The triglyceride-to-high density lipoprotein cholesterol ratio in overweight Korean children and adolescents

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Purpose: The triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio has recently been reported as a biomarker of cardiometabolic risk in obese children and adolescents. The purpose of this study is to describe the TG/HDL-C ratio and related factors in overweight and normal weight Korean children and to evaluate whether the high TG/HDL-C ratio is associated with insulin resistance in overweight children and adolescents.

Methods: Data from 255 overweight (aged 8.7±2.0 years) and 514 normal weight (aged 8.9±1.8 years) children and adolescents were evaluated. Glucose, insulin, total cholesterol (TC), HDL-C and TG levels were measured after overnight fasting, and the TG/HDL-C ratio, non–HDL-C and the homeostasis model assessment of insulin resistance (HOMA-IR) were calculated.

Results: The TG/HDL-C ratio was higher in overweight group compared to normal weight group ($P<0.001$). Among overweight children and adolescents, alanine aminotransferase ($P=0.018$), non–HDL-C ($P<0.001$), and HOMA-IR ($P=0.004$) were different between the TG/HDL-C ratio tertile groups. The prevalence of elevated HOMA-IR was increased with increasing TG/HDL-C ratio tertiles (P for trend=0.003). On regression analysis adjusted for age and sex, the BMI ($\beta=0.402$, $P=0.001$) and TG/HDL-C ratio ($\beta=0.251$, $P=0.014$) were independently associated with HOMA-IR (adjusted $R2=0.324$). The TG/HDL-C ratio of 2.0 or more showed higher sensitivity (55.6%) and specificity (72.9%), when compared to TC (≥200 mg/dL), non–HDL-C (≥145 mg/dL), and LDL-C (≥130 mg/dL) for identifying overweight children with elevated HOMA-IR.

Conclusion: The TG/HDL-C ratio is independently associated with insulin resistance in overweight children and adolescents, and it can be useful in identifying those at higher cardiometabolic risk.

Keywords: Dyslipidemia, Obesity, Hypertriglyceridemia, Insulin resistance, Child, Adolescent

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Introduction

With increased consumption of high-calorie food and sedentary life styles, the prevalence of obesity in children has increased worldwide[1]. Childhood obesity is associated with cardiovascular risk factors including dyslipidemia, hypertension, and insulin resistance[2,3]. Dyslipidemia is related with the initiation and progression of atherosclerosis[4]. Atherosclerosis begins in childhood with fatty streaks, and progress to fibrous plaques, which might rupture and cause ischemic organ damage, in adulthood[5]. It is important to identify those with higher risk for atherosclerosis to prevent its long-term complications and premature mortality.

Triglycerides (TGs) are major components of triglyceride-rich lipoproteins (TRLs) which

are synthesized from the liver and intestinal enterocytes. Epidemiologic studies have demonstrated that elevated TGs are independently associated with increased cardiovascular risk[6]. Recent genetic studies also provide evidence that TGs and TRLs are in the causal pathway of cardiovascular disease (CVD)[7].

The triglyceride-to-high density lipoprotein cholesterol (TG/HDL-C) ratio was associated with insulin resistance and impaired glucose tolerance (IGT) in obese youths[8,9]. The TG/HDL-C ratio was also suggested as a marker of endothelial dysfunction and structural vascular changes in obese children and adolescents[10-12]. The aims of this study are (1) to describe the TG/HDL-C ratio and related factors in overweight vs. normal weight Korean children, (2) to evaluate whether the high TG/HDL-C ratio is associated with insulin resistance in overweight children.

Materials and methods

1. Participants

Data from 769 Korean children (255 overweight children, aged 8.7±2.0 years, and 514 normal weight children, aged 8.9±1.8 years) who visited CHA Bundang Medical Center between March 2014 and April 2015, were retrospectively evaluated. Children with chronic disorders, including diabetes mellitus and thyroid disorders, or those under growth hormone treatment, were excluded. Glucose, insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and TG levels were measured after overnight fasting, and the TG/HDL-C ratio,

non–HDL-C (HDL-C subtracted from TC) were calculated. Insulin resistance was measured by homeostasis model assessment of insulin resistance (HOMA-IR) in a subgroup of children (32 normal weight and 74 overweight children). This study was approved by Institutional Review Board of CHA Bundang Medical Center and informed consent was waived (CHAMC 2016-08-014).

2. Definitions

Overweight was defined by body mass index (BMI) ≥85th percentile, and central obesity by waist circumference ≥90th percentile according to Korean reference data[13]. Height standard deviation score (SDS) and BMI SDS was calculated based on 2007 Korean growth standard[13].

Hypertriglyceridemia was defined by TG ≥130 mg/dL (≥10 years of age) or ≥100 mg/dL (<10 years of age), and hypo-HDL-cholesterolemia was defined by HDL-C <40 mg/dL[14]. High non–HDL-C was defined by non–HDL-C ≥145 mg/dL, and high TC by TC ≥200 mg/dL[14]. High TG/HDL-C ratio was defined by TG/HDL-C in the highest tertile group (TG/HDL-C ratio ≥2). LDL-C was calculated by Friedewald formula[15], and high LDL-C was defined by LDL-C ≥130 mg/dL[16]. HOMA-IR was calculated with the following formula: [fasting glucose (mmol/L) × fasting insulin (mU/L)]/22.5[17], and high HOMA-IR was defined by HOMA-IR ≥ 3[18].

Table 1. Clinical and metabolic characteristics of normal weight and overweight children

Characteristic	Normal weight (n=514)	Overweight (n=255)	P-value
Female sex	418 (81.3)	178 (70.8)	
Age (yr)	8.9±1.8	8.7±2.0	0.106
BA–CA	0.9±2.2	0.9±3.2	0.824
Height SDS	0.3±1.0	0.9±1.0	<0.001
BMI SDS	-0.02±0.8	1.7±0.5	<0.001
Waist circumference	69.1±7.1 (n=25)	79.2±10.0 (n=77)	<0.001
SBP (mm/Hg)	104.3±8.8 (n=30)	109.7±9.7 (n=127)	0.006
DBP (mm/Hg)	58.0±8.5 (n=30)	61.3±9.8 (n=127)	0.092
AST (IU/L)	24.3±5.6	24.5±8.3	0.681
ALT (IU/L)	14.9±6.5	22.6±20.1	<0.001
Glucose (mg/dL)	95.8±6.8	96.9±6.9	0.027
Total cholesterol (mg/dL)	170.3±29.8	172.3±29.0	0.053
HDL-C (mg/dL)	58.6±11.2	53.0±11.3	<0.001
Non HDL-C (mg/dL)	111.7±27.9	119.3±27.6	<0.001
Triglycerides (mg/dL)	74.2±36.3	100.0±26.7	<0.001
LDL-C (mg/dL)	96.9±26.4	100.1±26.7	0.117
TG/HDL ratio	1.4±0.9	2.0±1.9	<0.001
HOMA-IR	2.4±1.6 (n=32)	3.3±2.3 (n=74)	0.067

Values are presented as number (%) or mean±standard deviation.
BA–CA, bone age minus chronological age; BMI SDS, body mass index standard deviation scores; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG/HDL, triglyceride-to-high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance.

3. Statistical analysis

Data are described as means±standard deviations for continuous variables. Categorical variables were expressed as proportion (%) and were compared by chi-square test. First, we examined the differences in metabolic parameters between normal weight and overweight group. Between-group differences were tested using independent sample t-test. Second, TG/HDL-C ratio tertile groups were divided, and 1-way analysis of variance with Bonferroni *post hoc* test was used to compare variables between groups. To describe the trend of metabolic parameters with increasing TG/HDL-C ratio, P for trend was calculated from TG/HDL-C ratio tertile groups by analysis of covariance.

Table 2. Prevalence of abnormal metabolic parameters in normal weight vs. overweight children

Variable	Normal weight (%)	Overweight (%)	P-value
Central obesity[*]	20.0	84.4	<0.001
Glucose ≥100 mg/dL	27.6	35.7	0.220
Total cholesterol ≥200 mg/dL	11.9	17.3	0.410
HDL-C <40 mg/dL	3.7	13.2	<0.001
Non–HDL-C ≥145 mg/dL	9.1	16.1	0.004
Hypertriglyceridemia[†]	13.8	31.8	<0.001
LDL-C ≥130 mg/dL	8.8	12.2	0.137

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[*]Waist circumference ≥90th percentile. [†]TG ≥130 mg/dL for ≥10 years of age or ≥100 mg/dL for <10 years of age.

The relationship between TG/HDL-C ratio and HOMA-IR in overweight children was evaluated by linear regression analysis after adjusting for age, sex, and BMI, as well as by Pearson correlation analysis. Because the HOMA-IR was not normally distributed, it was natural log transformed before correlation or regression analysis.

We also calculated the sensitivity and the specificity of each metabolic parameter for identifying high HOMA-IR in overweight children. The sensitivity was calculated by the proportion of children having high HOMA-IR who were correctly identified by the metabolic parameters, and the specificity was measured by the proportion of children without high HOMA-IR who were correctly screened by the metabolic parameters.

The IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA) was used for all statistical analysis. A P-value of <0.05 was considered significant.

Results

1. Clinical characteristics of participants

Table 1 shows the characteristics of normal weight and overweight children. The systolic blood pressure ($P=0.006$), alanine aminotransferase (ALT) ($P<0.001$), and glucose ($P=0.027$) level was significantly increased in overweight children compared to normal weight children. Overweight children showed lower HDL-C ($P<0.001$), and higher non–HDL-C ($P<0.001$) and TG ($P<0.001$) levels than normal weight children. The TG/HDL-C ratio was also higher in overweight

Table 3. Metabolic parameters of overweight children according to tertiles of TG/HDL-C ratio

Characteristic	TG/HDL ratio tertile			P-value
	<1.17 (n=84)	≥1.17, <2.0 (n=81)	≥2.0 (n=90)	
Female sex	51 (60.7)	59 (72.8)	68 (75.6)	0.080
Age (yr)	8.3±1.8	8.9±2.2	9.0±1.9	0.064
Height SDS	0.8±1.2	0.9±0.9	1.1±1.0	0.147
BMI SDS	1.6±0.5	1.7±0.5	1.7±0.6	0.361
Waist circumference	75.9±9.1 (n=30)	78.8±8.6 (n=24)	83.2±10.6 (n=22)	0.070
SBP (mm/Hg)	108.6±10.9 (n=39)	109.8±8.6 (n=41)	110.7±9.6 (n=47)	0.627
DBP (mm/Hg)	58.9±10.1 (n=39)	62.4±10.9 (n=41)	62.4±8.1 (n=47)	0.183
AST (IU/L)	23.7±6.1	24.0±6.5	25.8±10.9	0.200
ALT (IU/L)	18.9±11.8	21.2±10.6	27.2±29.6[*,†]	0.018
Glucose (mg/dL)	97.1±8.2	97.2±6.4	96.6±6.0	0.858
Total cholesterol (mg/dL)	171.8±23.2	173.2±30.4	171.9±23.5	0.939
HDL-C (mg/dL)	61.5±11.1	53.3±7.3	44.8±8.3[*,†]	<0.001
Non–HDL-C (mg/dL)	110.3±29.4	119.9±27.9[*]	127.1±23.1[*,†]	<0.001
Triglycerides (mg/dL)	50.5±10.8	81.0±14.8	152.1±76.1[*,†]	<0.001
LDL-C (mg/dL)	100.2±28.8	103.7±27.7	96.7±23.6	0.224
HOMA-IR	2.7±1.3 (n=23)	2.5±1.6 (n=26)	4.5±3.2[*,†] (n=25)	0.004

Values are presented as number (%) or mean±standard deviation.
TG/HDL, triglyceride-to-high density lipoprotein cholesterol; BMI SDS, body mass index standard deviation scores; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance.
[*]$P<0.05$ compared with 1st tertile group. [†]$P<0.05$ compared with 2nd tertile group.

group compared to normal weight group (2.0±1.9 vs. 1.4±0.9, $P<0.001$) (Table 1).

The prevalence of hypo-HDL-cholesterolemia (13.2% vs. 3.7%, $P<0.001$), high non–HDL-C (16.1% vs. 9.1%, $P<0.001$), and hypertriglyceridemia (31.8% vs. 13.8%, $P<0.001$) was increased in overweight children compared to normal weight children (Table 2).

2. Trend of metabolic parameters according to TG/HDL–C ratio tertiles in overweight children

Table 3 describes the metabolic parameters of overweight children according to tertiles of TG/HDL-C ratio. BMI SDS showed no significant differences between the TG/HDL-C ratio tertile groups. However, ALT was higher in the third tertile group compared to the first and second tertile groups ($P=0.006$ and 0.049 vs. first and second tertile group, respectively). Non-HDL-C level was lower in the first tertile group compared to second and third tertile group ($P=0.020$ and $P<0.001$ vs. second and third tertile group, respectively). The HOMA-IR was significantly higher in the highest tertile group when compared to the first and second tertile groups ($P=0.008$ and $P=0.002$ vs. first and second tertile group, respectively). The prevalence of high HOMA-IR increased with increasing TG/HDL-C ratio tertiles (P for trend=0.003).

3. Association between TG/HDL–C ratio and HOMA–IR in overweight children

The TG/HDL-C ratio correlated with HOMA-IR in overweight children ($r=0.282$, $P=0.016$). On regression analysis adjusted for age and sex, the BMI ($\beta=0.402$, $P=0.001$) and TG/HDL-C ratio ($\beta=0.251$, $P=0.014$) were independently associated with log transformed HOMA-IR (adjusted R^2 of the model=0.324).

4. Sensitivity and specificity of metabolic parameters for identifying high HOMA–IR in overweight children

The TG/HDL-C ratio (≥2.0) showed higher sensitivity (55.6%) and specificity (72.9%) for identifying overweight children with high HOMA-IR when compared to TC (≥200 mg/dL), non–HDL-C (≥145 mg/dL), and LDL-C (≥130 mg/dL). The specificity of high TG/HDL-C was better than that of hypertriglyceridemia in identifying overweight children with high HOMA-IR (72.9% vs. 64.2%, Table 4).

Discussion

Our study showed strong association between the TG/HDL-C ratio and the parameter of insulin resistance. The TG/HDL-C ratio was higher in overweight children than normal weight children, and the prevalence of high HOMA-IR was increased with increasing TG/HDL-C ratio tertiles in overweight children. The BMI and TG/HDL-C ratio were independently associated with HOMA-IR after adjusting for age and sex in overweight children.

Elevated TG levels have been known as a biomarker of cardiovascular risk, but the specific role of TGs has been controversial until recently. Recent genetic evidences from mutational analysis, genome wide association studies, and Mendelian randomization studies suggest that TGs and TRLs play a pathogenic role in atherosclerosis, rather than simply being a biomarker[6,7]. In a meta-analysis, mutation in lipoprotein lipase that results in high TG levels increased the risk of ischemic heart disease nearly fivefold[19].

LDL-C has been the primary target to reduce the cardiovascular risk, but recent studies show high residual risk among patients treated with statins[20]. In fact, the most prevalent pattern in patients presenting with CVD event is characterized by elevated TG, decreased HDL-C, and normal to mildly elevated LDL-C, the profile commonly seen in individuals with insulin resistance and metabolic syndrome[21].

Lipoproteins must enter into the intima of arteries to cause atherosclerosis. Small dense LDL particles are more atherogenic, and the LDL particle size and the total LDL particle number, rather than routinely measured LDL-C levels, are more important[22]. TRLs are a key determinant of heterogeneity of LDL size and plasma TG level shows strong inverse relationship with LDL particle size[23]. It was also reported that TG/HDL-C ratio and non–HDL-C can identify overweight youth with atherogenic LDL particles[24].

Non–HLD-C reflects the cholesterol content in all potential atherogenic lipoproteins, including LDL-C, VLDL remnants, and chylomicron remnants[7,21]. It can also be measured from nonfasting samples. The non–HDL-C was reported to be more effective for CVD prediction than LDL-C especially when TGs are elevated, and recent guidelines recommend that non–HDL-C should be the target in the management of cardiovascular risk[25].

Overweight children had higher systolic blood pressure, ALT, glucose, non–HDL-C and TG levels in our study. The earliest stages and progression of atherosclerosis are influenced by dyslipidemia, hypertension, smoking, obesity, and diabetes mellitus. Controlling these risk factors should be beneficial for the prevention of atherosclerosis progression. The earlier the

Table 4. Sensitivity and specificity of metabolic parameters for identifying high HOMA-IR (≥3) in overweight children

Variable	Sensitivity (%)	Specificity (%)
Total cholesterol ≥200 mg/dL	15.4	56.8
Non–HDL-C ≥ 145 mg/dL	33.3	59.6
LDL-C ≥ 130 mg/dL	33.3	59.5
Hypertriglyceridemia*	56.0	64.2
TG/HDL-C ≥2.0	55.6	72.9

HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG/HDL-C, triglyceride-to-high-density lipoprotein cholesterol.
*TG ≥130 mg/dL for ≥10 years of age or ≥100 mg/dL for <10 years of age.

primary prevention begins, the better the result. Pediatricians should be involved in the prevention and control of these risk factors in children and adolescents[5].

Pacifico et al.[12] suggested that TG/HDL-C ratio help identifying children at high risk for structural vascular change and metabolic derangement. The odds ratio of central obesity, insulin resistance, high high-sensitivity C-reactive protein, nonalcoholic fatty liver disease, metabolic syndrome, and elevated carotid artery intima-media thickness (cIMT) values were increased significantly, as TG/HDL-C ratio tertiles increased[12]. Manco et al.[8] reported that TG/HDL-C ratio ≥2.2 was significantly associated with IGT in children and adolescents, and the TG/HDL-C ratio, rather than TG level, can be used to identify those with at risk of IGT. Our result also showed independent association between the TG/HDL-C ratio and HOMA-IR after adjusting for age, sex and BMI.

The TG/HDL-C ratio may also predict insulin resistance mediated organ damage. Di Bonito et al.[26] analyzed data from 5,505 children who were divided by non–HDL-C (≥130 mg/dL) or TG/HDL-C ratio (≥2.2). The odds ratios for insulin resistance, high blood pressure, metabolic syndrome, liver steatosis, increased cIMT, and left ventricular hypertrophy, were higher in children with high TG/HDL-C ratio compared to those with high non–HDL-C, suggesting that the TG/HDL-C ratio identify individuals with atherogenic dyslipidemia, cardiometabolic risk, and preclinical signs of organ damage[25].

The prevalence of hypertriglyceridemia (TG≥150 mg/dL) was 21.7% in obese Turkish children[2], and 21.5% in overweight Korean children[27]. In the present study, the prevalence of hypertriglyceridemia (TG≥130 mg/dL for ≥10 years of age or ≥100 mg/dL for <10 years of age) was 13.8% in normal weight group, and 31.8% in overweight group. Although hypertriglyceridemia is very common in overweight or obese children, TC, and non–high-density lipoprotein cholesterol (non–HDL-C) are commonly used screening tools for identifying children with dyslipidemia, and TG levels are less commonly measured in children.

In our study, TC and non–HDL-C were not sensitive to identify overweight children with increased insulin resistance. Recent guidelines recommend universal screening for dyslipidemia by nonfasting TC or non–HDL-C between age 9 and 11 years, however, targeted screening by the measurement of fasting lipid profile is recommended in children with BMI ≥95th percentile or adolescents with BMI ≥85th percentile, as well as those with family history of dyslipidemia or premature CVD[14,16,28].

It is not always easy to obtain fasting blood samples from children, and especially TG levels have high within-person variability[6]. Recent data shows that nonfasting as well as fasting serum TGs are independently associated with cardiovascular risk[29]. Postprandial TRLs are considered particularly proatherogenic, and studies suggested that nonfasting TGs are superior to fasting TGs as a cardiovascular risk predictor[30]. The practice of measuring fasting TG levels has been questioned recently[31].

Di Bonito et al.[26] used the TG/HDL-C ratio cutoff of 2.2 or higher based on the 75th percentile of 5,505 children including 4,417 obese children. The cut point of TG/HDL-C used in the studies by Pacifico et al.[12] was 1.98 or higher, defined by the cutoff of the highest tertile among 548 children including 391 overweight/obese children[8,26]. In our study, we defined high TG/HDL-C ratio by TG/HDL-C ≥2.0, according to the cut point of the highest tertile among 255 overweight children.

Limitation of our study is small sample size, especially the waist circumference, blood pressure and HOMA-IR was measured only in a subgroup of participants, and that the insulin resistance was measured by HOMA-IR, not by more accurate method.

In conclusion, the TG/HDL-C ratio is independently associated with insulin resistance in overweight children and adolescents. Our results support that TG levels should be included in screening obese children and adolescents at higher cardiometabolic risk.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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