RESEARCH PAPER

Triglyceride and Non-High-Density Lipoprotein Cholesterol as Predictors of Cardiovascular Disease Risk Factors in Chinese Han Children

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Objective: To investigate the role of serum cholesterol and triglyceride in the assessment of cardiovascular disease risk factors in children and adolescents.

Design: Case-control study.

Setting: Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China.

Subjects: Children from 6 years to 17 year old. 188 with simple obesity, and 431 with obesity and metabolic abnormalities. 274 age and gender-matched healthy children as controls.

Methods: Receiver operating characteristic curves were used to analyze the detection of cardiovascular disease risk factors by cholesterol and triglyceride in children and adolescents.

Results: The ranges of areas under receiver operating characteristic curves (AUC) for triglyceride and non-high-density lipoprotein cholesterol were 0.798-0.860 and 0.667-0.749, respectively to detect cardiovascular disease risk factors. The ranges of AUC for low-density lipoprotein cholesterol, total cholesterol, and high-density lipoprotein cholesterol were 0.631-0.718, 0.596-0.683, and 0.292-0.376, respectively.

Conclusions: Triglyceride and non-high-density lipoprotein cholesterol are better than low-density lipoprotein cholesterol as predictors of cardiovascular disease risk factors in Chinese Han children and adolescents.

Key words: *Cardiovascular disease, Children, Cholesterol, Lipids, Risk factors, Triglyceride.*

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Although atherosclerosis manifests clinically in middle and late adulthood, it is known to have a long asymptomatic phase of development, that begins early in life, often during childhood, and is significantly related to dyslipidemias. Dyslipidemia, characterised by elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C) and triglyceride (TG) levels as well as low high-density lipoprotein cholesterol (HDL-C) concentration, is well-known cardiovascular disease (CVD) risk factor [1].

With respect to lipid profiling for CVD risk assessment, LDL-C levels are widely targeted for primary prevention and intervention. At present, however, some investigators have suggested that non-HDL cholesterol may be superior to LDL cholesterol alone as a predictor of CVD risk factors in adolescents [2] and adults [3], largely because cholesterol-enriched very-low-density lipoprotein and intermediate-density lipoprotein have been shown to be atherogenic in addition to LDL. As for TG, the relationship between TG and CVD risk factors is controversial. In some studies, the relationship is not statistically significant after controlling for other lipids, particularly HDL-C [4-6]. However, several meta-analyses have concluded that TG is a CVD risk factor independent of HDL-C and other risk factors [7-9].

As clusters of risk factors for CVD are stable characteristics that tend to track fairly well from childhood into adulthood [10], preventive efforts that start in childhood are necessary, as they could delay progression to clinical disease. It is, thus important is to identify early the cardiovascular risk factors in children and adolescents. The associations between lipid parameters and CVD risk factors has been described in population groups [2,11] but similar studies in children and adolescents in China are relatively sparse. We therefore conducted this study to compare the predictive value of serum cholesterol and triglyceride in CVD risk factors in children and adolescents.

METHODS

Children and adolescents between 6 and 17 years of age (*n*=619) who were referred to our endocrinology department between September 2008 to September 2010 with the complaint of obesity were enrolled in this study. Subjects were eligible if they were healthy and had a body-mass index (BMI) that exceeded the 95th percentile for their age and sex [12]. According to the presence or absence of metabolic abnormalities, the total 619 cases were divided into the Simple obesity group and the Obesity with metabolic abnormalities group. The control group consisted of 274 healthy children and adolescents, all of whom were recruited by the Department of Child Care for health examination. Exclusion criteria consisted of the known presence of diabetes or other endocrine metabolic or kidney diseases, and the use of medication that alters blood pressure, glucose, or lipid metabolism.

Consent was obtained from the parents and the Ethics committee of the Children Hospital of Zhejiang University School of Medicine.

The participants were classified as having metabolic abnormalities if they met one or more of the following criteria for age and sex: elevated systolic blood pressure (SBP) or diastolic blood pressure (DBP) (a value that exceeded 95th percentile for age and sex) [13], abnormal fasting blood glucose (FBG) (glucose level >126 mg/dL) [14]; and dyslipidemia. The diagnosis of dyslipidemia was achieved if any of the following was found: a TC level >5.18mmol/L; a TG level >1.47mmol/L; an LDL-C level >3.37mmol/L; a non-HDL-C level >3.76 mmol/L or a HDL-C level <1.03 mmol/L [15,16].

Body height was measured to the nearest 1 mm, with the participants in bare or stocking feet standing upright against a stadiometer. With the participants lightly dressed, bodyweight was measured to the nearest 0.1 kg by a medical digital scale. Waist circumference (WC) was measured to the nearest 1 mm by placing a tape measure around participant's body in the horizontal plane, at the level of the midpoint between the lowest rib and the iliac crest on bare skin when in a state of expiration. We used the standard hydrargyric cuff sphygmomanometer for blood pressure measurement. The measurements were done by practitioners who received professional training. Every participant was seated and in a relaxed state for at least 10 min before measurement. Each underwent blood pressure measurement three times, the gap between the highest and lowest value was below 4 mmHg, the average value of the three values was used, or another measurement was made after the subject had rested.

Baseline blood samples were obtained from subjects at 8 A.M., after a 10-hour overnight fast, with the use of an indwelling venous line for measurement of levels of glucose and lipids (TC, TG, LDL-C, HDL-C). Blood glucose was measured using a glucose oxidase method. The concentrations of serum TC and TG were detected by the routine enzymatic method. Plasma HDL-C and LDL-C concentration were determined by the direct measurement method.

BMI was calculated as body weight/(body height)^2 , waist-to-height radio (WHtR) was calculated as WC/height, and non-HDL-C was calculated as total cholesterol minus HDL-C. Age- and sex-specific BMI *Z*-scores, WC *Z*-scores, and WHR *Z*-scores were used as continuous dependant variables for each model [17].

Statistics analysis: Statistical analyses were conducted using SPSS software (version 17.0). Quantitative data with normal distributions were presented as mean ± SD. Chi-square test was used to compare proportions between the groups. Continuous variables were analyzed with Student's *t* test. Differences were considered statistically significant if $P<0.05$. Receiver operating characteristic (ROC) curves were used to analyze the detection of cardiovascular risk factors by cholesterol and triglyceride in children and adolescents.

RESULTS

The descriptive characteristics of the sample are presented in ***Table* I**. Children in Group 3 exhibited higher BMI; BMI *Z*-scores; WC and WC *Z*-scores than the ones in Group 2.

There was a trend of increased cardiovascular risk in obese children. SBP; DBP; FBG; TG; LDL-C and non-HDL-C increased stepwise, whereas HDL-C decreased stepwise in Group 1, Group 2 and Group 3. Compared to Group 1 and Group 2, Group 3 had significantly higher TC levels, while no significant difference was apparent in TC level between Group 1 and Group 2 (***Table* II**).

***Fig.*1** displays the areas under the curves (AUC) for each lipid parameter as a predictor of cardiovascular risk factors and comparisons of the AUC between Group 2 and Group 3. For the identification of CVD risk, AUC for TG, non-HDL-C, LDL-C and TC were 0.829 (95% confidence interval [CI]: 0.798-0.860), 0.708 (95% CI: 0.667-0.749), 0.675 (95% CI: 0.631-0.718), 0.639 (95% CI:0.596-0.683), respectively. These AUC were significantly greater than 0.5, in detecting ardiovascular risk factors as compared to HDL-C with an area of 0.334 (95% CI: 0.292-0.376). All plasma lipid parameters performed significantly better among those in the Group 3 cohort than the Group 2 cohort ($P<0.05$).

TABLE I BASELINE CHARACTERISTICS OF THE STUDY POPULATION

	Control Group (Group 1)	*Simple Obesity Group (Group 2)*	*Obesity with Metabolic Abnormalities Group (Group 3)*
Gender (M/F)	191/83	147/41	311/120
Age (y)	10.29 ± 2.82	10.35 ± 1.82	10.67 ± 2.12
BMI (kg/m^2)	16.79 ± 1.83	27.00 ± 3.63**	27.87 ± 3.58$^{** \#\#}$
BMI *Z*-scores	(-0.20 ± 0.52)	3.06 ± 1.21**	3.32 ± 1.46$^{**\#}$
WC (cm)	57.88 ± 7.41	85.08 ± 10.80**	88.51 ± 11.41$^{**\#\#}$
WC *Z*-scores	(-0.38) ± 0.53	2.36 ± 1.61**	2.84 ± 1.32$^{**\#\#}$
WHtR	0.41 ± 0.03	0.59 ± 0.11**	0.60 ± 0.08**
WHtR *Z*-scores	(-0.32) ± 0.57	2.78 ± 2.75**	3.04 ± 1.41**

*BMI, Body mass index; WC, waist circumstance; WHtR, waist-to-height; Compared to Group 1 *represents P<0.05, ** represents P<0.01, Compared to Group 2 $^{\#}$represents P<0.05, $^{\#\#}$represents P<0.01.*

TABLE II CARDIOVASCULAR RISK FACTORS OF THE STUDY POPULATION

	Control Group (Group 1)	*Simple Obesity Group (Group 2)*	*Obesity with Metabolic Abnormalities Group (Group 3)*
SBP (mmHg)	91.04 ± 11.09	108.10 ± 11.21**	114.12 ± 13.88$^{**\#\#}$
DBP (mmHg)	64.83 ± 7.44	66.99 ± 7.39**	69.13 ± 8.99$^{**\#\#}$
FBG (mmol/L)	4.83 ± 0.47	4.91 ± 0.33*	5.13 ± 0.75$^{**\#\#}$
TC (mmol/L)	3.97 ± 0.58	4.05 ± 0.62	4.50 ± 0.95$^{**\#\#}$
TG (mmol/L)	0.75 ± 0.28	0.95 ± 0.28**	1.70 ± 0.89$^{**\#\#}$
HDL-C (mmol/L)	1.49 ± 0.28	1.36 ± 0.34**	1.21 ± 0.31$^{**\#\#}$
LDL-C (mmol/L)	2.09 ± 0.52	2.25 ± 0.51**	2.67 ± 0.74$^{**\#\#}$
non-HDL-C (mmol/L)	2.48 ± 0.55	2.69 ± 0.60**	3.29 ± 0.89$^{**\#\#}$

*SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol. Compared to Group 1*represents P<0.05, **represents P<0.01, Compared to Group 2$^{\#\#}$represents P<0.05, $^{\#\#}$represents P<0.01.*

DISCUSSION

Our study shows a strong correlation between childhood obesity and early-onset dyslipidemia, hypertension, and hyperglycemia. These conditions, when manifested in childhood, track into in adult life because obese children are more likely to become obese adults [18].

We plotted the ROC curves for serum cholesterol and triglycerides. The area under the ROC curve was largest for TG, indicating the model was superior to the other CVD risk-prediction models. In the past, the role of elevated triglycerides as an independent CVD risk factor has been debated. However, emerging evidence points to elevated triglyceride levels as a risk factor for cardiovascular disease that is independent of HDL cholesterol levels. One recent study consisting of 909 public parochial suburban schoolchildren aged 6 to 18 years, found that over a follow-up of 26 years, adult CVD was associated with pediatric high TG (odds ratio [OR], 5.85; 95% CI, 2.3-14.7) by stepwise logistic regression [19], supporting the hypothesis that TG would be an independent risk factor for CVD. A meta-analysis of prospective studies has shown that for each 1 mmol/L increase in TG, CVD risk increases by 12% in men and 37% in women, irrespective of HDL-C and other risk factors [20]. Since an area under the curve above 0.7 indicates a reasonably good clinical test, monitoring the levels of TG among children and adolescents at increased risk of obesity may be clinically useful in detecting their CVD risk factors.

Recent studies involving subjects of different age groups have also shown the importance of non-HDL-C as a reliable, less costly parameter that is strongly correlated with cardiovascular risk because non-HDL-C includes all atherogenic lipid subfractions [21]. Data from the

WHAT IS ALREADY KNOWN?

- Role of dyslipidemia in the assessment of cardiovascular disease risk factors in children and adolescents.

WHAT THIS STUDY ADDS?

- Triglyceride and non-high density lipoprotein cholesterol are better than low-density lipoprotein cholesterol as predictors of cardiovascular disease risk factors in Chinese Han children and adolescents.

Bogalusa Heart Study suggest that childhood non-HDL-cholesterol levels persist and best predict adult dyslipidemia and other CVD risks [22]. Another recent study, using data from the Framingham Heart Study, showed that non-HDL-C was a better predictor of cardiovascular disease risk than LDL-C [23]. These findings are consistent with the findings of the present study, in which non-HDL-C was shown to outperform LDL-C. Another major advantage of non-HDL-C is that it can be accurately calculated in a non-fasting state and is therefore very practical to obtain in clinical practice. In 2011, the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents released its summary report, which recommends non-HDL-C as a predictor of CVD risk [15]. In addition, non-HDL-C is included in the diagnostic criteria of metabolic syndrome by Chinese Society of Pediatrics [16].

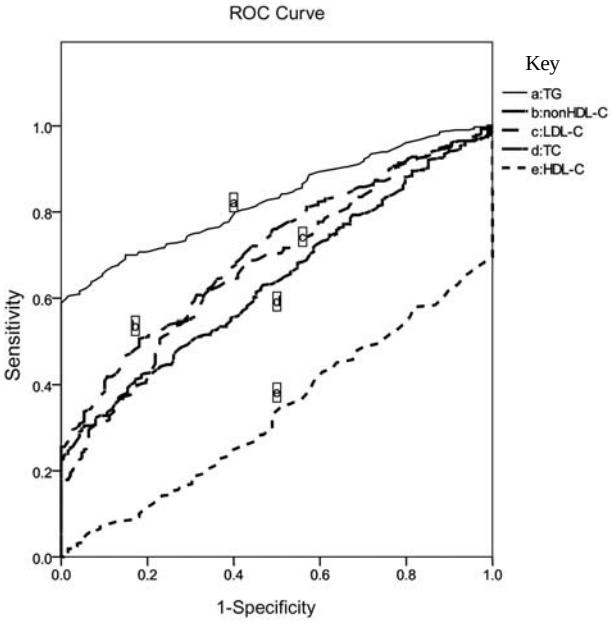

FIG. 1 *Receiver operating characteristic curves (ROC) constructed using the lipid parameters.*
TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

Given the unrelenting rise in childhood obesity rates, we have to brace ourselves for the onslaught of dyslipidemia and other metabolic disorders in children and adolescents in the very near future. Recently, the American Academy of Pediatrics issued a policy statement on lipid screening and cardiovascular health in childhood [24]. A fasting lipid profile is the recommended approach to screening, because there is currently no noninvasive method to assess atherosclerotic CVD in children and the first screening should preferably take place after 2 years of age but no later than 10 years of age. Our current study suggests that pediatric screening for lipid parameters in children and adolescents has a crucial predictive value for CVD risk factors, especially serum triglyceride and non-HDL-C.

Contributors: WZ: had primary responsibility for patient screening, enrollment, outcome assessment, preliminary data analysis and writing the manuscript. CW and JF: participated in the development of the protocol and analytical framework for the study and contributed to the writing of the manuscript. LL: supervised the design and execution of the study and contributed to the writing of the manuscript.

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REFERENCES

1. Jago R, Harrell JS, McMurray RG, Edelstein S, EI Ghormli L, Bassin S. Prevalence of abnormal lipid and blood pressure values among an ethnically diverse population of eighth-grade adolescents and screening implications. Pediatrics. 2006;117: 2065-73.
2. Srinivasan SR, Frontini MG, Xu J, Berenson GS. Utility of childhood non-high-density lipoprotein cholesterol levels in predicting adult dyslipidemia and other cardiovascular risks:The Bogalusa Heart Study. Pediatrics. 2006;118:201-6.
3. Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation. 2005;112:3375-83.
4. Austin MA. Epidemiologic associations between hypertriglyceridemia and coronary heart disease. Semin Thromb Hemost. 1988;14:137-42.
5. Austin MA. Plasma triglyceride as a risk factor for

coronary heart disease. The epidemiologic evidence and beyond. Am J Epidemiol. 1989;129:249-59.
6. Freedman DS, Gruchow HW, Anderson AJ, Rimm AA, Barboriak JJ. Relation of triglyceride levels to coronary artery disease: the Milwaukee Cardiovascular Data Registry. Am J Epidemiol. 1988;127:1118-30.
7. Abdel-Maksoud MF, Hokanson JE. The complex role of triglycerides in cardiovascular disease. Semin Vasc Med. 2002;2:325-33.
8. Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Whitlock G. Asia Pacific Cohort Studies Collaboration. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. Circulation. 2004;110:2678-86.
9. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation. 2007;115:450-8.
10. Bao W, Srinivasan SR, Wattigney WA, Berenson GS. Persistence of multiple cardiovascular risk clustering related to syndrome X from childhood to young adulthood. Arch Intern Med. 1994;154:1842-7.
11. Morrison JA, Glueck CJ, Horn PS, Yeramaneni S, Wang P. Pediatric triglycerides predict cardiovascular disease events in the fourth to fifth decade of life. Metabolism. 2009;58:1277-84.
12. Group of China Obesity Task Force. Body mass index reference norm for screening overweight and obesity in Chinese children and adolescents. China J Epidemiol. 2004;2:97-102.
13. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: A Working Group Report From the National High Blood Pressure Education Program. Pediatrics. 1996;98:649-58.
14. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S. The metabolic syndrome in children and adolescents. Lancet. 2007;369:2059-61.
15. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128: S213-56.
16. The Subspecialty Groups of Endocrinology and Genetic Disease, Pediatric Cardiology and Child Health Care, The Society of Pediatrics, Chinese Medical Association. Definition and prevention recommendations of metabolic syndrome in children and adolescents. China J Pediatr. 2012; 50.
17. Xue Feng Chen, Li Liang, Jun Fen Fu, Chun Xiu Gong, Feng Xiong, Ge Li Liu, *et al*. Study on physique index set for Chinese children and adolescents. Chlin J Epidemiol. 2012; 33:449-54.
18. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med. 1997;337:869-73.
19. Morrison JA, Glueck CJ, Wang P. Childhood risk factors predict cardiovascular disease, impaired fasting glucose plus type 2 diabetes mellitus, and high blood pressure 26 years later at a mean age of 38 years: the Princeton–lipid research clinics follow-up study. Metabolism. 2012;61:531-41.
20. Abdel-Maksoud MF, Hokanson JE. The complex role of triglycerides in cardiovascular disease. Semin Vasc Med. 2002;2:325-33.
21. Srinivasan SR, Myers L, Berenson GS. Distribution and correlates of non-high-density lipoprotein cholesterol in children: the Bogalusa heart study. Pediatrics. 2002;1103:e29.
22. Freedman DS, Khan LK, Dietz WH, Srinivasan SR, Berenson GS. Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. Pediatrics. 2001;108:712-8.
23. Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. Am J Cardiol. 2006;98:1363-8.
24. Daniels SR, Greer FR, Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008;122:198-208.