GENETIC DISORDERS CAUSING HYPERTRIGLYCERIDEMIA IN CHILDREN AND ADOLESCENTS

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ABSTRACT

Primary disorders of lipid metabolism causing hypertriglyceridemia (HTG) result from genetic defects in triglyceride synthesis and metabolism. These disorders, with the exception of mutations in the lipoprotein lipase complex, are often unmasked by precipitating factors including obesity, diabetes, or medications. Physical findings can include eruptive, palmer, or tuberoeruptive xanthomas. Other lipid abnormalities may or may not be present. Each of the genetic causes of HTG is associated with an increased risk of developing recurrent pancreatitis; some may also increase the risk of premature cardiovascular disease. Appropriate management begins with proper recognition of the disorder. Pharmacotherapies for TG lowering, although not approved for use in children <18 years-of-age in the U.S., are available and may be beneficial in select disorders. We review the genetic disorders causing HTG in children and adolescents, discuss their clinical presentation, associated complications, and management, and conclude with novel therapies in development.

INTRODUCTION

Triglycerides (TGs) constitute one of the major lipid groups. Excessive accumulation of TG in the blood leads to hypertriglyceridemia. TG concentrations of > 500 mg/dL account for <0.2% of the HTG cases in children, but when encountered should prompt consideration of mutations in the lipoprotein lipase (LPL) complex, termed the familial chylomicronemia syndrome (FCS) or the co-existence of genetic and secondary forms of HTG, termed the multifactorial chylomicronemia syndrome (MFCS), a far more common cause of severe HTG. Secondary causes of HTG include unrecognized or poorly controlled diabetes, obesity, metabolic syndrome, and medications (including atypical antipsychotics and estrogens) (Table 1). Appropriate management of the patient with HTG requires knowledge of the likely cause of the HTG, in order to prevent its complications. Our focus is to review the pathogenesis, genetics, presentation, and diagnosis of inherited HTG disorders in children and adolescents.

Table 1. Secondary Causes Hypertriglyceridemia in Children and Adolescents
Diet with excess calories, high glycemic load, and/or sucrose- or fructose-containing beverages
Endocrine Disorders (uncontrolled type 1 and type 2 diabetes mellitus, obesity, metabolic syndrome, hypothyroidism, hypercortisolism, lipodystrophies)
Medications (steroids, oral estrogen, second generation antipsychotics, antidepressants, retinoic acid derivatives, rosiglitazone, thiazide diuretics, beta-blockers, bile acid sequestrants, sirolimus, PEG-asparaginase, antiretroviral therapy)
Pregnancy
Renal disease (nephrotic syndrome, renal failure)
Liver disease (acute hepatitis)
Excessive alcohol intake
Chronic inflammatory conditions (systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome)

CLASSIFICATION OF HYPERTRIGLYCERIDEMIA

The classification of HTG in children and adolescents, as published by the National Expert Panel on Cholesterol Levels in Children (1) and the Expert Panel on Cardiovascular Health Risk Reduction in Children (2), includes definitions of borderline and high TG based upon the 75th and 95th percentiles of TG in children, respectively. Unfortunately, this classification does not emphasize severe TG levels. Table 2 presents a classification that combines the former recommendations with the 2010 Endocrine Society guidelines on HTG (3) to focus attention on the very high levels of TG seen in primary HTG (4).

Hegele et al suggested a simplified classification to facilitate clinical decision-making (5). This classification uses a general population-derived distribution of plasma TG levels to define mild-to-moderate HTG if TG are 175-885 mg/dL (2-9.9 mmol/L with severe HTG defined as >885 mg/dL (10 mmol/L). The latter helps to identify those who are at increased risk of pancreatitis, who more likely to have an underlying genetic cause for HTG, and who would benefit from referred to a lipid specialist.

Table 2. Classification of Hypertriglyceridemia (mg/dL) in Children and Adolescents						
Age	**Normal**	**Borderline**	**High**	**Very high**	**Severe**	**Very Severe**
0-9 yrs	<75	≥75-99	≥100-499	≥500-999	≥1000-1999	≥2000
10-19 yrs	<90	≥90-129	≥130-499	≥500-999	≥1000-1999	≥2000

Definitions integrated from the National Expert Panel on Blood Cholesterol Levels in Children, Expert Panel on Cardiovascular Risk Reduction in Children, and the Endocrine Society Statement on Evaluation and Treatment of Hypertriglyceridemia.

TRIGLYCERIDE DISORDERS IN CHILDHOOD AND ADOLESCENTS

Evaluation of HTG in infancy should include screening for secondary causes of HTG, particularly disorders affecting the thyroid, liver, and kidney function. Preterm and critically ill infants may be particularly prone to HTG because of immaturity, limited adipose stores, and reduced lipoprotein lipase (LPL) activity (6). In this setting, HTG may be exacerbated by stress, sepsis, selective medications, and use of intravenous fat (lipids) as a nutritional supplement. Infants with unexplained hypoglycemia and HTG should be evaluated for glycogen storage disease type I (GSD type I) especially when accompanied by hepatomegaly, lactic acidosis, and hyperuricemia.

Transient infantile hypertriglyceridemia (HTGTI) is an autosomal recessive hereditary disorder caused by the inactivation and variant of glycerol-3-phosphate dehydrogenase 1 located on chromosome 12q12-q13. The GPD1 gene encodes intracytoplasmic NAD-dependent GPD1, which plays an essential role in lipid and carbohydrate metabolism. In addition to HTG other manifestations include hepatomegaly, elevated liver transaminases, and hepatic steatosis in early infancy. While the HTG may normalize with age, mild HTG accompanied by elevated liver transaminases, a fatty liver, and even cirrhotic have been reported (7).

Genetic causes of HTG can result from rare mutations in the lipoprotein lipase (LPL) complex, where it is termed the familial chylomicronemia syndrome (FCS). More than 95% of patients with HTG have a multigenic susceptibility component, termed multifactorial chylomicronemia (MCM) (5). Multigenic hypertriglyceridemia has a complex etiology, consisting of an excess burden of common small-effect variants, in addition to rare heterozygous large-effect variants in genes either directly or indirectly associated with plasma triglyceride concentration (8). Causes of inherited forms of severe HTG are discussed below and summarized in Table 3.

Table 3. Summary of Primary Hypertriglyceridemia Disorders

Lipid Disorder	Molecular Defect	Incidence	Lipoprotein Abnormality	Lipid Profile	Presentation
*Familial Chylomicronemia Syndrome (FCS)	homozygous or compound heterozygous mutations in lipoprotein lipase (LPL) *	1 per 1,000,000	↑↑ Chylomicrons,	↑↑ TG (>1000 mg/dL) and post prandial HTG > 10,000 mg/dL	Early onset ↑↑ TG, eruptive xanthomas, recurrent pancreatitis
**Familial Combined Dyslipidemia	Unknown	1/200	↑ VLDL, ↑ LDL	↑ TG ↑ LDL-C, ↓HDL-C, ↑ small dense LDL	Often seen with obesity, insulin resistance, hypertension
**Familial Hypertriglyceridemia	Unknown	1/500	↑↑ VLDL	↑ TG (200-1000 mg/dL)	Family members usually affected
**Dysbetalipoproteinemia	Abnormal Apo E	1/5000	↑ Chylomicrons, ↑ VLDL remnants IDL)	↑ TG (250- 600 mg/dL); ↑ Total cholesterol	Palmer and tuberoeruptive xanthomas

* Rare causes include mutations in apo CII, apo A-V, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein (GPIHBP1), or lipase maturation factor-1(LMF-1) or the presence of circulating inhibitors to LPL.
**Generally present in adulthood unless precipitated by a secondary cause (obesity, insulin resistance)

Familial Chylomicronemia Syndrome (FCS)

GENETICS AND PATHOGENESIS

FCS has an estimated prevalence of approximately 1 in 500,000 to 1,000,000 (9, 10). FCS results from a mutation in one or more genes of the lipoprotein lipase (LPL) complex and affects catabolism of chylomicrons and very low-density lipoproteins (VLDL). The most common gene affected is LPL (accounts for 95% of these cases), in which homozygotes or compound heterozygotes inherit two defective LPL alleles. The LPL gene is composed of 10 exons and is located on chromosome 8p22. The first mutation was described in 1989, and since that time, over 100 mutations that result in LPL deficiency have been reported (11, 12). Most mutations occur in exons 3, 5, and 6, which are responsible for the catalytic coding region of the LPL gene (11). The LPL enzyme and its cofactor, apolipoprotein (apo) C-II, act on the luminal surface of the capillary endothelium and are responsible for liberating free fatty acids from the TG in dietary-derived chylomicrons and VLDL produced in the liver. When any part of the LPL complex is defective, there is a massive accumulation of chylomicrons in the blood, hence the name FCS. A lesser amount of TG from VLDL may also contribute to the observed HTG.

FCS may also be caused from loss of function mutations in apo C-II, the cofactor for LPL, glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein (GPIHBP1), which helps to anchor chylomicrons to the endothelial surface (13), and LMF1 factor 1, an endoplasmic reticulum chaperone protein required for post-translational activation of LPL (14). Apo A-V plays a role in stabilizing the lipoprotein-enzyme complex thereby enhancing lipolysis; thus, defective or absent apo A-V can result in reduced efficiency of LPL-mediated lipolysis (15, 16). Circulating inhibitors to the LPL enzyme (17) have been described. Each of the above has an indistinguishable clinical phenotype (18).

PRESENTATION AND DIAGNOSIS

The presentation of FCS in infancy is suspected by a creamy appearance of the blood on routine blood draw or fingerstick caused from TG accumulation secondary to decreased clearance of chylomicrons from the plasma. If the diagnosis is not made from observation of a lipemic blood sample, the disease often presents as severe abdominal pain from acute pancreatitis. Recurrent abdominal pain and pancreatitis are common. The diagnosis of FCS is supported by the presence of markedly elevated TG concentrations and chylomicrons, the latter which are normally rapidly cleared from the plasma following a meal. Laboratory data will also show marked reductions in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) concentrations (10). Homozygous or compound heterozygous individuals who have absent or markedly reduced LPL activity typically have serum TG concentrations that can reach 10,000 or higher (11). In contrast, heterozygous carriers have normal to moderately reduced LPL activity, are usually asymptomatic, and may have normal or mildly elevated fasting TG concentrations that can range from 200 to 750 mg/dL. As a result, presentation and diagnosis may occur later in childhood.

Physical signs may include lipemia retinalis and eruptive xanthomas, the latter generally located over the buttocks and extensor surfaces (12).

Hepatosplenomegaly can occur from the accumulation of chylomicrons in the liver and spleen (12). Complications of LPL deficiency may include multiple episodes of pancreatitis leading to pancreatic calcification, diabetes mellitus, and steatorrhea, especially in those who are unable or unwilling to comply with a very low-fat diet (19).

Reduction or absent LPL activity can be measured after intravenous heparin administration in the presence of normal apo C-II levels (20). Heparin is a competitive agonist of LPL; absence of LPL activity after an intravenous heparin bolus is diagnostic (21). Molecular genetic analysis is also available, but is not necessary for treatment.

The following disorders may result in the multifactorial chylomicronemia syndrome (MFCS) that result from the co-existence of genetic and secondary forms of HTG.

Familial Combined Hyperlipidemia (FCHL)

GENETICS AND PATHOGENESIS

FCHL is one the most common causes of genetic hyperlipidemia with a prevalence of 0.5% to 2% in the population (22, 23). In a pediatric clinic population, FCHL has been shown to be 3 times more prevalent than familial hypercholesterolemia (24). FCHL is a genetically complex disease whose phenotype is usually determined by the interaction of multiple susceptibility genes and the environment. Genome wide association studies (GWAS) and linkage approaches have been utilized to screen the genome in FCHL families from various populations to identify loci linked to the phenotype. At least 35 genes have been implicated in the development of FCHL (polygenic disorder). One chromosomal locus that has been consistently linked to FCHL is 1q21–23 (25). Another commonly linked gene in FCHL is the ubiquitous transcription factor upstream stimulatory factor 1 (USF1), which has numerous target genes related to lipid and glucose metabolism (26). A detailed review of gene associations in FCHL is available (25). In general, the genes that have been implicated are primarily those involved in an overproduction of VLDL and apoB-100 by the liver, a reduction of fatty acid uptake by adipose tissue, and a decrease in clearance of chylomicron remnants. For those with TG 2-10 mmol/L (<885mg/dL), biochemical screening and counselling for family members is recommended, but routine genetic testing is not warranted (27).

PRESENTATION AND DIAGNOSIS

The lipid profile found in individuals with FCHL is variable. In addition to high TG concentrations, LDL-C may be normal or elevated and HDL-C levels low. There is also an increase in small dense LDL (sdLDL) particles, due to the delayed clearance of VLDL (28, 29). Elevated levels of apo B (> 90 percentile) and sdLDL particles are now considered diagnostic criteria for FCHL in adults (28), although neither is routinely assessed in clinical practice. The presence of elevated TG and apo B levels in at least 2 family members is also considered necessary for a definitive diagnosis of FCHL (30).

FCHL presents in childhood when unmasked by weight gain (31), and is also influenced by age (31). As a result, in normal weight individuals, the presentation can be delayed. Thus, it is possible that children with normal lipid values but a family known to have FCHL should be retested as young adults (31). Unique physical findings in FCHL are lacking, but affected individuals often exhibit obesity, signs of insulin resistance, and hypertension (32). The diagnosis is made from a characteristic fasting lipid profile and, if available, a reliable family history of dyslipidemia and early CVD (33).

The association of FCHL with premature CVD is well established and CVD risk factors such as visceral adiposity, insulin resistance, impaired glucose tolerance, and hypertension are often present (34, 35). Therefore, identifying this disorder is of particular importance for management of future cardiovascular health.

Familial Hypertriglyceridemia (FHTG)

While FHTG was previously thought to be distinct from FCHL, more recent genetic characterization of individuals with familial forms of HTG indicates that both disorders are polymorphisms in multiple genes associated with HTG. Nevertheless, it is important to note that FCHL as originally described is associated with a very high prevalence of premature CVD (34-36). Thus, distinguishing clinical FCHL from FHTG may be useful for assessing cardiovascular risk.

PATHOGENESIS AND GENETICS

Familial hypertriglyceridemia (FHTG) is a polygenic disorder with a prevalence of approximately 1 per 500 (23). The genetic defect causing FHTG has not been identified, but studies in a Mexican-American cohort have identified genetic susceptibility loci on chromosomes 6, 7, and 15 that are linked to elevated TG levels (37, 38). The primary abnormality in FHTG is an overproduction of VLDL by the liver and impaired catabolism of TG-rich lipoproteins where normal numbers of very large triglyceride-enriched VLDL particles are secreted (32, 39). FHTG has also been associated with a defective regulation of bile acid synthesis, resulting in abnormally high production rate of bile acids, which associates with the subsequent development of HTG (40). Unlike FCHL, hepatic apoB-100 production is not increased and, as such, there is no overproduction of LDL. Prior work suggested that there is no increased CVD risk (23), but recent data shows baseline TG levels predicted subsequent CVD mortality after 20 years of follow up among relatives in FHTG families (34).

Most individuals with mild-to-moderate HTG, including those with FHTG, as well as severe elevations of TG are polygenic, with a stepwise increase in the prevalence of genetic determinants as the HTG phenotype became more severe. For individual patients, however, genetic testing alone cannot accurately predict phenotypic expression of HTG severity. At present clinical decisions regarding diet and use of lipid lowering medication should be based on the severity of the HTG, without the need for extensive genetic testing (41).

PRESENTATION AND DIAGNOSIS

TG levels are usually normal in childhood. Although FHTG is not usually expressed until adulthood, with the rise in childhood obesity FHTG has been diagnosed at an earlier age (42-44). The phenotype is usually asymptomatic HTG (42-44) with TG levels between 250 and 1000 mg/dL, normal-to-mildly elevated total cholesterol concentrations and low-to-normal LDL-C and HDL-C levels (45). The diagnosis of FHTG is made by obtaining a detailed family history and examination of fasting lipoprotein profiles of the patient and relatives.

Dysbetalipoproteinemia (Remnant Removal Disease)

PATHOGENESIS AND GENETICS

Dysbetalipoproteinemia is a autosomal recessive disorder with an estimated prevalence of 1 in 1000 to 1 in 2500 individuals (46). It is caused by a homozygous mutation in the apoE2 genotype (approximately 1% of population) or a dominant negative mutation in the apo E gene, which serves as a ligand for chylomicrons, intermediate-density lipoproteins, and VLDL receptors in the liver. In the

presence of a secondary insult (concomitant genetic mutation, medication, or environment) there is abnormal uptake and metabolism of remnant particles (chylomicrons, intermediate-density lipoprotein, and VLDL) with subsequent accumulation of each in the blood. This disorder is an excellent example of the interaction of genetics and environment as the genetic abnormality is quite common but the expression of the clinical manifestations requires another abnormality which is frequently another disease or medication that effects lipid metabolism.

Isoform apoE4 is associated with an increase in LDL-cholesterol levels and thus a higher cardiovascular risk compared to apoE3; whereas apoE2 is associated with a mild decrease in LDL-cholesterol levels. Several rare APOE gene variants have been reported in different types of dyslipidemias including dysbetalipoproteinemia, familial combined hyperlipidemia (FCH), lipoprotein glomerulopathy, and autosomal dominant hypercholesterolemia due to molecular alterations in three main genes: LDLR, APOB and PCSK9. Clinical presentation of lipid disorders associated with APOE variants often strongly overlap related to common genetic and environmental factors (47).

PRESENTATION AND DIAGNOSIS

A secondary insult such as obesity, diabetes, or estrogen use is necessary for expression in childhood. The diagnosis of dysbetalipoproteinemia remnant removal disease should be suspected when total cholesterol and triglyceride levels (range from 300 to 1000 mg/dl) are roughly equal in magnitude (48).

Dysbetalipoproteinemia has been documented in the pediatric age group (44, 49, 50). A case series of 3 children from Vancouver, British Columbia, Canada demonstrated early presentation of the disorder (age range, 10–11 y) due to precipitating factors including hypothyroidism, partial LPL deficiency, and concurrent familial hypercholesterolemia (50). Each child presented with palmar and tuberoeruptive xanthomas.

Palmer crease xanthomas (lipid deposits in the palmar creases) are pathognomonic for this condition, although eruptive xanthomas are possible on pressure sites like the elbows, knees, and buttocks (48). A 30-y retrospective review of lipid disorders from a single clinical practice identified 105 patients with dysbetalipoproteinemia. Palmar crease xanthomas occurred in 20% of patients, cutaneous xanthomas in 18%, and tendon xanthomas in 13% (48).

The diagnosis of dysbetalipoproteinemia is confirmed by documenting elevated remnant lipoproteins, abnormal gel electrophoresis mobility, or by identifying the genetic defect (Arg145 →Cys) in apoE2 (51). Despite having normal or low LDL cholesterol and apo B concentrations, individuals with dysbetalipoproteinemia often have an elevated CVD risk due to the increased remnant particles (52, 53). Affected individuals also are at increased risk for peripheral vascular disease (53).

Current lipid-based diagnostic methods have important limitations. A 3-step algorithm has been proposed for the diagnosis of dysbetalipoproteinemia using total cholesterol and TG as a first step, the non-HDL-C/apo B ratio as a second screening criterion, and finally the APOE genotype, lipoprotein ultracentrifugation, or electrophoresis as a confirmatory test (54).

SCREENING AND DIAGNOSIS

Most cases of HTG are diagnosed in childhood most often because a family member had experienced a premature cardiac event, because their siblings were known to have elevated TG levels, or because abnormal test results were obtained during a routine examination (44).

Screening for dyslipidemia is recommended in children ≥ 2 years who have one or more of the following: (1) parents, aunts, uncles and/or grandparents (men ≤ 55 years old, women ≤ 65 years old) who have had a heart attack, treated angina, coronary artery bypass, graft/stent/angioplasty, stroke, or sudden cardiac death; (2) parents who have high blood cholesterol levels (>240 mg/dl); or (3) parental/grandparental family history is not known, or (4) the patient has two or more other risk factors for CAD (including hypertension, cigarette smoking, low HDL cholesterol, obesity (>30% overweight), physical inactivity and diabetes mellitus (1, 55, 56).

With newer recommendations of universal lipid screening between 9-11 years (2), it is likely that dysbetalipoproteinemia, and also FCHL or FHTG, may be detected more often in childhood. Any presentation of acute pancreatitis should prompt the need for a lipid profile. A fasting lipid profile (>12hours) should be obtained if TG are elevated in the non-fasting state. Cut points for normal and elevated TG levels are listed in Table 2.

Disorders of severe HTG are diagnosed based upon the degree of TG elevation and associated lipoprotein abnormalities (if any), the clinical features (if present), and a reliable family history, when available. Genetic testing is available for suspected cases of FCS and dysbetalipoproteinemia but is not necessary for treatment.

MANAGEMENT OF HTG

Secondary causes of HTG, including a variety of medications, are common. Therefore prior to implementation of a management plan, evaluation of secondary causes of HTG is recommended. When present, optimum treatment of secondary conditions, such as hypothyroidism, may be sufficient to correct the HTG. Medications known to cause elevations of TG should either be discontinued, if possible, or an alternative medication used.

Lifestyle Intervention

Adoption of a healthy lifestyle, including dietary modification, optimizing body weight, smoking avoidance/cessation, and physical activity, is the primary strategy for managing HTG in youth (2). Specific dietary recommendations include reducing simple carbohydrates including sugar sweetened beverages (56), substituting monounsaturated and n-6 polyunsaturated fatty acids for carbohydrate (57), and decreasing carbohydrate rich foods like white bread, rice and pasta (58). Thirty- sixty minutes of daily moderate to vigorous physical activity is also recommended for children between 2-21 years of age with TG elevations (2) as this degree of activity effectively reduces TG (59). Lifestyle recommendations for TG lowering are summarized in Table 4.

Table 4. Lifestyle Recommendations for Triglyceride Lowering in Children and Adolescents
1) Daily caloric intake should be < 25%–30% of calories from fat, <7% from saturated fat, <200 mg/dL of cholesterol*, decrease trans fat
2) Avoid sugar intake (ice cream, candy, baked goods) and sugar sweetened beverages (pop, juice, sports drinks)
3) Replace simple carbohydrates (white bread, white pasta, white rice) with complex carbohydrates (wheat bread, whole grain pasta, brown rice)
4) Replace carbohydrates with monounsaturated fat (olive oil, canola oil, nuts, seeds)
5) Increase omega 3 fatty acids (fish)
6) 30-60 minutes of moderate to vigorous exercise daily

* More severe elevations of TG may require reduction of fat to 10-15% of daily calories equivalent to ~10-25 grams/day. This is considered a very low-fat diet and should be done in consultation with a nutritionist and a pediatric lipidologist.

The goal of treatment in patients with FCS and MCS differs from other causes of severe HTG because these patients cannot metabolize TGs and fats. Additionally, the primary goal is prevention of pancreatitis by reducing TG concentrations in the blood. This may require a very-low-fat diet (<10-15% daily caloric intake from fat or <15-20 g/day total fat) along with restriction of simple, refined carbohydrates, though this is often difficult to maintain (60). Total carbohydrate limited to <60% daily caloric intake, adolescents advised to avoid alcohol and reproductive age females counselled about the use of oral contraceptives. Such diets should ensure 2-4% daily caloric intake of alpha linolenic and linolenic acid to meet essential fatty acid (EFA) needs.

As a way to increase calorie intake, medium chain triglycerides (MCTs), e.g., chain length of 10 and 12 carbons, can be considered. MCTs can be either added to infant formula or given as an oral solution to supplement fat calories. Dietary MCTs are directly absorbed into the portal vein and do not require transport by chylomicrons and as a result do not increase TG concentrations. Rouis et al. describe a unique patient with clinical features of LPL deficiency with a complete resolution of clinical symptoms with MCT oil and omega 3 fatty-acid therapy (61). It should be noted MCT oil does not contain EFAs (62).

Drug Treatment

Pharmacological management is sometimes useful in disorders resulting in severe HTG to prevent pancreatitis and/or reduce risk of CVD. Medications commonly used for TG lowering are presented in Table 5. It should be noted that although prescribed (55, 63-65), none are FDA approved for use in children and adolescents (<18 years of age) and may not be effective. In patients with FCS drug therapy with the drugs listed in table 5 are usually not effective and omega-3-fatty acids contribute to the dietary fat intake.

Table 5. Medications used for Triglyceride Lowering			
Medication	**Mechanism of Action**	**Lipoprotein Effects**	**Side Effects**
Fibric Acid Derivatives*	Agonist for PPAR alpha nuclear receptors that upregulate LPL and down regulate apo C-III causing ↑degradation of VLDL and TG	↓ TG (30-60%), ↑ HDL-C ↑ LDL particle size.	Cholesterol gallstones. Contraindicated in liver and gall bladder disease. Use caution in renal disease
Omega 3 fatty acids (fish oil) *	Decreases hepatic fatty acid and TG synthesis and VLDL release	↓ TG (20-50%), ↑ HDL-C, ↑ LDL-C, ↑ LDL particle size.	Fishy taste and burping
Nicotinic Acid*	↓ VLDL and LDL production and HDL degradation	↓ TG (10-40%), ↓ LDL-C, ↑ HDL-C, ↓ lipoprotein (a) ↑ LDL particle size.	Dose dependent hepatotoxicity, worsening glucose metabolism, and hyperuricemia.

*Not FDA approved for <18 years of age

Fibric acid derivatives (fenofibrate, gemfibrozil) lower blood TG levels by reducing VLDL production and promoting catabolism of TG through enhanced LPL activity. In general, fibrates lower TG concentrations by 30-60% (66, 67). They have a modest effect on increasing HDL-C levels but can increase LDL particle size. Since FCS results from a lack of LPL activity, a response to fibrates is not expected in FCS. Fibrates are usually effective in MCS as there is typically some LPL activity. Rare side effects include dyspepsia, diarrhea, an increase in transaminases, cholelithiasis, and deep venous thrombosis. Fibrates must be used with caution in patients with renal dysfunction and gall bladder disease. In most cases, fenofibrate is used, but gemfibrozil is preferred in renal insufficiency.

Long chain omega 3 fatty acids inhibit diacyl glycerol acetyl transferase (DGAT), reduce VLDL-TG synthesis, and increase the rate of peroxisomal beta oxidation in the liver. In adults, omega 3 fatty acids lower TG levels by 20-50% (68). These effects are primarily seen with prescription fish oils which contain approximately 465 mg of eicosapentaenoic acid (EPA) and 375 mg of docosahexaenoic acid (DHA) and require taking at least 2 grams of omega 3 fatty acids per day. Over the counter preparations have variable quantities of EPA and DHA resulting in variable TG lowering effects. Two small studies in children with hypertriglyceridemia did not find significant lowering of the TG levels (69, 70), however, the studies were likely underpowered. When using omega- 3 fatty acids in patients with severe hypertriglyceridemia it is important to ensure that the total fat intake is within the fat allowance permitted. Four capsules of omega-3 fatty acids provide 4 grams of fat/day.

Niacin lowers TGs 10-30%, increases HDL cholesterol by 10-40% and lowers LDL cholesterol by 5-20%. The most common complaint with its use is flushing due to the release of prostaglandin E2 in the skin. Flushing typically occurs 15-60 minutes after ingestion and can last up to 30 minutes. Aspirin 30 minutes before niacin can reduce flushing. Children often do not tolerate niacin.

Patients with LPL deficiency can be offered a trial of fibric acid derivatives but the response is quite variable since these agents work to lower plasma TG primarily by upregulating LPL activity, which is deficient in this condition (71). Omega 3 fatty acids lower plasma TGs in certain conditions of HTG, but they may actually aggravate the severe HTG of FCS and are therefore contraindicated in LPL deficiency (61).

Volanesorsen is an antisense oligonucleotide (ASO) which binds to and induces degradation of APO C3 mRNA in the hepatocyte, resulting in reduced apo C-III protein synthesis. The drug is administered by sub-cutaneous injection and mostly cleared through the kidney. Short term clinical trials demonstrated improved lipid profiles following weekly Volanesorsen injection in patients with severe HTG due to heterogeneous causes of HTG.

APPROACH, a phase 3, double-blind clinical trial randomized 66 patients with familial chylomicronemia syndrome to Volanesorsen or placebo for 52-week to evaluate the safety and effectiveness. Patients receiving Volanesorsen had a 77% decrease in mean TG levels, corresponding to a mean decrease of 1,712 mg/dL (19.3 mmol/L). TG levels less than 750 mg/dL were achieved in 77% of patients with FCS. Thrombocytopenia and injection-site reactions were common adverse events (72).

The COMPASS trial was a randomized, placebo-controlled, double-blind, phase 3 study done at 38 international clinical sites. Subjects were 18 years-of-age or older with multifactorial severe HTG or FCS, who had a BMI of $\leq$45 kg/m^2 and fasting plasma TG $\geq$500 mg/dL. Subjects were randomly assigned to subcutaneous Volanesorsen or placebo once a week for 26 weeks. Volanesorsen reduced mean plasma TG concentration by 71.2% from baseline to 3 months compared with the placebo group, representing a mean absolute reduction of fasting plasma TG of 869 mg/dL. The most common adverse event were injection-site reactions (average of 24% of all Volanesorsen injections vs 0.2% of placebo injections), which were all mild or moderate. One participant in the Volanesorsen group had thrombocytopenia and one patient experienced serum sickness (73). Rejected in 2018 by the U.S. FDA due to adverse effects on platelets, the EMA approved Volanesorsen for treatment of FSC in Europe the following year.

Acute management of HTG requires maintaining NPO status, especially if there is concomitant pancreatitis. A short-term insulin infusion can be tried especially in patients with diabetes, as insulin enhances LPL activity. An intravenous infusion of regular insulin at a rate of 0.1 to 0.3 units/kg/hour while monitoring blood glucose levels will result in a reduction of TG levels down by 40-80% in 24-48 hours (74-78). TG levels can be measured every 12-24 hours during insulin infusion, and glucose levels should be monitored every hour.

In individuals with primary HTG who have continued pancreatitis, plasmapheresis has been utilized. In this procedure plasma is separated from the blood and processed to eliminate selective components. The plasma is then reinfused, though on occasions it may be completely eliminated and replaced by an isovolumetric solution. Plasmapheresis can be carried out as either an emergency or a scheduled procedure. In situations where urgent, rapid and efficient reduction in TG levels is needed, such as in pancreatitis, plasmapheresis has proven a valid and safe technique and results in reductions of TG as much as 60% (79). A multicenter study recently published data demonstrating success using plasmapheresis to prevent pancreatitis in those who fail medical therapy (80).

Novel Therapies

Novel therapies for treatment of HTG are in development (Table 6). These agents increase clearance or reduce the production of triglyceride rich lipoproteins. Their clinical efficacy, cost-effectiveness, and indications, especially in children, have not yet been established.

Table 6. Triglyceride Lowering Agents in Development

Mechanism of action	Class/Drug	TG Lowering	Predominant Side Effects
Decreased production of TG/TRLP	MTP inhibitor (lomitapide)	35-65%	Mild GI side effects, transaminitis
	Apo B ASO (mipomersen)	8-10%	Injection site reactions, flu like symptoms and transaminitis
Increased TG/TRLP catabolism	ANGPTL3 mAb (evinacumab)	77-83%	Flu-like symptoms, dizziness, myalgia, nausea
	ANGPTL3 ASO (vupanorsen)	40-50%	Injection site reactions

COMPLICATIONS OF HTG

Cardiovascular Disease

Children and adolescents with persistently moderate to high levels of TG may be at increased risk for premature cardiovascular disease during adulthood. However, the extent to which HTG independently contributes to CVD has long been debated and remains unknown (3, 81-83). Some studies have shown an independent relationship between HTG and CVD, but effect sizes are small but significant when adjusted for both HDL and non-HDL-C (84, 85).

In FCHL the increased CVD risk in probands and first degree relatives is largely attributed to the increase in apo B (34) and/or lipoprotein (a) (86). Likewise, in dysbetalipoproteinemia the increased CVD risk is attributed to increased remnant lipoprotein particles (52, 53). A recent systematic review and meta-analysis of observational studies evaluating HTG and CVD found that fasting HTG was associated with an increase in cardiovascular death (odds ratios (OR) 1.80; 95% confidence interval (CI) 1.31-2.49), cardiovascular events (OR, 1.37; 95% CI, 1.23-1.53), and myocardial infarction (OR, 1.31; 95% CI, 1.15-1.4 (87).

To address a causal role for TG in the development of CVD, several Medellin randomization studies have been conducted. While TG raising variant alleles have been associated with clinical CVD endpoints, in most cases, a second lipid disturbance—usually depressed HDL-C—was concurrently associated (88). It appears TG may be part of a joint phenotype or a biomarker of metabolic risk that leads to CVD.

Pemafibrate, a selective peroxisome proliferator-activated receptor α modulator, has previously been shown to reduce TG levels and improves other lipid levels. In a multinational, double-blind, randomized, controlled trial of patients with type 2 diabetes, mild-to-moderate HTG (TG level, 200 to 499 mg/dL) and low HDL (HDL-C <40 mg/dL) Pemafibrate lowered TG, VLDL cholesterol, remnant cholesterol, and apolipoprotein C-III levels. However, the incidence of cardiovascular events was not lower among those who received Pemafibrate than among those who

received placebo (89). In a separate trial, Pemafibrate did not decrease liver fat content but had significant reduction in magnetic resonance imaging-estimated proton density fat fraction-based liver stiffness (90).

Pancreatitis

FCS commonly presents with spontaneous pancreatitis in the first decade of life as a result of the degree of TG elevation. In contrast, FHTG and dysbetalipoproteinemia usually require a secondary risk factor to incite pancreatitis in adolescence (42, 50).

HTG accounts for 1-4% of cases of acute pancreatitis (91). Though the exact mechanism of inciting pancreatitis is unknown, TG-rich chylomicrons are thought to impair circulatory flow in capillary beds of the pancreas causing ischemia and triggering an inflammatory response (11, 12). HTG is the most common cause of pancreatitis not due to gallstones or alcohol abuse (1, 2, 55, 92).

Pancreatitis generally occurs when TG levels exceed 1000-1500 mg/dL (93, 94) but TG between 200-1000 mg/dL can be seen in the early stages of acute pancreatitis of any etiology (95, 96). The risk of developing acute pancreatitis with serum TG >1000 and >2000 mg/dL is 5% and 10% to 20%, respectively (94). The presentation of pancreatitis usually includes abdominal pain, vomiting, and ileus (97). When the diagnosis is suspected, serum TG levels should be measured since elevated concentrations in the blood can diminish rapidly. Thus, a delay in obtaining TG concentration may lead to falsely low levels. Prevention of pancreatitis relies on consistent TG lowering. Lowering levels to < 500 mg/dL effectively prevents recurrences of pancreatitis in most affected individuals (94). Prevention of pancreatitis is crucial since mortality from pancreatitis can be as high as 20% (98).

CONCLUSIONS

Identification of genetic causes of severe HTG in pediatric patients is important given the risk for pancreatitis and/or early CVD. Lifestyle modification is central to prevention, but often is not sufficient. While medications can be helpful in lowering TG, in some disorders they have no benefit. Novel therapies may be on the horizon. Whether these therapies will be beneficial in treating primary disorders of HTG in children and adolescents and their associated complications remains to be seen.

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