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Focused Clinical Practice Update

The Detection, Evaluation, and Management of Dyslipidemia in Children and Adolescents: A Canadian Cardiovascular Society/Canadian Pediatric Cardiology Association Clinical Practice Update

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ABSTRACT

Atherosclerosis begins in youth and is directly linked with the presence and severity of cardiovascular risk factors, including dyslipidemia. Thus, the timely identification and management of dyslipidemia in childhood might slow atherosclerotic progression and decrease the risk of cardiovascular disease in adulthood. This is particularly true for children with genetic disorders resulting in marked dyslipidemia, including familial hypercholesterolemia, which remains frequently undiagnosed. Universal and cascade screening strategies can effectively identify cases of pediatric dyslipidemia. In the clinical evaluation

RÉSUMÉ

L'athérosclérose commence chez les jeunes et est directement liée à la présence et à la gravité des facteurs de risque cardiovasculaire, dont la dyslipidémie. Ainsi, l'identification et la gestion opportunes de la dyslipidémie durant l'enfance pourraient ralentir la progression de l'athérosclérose et diminuer le risque de maladie cardiovasculaire à l'âge adulte. Cela est particulièrement vrai pour les enfants atteints de troubles génétiques entraînant une dyslipidémie marquée, notamment l'hypercholestérolémie familiale, qui reste fréquemment non diagnostiquée. Les stratégies de dépistage universel et en cascade

Atherosclerosis, the pathobiological basis of cardiovascular (CV) disease (CVD), begins in youth and is directly linked with the presence and severity of CV risk factors, such as dyslipidemia.[1,2] Timely identification and management of dyslipidemia in childhood is imperative, particularly for at-risk populations, including in those with severe and lifelong dyslipidemias due to inherited lipid disorders such as familial hypercholesterolemia (FH). This Canadian Cardiovascular Society clinical practice update provides an approach to the detection, evaluation, and management of pediatric dyslipidemia. The evidence base supporting the rationale for identifying and treating pediatric lipid disorders is emphasized and existing knowledge gaps are highlighted. Expert opinions by the writing group are provided throughout and are summarized along with key points in Table 1. This clinical practice update has been endorsed by the Canadian Pediatric Cardiology Association.

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See page 1178 for disclosure information.

Definition, Epidemiology, and Genetics

Dyslipidemia is seen with increasing prevalence in young Canadians. Pediatric dyslipidemias can result either from inherited factors, including several monogenic (ie, single-gene

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of children with dyslipidemia, evaluating for secondary causes of dyslipidemia, including medications and systemic disorders is essential. The first line therapy generally centres around lifestyle modifications, with dietary changes specific to the dyslipidemia phenotype. Indications for medication depend on the severity of dyslipidemia and an individualized assessment of cardiovascular risk. Despite an expanding evidence base supporting the detection and timely management of pediatric dyslipidemia, numerous knowledge gaps remain, including a sufficient evidence base to support more widespread screening, thresholds for initiation of pharmacotherapy, and treatment targets. Further studies on the most appropriate age for statin initiation and long-term safety studies of statin use in youth are also required. The most pressing matter, however, is the development of knowledge translation strategies to improve the screening and detection of lipid disorders in Canadian youth.

peuvent identifier efficacement des cas de dyslipidémie pédiatrique. Dans le cadre de l'évaluation clinique d'enfants atteints de dyslipidémie, il est essentiel de rechercher les causes secondaires de la dyslipidémie, notamment la médication et les troubles systémiques. Le traitement de première intention est généralement axé sur la modification du mode de vie, avec des changements diététiques adaptés au phénotype de la dyslipidémie. Les indications pour la médication dépendent de la gravité de la dyslipidémie et d'une évaluation individuelle du risque cardiovasculaire. Malgré l'enrichissement de la base de données probantes soutenant la détection et la prise en charge opportune de la dyslipidémie pédiatrique, de nombreux manques persistent, incluant une base de données probantes de taille suffisante pour soutenir un dépistage plus répandu, l'établissement des seuils d'initiation de la pharmacothérapie et les objectifs de traitement. D'autres études portant sur l'âge le plus approprié pour l'initiation des statines et des études sur la sécurité à long terme de l'utilisation des statines chez les jeunes sont également nécessaires. La préoccupation la plus urgente, cependant, demeure l'élaboration de stratégies d'application des connaissances pour améliorer le dépistage et la détection des troubles lipidiques chez les jeunes Canadiens.

dyslipidemias), or increasingly from nongenetic factors, particularly poor dietary habits and inactivity.[3] For reference, suggested normative, borderline, and abnormal pediatric lipoprotein levels are provided in Table 2.

There are 25 monogenic dyslipidemias that present in childhood, and the most common are described in Table 3.[4] FH, one of the most common monogenic dyslipidemias in children, is inherited in an autosomal codominant fashion.[5] The heterozygous form has a prevalence of up to 1 in 90 in parts of Quebec, likely due to enrichment in the colonizing ancestral population (founder effect), and a prevalence of approximately 1 in 300 in the rest of Canada, occurring in all ancestries including indigenous people.[6] FH is diagnosed by either genetic testing or using phenotypic criteria (ie, elevated low-density lipoprotein [LDL] cholesterol [LDL-C] plus a family history of elevated LDL-C), premature coronary artery disease (CAD) and/or genetic diagnosis.[6] Numerous definitions for FH exist. An LDL-C cut-point of 4.0 mmol/L has been suggested in children to define definite FH in the presence of a known causative gene mutation. Probable FH is considered at the same LDL-C cut-point of 4.0 mmol/L in the presence of a first-degree relative with high LDL-C or premature atherosclerotic CVD.[7] In children, testing has previously been recommended from age 2 years, or earlier if the much rarer and more severe homozygous form of FH is suspected.[8-10] Despite the ease of diagnosing probable FH, most cases unfortunately remain undiagnosed.[5] Identifying and treating FH early reduces cumulative LDL-C burden (and thus atherosclerotic burden), providing health and socioeconomic benefits.[5,8]

Other primary pediatric dyslipidemias include severe hypertriglyceridemia,[11] combined hyperlipidemia, depressed high-density lipoprotein cholesterol (HDL-C), and elevated lipoprotein(a) (Lp[a]; Table 3). Although some of these have characteristic clinical manifestations that are variably present, pediatric dyslipidemias typically are clinically silent apart from laboratory values and family histories of early onset dyslipidemia and premature CVD.[4] Genetic testing might help diagnose FH and other monogenic dyslipidemias and facilitate cascade screening. It is reasonable to consider genetic testing when a diagnosis of FH or other monogenic dyslipidemias is clinically suspected.[12] It is important to consider, however, that clinical availability of genetic testing, although improving, is not universal, and testing requires necessary personnel with the expertise to accurately interpret the results and counsel the patient and family. Moreover, although genetic testing helps to confirm diagnoses and facilitate cascade screening, it does not, at this time, affect treatment strategy.

Pediatric severe hypertriglyceridemia can be caused by an autosomal recessive (biallelic) disorder associated with reduced function of either lipoprotein lipase or one of its activating proteins or binding partners.[11] Chylomicronemia might also have a polygenic basis in many patients.[8] Combined hyperlipidemia, characterized by elevated triglycerides, LDL-C, and apolipoprotein B, is quite common but is most often polygenic.[11] Drastically reduced HDL-C is a feature of such multisystem syndromic autosomal recessive conditions such as Tangier disease or lecithin cholesterol acyl transferase deficiency.[4] Elevated Lp(a) is strongly genetically determined with a minimal influence of secondary factors.[13] Lp(a) increases the risk of vascular disease in adults and possibly stroke in children and could be measured when there is premature vascular disease without obvious risk factors. However, there currently are no specific approved treatments for elevated Lp(a) in children.[13]

Secondary dyslipidemias (Table 4) account for a growing burden of pediatric dyslipidemia. The most common is obesity-related dyslipidemia, rapidly outpacing all other etiologies of lipid disturbances.[3] Obesity-related dyslipidemia typically presents with mild-to-moderate hypertriglyceridemia and low HDL-C, but the underlying CV risk relates to increased numbers of small, dense LDL particles. Secondary dyslipidemias are associated with specific lifestyle and environmental factors, medical conditions, and medications (Table 3). Secondary causes of dyslipidemia should always be considered, even when a primary dyslipidemia appears certain.

A potential direct or contributory role of secondary risk factors should be ascertained with a careful history and physical examination. Reduction, elimination, or correction of underlying or contributing causes of dyslipidemia are central to the management plan.

Expert opinion: When accessible, genetic testing is useful to achieve definitive diagnoses of FH and other genetic dyslipidemias. However, clinical diagnosis can be made independent of genetic testing using available nongenetic criteria.

Rationale for Screening and Treatment of Pediatric Dyslipidemia

Landmark autopsy studies and subsequent noninvasive assessments have reliably shown that atherosclerosis begins in youth and is associated with the presence and severity of modifiable and nonmodifiable CV risk factors, including dyslipidemia[1,2] that in turn track from childhood to adulthood.[14] The identification and management of dyslipidemia in childhood might serve to delay the onset and slow the progression of atherosclerotic CVD, particularly in high-risk populations.

Lipid disorders are often clinically silent throughout childhood and, thus, can be easily missed. For example, although heterozygous FH is the most common inherited lipid disorder (present in approximately 1:300 people),[6,15] it remains profoundly underdiagnosed, with an estimated 90% of cases undetected.[5] Unfortunately, selective screening strategies on the basis of family history, as previously recommended,[16] miss approximately 30%-60% of dyslipidemic youth.[17] Thus, in 2011, the National Heart, Lung, and Blood Institute convened an Expert Panel that was adopted by the American Academy of Pediatrics and the National Lipid Association ("Expert Panel guidelines") that recommended universal nonfasting lipid screening of all children between 9 and 11 years of age and again at 17-21 years of age, with the aim of improving the detection of inherited lipid disorders such as FH.[10]

Optimizing the early identification of lipid disorders in youth is imperative because numerous randomized and prospective observational studies have consistently shown that statin treatment in children with FH effectively lowers LDL-C and might significantly slow early atherosclerotic progression and reduce premature atherosclerotic CVD risk.[18,19] Evidence supporting the favourable effect of early statin treatment in childhood on markers of early atherosclerosis is largely derived from placebo-controlled randomized controlled trials (RCTs) on the effect of simvastatin[20] on flow-mediated dilation of the brachial artery and pravastatin on carotid intima media thickness.[21] Recently, Luirink et al., in a 20-year follow-up of children with FH initially enrolled in the pravastatin placebo-controlled RCT, reported that carotid intima media thickness was no different between the pediatric FH cohort who had received statin therapy since childhood and their unaffected siblings without FH.[22] Moreover, a CV event occurred in only 1 patient (who had stopped statin therapy at the end of the initial trial), with no deaths from CV causes during the follow-up period. In contrast, among the participants' affected parents with FH who had not started statin treatment until adulthood, 26% had CV events and 7% had CV death by age 40 years. Taken together, the evidence to date provides an emerging rationale for the early initiation of statin treatment for children with FH, with the potential for significantly reducing atherosclerotic CVD risk. Of note, data supporting early treatment of other phenotypes of pediatric dyslipidemia are less robust.

Table 1. Key points and expert opinions

1. Atherosclerosis begins in youth. Its presence and severity is linked to the presence and severity of CV risk factors including dyslipidemia.
2. FH is common (approximately 1:300) but remains vastly underdiagnosed.
3. Identification and treatment of FH in childhood significantly reduces, and possibly normalizes, CV risk in adulthood.
4. When accessible, genetic testing is useful to achieve definitive diagnoses of FH and other genetic dyslipidemias. However, clinical diagnosis can be made independent of genetic testing using available nongenetic criteria.
5. Because of the prevalence of FH, ease of detection, and effective treatment options, we recommend universal lipid screening (fasting or nonfasting, non-HDL-C or LDL-C) to be performed within the first decade of life (after 2 years old), coupled with cascade screening for identified cases of probable/definite FH or other monogenic lipid disorders. Selective screening at any time should be considered for children with identified CV risk factors or risk conditions, or a positive family history of premature CVD or dyslipidemia.
6. Decisions regarding diagnosis and the need for pharmacological therapy are on the basis of the average of results from at least 2 fasting lipid profiles obtained at least 2 weeks but no more than 3 months apart.
7. A thorough history and physical examination, with additional investigations as needed, are required to exclude secondary causes of pediatric dyslipidemia.
8. Lifestyle and dietary management serve as the first-line treatment strategy in nearly all cases of pediatric dyslipidemia. If lipid-lowering medications are started, lifestyle and dietary management continue to be important.
9. Referral to a pediatric lipid specialist may be considered to facilitate lifestyle or pharmacotherapy management, or if there is marked dyslipidemia at diagnosis (LDL-C $\geq$ 4.1 mmol/L or triglyceride levels $\geq$ 5.5 mmol/L) or dyslipidemia in the setting of risk factors or at-risk conditions (Table 5).
10. Statin therapy is reasonable, beginning at age 8-12 years when LDL-C remains above specific treatment thresholds despite lifestyle management (Fig. 2). Routine safety monitoring and LDL-C treatment targets should be incorporated (Fig. 3).
11. Patients with persistent hypertriglyceridemia (2.3-5.5 mmol/L) despite lifestyle interventions or severe (> 5.5 mmol/L) hypertriglyceridemia at diagnosis may be considered for pharmacotherapy in addition to strict dietary management, including the use of prescription omega-3 fatty acids or fibrates, although evidence of benefit and safety are limited for children, and evaluation and management by a lipid specialist is recommended.

CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Screening Strategies

Identification of dyslipidemia with a nonfasting lipid panel is simple and can easily be included in routine primary care medical practice. Strategies used in practice are: (1) selective vs universal screening; and (2) cascade/reverse-cascade screening. An approach to incorporating these strategies is provided in Figure 1.

Selective vs universal screening

Selective lipid screening is indicated for children older than 2 years of age who have a positive family history of

Table 2. Acceptable, borderline-high, and high plasma lipid and lipoprotein concentrations

Category	Acceptable	Borderline	Abnormal
TC	< 4.4 mmol/L	4.4 to < 5.2 mmol/L	≥ 5.2 mmol/L
LDL-C	< 2.8 mmol/L	2.8 to < 3.4 mmol/L	≥ 3.4 mmol/L
Non-HDL-C	< 3.10 mmol/L	3.10 to < 3.75 mmol/L	≥ 3.75 mmol/L
Triglycerides*			
0-9 years	< 0.8 mmol/L	0.8 to < 1.1 mmol/L	≥ 1.1 mmol/L
10-19 years	< 1.0 mmol/L	1.0 to < 1.5 mmol/L	≥ 1.5 mmol/L
HDL-C	> 1.2 mmol/L	1.0 to 1.2 mmol/L	< 1.0 mmol/L

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

Adapted from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute.[10]

*Normative values are for fasting triglyceride levels.

premature CVD (defined as a history of angina, myocardial infarction, coronary artery disease, or sudden cardiac death in a parent, grandparent, aunt, or uncle at younger than 55 years of age for men and younger than 65 years of age for women).[10] Selective screening also applies to children with medical conditions (such as type 2 diabetes mellitus and chronic kidney disease) or risk factors for premature CVD (such as obesity, hypertension, and smoking status).[10,23] Selective screening on the basis of family history is imperfect and might miss 30%-60% of children with dyslipidemias, particularly because accurate and reliable measures of family history are frequently not available.[5,10,24] On the basis of this, the Expert Panel guidelines recommended universal screening at age 9-11 years and again between ages 17 and 21 years.[10,25] Despite this recommendation, screening rates, including in Canada, remain low.[26] The 9- to 11-year-old timing for screening was selectively chosen because lipoprotein values physiologically decrease through the teenage years.[27] However, because Canadian children infrequently attend routine primary care visits outside of early childhood, performing universal screening at a younger age (1-5 years old) might be more prudent in the Canadian context, particularly because the primary goal of this screening is to identify FH, which results in lifelong dyslipidemia.

Cascade and reverse-cascade screening

Family-based cascade testing is the strategy in which first-degree relatives of individuals with FH are tested.[24] Identifying genetic mutations facilitates cascade screening, because the presence and severity of dyslipidemia can be variable among individuals with the same disease-causing mutation.[5] Thus, although not universally easily accessible across Canada, genetic testing might facilitate cascade screening when facing a clinical diagnosis of probable/definite FH.[9] Reverse-cascade screening is an important extension of universal screening in childhood, in which parents and grandparents of identified childhood cases are also screened.[28] This allows for the identification and treatment of adults with FH before the occurrence of CVD events. For example, incorporating FH screening into primary care evaluations might not only allow for the detection of FH in young children, but also effectively identify disease in their relatively young affected parent before the development of manifest CVD.[28]

Cost-effectiveness of screening

Universal screening of children for lipid disorders has been implemented is some countries, such as the United States, Slovenia, and Australia. Linking screening to immunization might improve cost-effectiveness and uptake rates.[24] However, the cost-effectiveness of universal screening approaches, particularly in the Canadian context, requires further study.[5] In contrast, cascade/reverse-cascade screening, although highly cost-effective, is by itself unlikely to have the desired effect considering the low rate of identified index cases.[24] To this end, a recent cost-utility analysis in the United Kingdom showed that a strategy involving universal lipid screening at 1-2 years of age, followed by diagnostic genetic testing and reverse cascade testing on the basis of the results, was the most cost-effective model for FH case-finding, supporting the implementation of a universal lipid screening program linked with genetic and cascade testing.[29]

Expert opinion: Because of the prevalence of FH, ease of detection, and effective treatment options, we recommend universal lipid screening (fasting or nonfasting, non-HDL-C or LDL-C) to be performed within the first decade of life (after 2 years old), coupled with cascade screening for identified cases of probable/definite FH or other monogenic lipid disorders. Selective screening at any time should be considered for children with identified CV risk factors or risk conditions, or a positive family history of premature CVD or dyslipidemia.

Evaluation of Pediatric Dyslipidemias

The clinical evaluation of patients with dyslipidemia involves a thorough assessment of possible primary and secondary etiologies (Tables 3 and 4).[3,10] The history and physical examination centre on identifying potential secondary causes of dyslipidemia. Symptoms suggestive of diabetes, liver, renal or thyroid disease, medication use, diet and exercise, and a complete family history emphasizing premature CVD and risk factors should be elicited. A history of recurrent abdominal pain suggestive of pancreatitis might suggest severe hypertriglyceridemia.[30]

Table 3. Primary genetic dyslipidemias

Primary lipid disturbance	Threshold level(s)	Disease name	Associated clinical features	Inheritance	Prevalence	Causal gene / location	Comments
↑ LDL-C	> 4.1 mmol/L (> 3.5 mmol/L with positive family history)	HeFH	Often none in children; rarely xanthelasmas, corneal arcus, tendon xanthomas	AD	1:300 in most of Canada; up to 1:90 in some parts of Quebec	*LDLR* / 19p13.3	> 90% of classical HeFH cases; 50% and 25% of first- and second-degree relatives are affected
						APOB / 2p24	5%-10% of HeFH cases, also called "familial defective apo B"
						PSCK9 / 1p32.3	< 1% of FH cases; rare gain-of-function variants
		Severe mutation-negative hypercholesterolemia	Biochemical only	Often polygenic	1:50-100	Numerous small effect common polymorphisms	No clear inheritance pattern; suspicion is raised if sequencing shows no monogenic variant for HeFH, no standardized genetic testing presently
↑ LDL-C	> 8.0 mmol/L	HoFH	Xanthelasmas, corneal arcus, tendon xanthomas, early ASCVD, aortic valve disease	AR	1:160,000-300,000	Same genes as for HeFH plus *LDLRAP1* / 1p36	Most patients are compound heterozygotes (ie, 2 different variants) with equal clinical severity to simple homozygotes (ie, 2 copies of the identical variant)
↑ TG	> 10.0 mmol/L	FCS	Lipemia retinalis, hepatosplenomegaly, eruptive xanthomas, abdominal pain, nausea, vomiting, pancreatitis	AR	1:300,000-500,000	*LPL* / 8p22	Approximately 80% of FCS cases are LPL deficiency with biallelic variants; most patients are compound heterozygotes (ie, 2 different variants) with equal clinical severity to simple homozygotes (ie, 2 copies of the identical variant)
						APOC2 / 19q13.2	Classical apolipoprotein C-II deficiency, 2%-5% of FCS cases
						APOA5 / 11q23	2%-5% of FCS cases
						GPIHBP1 / 8q24.3	3%-6% of FCS cases
						LMF1 / 16p13.3	2%-5% of FCS cases
↑ TG	> 6.0 mmol/L	Transient infantile HTG	Failure to thrive; abdominal pain	AR	< 1:500,000-1,000,000	*GPD1* / 12q12	Very LDL-C levels are mainly elevated; lipid profiles improve as the child ages
↑ TC with ↑ TG	TC > 5.0 and TG > 4.0 mmol/L	Dysbetalipoproteinemia	Usually none, palmar xanthomas, tuberous xanthomas	AR or AD	1:10,000	*APOE* / 19q13	Heterozygous *APOE* rare pathogenic variants or homozygosity for common E2 isoform are predisposing factors
		Combined hyperlipidemia	Biochemical only	Polygenic	1:50-100	Numerous common SNPs	No clear inheritance pattern; apolipoprotein B level is also elevated and HDL-C is depressed
↓ HDL-C	< 0.3 mmol/L	Tangier disease	Orange tonsils, hepatosplenomegaly	AR	< 1:100,000	*ABCA1* / 9q31	Controversial relationship with early ASCVD
		LCAT deficiency / fish eye disease	Corneal opacity, renal involvement	AR	< 1:100,000	*LCAT* / 16q22	Controversial relationship with early ASCVD
		Hypoalphalipoproteinemia	Sometimes xanthomas, corneal arcus	AD	< 1:100,000	*APOA1* / 11q23	Predisposes to premature ASCVD in adulthood
↑ Lp(a)	> 50 mg/dL (> 120 nmol/L)	Hyperlipoproteinemia(a); elevated Lp(a)	None in childhood	Autosomal codominant	1:50	*LPA* / 6q26	Predisposes to premature ASCVD in adulthood; essentially no clinical end points in children

AD, autosomal dominant; AR, autosomal recessive; ASCVD, atherosclerotic cardiovascular disease; FCS, familial chylomicronemia syndrome; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous (monoallelic) familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; HTG, hypertriglyceridemia; LCAT, lecithin cholesterol acyl transferase; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LPL, xlipoprotein lipase; SNP, single nucleotide polymorphism; TC, total cholesterol; TG, triglycerides.

Table 4. Selected secondary causes of and contributors to pediatric dyslipidemia

Condition/disorder	Biochemical disturbance				
	↑ LDL-C	↑ TG	↑ non HDL-C	↑ Apo B	↓ HDL-C
Obesity		×	×	×	×
Metabolic syndrome		×	×	×	×
Diabetes, particularly type 2		×	×	×	×
Positive caloric balance plus poor diet		×	×	×	×
Renal disease					
Uremia		×	×	×	×
Nephrotic syndrome	×	×	×	×	×
Liver disease					
Hepatosteatosis		×	×	×	×
Primary biliary cirrhosis	×		×	×	×
Hypothyroidism	×		×	×	
Autoimmune disorders					
Paraproteinemias		×	×	×	×
Systemic lupus erythematosis		×	×	×	×
Medications					
Corticosteroids	×	×	×	×	×
High estrogen oral contraceptive		×	×	×	
Isotretinoin	×	×	×	×	×
Bile acid sequestrants		×			×
Cyclophosphamide	×	×	×	×	×
Atypical antipsychotic medications	×	×	×	×	×

Apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Table 5. Risk factors and conditions stratified according to risk category

Category	Condition or risk factor associated with increased risk of atherosclerotic cardiovascular disease	Diagnosis associated with increased risk of non-atherosclerotic coronary artery events
Very high risk	• Homozygous FH	
High risk	• Heterozygous FH • Diabetes mellitus, type 1 and type 2 • Chronic kidney disease/post renal transplant • Status-post stem cell transplant (childhood cancer survivor) • Hypertension requiring drug therapy • Cigarette smoker • Severe obesity	• Kawasaki disease with persistent aneurysms • Post heart transplant—especially with vasculopathy
Moderate risk	• Obesity • Insulin resistance with comorbidities (dyslipidemia, NAFLD, PCOS) • Hypertension not requiring drug therapy • Status-post chest radiation (childhood cancer survivor) • Elevated lipoprotein(a) • Nephrotic syndrome • Coarctation of the aorta • Aortic stenosis	
At risk	• White coat hypertension • Pulmonary hypertension • Chronic inflammatory conditions (JIA, SLE, IBD, HIV) • Hypertrophic and other cardiomyopathies • Childhood cancer survivor (status post cardiotoxic chemotherapy only) • Psychiatric conditions (including major depressive disorders and bipolar disorder) • Cystic fibrosis	• Coronary artery translocation for ALCAPA, TGA • Kawasaki disease with regressed large coronary aneurysms

ALCAPA, anomalous left coronary artery from the pulmonary artery; FH, familial hypercholesterolemia; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovarian syndrome; SLE, systemic lupus erythematosus; TGA, transposition of the great arteries.

Data from de Ferranti SD, et al.,[36] Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute,[10] and Khoury et al.[23]

Physical examination should include plotting height, weight, and body mass index on standardized growth charts, measuring blood pressure, assessing pubertal stage, excluding goiter or hepatosplenomegaly, and identifying signs of insulin resistance such as acanthosis nigricans. The presence of acanthosis nigricans should prompt a more detailed evaluation for insulin resistance and/or metabolic syndrome. Physical findings of dyslipidemia, such as corneal arcus, xanthelasmas or tendon xanthomas are rare in children with heterozygous FH or other forms of dyslipidemia; their presence points to homozygous FH.[31] Lipemia retinalis and eruptive xanthomas over extensor surfaces and buttocks are suggestive of significant hypertriglyceridemia.[30]

The initial biochemical evaluation should include a complete blood count, lipid profile, thyroid stimulating hormone, liver and renal function, urinalysis, fasting glucose, glycated hemoglobin, and other investigations as guided by the clinical assessment. Measurement of LDL particle size and number is not routinely completed, but can be used when a more detailed evaluation of CV risk is required.[32] From a pediatric perspective, determination of Lp(a) levels might further inform CV risk assessment, because Lp(a) shows strong genetic inheritance, is associated with family history of CVD, and the clinical implications of FH have been shown to be further exacerbated by concomitant increased Lp(a).[33-35] However, limitations remain concerning Lp(a) measurement, including a lack of universally available Lp(a) assays and a lack of measurement standardization.[34] Moreover, there is no evidence-based Lp(a) cut-point by which a child with dyslipidemia might be identified as having an incrementally increased future CVD risk. Categorizing the patient's risk conditions for premature CVD (Table 5) is instrumental in guiding treatment decisions.[36]

Expert opinion: A thorough history and physical examination, with additional investigations as needed, are required to exclude secondary causes of pediatric dyslipidemia.

Non-HDL-C level has been identified as a significant predictor of the presence and persistence of dyslipidemia, because it represents the apolipoprotein B-containing lipoproteins. Moreover, it can be accurately calculated in the nonfasting state. Therefore, despite management algorithms focused on LDL-C and triglyceride levels, non-HDL-C is a useful measure for an initial lipid screen.[10]

Expert opinion: Decisions regarding diagnosis and the need for pharmacological therapy are on the basis of the average of results from at least 2 fasting lipid profiles obtained at least 2 weeks but no more than 3 months apart.

Approach to Management

Diet and lifestyle counselling

Important elements of dietary recommendations for all children with dyslipidemia include: (1) maintenance of a healthy diet according to Canada's food guide for age, which is high in whole fruit, nonstarchy vegetables, legumes, fish, nuts, vegetable oils, whole grains, and yogurt; (2) avoidance of trans-fats; (3) limited saturated fat intake in favour of vegetable oils; and (4) limited intake of highly processed foods, red and processed meats, refined carbohydrates, and salt. Whenever possible, consultation with a registered dietitian is recommended. Encouraging adherence to Canada's Movement guidelines for children and youth[37] and avoidance of smoking are also key.

LDL-C reduction

The recommended dietary approach to address elevated LDL-C is graded.[10,38] For example, the American Heart Association suggests the first step is the **C**ardiovascular **H**ealth **I**ntegrated **L**ifestyle **D**iet (CHILD)-1 diet which includes maintaining total calories from fat $< 30\%$ and saturated fat at 8%-10% of daily caloric intake. Should elevation in LDL-C persist, further reduction in saturated fat to $< 7\%$ and monounsaturated fat to $< 10\%$ (CHILD-2 diet) is recommended.

Because evidence-based dietary supplements can also lead to improvement in LDL-C, including them in the dietary approach is recommended. Phytosterols (sterols and stanols) are bioactive compounds found in plants. Intake of 2 g/d is shown to result in an 8%-10% decline in LDL-C,[39] even in individuals receiving statin therapy.[40] To achieve intake of 2 g daily, use of a dietary supplement or consumption of foods enriched with these compounds is necessary. These are likely best consumed with a meal.[41] Supplementation with the soluble fibre, psyllium, results in a 5%-10% decline in LDL-C in a dose-dependent manner, even in those receiving statin therapy.[42] Incorporation of plant sterols (2 g/d) and psyllium fibre (6 g/d; for ages 2-12 years and 12 g/d for older than 12 years) are recommended for children with hypercholesterolemia in the Expert Panel guideline.[10] Although effective in lowering LDL-C, the effect of dietary phytosterol and fibre supplementation on CVD risk is not known.

Triglycerides

Patients with moderately elevated triglycerides typically respond to lifestyle changes, including a diet low in sugar and refined carbohydrates in favour of complex carbohydrates, low in fat, and high in fibre.[10,43] Optimizing intake of foods rich in omega-3 fatty acids is often recommended. Regular physical activity should be recommended. Secondary causes, such as obesity or uncontrolled diabetes, should be addressed. This includes involvement of multidisciplinary dedicated obesity management programs as needed. Significant restriction of fat is important for those with lipoprotein lipase deficiency and severe hypertriglyceridemia (> 10 mmol/L) to prevent pancreatitis.[43]

Expert opinion: Lifestyle and dietary management serve as the first-line treatment strategy in nearly all cases of pediatric dyslipidemia. If lipid-lowering medications are started, lifestyle and dietary management continue to be important.

Pharmacologic therapy

Consideration of drug therapy for dyslipidemia should follow a reasonable trial of management focused on heart-healthy behaviours and dietary modifications as described previously. Pharmacologic therapy in pediatric patients is reserved for patients with severe, persistent dyslipidemias within the setting of other risk conditions or risk factors, most commonly FH (Table 5). For patients with very high lipid levels, multiple risk factors/conditions, or a positive family history of premature CVD, medication can be pursued concomitantly with lifestyle management.

Expert opinion: Referral to a pediatric lipid specialist may be considered to facilitate lifestyle or pharmacotherapy management, or if there is marked dyslipidemia at diagnosis (LDL-C $\geq$ 4.1 mmol/L or triglyceride levels $\geq$ 5.5 mmol/L) or dyslipidemia in the setting of risk factors or at-risk conditions (Table 5).

For LDL-C management with statins, most often for those with FH, the ideal age to start is between 8 and 12 years, on the basis of the ages of children enrolled in statin RCTs to date[18] and evidence that earlier treatment has been associated with a reduction in markers of early atherosclerosis.[44] Recommendations are provided in Figure 2. Periodic safety monitoring of liver enzymes, muscle and other symptoms, counselling regarding pregnancy prevention and drug interactions, and reinforcement of lifestyle measures is recommended, as outlined in Figure 3. Shared decision-making with the family regarding starting medication is required, incorporating education and counselling, and addressing concerns. Patients not meeting a minimal target LDL-C level of 3.4 mmol/L, or 2.6 mmol/L for higher-risk patients (such as those with type 2 diabetes mellitus)[36] might benefit from an increased statin dose or the additional use of ezetimibe, although evidence to support these treatment targets is lacking, and treatment of FH in childhood with statins has resulted in favourable slowing of early markers of atherosclerosis despite high residual LDL-C levels.[22] The use of additional medications, including bile acid sequestrants, are typically not required and often have a low uptake because of significant side effect profiles. Pharmacologic management of children with homozygous FH should begin immediately upon diagnosis and be led by lipid specialists. In addition to statin therapy, management of these patients often includes proprotein convertase subtilisin/kexin type 9 serine protease inhibitors and LDL-C apheresis.

In children ages 8 years and older, statin use has been shown to be associated with similar short- to medium-term safety profiles as seen in adults.[18] Moreover, 20-year follow-up data have recently been published, suggesting a reassuring extension of these safety data.[22] The most recent Cochrane review on statin use in children with FH showed little or no difference between treatment and placebo regarding liver function, creatinine kinase, myopathy, sex hormone levels or puberty status, or clinical adverse events.[18] No clinical trials to date in children and adolescents have reported rhabdomyolysis (degeneration of skeletal muscle tissue) as a result of statin treatment.[18] Nonetheless, the use of statin therapy in younger children (younger than 8 years of age) and the long-term safety of statin use in all children requires ongoing study. The risk of developing insulin resistance or type 2 diabetes mellitus due to statin use has gained increased attention in recent years. In adults, meta-analysis data show that treatment with statins of 255 adult patients for 4 years would be required to result in 1 incident case of type 2 diabetes mellitus.[45] The risk of diabetes mellitus development appears to be dependent on the presence of specific baseline risk factors, such as the presence of insulin resistance and obesity,[46] although recent work has suggested that the highest relative risk of new-onset diabetes (compared with those not treated with statins) are in patients with lower hemoglobin A1c percentages.[47] Although the risk of new-onset diabetes mellitus in pediatric patients treated with statins requires further study, it is important to note that in the 20-year follow-up by Luirink et al., 1/184 statin-treated patients with heterozygous FH developed type 2 diabetes mellitus, compared with 2/77 unaffected siblings.[22] Moreover, there has been some suggestion that FH-causing genetic mutations might mediate the risk of diabetes development, although this requires further study.[48]

Expert opinion: Statin therapy is reasonable, beginning at age 8-12 years when LDL-C remains above specific treatment thresholds despite lifestyle management (Fig. 2). Routine safety monitoring and LDL-C treatment targets should be incorporated (Fig. 3).

For patients with hypertriglyceridemia, supplementation with omega-3 fatty acids might be of benefit. Pharmacological doses of 2-4 g/d of long chain omega-3 fatty acids reduce triglyceride levels by up to 30% in adults,[43] and the use of icosapent ethyl (the ethyl ester of eicosapentaenoic acid [EPA]) has resulted in reductions in CVD events (compared with mineral oil) in adults in the **Reduction** of **C**ardiovascular **E**vents With Icosapent Ethyl-**I**ntervention **T**rial (REDUCE-IT) trial.[49] However, it is important to note that other omega-3 fatty acid prescription formulations that contain EPA and docosahexaenoic acid have not shown similar reductions in CVD events.[50] In addition, small randomized trials in children/adolescents have not shown statistically significant improvements in triglyceride levels compared with placebo.[51] Although more costly, the choice of a Health Canada-approved product with appropriate

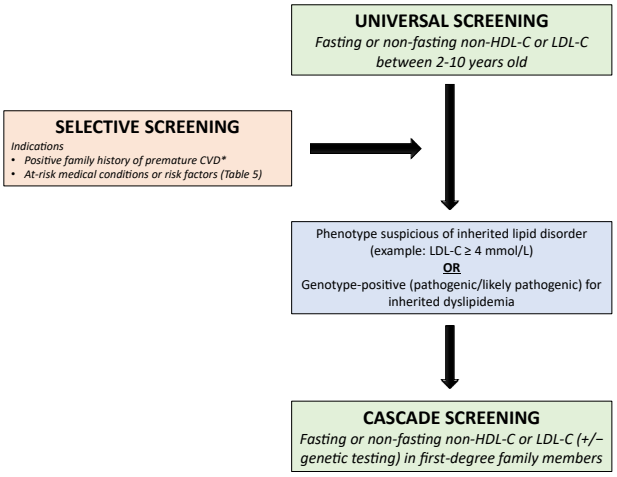

Figure 1. Incorporation of universal, selective, and cascade screening in the diagnosis of pediatric dyslipidemia. CAD, coronary artery disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol. * Premature CVD: history of angina, myocardial infarction, CAD, or sudden cardiac death in a parent, grandparent, aunt, or uncle at younger than 55 years of age for men and younger than 65 years of age for women.

omega-3 fatty acid content is important,[52] and prescription formulations should be used, because over-the-counter supplementations often have lower levels of EPA and docosahexaenoic acid, might not have undergone the same regulatory safety monitoring as prescription products, and might contain potentially harmful additional components, such as toxins and oxidized fatty acids.[53]

For patients who require treatment for hypertriglyceridemia, fibrates may be considered by pediatric lipid specialists, particularly for those with moderate-severe elevations (> 5.5 mmol/L) or worse.[10] Evidence regarding benefit and safety in children and adolescents is very limited and equivocal. Clinicians should be mindful of concomitant liver or kidney disease and drug interactions that increase the risk of muscle toxicity (particularly when used in combination with statin therapy). This is particularly relevant for gemfibrozil. The interactions with statin therapy and myopathy/rhabdomyolysis risk associated with fenofibrate is markedly lower.[46,54]

Expert opinion: Patients with persistent hypertriglyceridemia (2.3-5.5 mmol/L) despite lifestyle interventions or severe (> 5.5 mmol/L) hypertriglyceridemia at diagnosis may be considered for pharmacotherapy in addition to strict dietary management, including the use of prescription omega-3 fatty acids or fibrates, although evidence of benefit and safety are limited for children, and evaluation and management by a lipid specialist is recommended.

Patients with familial combined dyslipidemia might merit drug treatment with either a statin or a fibrate depending on the severity of dyslipidemia after a trial of lifestyle modification, as outlined previously and in Figure 2.[10] Selected patients with combined dyslipidemia of obesity (high non-HDL-C, low HDL-C, and high triglycerides) might meet

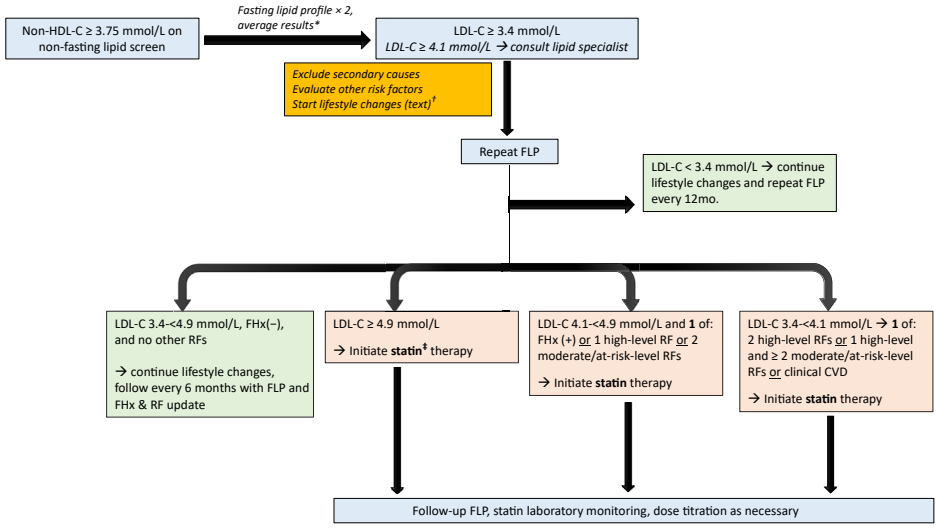

Figure 2. Pediatric statin treatment indications and thresholds. See Table 5 for high-, moderate-, and at-risk level risk factors and conditions. To convert to mg/dL, multiply by 38.67. CVD, cardiovascular disease; FHx (–) and (+), family history negative and positive; FLP, fasting lipid profile; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RF, risk factor. * Repeat FLP between 2 weeks and 3 months of initial testing. † Consider use of dietary supplements (phytosterols and psyllium). ‡ Statins typically are initiated starting at 8-12 years of age. Note that statin treatment thresholds in the pediatric population are largely based on expert opinion. Data from de Ferranti et al.[36] and Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute.[10] Modified from Khoury and McCrindle[19] with permission from Elsevier.

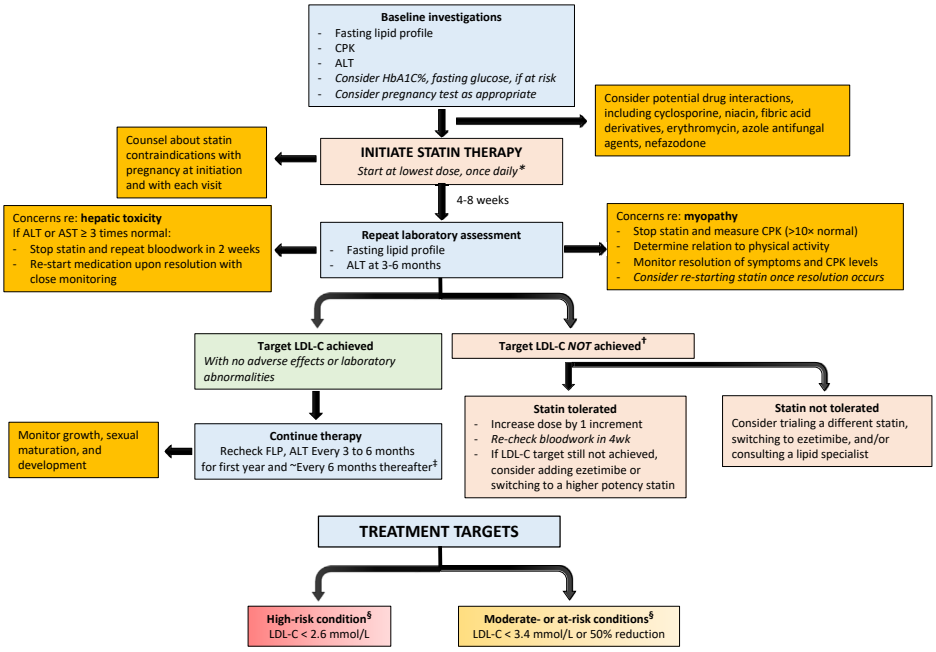

Figure 3. Statin monitoring and treatment algorithm. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; HbA1c%, hemoglobin A1c percentage; LDL-C, low-density lipoprotein cholesterol. * Atorvastatin 10 mg once daily or rosuvastatin 5-10 mg once daily are often used and have the strongest evidence basis, although statin choice is practitioner-dependent. † Assess adherence at each visit. ‡ Consider annual assessment of HbA1c and/or fasting glucose, if the patient is at-risk for type 2 diabetes mellitus development. § See Table 5. Note that treatment targets lack a robust evidence basis in the pediatric population and are largely based on expert opinion. Data from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute[10] and de Ferranti et al.[36] Reproduced from Khoury and McCrindle[19] with permission from Elsevier.

criteria for a statin, because this is a prevalent high-risk dyslipidemia associated with increased numbers of atherogenic small, dense LDL particles.[55] The presence of increased numbers of small, dense LDL particles can be inferred in the presence of a high triglyceride/HDL-C ratio (inverse association),[56] or LDL particle size and number can be measured directly using specialized laboratory techniques such as nuclear magnetic resonance, when available.[32,55] Isolated low HDL-C is usually managed by addressing other risk factors and optimizing healthy lifestyle behaviours. Patients with type 1 or 2 diabetes have lower LDL-C thresholds for starting a statin (Fig. 2).

Current Knowledge Gaps and Future Directions

Numerous knowledge gaps remain with respect to the screening and management of pediatric lipid disorders. First, the optimal timing and strategy for lipid screening in youth requires further study. The cost-effectiveness of universal lipid screening within the Canadian context is not currently known. Specifically, the clinical and economic effect of the increased identification of milder forms of pediatric dyslipidemia within the context of limited resources and access to pediatric dietitians and lipid subspecialists must be explored. To this end, it is imperative that primary care practitioners be enabled to manage lipid disorders in youth, with ready access to registered dietician support, for all but the most severe situations. Risk stratification and current thresholds for the initiation of pharmacotherapy are empiric and on the basis of expert opinion. Moreover, the utility of additional biochemical risk stratification tools in children, including Lp(a), require further study. Evidence-based treatment targets must be established. The appropriate age for starting statin therapy has not been established, although the evidence to date suggests that earlier treatment is beneficial.[44] Moreover, the safety of statin initiation in children younger than 8-10 years of age requires further study and the long-term safety of statin use in youth requires continued examination.

Conclusions

The single most effective future endeavour must be the promotion of systematic strategies dedicated to the identification of Canadian youth with FH. Doing so will result in dramatic improvements in the detection of what is currently a vastly underdiagnosed and easily treatable condition. Such an undertaking has the potential to reduce CV risk and improve future CV health in this population of Canadians more than any novel treatment. Thus, the primary call to action and key message from this statement for Canadian primary care practitioners and health policy makers is that FH and other high-risk pediatric lipid disorders are common and their detection and timely treatment might normalize long-term atherosclerotic risk. Finally, emerging clinical trial data might soon provide evidence supporting use of novel lipid-lowering drugs, including biologic agents that target proprotein convertase subtilisin/kexin type 9 serine protease in the pediatric age group,[57,58] thereby broadening treatment options for these patients.

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