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Review

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Hypertriglyceridemia in Obese Children and Adolescents

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The increasing prevalence of obesity in children and adolescents is a serious public health concern. Hypertriglyceridemia is common in obese children and adolescents, and elevated triglyceride (TG) level is a known biomarker of cardiometabolic risk. Results from genetic studies suggest that TG and TG-rich lipoproteins and, more specifically, remnant cholesterol are in the causal pathway of cardiovascular disease. However, simultaneous measurement of all remnants has not yet been established, and plasma TG level can be used as a useful marker of remnant cholesterol. Adipose tissue dysfunction, including impaired adipocyte TG storage and release of fatty acids, mediates the development of obesity-related complications. The prevalence of hypertriglyceridemia increases in overweight or obese children and is associated with other cardiometabolic risk factors. Recently, the TG/high-density lipoprotein cholesterol (HDL-C) ratio was recognized as a marker of structural vascular changes and insulin resistance in obese youth. Recent guidelines recommend universal lipid screening with nonfasting non-HDL-C measurement in children at 9–11 years of age; however, fasting lipid profiles should be measured in obese children and overweight adolescents and in those with high non-HDL-C in universal screening. The primary approach to lower TG in children includes dietary and lifestyle modifications; however, children with severe hypertriglyceridemia should also be referred to a pediatric lipid specialist.

Key words: Hypertriglyceridemia, Obesity, Child

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INTRODUCTION

Obesity results from chronic energy imbalance involving dietary intake and physical activity.[1] The increasing prevalence of obesity in children and adolescents is considered as one of the most series public health concerns in this century.[2] Childhood obesity can adversely affect many organs and increases the risk of chronic diseases, including dyslipidemia, diabetes, and cardiovascular disease (CVD).[2,3]

According to a study that included 230,000 Norwegian adolescents, adolescent obesity was associated with increased mortality in middle age from several causes, including ischemic heart disease.[4] Childhood body mass index (BMI) showed strong tracking to adulthood, and childhood BMI was independently related with carotid intima-media thickness (cIMT) in adulthood.[5] According to a large population-based U.S. study, the overall prevalence of dyslipidemia in normal weight adolescents was 14.2%, which increased to 42.9% in obese youth.[6] In obese adolescents, the prevalence of high triglyceride (TG), low high-density lipoprotein cholesterol (HDL-C), and high low-density lipoprotein cholesterol (LDL-C) was 24.1%, 20.5%, and 14.2%, respectively, suggesting that hypertriglyceridemia is one of the most common lipid abnormalities in obese youth.[6] LDL-C is known to be a critical risk factor for early CVD and has been considered the primary target for risk reduction.[7] However, patients treated with statins showed residual risk, and the most commonly observed lipid pattern in obese patients

with CVD was high TG, low HDL-C, and normal to mildly elevated LDL-C.[8]

TRIGLYCERIDES AND CARDIOVASCULAR RISK

An elevated TG level is a known biomarker of cardiovascular risk, and hypertriglyceridemia is a component of metabolic syndrome.[9,10] However, the specific role of TG has long been controversial, at least partially due to the high within-person variability compared to more stable factors such as HDL-C.[10] Recent genetic studies suggest that TGs and TG-rich lipoproteins (TRLs) are causally related to CVD, rather than simply being a biomarker.[11,12] Genome-wide association studies also reported causal associations between raised TGs and coronary artery disease.[11,13] In comparison, a Mendelian randomization study showed that genetically reduced nonfasting plasma TG level leads to reduced mortality.[14]

Remnant cholesterol is defined as the cholesterol content of all TRLs.[15] Simultaneous measurement of all remnants has not been established; however, remnant cholesterol can be calculated as HDL-C and LDL-C subtracted from nonfasting total cholesterol (TC).[16] Even though plasma TG level is a useful marker of remnant cholesterol, it has been recently suggested that remnant cholesterol, rather than TGs, is in the causal pathway of atherosclerosis and CVD.[16] Remnant lipoproteins can enter the arterial intima, similar to LDL, and remnants tend to be preferentially trapped in the intima, leading to inflammation, foam cell formation, atherosclerotic plaque formation, and finally CVD.[16]

INSULIN RESISTANCE AND OBESITY-RELATED COMPLICATIONS

Adipose tissue dysfunction, including impairment of adipocyte TG storage and release of fatty acids, mediates the development of obesity-related complications.[17] Individuals with the ability to recruit healthy subcutaneous adipocytes in response to excess energy intake are relatively protected from obesity-associated morbidity.[18] However, individuals with limited adipocyte recruitment ability will store excess fat in ectopic depots, such as the liver, visceral fat, and muscle, and are prone to metabolic complications of obesity.[18,19]

The difference in insulin sensitivity is related to different lipid partitioning patterns, and insulin resistance is associated with increased lipid deposition in the visceral and intramyocellular compartments.[19,20] Intramyocellular and extramyocellular lipid deposition increased in obese adolescents and were directly associated with peripheral insulin sensitivity.[21] A hypothesis has been suggested that unifies these concepts and proposes that the intracellular accumulation of lipids in muscle and liver triggers novel protein kinase C activation and subsequent insulin signaling impairment.[21] This hypothesis accounts for the mechanism of insulin resistance in obesity and type 2 diabetes and the insulin-sensitizing effects of thiazolidinediones.[22]

Visceral adiposity has also been reported to be related to atherogenic metabolic profiles in children.[19] Intramyocellular lipid assessment in a clinical setting is not practical, but measuring waist circumference, an indirect measure of visceral fat, can easily be performed and used to identify children with higher metabolic risk. The hypertriglyceridemic waist phenotype, coexistence of elevated TG level and abdominal obesity, has been suggested to identify individuals at high risk for CVD.[23]

HYPERTRIGLYCERIDEMIA IN CHILDREN AND ADOLESCENTS

Studies on hypertriglyceridemia in children are currently limited. Recent reports on the prevalence of dyslipidemia in children and adolescents are shown in Table 1. In a large population-based U.S. study, the prevalence of hypertriglyceridemia was 5.9% in normal weight children, which showed stepwise increase to 13.8% and 24.1% in overweight and obese children, respectively.[6] The prevalence of hypertriglyceridemia in children and adolescents is reported to be 5.9% to 8.6% in the general population, which is comparable to other components of dyslipidemia.[24-27] However, the prevalence of hypertriglyceridemia increases up to 13.8%–31.8% in overweight or obese children and adolescents and seems to be higher than other components of dyslipidemia, suggesting that hypertriglyceridemia could be the most common lipid abnormality among overweight or obese youth (Table 1).[28-30]

In a study of 139 Argentinian children, a status of overweight or

Table 1. Summary of studies on the prevalence of dyslipidemia in children and adolescents

Study (year), country	Number	Age (yr), range	BMI (%)	High TC (%)	High non-HDL-C (%)	High TG (%)	Low HDL-C (%)	High LDL-C (%)
General population								
NHANES (1999–2006)[6], United States*	2,125 (68% Of total 3,125)	12–19	Normal	-	-	5.9	4.3	5.8
NHANES (2011–2014)[24], United States†	4,638	6–19	-	7.4	8.4	-	13.4	-
Turkish school-children (2007)[25], Turkey‡	2,896	7–18	-	11.8	10.4	7.5	6.6	11.9
KNHANES (2011–2014)[26], Korea§	2,935	10–19	Normal, 74; overweight, 13; obese, 13	-	-	8.6	18.2	-
CASPIAN-III study (2009–2010)[27], Iran‖	5,625	10–18	Normal, 81 (M)/86 (F); overweight, 9 (M)/7 (F); obese, 10 (M)/8 (F)	M, 6.4; F, 5.0	-	M, 8.1; F, 7.9	M, 6.2; F, 5.3	M, 33.4; F, 36.9
Overweight or obese children								
NHANES (1999–2006)[6], United States*	1,000 (32% Of total 3,125)	12–19	Overweight, 15; obese, 17	-	-	Overweight, 13.8; obese, 24.1	Overweight, 8.3; obese, 20.5	Overweight, 8.4; obese, 14.2
Casavalle et al. (2014)[28], Argentina¶	139	8–14	Overweight, 22; obese, 78	11.5	15.8	31.7	29.5	10.1
Elmaoğulları et al. (2015)[29], Turkey	823	2–18	Obese (BMI ≥ 95th percentile)	18.6	-	21.7	19.7	13.4
Yoo et al. (2017)[30], Korea†	255	Mean ± SD, 8.7 ± 2.0	Overweight (BMI ≥ 85th percentile)	17.3	16.1	31.8	13.2	12.2
Pediatric stroke patient								
International Pediatric Stroke study (2003–2013)[31], International†	482	0–19	Overweight or obese, 33	10.0	23.1	44.5 (< 10 yr), 32.9 (≥ 10 yr)	39.8	10.7

Cutoff values (mg/dL): *LDL-C ≥ 130, low HDL-C ≤ 35, and TG level ≥ 150; †NHLBI expert panel (2011): TC ≥ 200, LDL-C ≥ 130, non-HDL-C ≥ 145, HDL-C < 40, TG ≥ 100 (0–9 years), and ≥ 130 (10–19 years); ‡TC > 200, LDL-C > 130, non-HDL-C > 150, HDL-C < 35, TG > 140; §TG ≥ 150, HDL-C < 40 (boys aged 10–19 years and girls ≤ 16 years), and < 50 (girls aged ≥ 16 years); ‖TC, LDL-C,TG, higher than the level corresponding to the age- and gender-specific 95th percentile, and/or HDL-C lower than the age- and gender-specific 5th percentile; ¶TC ≥ 200, LDL-C ≥ 130, non-HDL-C > 145, recommended by National Cholesterol Education Program.
BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; KNHANES, Korea National Health and Nutrition Examination Survey; CASPIAN, Childhood and Adolescence Surveillance and Prevention of Adult Noncommunicable Disease; M, male; F, female; SD, standard deviation.

obesity increased the odds ratios of hypertriglyceridemia, low HDL-C, and metabolic risk factors, and dyslipidemia was more commonly detected in subjects with central obesity, family history of dyslipidemia, and type 2 diabetes.[28] Among 823 obese Turkish children and adolescents, the prevalence of dyslipidemia increased with increasing BMI, and hypertriglyceridemia was the most common type of dyslipidemia.[29] Hepatosteatosis was more commonly observed in patients with dyslipidemia, and the level of insulin resistance was higher in subjects with both dyslipidemia and hepatosteatosis.[29]

A study that included children in the International Pediatric Stroke study showed that dyslipidemia was more common in children with arterial ischemic stroke compared to the data from the National Health and Nutrition Examination Survey (NHANES) (38.4% vs. 21%), and that 44.5% of children and 32.9% of adolescents with arterial ischemic stroke had hypertriglyceridemia, suggesting that the prevalence of dyslipidemia, including hypertriglyceridemia, might be higher in children with arterial ischemic stroke than in the general population.[24,31]

TG/HDL-C RATIO AND RELATED FACTORS IN OBESE YOUTH

Recent genetic studies suggested that low HDL-C is not causally related to CVD, but is likely an innocent bystander.[13,15] However, most studies in children and adolescents report the associations

Table 2. Summary of recent studies on TG/HDL-C ratio in children and adolescents

Author (year), country	Number (age, yr*)	Result
Giannini et al. (2011)[32], United States	1,452 (13.1 ± 2.9)	The TG/HDL-C ratio was associated with insulin resistance in obese Caucasian youth, and the OR for insulin resistance was 6.02 in those with TG/HDL-C higher than 2.27.
Yoo et al. (2017)[30], Korea	769 (overweight, 8.7 ± 2.0; normal, 8.9 ± 1.8)	The TG/HDL-C ratio correlated with HOMA-IR in overweight children (r = 0.282, *P* = 0.016). The specificity of high TG/HDL-C was better than that of hypertriglyceridemia for identifying overweight children with high HOMA-IR (72.9% vs. 64.2%).
KNHANES (2011–2014)[26], Korea	2,935 (10–19)	TG/HDL-C ratio (0.891 [95% CI, 0.891–0.892]) showed the highest predictability for CMRF clustering. The TG/HDL-C ratio cut-off points for predicting MetS and CMRF clustering were 2.64 (sensitivity, 95.1%; specificity, 86.4%) and 2.63 (sensitivity, 74.4%; specificity, 90.5%), respectively.
Pacifico et al. (2014)[33], Italy	548 (6–16)	Increased cIMT was associated with high TG/HDL-C ratio (OR, 1.81; 95% CI, 1.08–3.04; *P* < 0.05) in a stepwise multivariate logistic regression analysis.
Urbina et al. (2013)[34], United States	893 (10–26)	The high TG/HDL-C ratio group had the stiffest vessels (all *P* < 0.03, based on analysis of variance).
CARITALY study (2003–2013)[35], Italy	5,505 (5–18)	The ORs for insulin resistance, high blood pressure, metabolic syndrome, presence of liver steatosis, and increased cIMT were higher in children with high TG/HDL-C compared to children with high non-HDL-C.

*Values are presented as mean ± standard deviation or range.
TG/HDL-C, triglyceride to high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; KNHANES, Korea National Health and Nutrition Examination Survey; CI, confidence interval; CMRF, cardiometabolic risk factor; MetS, metabolic syndrome; cIMT, carotid intima-media thickness; OR, odds ratio; CARITALY, CARdiometabolic risk factors in overweight and obese children in ITALY.

between TG/HDL-C ratio, not TG itself, and metabolic risk factors. Table 2 summarizes recent reports on the TG/HDL-C ratio and related factors in children and adolescents.

The TG/HDL-C ratio was associated with insulin resistance in obese Caucasian youth, and the odds ratio for insulin resistance was 6.02 in those with high TG/HDL-C (> 2.27).[32] Our previous study also showed that TG/HDL-C ratio (≥ 2.0) showed higher sensitivity (55.6%) and specificity (72.9%) than TC, non-HDL-C, and LDL-C in identifying overweight children with increased homeostasis model assessment of insulin resistance (HOMA-IR).[30] A recent study that used data for 2,935 adolescents from the 2011 to 2014 Korean NHANES reported that TG/HDL-C ratio showed the highest predictability for clustering of cardiometabolic risk factors (Table 2).[26]

The TG/HDL-C ratio was recognized as a suggestive marker of structural vascular changes and insulin resistance in obese youth. A study on the association of TG/HDL ratio with cIMT in children and adolescents showed that the odds ratios for insulin resistance increased with increasing TG/HDL-C ratio tertile, and that increased cIMT was independently associated with a high TG/HDL-C ratio.[33] A longitudinal school-based study indicated that the high TG/HDL-C ratio was an independent determinant of arterial stiffness in obese youth.[34] Additionally, a recent study suggested that a TG/HDL-C ratio ≥ 2.2 can be used as an accurate screening parameter of insulin resistance, metabolic syndrome, and increased cIMT (Table 2).[35]

LIPID SCREENING AND DYSLIPIDEMIA DIAGNOSIS IN CHILDREN AND ADOLESCENTS

Non-HDL-C, calculated as TC minus HDL-C, reflects the sum of highly atherogenic lipoprotein particles.[36] Recent guidelines recommend universal lipid screening with nonfasting non-HDL-C measurement in all youth between the ages of 9–11 and 17–21 years.[37] If the non-HDL-C is 145 mg/dL or higher, a fasting lipid profile measurement should be performed.[37] Lipid screening of dyslipidemia is not recommended for ages less than 2 years. However, a fasting lipid profile should be measured in obese children (BMI ≥ 95th percentile) aged 2–8 years and in overweight adolescents (BMI ≥ 85th percentile) aged 12–16 years, and those in these age group with a family history of myocardial infarction, stroke before the age of 55 in males or the age of 65 in females, or risk factors such as hypertension, diabetes mellitus, Kawasaki disease, or nephrotic syndrome.[38]

Hypertriglyceridemia can be diagnosed if TG level is ≥ 100 mg/dL in children (< 10 year) or ≥ 130 mg/dL in adolescents (10–19 year) based on an average of two fasting measurements.[37] Ethnic differences in TG level and related factors have been reported, and further investigation is needed to develop ethnicity-specific cutoffs.[32]

Secondary causes of hypertriglyceridemia, such as hypothyroidism, polycystic ovarian syndrome, and medication effects, should also be ruled out.[36] A correction between underlying causes could result in normalization of TG level for all of these cases.

PEDIATRIC HYPERTRIGLYCERIDEMIA MANAGEMENT

The primary approach for reducing and managing TG in children includes dietary and lifestyle modifications.[36] In addition, the primary aim of hypertriglyceridemia management is weight control for obese children and adolescents. Reduced caloric intake with or without increased exercise resulted in significant reduction of TG level as well as weight loss and improvement of other metabolic profiles.[39] In another report from the Young Finns study, childhood dietary patterns remained stable over the life course and were associated with cardiovascular risk factors and measures of subclinical atherosclerosis, suggesting that childhood nutrition might have significant influence on the progression of CVD.[40]

Dietary modification with a cardiovascular health integrated lifestyle diet (CHILD)-1 and then CHILD-2 TG should be recommended for children with hypertriglyceridemia.[33,37] Simple sugars need to be substituted for complex carbohydrates, sugar-sweetened beverages should be excluded, and fish consumption is encouraged to increase the intake of omega-3 fatty acids.[36] Lifestyle changes, including increasing physical activity to 60 minutes per day, reducing screen time to less than 2 hours per day, attaining ideal body weight ($\leq$ 85th percentile), and optimizing blood pressure, should be encouraged for all patients with increased TG level.[36,37]

Medication is rarely indicated for children with hypertriglyceridemia who respond well to weight loss and lifestyle changes.[37] However, children with severe hypertriglyceridemia (TG > 500 mg/dL) should be referred to a pediatric lipid specialist, and the symptoms of pancreatitis should be counseled.[41] Although fibric acid derivatives are commonly used as TG lowering agents in adults, these have not yet been approved for children by the Food and Drug Administration (FDA).[37,42] Although a high dose of omega-3 fatty acids has been shown to decrease TG level by 20%–30% in adults, prescription of omega-3 fatty acids for children is not currently approved by the U.S. FDA.[43]

CONCLUSION

Hypertriglyceridemia is common in obese children and adolescents and may increase the patient's future cardiovascular risk. Although universal screening with nonfasting non-HDL cholesterol is recommended, TGs should also be measured in obese children and adolescents. Early detection and intervention with lifestyle modification have been helpful approaches for obese children and adolescents with increased TG level.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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