Approach to Hypertriglyceridemia in the Pediatric Population

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Practice Gaps

There is paucity of information regarding identification and management of hypertriglyceridemia in children. In this review article, we discuss the etiologic origin, diagnosis, and therapeutic approach of a commonly encountered pediatric problem that lacks clear-cut guidelines.

Objectives

After completing this article, readers should be able to:

1. Describe the pathophysiology of hypertriglyceridemia.
2. Recognize causes of hypertriglyceridemia.
3. Discuss management of pediatric hypertriglyceridemia.

Abstract

Hypertriglyceridemia is increasingly identified in children and adolescents, owing to improved screening and higher prevalence of childhood obesity. Hypertriglyceridemia can result from either increased triglyceride (TG) production or reduced TG clearance. The etiologic origin can be primary (genetic) or secondary, but it is often multifactorial. Management is challenging because of the interplay of genetic and secondary causes and lack of evidence-based guidelines. Lifestyle changes and dietary interventions are most important, especially in hypertriglyceridemia associated with obesity. Dietary restriction of fat remains the mainstay of management in primary hypertriglyceridemia. When fasting TG concentration is increased above 500 mg/dL (5.65 mmol/L), fibrates may be used to prevent pancreatitis. Omega-3 fatty acids are often used as an adjunctive therapy. When the fasting TG concentration is less than 500 mg/dL (5.65 mmol/L) and if the non–high-density lipoprotein cholesterol level is above 145 mg/dL (3.76 mmol/L), statin treatment can be considered.

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ABBREVIATIONS

ApoB-48	apolipoprotein B-48
ApoB-100	apolipoprotein B-100
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FA	fatty acid
FDA	Food and Drug Administration
FFA	free FA
HDL	high-density lipoprotein
IDL	intermediate-density lipoprotein
LDL	low-density lipoprotein
LPL	lipoprotein lipase
NHLBI	National Heart, Lung, and Blood Institute
OTC	over-the-counter
TG	triglyceride
VLDL	very low-density lipoprotein

INTRODUCTION

The term *hypertriglyceridemia* indicates an increased plasma fasting triglyceride (TG) concentration that is above the 95th percentile for age and sex. (1)(2) A TG level greater than or equal to 100 mg/dL (1.13 mmol/L) and a level greater than or equal to 130 mg/dL (1.47 mmol/L) are considered above the 95th percentile for children of ages 0 to 9 years and 10 to 19 years, respectively. (3)(4)(5) An estimated 10% of US children and adolescents between 12 and 19 years of age have increased serum TG levels greater than 150 mg/dL (1.69 mmol/L). (3)(6)(7) By extrapolating the adult guidelines, hypertriglyceridemia can be considered mild to borderline high (150–199 mg/dL [1.69–2.25 mmol/L]), moderate to high (200–499 mg/dL [2.26–5.64 mmol/L]), very high (500–999 mg/dL [5.65–11.29 mmol/L]), severe (1000–1999 mg/dL [11.30–22.59 mmol/L]), and very severe (>2,000 mg/dL [>22.60 mmol/L]). (5)(6)(7) Hypertriglyceridemia in children parallels the increasing incidence in childhood obesity, metabolic syndrome, type 2 diabetes, sedentary lifestyle, high-fat and high-carbohydrate diet, and medication use. (8) There is a paucity of literature on pediatric hypertriglyceridemia. With increased universal lipid screening, the number of cases of hypertriglyceridemia identified will increase.

BRIEF OVERVIEW OF TG METABOLISM

Understanding TG metabolism is fundamental for prompt identification and management of hypertriglyceridemia. Factors that stimulate hepatic lipoprotein synthesis or inhibit TG removal generally lead to increased plasma cholesterol and TG levels. Hypertriglyceridemia results from an increase in the circulating TG-rich lipoproteins (ie, plasma very low-density lipoprotein [VLDL], chylomicrons), which are produced by the liver or absorbed from food. Chylomicrons transport dietary lipids and are synthesized within enterocytes. Chylomicrons contain a truncated form of apolipoprotein B, called *apolipoprotein B-48* (ApoB-48), which is only 48% of the length of the complete molecule. ApoB-48 allows for production and secretion of chylomicrons. VLDL is synthesized within the hepatocytes and contains atherogenic apolipoprotein B-100 (ApoB-100), chylomicron remnants, free fatty acids (FFAs), and de novo fatty acids (FAs). (5) Both chylomicron and VLDL transport and deliver TGs to tissues to use as FFAs for energy and storage (Fig 1).

Dietary cholesterol, FAs, and fat-soluble vitamins are absorbed in the proximal small intestine. TGs are formed in the enterocytes upon hydrolysis of these dietary fats. The longer-chain FAs are incorporated into nascent chylomicrons in the intestinal mucosal cells, whereas medium-chain FAs with fewer than 10 carbon atoms directly enter the liver through the portal vein. The chylomicron consists of 80% to 95% TGs, along with cholesteryl esters, retinyl esters, phospholipids, cholesterol, ApoB-48, and other apolipoproteins. Chylomicrons enter the thoracic duct via the lymphatic system, then travel to the vena cava and circulate. In the lymph and blood, chylomicrons acquire other apoliporoteins, such as apolipoprotein C-II, apolipoprotein C-III, and apolipoprotein E. (5) Depending on the fat content of a meal, TG levels can increase as much as 100% postprandially.

VLDL is synthesized in the hepatocytes and transport TGs and cholesterol to peripheral tissues. The VLDL TG content is derived from chylomicron remnants, plasma FFA, and de novo FAs synthesized from carbohydrates (Fig 2). VLDL has more cholesterol relative to TGs, with a TG-to-cholesterol ratio of 5:1, in comparison to chylomicrons, which have a TG-to-cholesterol ratio of 10:1. (5) Both endothelial lipoprotein lipase (LPL) and hepatic TG lipase can release FFA and glycerol from VLDL TGs. The

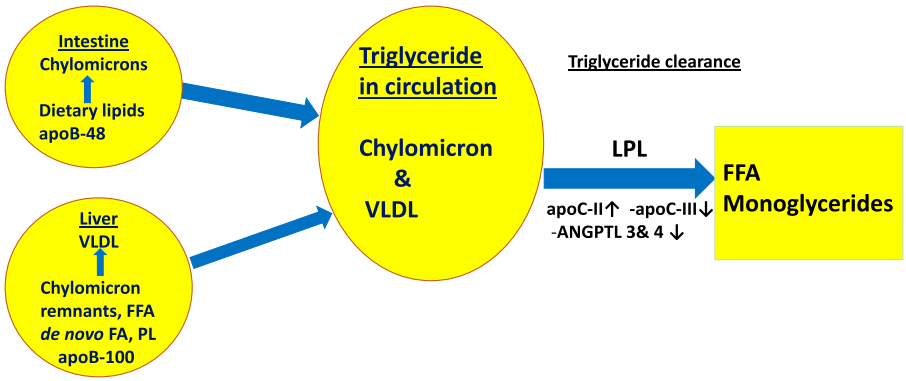

Figure 1. Triglyceride synthesis. ANGPTL=angiopoietin-like, apoB-48=apolipoprotein B-48, apoB-100=apolipoprotein B-100, apoC-II=apolipoprotein C-II, apoC-III=apolipoprotein C-III, FA=fatty acid, FFA=free FA, LPL=lipoprotein lipase, PL=phospholipid, VLDL=very low-density lipoprotein.

remaining VLDL (ie, VLDL remnants), also referred to as *intermediate-density lipoproteins* (IDLs), become TG depleted, decrease in size, and form cholesterol-enriched small, dense low-density lipoprotein (LDL) particles. ApoB-100 is the principal apolipoprotein on all atherogenic lipoprotein particles (ie, LDL, VLDL, and IDL).

The Role of LPL

LPL located on the capillary endothelial cells breaks down TGs from TG-rich lipoproteins into FFAs and monoglycerides. LPL is activated by apolipoprotein C-II and inhibited by apolipoprotein C-III and angiopoietin-like proteins 3 and 4 (Fig 1). Glycosylphosphatidylinositol-anchored high-density lipoprotein (HDL)-1 transports LPL into the luminal surface of capillary endothelial cells, and this complex interacts with lipase maturation factor. Thus, defects in apolipoprotein C-II or LPL can lead to defects in chylomicron clearance. Insulin is a potent activator of LPL and, hence, insulin-resistant and/or insulinopenic states are associated with reduced LPL activity. Lack of LPL enzyme activity, lack of LPL protein production, or both can result in hypertriglyceridemia (predominantly hyperchylomicronemia).

Obesity and Dyslipidemia

There is increased VLDL TG production in the setting of visceral obesity and insulin resistance due to excess FFA flux to the liver from high-fat diets, excess adipose tissue release of FFAs, and increased de novo TG production from high carbohydrate intake and hyperinsulinemia. Simple sugars undergo glycolysis to generate acetyl coenzyme A molecules, which are the building blocks for FA synthesis.

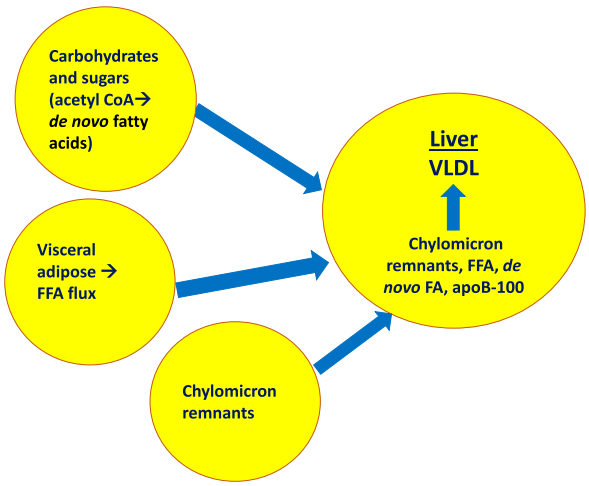

Figure 2. Synthesis of very low-density lipoprotein. apoB-100=apolipoprotein B-100, CoA=coenzyme A, FA=fatty acid, FFA=free FA, VLDL=very low-density lipoprotein.

Atherogenic Dyslipidemia

LPL is the major enzyme involved in hydrolysis of TGs and is primarily expressed in myocyte and adipocyte vascular beds. LPL hydrolyzes TGs trafficked in the large TG-rich chylomicrons and VLDLs. Lipolysis reduces the particle size and releases apolipoprotein A-I molecules on chylomicron surfaces, which become available for lipidation or renal catabolism. A large quantity of phospholipids is also released, which attaches to phospholipid transfer proteins and serves as a reservoir for use by maturing HDL particles. Since LPL is the primary enzyme involved in the hydrolysis of TGs, LPL deficiency and/or inhibition leads to severe hypertriglyceridemia. Increased TG levels are associated with decreased HDL cholesterol levels and increased concentrations of proatherogenic small, dense LDL particles. (9)

CAUSES OF HYPERTRIGLYCERIDEMIA

Hypertriglyceridemia is secondary to either increased TG production or reduced TG clearance. The etiologic origin could be primary or secondary and is often multifactorial.

Primary Causes

Table 1 illustrates the causes of primary (genetic) hyperlipidemias. The traditional Fredrickson classification describes the pattern of increased lipoproteins as type I (chylomicrons), type IIa (LDL), type IIb (LDL and VLDL), type III (IDL), type IV (VLDL), and type V (VLDL and chylomicrons). (10) All except type IIa exhibit increased serum TG levels. A 2-hit hypothesis is often proposed for the manifestation of hypertriglyceridemia, the first "hit" being genetic predisposition and the second "hit" being hormonal or environmental factors (such as obesity, hypothyroidism, estrogen status, or diabetes) that play a permissive role.

Type I Hyperlipoproteinemia (Hyperchylomicronemia Syndrome). Type I hyperlipoproteinemia usually manifests in infancy and childhood *(a)* secondary to homozygous or compound heterozygous mutations in the *LPL* gene, causing LPL deficiency, (11) or *(b)* owing to loss of function mutations in the genes that encode the cofactors essential for LPL activity—that is, *APOC2, APOA5, LMF1,* and *GP1HBP1.* (11)(12) These result in decreased hydrolysis of TGs transported in chylomicrons and VLDL at the tissue capillary endothelial surface. (13)(14) Affected patients experience recurrent attacks of acute pancreatitis, eruptive xanthomas, and lipemia retinalis. Inheritance is autosomal recessive, and history of consanguinity may be present. LPL deficiency has a prevalence of $1:10^6$ in the US population. Rarely, type I hyperlipoproteinemia could be due to circulating LPL autoinhibitors, (11)(15)(16)(17)(18)(19)(20)(21)(22)(23) which impair LPL activity as described in the context of autoimmunity.

TABLE 1. **Characteristics of Primary Hyperlipidemias**

FREDRICKSON CLASSIFICATION	INHERITANCE	LIPID ABNORMALITY[a]	CLINICAL FEATURES	CAUSES
Type I[b]	Autosomal recessive	TG ↑ (chylomicron ↑) TC:TG ratio >10:1 — — —	Chylomicronemia syndrome: eruptive xanthomas, recurrent pancreatitis, lipemia retinalis	LPL deficiency ApoC-II deficiency LMF1 deficiency GP1HBP1 deficiency ApoA5 deficiency
Type IIa	Autosomal dominant	LDL ↑, TG normal	Premature CVD, tendon xanthomas	Familial hypercholesterolemia
Type IIb	Polygenic	TG ↑ (VLDL ↑) ApoB-100 ↑ HDL ↓, LDL normal or ↑	Early CVD in family members	Familial combined hyperlipidemia[c]
Type III	Polygenic ApoE2/E2 homozygosity	TG ↑ (VLDL ↑, chylomicrons ↑), IDL ↑, TC ↑, LDL normal	Premature CVD, palmar or tuberoeruptive xanthomas	Dysbetalipoproteinemia[c]
Type IV	Autosomal dominant	TG ↑ (VLDL ↑), ApoB-100 normal HDL ↓ or normal, LDL normal or ↓	Hypertriglyceridemia in family members, may have increased CVD risk	Familial hypertriglyceridemia[c]
Type V	Autosomal dominant	TG ↑ (VLDL ↑, chylomicron ↑)	Hypertriglyceridemia in family members Minimal CVD risk	Familial hypertriglyceridemia[c]

ApoA5=apolipoprotein A-5, APoB-100=apolipoprotein B-100, ApoC-II=apolipoprotein C-II, ApoE2=apolipoprotein E2, CVD=cardiovascular disease, GP1HBP1=glycosylphosphatidylinositol-anchored HDL-1, HDL=high-density lipoprotein, IDL=intermediate-density lipoprotein, LDL=low-density lipoprotein, LMF1=lipase maturation factor-1, LPL=lipoprotein lipase, TC=total cholesterol, TG=triglyceride, VLDL=very low-density lipoprotein.

[a] *Predominant type of TG-containing lipoprotein (ie, VLDL vs chylomicron) increase is depicted in parentheses.*

[b] *Patients with heterozygous mutations may present with mild to moderate TG level increases.*

[c] *Manifests in childhood owing to complex interactions of genetic and environmental factors (ie, weight gain, medications, metabolic perturbations)—that is, the second "hit."*

Familial Hypertriglyceridemia. Familial hypertriglyceridemia is caused by excessive TG synthesis, which can manifest as type IV or type V hyperlipoproteinemia and is thought to affect 1% of the population. Those with type IV hyperlipoproteinemia have increased concentration of VLDL in the circulation, due to either increased production or decreased catabolism of VLDL, (6) and can have a TG level between 250 and 1,000 mg/dL (2.82–11.30 mmol/L). Type V hyperlipoproteinemia results from an increased production of both VLDL and chylomicrons. These patients have a TG level that exceeds 1,000 mg/dL (11.30 mmol/L) (similar to type I hyperlipoproteinemia), with pancreatitis as a major concern. These are autosomal dominant disorders. There will be a history of pancreatitis in multiple family members but a variable history of premature cardiovascular disease, likely dependent on whether they have predominant increases in chylomicrons and/or VLDL. Although familial hypertriglyceridemia is generally not fully expressed until adulthood, hypertriglyceridemia manifests at younger ages in patients with familial hypertriglyceridemia because of complex interactions of genetic and environmental factors, such as childhood obesity, diabetes, and medications (ie, the second "hit").

Familial Combined Hyperlipidemia. Familial combined hyperlipidemia is also known as type IIb hyperlipoproteinemia and is characterized by an overproduction of VLDL and ApoB-100 by the liver and a decrease in clearance of chylomicron remnants. (6) The prevalence is around 1% to 5.7% of the population. Patients present with increased levels of ApoB-100 (>130 mg/dL) and non–HDL cholesterol. Patients may manifest an increase in either TG or LDL cholesterol level or both. Familial combined hyperlipidemia is associated with a strong family history of premature cardiovascular disease. Patients and family members can have increased LDL cholesterol and TG levels, increased TG levels alone, or increased LDL cholesterol levels alone.

Dysbetalipoproteinemia (Type III Hyperlipoproteinemia). Manifests with accumulation of IDL with near-equivalent increase of both cholesterol and TGs, usually in the range of 300 to 500 mg/dL (3.39–5.65 mmol/L). This is rare (prevalence of 1 in 10,000). It is due to homozygous mutation

in apolipoprotein E (ApoE2/E2 homozygosity). Usually, this manifests after 20 years of age and, rarely, a second "hit" may precipitate the hypertriglyceridemia earlier. (24)

Mutations in the nuclear bile acid receptor "FXR" (farnesoid X receptor) cause progressive familial intrahepatic cholestasis and can manifest as moderate hypertriglyceridemia. (25) Primary hypoalphalipoproteinemias, including Tangier disease (lecithin cholesterol acyltransferase deficiency), can appear with moderate hypertriglyceridemia at presentation. (26)

Secondary Causes

Secondary causes are listed in Table 2. Oftentimes, secondary hypertriglyceridemia is due to an interplay of combinations of these conditions (hormonal and environmental), along with genetic causes. (6)(27)(28)(29)

Dyslipidemia of Obesity and Insulin Resistance. Insulin resistance promotes FFA release from adipose tissue into the portal circulation, which, in turn, increases hepatic TG production and secretion of TG-rich VLDL. Thereupon, excessive TG deposition in the liver, skeletal muscle, and visceral adipose tissue promotes insulin resistance. Consumption of a high-carbohydrate diet in the face of an insulin-resistant state begets chronic stimulation of VLDL overproduction. Insulin is a potent stimulator of LPL, which regulates postprandial TG excursions, and therefore, LPL activity is impaired in insulin-resistant individuals.

Diabetes Mellitus. Both type 1 and type 2 diabetes mellitus can cause hypertriglyceridemia. LPL activity will be reduced in poorly controlled type 1 diabetes mellitus. Owing to insulinopenia, there is increased FFA flux from adipose tissue, which drives hepatic VLDL production. Patients with type 2 diabetes mellitus also have all these metabolic disturbances, along with an array of biochemical perturbations related to obesity and insulin resistance.

TABLE 2. **Causes of Secondary Hypertriglyceridemia**

Obesity
Metabolic syndrome
Uncontrolled diabetes
Hypothyroidism
Hypercortisolemia
Nonalcoholic fatty liver disease
Liver disease
Glycogen storage disorders
Lipodystrophy: genetic or acquired
Renal disease
Excessive alcohol intake
Infections
Autoimmune disease: eg, dermatomyositis
Medications: steroids, glucocorticoids, oral estrogens, diuretics, thiazides, protease inhibitors, antipsychotics, antidepressants, estrogen-receptor blockade, retinoids, immunosuppressants (eg, rapamycin, cyclosporine), β-blockers, bile acid sequestrants

COMPLICATIONS OF HYPERTRIGLYCERIDEMIA

Pancreatitis

The risk of pancreatitis is far more worrisome once serum TG concentrations exceed 1,000 mg/dL (11.30 mmol/L). (5)(7) The mechanisms include pancreatic capillary bed ischemia due to TG-rich chylomicron sludge; subsequent release of pancreatic lipases from the damaged pancreatic acini further increasing production of proinflammatory FFAs, which leads to free radical damage and inflammation; and premature activation of pancreatic trypsinogen to trypsin, which promotes activation of other digestive enzymes, resulting in autodigestion of the gland. (30)(31)(32) If pancreatitis is suspected, hospitalization is required for rapid lowering of TG levels. Noncompliance with a low-fat diet can cause recurrent pancreatitis in those with quantitative or qualitative defects of LPL, as seen in type I hyperlipidemia. Pancreatitis is associated with clinically significant morbidity and mortality, (33) and recurrent pancreatitis may lead to chronic exocrine and endocrine pancreatic insufficiency (ie, fat malabsorption, failure to thrive, and insulin-dependent diabetes).

Cardiovascular Risk

Hypertriglyceridemia is considered to be an independent risk factor for coronary artery disease. (34) Increased TG levels are associated with decreased HDL cholesterol levels; increased concentrations of proatherogenic small, dense LDL particles; increased non–HDL cholesterol levels; and increased concentrations of ApoB-100. (7)(9) Cardiovascular risk is associated with atherogenic dyslipidemia and other diseases with cardiovascular risk, such as diabetes and obesity. (6)(7)

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease is associated with obesity and visceral adiposity. Even though metabolic syndrome is associated with nonalcoholic fatty liver disease, hypertriglyceridemia is not universally reported in pediatric nonalcoholic fatty liver disease. Hypertriglyceridemia in this

scenario can be associated with fat accumulation in the liver and increased transaminase levels.

MANAGEMENT

There is a paucity of data on a systematic approach to management of hypertriglyceridemia in pediatric patients and therefore, the approach is mostly based on current adult hypertriglyceridemia management guidelines that are tailored for the pediatric population. (4)(7)(29)(35)

There are no specific screening guidelines for hypertriglyceridemia, per se. There is also controversy regarding the existing guidelines. Table 3 summarizes the National Heart, Lung, and Blood Institute (NHLBI) expert panel guidelines (4) for dyslipidemia screening. These have been endorsed by the American Academy of Pediatrics and the American Heart Association. NHLBI guidelines recommend universal screening for all children between 9 and 11 years of age and again between ages 17 and 21 years by using a nonfasting lipid profile. Selective (targeted) screening is recommended between ages 2 and 8 years and 12 and 16 years for children with risk factors for premature cardiovascular disease. (4) The US Preventive Services Task Force determined that there is insufficient evidence for or against lipid screening in children and adolescents. (36)

When using nonfasting lipid profiles, risk assessment determination is performed by using the non–HDL cholesterol component (calculated by subtracting the HDL cholesterol level from the total cholesterol level). There is more emphasis on recognition of non–HDL cholesterol because it represents all atherogenic lipoprotein particles. Since dietary fats and carbohydrates can increase serum TG concentrations, fasting for 8–12 hours prior to testing is recommended for evaluation of hypertriglyceridemia. (7) It is important to keep in mind that if the TG concentration is more than 400 mg/dL (4.52 mmol/L), LDL cholesterol calculation by using the Friedewald equation [LDL = Total cholesterol − HDL − (TGs ÷ 5)] is inaccurate. (5)

Primary hypertriglyceridemia diagnosis is based on increased fasting TG concentration in association with family history of dyslipidemia, pancreatitis, and cardiovascular disease, along with associated risk factors and clinical features. It is important to exclude secondary causes of hypertriglyceridemia in all patients. (7) Patients with hypertriglyceridemia associated with obesity and metabolic syndrome need to be evaluated for other associated comorbid conditions, such as hypertension, diabetes, and nonalcoholic fatty liver.

LIFESTYLE MODIFICATION

Patients with secondary hypertriglyceridemia should follow a 6-month trial period of weight management, including dietary counselling and physical activity, since obesity and insulin resistance play a central role (NHLBI expert panel recommendation). (4) A multimodal intervention involving dietary modification, increasing physical activity, and behavioral changes is recommended. Children and adolescents with both primary and secondary hypertriglyceridemia are advised to follow a restricted diet with less than 25% to 30% of calories from fat, less than 7% of calories from saturated fat, less than 200 mg per day of cholesterol, and avoidance of trans fats consumption. Current guidelines also advocate replacement of simple carbohydrates with complex carbohydrates, limiting intake of sugar and sugar-sweetened beverages, and increasing the dietary intake of fish to increase omega-3 fatty acid consumption. (4) A high intake of natural dietary fiber, especially water-soluble fiber, is advocated. Institute of Medicine Dietary Reference Intake recommends consumption of 14 g of dietary fiber per 1,000 kcal.

The more common forms of increased TG levels are usually secondary to de novo hepatic TG synthesis and production of VLDL, in which restricting intake of dietary carbohydrates—especially simple sugars—and increasing dietary fiber intake will be effective. Intake of mono- and polyunsaturated FAs and omega-3 FAs is encouraged.

Performing moderate to intense physical activity for 30 to 60 minutes daily can reduce the TG level. Weight loss is expected to improve insulin sensitivity, reduce FFA release from adipose tissue, and enhance activity of LPL, leading to better clearance of TGs. Moreover, a healthy diet with fewer refined carbohydrates and less saturated fat will reduce endogenous synthesis of VLDL and LDL cholesterol.

PHARMACOLOGICAL MANAGEMENT

There are no Food and Drug Administration (FDA)–approved TG level–lowering medications for use in children younger than 18 years of age, and there are no established indications for their use in children. (6) Nevertheless, extrapolation of adult guidelines is judiciously applied in this scenario. (6)(7)(29) When fasting TG concentration is greater than 500 mg/dL (5.65 mmol/L), primary pharmacological agents for treating hypertriglyceridemia, such as fibrates, niacin, and omega-3 FAs, are used to prevent pancreatitis. (28) However, the safety and effectiveness data

TABLE 3. **NHLBI Guidelines for Pediatric Dyslipidemia Screening**

TYPE OF SCREENING AND AGE	LIPID PROFILE	CRITERIA TO SCREEN	WHEN TO REPEAT
Universal			Normal: repeat at 17–21 y of age
9–11 y	Nonfasting[a]/fasting	Universal	Borderline: repeat after 1 y
17–21 y	Nonfasting[a]/fasting	Universal	Abnormal[b]: perform FLP twice[c]
Selective			
2–8 y	Fasting	Positive family history of premature CVD[d] Parent has TC ≥240 mg/dL (≥6.22 mmol/L) or known dyslipidemia Child has diabetes, hypertension, BMI ≥ 95th percentile, smokes cigarettes, or is exposed to secondhand smoke Child has a moderate- to high-risk medical condition[e]	Abnormal[b]: perform FLP twice[c]
12–16 y	Fasting	New knowledge of positive family history of premature CVD[d] New knowledge of parent with TC ≥240 mg/dL (≥6.22 mmol/L) or known dyslipidemia Patient has diabetes, hypertension, BMI ≥85th percentile or smokes cigarettes Patient has a moderate[e]- or high-risk[f] medical condition	Abnormal[b]: perform FLP twice[c]

According to reference 4. BMI=body mass index; CVD=cardiovascular disease; FLP=fasting lipid profile; HDL=high-density lipoprotein; LDL=low-density lipoprotein; NHLBI=National Heart, Lung, and Blood Institute; TC=total cholesterol; TG=triglyceride.

[a] *Disregard TG and LDL cholesterol in the nonfasting sample.*

[b] *Abnormal lipid screening results are as follows: For nonfasting screening, results are abnormal if non-HDL level is >145 mg/dL (>3.76 mmol/L) or if HDL level is <40 mg/dL (<1.04 mmol/L); for fasting screening, results are abnormal if LDL cholesterol level is >130 mg/dL (>3.37 mmol/L), if non–HDL cholesterol level is >145 mg/dL (>3.76 mmol/L), if HDL cholesterol level is <40 mg/dL (<1.04 mmol/L), if TG level is >100 mg/dL (>1.13 mmol/L) if the child is <10 years of age, or if TG level is >130 mg/dL (>1.47 mmol/L) if the child is >10 years of age.*

[c] *Repeat fasting lipid profile after 2 weeks but within 3 months (average the results).*

[d] *Positive family history of CVD indicates that a parent, grandparent, aunt/uncle, or sibling has a history of myocardial infarction, angina, stroke, or coronary artery bypass graft, stent, or angioplasty at <55 years of age for male patients or <65 years of age for female patients.*

[e] *Moderate-risk condition indicates Kawasaki disease with regressed coronary aneurysms, chronic inflammatory disease (systemic lupus erythematosus, juvenile rheumatoid arthritis), HIV infection, or nephrotic syndrome.*

[f] *High-risk condition indicates diabetes mellitus type 1 and type 2, chronic kidney disease and/or end-stage renal disease or postrenal transplant, postorthotopic heart transplant, or Kawasaki disease with current aneurysms.*

for these agents for treating hypertriglyceridemia in children are lacking. (37)(38) For patients with moderate hypertriglyceridemia (200–499 mg/dL [2.26–5.64 mmol/L]), treatment is targeted toward reducing the non-HDL cholesterol level (3)(7)(39) by using a statin. (28)

Fibrates

Fibrates, a class of lipid level–lowering drugs, are the first-line management when the TG concentration is greater than 500 mg/dL (5.65 mmol/L) to reduce the pancreatitis risk. (6)(12)(38) This is not an FDA-approved indication for patients under 18 years of age; for these patients, a pediatric lipid specialist should be consulted. Fibrates activate the peroxisome proliferator–activated receptor-α and reduce hepatic VLDL synthesis. Fibrates also augment the activity of LPL, leading to enhanced hydrolysis of TG-rich lipoproteins. In adults with isolated hypertriglyceridemia, fibrates reportedly reduce plasma TG concentration by 40% to 60%. (15) Gemfibrozil (600 mg administered twice daily) and fenofibrates (nanocrystal formulation administered at a dose of 145 mg daily or micronized capsules administered at a dose of 200 mg daily as fenofibric acid 135 mg) are the available fibrate therapies. Fibrates can cause myopathy, especially when used in conjunction with a statin. They have to be used with caution in patients with mild to moderate renal disease and are contraindicated in severe renal impairment. Fibrates can be used in patients with dyslipidemia and nonalcoholic fatty liver disease. Owing to their risk for development of cholesterol gallstones, fibrates are contraindicated in patients with gallbladder disease. (20)

Niacin (Nicotinic Acid)

Nicotinic acid reduces plasma TG levels by 5% to 40%. It also reduces LDL cholesterol and lipoprotein(a) levels.

Niacin increases the plasma HDL cholesterol level by 10% to 40%. (35) Niacin curtails TGs by inhibiting diacylglycerol acyltransferase-2, which is an enzyme that converts diacylglycerol to TGs, thereby reducing FFA flux from the adipose tissue. It can increase the breakdown of TG-rich lipoproteins ApoB-100 and ApoB-48. The main adverse effect of niacin is the flushing that occurs 15 minutes after ingestion, due to the release of prostaglandin F2, which can be prevented in adults by giving the patient aspirin 15 minutes before administering niacin. (35)(40) However, owing to concerns of Reye syndrome, aspirin is not advocated for use in children. To date, there has been only 1 clinical trial in pediatrics involving the use of niacin (41), in which numerous adverse effects were reported in 76% of patients, including flushing, abdominal pain, vomiting, headache, and increased liver enzyme levels. (37)(41)

Omega-3 FAs

Long-chain omega-3 FAs can be used as an adjunctive therapy when TG concentration is greater than 500 mg/dL (5.65 mmol/L). It has to be kept in mind that a TG-lowering effect is entirely dependent on the omega-3 content (ie, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] content). When compared to prescription fish oil products that contain specific amounts of EPA and DHA and/or a capsule, over-the-counter (OTC), unregulated fish oil supplements vary in concentration of EPA and DHA. In adults, when used in the form of EPA and DHA (approximately 465 mg EPA and 375 mg DHA), these therapies reduced TG levels by 20% to 50%. (35)(42) There are no pediatric dosing guidelines available. So far, to our knowledge, there have been 2 pediatric clinical trials in which omega-3 FAs were used. (43)(44) Even though the low-dose OTC fish oil trial (44) in patients with TG levels greater than 140 mg/dL (1.58 mmol/L) did not show TG level–lowering effectiveness, the trial in which 3 to 4 g of prescription omega-3-acid ethyl esters were used (approximately 3,360 mg DHA plus EPA administered per day) (43) demonstrated responders and nonresponders. However, there was no statistically significant improvement. Prescription-strength or OTC fish oil capsules may be used after confirming *(a)* that a patient has severe hypertriglyceridemia by obtaining several fasting baseline measurements and *(b)* a failure to control TG levels by means of diet and weight loss. Depending on the response, a decision can be made whether to continue or stop the treatment. Prescription fish oil products do not cause the fishy taste and burping experienced with OTC fish oil capsules. (35)

Statins

When TG levels are between 200 and 499 mg/dL (2.26–5.64 mmol/L), it is important to evaluate the non–HDL cholesterol level, as this reflects all atherogenic lipoprotein particles. (8) Statins are 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors and can be used for persistently increased non–HDL cholesterol levels, even after implementation of dietary and lifestyle changes. (8)(45) Commonly used statins include simvastatin 5 to 40 mg per day, atorvastatin 10 to 20 mg per day, rosuvastatin 5 to 20 mg per day, and pravastatin 20 to 40 mg per day. To our knowledge, there have not been many large, long-term studies on statin use in the pediatric population. The common side effects include headache, myalgia, and gastrointestinal symptoms, all of which eventually disappear with continued use. Some uncommon but potential side effects include muscle disorders (ie, myalgia, myopathy, rhabdomyolysis, myonecrosis, and myositis), increased serum transaminase levels, increased incidence of new-onset type 2 diabetes, and ill-defined cognitive dysfunction. These unstudied long-term risks in the pediatric population should be compared to the benefits when initiating statin treatment. Statins should be used cautiously in female patients because of potential teratogenicity. Drug interactions (ie, those that affect cytochrome P450) need to be kept in mind when prescribing statins.

SEVERE HYPERTRIGLYCERIDEMIA

Acute pancreatitis can be consequent to severe hypertriglyceridemia (ie, TG level > 1,000 mg/dL [11.30 mmol/L]). (5) Ideally, serum TG concentration should be less than 500 mg/dL (5.65 mmol/L) to prevent pancreatitis. Patients with severe hypertriglyceridemia tend to have exponential increases postprandially because of defective and already maximized LPL activity. (30) Children with pancreatitis can present with acute abdominal pain, nausea, vomiting, and ileus. Even though there are no established guidelines, oftentimes patients with severe hypertriglyceridemia are hospitalized on the basis of the presence or absence of symptoms. A TG level higher than 1,000 mg/dL (11.30 mmol/L) with abdominal pain or pancreatitis necessitates hospitalization. Severe hypertriglyceridemia in patients with uncontrolled diabetes and those with previous episodes of pancreatitis require admission when the TG level is higher than 1,000 mg/dL (11.30 mmol/L) (2). Insulin activates LPL and facilitates degradation and clearance of TG from the circulation (46) and, hence, insulin therapy is often used in the management of severe

hypertriglyceridemia, (47)(48)(49)(50)(51) especially in patients with uncontrolled diabetes. Plasmapheresis can reduce serum TG levels rapidly and can be used in symptomatic patients with severe hypertriglyceridemia and pancreatitis. Plasmapheresis is not required in the care of asymptomatic patients with severe hypertriglyceridemia. When the TG level is higher than 1,000 mg/dL (11.30 mmol/L), the predominant lipoprotein is chylomicron (52), the levels of which could be further worsened by any additional dietary fat intake; therefore, patients with TG levels higher than 1,000 mg/dL (11.30 mmol/L) should refrain from having dietary fat for 72 hours. Since chylomicrons are produced in the small intestine and are dependent on dietary fat for formation, (53) fasting will result in a rapid and robust decline in TG levels. When TG levels are lower than 1,000 mg/dL (11.30 mmol/L), the patient can then be placed on a diet that contains less than 10% to 15% of daily calories from fat.

CONCLUSIONS

A lack of pediatric-specific protocol and FDA-approved TG level–lowering drugs makes the management of hypertriglyceridemia in children difficult. Dietary restriction remains the mainstay of management, supplemented by TG level–lowering medications. A more rational approach needs to be followed in the pediatric setting.

SUMMARY

- On the basis of epidemiological studies and expert opinion, (3)(7) an estimated 10% of US children and adolescents between 12 and 19 years of age have increased serum TG concentrations (TG level >150 mg/dL [>1.69 mmol/L]).
- On the basis of expert opinion, (5)(7) hypertriglyceridemia diagnosis is based on fasting TG concentrations.
- On the basis of expert opinion, (5)(7) it is important to exclude secondary causes of hypertriglyceridemia in all patients.
- On the basis of expert opinion, (5)(7) the risk of pancreatitis is lower when TG concentration is less than 1,000 mg/dL (11.30 mmol/L).
- On the basis of expert opinion, (4) a 6-month trial period of weight management, including dietary counselling and physical activity, is recommended in patents with secondary hypertriglyceridemia—especially where obesity and insulin resistance play a central role.
- On the basis of some research evidence, consensus statements, and expert opinions, (3)(7)(39) for patients with TG levels between 150 and 499 mg/dL (1.69–5.64 mmol/L), the treatment goal is to target non-HDL cholesterol.
- On the basis of expert opinion, (5,7) for patients with very high triglycerides, (above 500 mg/dL), a fibrate can be used to reduce the pancreatitis risk.

References for this article are at http://pedsinreview.aappublications.org/content/38/9/424.

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1. A 9-year-old girl was found to have a fasting triglyceride level of 352 mg/dL (3.98 mmol/L) at a routine lipid profile screening. Her height and weight are at the 25th percentile, and her body mass index is at the 50th percentile. Which of the following is the most appropriate recommendation for lifestyle modification in this patient?
    A. Diet high in simple carbohydrates.
    B. Diet high in water-soluble natural fiber.
    C. Low omega-3 diet.
    D. Restrict saturated fat to 30% in the diet.
    E. Weight loss.
2. You have been evaluating a 6-year-old boy for hypertriglyceridemia. The patient's family history is clinically significant for severe hypertriglyceridemia in his father and uncle and the death of his maternal grandmother at 45 years of age due to myocardial infarction. The boy's fasting triglyceride level is 553 mg/dL (6.25 mmol/L). You began dietary and physical activity modifications and referred him to an endocrinologist. The boy's parents return today to discuss the endocrinologist's recommendations for treatment options. In discussing with them the potential side effects of the various pharmacological treatments of hypertriglyceridemia, which of the following is the most appropriate statement?
    A. Aspirin should be routinely given to children 15 minutes before niacin to prevent flushing.
    B. Fibrates are contraindicated in patients with kidney stones.
    C. Niacin is well tolerated in children, and side effects are uncommon.
    D. Omega-3 fatty acid supplementation with prescription fish oil capsules causes burping and fishy taste.
    E. Statins may cause muscle disorders and increased liver enzyme levels.
3. A 13-year-old boy with type 1 diabetes mellitus that is well controlled with insulin is brought to the clinic by his parents for evaluation. His fasting triglyceride level was 1,100 mg/dL (12.43 mmol/L). He is otherwise asymptomatic. Which of the following is the most appropriate next step in the care of this patient to prevent complications such as pancreatitis?
    A. Hold the insulin dose for 72 hours.
    B. Immediate hospitalization.
    B. Immediate plasmapheresis.
    D. Prescribe pancreatic enzymes.
    E. Restrict dietary fat for 72 hours.
4. A 10-year-old boy with a history of mood disorder, gastroesophageal reflux disease, allergic rhinitis, and intermittent asthma is seen for follow-up. At a routine lipid screening, his fasting triglyceride level is found to be 278 mg/dL (3.14 mmol/L). The patient is taking multiple medications for his chronic medical conditions. Which of the following medications he is taking is most likely to cause secondary hypertriglyceridemia?
    A. Albuterol.
    B. Loratadine.
    C. Methyphenidate.
    D. Omeprazole.
    E. Risperidone.
5. A 9-year-old girl is seen in the clinic as a new patient. A screening fasting lipid profile shows a triglyceride level of 250 mg/dL (2.82 mmol/L). She is otherwise healthy, with a body mass index at the 40th percentile. Her family history is unremarkable. Which of the following is the most appropriate next step in the care of this patient?

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A. Prescribe a statin.
B. Prescribe niacin.
C. Recommend a diet containing less than 10% to 15% dietary fat.
D. Recommend supplementation of omega-3 fatty acids with fish oil capsules.
E. Repeat the fasting lipid profile and plan further care based on the mean of the 2 results.

Approach to Hypertriglyceridemia in the Pediatric Population

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