Usefulness of the High Triglyceride-to-HDL Cholesterol Ratio to Identify Cardiometabolic Risk Factors and Preclinical Signs of Organ Damage in Outpatient Children

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OBJECTIVE—To evaluate whether the high triglyceride-to-HDL cholesterol (TG-to-HDL-C) ratio is associated with cardiometabolic risk (CMR) factors and preclinical signs of organ damage in an outpatient population of white children and adolescents.

RESEARCH DESIGN AND METHODS—The study population included 884 subjects (aged 6–16 years), of whom 206 (23%) were normal weight, 135 (15%) were overweight, and 543 (61%) were obese. Biochemical variables were analyzed in the whole sample, whereas homocysteine and left ventricular (LV) geometry and function were evaluated in 536 and 258 children, respectively.

RESULTS—The percentage of pubertal children ($P < 0.001$), as well as measurements of BMI, waist circumference, homeostasis model assessment of insulin resistance, white blood cell count, alanine aminotransferase (ALT), systolic blood pressure ($P < 0.0001$, for all), creatinine ($P < 0.001$), and diastolic blood pressure ($P < 0.02$), increased from the lowest to the highest tertile of the TG-to-HDL-C ratio. Age, sex, homocysteine, and glomerular filtration rate did not change. Moreover, interventricular septum thickness, relative wall thickness, and LV mass index ($P = 0.01$ to $P < 0.0001$) increased across tertiles of the TG-to-HDL-C ratio. Children with a TG-to-HDL-C ratio ≥2.0 showed a two- to threefold higher risk of elevated ALT levels and concentric LV hypertrophy than those with a TG-to-HDL-C ratio <2.0, independent of confounding factors.

CONCLUSIONS—The high TG-to-HDL-C ratio is associated with several CMR factors and preclinical signs of liver and cardiac abnormalities in the outpatient, white pediatric population. Thus, a TG-to-HDL-C ratio ≥2.0 may be useful in clinical practice to detect children with a worsened CMR profile who need monitoring to prevent cardiovascular disease in adulthood.

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There is growing interest in the identification of cardiovascular risk factors at an early stage of life because increased BMI (1), altered glucose homeostasis (2), and high blood pressure (3) in childhood are associated with a high risk of developing obesity, diabetes, hypertension, and coronary artery disease in adulthood. Few prospective studies have analyzed the abnormalities of the lipid profile from childhood to adulthood. The Bogalusa Heart Study (4) and the Muscatine Study (5) have demonstrated that the best predictor of lipid or lipoprotein levels in adulthood is the level observed in childhood, underscoring the importance of assessing the lipid profile early in life, although the cutoff to define dyslipidemia in children still is debated (6).

In adults, lipoprotein ratios are recognized as being more useful than isolated lipid values for cardiovascular disease risk assessment because they better reflect the interactions between lipid fractions (7). In particular, the triglyceride-to-HDL cholesterol (TG-to-HDL-C) ratio is closely related to both insulin resistance and cardiometabolic risk (CMR) in a white population (8).

The clinical and prognostic significance of the TG-to-HDL-C ratio in the pediatric population is, at present, unclear. Weiss et al. (9) have recently demonstrated that the TG-to-HDL-C ratio measured in late adolescence predicts a proatherogenic lipid profile in adulthood independently of obesity and weight gain. Whether a high TG-to-HDL-C ratio is able to detect CMR factors and preclinical signs of organ damage in the pediatric population has not yet been investigated. To address this issue, we explored the relationship between the TG-to-HDL-C ratio and CMR factors as well as its association with subclinical signs of liver and cardiac abnormalities in an outpatient, white pediatric population.

RESEARCH DESIGN AND METHODS

—All of the subjects who were consecutively observed in the outpatient unit of the pediatric department of Pozzuoli Hospital in the period between 2004 and 2010 were included in the study. The majority of the children were referred by their general practitioners for allergy problems, overweight, and obesity, as described elsewhere (10). After excluding subjects with gastrointestinal,

liver, cardiac, renal, urinary, and infectious diseases, the sample consisted of 884 children (435 boys and 449 girls), with an age range of 6–16 years. Of these subjects, 206 (23%) were normal weight, 135 (15%) were overweight, and 543 (61%) were obese. All of the children were apparently healthy, and none of the children had a history of alcohol consumption or diabetes or were under pharmacological treatment. Anthropometric measurements were obtained using standard methods. Sexual maturity was evaluated by the Tanner stage for pubic hair (stages I–V). Blood pressure was measured according to the fourth report of the National High Blood Pressure Education Program on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents (11).

Measurements
Fasting blood samples were taken from all participants. The determination of biochemical parameters was performed in the centralized laboratory of Pozzuoli Hospital. Fasting plasma glucose (FPG), insulin, total cholesterol, TGs, HDL-C, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine (colorimetric compensated Jaffe method) were determined using a Roche analyzer (Modular Analytics Serum Work Area, Mannheim, Germany). Homocysteine was determined by the immunoenzymatic method (Abbott, Abbott Park, IL). Insulin resistance was evaluated by the homeostasis model assessment of insulin resistance (HOMA-IR) index using the following standard formula: fasting insulin (units per liter) × fasting glucose (millimoles per liter)/22.5. Estimated glomerular filtration rate (eGFR) was calculated using the following updated Schwartz formula: 0.413 × height (centimeters)/serum creatinine (milligrams per deciliter).

Echocardiography
A total of 258 children underwent echocardiography. These children did not differ from the remainder of the children for age and sex distribution. Standard echocardiograms were obtained by a commercially available echocardiographic system with tissue Doppler imaging (TDI) capabilities (Artida/Aplio; Toshiba). All measurements were analyzed according to the recommendations of the American Society of Echocardiography. Left ventricular mass (LVM) was calculated according to the Penn convention and indexed for height$^{2.7}$ (LVMi). Relative wall thickness

(RWT) was calculated from LV posterior wall thickness (LVPWT), interventricular septum thickness (IVST), and LV diastolic diameter (LVDD) using the following formula: (PWT + IVST)/LVDD. Increased LVM was defined using age- and sex-specific quantiles as proposed by Khoury et al. (12). LV hypertrophy was identified by a cutoff higher than the 90th percentile. Increased RWT was defined by a value >0.375 (13), corresponding to the 90th percentile of our nonobese children. LV geometry was defined as normal geometry (normal LVMi and RWT), eccentric LV hypertrophy (increased LVMi and normal RWT), concentric remodeling (normal LVMi and increased RWT), and concentric LV hypertrophy (increased LVMi and RWT). LV function was analyzed by conventional and TDI echocardiography, as described elsewhere (13). Transmitral peak rapid filling velocity (E), peak atrial filling velocity (A), the E-to-A ratio, and isovolumic relaxation time (IRT) were obtained as measures of diastolic function. For TDI echocardiography, three major velocities were recorded at the annular site: peak positive systolic velocity and two peak negative velocities during the early (E_a) and late (A_a) phases of diastole. The E_a-to-A_a ratio also was calculated. All echocardiographic readings were made online by the same investigator who was blinded to the metabolic status of the children.

Definitions
Pubertal stage was defined by Tanner stages III–V. Overweight and obesity were defined using the International Obesity Task Force criteria (14). Impaired fasting glucose (IFG) was defined by an FPG ≥100 mg/dL. High blood pressure (above the 90th percentile for age, sex, and height) was defined according to the fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents (11). High waist circumference, high TGs, low HDL-C, and metabolic syndrome were defined using the cutoff proposed by Cook et al. (15). These values derive from the growth curves of U.S. children and adolescents that intercept the cutoff values of each single component of metabolic syndrome (Adult Treatment Panel III definition) in adult life.

Insulin resistance was defined by the 95th percentile of the HOMA-IR values obtained in healthy nonobese Italian children categorized according to Tanner stage (i.e., HOMA-IR >2.20 [stage I], >3.61

[stages II and III], and >3.64 [stages IV and V]), as described elsewhere (10). High ALT levels, as a surrogate of nonalcoholic fatty liver disease (NAFLD), were defined using sex-related cut points (i.e., >30 IU/L in boys and >19 IU/L in girls), as described elsewhere (16). High white blood cell (WBC) count was defined by a value ≥9.0 (10³/L), corresponding to the 80th percentile of our population (10). The study was approved by the local ethics committee, and informed consent was obtained from the parents of all participants.

Statistical analysis
Data are expressed as means ± SD or number (percentage). Given the skewed distribution of HOMA-IR, TGs, plasma creatinine, ALT, AST, and homocysteine, the statistical analysis of these variables was applied after log transformation and back transformation to natural units to allow presentation in the text and tables. Means were compared using ANOVA. χ^2 or Fisher exact tests, as appropriate, were used to compare proportions. To evaluate the CMR risk associated with a high TG-to-HDL-C ratio, we performed logistic regression analysis, controlled for age, sex, and pubertal stage, separately in nonobese and obese subjects. To assess the independent impact of some variables on high ALT levels and concentric LV hypertrophy, we performed a multiple logistic analysis with a forward stepwise selection procedure. A two-sided P value <0.05 was considered statistically significant. The statistical analysis was performed using SPSS for Windows, version 13.0 (SPSS, Chicago, IL).

RESULTS—To evaluate the relationship between the TG-to-HDL-C ratio and CMR factors, all children were stratified into tertiles of the TG-to-HDL-C ratio. Moving from the lowest to the highest tertile, we observed an increased percentage of pubertal stage (P < 0.0001), as well as increased levels of BMI, waist circumference, HOMA-IR, WBC count, ALT, systolic blood pressure (P < 0.0001, for all), FPG (P = 0.022), total cholesterol (P = 0.004), creatinine (P = 0.001), AST (P = 0.007), and diastolic blood pressure (P = 0.019) (Table 1). No significant difference was seen between tertiles for age, sex, homocysteine, and eGFR.

Echocardiographic variables
A statistically significant difference across tertiles was found in RWT (P = 0.009) and LVMi (P < 0.0001), whereas no difference

Table 1—Features of children according to tertiles of the TG-to-HDL-C ratio

| | TG-to-HDL-C ratio tertile | | | |
	<1.2	≥1.2 and <2.0	≥2.0	P
n (%)	315 (35)	297 (34)	272 (31)	
Male sex	159 (51)	142 (48)	134 (49)	0.805
Age (years)	10 ± 3	10 ± 3	10 ± 3	0.662
Pubertal stage	128 (41)	177 (60)	138 (51)	0.0001
BMI (kg/m^2)	22 ± 6	25 ± 5	29 ± 5	0.0001
BMI z score	−0.51 ± 0.92	0.03 ± 0.90	0.56 ± 0.87	0.0001
Obesity	131 (41)	184 (62)	228 (84)	0.0001
Waist circumference (cm)	74 ± 16	82 ± 16	91 ± 14	0.0001
Waist circumference z score	−0.46 ± 0.94	0.00 ± 0.96	0.53 ± 0.82	0.0001
FPG (mg/dL)	85 ± 7	86 ± 7	85 ± 8	0.022
HbA$_{1c}$ (%)	5.4 ± 0.3	5.4 ± 0.3	5.4 ± 0.3	0.223
HOMA-IR	1.9 ± 1.5	2.8 ± 2.0	3.7 ± 2.8	0.0001
Cholesterol (mg/dL)	158 ± 28	162 ± 32	167 ± 33	0.004
HDL-C (mg/dL)	60 ± 10	52 ± 9	43 ± 8	0.0001
TGs (mg/dL)	55 ± 12	78 ± 14	130 ± 45	0.0001
Homocysteine (mmol/L)	8.1 ± 3.0	8.3 ± 3.2	8.1 ± 3.2	0.625
WBC (10^3/L)	7.0 ± 2.2	7.5 ± 2.0	8.1 ± 2.2	0.0001
Creatinine (mg/dL)	0.52 ± 0.10	0.54 ± 0.10	0.54 ± 0.11	0.001
eGFR (mL/min per 1.73 m^2)	113 ± 17	110 ± 18	112 ± 17	0.150
ALT (IU/L)	21 ± 11	23 ± 13	30 ± 22	0.0001
AST (IU/L)	25 ± 7	24 ± 7	26 ± 9	0.007
Systolic blood pressure (mmHg)	104 ± 11	106 ± 12	110 ± 14	0.0001
Diastolic blood pressure (mmHg)	59 ± 8	60 ± 10	62 ± 10	0.019
Systolic blood pressure z score	−0.25 ± 0.91	−0.00 ± 0.97	0.34 ± 1.13	0.0001
Diastolic blood pressure z score	−0.16 ± 0.89	0.02 ± 1.06	0.17 ± 1.12	0.001

Data are means ± SD or n (%) unless otherwise indicated.

was observed between tertiles of the TG-to-HDL-C ratio for both systolic and diastolic function, evaluated with conventional and TDI echocardiography (Table 2). The prevalence of normal geometry, eccentric, LV hypertrophy, concentric remodeling, and concentric LV hypertrophy among children with a high TG-to-HDL-C ratio (≥2.0) was 24, 39, 33, and 58%, respectively (P = 0.001).

Relationship between a high TG-to-HDL-C ratio and CMR factors

To analyze the CMR profile associated with a high TG-to-HDL-C ratio (≥2.0) independent of obesity, we performed a logistic regression analysis separately in nonobese and obese children. Nonobese children with a high TG-to-HDL-C ratio showed a 3- to 58-fold increased risk of

insulin resistance, high waist circumference, high blood pressure, IFG, high WBC, and metabolic syndrome compared with those with a TG-to-HDL-C ratio <2.0. In obese children, those with a high TG-to-HDL-C ratio showed a 1.5- to 10-fold increased risk of insulin resistance, high blood pressure, and metabolic syndrome compared with those with a TG-to-HDL-C ratio <2.0 (Table 3).

Elevated ALT levels were predicted by high waist circumference, insulin resistance, and a high TG-to-HDL-C ratio. The independent predictors of concentric LV hypertrophy were a high TG-to-HDL-C ratio and high blood pressure (Table 4).

CONCLUSIONS—This study provides evidence that in an outpatient, white pediatric population, a high TG-to-HDL-C ratio is associated with an unfavorable CMR profile. In particular, children with a TG-to-HDL-C ratio ≥2.0 showed an increased risk of subclinical signs of liver and cardiac abnormalities independent of high waist circumference, high blood pressure, and insulin resistance.

In adults, there is growing interest in the TG-to-HDL-C ratio as a surrogate marker of atherogenic lipid abnormalities, namely small LDL cholesterol and small HDL-C (17), and of insulin resistance and high cardiovascular risk (8). In childhood, the clinical value of lipid ratios has been much less investigated. In a large sample of high school adolescents, Musso et al. (18) demonstrated that the TG-to-HDL-C ratio and high-sensitivity C-reactive protein positively correlated with BMI and waist circumference. Weiss et al. (9), using a longitudinal design, demonstrated that the TG-to-HDL-C ratio in late adolescence predicts small LDL and HDL particles in adulthood independent of obesity and weight gain. In a recent report performed in a large multiethnic cohort of obese youths, Giannini et al. (19) demonstrated that a high TG-to-HDL-C ratio is associated with insulin resistance in white girls and boys but not in African Americans or Hispanics. In the current study, we demonstrate that a high TG-to-HDL-C ratio is significantly associated with several CMR factors. In particular, in nonobese children, a TG-to-HDL-C ratio ≥2.0 is associated with a 3- to 58-fold increased risk of high waist circumference, high blood pressure, IFG, high WBC count, insulin resistance, and metabolic syndrome. In obese subjects a TG-to-HDL-C ratio

Table 2—Cardiac features of children according to tertiles of the TG-to-HDL-C ratio

| | TG-to-HDL-C ratio tertile | | | |
	<1.2	≥1.2 and <2.0	≥2.0	P
n	67	102	89	
Heart rate (bpm)	84 ± 11	84 ± 14	87 ± 12	0.218
LVDD (mm)	42 ± 5	41 ± 5	42 ± 5	0.215
RWT (mm)	0.35 ± 0.06	0.35 ± 0.05	0.37 ± 0.06	0.009
LVM (g)	91 ± 35	87 ± 33	104 ± 33	0.001
LVMi (g/h$^{2.7}$)	35 ± 11	34 ± 9	39 ± 10	0.0001
Ejection fraction (%)	63 ± 7	64 ± 5	64 ± 6	0.641
IRT (ms)	65 ± 8	66 ± 11	66 ± 9	0.873
E-to-A ratio	2.1 ± 0.6	2.1 ± 0.7	2.2 ± 0.8	0.587
E$_a$-to-A$_a$ ratio	2.4 ± 0.8	2.2 ± 0.7	2.3 ± 0.7	0.243
S$_a$ (cm/s)	10 ± 2	10 ± 2	10 ± 2	0.165

Data are means ± SD unless otherwise indicated. S$_a$, peak-positive systolic velocity.

Table 3—Odds ratios and 95% CIs of CMR factors associated with a high TG-to-HDL-C ratio in nonobese and obese subjects

Variable	Odds ratio (95% CI)^	P
Nonobese subjects		
Insulin resistance	2.62 (1.03–6.72)	0.044
IFG	7.81 (1.17–52.37)	0.034
High WBC	8.08 (1.41–46.40)	0.019
High blood pressure	4.51 (1.84–11.04)	0.001
High waist circumference	3.23 (1.48–7.01)	0.003
Metabolic syndrome	57.74 (9.49–351.42)	0.0001
Obese subjects		
Insulin resistance	1.45 (1.02–2.05)	0.037
High blood pressure	1.49 (1.03–2.17)	0.036
Metabolic syndrome	9.87 (6.17–15.78)	0.0001

^Controlled for age, sex, and pubertal stage.

≥2.0 is associated with a 1.5- to 10-fold higher risk of insulin resistance, high waist circumference, and metabolic syndrome. These results emphasize the clinical usefulness of the TG-to-HDL-C ratio, which is greater in nonobese than in obese children in whom the excess adiposity may likely mask the role of the single CMR factors.

A previous study performed in healthy Korean adults demonstrated that fasting plasma insulin and TG-to-HDL-C ratio concentrations were associated with elevated ALT and evidence of NAFLD (20). Of interest, Cali et al. (21) used magnetic resonance imaging to demonstrate a close association between fatty liver and an atherogenic lipid profile characterized by large VLDL, small dense LDL, and a decreased number of large HDL particles in obese children. Our results expand this observation, demonstrating that a high TG-to-HDL-C ratio, visceral adiposity, and insulin resistance are all independently associated with elevated ALT levels, which is recognized as a surrogate index of NAFLD. This finding also may have implications in terms of cardiovascular

risk because high ALT levels are considered to be a nontraditional marker of cardiovascular morbidity. There is in fact evidence that in overweight and obese children, NAFLD is associated with multiple cardiovascular risk factors (22).

The relationship between the TG-to-HDL-C ratio and LV geometry is unexplored. Our study provides the novel finding that a high TG-to-HDL-C ratio, independently of visceral adiposity and high blood pressure, is associated with concentric LV hypertrophy, a well-known cardiovascular risk factor. Although the pathophysiological significance of this association is not straightforward, some data from the literature may be helpful. First, in subjects with essential hypertension, low HDL levels are associated with LV hypertrophy (23). In addition, using proton magnetic resonance spectroscopy, Kankaanpää et al. (24) demonstrated accumulation of TGs in the myocardium of moderately obese subjects, which was more pronounced in those with elevated ALT levels. Collectively, these findings show that an atherogenic lipid phenotype (low HDL and high TGs) has a negative

impact on LVM and that it is associated with lipid deposition in the liver and the heart. Our finding of an independent association of a high TG-to-HDL-C ratio with liver and cardiac abnormalities supports the hypothesis that this lipid phenotype may represent a common substrate underlying both elevated ALT and LV hypertrophy.

The lack of clear cutoff values for the definition of dyslipidemia in childhood (6) may result in underdiagnosis and, consequently, undertreatment of children with lipid abnormalities who are at high risk for dyslipidemia in adulthood. We suggest that if confirmed in longitudinal studies, a high TG-to-HDL-C ratio might be used in clinical practice to identify children at risk for dyslipidemia and replace high TGs and low HDL in the definition of metabolic syndrome, also considering that the lipid cutoff levels in children still are debated.

The strength of our study was the large sample size, the comprehensive analysis of several CMR factors, and the evaluation of preclinical signs of liver and cardiac abnormalities. Some limitations can be envisaged. The cross-sectional design precludes us to establish whether a high TG-to-HDL-C ratio has any causative effect on cardiac and liver abnormalities as well as on their progression in adulthood. Follow-up of these children will clarify this issue. In addition, our sample was composed of outpatient children, most of whom were overweight or obese, which may have limited the generalizability of our results. Finally, ALT levels were used as a surrogate index of NAFLD; however, this proxy is widely accepted for epidemiological purposes, also considering that ALT levels are a major predictor of FLD (25).

In conclusion, our study demonstrates that a TG-to-HDL-C ratio ≥2.0 is associated with several CMR factors and proves to be useful in identifying children with a high risk of elevated ALT levels and concentric LV hypertrophy. These results, obtained in outpatient, white children with high prevalence of overweight, need to be replicated in the general pediatric population, and longitudinal evaluations will clarify whether a high TG-to-HDL-C ratio may be a good predictor of cardiovascular disease in adult life.

Table 4—Independent predictors of elevated ALT and concentric LV hypertrophy

Variable	Odds ratio (95% CI)	β	SE	P
Elevated ALT^				
High waist circumference	4.32 (2.88–6.50)	1.46	0.21	0.0001
High TG-to-HDL-C ratio	1.83 (1.32–2.54)	0.60	0.17	0.001
Insulin resistance	1.73 (1.23–2.41)	0.55	0.17	0.001
Concentric LV hypertrophy^^				
High blood pressure	3.05 (1.49–6.25)	1.12	0.37	0.002
High TG-to-HDL-C ratio	2.62 (1.30–5.28)	0.96	0.36	0.007

^Controlled for age, sex, pubertal stage, TGs, and HDL-C levels. ^^Controlled for age, sex, pubertal stage, high waist circumference, insulin resistance, TGs, and HDL-C levels.

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