



Screening and Management for Dyslipidemia in Korean Children and Adolescents

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Diagnosis

Cardiovascular disease (CVD) is the most common cause of death worldwide, and dyslipidemia is a major risk factor. Atherosclerosis can begin in childhood and continue into adulthood, thereby contributing to CVD development. Obesity is the most common cause of dyslipidemia, and the prevalence of childhood obesity and dyslipidemia is increasing worldwide, making it a public health concern. As clinical evidence has accumulated, guidelines for dyslipidemia in children have been continuously revised since 1992. The limitations of screening tests for individuals with a family history of dyslipidemia emphasize the necessity of universal screening, and non-HDL cholesterol assessment is recommended as a screening test for dyslipidemia in children. The guidelines for dyslipidemia in Korean children and adolescents published in 2017 recommend that non-HDL cholesterol screening tests be performed in non-fasting conditions at 9–11 years and 17–21 years of age. The main purpose of this article is to describe the history and rationale of lipid screening recommendations in children and adolescents and to review the currently recommended screening methods and treatments for dyslipidemia. (Ewha Med J 2022;45(3):e4)

Introduction

Dyslipidemia is a risk factor for cardiovascular disease (CVD), a major cause of morbidity and mortality worldwide. CVD is becoming more prevalent worldwide, and the CVD-associated mortality rate in Korea has steadily increased, similar to that in the United States (U.S.) [1,2]. Dyslipidemia is closely related to other CVD risk factors, such as obesity, diabetes mellitus (DM), hypertension, smoking, and metabolic syndrome (MetS) in children and young adults [3]. In Korea, as the smoking rate no longer increases and hypertension is well controlled, the incidence of cerebral hemorrhage has decreased. In contrast, the incidence of coronary artery disease and cerebral infarction has increased with an increase in the obese population [4]. Obesity is associated with an increased risk of developing insulin resistance [5]. An increase in the incidence of obesity is accompanied by an increase in MetS and DM, diseases associated with insulin resistance and dyslipidemia [6–9]. The prevalence of pediatric obesity in Korea increased from 8.6% in 2001 to 9.8% in 2017 [10]. The tendency of dyslipidemia to worsen in Korean children is also increasing. Based on the data of the Korea National Health and Nutrition Examination Survey (KNHANES) IV (2007–2009), the prevalence of total pediatric dyslipidemia was 19.7%, and according to KNHANES VII (2016–2018) data analysis, the proportion of

dyslipidemia among the pediatric population showed a tendency to worsen to 39.5% in boys and 29.7% in girls [11,12]. Approximately 20% of Korean children and adolescents aged 10–19 years have at least one type of dyslipidemia, and 56.1% of Korean obese adolescents have dyslipidemia [13]. Dyslipidemia in children and adolescents is closely related to atherosclerosis in childhood, as well as dyslipidemia, atherosclerosis, and CVD in adulthood. In addition, the first stage of CVD is atherosclerosis, which can begin in childhood, and its progression is associated with dyslipidemia [14]. Therefore, dyslipidemia is considered the most important risk factor for atherosclerosis compared to other risk factors, and aggressive diagnosis and treatment are important to lower the incidence and mortality associated with CVD [15]. Through early detection and intervention of dyslipidemia in childhood, pediatricians play a role in preventing the progression of dyslipidemia, which is very important for public health. This review focuses on the development process of pediatric lipid disorder screening guidelines, rationale for universal screening methods, and treatment for dyslipidemia in children and adolescents.

Definition of Dyslipidemia in Children and Adolescents

According to the type of increased lipid, dyslipidemia is classified into hypertriglyceridemia, hypercholesterolemia, combined hyperlipidemia (increased cholesterol and triglycerides [TG]), and hypo-HDL cholesterolemia [16]. The cutoff point for dyslipidemia in children and adolescents differs according to age, sex, and ethnicity. In 1992, the National Cholesterol Education Program (NCEP) and the American Academy of Pediatrics (AAP) suggested reference values corresponding to the 90–95th percentile for hypercholesterolemia (≥ 200 mg/dL) and hyper-LDL cholesterolemia (≥ 130 mg/dL) based on the distribution of serum lipid concentrations in children aged 6–19 years [17]. The criteria for using NCEP Panel III modified for children define hypertriglyceridemia as TG level ≥ 110 mg/dL and hypo-HDL cholesterolemia as HDL cholesterol < 40 mg/dL [18]. In 2011, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel revised the cutoff points initially developed by the NCEP and the AAP based on the population distribution [19]. The cutoff points of total cholesterol and LDL cholesterol suggested by the NHLBI, the AAP, and the NCEP were similar, but there was a difference in the cutoff points of TG and HDL cholesterol depending on the dyslipidemia research organization. The American Heart Association (AHA) recommends that TG ≥ 150 mg/dL and HDL cholesterol < 35 mg/dL be considered abnormal in children and adolescents [20]. The International Diabetes Federation (IDF) classified hypertriglyceridemia as a TG ≥ 150 mg/dL and hypo-HDL cholesterolemia according to sex and age, with HDL cholesterol < 40 mg/dL in children aged 10–15 years and HDL cholesterol < 40 mg/dL (boys) and < 50 mg/dL (girls) in children aged 16 years and older as standard values [21]. According to the AAP, based on the revision by the NHLBI, serum total cholesterol ≥ 200 mg/dL, LDL cholesterol ≥ 130 mg/dL, non-HDL cholesterol ≥ 145 mg/dL, TG ≥ 130 mg/dL (≥ 100 mg/dL in children under 10 years of age), and HDL cholesterol < 40 mg/dL were defined as dyslipidemia in children and adolescents [19].

According to the KNHNS, the 95th percentiles for total cholesterol, TG, LDL cholesterol, and non-HDL cholesterol were 203, 185, 129, and 145 mg/dL, respectively, and the 10th percentile for HDL cholesterol was 38 mg/dL in Korean children and adolescents [13,22]. The distribution of lipid levels in Korean children and adolescents was reported to be similar to that in American children and adolescents [23]. Based on this, the 2011 U.S. NHLBI guidelines were adopted to produce the guidelines for dyslipidemia in children and adolescents in Korea [19,24].

The diagnostic criteria for dyslipidemia in children and adolescents in Korea were based on

the NHLBI definition. The cutoff points for defining total cholesterol, LDL cholesterol, non-HDL cholesterol, TG, and HDL cholesterol levels in children and adolescents from the guidelines are presented in Table 1. According to the Korean Society of Pediatric Endocrinology (KSPE) Clinical Practice Guidelines Committee, total cholesterol ≥ 200 mg/dL, LDL cholesterol ≥ 130 mg/dL, non-HDL cholesterol ≥ 145 mg/dL, TG ≥ 130 mg/dL (≥ 100 mg/dL in children under 10 years of age), and HDL cholesterol < 40 mg/dL were defined as dyslipidemia in children and adolescents. Recommended cutoff points for diagnosing dyslipidemia in young adults are total cholesterol ≥ 225 mg/dL, LDL cholesterol ≥ 160 mg/dL, non-HDL cholesterol ≥ 190 mg/dL, TG ≥ 150 mg/dL, and HDL cholesterol < 40 mg/dL, as described in Table 2 [19].

Causes of Dyslipidemia in Children and Adolescents

The etiology of dyslipidemia can be classified into primary and secondary types [16]. Table 3 summarizes primary and secondary pediatric dyslipidemias [25]. Primary dyslipidemia is an inherited lipoprotein disorder that is often present in youth at a high risk of future CVD. Primary dyslipidemia is related to the production and degradation of specific proteins involved in the production, transport, and metabolism of lipoproteins, and abnormalities in specific genes have been identified. Secondary dyslipidemia is caused by a variety of diseases and conditions, including endocrine (hypothyroidism, DM, and pregnancy), exogenous (drugs, obesity, and alcohol), renal (nephrotic syndrome and chronic renal failure), hepatic (cholestasis, biliary atresia, hepatitis, and biliary cirrhosis), and immunological (human immunodeficiency virus infection/acquired immunodeficiency syndrome) conditions [25]. Obesity is a common cause of secondary dyslipidemia in children and adolescents. Various factors are involved in the pathophysiology of dyslipidemia in obese patients. In obese patients, increased fatty acid

Table 1. Definition of dyslipidemia for lipid cutoff levels in children and adolescents

Variable	Acceptable	Borderline	Abnormal
Total cholesterol (mg/dL)	< 170	170–199	≥ 200
LDL cholesterol (mg/dL)	< 110	110–129	≥ 130
Non-HDL cholesterol (mg/dL)	< 120	120–144	≥ 145
Triglycerides (mg/dL)			
0–9 yr	< 75	75–99	≥ 100
10–19 yr	< 90	90–129	≥ 130
HDL cholesterol (mg/dL)	> 45	40–45	< 40

Table 2. Cutoff levels for lipids in the diagnosis of dyslipidemia in young adults

Variable	Acceptable	Borderline	Abnormal
Total cholesterol (mg/dL)	< 190	190–224	≥ 225
LDL cholesterol (mg/dL)	< 120	120–159	≥ 160
Non-HDL cholesterol (mg/dL)	< 150	150–189	≥ 190
Triglycerides (mg/dL)	< 115	115–149	≥ 150
HDL cholesterol (mg/dL)	> 45	40–44	< 40

Table 3. Differential diagnosis of pediatric dyslipidemia

Primary disorders	Secondary disorders
Familial hypercholesterolemia	Hypothyroidism
Autosomal recessive	Diabetes
Hypercholesterolemia	Pregnancy
Autosomal dominant	Drugs
Hypercholesterolemia	Obesity
Familial ligand-defective apoB-100	Alcohol
Sitosterolemia	Nephrotic syndrome
Familial combined hyperlipidemia	Chronic renal failure
Familial hypertriglyceridemia	Cholestasis
Familial chylomicronemia syndrome	Biliary atresia
Hypoalphalipoproteinemia	Hepatitis
Dysbetalipoproteinemia	Biliary cirrhosis
	Human immunodeficiency virus infection/acquired immunodeficiency syndrome

flow from adipose tissue to the liver and hepatic *de novo* fatty acid synthesis are important contributors to elevated serum TG levels. Abundant TG prevent intrahepatic degradation of Apo B-100 and increase very-LDL formation and secretion, which is an important contributor to elevated serum TG levels. The pro-inflammatory state is a characteristic observed in obesity, and cytokines produced in macrophages and adipokines produced in adipocytes affect lipid metabolism [26]. Before considering primary dyslipidemia, the cause of the secondary dyslipidemia must be excluded. If dyslipidemia persists even after the cause of secondary dyslipidemia has been treated, the patient may need dietary therapy and may need to consider medication [27].

Lipid Screening in Pediatric Populations

Pediatric lipid testing is based on evidence that the early identification and management of dyslipidemia in children can reduce the risk and severity of CVD in adulthood [28]. To date, a unified diagnostic criterion for dyslipidemia in children and adolescents has not yet been established worldwide. Guidelines for dyslipidemia in children were first developed by the NCEP of the NHLBI in 1992 [29]. They were created based on expert opinion and extrapolation of data collected from adults, and the composition did not include a complete formal review of evidence to grade evidence. Three categories were presented for lipid screening in the pediatric population: acceptable, borderline-high, and high. Population-based approaches focus on the identification and treatment of dietary and lifestyle problems in the entire population and the identification and treatment of high-risk children and adolescents. Individual approaches rely on family history. Children with first- and second-degree relatives with early onset coronary artery disease or stroke should be screened. The committee considered universal screening but decided that a selective screening approach would be more efficient, recognizing the effects of genes and the environment.

However, it is difficult to determine whether screening for dyslipidemia reduces the incidence

of myocardial infarction or stroke in adulthood in asymptomatic children and adolescents. Therefore, the US Preventive Services Task Force reported a grade I recommendation in its review of the evidence for cholesterol testing in children and adolescents [30]. This indicates that there is insufficient evidence for lipid testing in children and adolescents.

In 2011, the NHLBI published the results of a complete review and grading of evidence for the screening and treatment of CVD risk factors, including dyslipidemia, in children and adolescents [19]. In contrast to the previous guidelines, universal screening for lipid disorders was recommended. This is because studies have shown that using only a selective screening approach based on family history can potentially miss children and adolescents with significantly high cholesterol levels.

In 2017, the KSPE published guidelines for dyslipidemia in Korean children and adolescents [24]. These guidelines were determined in consideration of the country and existence of evidence by referring to the NHLBI recommendation level standards.

Screening in children and adolescents is aimed at reducing the incidence of CVD in adults by the early detection and management of dyslipidemia. Long-term follow-up studies have demonstrated that dyslipidemia in children and adolescents is an important predictor of dyslipidemia in adults [31]. Therefore, the purpose of the screening test is to identify children and adolescents with a very high risk of early CVD due to dyslipidemia.

Although family history of CVD is important in predicting future CVD, using a family history of dyslipidemia or early CVD to determine the need for dyslipidemia screening misses up to 60% of children with dyslipidemia. Therefore, the accuracy or reliability of information on family history is low, and the absence of a family history does not mean that there is no dyslipidemia in children and adolescents [19]. The Coronary Artery Risk Detection in Appalachian Communities Project found that using family history to determine the need for cholesterol testing in children missed many individuals with moderate dyslipidemia and failed to detect a significant number of potential genetic dyslipidemias requiring pharmacological treatment. Project HeartBeat! investigated the sensitivity, specificity, and positive predictive value of lipid tests in children using factors such as positive family history alone, body mass index (BMI) above the 85th percentile alone, and positive family history and BMI above the 85th percentile. The authors concluded that using one of the three screening criteria could miss a significant number of children with dyslipidemia [32]. Therefore, it is emphasized that universal cholesterol testing to prevent future atherosclerosis can be used to identify all children with severe dyslipidemia, allowing appropriate intervention and follow-up [33]. The pattern of normal cholesterol concentration does not change much after 2 years of age, but the lipid level decreases by 10%–20% during puberty and increases again in the 20s. Therefore, considering these normal change patterns, screening tests are required at the ages of 9–11 and 17–21 years for all children and adolescents, even if there is no clinical marker or family history.

The KSPE recommends non-HDL cholesterol assessment as a screening test. It is recommended that all children and adolescents be screened for non-HDL cholesterol under non-fasting conditions at the ages of 9–11 and 17–21 years. Screening for dyslipidemia is not recommended from birth to 2 years of age. Non-HDL cholesterol level is obtained by subtracting HDL cholesterol from total cholesterol [24]. It is less affected by fasting than LDL cholesterol and is a useful method for measuring lipoproteins that cause atherosclerosis. In children, non-HDL cholesterol appears to be a better predictor of CVD than LDL cholesterol [34]. According to a recent study using KNHNES data, the universal screening method using non-HDL cholesterol in obese adolescents above the 95th percentile of BMI, the current Korean screening test for lipid

disorders, was more effective in detecting familial hypercholesterolemia (FH) than the method of measuring total cholesterol [35].

In the initial stage, a fasting test is not required; if there are abnormal findings as a result of the primary test, a fasting test is recommended. It is also recommended that fasting lipid testing be performed at ages 2–8 and 12–16 years for individuals with risk factors for dyslipidemia [24].

After fasting for at least 9 h, total cholesterol, TG, HDL cholesterol, and LDL cholesterol levels are measured to diagnose dyslipidemia. Two or more fasting tests are performed at intervals of 2 weeks or more within 3 months, and the average value is used to diagnose dyslipidemia [19,36]. The risk factors for dyslipidemia are shown in Table 4 and are categorized into family history, high-risk factors, and moderate risk factors [24].

Treatment

Interventions for dyslipidemia include lifestyle modifications, such as healthy diet and regular physical exercise, and drug therapies. The increase in dyslipidemia among Korean children and adolescents has been greatly influenced by Western lifestyle [37]. Lifestyle modification is recommended for the treatment of dyslipidemia in children, and drug treatment is considered a secondary treatment when dyslipidemia cannot be corrected with lifestyle modifications [19,24].

1. Lifestyle modifications

Factors associated with dyslipidemia include alcohol consumption, smoking, diet, and obesity [19]. Obesity is one of the risk factors for dyslipidemia, and lifestyle modification to improve obesity is the priority in dyslipidemia treatment. Through lifestyle modifications, all children and adolescents should aim to reach their ideal body weight (BMI \leq 85th percentile for age and sex). The KSPE guidelines recommend that children and adolescents increase their activity by engaging in moderate or more physical activity for at least one hour each day. They also mention reducing sedentary lifestyles as much as possible, including watching television and playing video games. Smoking and alcohol drinking should also be strongly discouraged [24,36].

For children with dyslipidemia, the Cardiovascular Health Integrated Lifestyle Diet 1 (CHILD 1)

Table 4. Risk factors for dyslipidemia

Classification	Explanation
Family history	•Parent, grandparent, aunt, or uncle has a history of myocardial infarction, angina pectoris, coronary artery bypass surgery/stent/angioplasty, sudden death in male<55 years of age or female<65 years of age
High level risk factors	•Hypertension requiring medication •Smoking •BMI \geq 97th percentile •High risk conditions: type 1 and type 2 diabetes mellitus, chronic kidney disease/end-stage renal failure/kidney transplantation, heart transplantation, Kawasaki disease with aneurysm
Moderate level risk factors	•Hypertension that does not require medication •95th percentile \leq BMI<97th percentile •HDL cholesterol<40 mg/dL •Moderate risk conditions: Kawasaki disease with improved coronary aneurysm, chronic inflammatory disease (systemic lupus erythematosus, juvenile rheumatoid arthritis), human immunodeficiency virus infection, nephrotic syndrome

BMI, body mass index.

is recommended for 3–6 months, as suggested by the 2010 Dietary Guidelines for Americans to reduce the risk of CVD and provide the nutrition necessary for growth in children and adolescents [38]. CHILd 1 recommends exclusively breastfeeding up to 6 months of age and, if not possible, using iron-fortified formula. Breastfeeding should continue until at least 12 months of age, and juice should be limited to 120 mL/day. After 12 months, low-fat milk is recommended, the consumption of carbonated drinks should be limited, and drinking water is encouraged. The total fat content should be maintained at 30% of the total calories, saturated fatty acids at 8%–10%, and monounsaturated and polyunsaturated fatty acids at up to 20%. Individuals with a family history of obesity, heart disease, or hypercholesterolemia should consult their healthcare provider regarding low-fat milk intake after 12 months of age. After 2 years of age, daily fat intake should be limited to 25%–30% of the total daily caloric requirement, saturated fat to 8%–10%, and unsaturated fat to 20%. The cholesterol intake should be limited to 300 mg/day. The recommended amount of dietary fiber is 14 g/1,000 kcal, and salt intake should be limited [24].

If dyslipidemia is not controlled by CHILd 1 within 3 months, CHILd 2-LDL and CHILd 2-TG are performed. Compared to CHILd 1, CHILd 2 reduces cholesterol from 300 mg to 200 mg and saturated fatty acids from 8%–10% to 7%. CHILd 2-LDL is performed in children with high LDL cholesterol levels. If TG levels are high, CHILd 2-TG is performed, reducing the intake of simple carbohydrates, replacing simple carbohydrates with complex carbohydrates, and increasing the intake of omega-3 fatty acids. CHILd 2 reduces cholesterol from 300 mg to 200 mg and saturated fatty acids from 8%–10% to 7% compared to CHILd 1. CHILd 2-TG involves reducing sugar intake and increasing the intake of omega-3 fatty acids in the CHILd 2-LDL diet [3].

2. Drug therapy

Drug treatment is recommended for children and adolescents aged ≥ 10 years when lifestyle and dietary changes for 6–12 months are not effective [19,24,36]. Decisions on drug treatment should be based on the average fasting blood lipid concentration measured twice, at least 2 weeks apart, within the last 3 months. Drug treatment for dyslipidemia according to age is summarized in Table 5.

Children younger than 10 years do not usually start statin therapy. However, some experts recommend starting statins at 8 or 10 years of age. Its use is limited to cases of homozygous familial

Table 5. Drug treatment for dyslipidemia in children and adolescents

Ages	Treatments
Newborn – 9 years old	<ul style="list-style-type: none"> Lipid lowering therapy is limited to cases of homozygous familial hypercholesterolemia, LDL cholesterol ≥ 400 mg/dL, primary hypertriglyceridemia (≥ 500 mg/dL), cardiovascular disease, and heart transplantation.
10–21 years old	<ul style="list-style-type: none"> Immediately refer to an expert <ul style="list-style-type: none"> - LDL cholesterol ≥ 250 mg/dL or triglycerides ≥ 500 mg/dL Statin treatment <ol style="list-style-type: none"> LDL cholesterol ≥ 190 mg/dL LDL cholesterol between 160–189 mg/dL with a family history of premature CVD or one or more high-level risk factors, or at least two moderate-level risk factors LDL cholesterol between 130–159 mg/dL with two or more high-level risk factors, or at least one high-level risk factor and two moderate-level risk factors Omega-3 fatty acids (fish oil) <ul style="list-style-type: none"> - Triglycerides ≥ 200–499 mg/dL, non-HDL cholesterol ≥ 145 mg/dL Consider treatment with statins, fibrates, or niacin <ul style="list-style-type: none"> - If non-HDL cholesterol ≥ 145 mg/dL even after LDL cholesterol has reached target

CVD, cardiovascular disease.

hypercholesterolemia (HoFH), LDL cholesterol ≥ 400 mg/dL, and primary hypertriglyceridemia (TG ≥ 500 mg/dL) [24]. Initiation of statin therapy from childhood in patients with FH resulted in a slower progression of carotid intima-media thickness and a reduced risk of CVD in adulthood [39]. The use of statin preparations may be considered when LDL cholesterol does not improve after 6 months of lifestyle modifications and dietary changes in children aged ≥ 10 years [19]. If LDL cholesterol is < 250 mg/dL or TG level is 500 mg/dL in children aged 10 years or older, CHILD 1 or CHILD 2 is performed for 3–6 months, and BMI is at or above the 85th percentile, then increasing physical activity and reducing sedentary lifestyle are recommended. If the lipid concentration does not reach the target level despite these lifestyle modifications and dietary changes, drug treatment is considered [29].

The goal of hyper-LDL cholesterol treatment in children and adolescents is to maintain it below the 95th percentile (≤ 130 mg/dL) [19]. In children at a high risk of atherosclerosis, such as individuals with chronic kidney disease, type 1 and type 2 DM, Kawasaki disease with coronary aneurysm, and heart transplantation, drug therapy to reduce LDL cholesterol should be considered [40]. Children with HoFH and LDL cholesterol > 500 mg/dL should undergo LDL separation every 2 weeks [29].

For patients aged 10 years or older, statins, fibrates, or niacin may be considered if non-HDL cholesterol is ≥ 145 mg/dL, even if LDL cholesterol is within the target range [24]. For hypertriglyceridemia, when the TG is 200–499 mg/dL and non-HDL cholesterol is ≥ 145 mg/dL, intake of omega-3 fatty acids can be increased along with lifestyle control, but there are still concerns about safety due to insufficient studies in children [41]. The main effects of current dyslipidemia treatments are summarized in Table 6 [24,36]. Statins and acid-binding resins are currently the main drugs used for the treatment of dyslipidemia in children.

Statin are approved for use in children over 10 years of age by the U.S. Food and Drug Administration (FDA) and are the initial treatment of choice for children with elevated LDL cholesterol or non-HDL cholesterol levels. Statins reduce intracellular cholesterol levels by inhibiting hydroxymethylglutaryl coenzyme A reductase, the rate-limiting enzyme in the synthesis of cholesterol, and decrease LDL cholesterol levels by upregulating LDL receptors [42]. Statins should be started at the lowest dose administered once daily. The target level of LDL cholesterol is < 130 mg/dL, and it is ideally maintained below 110 mg/dL [43]. If the LDL

Table 6. Major effects of current medications for dyslipidemia

Type of medication	Major effects	Adverse effects	Medications	FDA approval in pediatrics
HMG-CoA reductase inhibitors	↓ LDL-C, TG, VLDL synthesis ↑ Hepatic LDL receptors, HDL-C	Increased liver enzyme and creatine kinase, myopathy, rhabdomyolysis	Lovastatin 20–80 mg/day Simvastatin 20–80 mg/day Pravastatin 20–80 mg/day Atorvastatin 5–80 mg/day	Approved
Bile acid sequestrants	↓ LDL-C, bile excretion ↑ TG	Trouble of gastrointestinal tract; gas, bloating, constipation, cramps	Cholestyramine 8–16 g/day Colestipol 2.5–20 g/day Colesevelam 1.25–4.375 g	Evidence-based studies in children are lacking but used in clinical practice
Cholesterol absorption inhibitors	↓ LDL-C ↑ HDL-C	Trouble of gastrointestinal tract, myopathy, headache	Ezetimibe 10 mg/day	Not approved
Fibric acid derivatives	↓ TG ↑ HDL-C	Dyspepsia, constipation, myositis, anemia	Gemfibrozil 1,200 mg/day Fenofibrate 48–145 mg/day	Not approved
Nicotinic acid	↓ TG and LDL-C	Flushing, hepatic toxicity	Niacin 1,000–2,250 mg/day	Not approved
Omega-3-fish oil	↓ TG, VLDL production	Gastrointestinal trouble	DHA 2–4 g (adults)	Not approved

FDA, Food and Drug Administration; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; DHA, docosahexaenoic acid.

cholesterol level does not reach the target level, the dose of the drug can be increased once, and the blood test is repeated after 4 weeks. If the LDL cholesterol level still does not reach the target concentration, the dose may be increased one more time or a bile acid sequestrant or cholesterol absorption inhibitor may be added [44]. Statins have been reported to be effective in reducing cholesterol levels by 20%–50% compared to baseline, have no effect on growth in children, and rarely cause side effects. The side effects of statins include myopathy and elevated liver enzyme levels. Therefore, it is necessary to monitor the levels of alanine aminotransferase, aspartate aminotransferase, and creatinine kinase every 3–6 months [45]. Hazardous liver enzyme levels are more than three times higher than the upper limit of normal levels. The risk of muscle toxicity is more than 10 times the upper limit of normal creatinine kinase levels, and the effect of physical activity should be considered. If abnormalities are found in blood tests or symptoms are reported, it is observed whether myopathy disappears after discontinuing the drug and follow-up shows a decrease in blood test values after 2 weeks. When abnormal levels are normalized, drug treatment can be started again with close examination [46].

Bile acid sequestrants are drugs that block the reabsorption of cholesterol in enterohepatic circulation. As they are not absorbed systemically, they can be used as a first-line treatment for dyslipidemia in children. However, compliance is poor owing to side effects of the digestive system, such as nausea, diarrhea, and constipation.

Ezetimibe is a cholesterol absorption inhibitor that reduces bile reabsorption and cholesterol absorption in enterohepatic circulation. This drug is approved for use as an adjuvant in children aged ≥ 10 years. In adult studies, ezetimibe has been reported to lower LDL cholesterol levels by 20%; however, studies in children and adolescents are not yet sufficient [47]. There have been no studies on the use of cholesterol absorption inhibitors as monotherapy in children and adolescents. In children aged 10–17 years with FH, the combined administration of simvastatin and ezetimibe resulted in a greater reduction in LDL cholesterol than simvastatin alone [48]. Niacin is a drug that increases HDL cholesterol and reduces LDL cholesterol and TG and is only used as an adjuvant treatment. However, niacin is not FDA-approved for pediatric patients with dyslipidemia and presents serious side effects such as flushing, itching, headache, and elevated aminotransferase levels, making it a limited treatment option for adolescents [49]. Fibric acid derivatives lower TG and increase HDL cholesterol. In children, fibrates are used to treat severe hypertriglyceridemia with a risk of acute pancreatitis. Fibrate may increase the therapeutic effect when combined with statins, but may cause rhabdomyolysis and is not approved by the FDA for dyslipidemia in children [41].

Omega-3 fatty acids reduce TG levels and may be considered in treatment of hypertriglyceridemia, but data on their effectiveness in pediatric patients are limited and are not FDA-approved for the treatment of pediatric dyslipidemia [50].

Conclusion

Atherosclerosis can begin in childhood and is associated with CVD onset in adulthood. Therefore, early detection and appropriate management of dyslipidemia in children and adolescents is the optimal way to reduce CV morbidity in adults. Clinical practice guidelines for dyslipidemia in children and adolescents have been developed to help clinicians reduce unnecessary care variability and to improve outcomes when managing dyslipidemia. Non-HDL cholesterol assessment, presented as a universal screening method for dyslipidemia in children, is a screening test that does not require fasting and is inexpensive; therefore, it can be conveniently performed

by pediatricians in the clinic. For these guidelines to be implemented in practice, clinicians should be alert and pay close attention to the risk of dyslipidemia in children and adolescents. Research on dyslipidemia in children and adolescents should be continued, and the development of updated clinical guidelines based on accumulated evidence is necessary.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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