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SECONDARY HYPERTRIGLYCERIDEMIA

Piers R Blackett MD. Department of Pediatrics, University of Oklahoma Health Sciences Center 1200 Children's Ave, Oklahoma City, Oklahoma 73104
Don P Wilson MD. Department of Pediatrics, Pediatric Endocrinology and Diabetes, Cook Children's Medical Center, 1500 Cooper St Floor 2, Fort Worth, TX 76104
Catherine McNeal, MD, PhD. Department of Pediatrics, Department of Internal Medicine, Division of Cardiology, Scott & White Healthcare, 2401 S. 31St St., Temple TX 76508

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ABSTRACT

Hypertriglyceridemia (HTG) is often secondary to obesity-related insulin resistance, but other common and rare causes should be considered. Genetic background, gestational conditions and nutrition in infancy and childhood contribute to HTG associated with formation of an atherogenic dyslipidemia consisting of high TG, low HDL-cholesterol, increased LDL particle number or apolipoprotein B and smaller LDL size and density. Very high TG levels generally result from defective disposal by lipoprotein lipase and can cause pancreatitis. Defining and treating the underlying cause are steps towards restoring the lipids and lipoproteins to normal. Renal, hepatic, endocrine, immune, and pharmacological causes are in the differential diagnosis. Rare diseases such as lipodystrophy and glycogen storage disease are particularly challenging and require specific management strategies. Prevention of acute pancreatitis by lowering TG is a priority when TG is very high (> 500mg/dl), and lifestyle modification is the basis of general management for cases with high and moderately high levels ranging from above the 95th percentile for age to 500 mg/dl. Since TG metabolism is associated with generation of an atherogenic dyslipidemia, predictors of coronary artery disease (CAD) such as LDL-C and non-HDL-C become targets when they exceed cut points. For complete coverage of all related aeas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

INTRODUCTION

This article is an overview of HTG causes that begin during gestation and present in childhood and adolescence, either interacting with genetic background or directly contributing to the TG levels. These disorders are common, such as obesity, or less common such as glycogen storage disease and lipodystrophy for which treatment can be more challenging. Also both common and rare pharmaceutical agents need to be considered as causes since treatment modification can contribute to reversing the HTG. Dyslipidemia presenting in adolescence is often associated with one or more components of the metabolic syndrome, i.e. obesity, hypertension and impaired glucose tolerance, and presents with high TG and low HDL-C. (1, 2) However, a wide variety of other causes can contribute to the differential diagnosis of HTG.

Genetic background, gestational factors, infant and childhood nutrition, demographic and environmental factors are important considerations. Also, understanding how TG is distributed among lipoproteins and how it influences lipoprotein composition and subsequent lipolysis, uptake by receptors and the arterial wall provides important background for understanding association with specific diagnoses and when treatment can be effective.

TG-RICH LIPOPROTEIN COMPOSITION

Triglyceride (TG) is normally located in the core of spherical circulating plasma lipoproteins. In the fasting state, VLDL (very low density lipoprotein) has 55% TG and 22% cholesterol, LDL (low density lipoprotein) has 5% TG and 50% cholesterol, and HDL (high density lipoprotein) has 5% TG and 20% cholesterol (3). Increases in hepatic production of VLDL account for the majority of HTG cases resulting in a disproportionate increase in TG. However, VLDL is 22% cholesterol, which also is increased when VLDL production is excessive or when its disposal is defective. In contrast, intestinally derived chylomicrons increase after meals and contain 90% triglyceride and only 3% cholesterol, but are efficiently catabolized by lipoprotein lipase, and their resulting remnant particles are taken up by hepatic receptors. Normally, TG reaches a peak 3 to 6 hours after a fat-containing meal and declines until there are no chylomicrons after ten hours of fasting. However, when disposal mechanisms are defective, chylomicrons account for very high TG levels and VLDL particles compete for lipolysis by lipoprotein lipase. Under these conditions the ratio of triglyceride to cholesterol approaches 10 to1, whereas the ratio is closer to 5 to1 when VLDL predominates. Excessive cholesterol enrichment of VLDL approaching a 1:1 ratio occurs when disposal of chylomicron and VLDL remnants are delayed – a defect usually presenting in adulthood and termed familial dysbetalipoproteinemia, a disorder attributed to variation in apoE's amino acid sequence. (4)

NON-HDL CHOLESTEROL IN HTG

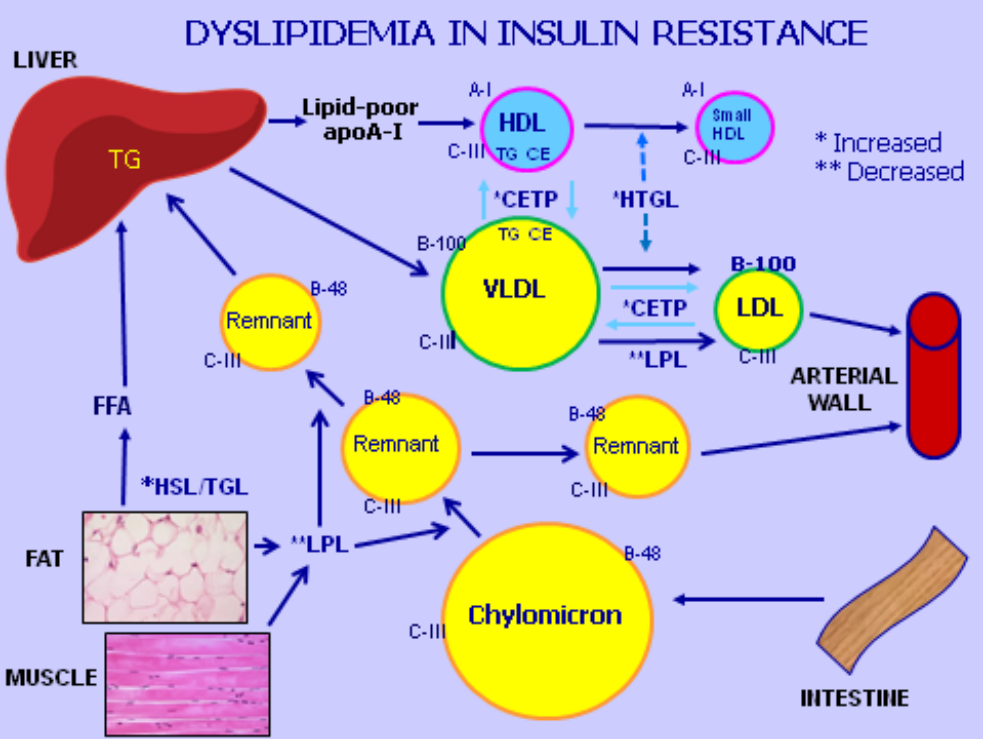
Since increased TG levels are often associated with atherogenic dyslipidemia, early lesion formation is likely. The Bogalusa Heart Study found that TG, total cholesterol and LDL-C in children and young adults aged 2 to 39 years of age were associated with post-mortem lesions in the coronary arteries and aorta (5), findings supported by the autopsy-based Pathological Determinants of Atherosclerosis in Youth (PDAY) study (6). However, the role for TG in atherosclerosis has remained less clear than for cholesterol. Adult cardiovascular disease has been associated with HTG in a meta-analysis (7), but in a second larger study the association was reduced by correcting for lipid and non-lipid risk factors. (8) Therefore risk attributed to intermediate TG elevation (150-499 mg/dL) is dependent on the cholesterol content of TG enriched particles in the non-HDL fraction, since cardiovascular risk is based on evidence that LDL-C and non-HDL-C predict end-points in adults.(9) The Bogalusa study showed that elevated TG in childhood is associated with subsequent intima media thickness in adulthood, but when adjusted for other lipid risk factors there was no association, whereas non-HDL-C remained predictive.(10) Consistently stronger prediction by non-HDL-C than LDL-C indicates that the cholesterol content of TG-rich lipoproteins (VLDL, IDL) represented by non-HDL-C can be regarded as a better predictor of risk than TG. This is also supported by the PDAY study in

which non-HDL-C was associated with fatty streaks and raised lesions (11), and risk factors, including non-HDL-C and low HDL-C, accelerated progression of flat fatty streaks to raised lesions in the second decade.(6) Childhood non-HDL-C, TG, apoB and apoB:apoA-I ratio all predicted carotid IMT after more than 20 years of follow-up, with non-HDL-C being superior to TG.(10) Therefore targeting non-HDL-C in cases with intermediate triglyceride levels is a useful and productive strategy endorsed by the 2011 NHLBI (National Heart Lung and Blood Institute) Expert Pediatric Committee recommendations.(9)

TG METABOLISM IN INSULIN RESISTANCE

Common secondary HTG occurs in insulin resistant states such as obesity and type 2 diabetes (T2D) and can often become modified or exacerbated by other secondary causes. Since the abnormal lipid metabolism in insulin resistance has been extensively studied it serves as a foundation for understanding secondary dyslipidemia and potential for exacerbation by other causes (figure 1).

Figure 1. Lipoprotein Metabolism in Insulin Resistance: A combination of excess production and disposal processes results in secondary HTG and atherogenic dyslipidemia in the insulin resistant state. Chylomicrons and VLDL production originating from the intestine and liver are increased. Mobilization of free fatty acids (FFA) from fat cells by hormone sensitive and TG lipases (HSL/TGL) provides the liver with substrate for VLDL formation. Dietary intake of fat provides the intestine with TG for chylomicron formation, which is upregulated in insulin resistance. Hepatic VLDL containing excess apoC-III relative to apoE is increased; apoC-III delays receptor-mediated hepatic uptake of VLDL and chylomicron remnants resulting in formation of intermediate density lipoproteins (IDL, not shown) and smaller and denser low density lipoproteins (LDL). Lipoprotein lipase (LPL) is inhibited by apoC-III and decreased by insulin resistance and/or deficiency. Cholesterol ester transfer protein (CETP) is upregulated resulting in exchange of TG and cholesterol ester (CE), leading to TG enrichment of LDL and HDL. Both become substrates for hepatic triglyceride lipase (HTGL), which is upregulated and acts on TG-enriched HDL and LDL to make them smaller, atherogenic and dysfunctional. Apolipoproteins A-I, B-48, B-100, C-I, C-II, C-III (C), and E are labelled and play important roles in lipoprotein metabolism.



HTG PREVALENCE

The prevalence of HTG in children aged 12 to 19 years, defined as levels above 150 mg/dL, is 10.2% and is higher in boys (11.2%) than girls (8.8%).(12). Abnormal TG levels for children are generally classified on the basis of cut points based on population norms recommended by the American Academy of Pediatrics and the American Heart Association.(13) The 50th to 95th percentile values for TG in children are presented in Table 1.(14)

Table 1. Triglyceride Levels for Males and Females 5-19 years of age

Percentile	Males			Females		
	5-9 yrs	10-14 yrs	15-19 yrs	5-9 yrs	10-14 yrs	15-19 yrs
50th	48	58	68	57	68	64
75th	58	74	88	74	85	85
90th	70	94	125	103	104	112
95th	85	111	143	120	120	126

Mean concentration of triglycerides (mg/dL). Adapted from: Tamir I, Heiss G, Glueck CJ, Christensen B, Kwiterovich P, Rifkind B. Lipid and lipoprotein distributions in white children ages 6–19 yrs: the Lipid Research Clinics Program Prevalence Study. J Chronic Dis. 1981; 34(1):27–39

Severe secondary hyper-TG, defined as levels above 500 mg/dL, presents a significant risk for acute pancreatitis, especially when lipoprotein lipase-mediated clearance is saturated (> 800 mg/dL) causing the triglyceride to attain very high levels often exceeding 1000 mg/dL, with

appearance of chylomicrons on standing plasma. Moderate HTG, defined as levels 150-499 mg/dL, is a risk factor for CVD. These children tend to be undertreated (14), despite potential for reversal [6] and primary prevention of cardiovascular disease. (9, 15, 16)

GENETIC BACKGROUND

Commonly encountered HTG is usually multigenic and results from small-effect variants (single nucleotide polymorphisms) in genes such as *APOA5, GCKR, LPL, and APOB* and together, more than 20% of susceptibility is accounted for by common and rare variants.(17) The population frequency of the HTG phenotype was shown in the Copenhagen General Population Study in which a small percentage have a non-fasting TG level greater than 1000 mg/dL, whereas the majority have intermediate levels ranging from greater than the 95th percentile to 500 mg/dL and higher, often secondary to an underlying disorder.(18)

Gene-Environment Interaction

Heterozygous relatives of cases with homozygous familial chylomicronemia carry loss-of-function mutations in genes such as *LPL*, *APOC2, APOA5, LMF1, and GPIHBP* are asymptomatic. Although they have close to normal lipids they may develop severe HTG (19) when exposed to exogenous factors such as alcohol, oral estrogen treatment, obesity and pregnancy posing a risk for acute pancreatitis (20, 21). These observations suggest that adolescent carriers, such as siblings of severely affected homozygotes, should be identified by genotyping to detect carriage of a single allele. If they are carriers, they should be advised on avoiding risk factors such as alcohol and pharmaceutical agents discussed further in this review.

Susceptibility to environmental factors is common; for example a typical case scenario occurs in a child with a mild increase in LDL-C who develops an increase in triglyceride and non-HDL-C during adolescence. The HTG is worsened by the onset of obesity and participation in social activities involving alcohol consumption and taking oral estrogens as birth control pills. Since insulin resistance and T2D have become more common in adolescence, the gene-environment interaction results in mixed dyslipidemia (22) with variable elevations in TG and cholesterol.(23) The interaction is common in cases with a pedigree suggestive of familial combined hyperlipidemia (FCHL) reported to have a prevalence of 1 per 100 and characterized by variable lipid profiles among family members with apparent dominant inheritance, but some have a high cholesterol and others have a high triglyceride or elevations in both. The phenotype has also been defined as having elevated apoB and TG levels in at least two affected family members, and has been associated with several variants including *USF1* (24), supporting a multigenic and not a monogenic origin as originally thought.(25)

Mendelian Randomization

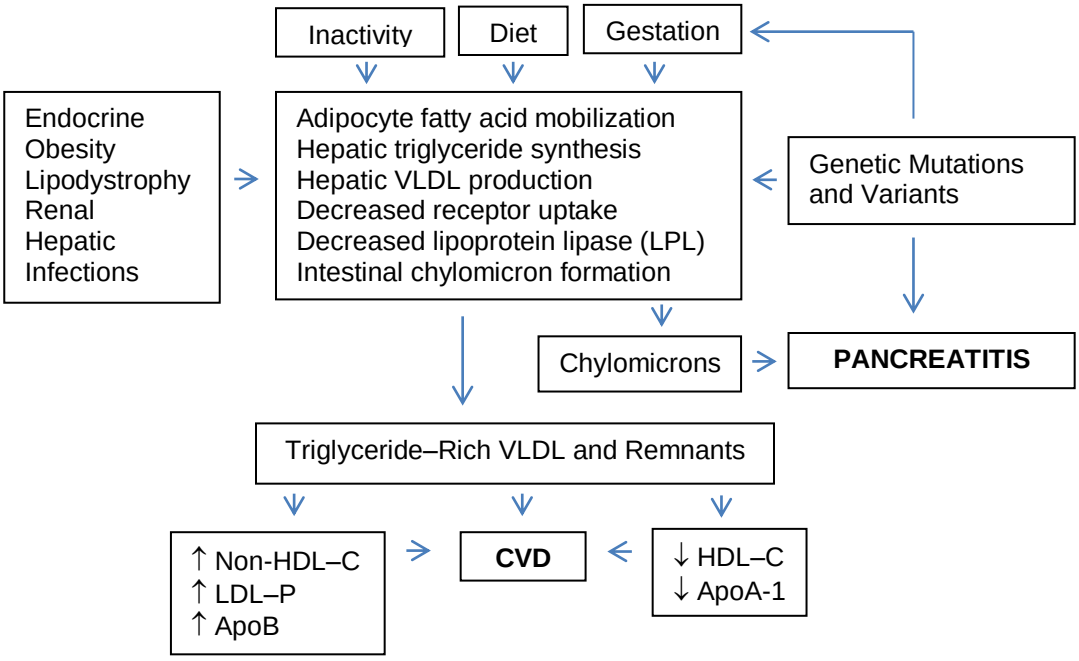
The important role of genetics in determining HTG associated risk is highlighted by recent Mendelian randomization studies in which individuals carrying a protective mutation are compared to unaffected carriers over a lifetime. Recent studies on loss of function *APOC3*

mutations are a classic example. As compared with non-carriers, carriers of *APOC3* mutations had 39% lower TG levels, 16% lower LDL cholesterol levels, and 22% higher HDL cholesterol levels.(26) The risk of coronary heart disease was reduced by 40% and was attributed to the lifetime effect of the normal or low levels.(26) These remarkable findings were replicated in a Danish study with similar reductions in TG and cardiovascular disease in individuals with the protective *APOC3* mutations.(27) Randomization occurs in populations when sorted according to genotype and provides study design analogous to that used in pharmaceutical trials, but with the added benefit that exposure to low levels in the genetically protected arm of the study begin at birth and continue over the lifespan. These landmark studies contribute evidence that a low TG and an associated improved lipid profile is beneficial, and supports interventions such as lifestyle, and pharmaceutical lowering when indicated, beginning at young ages.

DEVELOPMENTAL FACTORS

A sequence of factors, beginning during gestation, influence the development of hypertriglyceridemia (HTG) (Figure 2).

Figure 2. Developmental Influences. Metabolic processes are programmed during gestation and early childhood and are influenced by disease states and environmental factors such as dietary excess and inactivity. The HTG is associated with atherogenic dyslipidemia consisting of increased non-HDL-C (non-high density lipoprotein-cholesterol), LDL-P (LDL particle number), apoB (apolipoprotein B), decreased HDL-C (high density lipoprotein cholesterol) and decreased apoA-I.



Maternal nutrition and placental function affect nutrient supply for fetal growth and influence subsequent development of the metabolic syndrome.(28) Overweight children who were small for gestational age (SGA) have increased risk for components of the metabolic syndrome

compared to overweight children who were appropriate for gestation age (AGA). These effects on growth are attributed to restriction in intrauterine growth.(29) After gestational programming (29), nutritional and endocrine factors play a role during childhood and affect development of risk factors including dyslipidemia (Figure 1). Preterm infants have higher meal frequency than older children and adults, but less efficient fat digestion and absorption, making it difficult to cope with a high fat intake relative to their body weight.(30) Consequently, HTG is a frequent occurrence. Since pancreatic lipase and bile salt secretion is often inadequate for facilitating absorption of fat and its utilization as a source of energy, premature babies often fail to thrive and need exogenous fat as a component of total intravenous parenteral nutrition titrated according to the TG level. (31) If lipoprotein lipase is genetically defective plasma clearance is even more compromised and severe HTG occurs during lipid infusions. If clinical circumstances necessitate that fats be restricted, essential omega-3 and omega-6 fatty acids are supplied for development of the brain and retina, and medium chain TG are an effective energy source without raising TG levels since they are directly transported to the liver via the portal system.(32)

Increases in obesity, particularly as abdominal fat, during childhood predict the metabolic syndrome and compound the effect of an abnormal birth weight.(33) Also low adiponectin has been associated with insulin resistance, particularly in African American youth and compounds dyslipidemia.(34) The adrenal axis may be involved; urinary free cortisol is associated with the metabolic syndrome in children (35), but the role of cortisol is controversial.(36, 37) Conversion of cortisone to cortisol by 11 beta -hydroxysteroid dehydrogenase type 1 (11 beta -HSD1) results in cortisol excess leading to insulin resistance, hypertension, and dyslipidemia. Inhibition of the enzyme results in reversal of metabolic syndrome criteria providing potential for pharmaceutical intervention.(38) Normal puberty causes a transient increase in insulin resistance, attributed to maturational increases in sex and growth hormones, and may increase prevalence of both the metabolic syndrome and type 2 diabetes.(39)

MEDICAL CAUSES

Endocrine, hepatic, renal, and immune causes are suspected based on history and physical findings followed by confirmatory laboratory testing. Variable modification of the lipid profile occurs (Table 2).

Table 2. Secondary HTG Causes, lipid effects and mechanism

a). HTG (variable hypercholesterolemia)				
Disease	**Trigl**	**Chol**	**HDL-C**	**Mechanism**
Obesity	++	sdLDL + apoB	-	Hepatic production
Type 2 diabetes	++	sdLDL + apoB	-	Hepatic production and deficient disposal
Type 1 diabetes	+ or ++	+	-	Hepatic production and deficient disposal
NAFLD	++	sdLDL	_	Hepatic production of large VLDL
GSD 1	++	++		Hepatic production
Bile duct obstruction		+++		LpX formation from albumin, globulin & lipids.
Cushing's disease	+	+	-	Insulin resistance effects
Lipodystrophy	++		-	Secondary LPL deficiency and diabetes
Stress and trauma	+	+		Increased stress hormones
Pregnancy	+	+		Progesterone effects
CRI	++	+	-	Similar to metabolic syndrome
HIV	+	+		Inflammation, treatments, lipodystrophy
Rheumatoid arthritis	+	+		Inflammation, cytokines
Lupus	+	+		Inflammation, cytokines
Gammopathies	+	+		Antibodies to LDL-R and LPL
b) Hypercholesterolemia (variable HTG)				
Lysosomal acid lipase def.		++	-	Excess cholesterol synthesis (high liver enzymes and excess cholesterol storage),
Bile duct obstruction		+++		LpX formation from albumin, globulin & lipids.
Hypothyroidism	+	++		LDL receptor deficiency
Growth hormone deficiency		+		LDL receptor deficiency
Nephrotic syndrome	+	++		Increased synthesis (low fatty acids)
Saturated and trans fats		+		Dietary excess and LDL-R down-regulation
Anorexia nervosa		+		Nutrient deficiencies

Abbreviations: sdLDL = small dense LDL, NAFLD = non-alcoholic fatty liver disease, GSD = glycogen storage disease, LpX = lipoprotein X, LPL = lipoprotein lipase, CRI = chronic renal insufficiency, HIV = human immunodeficiency virus.

Obesity:
Obesity has prevailed as the most prominent cardiovascular risk beginning in childhood and dietary factors such as excessive consumption of refined carbohydrates, saturated fat and trans fatty acids not only contribute to weight gain but also cause dyslipidemia.(9) Children and adolescents are increasingly referred for obesity associated with dyslipidemia constituting HTG coupled with small dense LDL and low HDL-C (40, 41) , and with resistance to insulin in muscle and adipose tissue leading to increased plasma insulin and free fatty acids.(42) Consumption of high amounts of carbohydrate and fat, being physically unfit, and having close relatives with similar presentations and progression to T2D or manifestations of the metabolic syndrome is often evident.(43) Physical characteristics include being overweight or obese; the distribution of fat is generalized but consistently associated with an increased waist circumference, the latter strongly predicting adolescent-onset risk factors.(44, 45) The skin is hyper-pigmented and thickened at characteristic locations around the neck, knees, elbows and sites of friction. Indeed, the condition called acanthosis nigricans is associated with insulin resistance (46) and thought by many to be a central component of the metabolic syndrome for which American Indian and Hispanic ethnic groups are particularly predisposed, but Caucasians and African Americans also have high rates.(43)

Resistance to insulin action results in mobilization of adipocyte TG and increased fatty acid availability for uptake by muscle and an inverse association with insulin resistance.(47) The increased hepatic supply of fatty acids coupled with insulin-stimulated hepatic TG synthesis results in increased VLDL formation and HTG (42, 48) constituting a component of apoB-containing VLDL particles (49, 50); and increased chylomicron production contributes to the TG level (Figure 2).(51) The effect on lipoproteins is significant since it alters function in favor of atherogenesis. An entropic mechanism involves TG-rich particles exchanging their TG for cholesterol ester via cholesterol-ester transfer protein (CETP) thereby enriching LDL and HDL with TG; a process that is increased by insulin resistance.(52) Both LDL and HDL become substrates for hepatic TG lipase, which is up-regulated (53) leading to formation of small dense LDL and small HDL prone to degradation.(54, 55)

Type 2 Diabetes:
Atherogenic dyslipidemia with increased triglyceride and LDL-C but low HDL-C precedes adult-onset T2D in association with persisting insulin resistance. (56) LDL glycation and oxidation is increased (57, 58) accounting for increased atherogenesis (59). In the Treatment Options for T2D in Adolescents and Youth (TODAY) trial, 699 adolescents were studied in three treatment groups receiving Metformin alone, Metformin with Rosiglitazone and Metformin with intensive lifestyle. 21% had a high triglyceride or were on a lipid-lowering medication at baseline and 23 % had a high level after three years. During this same period apoB increased from a mean value of 76.6mg/dl to 80.1mg/dl associated with deterioration in glycemic control attributed to a decline in β-cell function. However, the intensive lifestyle arm had significantly lower TG levels after three years. (60) The data indicate that T2D in youth is severe with significant cardiovascular risk and difficult to control requiring a multidisciplinary approach (61)

Type 1 Diabetes:

Children with type 1 diabetes (T1D) tend to have elevations in TG and cholesterol when insulin supplies are insufficient, reflecting dependence of lipoprotein lipase on insulin for synthesis and secretion. Increased triglyceride and cholesterol correct after two weeks of the intensified insulin delivery (62), and the low HDL-C increases after two months.(63) When cases present with severe insulin deficiency and ketoacidosis, TG and cholesterol attain very high levels but normalize on standard treatment with insulin and intravenous fluids.(64, 65) These changes reflect the role of insulin in lipoprotein lipase transcription, synthesis and secretion. Intensified insulin delivery increases apoA-I and HDL-C even when control of the diabetes reflected by glycosylated hemoglobin remains unchanged.(66) However, the relatively normal lipid profiles seen in treated patients with T1D is a paradox since the risk for CVD persists and remains a frequent cause of death (67), but development of renal complications plays a compounding role.(68) Subcutaneous insulin bypasses physiological insulin delivery to the liver, and also results in a delayed plasma insulin peak compared to physiological insulin secretion from the pancreas (69), but the resulting delay in chylomicron clearance was not found to be associated with glucose control or elevated fasting TG in adolescents. (69) However, potentially atherogenic apoB-48 containing remnants are increased after a meal challenge (70) and increases in free fatty acids, a correlate of post-prandial TG, (71) are harmful to the endothelium by inducing pro-inflammatory effects.(72)

ApoC-III, a correlate of triglyceride, has been implicated in the pathogenesis of atherosclerosis (73) in hyperglycemic and insulin resistant states and may have an atherosclerotic role in T1D. The apoC-III promoter contains both a carbohydrate response element that is responsive to glucose fluctuations (74) and an insulin response element (75) making it susceptible to both glucose fluctuations and insulin deficiency since it is normally down-regulated by insulin. Observations in patients with T1D provide supportive evidence that increased apoC-III is associated with poor glucose control (76, 77) and being overweight.(78) In the DCCT/EDIC T1D cohort with a significant adolescent aged population at onset, apoC-III was associated with retinopathy (79) and albuminuria (79, 80), implicating apoC-III and associated TG-rich lipoproteins in microvascular disease.(81)

Lipodystrophy:

Congenital and autoimmune lipodystrophies (82) are a group of genetic and acquired disorders characterized by loss of body fat, which is either partial or generalized.(83) The degree of fat loss determines the severity of metabolic complications such as HTG, ectopic fat accumulation, insulin resistance and progression to diabetes. Loss of adipocytes results in progressive LPL deficiency and chylomicronemia. Reduction in fat intake is effective in reducing risk for pancreatitis; however, insulin resistance and high carbohydrate intake may result in excess VLDL production requiring the use of prescription omega-3 fatty acids and fibrates. Metformin is the drug of choice for diabetes but trial evidence is lacking for the specific use of glucose-lowering agents in lipodystrophy.(83) Loss of adipocytes also leads to acquired leptin deficiency and severe hyperphagia making dietary management of HTG, glucose intolerance and overt diabetes difficult. Recent availability of recombinant leptin (metreleptin, Amylin Pharmaceuticals) has greatly improved outcomes and quality of life; treatment trials for children are in process.

Although formation of leptin antibodies has attenuated the effects(84), follow-up studies suggest that low titers may not result in significant decline in the clinical response.

Hypothyroidism:
Overt hypothyroidism usually secondary to autoimmune or congenital hypothyroidism commonly presents in childhood and at onset is characterized by an increase in LDL-C and apoB because of a reduced number of LDL receptors (85). In subclinical hypothyroidism the lipid profile is characterized by normal or slightly elevated total cholesterol levels and LDL-C in adults (85) but this observation has been less evident in children. (86)

Growth Hormone:
Growth hormone deficiency and excess are both causes of hyperlipidemia. GH deficiency down-regulates the LDL receptor (87) and can result in elevations in total cholesterol and LDL-C that are reduced by treatment (88); whereas excess tends to mobilize fatty acids and increase VLDL triglyceride (89, 90), as seen in cases with acromegaly or gigantism in childhood.

Non-Alcoholic Fatty Liver Disease (NAFLD):
NAFLD, manifesting as ectopic fat deposition in the liver, is observed in obese children and adolescents in association with increased visceral fat and metabolic syndrome criteria. (91) The condition is associated with insulin resistance and high TG independent of intra-myocellular fat.(91)

Hepatitis C:
Hepatitis C is associated with steatosis and a unique dysmetabolic syndrome characterized by insulin resistance, inflammation-induced atherosclerosis but a low cholesterol level.(92) The virus interferes with distal steps in cholesterol synthesis and with apoB secretion, but risk for atherosclerosis is attributed to vascular inflammation. (93, 94)

Glycogen Storage Disease (GSD):
GSDs are associated with HTG (95, 96) and present as significant pediatric challenges since the onset is at an early age. Type I GSD is caused by a recessively inherited defect in glucose-6-phosphatase, and accounts for more than 60% of the GSD types involving the liver and results in the highest TG levels due to the most excessive VLDL production. It presents during the first year of life with severe hypoglycemia and hepatomegaly caused by the accumulation of hepatic glycogen. Increased VLDL production is associated with TG-rich particles containing excess apoC-III and apoE.(96) In addition, the metabolic consequences of impeded glucose formation and excessive anaerobic glycolysis manifest as hypoglycemia with lactic acidemia, hyperuricemia and dyslipidemia. Impaired growth factor production and acidosis result in poor growth and delayed puberty. Many of these effects, including impaired growth, can be reversed by sustained correction of hypoglycemia to normal with dietary sources of complex carbohydrate. Restoration of normoglycemia results in less stress-hormone induced stimulation of metabolic excesses derived from activated anaerobic glycolysis. Continuous complex carbohydrate feeding regimens are prescribed as frequent meals and supplementation with corn-starch.(97) However, to effectively normalize the TG, frequent corn-starch dosing is

needed to achieve blood glucose levels continuously above 75 mg/dL, especially at night.(95) This approach involves high carbohydrate intakes, which in the long term may increase VLDL production often resulting in requirement for lipid lowering medications.(96)

Nephrosis:

Nephrosis is associated with increased cholesterol synthesis and increased TG attributed to lipoprotein lipase inhibition. (98) A two-phase dyslipidemia occurs in which TG hydrolysis by lipoprotein lipase is impaired when albumin levels are too low to remove fatty acids at an adequate rate after hydrolysis (99). Association with atherosclerosis is in part attributed to increases in Lp(a) and apoC-III. (98, 100)

Findings in chronic kidney disease in children resemble those in adults and simulate atherogenic dyslipidemia seen in the metabolic syndrome. (101)

Immune:

Immune causes are rare in adults and children but should be considered in specific clinical situations. HIV (human immunodeficiency virus) is associated with partial lipodystrophy and insulin resistance. The lipid profile before treatment shows a high triglyceride, low HDL-C and small dense LDL (102), and subsequent treatment with protease inhibitors can make the situation worse (103). In gammopathies such as in Hodgkin's disease, antibodies can sequester factors required for LPL activity (104) or they can impede lipoprotein uptake by receptors (105). Although less frequent than in adults, monoclonal or oligoclonal gammopathies, predominantly IgG mediated, occur in children with various autoimmune diseases, hematologic diseases, malignancies, transplantations, and immunodeficiencies. (106)

PHARMACOLOGICAL CAUSES

Pharmacological agents have significant effects on plasma lipids. In some cases the mechanism is known but is frequently often uncertain or unknown. The potential for causing dyslipidemia is particularly important when the patient has a genetic background that interacts. Changing the medication or treating the dyslipidemia are both options, especially when the disease requires long term management. Each medication class has characteristic effects on the lipid profile but some such as glucocorticoids, oral estrogens and alcohol may increase HDL-C and others may increase both cholesterol and triglyceride (Table 2)

Table 2. Classes of Medications and Examples Causing Hypertriglyceridemia in Childhood.

Medication Class	TG	TC	HDL-C	Examples
Glucocorticoids	++	+	+	prednisone, hydrocortisone
Oral estrogens	+	+	+	ethinyl estradiol
Anabolic steroids	+	+	-	depo-testosterone, oxandrolone

Estrogen receptor blockade	+			tamoxifen
Retinoids	+		-	isotretinoin
Immune suppressants	+	+		cyclosporine, sirolimus, tacrolimus
Protease inhibitors	+		-	ritonavir, nelfinovir and indinivir
Diuretics	++		-	chlorthiazide, diuril
Antipsychotics	+		-	clozapine, olanzapine, cimetidine
Beta blockers	+		-	propranolol, labetelol
Bile acid sequestrants	+			pholestyramine, colestipol, cholesevelam
Alcohol	+		+	spirits, wines, beers

Glucocorticoids

Glucocorticoids, especially in high doses, cause significant combined dyslipidemia and the effects on lipids may be compounded by other medications, the disease itself, or the patient's genetic background. Lipid changes during treatment of chronic illnesses show elevations in triglyceride and LDL-C due to increased production, with variable changes in HDL-C but often lowering.(107) The effects may depend on the preparation used, dose and disease being treated. (108) Combination drug therapy with L-asparaginase, an inhibitor of lipoprotein lipase, used for the induction phase in leukemia therapy can cause marked elevations in TG and is also diabetogenic (109). Lipid-lowering to prevent acute pancreatitis and thrombotic events is possible without stopping the chemotherapy (109).

Estrogens

Oral estrogens such as ethinylestradiol usually prescribed with progestogen as oral contraceptives increase the production rate of apoB-containing lipoproteins but the increase is counterbalanced by an increased catabolic rate (110). This finding accounts for only a slight increase in cholesterol and triglyceride within the normal range in adolescent girls (111), however interaction with obesity is possible with respect to LDL-C and fasting glucose (112). Reducing the dose of estrogen from the previously prescribed high dose preparations was effective in offsetting cardiovascular risk, however interactions with other risk factors such as smoking may occur.(113)

Estrogen receptor blockade with Tamoxifen has been associated with mild hyper-TG in women treated for breast cancer or its prevention, but it has rare use in childhood except for treatment of pubertal gynecomastia.

Retinoids

Retinoids such as Isotretinoin (Accutane, 13-cis-retinoic acid) has an indication for severe nodular acne and can be prescribed for as long as 20 weeks, but careful monitoring is required. Severe HTG resulting from lipoprotein lipase inhibition frequently occurs, and can cause acute pancreatitis (114, 115). It acts via retinoic acid and retinoid x receptors (116) and there is also ongoing interest in use for cancer therapy and chemoprevention.(117)

Immune Suppressants

Cyclosporine (118), sirolimus (119) and tacrolimus are used in transplant patients and immune-mediated diseases in children requiring long term treatment and monitoring when indicated (120, 121). The mechanism is via down-regulation of hepatic 7alpha-hydroxylase and myocyte and adipocyte lipoprotein lipase down-regulation. (122)

Protease Inhibitors

Protease inhibitors are associated with HTG and low HDL-C and add to the effects of the lipodystrophy syndrome occurring before anti-retroviral treatment of human immunodeficiency virus infections in pediatric cases, particularly during adolescence (123). Drugs such as ritonavir, nelfinovir and indinivir cause more severe dyslipidemia than others (124). Nucleoside reverse transcriptase inhibitors can also cause TG and cholesterol elevations. (125)

Bile Acid Sequestrants

Bile acid sequestrants should be avoided in cases with mixed dyslipidemia since they elevate TG. (126) Fibrates or omega-3s, although effective in lowering TG, may transiently raise LDL-C during lipolysis of VLDL and conversion to LDL .

Diuretics

Diuretics including thiazides and loop diuretics such as furosemide alone or as combination therapy for hypertension raise cholesterol and TG and lower HDL-C in a dose dependent manner and more so in African Americans. (127)

Beta-Blockers

Beta-blockers increase TG and lower HDL-C especially preparations without alpha-blocking activity but have rare indication in childhood since combination therapy for hypertension does not have trial evidence, (128) but they are used for management of arrhythmias.

Antipsychotics

Antipsychotics have pediatric psychiatric indications and agents such as clozapine and olanzapine induce HTG. However, it is not clear if the effect is independent of HTG induced by increased appetite and resulting weight gain typical of this class of medications and may require prescription changes or behavioral modification when possible.

Anabolic Steroids

Covert use of anabolic steroids in adolescent athletes and should be suspected with HTG and unusually low HDL-C levels. Medical use of oxandrolone for growth or androgens for aplastic anemia is rare and seldom has an indication.

Alcohol

Alcohol consumption has dyslipidemic effects, particularly with chronic use (129), and promotes development of fatty liver disease and associated HTG (130), particularly in susceptible Hispanic adolescents (131) or in those with underlying genetic predisposition. .As with steroids

and estrogens, a typical presentation is with a markedly increased TG level with a higher than expected HDL-C (Table 2).

MANAGEMENT

General

Obesity and insulin resistance associated with dietary excess and inactivity should be assessed as potential targets in the therapeutic plan. If the identifiable cause(s) of secondary HTG cannot be modified, as in patients with severe disorders or on necessary drug therapy for their underlying diseases, lifestyle management is a priority. A six month trial of weight management by restricting excessive calories, saturated fat, and refined carbohydrate in the diet is recommended by the NHLBI Expert Panel (9). There is also consensus that diet, exercise and behavioral modalities should be used in combination for successful outcomes in children (132), which are dependent on self-motivation, family support and access to skilled instruction, preferably provided by a dietitian with pediatric experience. A comprehensive team approach for use of exercise and behavioral modalities is considered optimal. Successful programs serve as role models for providers, particularly from centers with resources for team approaches similar to those designed for obesity management.(133)

Drug Therapy

Treatment of the primary disorder is the first priority. More common disorders such as diabetes require specific therapies based on the diabetes type, severity and effect of lifestyle. Rare disorders require specific therapies such as complex carbohydrates for maintaining normoglycemia in GSD, and leptin therapy for lipodystrophy (discussed above). If pharmaceutical agents are the cause, modification of the treatment plan can be considered in consultation with the primary specialist.

Statins:
For commonly encountered dyslipidemia there is good reason to follow established guidelines.(9) If a six month trial of intensive lifestyle is not effective in reaching the recommended goal, the LDL-C and non-HDL-C become targets using appropriate agents such as statins. As discussed previously, non-HDL-C is a preferred target for individuals with mild to moderate TG elevations (150-499 mg/dl) as recommended by the 2011 expert NHLBI panel.(9) For LDL-C and non-HDL-C above 95th percentiles in the presence of HTG and at least one other risk factor, statin therapy is indicated selecting from approved statins for children over age 10 years.(9) The reported statin association with type 2 diabetes (134, 135) should be considered when obesity and associated genetic risk for diabetes is present.

It should be emphasized that when statin treatment is indicated for drug-induced hypercholesterolemia, care should be taken to avoid interactions with drugs that are metabolized by pathways utilizing cytochrome P450 enzymes, such as CYP3A4 for oxidation of Atorvastatin, Lovastatin and Simvastatin and CYP2C9 for Fluvastatin and Rosuvastatin.(136) Drugs such as amiodipine, clarithromycin, cyclosporine A, diltiazem, erythromycin, ketoconazole, itraconazole, mibefradil, midazolam, nefazodone, nifedepine, protease inhibitors, quinidine, sildefanil, terbinafine, verapamil and warfarin are CYP3A4 utilizers and will raise the statin levels when used together, thus increasing risk of toxicity. Likewise alprenolol, diclofenac, fluconazole, hexobarbitoal, n-desmethyldiazepan, tolbutamide and warfarin are CYP2C9 utilizers and will be incompatible with Fluvastatin and Rosuvastatin. Several of these drugs have common pediatric usage including certain antibiotics and antifungal agents.

Fibrates**:**
Based on adult evidence of harmful effects of TG-rich lipoproteins, small dense LDL and remnant lipoproteins derived from VLDL and chylomicrons (55, 137) and the metabolic effects of TG and associated increase in fatty acids (138) , pharmacological TG lowering in childhood is indicated for selected cases resistant to lifestyle. (9) Individuals with severe isolated HTG at risk for acute pancreatitis should have a trial of a TG-lowering agent such as fibrates, beginning with the lowest available dose while monitoring for adverse effects. Fibrates, approved for use over age 18 years, have limited trial evidence in children but a fibrate (bezafibrate, not available in the United States) was shown to be safe when used for children with familial hypercholesterolemia before statins were available for use.(139) It is however notable that few adult trials have shown benefit of fibrates on cardiovascular event reduction.

Niacin:
Adverse effects on the intestine, liver, glucose intolerance and low tolerability have resulted in reluctance to use of niacin in children, although adverse effects are reversible.(140)

Omega-3 Fatty Acids:
Omega-3-fatty acids have appeal as a potential TG-lowering agent for children because of their relatively low adverse effect profile and recent availability as a prescription grade preparation following purification to remove heavy metals and fatty acids.(141) Although adults have had up to 30% TG lowering with 4 gram doses, 2 gram doses are less effective and increased LDL-C is a recognized adverse effect. (142, 143) but the LDL-C to HDL-C ratio is unchanged.(144) A retrospective survey of children treated for TG lowering with omega-3 fatty acids at a dose of 0.5 to 1 gram per day, did not show significant TG lowering suggesting that prescription of relatively low doses may not be helpful.(145) The study supports use of higher doses in combination with lifestyle measures. A high purity prescription form of eicosapentaenoic acid ethyl ester, lowers TG while lowering LDL particle concentration and LDL-C in cases with TG over 500mg/L(146), but it is not yet available for use under 18 years of age, however it appears to be a reasonable consideration for testing in pediatric settings. The free fatty acid form as shown in the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial is effective for TG-lowering (147), but not yet available for use in children. Non-prescription marine omega-3s can be safely used if patients are instructed on what to look for on the label (e.g. distilled, USP approved) and specific marine sources with high concentrations are recommended (148).

Severe Secondary HTG:
Treatment for HTG with levels above 1000 mg/dl in patients with partial defects in chylomicron clearance by LPL or its co-factors requires total dietary fat restriction for 72 hours followed by dietary management in the longer term. The approach is similar to the management of homozygous familial chylomicronemia (149) for which there is more information (reviewed in another chapter). It should be recognized that small increments in fat can cause striking increases in plasma TG because when TG levels saturate LPL activity, any additional TG entering the plasma will face zero order kinetics and increase the TG in a non-linear fashion. TG can be substantially lowered by restricting dietary fat to less than 15% of the total daily caloric intake and cases vary in their response to fibrates depending on their effect on residual lipoprotein lipase and on suppression of hepatic TG production. Adherence to a very low fat diet requires supplementation with linoleic acid and fat-soluble vitamins (A, D, E and K), but frequent monitoring is advised. Supplemental medium chain triglycerides (MCT) (150) may be beneficial in providing additional calories and improving compliance. Fenofibrate can be helpful in cases with residual lipoprotein lipase activity and also may reduce hepatic TG production. New agents are being developed to increase clearance and/or reduce the production of triglyceride-rich

lipoproteins, but their clinical efficacy, cost effectiveness, and indications, especially in children, are yet to be established.

CONCLUSION

In addition to obesity and accompanying metabolic syndrome, other common and rare causes of secondary dyslipidemia require diagnosis-specific management strategies. Identification and prioritization of reversible causes and risk factors, use of comprehensive lifestyle approaches, and optimal choice of medications based on guidelines can lead to improved outcomes. Lifestyle modification with selective prescription of medications designed to reduce risk of cardiovascular disease is indicated for individuals with intermediate TG levels ranging from 150-499 mg/dL, but severely elevated levels imposing risk for acute pancreatitis, require more intense dietary restriction combined with TG-lowering medications. Since non-HDL-C is a known predictor of cardiovascular disease and represents an estimate of all atherogenic lipoprotein particles TG-rich lipoproteins, it is recommended as a preferred target especially in most cases with intermediate elevations.

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