, specific, and cost-effective screening alternative [13, 14].
4. Reverse cascade screening: when a child is diagnosed with dyslipidemia, the child's parents are tested [13, 14].

The National Heart, Lung, and Blood Institute (NHLBI), the American Academy of Pediatrics (AAP), and the Brazilian Society of Pediatrics (SBP) recommend universal screening for dyslipidemia in children at two time points: before puberty, approximately between nine and 11 years of age, since serum cholesterol levels change during puberty due to sexual maturation and the growth spurt; and between 17 and 21 years of age [9, 13, 14, 18, 19, 20, 23]. Children with risk factors for dyslipidemia and early CVD must be screened selectively between the ages of two and eight years and 12 and 16 years [9, 23]. Fasting for eight to 12 hours is recommended in hypertriglyceridemia testing, since fat and carbohydrate intake can elevate serum triglyceride levels [23].

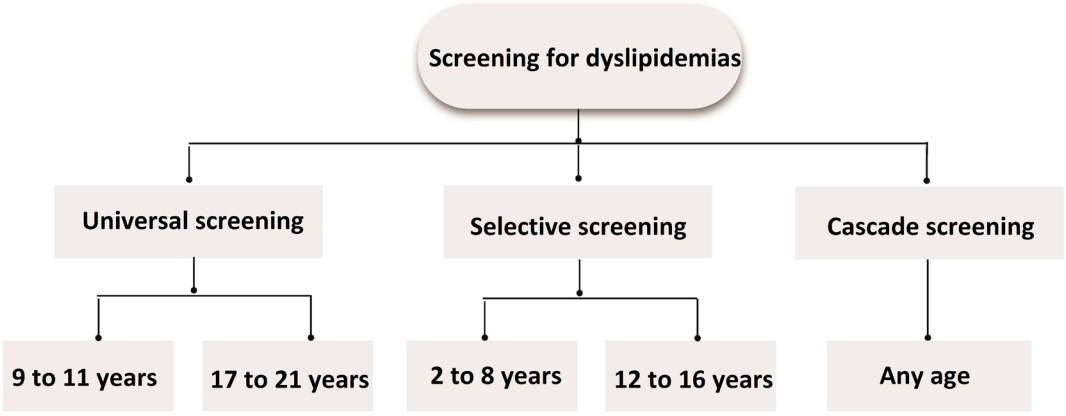


Figure 2. Screening for dyslipidemia.

FH must be investigated in patients with LDL-c above 160 mg/dL or non-HDL-c above 190 mg/dL. Presence of clinical signs of hypercholesterolemia, increased LDL-c in first-degree relatives, history of early coronary heart disease in first-degree relatives (women < 65 years and men < 55 years of age) [6], and family history of pancreatitis, must also be considered in interviews and physical examination [4, 9, 17, 20, 23]. Secondary dyslipidemia must be ruled out [9, 23]. If TC levels and its fractions vary widely during childhood and do not meet criteria for FH, tests must be repeated every three to six months [21].

Children and adolescents with a family history of hypercholesterolemia, FH, and LDL-c > 190 mg/dL must undergo genetic testing [6]. As mentioned previously, most of the identified genetic alterations are mutations in the LDLR gene. Response to lipid-lowering drug therapy depends on the identified genetic mutations. Thus, if a patient is suspected with homozygous FH in particular, genetic testing becomes a requirement [9, 21]. Children and adolescents diagnosed with FH must undergo cascade screening to find other possible cases of disease in the family [9, 21]. Figure 3 summarizes the above, in relation to the steps to carry out the investigation and differentiation of primary and secondary dyslipidemias.

Adoption of universal screening for dyslipidemia in health services is still low, indicating a need for more investment and education about the relevance of detecting dyslipidemia in children [24].

DIAGNOSIS

Diagnosis is based on clinical history, physical examination, and laboratory tests. Tests for TC, LDL-c, HDL-c, VLDL-c, non-HDL-c, and triglycerides must be performed. Fasting is not required in tests for non-HDL-c [9]. Reference values for total cholesterol dosage and fractions are described in table 2.

In case of TC levels ≥ 200 mg/dL, a second complete lipid profile must be performed within three months. At such time, other tests should be ordered to rule out secondary causes of dyslipidemia [13, 18, 19]. If altered values are found – TC ≥ 200 mg/dL and LDL-c ≥ 130 mg/dL – and secondary causes are ruled out, non-pharmacological therapy should be initiated for six months and a new tests for TC and fractions ordered. If LDL-c levels ≥ 130 mg/dL persist, FH must be considered in differential diagnosis [13].

Children with LDL-c levels ≥ 190 mg/dL on two consecutive tests within a three-month interval must be suspected for FH. If LDL-c ≥ 160 mg/dL and the patient has a family history of dyslipidemia or if LDL-c ≥ 130 mg/dL and the patient has a highly positive family history (parents died of CVD), FH must be considered and genetic tests ordered. Generally, in cases of heterozygous FH, TC levels are three times above the normal limit, while in homozygous FH TC levels range between 500-1000 mg/dL and may include clinical manifestations, such as xanthomas [13]. There are several references that define different diagnostic criteria for dyslipidemias, the main ones are listed in table 3.

TREATMENT OF PRIMARY DYSLIPIDEMIAS

Non-pharmacological treatment

Non-drug treatment is based on a multidisciplinary approach accompanied by a healthy, balanced diet, regular physical activity, and psychological support [9, 13, 21]. The involvement of all family members in lifestyle changes is of paramount importance for better compliance to treatment [1, 9, 13]. Nutritionist-supervised dietary interventions are recommended for individuals aged two years or older [9, 13].

The Mediterranean diet is a protective factor against CVD. It prescribes a high intake of fruits (citrus fruits, grapes, pomegra-

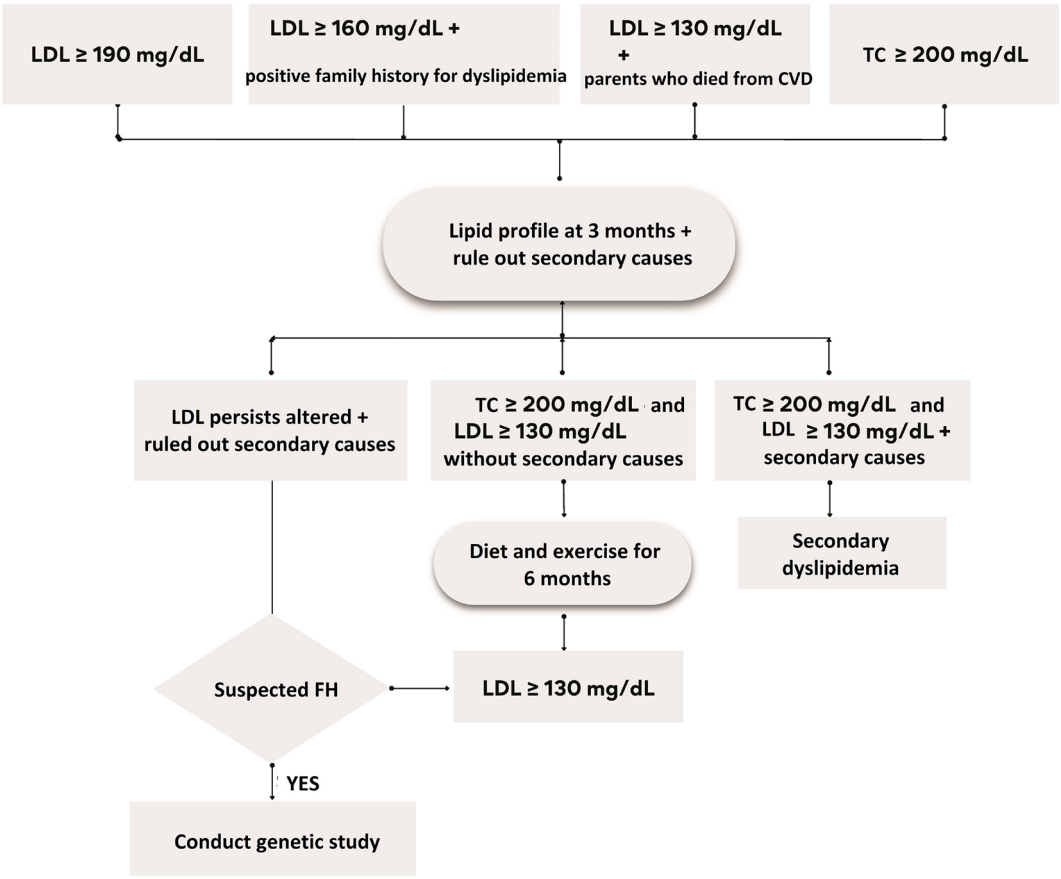


Figure 3. Dyslipidemia investigation flowchart.

Table 2. Reference values for lipid profiles (mg/dL) of children aged two to 19 years.

		Fasting			No fasting
Lipids		**Acceptable (mg/dL)**	**Borderline (mg/dL)**	**Altered (mg/dL)**	**Acceptable (mg/dL)**
Total cholesterol		< 170	170 – 199	≥ 200	< 170
LDL-C		< 110	110 – 129	≥ 130	< 110
HDL-C		> 45	40 – 45	< 40	> 45
Non-HDL-C		< 120	120 – 144	≥ 145	-
Triglycerides	0 – 9 years	< 75	75 – 99	≥ 100	< 85
	10 – 19 years	< 90	90 – 129	≥ 130	< 100

Source: Adapted[13,18,19,25].

nates), vegetables (cauliflower, tomatoes, broccoli, radish, fennel), herbs (sage, mint, oregano, ditamno), olive oil, cereals, fish, and a low intake of red meat and saturated fats. Its protective effect derives from the bioactive components found in these foods, phytochemicals and polyphenols, such as oleuropein, resveratrol, sulforaphane, anthocyanins, quercetin, and tannins. These bioactive components improve the lipid profile, and endothelial and thrombotic factors, among others [8].

Table 3. Diagnostic criteria for FH.

European Atherosclerosis Society (EAS)	LDL-c > 190 mg/dL in two tests, after 3 months of diet = highly suggestive LDL-c > 160 mg/dL after dietary intervention + family history of high LDL-c or early CVD in first degree relatives = highly suggestive LDL-c > 130 mg/dL in one test + relatives with genetic tests consistent with FH = suggestive
National Lipid Association (NLA)	LDL-c ≥ 160 mg/dL or non-HDL-c ≥ 190 mg/dL
American Heart Association (AHA)	LDL-c ≥ 160 mg/dL for children + first degree relatives with early CVD or with positive tests for genetic mutations that elevate LDL-c
Simon Broome criteria (United Kingdom)	Defined FH: TC >268 mg/dL or LDL-c > 160 mg/dL in individuals aged < 16 years + xanthomas in tendons of the patient or first degree or second degree relative or genetic evidence of LDLR or APOb or PCSK9 mutation. Possible FH: TC > 268 mg/dL or LDL-c > 160 mg/dL in individuals aged < 16 years and at least one of the following: family history of acute myocardial infarction in second degree relative aged < 50 years or in first degree relative aged < 60 years with family history of high cholesterol > 300 mg/dL in first or second degree adult relative or > 268 mg/dL in child or sibling aged < 16 years.
US MEDPED	TC ≥ 270 mg/dL despite family history TC ≥ 240 mg/dL + third degree relative with FH TC ≥ 230 mg/dL + second degree relative with FH TC ≥ 220 mg/dL + first degree relative with FH
Japan	LDL-c ≥ 140 + family history of early CVD or FH

Source: Adapted[9,13,16].
Make Early Diagnosis to Prevent Early Death (MEDPED).

Dietary interventions should commence with the Cardiovascular Health Integrated Lifestyle Diet 1 (CHILD-1) for six to 12 months, with fat intake restricted to less than 25-30% of total daily calories, with less than 8-10% of daily calories coming from saturated fats, less than 300 mg per day of cholesterol intake, and avoidance of trans fats [9, 18, 21, 23]. The Cardiovascular Health Integrated Lifestyle Diet 2 (CHILD-2) is specific for individuals with elevated LDL-c and TG, and prescribes a greater restriction of saturated fats (7%) and daily cholesterol intake to less than 200 mg, as well as higher intake of water-soluble fibers and plant sterols, such as corn, soy, canola, nuts, and cereals [7, 18].

The intake of complex carbohydrates is recommended, while the intake of sugar and sweetened beverages must be decreased [7, 26]. Increased intake of fish increases the supply of omega-3, and intake of fiber, especially water-soluble fiber, is recommended [1, 13, 14, 18, 23].

Studies show that consumption of ultra-processed food products is a predictor of elevated serum levels of TC and LDL-c in preschoolers. Children who eat only a meal a day also have higher levels of TC, LDL-c, and apolipoprotein B when compared to children who have more than a meal a day [8].

Studies show that dietary interventions with bioactive foods, such as nuts, may be recommended for children with primary dyslipidemia, since these foods help to modulate the lipid profile and the oxidative/anti-oxidative status [27, 28].

Moderate physical activity for 30 to 60 minutes a day, more often than twice a week, can lower triglyceride and cholesterol and increase HDL-c levels [8, 13, 23]. Studies show that longer screen time correlates with lower HDL-c and higher triglyceride levels [8, 21].

Pharmacological treatment

When lifestyle changes do not suffice, therapy with lipid-lowering drugs must be considered. Children and adolescents with homozygous FH must be referred to a specialist; if drug therapy fails, apheresis must be initiated [9, 21]. Figure 4 summarizes the treatment steps for homozygous and heterozygous FH.

Statins

Statins are 3-Hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors that decrease total cholesterol and increase LDLR expression on the surface of hepatocytes, thus reducing LDL-c levels [7, 16, 19, 23]. They may be prescribed to patients with persistently high levels of non-HDL-c, even after adoption of dietary and lifestyle changes [23]. Statins are the first-line treatment for pediatric dyslipidemia [1, 21]. They have shown better effect on cardiovascular outcomes and have their use justified in children older than two years with homozygous FH, despite adverse effect uncertainties [3, 9]. In heterozygous FH, studies advocate the use of statins in children aged 8-10 years [5, 9, 15, 16]. Statins effectively decrease LDL-c levels and cardiovascular events in adults and children [3, 5, 12, 14, 29].

Indications for the use of statins in the treatment of pediatric dyslipidemia include severe lipid abnormalities due to genetic disorders such as FH; FH with persistently elevated LDL-c (≥ 190) after 3 to 6 months of lifestyle modifications or family history of early CVD; TG above 500 mg/dL; and non-HDL-c cholesterol above 145 mg/dl [6, 16, 23].

The most commonly used statins are simvastatin 5 to 40 mg/day; atorvastatin 10 to 20 mg/day; rosuvastatin 5 to 20 mg/day; and pravastatin 20 to 40 mg/day [16, 23]. Treatment

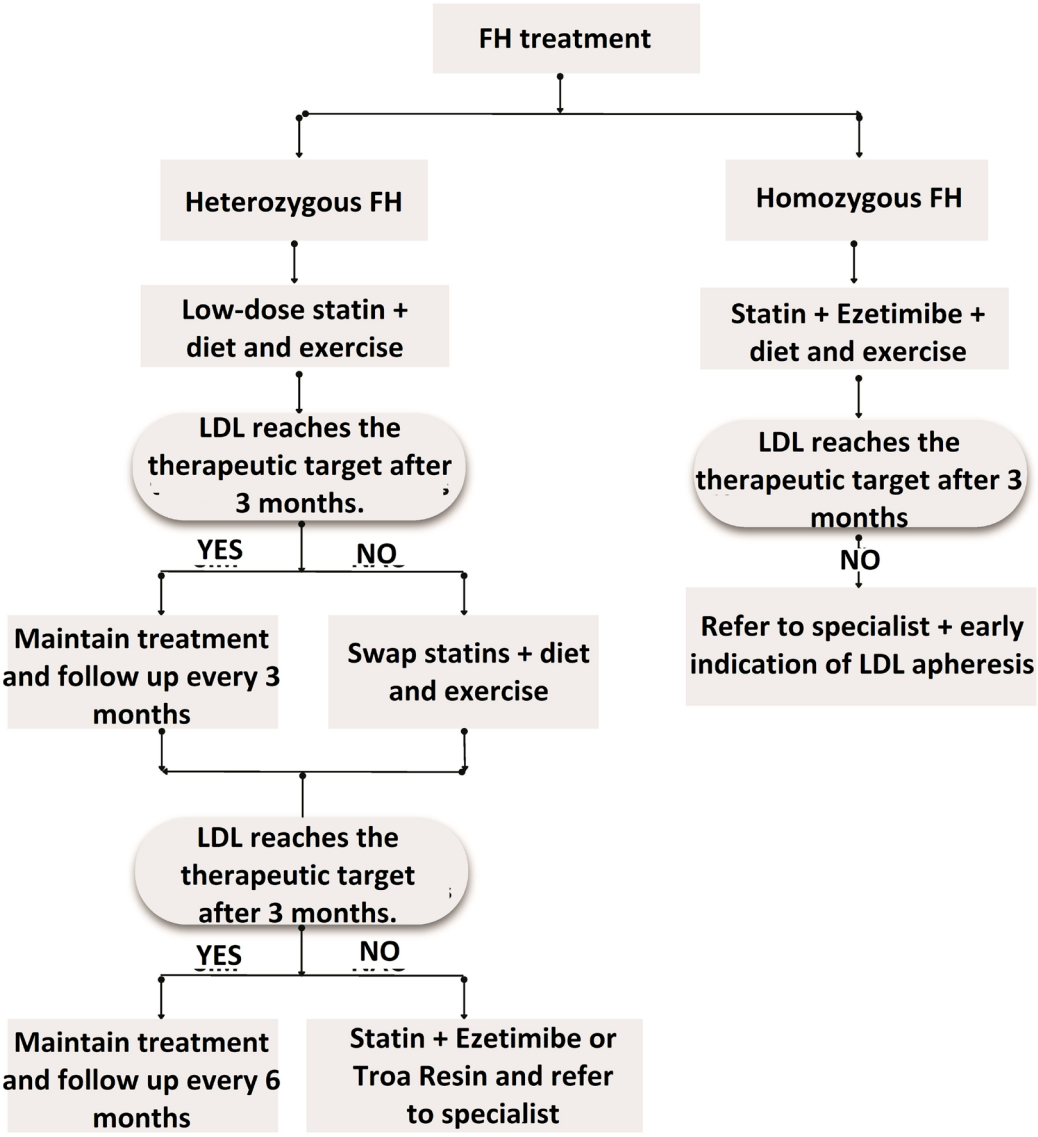


Figure 4. FH treatment flowchart.

must start at the lowest dose possible, and if LDL-c does not decrease satisfactorily, dose may be increased, the patient may be switched to a more potent statin, or another lipid-lowering drug may be added, usually ezetimibe or cholestyramine [1, 18, 21]. Statins can be administered once a day at night, since most LDL-c is synthesized at night [1]. Studies show that long-term treatment with statins prescribed to patients with FH has been associated with lesser increases of intima-media thickness [3, 5, 12, 14, 16, 17, 19]. Therapy with statins must be initiated upon the diagnosis of homozygous FH. Addition of ezetimibe might be needed in cases of severe disease [6, 9, 14, 16].

Adverse events associated with statins include gastrointestinal disorders, elevated liver transaminases and creatine phosphokinase (CPK), headache, constipation, and myalgia [3, 5, 6, 7, 17, 18, 19, 23, 30]. These adverse events are easily managed with temporary suspension of therapy [1, 17]. No impacts on sexual maturation and growth have been described [5, 6, 11, 12, 16, 17]. Statins must be used with caution in patients of childbearing age because of potential teratogenicity [1, 7, 12, 18, 23]. Statins must be discontinued three months before conception, during pregnancy, and lactation [9, 21].

Patients developing moderate statin intolerance should be prescribed another statin before progressing to other therapies [6]. Studies have shown that administration of rosuvastatin and atorvastatin on alternate days had similar efficacy on the lipid profile compared to a daily dose therapy, and decreased the incidence of myalgia, and elevated CPK and transaminases [30].

Fibrates

Fibrates activate peroxisome proliferator-activated receptor alpha and decrease hepatic synthesis of VLDL-c. They also increase lipoprotein lipase (LPL) activity, leading to increased hydrolysis of TG-rich lipoproteins [7, 23]. Fibrates have been cleared by the Food and Drug Administration (FDA) for use in patients over 18 years of age. They constitute the first-line therapy in the management of severe hypertriglyceridemia [23]. When serum TG levels are above 500 mg/dL, fibrates must be prescribed to prevent pancreatitis [18, 23].

Adverse effects include myopathy, especially when fibrates are prescribed in conjunction with a statin [19, 23]. Caution is required when prescribing the medication to patients with chronic kidney disease. A contraindication exists for individuals with kidney failure and cholelithiasis, the latter because of the risk of developing cholesterol stones [23].

Bile acid sequestrants

This drug class decreases intestinal absorption of cholesterol by binding to bile salts in the intestinal lumen, preventing enterohepatic circulation of bile acid molecules [1, 7, 16, 19]. Bile acid sequestrants have been approved for use in children over the age of ten years diagnosed with heterozygous FH. The most commonly used drugs are cholestyramine, colestipol, and colesevelam, the latter being more widely accepted for its better palatability [16, 19]. Tolerance to resins may be improved by dissolving them in fruit juice and taking them before a meal. Resins must not be given together with other medications, such as warfarin, thyroxine, and digoxin [7, 13]. Cholestyramine reduces LDL-c by approximately 10-20% in children with severe hypercholesterolemia [1, 7, 16].

Adverse effects include reduced vitamin D and folic acid, abdominal distension, abdominal pain, diarrhea, constipation, nausea, and vomiting [1, 7, 16, 17, 19, 21]. Unlike statins, they can be used safely during pregnancy [9].

Cholesterol absorption inhibitors

Ezetimibe blocks cholesterol absorption by inhibiting sterol transporter Niemann-Pick C1 Like 1 (NPC1L1) in the brush border of the small bowel. It has been approved for treatment of hypercholesterolemia in patients older than 10 years [7, 16]. The combination of ezetimibe and statin is superior to simvastatin alone [1, 7, 16]. The most relevant adverse effect of ezetimibe is the elevation of transaminase levels [17].

Niacin

Niacin acts by inhibiting diacylglycerol acyltransferase-2, an enzyme that converts diacylglycerol into TG, thus reducing the flow of free fatty acids (FFA) from adipose tissue [23]. It decreases triglyceride levels by 5% to 40%, reduces LDL-c and lipoprotein levels, and increases HDL-c levels by 10% to 40% [19, 23]. Adverse effects include niacin flush, which occurs 15 minutes after taking the medication due to the release of prostaglandin F2; abdominal pain; vomiting; headache; insulin resistance; and elevation of liver transaminases [1, 23].

Omega-3

Omega-3 long-chain fatty acids can be used in conjunction with other lipid-lowering drugs when serum TG levels are above 500 mg/dL or when TG levels cannot be managed with diet and weight loss alone [18, 23]. Effect is dependent on the levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Desired levels are approximately 465 mg of EPA and 375 mg of DHA [23]. Omega-3 fatty acids can reduce TG levels by 20% to 50% with daily intakes of 3 to 4 grams [7, 23, 31]. Omega-3 is also found in foods such as fish (salmon, herring, mackerel, and trout), fish oil, and plant products (flaxseed, chia seed, canola oil, soybean oil), and some nuts [31]. Side effects include diarrhea, eructation, nausea, and atrial fibrillation [31].

Orlistat

Orlistat is a medication often used for weight reduction in individuals with obesity and type 2 diabetes mellitus. It has been approved for use in children older than 12 years. Orlistat is a gastric and pancreatic lipase inhibitor that decreases fat absorption in the bowel by up to 30% [18, 32]. Studies have shown that decreased fat absorption allowed by Orlistat may decrease triglyceride levels in patients with type 1 hyperlipoproteinemia. No severe adverse effects or changes in growth and physical well-being of the children included in studies with the drug were described. Therefore, it is safe and effective at reducing serum TG levels in individuals with type 1 hyperlipoproteinemia, in association with a low-fat diet and supplementation with fat-soluble vitamins [32].

PCSK9 inhibitors

This human monoclonal antibody binds to circulating PCSK9 and reduces LDLR catabolism in hepatocytes, increasing LDLR expression and decreasing LDL-c levels. The most common representatives of this drug class are evolocumab and alirocumab, both approved by the FDA in 2015 for use in adults with hyperlipidemia, mainly FH. There is no approval for use in children yet, but clinical trials looking into its use in pediatric patients are in progress and showing promising results [13, 16, 29]. It is indicated for patients older than 12 years as additional therapy to other lipid-lowering drugs. Studies have shown a significant reduction in LDL-c levels in patients

without satisfactory response or with intolerance to statins, but the same effect was not seen in patients with absent LDLR [9].

Lomitapide

Lomitapide indirectly reduces circulating LDL-c by inhibiting microsomal triglyceride transfer protein (MTP), which, by binding TG molecules to apolipoprotein B-100 in the liver, leads to lower levels of LDL-c, VLDL-c, and IDL [14, 16]. It has been approved for use in adults with homozygous FH and used cautiously in pediatric patients [16]. Most adverse events are of a gastrointestinal nature, and include diarrhea, abdominal pain, liver dysfunction, and fatty liver disease [1, 16, 21].

LDL-apheresis

LDL-apheresis is prescribed to patients with homozygous FH unresponsive to drug therapy, even with optimized doses. It must be started early on, usually on patients aged five years [9, 13]. Three methods are available: simple plasma exchange, double membrane filtration, and selective methods to lower LDL-c. Recommended frequency of treatment is weekly or every two weeks, with LDL-c levels measured before and after apheresis [9, 19, 21]. This therapy may contribute to atheroma regression, angina stabilization, and improved patient outcomes [9, 21]. A single apheresis session can lower LDL-c levels by 55% to 70%. Side effects include hypotension, abdominal pain, hypokalemia, and iron deficiency [9].

Other therapies

Liver transplantation may be required for patients with severe dyslipidemia. Transplantation may dramatically reduce LDL-c levels, since the transplanted liver will provide functioning LDL-c receptors. Gene therapy is a potential new treatment under study that may be beneficial for patients with homozygous FH [19].

TREATMENT GOALS

The goal for patients under 18 years of age is to achieve serum LDL-c levels below 130 mg/dL or a 50% decrease from the prior LDL-c level measured. In children with risk factors, the recommended LDL-c level is < 100 mg/dL [9, 12, 16, 18].

FOLLOW-UP

Measurement of TC and fractions, transaminases, creatinine, creatine phosphokinase is recommended before initiation of treatment with hypolipemic drugs and during follow-up [9, 21]. Response to treatment must be assessed after the first month of drug therapy and consider symptoms, tolerance to medication, and potential workup changes and adverse effects. Once the ideal dose has been reached, patients must be followed every three months in the first year of treatment, and then every six months, with repetition of laboratory tests. Growth, weight gain, and sexual maturity must also be evaluated during follow-up visits [9, 21].

Patients must be periodically followed for risk of developing CVD with electrocardiograms, echocardiograms, or angiograms to evaluate contractility alterations and supra-aortic stenosis due to atherosclerosis and aortic regurgitation. Attention should also be paid to increased risk of renal artery stenosis, mesenteric ischemia, cerebrovascular disease, and peripheral arterial disease [14, 19].

TREATMENT OF SECONDARY DYSLIPIDEMIA

Drug treatment for secondary dyslipidemia is controversial. Literature about effectiveness of treatment is insufficient. Treatment of secondary dyslipidemia is based on dietary interventions and treatment of underlying metabolic disorders [3].

PREVENTION

Adoption of healthy eating habits, with low levels of cholesterol, saturated fats, and carbohydrates, improves the lipid profile and decreases cardiovascular risk [3, 6, 22]. A healthy diet and regular exercises, when started in childhood and adolescence, may have beneficial effects in adulthood, since evidence suggests that atherosclerosis starts in the early years of life and progresses slowly into adult age [8]. Additionally, when encouraged from childhood, healthy habits are more easily internalized in adulthood [13, 22]. Therefore, parents should adopt and encourage their children to adopt healthy habits. Smoking and spending too much time in front of the screens of cell phones, televisions, and tablets should be avoided [13, 21]. Pediatricians must discuss eating habits and assess the nutritional status of children during visits to prevent diseases in adulthood.

CONCLUSION

Approaches to dyslipidemias regarding screening and treatment are still a topic of controversy. FH is underdiagnosed, and efforts are needed to improve screening and early diagnosis of patients with the condition to prevent progression to CVD in adulthood. Universal screening is the most sensitive method to detect dyslipidemia, since data coming from family accounts for selective screening are often unreliable. Regarding treatment, longer-term studies are needed to evaluate the long-term effect of drug therapies on cardiovascular risk in adults. Further studies about new therapies for pediatric patients involving medications prescribed to adults are needed.

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