Hypertriglyceridemia in Children

Don P. Wilson, M.D., FNLA
Fellow, American Board of Clinical Lipidology
Director, Pediatric Cardiovascular Risk Prevention Clinic
Pediatric Endocrinology
Cook Children's Medical Center
Fort Worth, Texas

INTRODUCTION

Plasma Triglycerides (TG):

- **Are a measure of circulating triglyceride-rich lipoproteins (TRL) and their metabolic remnants.**

- **Are derived either from the diet or produced by the liver.**

Although genetic disorders that cause hyperTG are rare, significant elevations in plasma TG concentration are becoming increasingly recognized in children:

- **Who are sedentary**
- **Are overweight or obese**
- **Consume a high fat, high CHO diet**
- **For whom medications are prescribed for a variety of conditions**

In addition, there are a number of pediatric conditions that are commonly associated with hyperTG.

Common Secondary Causes of Dyslipidemia	
Condition	Screening Tests
Hypothyroidism	Free T4, TSH
Liver Diseases	CMP
Kidney Diseases	CMP / UA
Diabetes Mellitus	CMP / UA / Fasting or Random Glucose / HgbA1c
Obesity / Insulin Resistance	CMP / Fasting Glucose and Insulin
Medications	Corticosteroids, beta-blockers, bile acid resins, retinoids, oral estrogens (not transcutaneous), tamoxifen, protease inhibitors (especially ritonavir), sirolimus, asparaginase / prednisone combination therapy for ALL.

CMP=Comprehensive Metabolic Profile; UA=Urinalysis

DEFINITIONS

Abnormal serum triglyceride levels for children are generally classified on the basis of cutoff points suggested in AAP and AHA guidelines.

American Heart Association Guidelines for Primary Prevention of Atherosclerotic Cardiovascular Disease Beginning in Childhood. Circulation. 2003; 107:1562-1566.

Clinical Definition of Plasma Triglyceride Concentration			
Organization	Interpretation	nmol/L	mg/dL
2001 NCEP ATP III			
	Normal	<1.7	<150
	Borderline High	1.7-2.3	150-199
	High	2.3-5.6	200-499
	Very High	>5.6	≥500
2012 Endocrine Society			
	Normal	<1.7	<150
	Mild	1.7-2.3	150-199
	Moderate	2.3-11.2	200-999
	Severe	11.2-22.4	1000-1999
	Very Severe	>22.4	≥2000
2014 National Lipid Association			
	Normal	<1.7	<150
	Borderline High	1.7-2.3	150-199
	High	2.3-5.6	200-499
	Very High	>5.6	≥500
AAP /AHA			
0-9 years of age	Acceptable		<75 mg/dL
	Borderline		75-99 mg/dL
	High		>100 mg/dL
10-19 years of age	Acceptable		<90 mg/dL
	Borderline		90-129 mg/dL
	High		>130 mg/dL

NCEP=National Cholesterol Education Program Adult Treatment Panel III;
AAP= American Academy of Pediatrics; AHA= American Heart Association

Modified from: www.thelancet.com/diabetes-endocrinology Published online December 23, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70191-8

Distribution of Triglycerides for Males and Females 5-19 years of age

Mean concentration of triglycerides (mg/dL) in 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
Adapted from the Lipid Research Clinic Pediatric Prevalence Study.						

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

NHANES - 1999 to 2006

The prevalence of triglyceride levels > 150 mg/dL among all youths 12 to 19 years of age was 10.2%.

- **Boys 11.4%**
- **Girls 8.8%**

US Department of Health and Human Services, Centers for Disease Control and Prevention. Prevalence of abnormal lipid levels among youths: United States, 1999–2006. Morbidity and Mortality Weekly Report. 2010; 59:2.

Weight Category	TG >150 mg/dL
Normal (BMI 5th - 85th %)	5.9%
Overweight (BMI 85th - 94th %)	13.8%
Obese (BMI ≥ 95th %)	24.1%
Race / Ethnicity	
White, non-Hispanic	12.1%
Hispanic	9.3%
Black, non-Hispanic	3.7%

US Department of Health and Human Services, Centers for Disease Control and Prevention. Prevalence of abnormal lipid levels among youths: United States, 1999–2006. Morbidity and Mortality Weekly Report. 2010; 59:2.

NHANES -1999 to 2008

Triglyceride Levels in Children 12 to 19 Years of Age				
TG Concentration	**Normal**	**Mild-Mod**	**High**	**Missing**
Triglyceride Levels (mg/dL)	**<150**	**150-499**	**> 500**	
Sample (n)	2872	316	3	57
Weighted to US population (n)	29,168,008	3,464,483	59,946	465,332
Weighted % for each category	88.0%	10.5%	0.2%	1.4%
Abbreviations: NHANES, National Health and Nutrition Examination Survey.				

Christian JB, et al. Prevalence, Characteristics, and Risk Factors of Elevated Triglycerides in US Children. Clinical Pediatrics 2011; 50(12):1103-1109.

ETIOLOGY

Hypertriglyceridemia in childhood can be classified as:

- **Genetic**
- **Acquired**
- **Genetic and Acquired**

ETIOLOGY

Genetic abnormalities of triglyceride metabolism (LPL, APOC2, APOA5, LMF1,GPIHBP1 and GPD1), are rare and generally diagnosed soon after birth.

Copenhagen General Population Study

Subjects: >70,000 Adults Age: >20 years			Multigenic* and Small-Effect Variants							Can be Monogenic**					
% Popn	26%	46%	28%							0.1%					
Triglycerides															
mmol/L	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
mg/dL	<88	88-177	177-797							797-1329					
HyperTg			<-------- Mild to High -------->							<---------- Severe ---------->					
Risk			Increase in CVD							Chylomicronemia Pancreatitis CVD Risk Less Likely					

*LPL, APOA5, GCKR, APOB, LMF1, GPIHBP1, CREBH1, APOC2, APOE
**LPL, APOC2, APOA5, LMF1, GPIHBP1 AND GPD1

Modified from: Hegele, RA et al. The polygenic nature of hypertriglycerideaemia: implications for definitions, diagnosis, and management. www.thelancet.com/diabetes-endocrinology. Published online December 23, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70191-8

CLASSIFICATION

Historically disorders that cause hyperTG have been classified by the electrophoretic patterns of lipoprotein fractions (Fredrickson Classification).

The polygenic nature of most hyperTG states, however, precludes a meaningful classification based on genetic mutations.

Diagnosis	Fredrickson Classification	Primary Lipid Change	Primary Lipoprotein Change	Genetics
Familial Hyperchylomicronemia	Type 1	↑TG	↑Chylomicrons	**Monogenic**; autosomal recessive due to 2 mutant alleles of *LPL, APOC2, APOA5, LMF1, GPIHBP1*, or *GPD1*; presentation mainly in pediatric or early adulthood.
Familial Hypercholesterolemia	Type 2A	↑TC	↑LDL	Monogenic; autosomal codominant; heterozygous form results from 1 mutant allele of *LDLR*, *APOB*, or *PCSK9*; homozygous form results from 2 mutant alleles of these genes or of *LDLRAP1* (recessive).
Familial Combined Hyperlipoproteinemia	Type 2B	↑TC, ↑TG	↑VLDL, ↑LDL	**Polygenic**; high GRS* for hypertriglyceridemia; excess of rare variants in hypertriglyceridemia-associated genes; high GRS for LDL cholesterol.
Dysbetalipoproteinemia	Type 3	↑TC, ↑TG	↑IDL	**Polygenic**; high GRS for hypertriglyceridemia; excess of rare variants in hypertriglyceridemia-associated genes; *APOE E2/E2* homozygosity; or heterozygous rare mutations in *APOE*.
Primary Hypertriglyceridemia	Type 4	↑TG	↑VLDL	**Polygenic**; high GRS for hypertriglyceridemia; excess of rare variants in hypertriglyceridemia-associated genes.
Mixed Hypertriglyceridemia	Type 5	↑TC, ↑TG	↑VLDL, ↑Chylomicrons	**Polygenic**; high GRS for hypertriglyceridemia; excess of rare variants in hypertriglyceridemia-associated genes, with higher burden of risk alleles than for hyperlipoproteinemia type 4.

*GRS=polygenic genetic risk score

Adapted from: Hegele RA. Plasma lipoproteins: genetic influences and clinical implications. Nat Rev Genet 2009; 10:109-21.

Risk Factors for HyperTG in Childhood

In clinical practice hyperTg is most commonly encountered in children and adolescents who are:

- **Obese (BMI $\geq$ 95th %)**
- **Insulin resistance, clinically manifest by the presence of acanthosis nigricans, impaired or elevated fasting glucose, hypertension, and in girls, polycystic ovarian syndrome (PCOS)**

Risk Factor Tracking

Risk Factor	Tracking *	Comments
Obesity	Yes	BMI>99th %; 100% Obese as an adult BMI 95th – 99th %; 85% Obese as an adult
Risk Factor Clustering**	Yes	Insulin resistance Elevated triglycerides Reduced HDL-C Elevated blood pressure

* Childhood into Adulthood
** Obesity and Metabolic Syndrome

Adapted from: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, & National Heart, Lung, and Blood Institute, (2011). Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics, 128 Suppl 5, S213-56.

Clinical Manifestations

Clinical Manifestations of hyperTG

- **Pancreatitis**
- **Premature Cardiovascular Disease**

Pancreatitis

Pancreatitis is the most frequent acute complication described in individuals with severe hyperTG.

The literature suggests that fasting levels of TG > 500 mg/dL increases the risk of pancreatitis, although data to support the exact level of TG that precipitates pancreatitis is lacking.

Pancreatitis

Brunzell found that triglyceride-induced pancreatitis occurred at plasma levels >2000 mg/dl, but not if levels were maintained <2000 mg/dL.

He, therefore, recommended that TG <1000 mg/dL be used as a threshold for preventing pancreatitis.

Brunzell JD, Bierman EL. Med Clin North Am 66(2)455-68,1982.
Sandhu S et al. Lipids in Health and Disease 10:157,2011.

HyperTG and CVD Risk

Although the consequences of atherosclerotic CVD are seen only rarely in children, the early pathophysiological changes in arteries begin soon after birth and accelerate during adolescence.

HyperTG and Lifetime CVD Risk

There is evidence to suggest that elevated TG levels in childhood may be associated with atherosclerotic risk and subsequent cardiovascular events in adulthood.

Sarwar N, et al. Triglyceride and risk of coronary heart disease. Circulation 115; 450 - 458, 2007.

Frontini MG, Srinivasan SR, Xu J, Tang R, Bond MG, Berenson GS. Usefulness of childhood non-high density lipoprotein cholesterol levels versus other lipoprotein measures in predicting adult subclinical atherosclerosis: the Bogalusa Heart Study. Pediatrics 2008;121:924-9.

HyperTG and Lifetime CVD Risk

The Bogalusa Heart Study found that serum concentrations of TG, total cholesterol (TC), and LDL cholesterol in children and young adults (aged 2 to 39 years) were associated with lesions in the coronary arteries and aorta at autopsy.

Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults: the Bogalusa Heart Study. N Engl J Med.1998;338: 1650-1656.

HyperTG and Lifetime CVD Risk

The lifetime role of TG in atherogenic particle formation is supported by gene variants associated with classic hypertriglyceride phenotypes (IIb,III,IV,and V), whose expression is increased by hepatic fat deposition and insulin resistance.

HyperTG and Lifetime CVD Risk

The association of lifetime TG lowering providing protection from CVD is evident in recent studies on loss of function APOC-III mutations.

As compared with non-carriers, carriers of any of four APOC3 mutations had:

- **↓ Triglyceride levels (39%)**
- **↓ LDL cholesterol levels (16%)**
- **↓ APOC3 levels (46%)**
- **↑ HDL cholesterol levels (22%)**

The risk of coronary heart disease was reduced 40%.

The New England Journal of Medicine 2014;371:22-31.

HyperTG and Lifetime CVD Risk

TG, non-HDL-C, apoB and apoB:apoA-I ratio all predict carotid IMT after more than 20 years of follow-up.

Non-HDL-Cholesterol is superior to TG.

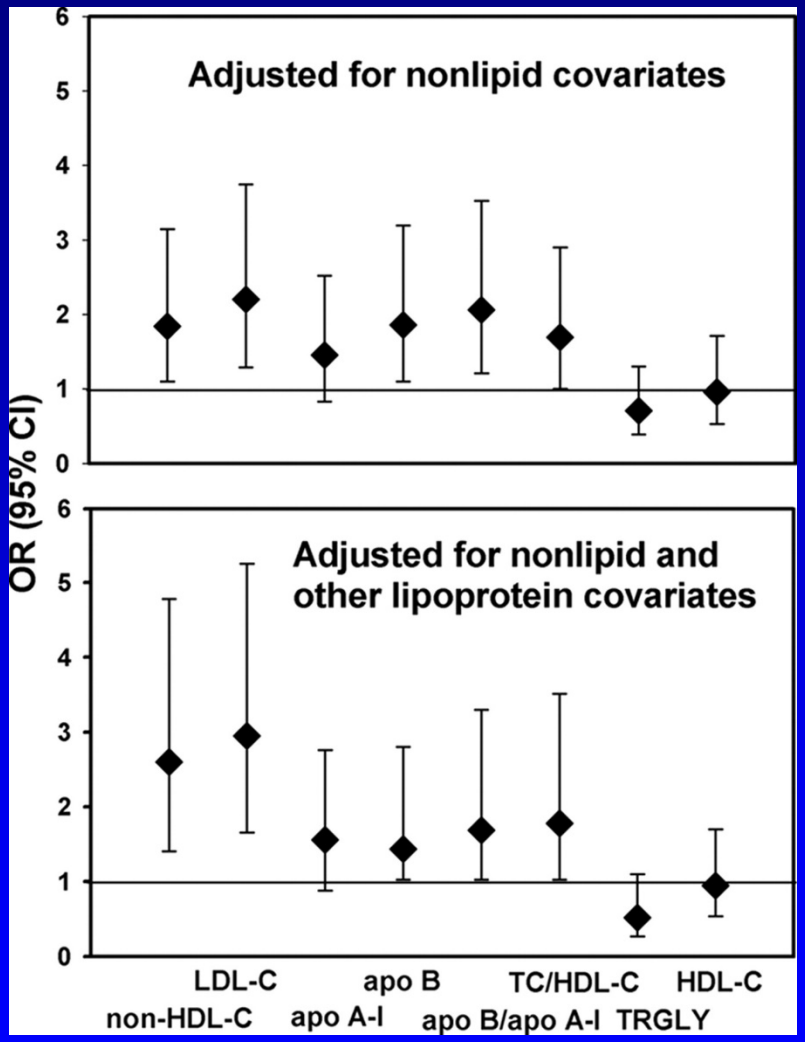
Circulation 2010;122:2514-20.
Pediatrics 2008;121:924-9.

HyperTG and Lifetime CVD Risk

Thus the combined effects of genetic and environmental factors, beginning before birth, promote insulin resistance and associated dyslipidemia, leading to early adult disease.

Nature Reviews Cardiology 2013;10:648-61.
Diabetologia 2006;49:755-65.
Journal of the International Association for the Study of Obesity 2000;24:330-9.
Journal of Clinical Lipidology 2013;7:65-81.

ORs and 95% CI for having excess adulthood carotid IMT (top versus bottom 9 deciles) by childhood lipoprotein measures (top versus bottom 3 quartiles) in the Bogalusa Heart Study cohort.



Frontini M G et al. Pediatrics 2008;121:924-929

PEDIATRICS®

HyperTG and Lifetime CVD Risk

Similar to adult meta-analysis, adjustment for established risk factors attenuate the association of TG with CVD evident in young adults with carotd IMT thickening.

Circulation 2007;115:450-8.

HyperTG and Lifetime CVD Risk

- Pediatric studies rely on surrogate markers, not hard end points.
- The prolonged time between initial detection of hyperTg and a CVD event.
- HyperTG is generally accompanied by atherogenic particles, best measured by non HDL-cholesterol, making direct causality difficult to prove.

Treatment of Hypertriglyceridemia

TG (mg/dL)	Normal	Mild-Moderate	High	Severe
	<150	**150-499**	**500-999**	**>1000**
Goal	Health Maintenance	CVD Risk Prevention	Avoid Pancreatitis	
Rx Target	TG < 150	Non HDL-C < 130	Triglycerides < 150	
Diet				
Fat*	25-30%	25-30%	15-30%	<10-15%
CHO*	55-60%	Avoid Excessive Consumption		
TG Lowering Rx				
	None	Consider statin as 1st line therapy	Consider Fibrate;O3FA;Niacin	Usually ineffective

* % of daily kcal/EER

TREATMENT
Acquired HyperTG

Individuals with acquired disorders, such as obesity and diabetes, should be encouraged to maintain a healthy weight as well as restrict excessive calories, fat and refined carbohydrate in their diet.

TREATMENT
Lifestyle Modifications

Depending upon the clinical context, lifestyle modifications can collectively decrease plasma triglyceride concentrations by up to 60%.

Int. J. Obes. Relat. Metab. Disord. 21 (Suppl. 1), S5-S9 (1997).
Am. J. Clin. Nutr. 56, 320-328 (1992).

TREATMENT
Acquired HyperTG

Alcohol and medications known to increase triglycerides, such as estrogens and glucocorticoids, should be avoided if possible.

Drug Therapy for HyperTG

Table 3. Summary of Dyslipidemic Agent Use by Triglyceride Levels and Age using i3 InVision Data Mart Database

TG Levels (mg/dL)	Niacin (%)[a]	Statin (%)[a]	Fibric Acid (%)[a]	Lovaza (%)[a]	No Treatment
Total	n = 120	n = 433	n = 126	n = 42	n = 64 578
<150	73.3	50.4	10.3	35.7	80.9
150-499	26.7	46.2	65.9	45.2	18.7
500+	0	3.5	23.8	19.1	0.3
5-11 years	n = 0	n = 51	n = 2	n = 4	n = 14 983
<150	0	66.7	0	25.0	84.5
150-499	0	33.3	100.0	75.0	15.3
500+	0	0	0	0	0.2
12-19 years	n = 120	n = 382	n = 124	n = 38	n = 49 595
<150	73.3	48.2	10.5	36.8	79.8
150-499	26.7	47.9	65.3	42.1	19.8
500+	0	3.9	24.2	21.0	0.4

[a]The sum of the percentages may not equal 100% because of rounding, and/or patients may be counted more than once if they have used more than one dyslipidemic agent.

Triglycerides >150 mg/dl
5-11 years of age = 0.1%
12-19 years of age = 0.7%

Jennifer B. Christian, Maneesh X. Juneja, Amy M. Meadowcroft, Spencer Borden and Kimberly A. Lowe. Prevalence, Characteristics, and Risk Factors of Elevated Triglyceride Levels in US Children. CLIN PEDIATR 2011 50(12): 1103-1109.

Drug Therapy for HyperTG

Table 4. Summary of Triglyceride Levels by Dyslipidemic Agent Use and Age using i3 InVision Data Mart Database

	TG Levels (mg/dL), Total (%)[a]			TG Levels (mg/dL), 5-11 years (%)[a]			TG Levels (mg/dL), 12-19 years (%)[a]		
	<150	150-499	500+	<150	150-499	500+	<150	150-499	500+
Total	n = 52587	n = 12414	n = 257	n = 12699	n = 2308	n = 32	n = 39888	n = 10106	n = 225
Niacin	0.2	0.3	0	0	0	0	0.2	0.3	0
Statin	0.4	1.6	5.8	0.3	0.7	0	0.5	1.8	6.7
Fibric acid	0	0.7	11.7	0	0.1	0	0	0.8	13.3
Lovaza	0	0.2	3.1	0	0.1	0	0	0.2	3.6
No treatment	99.4	97.5	84.0	99.7	99.1	100.0	99.3	97.1	81.8

[a]The sum of the percentages may not equal 100% because of rounding, and/or patients may be counted more than once if they have used more than one dyslipidemic agent.

Jennifer B. Christian, Maneesh X. Juneja, Amy M. Meadowcroft, Spencer Borden and Kimberly A. Lowe. Prevalence, Characteristics, and Risk Factors of Elevated Triglyceride Levels in US Children. CLIN PEDIATR 2011 50(12): 1103-1109.

TREATMENT
Severe HyperTG

While lipid lowering medications are generally not effective, triglycerides can be substantially lowered by restricting dietary fat to <15% of the total daily caloric intake.

Effective treatment requires strict, life-long adherence to a very low fat diet.

TREATMENT
Severe HyperTG

Adequate intake of linoleic acid and fat soluble vitamins (A, D, E, and K) should be monitored.

Supplemental medium chained triglycerides (MCT) may be beneficial in providing additional calories and improving compliance.

Novel Therapies for Treatment of HyperTG

Several novel therapies for treatment of hyperTG are in development.

These agents increase clearance or reduce the production of TRLs.

Agent	Target	Secretion	Catabolism	Expected mean reduction in TG
Dual PPAR α/δ agonist	Liver, Muscle, Adiocytes	Decreased	Increased	30
CETP inhibitor	Plasma	=	Increased	20
MTP inhibitor	Liver, Enterocyte	Decreased	=	30
DGAT-1 inhibitor	Liver, Enterocyte, Adipocytes	Decreased	=	40
DGAT-2 inhibitor	Liver	Decreased	=	40
ANGPTL inhibitor	Muscle, Adipocytes	=	Increased	40
ApoB antisense	Liver	Decreased	=	30
ApoC-III antisense	Liver	=	Increased	40
PCSK9 inhibitor	Liver	Uncertain	Increased	15
LPL gene replacement	Muscle, Adipocytes	=	Increased	40

Modified from: Hegele, RA et al. The polygenic nature of hypertriglycerideaemia: implications for definitions, diagnosis, and management. www.thelancet.com/diabetes-endocrinology Published online December 23, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70191-8

Novel Therapies for Treatment of HyperTG

Their clinical efficacy, cost-effectiveness, and indications, especially in children, are yet to be established.

Hypertriglyceridemia in Children Summary

Although monogenic causes are rare, significant elevations in plasma TG concentration are becoming increasingly recognized in children.

Hypertriglyceridemia in Children Summary

Obesity and insulin resistance, the most common cause of hyperTG in children, are frequently associated with high levels of TG, a low HDL-C and small dense LDL-C.

Non HDL-C is a clinically useful tool to measure these atherogenic particles.

Hypertriglyceridemia in Children Summary

Severe hyperTG (>1000 mg/dL) may cause acute pancreatitis, while mild to moderate elevations (150-499 mg/dL) may increase risk of premature CVD.