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Serum cystatin C levels are associated with triglycerides/high-density lipoprotein cholesterol ratio in adolescent girls ages between 16-19 years old

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Abstract. – OBJECTIVE: The pathophysiological role of cystatin C in cardiometabolic disorders is not completely explored in young population. On the other hand, together with the increase in obesity, dyslipidemia and insulin resistance (IR) are often observed even in youngsters. The aim of the study was to investigate the relationship between cystatin C and triglycerides-to-high-density lipoprotein cholesterol ratio (TG/HDL-c), as an indicator of dyslipidemia and a surrogate marker of IR in the cohort of adolescent girls ages between 16-19 years.

PATIENTS AND METHODS: A total of 99 girls were included in the study. Anthropometric and biochemical parameters were provided. Associations of biochemical markers with TG/HDL-c ratio were tested using univariable and multivariable ordinal regression analysis for TG/HDL-c ratio tertiles as dependent variable.

RESULTS: In univariate analysis, cystatin C levels were significantly associated with TG/HDL-c ratio (OR=1.813; 95% CI: 1.190-2.757, *p*=0.005). Furthermore, multivariate analysis revealed that cystatin C was an independent predictor of TG/HDL-c ratio when body mass index and high sensitivity C-reactive protein (i.e., markers that were significantly correlated with TG/HDL-c ratio in Spearman's correlation analysis) were included in the Model. Adjusted odds for cystatin C (OR=1.621; 95% CI: 1.028-2.552, *p*=0.037) demonstrated that rise in cystatin C by 0.1 mg/L increased the probability for higher TG/HDL-c tertile group by 1.621 times.

CONCLUSIONS: Serum cystatin C levels are associated with TG/HDL-c ratio in adolescent girls. Longitudinal studies are needed to confirm the causal relationship between cystatin C and TG/HDL-c ratio and to further explore its diagnostic and therapeutic potential in dyslipidemia and insulin resistance in young population.

Key Words:
Cystatin C, Cardiometabolic risk, Dyslipidemia, Inflammation.

Introduction

Adolescence represents a very challenging period of life since the transition to adulthood is accompanied with many changes. Sedentary lifestyle, smoking, increased alcohol intake, changes in eating habits, consumption of fast food, weight gain etc. favor an increased risk for obesity-related cardiometabolic disorders that often track into adulthood[1].

Given the rapid increase in overweight/obesity in young population, it is of great importance to early recognize high-risk youngsters and to treat them promptly in order to avoid or postpone cardiometabolic complications late in life. In line with this, regular physical activity[2] and healthy dietary pattern[3] are of urgent need to be implemented. In addition, a new look to some relatively old biomarkers might be beneficial in earlier diagnosis and treatment of those individuals.

It is well known that dyslipidemia highly correlates with obesity-related disorders[4-11]. Decreased high-density lipoprotein cholesterol (HDL-c) and increased triglycerides (TG) represent the hallmarks of dyslipidemia and a typical finding in insulin resistant state[12]. Accordingly, increased TG/HDL-c ratio, as an indicator of dyslipidemia and a surrogate marker of insulin resistance (IR) was shown to be reliable indicator of high cardiometabolic risk[13]. The high ratio of these two lipid parameters was shown to be

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an independent predictor of hypertension[14] and major adverse cardiovascular outcomes in female population[15]. Additionally, TG/HDL-c ratio negatively correlates with the circulating levels of small dense low-density lipoprotein cholesterol (LDL) particles, which are recognized as more atherogenic ones than larger LDL-particles[16].

Similarly, in children and adolescents the reliability of TG/HDL-c ratio in IR prediction was shown[12,17]. Furthermore, it was reported that this ratio reflects atherosclerotic disturbances better than TG and HDL-c, separately[17] and might be reliable in screening for metabolic disturbances[18].

On the other hand, although cystatin C has been widely used as a biomarker of renal function (i.e., even better than creatinine, since it is not influenced by muscle mass)[19,20] it was shown to exert many other metabolic properties in the last decade[21,22]. Researches that described that adipocytes, pre-adipocytes, macrophages and endothelial cells represent significant source of high level of cystatin C in circulation have shed a light on some novel roles of this biomarker in cardiometabolic disorders[22]. Not only that it was found to be increased in obesity[22], but also in the majority of states closely related to obesity, such as metabolic syndrome[23], type 2 diabetes mellitus[21], coronary heart disease[24].

However, the pathophysiological role of cystatin C in cardiometabolic disorders is not completely explored in young population since discordant results are presented so far[19,20,25]. As well, studies that examined the relationship between cystatin C and TG/HDL-c ratio in adolescent population are scarce. Therefore, in order to obtain deeper insight into the pathophysiological properties of cystatin C in dyslipidemia and IR, the objective of this study was to investigate its relationship with TG/HDL-c ratio in the cohort of adolescent girls ages between 16-19 years.

Patients and Methods

Study Population

This study included a cohort of 99 consecutively recruited adolescent girls from the third and fourth grade of two secondary schools in Podgorica. Each girl filled in a questionnaire, answering the questions about lifestyle habits (i.e., smoking, physical activity, alcohol use), medications use and illnesses.

Inclusion criteria were normal weight or overweight/obese otherwise healthy girls who voluntarily accepted participation in the study. Girls younger than 16 years and older than 19 years of age, girls with a history of alcohol use or any medications use, smoking, acute or chronic inflammatory disease or any other disease were excluded.

Institutional Ethical Committee approved the study protocol and the research was conducted in line with principles of the Declaration of Helsinki. Signed informed approval was provided by each girl, whereas for participants younger than 18 years of age parental written consent was obtained, also.

Anthropometric Measurements

Anthropometric parameters: waist circumference (WC), body weight and body height were taken. The body mass index (BMI) was calculated, as previously described[26]. Girls were considered to be normal weight if presented with BMI <25 kg/m^2, whereas those with BMI ≥ 25 kg/m^2 were regarded to be overweight/obese.

Biochemical Analyses

The blood samples were collected in the morning after an overnight fast of at least 8 hours[26]. Serum cystatin C and high sensitivity C-reactive protein (hsCRP) levels were determined nephelometrically (Behring Nephelometer Analyzer, Marburg, Germany). Standardized procedures were used for determination of serum levels of total cholesterol (TC), LDL-c, HDL-c, TG, glucose, total proteins and creatinine and were measured on automatic analyzer (Roche Cobas 400, Mannheim, Germany).

Statistical Analysis

After data distribution testing with Shapiro-Wilk test, results are expressed as median and the interquartile range: 25th percentile, 75th percentile. Comparisons among the TG/HDL-c tertiles groups were made by the Kruskal-Wallis test. Post hoc comparisons were performed by Mann-Whitney U test. Categorical data were presented as absolute frequencies and compared by Chi-square test for contingency tables. The correlation between TG/HDL-c and demographic and laboratory data was examined by Spearman's correlation analysis and data were presented as coefficient correlation (ρ). Univariable and multivariable ordinal regression analysis was employed to examine possible association of TG/HDL-c and cystatin C levels. TG/HDL-c levels

Table I. Basic demographic and laboratory data according to TG/HDL-c ratio tertiles.

	The first TG/HDL-c ratio tertile	The second TG/HDL-c ratio tertile	The third TG/HDL-c ratio tertile	p**
Adolescent girls No.	33	33	33	
Age, years	18 (17-19)	18 (17-19)	18 (17-19)	0.506
Weight, kg	65 (56-69)	70 (60-75)	72 (64-91)[a]*	0.009
Height, cm	167 (166-172)	168 (165-173)	169 (166-174)	0.692
BMI, kg/m^2	21.8 (19.8-25.2)	23.2 (20.8-26.4)	26.1 (22.3-30.9)[a]*	0.007
WC, cm	79 (75-83)	86 (74-93)	90 (79-100)[a]*	0.003
Glucose, mmol/L	5.1 (5.0-5.2)	5.0 (4.7-5.2)	5.0 (4.8-5.5)	0.379
Total proteins, g/L	73.0 (70.5-75.0)	73.0 (70.5-74.5)	73 (69-74)	0.769
Creatinine, µmol/L	57 (47-63)	58 (49-62)	52 (45-60)	0.665
TC, mmol/L	3.93 (3.54-4.34)	4.20 (3.83-4.63)	4.19 (3.76-4.73)	0.235
HDL-c, mmol/L	1.75 (1.41-1.95)	1.46 (1.33-1.60)[a]*	1.17 (1.01-1.35)[a†,b†]	< 0.001
LDL-c, mmol/L	2.05 (1.79-2.36)	2.27 (2.15-2.57)[a#]	2.48 (2.13-2.90)[a]*	0.008
TG, mmol/L	0.55 (0.44-0.64)	0.81 (0.69-0.90)[a†]	1.19 (0.96-1.39)[a†,b†]	< 0.001
Non-HDL-c, mmol/L	2.16 (1.81-2.54)	2.58 (2.45-2.79)[a]*	3.05 (2.63-3.45)[a†,b#]	< 0.001
TG/HDL-c ratio	0.33 (0.27-0.38)	0.53 (0.47-0.61)[a†]	0.88 (0.75-1.20)[a†,b†]	< 0.001
hsCRP, mg/L	0.33 (0.30-0.65)	0.62 (0.30-1.55)	0.78 (0.53-2.00)[a]*	0.013

Data are presented as median (interquartile range) and compared by Kruskal-Wallis test with post hoc Mann-Whitney test. **p for Kruskal-Wallis test. asignificantly different from the first TG/HDL-c tertile group. bsignificantly different from the second TG/HDL-c tertile group. *p<0.01; #p<0.05; †p<0.001. BMI-Body mass index; WC-Waist circumference; TC-Total cholesterol; HDL-cholesterol-High-density lipoprotein cholesterol; LDL-cholesterol-Low-density lipoprotein cholesterol; TG-Triglycerides; hsCRP-High-sensitivity C-reactive protein.

(dependent variable) were ranked according to tertile values. Variables which significantly correlated with TG/HDL-c were set as independent variables (predictors). Data from these analyses were given as the estimated odds ratio (95% Confidence Interval). A level of p less than 0.05 was defined as statistically significant.

Results

Female adolescents from the third TG/HDL-c tertile group were heavier, had higher BMI and WC than those from the first tertile group (Table I). As expected, there were statistically significant differences in HDL-c, LDL-c, TG and non-HDL-c levels between TG/HDL-c tertile groups. TG and non-HDL-c were the highest in the third tertile group, but they were also higher in the second compared to first tertile group. The opposite was obtained for HDL-c levels. HDL-c levels were the lowest in the third tertile group, but they were also lower in the second compared to first tertile group. Significantly higher LDL-c concentrations were in the second and in the third group than in the first one. HsCRP levels were higher in the third than in the first TG/HDL-c tertile group (Table I).

Figure 1 demonstrated significant differences in cystatin C levels among TG/HDL-c tertile groups (p=0.014). The highest cystatin C was obtained in the third group compared to the two other groups.

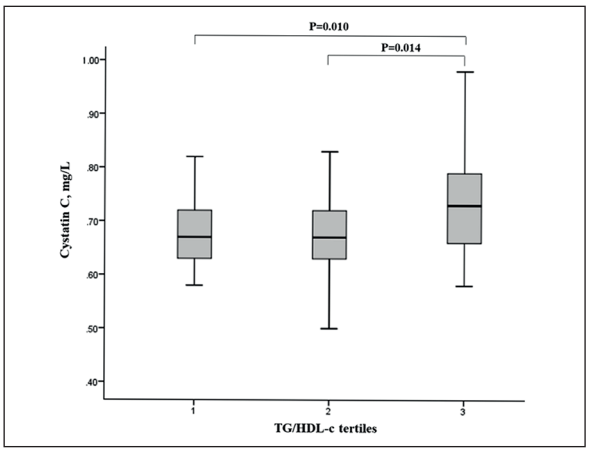

Figure 1. Cys C levels in adolescents according to TG/HDL-c ratio tertiles. Data are presented as median (interquartile range) and compared by Kruskal-Wallis test with *post hoc* Mann-Whitney test. p=0.014 for Kruskal-Wallis test. Cystatin C values for the first TG/HDL-c ratio tertile group was Median: 0.67, Interquartile range: 0.63-0.72; for the second group Median: 0.67, Interquartile range: 0.63-0.70 and for the third group Median: 0.73, Interquartile range: 0.66-0.79.

Unequal distribution of normal weight and overweight/obese adolescent girls were evident between all the three TG/HDL-c tertile groups (p=0.012) (Figure 2). No significant differences in distribution of normal weight and overweight/obese adolescent girls were seen between the first and the second TG/HDL-c tertile group (p=0.120) and between the second and the third group (p=0.138). However, significantly more overweight/obese adolescent girls than normal weight ones were found in the third than in the first tertile group (p=0.003).

Furthermore, when divided all girls into normal weight (i.e., with BMI <25 kg/m^2, n=54) and overweight/obese group (i.e., with BMI ≥25 kg/m^2, n=45), the median (interquartile range) for serum cystatin C levels were as follows: 0.66 (0.63-0.72) *vs.* 0.71 (0.66-0.80), p=0.009, respectively (data not presented).

Spearman's correlation analysis showed that weight, BMI, WC, LDL-c, TG, non-HDL-c, hsCRP and cystatin C correlated positively with TG/HDL-c ratio (Table II). Also, significant negative correlation was expected between HDL-c and TG/HDL-c ratio.

Ordinal regression analysis was performed to analyse in depth association of cystatin C and TG/HDL-c ratio. In univariate analysis, cystatin C levels were significantly associated with TG/HDL-c ratio (OR=1.813; 95% CI: 1.190-2.757, p=0.005). This result indicated that as cystatin C level increases by 0.1 mg/L, the probability of adolescents' classification in higher tertile TG/HDL-c ratio group raises 1.813 times. Furthermore, multivariate analysis revealed that cystatin C was an independent predictor of TG/HDL-c ratio when BMI and hsCRP (i.e., markers that were significantly correlated with TG/HDL-c ratio in Spearman's correlation analysis) were included in the Model. Adjusted odds for cystatin C (OR=1.621, 95% CI: 1.028-2.552, p=0.037) demonstrated that rise in cystatin C by 0.1 mg/L increased the probability for higher TG/HDL-c tertile group by 1.621 times.

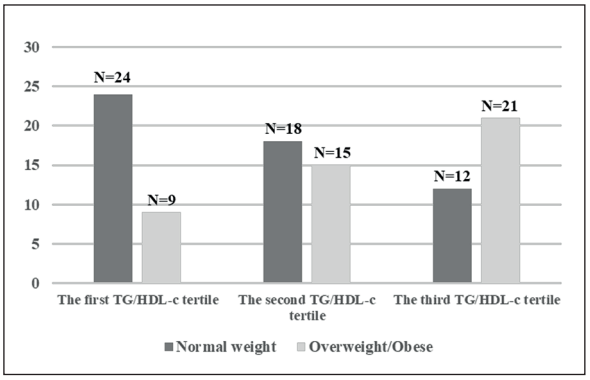

Figure 2. Absolute frequencies of normal weight *vs.* overweight/obese female adolescents in TG/HDL-c ratio tertile groups. p for Chi-square test for contingency tables is 0.012.

Table II. Correlation coefficients of TG/HDL-c ratio with tested markers.

	ρ	*P*
Age, years	-0.097	0.338
Weight, kg	0.287	0.004
Height, m	0.047	0.645
BMI, kg/m^2	0.309	0.002
WC, cm	0.327	0.001
Glucose, mmol/L	-0.030	0.762
Total proteins, g/L	-0.096	0.350
Creatinine, µmol/L	-0.125	0.238
TC, mmol/L	0.147	0.145
HDL-c, mmol/L	-0.656	< 0.001
LDL-c, mmol/L	0.294	0.003
TG, mmol/L	0.888	< 0.001
Non-HDL-c, mmol/L	0.516	< 0.001
hsCRP, mg/L	0.339	0.001
Cystatin C, mg/L	0.252	0.012

Data age given as coefficients of correlation Rho (ρ). BMI-Body mass index; WC-Waist circumference; TC-Total cholesterol; HDL-cholesterol-High-density lipoprotein cholesterol; LDL-cholesterol-Low-density lipoprotein cholesterol; TG-Triglycerides; hsCRP-High-sensitivity C-reactive protein.

Discussion

Our results demonstrate the association between cystatin C levels and TG/HDL-c ratio in the cohort of adolescent girls. To the best of our knowledge, this is the first study that observed the relationship of cystatin C with TG/HDL-c ratio in adolescent girls of narrow age range and one among the scarce ones generally in young population. Even more, this association remained significant when obesity (i.e., determined with BMI) and inflammation (i.e., determined with hsCRP) were included in the analysis. Thus, we assume that an early recognition of increased serum cystatin C levels in adolescence may help to detect the dysregulation of lipid metabolism, increased IR and concomitantly increased cardiometabolic risk for future event late in life. This may also enable physicians to treat promptly those high risk young individuals.

Although controversies exist in some studies[27], the association between cystatin C and some of individual lipid parameters was shown in adult population[21].

Similarly, Önerli Salman et al[20] also reported the positive association between cystatin C and TG, TC and LDL-c, but an inverse association with HDL-c in the cohort of children and adolescents ages between 6-18 years old. However, studies have shown that TG/HDL-c ratio better indicates atherosclerotic disturbances than TG and HDL-c, alone[17]. In line with this, cystatin C was reported to be associated with atherogenic index of plasma (i.e., log TG/HDL-c ratio) in adults[28].

Our results agree with Harada et al[29] who reported that subgroup of Japanese boys ages between 12 and 15 years old, who had high serum cystatin C levels displayed also the highest TG/HDL-c ratio. However, in subgroup of girls of similar age this statistical difference was not reached. Furthermore, Medeiros et al[30] reported the significant correlations between eGFR CysC (i.e., estimated glomerular filtration rate that used cystatin C levels in its equation) and TG, HDL-c and IR. However, the mentioned correlations were showed only in males, but not in females. The possible discordance in such findings might be related to a dissimilar age range of examined cohorts, variability in sample-size groups, as well as ethnic differences.

We have reported higher cystatin C levels in obese/overweight adolescent girls as compared with normal weight counterparts (data not presented) which is in line with our previous findings of its higher level in adult female population in other obesity-related disorders, such as metabolic syndrome[23] and fatty liver disease[26].

Indeed, increased adipose tissue (especially those in visceral compartment) may be one of the major culprits of increased oxidative stress and inflammation in obesity-related disorders[31-34]. Increased production of reactive oxygen species, with concomitant increase in pro-inflammatory cytokines secretion promotes IR state and dyslipidemia[31]. Knowing that cystatin C is secreted by all nucleated cells, but especially by adipocytes, macrophages and endothelial cells[22], the observed higher levels of this inflammatory biomarker in obesity-related disorders are not a surprise. Accordingly, in a prospective Malm Diet and Cancer study, Magnusson et al[35] explained that the association between cystatin C levels and incident metabolic syndrome might be mediated by visceral fat, given the fact that serum cystatin C levels independently correlated with abdominal obesity.

On the contrary, in a study that encompassed young population[20] there was no difference in serum cystatin C and creatinine levels between obese and normal weight participants. However, obese patients with metabolic syndrome displayed higher serum cystatin C levels than obese subjects without metabolic syndrome suggesting that higher cystatin C could be used as an earlier parameter than higher serum creatinine in the recognition of the adverse effects of dyslipidemia on renal function in young population with obesity.

This can be explained by several mechanisms. Accumulation of fat leads to hemodynamic changes (i.e., hyperfiltration, enhanced glomerular permeability, glomerular hypertension) and promotes oxidative stress, inflammation, apoptosis and concomitantly the occurrence of renal scarring[36]. Parallelly with the reabsorption of cholesterol and fatty acids by tubular epithelial cells, tubulointerstitial inflammation stimulates the generation of foam cells and damage of glomerular capillary endothelial and mesangial cells. In addition, the deposition of lipoproteins in the mesangial cells may promote production of matrix and subsequent glomerulosclerosis[20].

The strength of the current study lies in the fact that examined cohort comprised of girls with a narrow age range (i.e., between 16-19 years old), and thus we eliminated hormonal variations during childhood which might affect IR and inflammation markers. Moreover, we excluded some other factors which might be source of bias such as comorbidities, smoking and medications use.

The cross-sectional nature of this study represents its limitation and does not allow us to confirm the causality between cystatin C and TG/HDL-c ratio. Additionally, we were not able to explore the influence of sex hormones on serum cystatin C levels in this cohort of adolescent girls. This might add contribution to the elucidation of the other factors influencing cystatin C levels in adolescence. Furthermore, longitudinal studies comprising both sexes would be of benefit in better understanding the role of cystatin C in obesity-related disorders.

Conclusions

As far as we know, this is the first study that demonstrated the relationship of cystatin C with TG/HDL-c ratio in adolescent girls of narrow

age range and one among the rare ones generally in children and adolescents. The obtained results might suggest cystatin C as reliable biomarker of severity of dyslipidemia and insulin resistance in adolescent age, especially in those girls presented with obesity. Prospective studies are needed to further examine its causal effect on obesity-related disorders in young population.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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