Association Between Serum Uric Acid and Triglycerides in Chinese Children and Adolescents With Short Stature

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Research

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Abstract

Background: Elevated triglyceride (TG) levels are a biomarker of CVD risk. The relationship between serum uric acid (SUA) and TG in adults and obese children is well established. However, studies on children with short stature with SUA and TG are limited.

Aim: The aim of this study was to examine the relationship between SUA and TG in Chinese children and adolescents with short stature.

Methods: This study is a cross-sectional analysis of a cohort study. A total of 1095 children and adolescents with short stature (720 males and 375 females) were included. The related clinical characteristics, including body mass index (BMI), serum uric acid (SUA), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), were determined.

Results: The univariate analysis results showed a significant positive association between SUA and TG ($P < 0.001$). Furthermore, a smooth curve fitting after adjusting for potential confounders was performed, and a nonlinear relationship between SUA and TG was observed. A multivariate piecewise linear regression model revealed a significant positive association between SUA and TG when the SUA level was greater than 7 mg/dL (β 0.13, 95% CI 0.05, 0.22; $P = 0.002$). However, we did not observe a significant relationship between SUA and TG when the SUA level was lower than 7 mg/dL (β 0.01, 95% CI -0.01, 0.04; $P=0.799$).

Conclusion: This study described a nonlinear relationship between UA and TG in children and adolescents with short stature. When SUA rises to a certain level, there is a strong positive association between UA and TG. This finding suggests that elevated UA levels may be another risk indicator of cardiovascular disease in children and adolescents with short stature.

Background

Short stature is a common reason for referral to a growth and development specialist clinic to identify the cause. The factors affecting short stature are complex and diverse, including nutrition, hormonal regulation, pubertal development, and chronic disease during the foetal to adolescent period. Children and adolescents with short stature not only have height problems but also effects on their psychology and physiology[1, 2]. Several prospective large-scale studies and meta-analyses have reported that there is an inverse association between height and cardiovascular disease (CVD) risk[3-6]. Dyslipidaemia is one of the main risk factors for CVD, and there is a negative association between height and lipid profile in children and adults[7-9]. Hence, it is necessary to pay attention to the lipid profile of children with short stature, which is a risk factor for cardiovascular disease. Lipid levels in childhood can usually be traced back to adulthood. Although CVD usually develops in later years, it is well known that the accumulation

of intimal fat streaks is an early lesion of atherosclerosis, which accompanies dyslipidaemia from childhood[10-12].

Several studies have shown that elevated triglyceride (TG) levels are a biomarker of CVD risk[13-15], similar to high total cholesterol and low-density lipoprotein cholesterol (LDL-C). There is evidence showing that elevated residual cholesterol levels marked by elevated TG are another causal risk factor for cardiovascular disease and that all-cause mortality is increasing[16]. A meta-analysis involving 10,158 patients with coronary heart disease (CHD) among 262,525 participants in 29 western prospective studies showed that TG is highly associated with CVD[17]. Furthermore, assessment of lipid profiles in childhood can predict the risk of cardiovascular disease in adulthood[18]. The factors affecting TG are complex and diverse, and the relationship between serum uric acid (SUA) and TG in adults and obese children is well established[19-22]. However, studies on children with short stature with SUA and TG are limited. Our previous studies have shown that the lipid profile is related to insulin-like growth factor 1 (IGF-1) levels in children with short stature[23], and IGF-1 is related to SUA[24]. Therefore, the aim of this study was to investigate the relationship between SUA and TG in children and adolescents with short stature.

Methods

Subjects

The study group consisted of 1095 children and adolescents with short stature (720 males and 375 females) who were enrolled from March 2013 to March 2020 at the Department of Endocrinology, Affiliated Hospital of Jining Medical University. They were recruited as part of the Growth and Development Diseases in Shandong Province: a cohort follow-up study (GDDSD study, http://www.chictr.org.cn, ChiCTR1900026510). A cross-sectional analysis of a cohort study was performed in children and adolescents with short stature with an average age of 10.6 ± 3.3 years. All subjects with short stature, which is defined as the population whose height is more than two standard deviation scores (SDSs) below the corresponding mean height for a given age, sex, and race group[25]; normal weight and height at birth; and the absence of chronic disease were included in the study. The exclusion criteria were as follows: short stature with precocious puberty, congenital adrenal hyperplasia, cartilage dysplasia, and chromosomal or genetic abnormalities such as Turner syndrome.

The Human Ethics Committee of the Affiliated Hospital of Jining Medical University (Shandong, China) reviewed and approved this study. All families of the patients were informed of the purpose of this study, and the parents of all participants signed written informed consent.

Anthropometry measurements

The height and weight of the study subject were measured by a special individual at the growth and development specialist clinic in the morning with standard methods after taking off the shoes and

wearing light clothes. Height and weight were measured with a height measuring instrument (China Jiangsu Nantong Best Industrial Co., Ltd.) with an allowable error range of 0.1 cm and a weight scale (Wuxi Weigher Factory Co., Ltd., Jiangsu, China) with a precision of 0.1 kg. Height was expressed as the SDS based on Chinese children of normal values[26], and body mass index (BMI) was calculated as the ratio of weight in kilograms to the square of height in metres. BMI SDS was calculated according to 2009 growth charts for Chinese children and adolescents. The staging of puberty was assessed based on physical examination and Tanner stages[27]. Boys without pubic hair and a testicular volume less than 4 mL and girls without pubic hair and no breast development are conside red prepubertal.

Laboratory measurements

Fasting blood samples were obtained from all subjects to measure laboratory parameters. The lipid profile (including TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)) and kidney function (SUA, urea nitrogen (BUN) and creatinine) were detected by a biochemical autoanalyser (Cobas c702, Roche; Shanghai, China). Serum IGF-1 concentrations were assessed by a chemiluminescence assay (DPC IMMULITE 1000 analyser, SIEMENS, Germany) with an intra-assay and inter-assay coefficient of variation of 3.0% and 6.2%, respectively. IGF-1 SDS was calculated based on IGF-1 levels matched to age- and sex-matched healthy children and adolescents[28].

Statistical analysis

We present the continuous variables with a normal distribution as the mean ± standard deviation and a non-normal distribution as the median (interquartile range). Categorical variables are shown in numbers and percentages. To investigate the factors affecting TG, a univariate analysis model was performed. We then explored the association between SUA and TG using smooth curve fitting after adjusting for potential confounders. Finally, we further applied a multivariate piecewise linear regression to explore the threshold effect of SUA and TG. A two-sided $P < 0.05$ was considered statistically significant. All analyses were performed using EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) and R 3.4.3 (http://www.r-project.org).

Results

Clinical and biochemical characteristics of the subjects

The clinical and biochemical characteristics of all subjects are summarized in Table 1. A total of 1095 subjects with an average age of 10.6 ± 3.3 years old were analysed in this study, of which 65.75% were male and 624 (56.99%) were prepubescent. The mean height SDS of the subjects was -2.85 ± 0.84. The mean levels of TG and SUA were 68.73 ± 33.80 mg/dl and 4.70 ± 1.36 mg/dl, respectively.

Factors associated with TG in the subjects

The associations between TG levels and SUA and anthropometric and biochemical variables are displayed in Table 2 by univariate linear regression analysis. For the unadjusted model, a significant positive association between SUA and TG (P < 0.001) was observed. In addition, there was a positive relationship between age, body weight, TC (all P < 0.001) and pubertal stage (P = 0.009). We found that HDL-C was significantly negatively associated with TG (P < 0.001). In our study, we did not find any significant association between TG and sex, height SDS, BMI SDS, IGF-1 SDS, LDL-C, Cr or BUN (all P > 0.05).

Independent association of SUA and TG by multivariate piecewise linear regression

In this study, we analysed the relationship between SUA and TG by smooth curve fitting after adjusting for potential confounding factors, including age, sex, body weight, TC and pubertal stage. A nonlinear relationship was observed between SUA and TG, and there is a breakpoint, indicating that there are two stages of changes between SUA and TG (Figure 1). To present the relationship between SUA and TG more accurately, we use the linear regression and piecewise linear regression models at the same time and choose the model that is more suitable for the relationship between SUA and TG according to the P for the log likelihood ratio test.

As shown in Table 3, the result shows that the P for the log likelihood ratio test was less than 0.05, which indicates that a two-piecewise linear regression can better represent the relationship between SUA and TG. We further analysed the threshold effect according to curve fitting between SUA and TG and found that this inflection point of the SUA was 7 mg/dL. Specifically, TG levels increased as SUA increased when the SUA level was greater than 7 mg/dL (β 0.13, 95% CI 0.05, 0.22; P = 0.002). However, we did not observe a significant relationship between SUA and TG when the SUA level was lower than 7 mg/dL (β 0.01, 95% CI -0.01, 0.04; P=0.799).

Discussion

In this cross-sectional analysis of a cohort of children and adolescents with short stature, we observed that the levels of SUA were positively associated with TG after adjusting for potential confounding factors. Interestingly, we found a nonlinear relationship between SUA and TG in children and adolescents with short stature, and the SUA turning point level was 7 mg/dL.

SUA is the final product of human purine metabolism. High levels of UA are associated with many metabolic diseases. It is reported that hyperuricaemia in children and adolescents has been increasing in recent years, and UA levels > 5.5 mg/dl are considered abnormal[29]. The relationship between SUA and TG is controversial; a study has reported that there is a positive association between SUA and TG[19], while in another study, the relationship was not observed[30]. In our study, we found that SUA was positively associated with TG in children and adolescents with short stature, which was consistent with Ma W et al., who conducted a study of 261 Chinese patients with newly diagnosed moyamoya disease. In addition, a population-based observational study was undertaken in a rural area in the District of

Birbhum, West Bengal, India, and found that SUA was correlated with TG[30]. A cross-sectional study conducted by Lurbe E et al. in 333 obese Caucasian children aged 5-18 years found a positive association between SUA and TG[22]. Furthermore, Xu L et al. also found a positive association between SUA and TG in 597 patients with type 2 diabetes mellitus. However, Li L et al. conducted a cross-sectional study among 409 obese Chinese adults, and no significant associations were found between SUA and TG[30]. The differences in the clinical characteristics and recruitment criteria among these studies may explain this divergent result.

Interestingly, we further analysed the relationship between SUA and TG through smooth curve fitting and observed a nonlinear relationship between SUA and TG. TG levels increased as the SUA increased when the SUA level was greater than 7 mg/dL, whereas the relationship between SUA and TG was not observed. This means that when SUA rises to a certain level, there is a strong association with TG. Many clinical studies have shown that hyperuricaemia is related to cardiovascular disease[30-33], and it is also implied that SUA is related to the lipid profile. The underlying mechanism of elevated lipids caused by high levels of SUA is that SUA promotes lipid peroxidation, generates oxygen free radicals, and causes inflammation of blood vessel walls. High levels of SUA are considered to be a mediator of inflammatory endocrine disorders in adipose tissue, which may be one of the important factors in the development of dyslipidaemia[34].

Overweight or obese children are prone to dyslipidaemia, and previous studies have reported that there is a positive association between BMI and TG in adults and children[35-37]. However, our study did not find a relationship between BMI and TG in children and adolescents with short stature. This may be due to the relatively well-proportioned BMI of the subjects in our study. In addition, we did not find a relationship between height and TG in short children and adolescents. This is inconsistent with a previous study conducted by La Batide-Alanore, A. et al. among 865 nuclear families in the French STANISLAS cohort who volunteered to participate in free health examinations between 1993 and 1994 that found that height was negatively associated with TG in both parents and their offspring[38]. We consider that this may be because our study subjects are children and adolescents with short stature, and their height is below the limit of -2SDS.

Our study has several limitations that need to be considered. First, the cross-sectional analysis of the study does not allow us to determine causality. Second, the findings of this study are only applicable to Chinese short stature children and adolescents. Different results may be observed in other populations, such as obese children. Finally, we can further study the relationship between a low-purine diet and lipid profile improvement in children and adolescents with short stature.

Conclusions

In conclusion, our study described a nonlinear relationship between UA and TG in children and adolescents with short stature. When SUA rises to a certain level, there is a strong positive association

between UA and TG. This finding suggests that elevated UA levels may be another risk indicator of cardiovascular disease in children and adolescents with short stature.

Abbreviations

BMISDS: body mass index standard deviation scores; CVD: cardiovascular disease; HDL-C: high density lipoprotein-cholesterol; Height SDS: height standard deviation scores; IGF-1 SDS: insulin like growth factor-1 standard deviation scores; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; SUA: serum uric acid

Declarations

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Availability of data and materials

The datasets used and/or analysed in the current study are available from the corresponding authors upon reasonable request.

Authors' contributions

1. Y. C. carried out the studies and drafted the manuscript. Z. helped with the statistical analysis. M. Z. revised the manuscript. B. B. and H. T. participated in the concept and design of the study, revising it critically for important intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Human Ethics Committee of the Affiliated Hospital of Jining Medical University (Shandong, China) reviewed and approved this study. All families of the patients have been informed of the purpose of this study, and the parents of all participants have signed written informed consent.

Consent for publication

All authors have read and approved the content, and they agree to submit it for consideration for publication in the journal.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Clinical and biochemical characteristics.

	All
Number	1095
Sex (male %)	720 (65.75%)
Age (years)	10.6 ± 3.3
Height (cm)	131.44 ± 17.89
Height SDS	-2.85 ± 0.84
Body weight (kg)	31.80 ± 12.99
BMI (kg/m2)	17.57 ± 3.44
BMI SDS	-0.05 ± 1.26
IGF-1 (ng/mL)	198.00 (114.75-321.00)
IGF-1 SDS	-1.02 (-1.84–0.18)
TG (mg/dL)	68.73 ± 33.80
TC (mg/dL)	147.35 ± 26.76
HDL-C (mg/dL)	52.77 ± 11.91
LDL-C (mg/dL)	264.03 ± 14.96
SUA (mg/dL)	4.70 ± 1.36
Cr (μmol/L)	40.10 (34.02-46.40)
BUN (mmol/L)	4.40 (3.70-5.30)
Pubertal stage	
In prepuberty (%)	624 (56.99%)
In puberty (%)	471 (43.01%)

Abbreviations: Height SDS: height standard deviation scores; BMI SDS: body mass index standard deviation scores; IGF-1 SDS: insulin like growth factor-1 standard deviation scores; TG: triglyceride; TC: total cholesterol. HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein cholesterol; SUA: serum uric acid; BUN: blood urea nitrogen, Cr: creatinine. Normal distribution of data was presented as mean ± standard deviation; nonnormal distribution of data was presented as median (interquartile range) and categorical data using number (percentage). $P < 0.05$ is considered to be statistically significant.

Table 2 Association between TG and different variables

Variables	β	(95% CI)	P value
Age (years)	0.01	(0.01, 0.02)	< 0.001
Height SDS	-0.01	(-0.04, 0.02)	0.462
Body weight (kg)	0.01	(0.01, 0.01)	< 0.001
BMI SDS	0.01	(-0.02, 0.02)	0.853
IGF-1 SDS	-0.01	(-0.03, 0.01)	0.854
TC (mg/dL)	0.06	(0.03, 0.10)	< 0.001
HDL-C (mg/dL)	-0.35	(-0.43, -0.27)	< 0.001
LDL-C (mg/dL)	-0.01	(-0.01, 0.01)	0.827
SUA (mg/dL)	0.05	(0.04, 0.07)	< 0.001
Cr (μmol/L)	0.01	(-0.01, 0.01)	0.388
BUN (mmol/L)	-0.01	(-0.01, 0.00)	0.132
Sex			
Male	reference		
Female	0.01	(-0.04, 0.02)	0.461
Pubertal stage			
In prepuberty (%)	reference		
In puberty (%)	0.06	(0.02, 0.11)	0.009

Abbreviations: Height SDS: height standard deviation scores; BMI SDS: body mass index standard deviation scores; IGF-1 SDS: insulin like growth factor-1 standard deviation scores; TG: triglyceride; TC:

total cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein cholesterol; SUA: serum uric acid; BUN: blood urea nitrogen, Cr: creatinine; P < 0.05 is considered to be statistically significant.

Table 3 Threshold effect analysis for the relationship between SUA and TG

Models	TG	
	Adjusted β (95%CI)	P value
Model I		
One line slope	0.03 (0.01, 0.05)	< 0.001
Model II		
Turning point	7	
< 7 slope 1	0.01 (-0.01, 0.04)	0.799
> 7 slope 2	0.13 (0.05, 0.22)	0.002
LRT test	0.010	

Model I, linear analysis; Model II, non-linear analysis. LRT test, Logarithmic likelihood ratio test.(p-value<0.05 means Model II is significantly different from Model I, which indicates a non-linear relationship); Adjustment variables: age, sex, weight, TC, and pubertal stage. SUA: serum uric acid; TG: triglyceride; TC: total cholesterol; P< 0.05 is considered to be statistically significant.

Figures

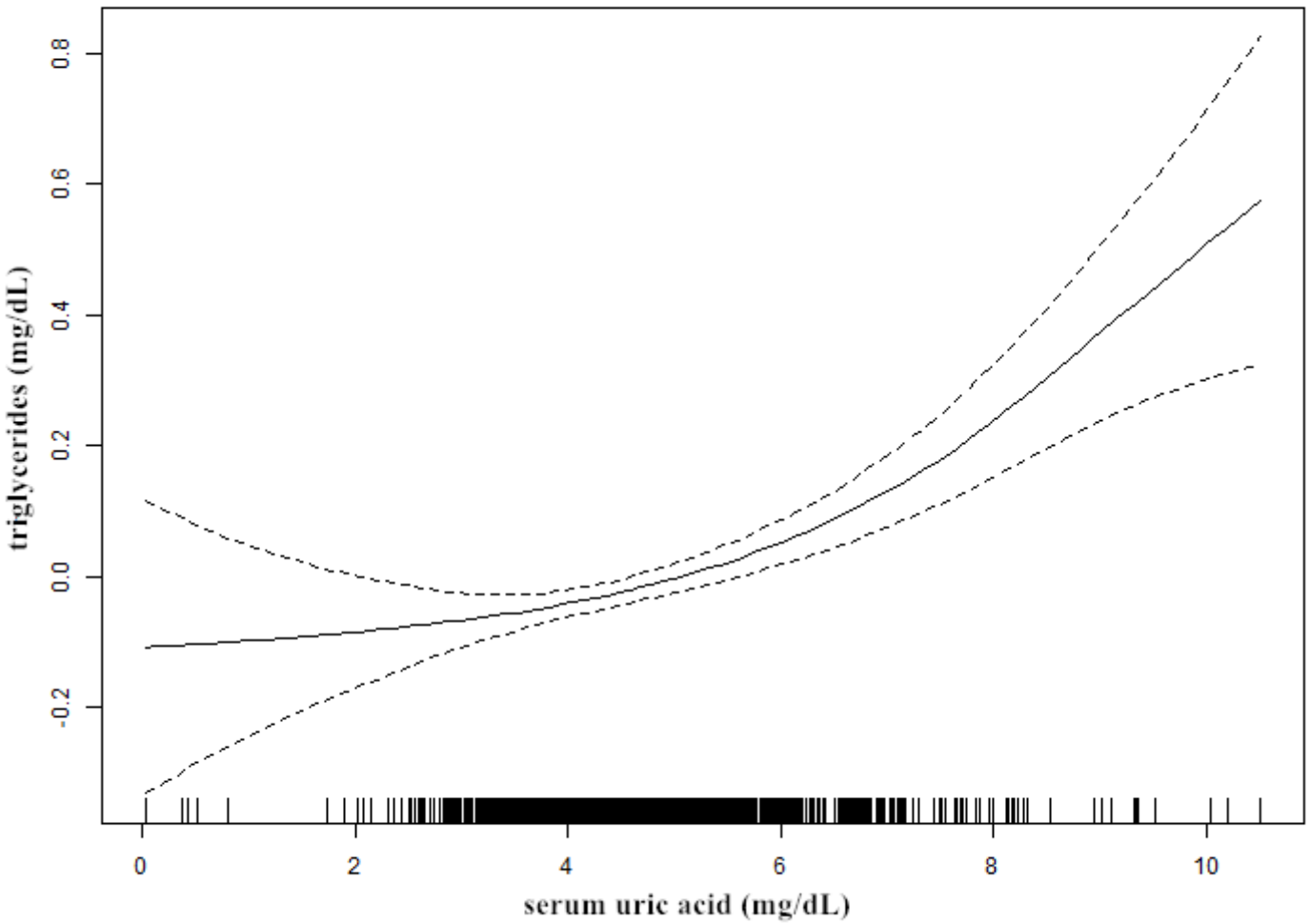

Figure 1

The relationship between SUA and TG by smooth curve fitting. Adjustment variables: age, sex, weight, TC, pubertal stage. SUA: serum uric acid; TG: triglyceride; TC: total cholesterol.