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Chapter

Statin Therapy in Children

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Abstract

Landmark studies such as the Bogalusa Heart study, Pathobiological Determinants of Atherosclerosis in Youth study, and Muscatine and Young Finns studies established that the atherosclerotic process begins in childhood. Early precursors of atherosclerosis may increase risk of cardiovascular morbidity in adulthood. Follow-up studies of children with familial homozygous hypercholesterolemia showed that initiation of statin therapy slowed the progression of carotid intima-media thickness and reduced cardiovascular disease risk. Despite the growing evidence on the efficacy of statins and a rising prevalence of dyslipidemia, there are concerns regarding long-term safety and efficacy. Moreover, data on statin use in children with secondary dyslipidemia are sparse. This chapter provides a comprehensive review of the current state of literature on the indications, contraindications, efficacy and safety data on the use of statins in pediatric dyslipidemia.

Keywords: pediatric dyslipidemia, HMG Co-A reductase inhibitors, low-density lipoprotein cholesterol, cardiovascular risk factors

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in the United States [1]. Atherosclerosis, a silent precursor of CVD has its origins from early in childhood [2, 3]. Some dyslipidemias such as familial hypercholesterolemia (FH) and familial combined hyperlipidemia (FCH) are highly prevalent clinically silent disorders. Elevated lipid levels in childhood track well into adulthood [4]. In 2011, the National Heart, Lung, and Blood Institute (NHLBI) convened an expert panel on Cardiovascular Health and Risk Reduction in Children and Adolescents, which recommended for universal lipid screening in the pediatric population [5]. The universal lipid screening leads to identification of a large number of children with previously unrecognized dyslipidemia. Statins are one of the most potent classes of lipid lowering medications for CV risk reduction. This chapter describes the current screening and management guidelines, efficacy and adverse effects of statin therapy in pediatric dyslipidemia.

1.1 Mechanism of action of statins

The primary mechanism of action of statins is inhibition of the enzyme-3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This is a rate-limiting step in the biosynthesis of cholesterol. Reduced intrahepatic cholesterol leads to decreased VLDL assembly. The hepatocyte cholesterol depletion leads to upregulation of sterol regulatory binding element proteins (SREBPs), the nuclear transcription factors that regulate LDL receptors (LDL-R). Upregulation of LDL-R

on the surface of the hepatocyte in turn results in increased uptake and degradation of low-density lipoprotein cholesterol (LDL) [6]. They reduce the secretion of apoB, which affects the rate at which HMG CoA reductase is available to synthesize cholesterol again [7].

Statins induce inhibition of the Rho-signaling pathway, activate peroxisome proliferator-activated receptor alpha (PPARα) and improve HDL levels by increased production of apoA-I, the major apolipoprotein of HDL [8, 9]. Decrease in isoprenylation of signaling molecules, such as Ras, Rho, and Rac, leads to the modulation of various signaling pathways. By inhibiting mevalonic acid synthesis, statins prevent the synthesis of isoprenoid intermediates farnesyl pyrophosphate and geranyl geranylpyrophosphate [10]. It has been long established that a pro-inflammatory environment is necessary for plaque progression and advancement of atherosclerosis, and these intermediates are known to have a pro-inflammatory effect. Statins can inhibit posttranslational modification of Ras and Rho, which regulate cell proliferation, differentiation, apoptosis, and the cytoskeletal modifications [11]. Statins have also been proposed to be beneficial to prevent progression of atherosclerosis by their pleiotropic effect [12]. Experimental models have suggested reduction in T-cell clustering with the use of statins, thereby proposing an immunomodulatory effect [13].

1.2 Risk factors and medical conditions

Table 1 lists the medical risk factors and conditions to be considered while screening for dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. The terminology from this table will be used throughout the chapter.

1.3 Current screening recommendations for pediatric dyslipidemia

Although the atherosclerotic process begins in childhood, most pediatric lipid disorders do not have any obvious clinical manifestations [2, 3]. Screening based on family history alone can miss up to 30–60% dyslipidemias [5, 14]. In higher risk

Positive family history: parent, grandparent, aunt, uncle, sibling with any of these before the age 55 Y in a male or 65 Y in a female: myocardial infarction, stroke, angina, coronary artery bypass, stent, angioplasty, sudden cardiac death, parent with total cholesterol >240 mg/dL	
High risk factors: • Hypertension requiring drug therapy (BP ≥ 99th% ile + 5 mmHg) • Current cigarette smoker • BMI ≥ 97th%ile	**Moderate risk factors**: • Hypertension not requiring drug therapy • BMI ≥ 95th%ile, < 97th%ile • HDL–C < 40 mg/dL
High risk medical conditions: • Diabetes mellitus, type 1 and type 2 • Chronic renal disease/end-stage renal disease/ postrenal transplant • Postorthotopic heart transplant • Kawasaki disease with current aneurysms	**Moderate risk medical conditions**: • Kawasaki disease with regressed coronary aneurysms • Chronic inflammatory disease • Human immunodeficiency virus (HIV) infection • Nephrotic syndrome

Abbreviations: BP, blood pressure; BMI, body mass index.
Adapted from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute 2011.

Table 1.
Cardiovascular risk factors and high-risk medical conditions.

adult patients, especially those with disorders such as FH, statin therapy has been retrospectively associated with reducing risk of major cardiovascular events [15]. In the absence of clear history or physical examination findings, recognition of children with lipid disorders needs universal screening. The United States NHLBI, the American Academy of Pediatrics and the American Heart Association have all endorsed selective risk based screening and universal screening [5, 16, 17]. International Organizations such as the European Atherosclerosis Society recommend selective and cascade screening [18]. In contrast, the United States Preventive Services Task Force (USPSTF) concluded that current evidence is insufficient to assess the benefits or harms of screening for lipid disorders in children and adolescents, even though it acknowledges the importance of early identification of dyslipidemias [19]. For many CV risk factors like dyslipidemia, hypertension, and obesity, it is difficult to conduct large, long-term studies because of the time, cost and expected difficulties in study adherence. Recently, relatively long term follow up studies indicated that the initiation of statin therapy during childhood in patients with FH slowed the progression of carotid intima-media thickness and reduced the risk of cardiovascular disease in adulthood [20].

Screening can be performed either with a fasting or non-fasting serum lipid profile. The triglyceride (TG) levels are the most affected component of the lipid profile by non-fasting status. The LDL and non-HDL (TC-HDL) are mostly unaffected by the non-fasting status and can therefore be used for screening purposes [21, 22]. Cholesterol and LDL tend to increase until 2 years and plateau until adolescence. A 10–20% reduction of TC and LDL occurs in both normal children as well as children with genetic dyslipidemias during puberty, and can result in false negatives during this time [23]. Therefore, it is important to universally screen for lipid disorders between ages 9–11 Y and repeat between ages 17–19 Y. **Table** 2 depicts lipid values very by age, according National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels in Children.

Up to 12 months, no routine screening of lipid profiles is recommended in infancy. Between 2 and 8 Y and 12 and 16 Y, a fasting lipid profile (FLP) is recommended if there is a positive family history, if the child has a moderate or high-risk medical condition or a high risk factor. Between 9 and 11 Y and 17 and 21 Y, universal screening is recommended. If on a non-fasting sample, the non-HDL ≥ 145 mg/dL or HDL < 40 mg/dL, it is recommended to repeat an FLP twice within 2 weeks to 3 months and average the results. Values to address on the FLP

Categories	Acceptable	Borderline high	High
Total cholesterol	<170	171–199	>200
LDL	<110	110–129	≥130
Non-HDL	<120	120–144	≥145
TG (0–9 Y)	<75	75–99	≥100
TG (10–19 Y)	<90	90–129	≥130
HDL	>45	40–45	<40

Abbreviations: TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride.
Values from the National Cholesterol Education Program [24]. All fasting values in mg/dL. To convert to SI units, divide total cholesterol, LDL, HDL, and non-HDL by 38.6, and for TG, divide by 88.6.
High and borderline-high values are indicative of approximately the 95th and 75th percentiles for age.

Table 2.
Lipid values by age.

after averaging the results include LDL ≥ 130 mg/dL, non-HDL ≥ 145 mg/dL, HDL < 40 mg/dL, TG ≥ 100 mg/dL if <10 years; ≥ 130 mg/dL if ≥10 years [5].

1.4 Diagnostic considerations in pediatric dyslipidemia

Dyslipidemia could be primary or secondary. Primary lipid disorders include monogenic conditions like FH or familial hypertriglyceridemia. Some genetic dyslipidemias like FCH do not have a recognized genetic defect yet, and have variable degrees of dyslipidemia and varying patterns of increase of TG and LDL within the same family. Obesity can exacerbate the expression of dyslipidemia in children with this underlying genotype. Lipid disorders could also be secondary to the underlying untreated medical conditions. Some considerations include diabetes mellitus, hypothyroidism, hypercortisolism, metabolic syndrome, growth hormone deficiency, pregnancy, drug and medication use, acute and chronic hepatitis, nephrotic syndrome, chronic kidney disease etc. [25–31].

After ruling out secondary dyslipidemias, primary dyslipidemias are to be considered. Primary lipid disorders can be broadly categorized by the predominantly affected component of the lipid profile. **Table** 3 depicts patterns of inheritance, predominant affected lipoprotein and prevalence in the more commonly encountered primary dyslipidemias. Of these conditions, the most prevalent conditions are heterozygous FH (HeFH 1:300) and FCH (1:100).

1.5 Lifestyle management of dyslipidemia

Dietary management and lifestyle changes are the cornerstone of therapy for many secondary dyslipidemias. A registered dietitian nutritionist is central to implementing lifestyle changes, trained to assess the child's nutritional status and make practical modifications to facilitate behavioral changes. In children and adolescents with obesity, moderate, gradual weight reduction has been shown to improve dyslipidemia and decrease insulin resistance.

The NCEP has proposed a stepwise dietary regulation for children with elevated LDL levels. For all children more than 1 year of age and older, the Cardiovascular Health Integrated Lifestyle Diet (CHILD)-1 diet is the first step (Step 1 diet); this constitutes total fat (25–30% of total daily calories), saturated fat (8–10% of daily kcal/estimated energy requirements), avoiding trans-fat, <300 mg/day from cholesterol, dietary fiber (14 g/1000 kcal), fat-free unflavored milk, limiting sodium intake and sweetened juice (no added sugar) <120 mL/day. Polyunsaturated fatty acids up to 10% of daily calories, and monounsaturated fatty acid intake of 10–15% of daily caloric intake is recommended [5].

If the CHILD-1 modifications do not show the desired lipid changes within 3 months of initiation, the next step is to advance to the CHILD-2 diet (Step 2 diet), which further restricts saturated fat. The CHILD-2 diet consists of 25–30% of total calories from fat, <7% from saturated fat, <10% from monounsaturated fat, and avoiding trans-fat. The CHILD-2 diet specific for LDL lowering (CHILD-2-LDL) also recommends use of fiber supplementation and plant stanols/sterols: plant sterol and stanol esters up to 2 g/day, water-soluble fiber psyllium, dose of 6 g/day (2–12 years) and 12 g/day (>12 years). The CHILD 2 diet specific to TG lowering (CHILD-2-TG) recommends decreasing sugar and sugar-sweetened beverages, replacing simple with complex carbohydrates, and increasing dietary fish to increase omega-3 fatty acid intake [5].

The expert panel also recommends at least 1 h of moderate-to vigorous physical activity every day of the week, with vigorous, intense physical activity on at least 3

Name	Genetic defect	Pattern of inheritance	Incidence	Lipid profile/lipoprotein pattern
Disorders with elevated LDL				
Familial homozygous hypercholesterolemia	LDL-R Gain of function PCSK9 Familial defective apo B-*100*	AD	1:1,000,000	↑↑ ↑ TC ↑ ↑ LDL
Familial heterozygous hypercholesterolemia	Same as above	AR	1:300–400	↑ TC ↑ LDL
Autosomal recessive hypercholesterolemia	LDL-R Adaptor protein	AR	<1:1,000,000	↑ TC ↑ LDL
Sitosterolemia	*ABCG5* *ABCG8*	AR	<1:1,000,000	↑ TC ↑ LDL ↑ serum sitosterol, campesterol
Lysosomal acid lipase deficiency	LIPA gene defect	AR	1:40,000–300,000	↑ LDL
Cholesterol 7α-Hydroxylase deficiency	CYP7A1 gene	Semi-dominant	<1:1,000,000	↑ TC ↑ LDL ↑TG
Familial combined hyperlipidemia	Unknown	AD	1:100–200	↑ TC ↑ LDL ↑VLDL ↑TG, Chylomicrons, ↑ VLDL remnants
Dysbetalipoproteinemia	apoE	AR	1:5000	↑ ↑ TC ↑ ↑ LDL ↑↑ IDL ↑↑ TG ↑ Chylomicrons
Disorders with elevated TG				
Familial hypertriglyceridemia	Unknown	AD	1:500	↑ TC ↑↑ TG
Familial chylomicronemia	LPL deficiency apoC-II deficiency apoA5 and *GPIHBP1* loss-of-function	AR	1 out of 1,000,000	↑ TC ↑↑↑ TG
Disorders with reduced HDL				
Hypoalphalipoproteinemia	APOA1	AD	<1:1,000,000	↓ HDL ↓ or normal TG
Tangier disease	ABCA1	AR	<1:1,000,000	↓ HDL normal or ↑ TG
Lecithin cholesterol acyl transferase deficiency	*LCAT* (16q22.1)	AR	<1:1,000,000	↓ HDL

Abbreviations: TC, total cholesterol; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; TG, triglyceride; AD, autosomal dominant; AR, autosomal recessive; LDL-R, LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; apoB, apolipoprotein; ABCG, ATP-binding cassette sub-family G member; LIPA, lysosomal acid lipase type A; LPL, lipoprotein lipase; GPIHBP1, *glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1;* LCAT, *lecithin cholesterol acyl transferase.*

Table 3.
Characteristic features of primary dyslipidemias.

of these days in agreement with the 2008 Physical Activity Guidelines for Americans from the U.S. [5].

1.6 Laboratory evaluations prior to statin therapy

Suggested serum testing prior to initiation of statin therapy include testing to rule out secondary causes of dyslipidemia—serum albumin, blood glucose level or

hemoglobin A1C, renal function tests, serum thyroid-stimulating hormone, free T4 concentration, and a pregnancy screen. These tests are to be done as deemed clinically necessary. Liver function studies, serum creatinine kinase (CK) levels are useful to obtain at baseline to monitor for future potential adverse effects.

1.7 Indications for statin therapy in pediatrics

Children with average LDL-C ≥ 190 mg/dL have a high likelihood of FH and almost certainly require pharmacotherapy, as diet and exercise modifications can maximally reduce lipids by ~10–20% [32]. Fasting TG level of ≥500 mg/dL (which may indicate postprandial elevations to >1000 mg/dL and risk of pancreatitis) are also best referred and managed by a lipid specialist. Referral may ultimately be required if LDL levels remain elevated beyond ≥160 mg/dL despite 6 months of lifestyle interventions. Once the lipid profile has been repeated within a 2 week to 3-month period, the following average values currently are recommended to start statin therapy concomitantly with diet and lifestyle modifications.

In children <10 years of age:

- Homozygous familial hypercholesterolemia (HoFH) with LDL typically above 400 mg/dL
- CVD within the first two decades of life/post cardiac transplantation
- LDL ≥190 mg/dL + positive family history, OR 1 high risk factor/condition, OR 2 moderate risk factors/conditions

In children ≥10 years:

- LDL ≥ 190 mg/dL
- LDL ≥ 160 mg/dL + positive family history, OR 1 high risk factor/condition, OR 2 moderate risk factors/conditions
- LDL ≥130 mg/dL + 2 high risk factors/conditions, OR 1 high risk factor/condition and 2 moderate risk factors/conditions, OR clinical CVD

1.8 Expected effects of statin therapy

Aside from PCSK9 inhibitors, statins are the most potent class of lipid lowering agents. The expected effects of statin therapy on TC and LDL levels are dependent on their potency and dosing. Most statins have a mild effect on increasing HDL by 2–5%, and on decreasing TG levels by up to 40%. **Table** 4 outlines the starting dosing, properties and potency by expected effects on LDL reduction of some of the commonly used statins in pediatrics. Although the statins with longer half-lives inhibit the enzyme for a longer time, even with statins that have a shorter half-life are effective at reducing the LDL levels because they reduce overall serum levels of lipoproteins with a half-life of approximately 2–3 days. For this reason, all statins can be administered in once a day dosing. The general principal behind statin therapy in pediatrics is to use the lowest effective doses of a statin. Currently, the maximum daily dose studied in pediatrics is for 40 mg of lovastatin, pravastatin, and simvastatin; 20 mg of atorvastatin and rosuvastatin; and 80 mg of fluvastatin.

Statin	Typical dose (mg)	Maximum dose (mg)	Half-life (h)	Lipophilicity	Fecal excretion (%)	Renal excretion (%)	Effect on LDL reduction (%)
Atorvastatin	5–10	80	15–30	Lipophilic	>98	<2	38–54
Fluvastatin	20	80	0.5–2.3	Lipophilic	93	6	17–33
Lovastatin	10	80	2.9	Lipophilic	83	10	29–48
Pravastatin	5–20	40	1.3–2.8	Hydrophilic	70	20	19–40
Rosuvastatin	5–10	40	19	Hydrophilic	90	10	52–63
Simvastatin	5–10	40	2–3	Lipophilic	60	13	28–41

Abbreviation: LDL, low-density lipoprotein cholesterol.

Table 4.
Starting doses and properties of statin drug therapy.

In the United States, pravastatin and pitavastatin have FDA approval for children age ≥ 8 years with HeFH. Lovastatin, simvastatin, fluvastatin, atorvastatin and rosuvastatin have been approved for children ≥10 years with FH. At the higher prescribed doses, atorvastatin and rosuvastatin are more potent than the other approved medications [33]. Key randomized clinical trials for each of these statins in the order of approval for pediatric use are summarized in **Table** 5.

1.9 Special considerations for high-risk conditions

As diabetes is considered a CV risk factor, intensive lipid management is suggested for these patients. In addition to maintaining the best glycemic control possible, the American Diabetes Association recommends starting treatment with statins for LDL ≥ 160 mg/dL and considering treatment for LDL ≥ 130 mg/dL with additional risk factors basing the treatment decision on the child's complete CVD risk profile, including assessment of blood pressure, family history, and smoking status with a goal of lowering LDL to under 100 mg/dL [48].

In nephrotic syndrome, chronic kidney disease and polycystic ovarian syndrome as well LDL ≥ 160 mg/dL maybe a threshold for initiating statin treatment in addition to adequate mediation therapy for the underlying condition, lifestyle and diet therapy. In Kawasaki disease, patients >2 years old without persistent coronary artery abnormalities should undergo lipid screening 1 year after the acute phase, and if normal, universal screening can be considered. Patients with coronary artery aneurysms should undergo annual screening and treated for levels ≥160 mg/dL.

1.10 Challenges in pediatric dosing

Thus far, statins are only available in pill form. With the exception of simvastatin oral suspension, other liquid preparations or flavoring are not readily available which maybe an issue for children with sensory issues or difficulty swallowing a pill. A disintegrating formulation of simvastatin is available, and this may be helpful in younger children. Although compounding the medication at local pharmacies is an option, several logistical issues limit this accessibility. Some of the extended release preparations such as Lovastatin and fluvastatin are rarely used in children, and should not be crushed. Fluvastatin is available as a capsule but the contents are not to be separated per manufacturer's instructions.

Group	Study design	Test group	N	Age	Condition	Duration	Outcomes
				Atorvastatin			
McCrindle et al. [34]	Placebo controlled RCT	10−20 mg	187	10–17 Y	HeFH or severe hypercholesterolemia	6 months	TC ↓ 32% LDL ↓ 40% TG ↓ 12% ApoB ↓ 34% HDL ↑ 2.8%
Gandelman et al. [35]	No	5–10 mg	39	6–10 Y (TS 1) 10–18 Y (TS 2)	HeFH	8 weeks	TC ↓ 34.1–35.6% LDL ↓ 40.7–39.7% TG ↓ 6–21.1%
Canas et al. [36]	Placebo controlled RCT	10–20 mg	42	10–20Y	T1D	6 months	TC ↓ 21% LDL ↓ 32% Non-HDL ↓ 31% ApoB ↓ 26%
Langslet et al. [37]	No	5 mg or 10 mg, ↑ up to 80 mg	272	6–15 Y	HeFH	3 years	LDL ↓ 43.8% TS 1 and 39.9% for TS ≥2
				Fluvastatin			
Van der Graaf et al. [38]	No—single arm study	80 mg	85	10–16 Y	HeFH	2 years	TC ↓ 27.1% LDL ↓ 33.9% TG ↓ 5.3% ApoB ↓ 24.2%
				Lovastatin			
Lambert et al. [39]	Controlled multicenter RCT	10, 20, 30 and 40 mg doses	69	<17Y (boys only)	FH	8 weeks	TC ↓ 17–29% LDL ↓ 21–36% ApoB ↓ 19–28%
Stein et al. [40]	Placebo controlled RCT	10, 20 and 40 mg	132	10–17 Y (boys only)	HeFH	1 year	TC ↓ 13, 19 and 21% LDL ↓ 17%, 24 and 27% TG ↓ 4, 8 and 6% ApoB ↓ 23% (in 40 mg/d)
Claus et al. [41]	Placebo controlled RCT	20 mg for 4 weeks, then 40 mg	54	10–17 Y (girls only)	HeFH	24 weeks	TC ↓ 17–22% LDL ↓ 23–27% ApoB ↓ 20–23%

Group	Study design	Test group	N	Age	Condition	Duration	Outcomes
				Pravastatin			
Knipscheer et al. [42]	Placebo controlled RCT	5, 10 and 20 mg	72	8–16 Y	FH	12 weeks	TC ↓ 24.6% LDL ↓ 32.9% ApoB ↓ 26.8% HDL ↑ 10.8%
				Rosuvastatin			
Avis et al. [43]	Placebo controlled RCT	5, 10 and 20 mg	177	10–17 Y	FH	52 weeks	TC ↓ 27.1% LDL ↓ 33.9% TG ↓ 5.3% ApoB ↓ 24.2%
Braamskamp et al. [44]	Open label multicenter intention to treat analysis	5–20 mg	197	6–17 Y	HeFH	24 months	TC ↓ 32% LDL ↓ 43% TG ↓ 5% ApoB ↓ 36% Most adverse events mild
Stein et al. [45]	Placebo controlled cross over RCT	20 mg	13	7–15 Y	HoFH	24 weeks	Reduction of 22.3% LDL on rosuvastatin versus placebo with apheresis or ezetimibe
				Simvastatin			
de Jongh et al. [46]	Placebo controlled RCT	10–40 mg	50	9–18 Y	FH	28 weeks	TC ↓ 30% LDL ↓ 39.8% TG ↓ 16.7% FMD improved in simvastatin group
García-de-la-Puente [47]	Placebo controlled cross over RCT	5–10 mg	25	4–17 Y	Hyperlipidemia secondary to renal disease	6 months	TC ↓ 23.3.4% LDL ↓ 33.1% TG ↓ 21%

Abbreviations: TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; apoB, apolipoprotein B; N, number of participants; Y, years; HoFH, familial homozygous hypercholesterolemia; HeFH, familial heterozygous hypercholesterolemia; FH, familial hypercholesterolemia; RCT, randomized control trial; TS, tanner stage; mg, milligram; T1D, Type 1 diabetes mellitus.

Table 5.
Prominent pediatric clinical trials with lipid lowering effects of statins.

1.11 Considerations for statin bioavailability

1.11.1 Factors affecting absorption

Recently, ontogenic and genetic factors have been described as potential variables influencing systemic availability of statins [49]. As statins are orally delivered, the gastric milieu and intestinal transport can have effects on the efficacy, and may have population and individual level variability in efficacy. Influx transport proteins such as OATP1A2 and OATP2B1, which are pH dependent, are shown to have an effect at the level of the enterocyte for absorption of statins [50]. Variations in MRP2 (*ABCC2* c.1446C>G), an efflux transporter has been shown to decrease the bioavailability of pravastatin [51]. Co-ingesting statins with food has also shown to have some variability in bioavailability that affects some statins more than others. For instance, absorption of fluvastatin, pravastatin and rosuvastatin is delayed when taken with food [52–55]. In contrast, package inserts of lovastatin state that levels are lower when administered under fasting conditions. Timing of food intake appears to have no effect on simvastatin.

Timing of administration has also shown to have some effect on bioavailability. This is due to multiple factors including diurnal cholesterol biosynthesis peak at nighttime and early morning and possibly the difference in gastric emptying, absorption and distribution. Reduction in both peak concentration as well as overall area under the curve (AUC) distribution have been described with evening administration of pravastatin and atorvastatin [56, 57]. Fluvastatin concentrations have been reportedly higher when dosed in the evening [58] while rosuvastatin remained unaffected [59]. Although statins are best given in the evening to coincide with the peak cholesterol biosynthesis at night, and the long-acting statins, atorvastatin and rosuvastatin, may be given any time, in clinical practice, the difference in efficacy in relation to the timing is negligible.

As with most oral medications, first pass metabolism is another factor with the potential to influence bioavailability and toxicity. Depending upon the statin, when the enterocyte is the level at which first-pass occurs, the bioavailability may be reduced, reducing toxicity but overall efficacy as well. If the first pass occurs at the level of the liver, since the hepatocytes are the primary target for the statins, a more favorable risk profile is potentially created. If the hepatocytes have more primary exposure, reduction in systemic availability and increased hepatic exposure should lead to lesser adverse effects while enhancing action at the target organ level, creating a more favorable safety profile [60].

1.11.2 Factors affecting metabolism

Of the multiple cytochromes that have been shown to have *in-vitro* capacity of metabolizing statins, CYP3A4 has been the most important, especially for simvastatin, lovastatin, and atorvastatin [61, 62]. Rosuvastatin is able to strongly inhibit CYP2C9 activity [63]. Clinically, the co-administration of CYP3A4 inhibitors like clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal, grapefruit, etc. can lead to significant elevations in statin levels, and have the risk of higher toxicity. Inducers of CYP3A4 including phenobarbital, phenytoin, rifampicin, St. John's Wort and glucocorticoids can reduce the bioavailability of statins [64].

While considering drug interactions, concomitant administration of other lipid lowering therapy has to be kept in mind, especially for treatment of conditions such as FCH. For instance, gemfibrozil, which is used to lower TG levels, can engage with the OATP1B1-mediated transport of the statin into the hepatocyte and gut

cells. It can also catalyze glucuronidation. The net effect is these interactions are a higher concentration of systemic statin level and a greater risk of adverse effects [62, 65].

1.11.3 Factors affecting elimination

Elimination can be significantly impacted by half-lives as mentioned in **Table** 4. Some statins including atorvastatin and simvastatin undergo conjugation while pravastatin, rosuvastatin, and pitavastatin do not undergo extensive conjugation. Biliary excretion of the UGT-conjugated statins occurs through—multidrug resistance 1 (MDR1; *ABCB1*), multidrug resistance-associated protein 2 (MRP2; *ABCC2*), breast cancer resistance protein (BCRP; *ABCG2*), bile salt exporting pump (BSEP; *ABCB11*) [60]. Although these efflux transporters have had *in vitro* effects, the *in vivo* effects of variants of these transporters are not well studied. Renal clearance is less significant than the biliary elimination of statins [55, 66, 67]. Of the statins, pravastatin is the most renally cleared at around 20% [68].

1.12 Adverse effects of statin therapy

Of all the classes of lipid lowering medications, statins are best tolerated with least reported adverse events [69]. The safety profile of statins has been well studied in adults. Most studies studying the safety and efficacy of statins are in children with FH. The most commonly reported side effects including muscle related adverse events and hepatic transaminase occur relatively infrequently. When statin treatment was starting to be recommended as young as 8 years of age, there were fair concerns about the effects on cognition, growth and development, metabolic rate with potential for decades of exposure to this medication.

Multiple studies have shown no adverse effects of statins on growth and sexual maturation [70]. In addressing the overall safety profile of statins, a recent meta-analysis showed that statin treatment was effective for treating FH, with a good short-term safety profile [69]. The 10- and 20-year follow-up studies on the use of statins in pediatric dyslipidemias did not report significant serious adverse events [20, 71]. There is a dearth of large long-term randomized controlled trials to establish the long-term safety issues of statins.

1.12.1 Rhabdomyolysis/myopathy

Lipophilic statins are more prone to causing myopathy as they attain greater intramuscular concentrations compared to hydrophilic statins. Pravastatin and rosuvastatin are hydrophilic, others are lipophilic. However, fluvastatin, a lipophilic statin has reportedly lower side muscle-related side effects. Non-specific muscle aches and weakness has been described with all the statins. An extensive systematic review on statin safety in adults determined rhabdomyolysis to be rare at 3 per 100,000 person-years for atorvastatin, simvastatin, lovastatin, pravastatin, and fluvastatin [72]. In children, three large systematic reviews did not find any difference between the statin group and control group for rhabdomyolysis (CK levels increased 10 fold from upper limit of normal) [69, 73, 74]. *Clinically important rhabdomyolysis* is evidence of muscle cell destruction or enzyme leakage, regardless of the CK level, considered to be causally related to a change in renal function. In practice, when CK levels are up trending and elevated to >10 upper limit of normal, with or without co-existent myoglobinuria and/or renal injury, it is recommended to stop the statin [75]. Given that this is a rare side effect, common causes including exercise, cold exposure, trauma, seizures, hypothyroidism, recent infections/myositis,

autoimmune etiologies etc. need to be considered. Therapy can be commenced, preferably with a different statin when the CK levels normalize.

Statin induced myopathy is exceedingly rare in children with FH. In adults, myopathy, which includes myalgia and an increase in serum CK levels, occurs in approximately 0.1–1% of patients using statins. The risk factors associated with this are concomitant renal insufficiency, hepatic dysfunction, hypothyroidism, polypharmacy and intake of CYP3A4 inhibitors [76]. Of the reported cases, a co-existent polymorphism in SLCO1B1 resulting in decreased transport of statins into the hepatocytes, thereby increasing systemic toxicity was discovered, especially with lipophilic statins like simvastatin. Statin induced myopathy was 4.5 and 16.9 times more likely in heterozygote and homozygote carriers with this polymorphism [77].

1.12.2 Hepatic dysfunction

This is a rare side effect in statins, and in adult studies, the overall incidence of persistent transaminase elevation is considered to be about 0.5–3%. The Scandinavian Simvastatin Survival Study as well as the Heart Protection Study Collaboration group, as well as the Air Force/Texas Coronary Atherosclerosis Prevention Study, which were large randomized trials that studied simvastatin and lovastatin in large populations did not find significant differences in persistent hepatic transaminases between statin and placebo therapy in adults [78–80]. In children, three large systematic reviews did not find any difference between the statin group and control group for incidence of transaminitis (over 3-fold increase in alanine transferase or aspartate aminotransferase) [69, 73, 74].

Previously, patients receiving statins routinely measured liver function studies for monitoring transaminase elevation. In 2012, the FDA withdrew this requirement, and in practice, liver enzymes are measured as clinically needed. The examiner should inform the patient/parent to report symptoms of jaundice, malaise and fatigue as a sign of potential hepatotoxicity. In practice, if transaminase levels are found to be greater than 3 times the baseline either in symptomatic patients or during routine evaluation, the test should be repeated and other etiologies ruled out as well, given the rare incidence. During the work up process, one should consider discontinuation or dose reduction based on the presentation. Currently, the benefit of statin therapy far outweighs the risk of liver- and muscle-related adverse events.

1.12.3 Teratogenicity/need for contraception

Traditionally, animal studies have shown the potential of teratogenicity with statins due to disruption of cholesterol synthesis [81, 82]. Human studies in this regard are lacking, and the data we have so far is derived mostly from small cohort studies and case reports [83]. Contrastingly, some cohort studies did not find a significant teratogenic effect from maternal use of statins in the first trimester [84]. A meta-analysis of 6 controlled studies including a total of 618 women failed to find an increase in the risk of birth defects [85]. Many of these studies, however, were small, short term and insufficiently powered, making it difficult to generalize the results. At this time, women of childbearing age, as well as pubertal girls should be advised about concerns of teratogenicity with statin use in pregnancy, and counseled on the importance of concomitant contraceptive use.

1.12.4 Risk of type 2 diabetes mellitus (T2DM)

One of the concerning long-term side effects of statin treatment in children has been the higher risk of developing T2DM. A meta-analysis of RCTs in ~91,000

adult patients showed that statin therapy was associated with a 9% increase in the incidence of T2DM. Although there was a slightly increased risk of development of diabetes, the absolute risk as well as the comparative risk when measured against risk of coronary risk reduction was low [86]. In contrast, other studies in patients with FH treated with statins did not show a higher risk [87]. In pediatrics, the available data have been mostly reassuring, with two large 10- and 20-year follow-up studies not showing a significant increase in the incidence of T2DM when compared to the general population incidence [20, 71].

1.12.5 Concerns for non-specific effects on reduced cholesterol synthesis

Cholesterol is utilized by ubiquitously, and has a number of biological functions in other cells in the body; therefore, many non-hepatic cells also are capable of synthesizing LDL-R for uptake of cholesterol. Cholesterol is a precursor for both steroid and sex hormones. However, the use of statins has not been associated with adverse effects on the production of hormones that depend on normal sterol level availability, for instance, the adrenal hormones [74]. Fetal and neonatal cholesterol levels are lower, suggesting that an optimal homeostatic mechanism exists in which even during periods of high metabolic demand, lower levels of cholesterol are sufficient to support normal biological function [88]. Although some variations in dehydroepiandrosterone sulfate (DHEAS) and luteinizing hormone (LH) levels are reported in the literature, these differences were too small to have clinical relevance, given that the studied children did not have any growth or pubertal abnormalities [74].

2. Conclusions

Pediatric dyslipidemia could be due to monogenic, secondary or polygenic causes. Fatty plaques, the precursors of atherosclerosis and exposure to cardiovascular risk factors begin in childhood and progress into adulthood. All children with dyslipidemia benefit from diet and lifestyle modifications but the effect is limited in children with markedly elevated LDL levels. Statins are first line pharmacotherapeutic agents for elevated LDL concentrations with a favorable safety profile and robust short-term data with benefits outweighing the risks. Long-term data are needed in children to better understand the safety and efficacy of these medications.

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

BP	blood pressure
BMI	body mass index
TC	total cholesterol
LDL	low density lipoprotein cholesterol
HDL	high density lipoprotein cholesterol
TG	triglyceride
AD	autosomal dominant

AR	autosomal recessive
LDL-R	LDL receptor
NHLBI	National Heart Lung and Blood Institute
NCEP	National Cholesterol Education program
USPSTF	United States Preventive Services Task Force
HoFH	familial homozygous hypercholesterolemia
HeFH	familial heterozygous hypercholesterolemia
FCH	familial combined hyperlipidemia
HMG-CoA reductase	3-hydroxy-3-methylglutaryl-coenzyme A reductase
PCSK9	proprotein convertase subtilisin/kexin type 9
apoB	apolipoprotein
ABCG	ATP-binding cassette sub-family G member
LIPA	lysosomal acid lipase type A
LPL	lipoprotein lipase
GPIHBP1	glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1
LCAT	lecithin cholesterol acyl transferase
CVD	cardiovascular disease
CK	creatinine kinase

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