

Hyperuricemia in obese children and adolescents: the relationship with metabolic syndrome

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Abstract

The prevalence of hyperuricemia in obese children and adolescents and its association with metabolic syndrome are largely unknown. The objective of our study was to characterize hyperuricemia in relation to metabolic syndrome in Japanese children and adolescents with obesity. Between 2005 and 2008, we performed a cross-sectional study of 1,027 obese children and adolescents aged 6-14 years. Based on the reference value of serum uric acid we had established previously, hyperuricemia was defined as one standard deviation over the mean value at each age. The diagnosis of metabolic syndrome was made based on the Japanese criteria for children. A total of 213 children and adolescents (20.7%) was found to have hyperuricemia. The prevalence of hyperuricemia was significantly higher in the male gender and older age group. Sixty-five out of 213 subjects with hyperuricemia (30.5%) had metabolic syndrome, whereas 111 out of 814 subjects without hyperuricemia (13.6%) had metabolic syndrome. The most common abnormal component of metabolic syndrome was triglyceride, followed by diastolic blood pressure, systolic blood pressure, fasting blood glucose, and HDL-cholesterol. Such a tendency was almost identical between the two groups. We concluded that considering the association between hyperuricemia and metabolic syndrome in obese Japanese children and adolescents, the role of hyperuricemia in metabolic syndrome should receive more attention, beginning in early childhood.

Introduction

The prevalence of hyperuricemia in adults has increased over the last several decades, especially in developed countries.¹ In Japanese men, hyperuricemia is estimated to

have increased from 5% in the 1960s to 20% in the 1990s.² Although the serum uric acid (UA) level is not part of any definition of metabolic syndrome (MetS), a number of studies has shown strong associations between UA levels and MetS or its components.^{3,7} For example, in the U.S. National Health and Nutrition Examination Survey (NHANES) of 1988-1994, the prevalence of MetS was found to increase substantially with increasing levels of serum UA.⁵ The pathogenesis of the link is not defined fully, but insulin resistance is thought to play a pivotal role.³ There is little information, however, on the relationship between hyperuricemia and MetS in children and adolescents. This is partly because of the difficulty of establishing control or reference values for UA in children, since UA values are highly dependent on age.⁸ Furthermore, unified diagnostic criteria of MetS for children have been established only recently.^{9,10} The aim of our present study was to identify the association of hyperuricemia and MetS in obese children and adolescents based on our own reference value for UA and the Japanese criteria for pediatric MetS.

Materials and Methods

Study population

We enrolled children and adolescents aged 6-14 years, who were diagnosed at a regular school examination (height, weight, and waist circumference) in Amagasaki city between 2005 and 2008 as being obese, and who subsequently underwent a medical examination. The medical examination included blood pressure (BP), and blood tests at a fasting condition including glucose, triglyceride, HDL-cholesterol, and UA. Blood pressure was measured with a mercury-gravity manometer using the right arm of the subjects who set in a relaxed position. The mean of the duplicate measurements was taken as the record of BP. Obesity was defined by the obesity index $\geq 20\%$ of that calculated by the formula: $(\text{subject's weight} - \text{standard weight}) \div \text{standard weight} \times 100$.¹¹ Here, the standard weight denotes the age-height-related standard of weight based on the 1990 school year data of the Japanese Ministry of Education, Culture, Sports, Science, and Technology.¹¹ UA values were measured with a uricase kit (Ono Pharmaceutical, Tokyo, Japan) using the uricase-peroxidase method.¹² We had previously established the reference value of UA in Japanese children at various ages.⁸ Based on the reference value of each age group, hyperuricemia was defined as exceeding the mean plus one standard deviation. Namely, the cut-off levels are 5.9 mg/dL for 6-8 years (both genders), 6.1 mg/dL for 9-11 years (both gen-

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ders), 7.0 mg/dL (males), and 6.2 mg/dL (females) for 12-14 years. The diagnostic criteria for MetS for Japanese children included a waist circumference ≥ 80 cm and/or a waist circumference-to-height ratio ≥ 0.5 as a prerequisite. In addition, for positivity at least two of the following three components are necessary: systolic BP ≥ 125 mmHg and/or diastolic BP ≥ 70 mmHg; HDL-cholesterol < 40 mg/dL and/or triglyceride ≥ 120 mg/dL; blood glucose ≥ 100 mg/dL.¹⁰ A total of 1,027 children and adolescents were enrolled finally, after excluding those with incomplete data and those already physician-diagnosed with type II diabetes mellitus or hypertension. Our study was approved by the ethical committee for epidemiological study at Nara Women's University.

Statistics

Differences in the prevalence of hyperuricemia according to gender and age were examined by the Chi-square test and one-way analysis of variance (ANOVA), respectively. In MetS-positive and -negative subjects with hyperuricemia, differences in demographic factors and components of MetS were also determined by the Chi-square test. Logistic regression analysis was performed to determine the association between presence or absence of hyperuricemia and demographic factors or components of MetS. The statistical analysis were done using "StatMate 3" (ATMS, Tokyo, Japan). $P < 0.05$ were considered significant.

Results

Prevalence of hyperuricemia in relation to age and gender

Age and gender distributions of subjects with hyperuricemia are summarized in Table 1. The total prevalence of hyperuricemia was significantly higher ($P<0.01$) in males (24.4%) than in females (15.2%). Furthermore, the percentages of subjects with hyperuricemia increased with age regardless of gender ($P<0.001$). In fact, the percentages of hyperuricemia were highest in the age group of 12-14 years in both genders.

Prevalence and components of metabolic syndrome in subjects with hyperuricemia

In total, 176 out of 1,027 subjects (17.1%) met the diagnostic criteria for MetS (data not shown). As shown in Table 2, 65 out of 213 subjects with hyperuricemia (30.5%) had MetS. There were no gender or age differences in the frequency of MetS. The positivity of every component of MetS was significantly higher in the MetS-positive group.

Association between hyperuricemia and demographic factors or components of metabolic syndrome

Logistic regression analysis revealed that hyperuricemia was independently associated with male gender, older age, degree of obesity, systolic BP, and HDL-cholesterol. On the other hand, no association was found between hyperuricemia and waist circumference, diastolic BP, triglyceride, or fasting blood glucose (Table 3).

Discussion

Recent studies have documented the association among hyperuricemia, obesity, and MetS in adults.^{3,7} In particular, increased serum UA levels are associated with a risk of cardiovascular disease or renal disease.^{13,14} Several investigators have shown that insulin resistance plays a central role in the link between MetS and hyperuricemia.^{3,15,16} Insulin resistance is thought to cause decreased excretion of UA.^{17,18} Accordingly, the amelioration of insulin resistance by either a low-energy diet or an insulin-sensitizing agent was found to decrease serum UA levels.¹⁹

There are several large-population studies on the prevalence of MetS during childhood.^{20,21} The reported rates differ widely; for example, 0.2-6.4%, depending on the study population and the definition of MetS.²²⁻²⁵ The prevalence increased, range: 15.6% to 35.7%, when subjects were restricted to obese children and adolescents.^{24,26-28} In NHANES III, for example, the

Table 1. Number of subjects with hyperuricemia in relation to age and gender.

Gender Age	Male		Female		Total	
	Total	Hyperuricemia	Total	Hyperuricemia	Total	Hyperuricemia
6-8 yr	156	20 (12.8)*	122	8 (6.6)	278	28 (10.1)
9-11 yr	310	70 (22.6)	189	26 (13.8)	499	96 (19.2)
12-14 yr	154	61 (39.6)	96	28 (29.2)	250	89 (35.6)
Total	620	151 (24.4)	407	62 (15.2)	1027	213 (20.7)

*Numbers in parentheses indicate the percentage.

Table 2. Metabolic syndrome and its components in subjects with hyperuricemia.

	Number	Metabolic syndrome		P*
		(+)	(-)	
Total number (%)	213	65 (30.5) [§]	148 (69.5)	
Gender				0.97
Male	151 (70.9)	46 (30.5)	105 (69.5)	
Female	62 (29.1)	19 (30.6)	43 (69.4)	
Age (year) (mean±s.d.)	11.0±1.9	11.2±2.0	10.9±2.1	0.33
Systolic blood pressure (SP)				<0.001
<125 mmHg	164 (77.0)	36 (55.4)	128 (86.5)	
≥125 mmHg	49 (23.0)	29 (44.6)	20 (13.5)	
Diastolic blood pressure (DP)				<0.001
<70 mmHg	120 (56.3)	10 (15.4)	110 (74.3)	
≥70 mmHg	93 (43.7)	55 (84.6)	38 (25.7)	
Blood pressure				<0.001
SP<125 mmHg and DP<70 mmHg	99 (46.5)	4 (6.2)	95 (64.2)	
SP≥125 mmHg and/or DP≥70 mmHg	114 (53.5)	61 (93.8)	53 (35.8)	
HDL-cholesterol				<0.01
≥40 mg/dL	174 (81.7)	46 (70.8)	128 (86.5)	
<40 mg/dL	39 (18.3)	19 (29.2)	20 (13.5)	
Triglyceride (TG)				<0.001
<120 mg/dL	115 (54.0)	7 (10.8)	108 (73.0)	
≥120 mg/dL	98 (46.0)	58 (89.2)	40 (27.0)	
Lipids				<0.001
HDL≥40 mg/dL and TG<120 mg/dL	109 (51.1)	4 (6.2)	105 (70.9)	
HDL<40 mg/dL and/or TG≥120 mg/dL	104 (48.9)	61 (93.8)	43 (29.1)	
Fasting blood glucose				<0.001
<100 mg/dL	190 (89.2)	45 (69.2)	145 (98.0)	
≥100 mg/dL	23 (10.8)	20 (30.8)	3 (2.0)	

[§]Numbers in parentheses indicate the percentage; * χ^2 test.

prevalence of MetS in overweight adolescents (body mass index [BMI] ≥95th percentile) and in adolescents at risk of being overweight (85th percentile ≤ BMI <95th percentile) was 32.1% and 7.1%, respectively.²³ On the other hand, there is limited information about the association between hyperuricemia and obesity or MetS in children and adolescents. In NHANES (1999-2002), the prevalence of MetS increased substantially along with the increase of serum UA concentrations.²⁹ Using 120 obese children in the United States, Pacifico *et al.* demonstrated an independent association between UA concentrations and the presence of MetS.²⁷ Notably, they have also shown that increased UA levels are associated with carotid atherosclerosis. Such an association between hyperuricemia and components of MetS has been seen in Asian countries.^{30,31} Furthermore, longitudinal data from the Bogalusa Heart Study

indicated that obesity and MetS in childhood were predictors of elevated UA in adulthood.³² Another Bogalusa Heart Study demonstrated that an elevated serum UA level is associated with higher BP in childhood, which persists into adulthood.³³

Most of the previous studies, however, have used the criteria of MetS established for adults with their own cut-off values. Therefore, in our study we adopted the criteria of MetS recently established for children by the Japanese Ministry of Health, Labor, and Welfare.¹⁰ As for defining hyperuricemia of childhood, we used the reference values of UA in children at different ages established by ourselves.⁸ MetS was found in 17.1% of a total population, which was within the ranges of findings in previous studies, although the definition of MetS was different.^{24,26-28} On the other hand, the prevalence of MetS in a hyperuricemic population was

Table 3. Association between hyperuricemia and demographic factors and components of metabolic syndrome.

	Number	Hyperuricemia		β coefficient	Odds ratio [95%CI]	P
		(+)	(-)			
Total number (%)	1027	213 (20.7) [§]	814 (79.3)			
Gender				-0.49	0.61 [0.43-0.87]	<0.01
Male	620 (60.4)	151 (70.9)	469 (57.6)			
Female	407 (39.6)	62 (29.1)	345 (42.4)			
Age (year) (mean \pm s.d.)	10.0 \pm 2.1	11.0 \pm 2.1	9.7 \pm 2.0	0.27	1.31 [1.21-1.42]	<0.001
Obesity index (%)				0.68	1.98 [1.49-2.62]	<0.001
20 \leq <30	210 (20.4)	26 (12.2)	184 (22.6)			
30 \leq <50	633 (61.6)	119 (55.9)	514 (63.1)			
50 \leq	184 (18.0)	68 (31.9)	116 (14.3)			
Waist circumference				-0.14	0.87 [0.45-1.69]	0.68
<80 cm and W/H* <0.5	81 (7.9)	15 (7.0)	66 (8.1)			
\geq 80 cm or W/H \geq 0.5	946 (92.1)	198 (93.0)	748 (91.9)			
Systolic blood pressure				0.55	1.74 [1.12-2.69]	<0.05
<125 mmHg	896 (87.2)	164 (77.0)	732 (89.9)			
\geq 125 mmHg	131 (12.8)	49 (23.0)	82 (10.1)			
Diastolic blood pressure				-0.0004	0.99 [0.92-1.08]	0.99
<70 mmHg	694 (67.6)	121 (56.8)	573 (70.4)			
\geq 70 mmHg	333 (32.4)	92 (43.2)	241 (29.6)			
HDL-cholesterol				0.94	2.57 [1.56-4.22]	<0.001
\geq 40 mg/dL	932 (90.7)	174 (81.7)	758 (93.1)			
<40 mg/dL	95 (9.3)	39 (18.3)	56 (6.9)			
Triglyceride				0.35	1.41 [0.99-2.01]	0.053
<120 mg/dL	697 (67.9)	115 (54.0)	582 (71.5)			
\geq 120 mg/dL	330 (32.1)	98 (46.0)	232 (28.5)			
Fasting blood glucose				-0.28	0.76 [0.44-1.30]	0.32
<100mg/dL	930 (90.6)	189 (88.7)	741 (91.0)			
\geq 100 mg/dL	97 (9.4)	24 (11.3)	73 (9.0)			

[§]Numbers in parentheses indicate the percentage; * W/H= Waist circumference (cm)/body height (cm).

30.1%; almost twice that in a non-hyperuricemic population (13.6%). Among the demographic factors and components of MetS, age, degree of obesity, systolic BP, and HDL-cholesterol were significantly associated with positivity of hyperuricemia. However, the results of the association between UA levels and each component of MetS were not consistent among studies, presumably owing to the difference of ethnicity and cut-off values.^{25-27,29}

There are several limitations in our study. First, subjects of the present study were restricted to those with obesity. For the diagnosis of obesity, we used the obesity index commonly used in Japan instead of BMI.¹¹ The reason is that the obesity index is thought to be practical, as it does not need to take age-related changes seen in the BMI standard for childhood into consideration.³⁴ Further investigation on hyperuricemia and MetS in non-obese children and adolescents is necessary. Second, since this is a cross-sectional study, the relation of hyperuricemia to the future occurrence of lifestyle-related disorders was not elucidated. Finally, information about the lifestyles of the subjects, especially diet, is lacking. The habit of frequently eating purine-rich food may cause hyperuricemia and MetS simultaneous-

ly.³⁵ In spite of these limitations, the present study is, as far as we know, the first large cohort study for delineating the association of hyperuricemia and MetS in obese children and adolescents based on the pediatric criteria. Considering the high prevalence of MetS in hyperuricemic children and adolescents, pediatricians should pay more attention to the association between hyperuricemia and MetS. Efforts to reduce the morbidity of hyperuricemia through the management of lifestyles, especially in obese children, are necessary.

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