# Microalbuminuria Is Associated with Lower Weight and Taller Height in Adolescence

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Microalbuminuria (MA) is a well-known predictor of cardiovascular disease and mortality in adults. However, these relationships remain unclear in adolescents. A few studies on association between MA and obesity have been conducted in adolescents. However, the association between MA and growth parameters such as height has not been studied, despite the fact that adolescence is a period of rapid physiological change. We, therefore, aimed to evaluate the association between MA and growth parameters, and the association between MA and obesity related cardiovascular risk factors after adjusting for growth. The study included 1,459 adolescents (847 boys and 612 girls) aged 12-18 years who participated in the Korean National Health and Nutrition Examination Survey (2011-2013). A urine albumin/ creatinine ratio (UACR) of 30-299 mg/g in a morning urine sample was considered to reflect MA. MA was detected in 53 (3.6%) including 24 girls. Height z-score of adolescents with MA was greater than that of normoalbuminuric adolescents (0.87 vs. 0.38; P < 0.01). Upon multiple regression analysis, UACR was associated with lower weight z-score ( $\beta = -0.100$ , P < 0.01) and higher height z-score ( $\beta = 0.069$ , P < 0.01). In term of cardiovascular risk factors, the UACR was not associated with fasting glucose, high-densitylipoprotein cholesterol, or triglyceride levels. Adolescents with MA tend to be thin and tall. MA is not a useful screening method for obesity-related cardiovascular risk in adolescents, but instead MA is associated with taller height and lower weight, growth-related parameters in adolescence.

**Keywords:** adolescent; albuminuria; body height; body weight; cardiovascular disease Tohoku J. Exp. Med., 2017 November, **243** (3), 151-157. © 2017 Tohoku University Medical Press

## Introduction

Microalbuminuria (MA) refers to a situation in which urine albumin excretion is abnormally high, and often goes undetected. The condition is a useful predictor of the onset of diabetic nephropathy, and can be used to monitor disease progression (Viberti et al. 1982; Chavers et al. 1989). MA predicts cardiovascular disease in nondiabetic adults (Gerstein et al. 2001; Verhave et al. 2004; de Zeeuw et al. 2006) and has been suggested to be a valuable screening tool for such disease (Tsioufis et al. 2010).

In adolescents, however, any relationship between MA and cardiovascular risk factors (hypertension, dyslipidemia, glucose intolerance, and obesity) remains unclear; a few studies have explored this topic and the results have been inconsistent, especially in obesity. Some studies found that obese adolescents were more likely to develop MA as adults (Csernus et al. 2005; Burgert et al. 2006; Invitti et al. 2006). On the other hand, recent large-scale studies came to the opposite conclusion (Nguyen et al. 2008; Gurecka et al. 2015). For example, in the National Health and Nutrition Examination Survey, the prevalence of MA was lower in obese than in normal-weight adolescents unlike adults (Nguyen et al. 2008).

When studying anthropometric indices in adolescents, it is thus essential to consider the fact that adolescence is a period of rapid physiological change. It is important to monitor growth in adolescence. So far, there has been no study of MA considering height as well as weight.

In the present study, we evaluated the associations of MA not only with the body mass index (BMI), but also with growth parameters such as the weight and height z-scores. In addition, we explored associations between MA and cardiovascular risk factors (including hyperglycemia, hypertension, and dyslipidemia) after adjusting for growth parameters. To this end, we used a large dataset from the Korean National Health and Nutrition Examination Survey (KNHANES) on healthy adolescents.

## Methods

## Study population

We performed a cross-sectional study on data collected in the second and third years (2011, 2012) of the fourth KNHANES and the first year (2013) of the fifth KNHANES; this nationally representative

Received July 18, 2017; revised and accepted October 19, 2017. Published online November 10, 2017; doi: 10.1620/tjem.243.151. Correspondence: Sochung Chung, M.D., Ph.D., Department of Pediatrics, Konkuk University Medical Center, Konkuk University School of Medicine, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, Korea. e-mail: scchung@kuh.ac.kr survey featured a health examination, a health interview, and a nutritional survey. A total of 2,119 adolescents (12-18 years of age) participated, of whom 1,493 completed the health examination and health interview. We excluded 31 adolescents who fasted for < 8 h before blood sampling, who were pregnant, who were menstruating on the day of examination, or for whom a urine nitrate test was positive. We also excluded three adolescents with urine albumin/creatinine ratios (UACRs) > 300 mg/g because they may have had primary renal disease. Data from 1,459 adolescents were finally analyzed. No subject was taking any anti-hypertensive medication or lipid-lowering drug.

This study was approved by the Institutional Review Board of Konkuk University Medical Center, Seoul, Korea (IRB No. KUH1090053).

#### Anthropometric and laboratory measurements

Anthropometric indices were measured and blood and urine samples were processed, using standardized protocols. Height was measured to the nearest 0.1 cm in the standing position with the occiput, back, buttocks, and heels touching a wall by stadiometer (Seca, Germany). Body weight was measured digitally to the nearest 0.1 kg with each subject wearing a light gown without shoes using a calibrated digital scale (G-tech, Korea). Waist circumference (WC) was measured to the nearest 0.1 cm along the middle horizontal line between the inferior margin of the last rib and the iliac crest, at the end of normal expiration, without compression. Blood pressure (BP) was measured three times, by trained staff, using a mercury sphygmomanometer (Baum, USA). The BMI was the body weight divided by the square of the height (kg/m<sup>2</sup>). The height, weight, and BMI z-scores were calculated based on the 2007 Korean reference values (Lee et al. 2008).

Serum glucose was measured using the hexokinase/UV method. Total cholesterol, high-density-lipoprotein cholesterol (HDL-c), and triglyceride were measured by enzymatic methods. Low-densitylipoprotein cholesterol (LDL-c) levels were calculated with the aid of the Friedewald equation (Friedewald et al. 1972). A first-morning urine sample was collected using a clean-catch technique. Urine albumin levels were measured by a turbidimetric method. Urine creatinine levels were measured by the Jaffe method, and were rateblanked and compensated method.

#### Definitions of study variables

MA was defined as UACR  $\geq$  30 mg/g but < 300 mg/g, as in adults (American Diabetes Association 2001). Metabolic syndrome was diagnosed using the criteria of the International Diabetes Federation (Zimmet et al. 2007): central adiposity plus at least two of hypertension, a high triglyceride level, a low HDL level, an impaired fasting glucose level, and/or diabetes mellitus. The frequencies of physical activity and smoking status were explored using a questionnaire. We defined ever-smokers as smokers.

#### Statistical analyses

Data are expressed as means  $\pm$  standard deviations for continuous variables, and as percentages for categorical variables. Student's t-test and the  $\chi^2$  test were used to compare continuous and categorical variables, respectively. The UACR and urine albumin levels, which were not normally distributed, are presented as medians with interquartile ranges, and were compared with the aid of the Mann-Whitney U-test. UACR levels were logarithmically transformed prior to analysis to normalize the skewed distribution. Associations between logtransformed UACRs and other variables were assessed by calculating Pearson's correlation coefficients, and then subjected to multiple regression analysis using age, sex, the height z-score, the weight z-score, the systolic BP, the fasting glucose level, and the HDL-c and triglyceride levels, as independent variables. A *P* value < 0.05 was considered to reflect statistical significance. All statistical analyses were performed with the aid of SPSS software (version 17.0).

#### Results

Anthropometric parameters and biochemical profiles by MA status

Table 1 shows the baseline anthropometric, clinical, and biochemical characteristics by MA status. MA was detected in 3.6% of subjects (53/1,459), who were younger than the normoalbuminuria (NA) group (13.8 vs. 14.8 years of age; P < 0.01). The two groups did not differ in terms of sex.

The height z-score of the MA group was greater than that of the NA group (0.87 vs. 0.38; P < 0.01). The weight z-score of the MA group did not differ significantly from that of the NA group (0.13 vs. 0.18; P = 0.77). The MA group had a lower BMI z-score (-0.32 vs. 0.01; P = 0.03) and a WC/height ratio (0.41 vs. 0.43; P < 0.01) than the NA group.

Biochemically, the MA group had a higher HDL-c level (53.5 vs. 49.6 mg/dL; P < 0.01) and a lower triglyceride level (68.3 vs. 82.6 mg/dL; P = 0.03). No significant difference in any of BP; the fasting glucose, total cholesterol, and LDL-c levels; metabolic syndrome status; smoking status; or frequency of physical activity was apparent between the MA and NA groups.

#### Factors associated with the UACR

On correlation analysis, the UACR was associated with younger age (r = -0.058, P = 0.03), lower weight z-score (r = -0.136, P < 0.01), lower BMI z-score (r = -0.175, P < 0.01), and lower WC/height ratio (r = -0.190, P < 0.01), but not with the height z-score. The UACR was associated with higher HDL-c level (r = 0.108, P < 0.01) and with lower triglyceride level (r = -0.098, P < 0.01). The UACR was not significantly associated with any of BP or the fasting glucose, total cholesterol, or LDL-c levels (Table 2).

We divided the study population into non-overweight and overweight based on BMI 85 percentile and did subgroup analysis. In non-overweight group, the UACR was associated with younger age (r = -0.079, P < 0.01), lower weight z-score (r = -0.107, P < 0.01), lower BMI z-score (r = -0.164, P < 0.01), and lower WC/height ratio (r = -0.194, P < 0.01). The UACR was associated with higher HDL-c level (r = 0.102, P < 0.01) and with lower triglyceride level (r = -0.086, P < 0.01). In overweight group, the UACR was not associated any variables (Table 2).

On multiple regression analysis, the UACR was associated with younger age ( $\beta = -0.018$ ; P = 0.01), the male

Characteristics	Normoalbuminuria	Microalbuminuria	Р
	(n = 1,406)	(n = 53)	
Age (years)	$14.8\pm2.0$	$13.8\pm1.9$	< 0.01
Male (%)	818 (58.2)	29 (54.7)	0.62
Height z-score	$0.38 \pm 1.02$	$0.87\pm0.96$	< 0.01
Weight z-score	$0.18 \pm 1.07$	$0.13\pm0.95$	0.77
BMI (kg/m <sup>2</sup> )	$21.0\pm3.6$	$19.5\pm3.1$	< 0.01
BMI z-score	$0.01\pm1.09$	$-0.32\pm0.95$	0.03
WC/height	$0.43\pm0.05$	$0.41\pm0.04$	< 0.01
Systolic BP (mm Hg)	$108.1\pm10.0$	$106.5\pm9.5$	0.25
Diastolic BP (mm Hg)	$66.9\pm9.0$	$66.3\pm9.0$	0.65
Fasting glucose (mg/dL)	$89.4\pm 6.5$	$89.2\pm6.4$	0.81
Total cholesterol (mg/dL)	$156.5\pm26.3$	$157.9\pm32.5$	0.71
HDL-c (mg/dL)	$49.6\pm9.4$	$53.5\pm8.6$	< 0.01
LDL-c (mg/dL)	$90.4\pm22.5$	$90.6\pm28.0$	0.94
Triglyceride (mg/dL)	$82.6\pm45.9$	$68.3\pm36.2$	0.03
Metabolic syndrome (%)	26 (1.8)	1 (1.9)	1.00
Smoker (%)*	231 (16.5)	6 (11.3)	0.32
Physical activity $\geq 3$ /week (%)*	456 (32.5)	17 (32.1)	0.94
Urine albumin (mg/mL)**	6.6 (3.0-13.1)	108.8 (86.3-167.3)	< 0.01
Urine creatinine (mg/dL)	$215.1\pm92.8$	$225.2\pm99.7$	0.44
UACR (mg/g)**	3.0 (1.7-5.7)	46.8 (38.8-96.6)	< 0.01

Table 1. Baseline characteristics by microalbuminuria status.

Value are shown as means with standard deviations for normally distributed variables.

\*Five adolescents who did not respond were excluded.

\*\*For skewed variables values are shown as medians with interquartile ranges.

BMI, body mass index; WC, waist circumference; BP, blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; UACR, urine albumin urine creatinine ratio.

gender ( $\beta = -0.161$ ; P < 0.01), lower weight z-score ( $\beta = -0.100$ , P < 0.01), and higher height z-score ( $\beta = 0.069$ , P < 0.01). In terms of other cardiovascular risk factors, the UACR was not associated with fasting glucose level or the lipid profile. High systolic BP showed trend of association with MA but not significant statistically (Table 3).

#### *Relationship between height and weight of the MA group*

We compared the growth parameters of the MA and NA groups by placing the height z-scores on the X-axis and the weight z-scores on the Y-axis (Fig. 1). No MA subject was located in quadrant 2, which represents subjects of above-average weight, but below-average height, adjusted for age and sex. The regression line for the MA group lay below that for the NA group.

### Discussion

In the present study, we found that adolescents with MA had lower weight z-scores but greater height z-scores than those exhibiting NA. After adjusting for growth parameters, no traditional cardiovascular risk factor was associated with MA.

MA is known to be associated with obesity and other cardiovascular risk factors in adults. However, associations between MA and anthropometric index values are more complicated in adolescents.

MA was associated with lower weight z-score in adolescents in this study, unlike the findings in adults (Konta et al. 2013; Ren et al. 2016). In adults obesity has been suggested to induce MA via several potential mechanisms (sys-

Table 2.	Correlations	between	logarithm	ically	transforme	d urine	albumin/	creatinine	ratios
	and other var	iables acc	ording to	BMI	category.				

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	Total	Non-overweight	Overweight
	(n = 1,459)	(BMI < 85%)	$(BMI \ge 85\%)$
		(n = 1,203)	(n = 256)
Age (years)	-0.058*	-0.079**	0.055
Height z-score	0.030	0.046	0.006
Weight z-score	-0.136**	-0.107**	0.006
BMI z-score	-0.175**	-0.164**	0.002
WC/height	-0.190**	-0.194**	-0.060
Systolic BP (mm Hg)	-0.049	-0.049	0.078
Diastolic BP (mm Hg)	-0.010	-0.004	0.001
Fasting glucose (mg/dL)	-0.036	-0.027	-0.030
Total cholesterol (mg/dL)	-0.008	0.003	0.009
HDL-c (mg/dL)	0.108**	0.102**	-0.010
LDL-c (mg/dL)	-0.016	-0.007	0.035
Triglyceride (mg/dL)	-0.098**	-0.086**	-0.046

BMI, body mass index; WC, waist circumference; BP, blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c low-density lipoprotein cholesterol. \* P < 0.05, \*\* P < 0.01.

Table 3. Multiple regression and creatinine ratios.	alysis of logarithmically	transformed urine albumin/
	β	Р
Age (years)	-0.018	0.01
Male	-0.161	< 0.01
Height z-score	0.069	< 0.01
Weight z-score	-0.100	< 0.01
Systolic BP (mm Hg)	0.003	0.05
Fasting glucose (mg/dL)	-0.002	0.41
HDL-c (mg/dL)	0.001	0.40
Triglyceride (mg/dL)	-0.001	0.06

BP, blood pressure; HDL-c, high-density lipoprotein cholesterol.

temic inflammation, cytokine production, and hyperfiltration) (Scaglione et al. 1995; Tsioufis et al. 2005).

The reason for the observation that leaner children are more likely to have MA is unknown (Bangstad et al. 1993). The decrease in UACR as the weight z-score fell was not attributable to a rise in urine creatinine excretion which reflects body composition. We found that both the spot urine albumin level as well as UACR were associated with lower weight z-score (data not shown). This negative relationship was not attributable to a difference in the extent of physical activity between obese and normal-weight adolescents either. It has been suggested that obese children are less active and thus excrete less albumin (Hirschler et al. 2010). However, overweight adolescents reported more physical activity than those of normal weight in our study (data not shown), and no difference in physical activity levels between the MA and NA groups was apparent. Adverse causality may be in play because the study was cross-sec-



Fig. 1. Difference in the relationship between height and weight z-scores according to microalbuminuria status. A scatter plot shows the correlations between the height and weight z-scores in 53 microalbuminuric adolescents ( $\blacklozenge$ ) and 1,406 normoalbuminuric adolescents ( $\diamondsuit$ ). The solid line (y = 0.602 \* x - 0.391, P < 0.01) is the linear regression line for the microalbuminuric group, and the dotted line (y = 0.544 \* x - 0.030, P < 0.01) that for the normoalbuminuric group.

tional in nature; MA induced a lean stature. MA may be associated with renal physiology in children. Gracchi et al. (2016) showed that the prevalence of MA in toddlers was comparable to that in adults, and suggested that MA was congenital (Gracchi et al. 2016). This congenital trait, leakage of albumin into the urine, may be associated with weight loss. A prospective study is required to determine the relationship between albumin excretion and growth parameters; follow-up should commence in infancy and continue for many years.

Height in adolescents is an important growth parameter, and indicator of adequate nutrition. Previous studies investigated the association between MA and obesity in terms of BMI or weight (Bangstad et al. 1993; Nguyen et al. 2008; Hirschler et al. 2010; Cho and Kim 2017). They did not focus on height. Assessing weight without height overlooks many pathologic conditions in adolescents. To the best of our knowledge, this is the first research which showed that MA was associated with higher height z-score. It suggested that adolescents with MA do not grow up less. Adolescents with MA were indeed taller than others. However, the final heights in adulthood should be compared. The relationship between MA and the height z-score in young adults warrants further study.

The associations between MA and cardiovascular risk factors have been extensively studied in adults; MA is a known predictor of cardiovascular disease and mortality (Damsgaard et al. 1990; Roest et al. 2001). However, pediatric researchers have come to conflicting conclusions. Rademacher et al. (2008) found that the urine albumin level was associated only with higher fasting insulin level. Hanevold et al. (2008) showed that the urine albumin level correlated with high systolic BP in African-American males. In addition, Invitti et al. (2006) found that MA was associated with metabolic syndrome. However, one large study found no association between MA and any cardiovascular risk factor (Gurecka et al. 2015). Cho and Kim (2017) studied the associations with similar study population to ours, and suggested that MA can be a helpful cardiovascular disease risk marker. It is opposed to our conclusion. They showed that MA was associated with high HbA1c, while relationship between MA and obesity was negative, as same as our result; mean UACR with obese adolescents was lower than that for non-obese adolescents. We do not agree focusing high HbA1c regardless of negative association between MA and obesity. In the present study, we showed that MA was negatively associated with obesity, and was not associated with fasting glucose, HDL-c, and triglyceride levels after adjusting for growth parameters. Therefore, MA is not useful screening method for cardiovascular diseases in adolescents.

The association between MA and variables was different according to BMI category. In non-overweight group, the association between MA and growth parameters was same as total population. While in overweight group, MA was not associated with any growth parameters and cardiovascular risk factors.

There were several strengths to our work. We used a large dataset from healthy adolescents. In addition, the survey data were of high quality, and included valuable information on physical activity. Furthermore, the anthropometric data included height and weight z-scores; these are important when analyzing subjects who are growing rapidly. However, our work had certain limitations. First, the study was cross-sectional in nature; it was thus impossible to establish causal relationships between MA, on the one hand, and growth parameters or cardiovascular risk factors, on the other. Second, only single morning urine samples were collected; the prevalence of MA may thus have been overestimated. A large percentage of MA might be isolated and transient, being attributable to strenuous exercise or febrile illness (Davies et al. 1984; Bangstad et al. 1993). However, repeat urine collections cost time and money. Moreover, the UACR of early-morning urine samples was reported to correlate very well with the 24-h urine albumin excretion level (Elises et al. 1988). Third, orthostatic proteinuria might be included in our MA populations even if we collected the first urine in the morning. Some studies suggested that orthostatic proteinuria is more prevalent among non-obese adolescents, especially girls (Davies et al. 1984; Nguyen et al. 2008).

In conclusion, we show that adolescents with MA are thinner and taller than those with NA. MA is not associated with traditional cardiovascular risk factors, and it is not useful screening method for obesity related cardiovascular diseases in adolescents.

## **Conflict of Interest**

The authors declare no conflict of interest.

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