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Urinary Adiponectin and Fibroblast Growth Factor 21 Assay for Pediatric Metabolic Syndrome Screening

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Abstract

Urinary Adiponectin and Fibroblast Growth Factor 21 Assay for Pediatric Metabolic Syndrome Screening

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Background: Predicting pediatric metabolic syndrome is important for controlling various diseases and quality of life in obese children. To make a diagnosis of pediatric metabolic syndrome, measurement of several invasive blood biomarkers is needed. Although serum adiponectin and fibroblast growth factor 21 (FGF-21) are known to be related to obesity and metabolic syndrome, limited data on their usefulness as noninvasive urinary biomarkers have been reported. Therefore, we investigated the usefulness of urinary adiponectin and FGF-21 in the diagnosis of pediatric metabolic syndrome.

Methods: Urine samples from children and adolescents aged 13-15 years that were stored by the Korean Center for Disease Control were used. A total of 93 obese children with body mass index (BMI) > 99th percentile and 92 normal children with BMI between the 25th and 75th percentiles were selected. All obese and normal children were matched by age and sex. The physical data of all children, including height, body weight, waist circumference, and systolic and diastolic blood

pressure, were examined. Urinary creatinine, urinary albumin, serum fasting glucose, serum high-density lipoprotein cholesterol (HDL), and serum triglyceride were measured from urine and venous blood samples. Urinary adiponectin and FGF-21 levels were measured using enzyme-linked immunosorbent assay. Metabolic syndrome was defined according to the International Diabetes Federation criteria and the 2007 Korean National Growth Charts.

Results: **:** Pediatric metabolic syndrome was identified in 30 of 93 obese children and in none of the normal children. The median BMI and waist circumference of children with metabolic syndrome were 34.35 kg/m^2 and 106.0 cm, respectively, and those of normal children were 20.6 kg/m^2 and 69.4 cm, respectively. The creatinine-adjusted urinary adiponectin and FGF-21 levels were significantly higher in obese children (urinary adiponectin/creatinine: median level 3.5 vs. 1.3 mg/g, $P < 0.001$; urinary FGF-21/creatinine: median level 68.7 vs. 31.7 mg/g, $P < 0.001$). In logistic linear regression, creatinine-adjusted urinary adiponectin had a positive effect on metabolic syndrome, although not statistically significant (urinary adiponectin/creatinine: odds ratio [OR] = 1.189, $P = 0.192$), whereas it had a significant effect on obesity (OR = 1.722, $P = 0.009$). The area under the curve of creatinine-adjusted urinary adiponectin as an alternative to HDL for the diagnosis of metabolic syndrome was 0.700, and that of creatinine-adjusted urinary FGF-21 as an alternative to triglyceride was 0.644.

Conclusions: Urinary adiponectin and FGF-21 assays can be useful alternatives to invasive blood tests for metabolic syndrome screening in the pediatric population.

Keywords: Pediatrics, Metabolic syndrome, Adiponectin, FGF-21, Biomarker

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목 차

INTRODUCTION

Obesity and metabolic syndrome have become serious health problems in modern society. In the United States, more than 66% of all adults are classified as overweight or obese (1). The prevalence of obesity and metabolic syndrome is also rapidly increasing in other industrialized societies and in many developing countries (1-3). Furthermore, the increasing prevalence of obesity is not limited to the adult population, but is also observed in children and adolescents (2, 4). For example, according to the 2005 National Anthropometric Survey and 2017 Korean National Growth Charts for children and adolescents in South Korea, the prevalence of obesity among adolescents and children has steadily increased from 9.7% in 2005 to 11.8% in 2017 (5, 6). It is well known that obesity is a significant risk factor for a wide range of diseases in adults, including hypertension, type 2 diabetes mellitus, dyslipidemia, obstructive sleep apnea, nonalcoholic fatty liver disease, degenerative joint disease, and some malignancies (1, 7-9). Similarly, pediatric obesity and metabolic syndrome can induce many serious complications that can progress to serious health concerns in adulthood (2, 4). In both children and adults, body mass index (BMI) and waist circumference do not reflect the real physiological and endocrinological mechanisms of obesity and metabolic syndrome; therefore, they cannot be effectively used for the early identification and management of metabolic syndrome and the treatment of obesity, for the clinical evaluation of patients over time or with intervention, or for informing research (10). Furthermore, there are yet no consensus guidelines or diagnostic criteria for metabolic syndrome in the pediatric population, although > 40 definitions of pediatric metabolic syndrome have been reported (2). To make a diagnosis of metabolic syndrome

according to the International Diabetes Federation (IDF) criteria for pediatric metabolic syndrome (Table 1), invasive blood tests, which can be painful and distressful to pediatric patients, are needed for the measurement of markers including high-density lipoprotein cholesterol (HDL), glucose, and triglyceride (TG).

Nowadays, more serum biomarkers that are purported to be related to obesity and metabolic syndrome are being developed and used, such as leptin (11, 12), adiponectin (10-14), fibroblast growth factor 21 (FGF-21) (15-17), and ghrelin (18). However, there are only a few known noninvasive urinary biomarkers for metabolic syndrome, including urinary adiponectin (19-22) and urinary albumin-to-creatinine ratio (UACR, microalbuminuria) (23, 24), and these urinary biomarkers have not been investigated in the pediatric and adolescent populations. Therefore, the aim of our study was to evaluate the relationship of the levels of urinary adiponectin and FGF-21, measured using noninvasive urinary immunoassays, to metabolic syndrome in the pediatric population in Korea.

METHODS

Identification of the pediatric obesity cohort

We identified 93 children (53 boys and 40 girls) whose BMI exceeded the 99th percentile of the overall pediatric population (obesity group). To form the control group, we identified 92 children (47 boys and 45 girls) whose BMI ranged between the 25th and 75th percentiles of the overall pediatric population. The age of the children in the obesity and control groups ranged from 13 to 15 years (median, 14 years). The following physical information was extracted from the

database for all individuals: height, body weight, hip and waist circumference, and systolic and diastolic blood pressure values. The corresponding frozen serum and urine samples (N = 184) with no identifiable information were obtained from school medical examinations. We obtained approval from the Institutional Review Board of Seoul National University Hospital for use of available specimens with no identifiable information for the evaluation of a new in vitro diagnostic method, without obtaining informed consent.

Analysis of urinary adiponectin and FGF-21

The serum levels of the following markers were measured from the serum samples using a routine automated chemistry analyzer: glucose, cholesterol, HDL cholesterol, TG, aspartate transaminase, and alanine transaminase. The levels of the following markers were measured from the urine specimens: adiponectin, FGF-21, albumin, and creatinine. Urine adiponectin and FGF-21 levels were measured using an adiponectin enzyme-linked immunosorbent assay (ELISA) kit and an FGF-21 ELISA kit (Adipogen Corporation, San Diego, CA, USA), respectively. Urine albumin and creatinine levels were measured using routine automated chemistry analyzers. Urinary adiponectin, FGF-21, and albumin levels were adjusted for urinary creatinine excretion, calculated as creatinine-adjusted adiponectin (UAd/Cr, mg/g), creatinine-adjusted FGF-21 (UFGF-21/Cr, mg/g), and UACR (mg/g). The classification of the pediatric subjects into the metabolic syndrome group was based on physical measurements and several blood biomarkers such as HDL, TG, and glucose levels, using the IDF definition for children and

adolescents aged 10-16 years (Table 1) *(2)*, although there are no consensus guidelines or diagnostic criteria for metabolic syndrome in the pediatric population *(2, 25)*. Physical measurements and serum levels of biomarkers were evaluated relative to the 2007 Korean National Growth Chart data *(5, 26)*.

RESULTS

Metabolic syndrome was identified in 30 of 93 children in the obesity group and in none of the children in the control group. The median BMI and waist circumference of children with metabolic syndrome was 34.4 kg/m^2 and 106.0 cm, respectively, compared with 20.5 kg/m^2 and 69.4 cm, respectively, in children in the control group. UAd/Cr and UFGF-21/Cr and nonadjusted urinary adiponectin and FGF-21 levels were higher in the obese group than in the control group (Figure 1). Sex-specific differences were identified: UAd/Cr levels were higher in the male group than in the female group ($P < 0.001$), regardless of obesity status, whereas UFGF-21/Cr levels was also higher in the male group but without statistical significance ($P = 0.063$). UAd/Cr and UFGF-21/Cr were also significantly higher in the metabolic syndrome obesity group (Table 2), with UAd/Cr levels of 3.5, 2.5, and 1.3 mg/g ($P < 0.001$), and UFGF-21/Cr levels of 45.3, 36.6, and 21.9 mg/g ($P < 0.001$) in the metabolic syndrome obesity, non-metabolic syndrome obesity, and normal groups, respectively. UACR was not significantly different among all three groups (5.5, 6.1, and 6.2 mg/g; $P = 0.546$), but showed a higher value only in the female group ($P = 0.019$).

We also specifically compared the data of children with metabolic syndrome with those of the non-metabolic syndrome group, which included children with non-metabolic syndrome obesity and normal children. Among the noninvasive urinary biomarkers, only UAd/Cr (3.5 vs. 1.8 mg/g, P = 0.031) and UFGF-21/Cr (45.3 vs. 25.7 mg/g, P = 0.014) were significantly higher in children with metabolic syndrome than in children in the non-metabolic syndrome group, whereas UACR did not show a significant difference (Table 3).

The cutoff value, sensitivity, and specificity of UAd/Cr and UFGF-21/Cr for the discrimination of the obesity or metabolic syndrome group versus the control group were calculated from receiver operating characteristic (ROC) curve analysis in both sexes (Table 4), and the values of these variables in the different groups are summarized in Figure 2. The highest area under curve (AUC) for the identification of obesity was shown by UFGF-21/Cr (0.678, $P < 0.001$). In the metabolic syndrome and non-metabolic syndrome groups, the maximum AUC value was 0.641 (P = 0.011), shown by UFGF-21/Cr. The male group showed significantly higher AUC value of UFGF-21/Cr for the identification of metabolic syndrome (0.676, P = 0.013), whereas the female group had no significant results. Logistic regression analysis confirmed the positive predictive value of UAd/Cr for obesity, with an odds ratio (OR) of 1.722 (P = 0.009), and the OR was higher in the female group (5.2803 vs. 1.8815). Conversely, UFGF-21/Cr did not show significant results. All urinary biomarkers including UACR had no significant predictive value for metabolic syndrome in multivariate logistic regression, including UAd/Cr (OR = 1.189, P = 0.1924) (Table 5).

As three blood test results (HDL, TG, glucose) are needed in the IDF criteria for pediatric metabolic syndrome, and the invasiveness

of these tests makes them not suitable for the screening of children, we attempted to replace the invasive variables with noninvasive urinary FGF-21 and adiponectin based on the calculated cutoffs, and evaluated the AUC values from ROC curve analysis (Figure 3). Although alternative-to-glucose biomarkers showed low AUC values (< 0.533), alternative-to-HDL and alternative-to-TG biomarkers showed relatively high AUC values (0.712 for UAd/Cr as an alternative to HDL, 0.645 for UFGF-21/Cr as an alternative to TG). A sex-specific difference was identified in several alternative biomarkers: UAd/Cr as an alternative to HDL showed higher AUC in the female group than in the male group (0.739 vs. 0.685), whereas UFGF-21/Cr as an alternative to TG showed higher AUC in the male group (0.700 vs. 0.638).

DISCUSSION

Adiponectin is a polypeptide hormone secreted by adipose tissue (also called an adipokine) that constitutes 0.01% of total plasma protein. Adipokines such as adiponectin and leptin, which can be dysregulated in the obese state, have been known to enhance insulin sensitivity and glomerular function (27). Many studies have identified reduced serum levels of adiponectin (hypoadiponectinemia) in individuals with metabolic syndrome and obesity (1, 8, 28-31). Previous studies have also reported paradoxically decreased plasma levels of adiponectin in obese individuals (31-33), although adipokines are secreted only from adipose tissue (32). Decreased plasma levels of adiponectin have also been reported in studies in pediatric obesity. In their study of 104 sex- and age-matched Italian children (mean age 10.7 years), Cambuli et al. reported that serum adiponectin levels at

baseline were markedly decreased ($P < 0.0001$) in overweight and obese children compared with the levels in the weight-appropriate control group (10). Weiss et al. also reported decreased plasma adiponectin levels with increasing obesity in children and adolescents, and that the severity of obesity and the prevalence of metabolic syndrome were strongly associated ($P = 0.009$) (13). However, there are few reports on urinary adiponectin excretion in the pediatric population thus far, whereas several studies have identified increased urinary adiponectin excretion in adult patients with obesity, cardiovascular disease, diabetes mellitus, and renal disease (19-22). Increased urinary excretion of adiponectin may be caused by glomerular dysfunction, which results from obesity-related hypoadiponectinemia and glomerular podocyte dysfunction (27). As this phenomena can be one of the signs of diabetic nephropathy from glomerular sclerosis (20), early screening and diagnosis of pediatric metabolic syndrome is needed for clinical management.

FGF-21 is a polypeptide hormone that is preferentially produced in the liver (15). This hormone has potent effects on lipid and glucose metabolism, insulin sensitivity, and energy balance (17). Increased plasma FGF-21 levels have been reported in adult patients with obesity, insulin resistance, and diabetes (15-17, 34, 35). Serum FGF-21 levels have also been reported to be correlated with BMI, hepatic insulin resistance index, and hemoglobin A1c value (17, 36). However, there are no data thus far on urinary FGF-21 excretion in adults and children with metabolic syndrome.

Although BMI and waist circumference are well known noninvasive physical measurements for identifying obesity and metabolic syndrome (2), various biomarkers for metabolic syndrome are still required to make an exact diagnosis and to improve the specificity and

sensitivity for the condition. Specific and sensitive biomarkers may also by useful for the early diagnosis of metabolic syndrome, as well for evaluating the effectiveness of interventions. Early detection of metabolic syndrome would be particularly helpful for disease risk management and for monitoring the status of diseases with long-duration clinical therapies, especially in pediatric patients. Furthermore, certain biomarkers could inform the development of new treatment options for obesity, including hormonal therapy as well as therapies targeting specific causative pathways and molecules (37). New directions in the pharmacological treatment of obesity and metabolic syndrome might include the maintenance and regulation of adipose-derived hormones, particularly adipokines, which are produced by fat cells in the body and are known to affect appetite and the energy balance, in addition to being related to the reproductive function (38). The role of the gastrointestinal hunger hormone ghrelin has also been evaluated within the context of the potential of targeted pharmaceutical treatment of eating/wasting disorders and cachexia (39). Moreover, increased plasma adiponectin induced by blockade of the renin-angiotensin system has been reported to reduce the incidence of coronary arterial disease in subjects with metabolic syndrome; however, further large-scale clinical trials are needed (40).

Although noninvasiveness is a requirement for many screening methods for pediatric diseases, the diagnostic criteria for pediatric metabolic syndrome, including the IDF definition and that by Cook et al. (2), include several invasive blood biomarkers such as serum HDL, TG, and fasting glucose. These serum biomarkers should be measured for the exact diagnosis and clinical management of metabolic syndrome; however, invasive blood sampling may not be suitable for pediatric screening, as it can be painful and distressful for children. Furthermore,

as the prevalence of metabolic syndrome in overweight children was reported to be only 11.9% (range 2.8-29.3%) (2), and less than one-third of obese children satisfied the diagnostic criteria of pediatric metabolic syndrome in our study, more information other than physical measurements (e.g., waist circumference and BMI) is needed to screen for metabolic syndrome in the pediatric population. Accordingly, it has been reported that noninvasive urinary biomarkers may be available for the screening of pediatric metabolic syndrome and other systemic diseases, including kidney and cardiovascular diseases (19-22, 41). Children identified to have metabolic syndrome during screening could be referred to a physician for further assessment and for the identification of other risk factors, as well as for establishing an annual follow-up schedule to monitor the disease status, which includes invasive blood tests.

In our study, we identified significantly higher levels of urinary adiponectin and FGF-21 in children with metabolic syndrome than in the non-metabolic syndrome obesity group and the control group with a normal body weight. UAd/Cr and UFGF-21/Cr were significantly higher in children with metabolic syndrome than in both the normal control group and the non-metabolic syndrome obese group. Conversely, UACR (microalbuminuria), previously known as one of the urinary biomarkers for adult and elderly metabolic syndrome (42, 43), showed no significant difference between the pediatric metabolic syndrome group and the control group. In previous reports, plasma adiponectin level was paradoxically decreased in obese subjects (10, 13, 29, 32), whereas urinary adiponectin excretion was higher in all patients with diabetes mellitus and cardiovascular disease. This may possibly be due to increased glomerular dysfunction, which may need early management for the preservation of kidney function.

In this study, we observed a sex-specific difference in the levels of UAd/Cr and UFGF-21/Cr regardless of obesity status or metabolic syndrome diagnosis. Furthermore, as alternative biomarkers to several blood test markers for the diagnosis of metabolic syndrome, they showed higher AUC values in the male group (Figure 3). Several reports have demonstrated a sex-specific difference in the levels of these biomarkers in the plasma of adults (15, 44, 45); however, there was no specific evidence demonstrating different levels of urinary excretion. All reports identified higher plasma adiponectin and FGF-21 levels in the female group than in the male group. In our study, we observed a contrasting result in that the urinary levels of adiponectin and FGF-21 were relatively higher in the male group than in the female group. These sexual dimorphisms may be derived from sex-specific body adiposity and sex hormone differences; however, no specific cause or physiological mechanism has yet been identified (45). Although further studies are needed to elucidate these sex-specific differences in urinary biomarkers, different cutoff points for each sex can be identified to enhance the sensitivity of metabolic syndrome screening in the pediatric population.

When evaluated as alternatives to invasive blood biomarkers for the diagnosis of metabolic syndrome, UAd/Cr and UFGF-21/Cr showed relatively good AUC values as alternatives to HDL and TG, but not to glucose (Figure 3). Although adiponectin and FGF-21 are correlated with glucose metabolism in various pathways, the urinary excretion of both hormones seem to have no specific association with the serum glucose level in the pediatric population. It might be possible to replace two invasive biomarkers, HDL and TG, by noninvasive urinary biomarkers for the screening of pediatric metabolic syndrome, especially in the male group; however, further studies with larger samples and

including various ages of the pediatric population are needed. Furthermore, new criteria for the screening and diagnosis of pediatric metabolic syndrome using noninvasive biomarkers for children may also need to be established.

In this study, we used simple commercial immunoassay kits that can be incorporated as part of routine laboratory analyses in local clinics and even in the patients' home. Urine analysis provides a more feasible point-of-care testing than analyses based on blood samples obtained by venipuncture, which are relatively laborious, expensive, and stressful to patients. Moreover, urinary creatinine levels are routinely evaluated as a component of health checkups. An increase in BMI in childhood is more strongly associated with unfavorable circulating levels of obesity biomarkers than an increase in BMI later in adulthood (46). Therefore, preventing weight gain in childhood and early management of pediatric metabolic syndrome should be considered an important public health initiative through screening tests in routine school health examinations.

In conclusion, urinary adiponectin and FGF-21 assays could be useful screening tools for pediatric obesity and metabolic syndrome owing to their simple and noninvasive nature. UAd/Cr and UFGF-21/Cr may be reliable biomarkers for pediatric metabolic syndrome screening. These biomarkers, which are measured using a handheld immunoassay device, would allow readily assessing the risks of complications from obesity in children and adolescents.

Table 1. Diagnostic criteria for pediatric metabolic syndrome (age 10-16 years) from the International Diabetes Foundation

Variables	IDF definition ages 10-16 years
Defining criteria	Central obesity plus at least 2 out of 4 criteria
Central obesity	WC $\geq 90^{th}$ percentile or adult cut-off if lower
Hypertension	SBP $\geq$ 130 mmHg or DBP $\geq$ 85 mmHg or treatment with anti-hypertensive medication
Hypertriglyceridemia	TG $\geq$ 150 mg/dL
Low HDL	HDL < 40 mg/dL
Impaired glucose	FPG $\geq$ 100 mg/dL or known T2DM

WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL, high density lipoprotein; FPG, fasting plasma glucose; IDF, International Diabetes Foundation; T2DM, type 2 diabetes mellitus.

Table 2. Descriptive characteristics (median and 95% confidence interval) of serum and urinary biomarkers in the non-metabolic syndrome obesity, metabolic syndrome obesity, and control groups

Biomarkers	obesity group (n = 30)		Non-metabolic syndrome obesity group (n = 63)		Normal group (n = 92)		*P*-value**
Weight	99.4	(89.5-106.3)	88.3	(86.6-93.5)	54	(52.6-55.9)	< 0.001
BMI	34.4	(33.4-35.7)	32.9	(32.4-33.9)	20.6	(20.3-20.8)	< 0.001
Waist circumference	106.0	(104.1-108.9)	102.0	(99.5-103.7)	69.4	(68.5-70.5)	< 0.001
AST	24.0	(20.2-31.3)	21.0	(19.3-24.7)	18.0	(17.0-19.0)	< 0.001
ALT	25.5	(19.0-47.3)	25.0	(21.0-31.7)	11.0	(11.0-12.0)	< 0.001
Glucose	96.5	(92.4-99.8)	92.0	(89.2-94.0)	94.0	(91.0-95.0)	0.002
HDL	39.0	(36.0-42.8)	48.0	(45.0-49.0)	54.0	(52.0-56.0)	< 0.001
TG	173.0	(147.1-191.0)	96.0	(89.3-104.5)	58 .0	(50.7-70.0)	< 0.001
Systolic blood pressure	130	(130-130)	120	(120-130)	110	(110-120)	< 0.001
Diastolic blood pressure	80	(80-90)	80	(70-80)	70	(7-80)	< 0.001
UACR (mg/g)	6.1	(4.9-7.0)	5.5	(4.5-6.7)	6.22	(5.0-7.2)	0.546
Urinary adiponectin (ng/dL)	3.9	(2.3-6.2)	3.8	(2.6-5.0)	2.4	(1.6-3.3)	0.045
Urinary FGF-21 (ng/dL)	58.1	(48.9-87.4)	59.3	(47.0-72.0)	44.0	(31.4-50.8)	0.018
Urinary Adiponectin/Cr*(mg/g)	3.5	(1.7-4.0)	2.5	(1.9-3.3)	1.3	(0.7-1.8)	< 0.001
Urinary FGF-21/Cr (mg/g)	45.3	(27.8-59.4)	36.6	(28.0-49.2)	21.9	(13.3-26.1)	< 0.001

*Creatinine; **Kruskal-Wallist est; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TG, triglyceride; HDL, high-density lipoprotein; UACR, urine albumin-to-creatinine ratio; FGF-21, fibroblast growth factor 21.

Table 3. Descriptive characteristics (median and 95% confidence interval) of serum and urinary biomarkers in the metabolic syndrome and non-metabolic syndrome groups

Biomarkers	Metabolic syndrome group (n = 30)		Non-metabolic syndrome group (n = 155)		*P*-value**
Weight	99.4	(89.5-106.3)	59.5	(57.5-65.1)	< 0.001
BMI	34.4	(33.4-35.7)	21.7	(21.1-22.1)	< 0.001
Waist circumference	106.0	(104.1-108.9)	74.7	(72.0-79.5)	< 0.001
AST	24.0	(20.2-31.3)	19.0	(19.0-20.0)	< 0.001
ALT	25.5	(19.0-47.3)	14.0	(12.0-15.0)	< 0.001
Glucose	96.5	(92.4-99.8)	93.0	(92.0-94.0)	0.004
HDL	39.0	(36.0-42.8)	50.0	(49.0-52.6)	< 0.001
TG	173.0	(147.1-191.0)	76.5	(69.0-83.6)	< 0.001
Systolic blood pressure	130	(130-130)	120	(110-120.)	< 0.001
Diastolic blood pressure	80	(80-90)	70	(7-80)	< 0.001
UACR (mg/g)	6.1	(4.9-7.0)	5.8	(5.0-6.8)	0.559
Urinary adiponectin (ng/dL)	3.9	(2.3-6.2)	2.8	(2.4-3.7)	0.169
Urinary FGF-21 (ng/dL)	58.1	(48.9-87.4)	48.9	(42.5-56.7)	0.057
Urinary adiponectin/Cr*(mg/g)	3.5	(1.7-4.0)	1.8	(1.4-2.1)	0.031
Urinary FGF-21/Cr (mg/g)	45.3	(27.8-59.4)	25.7	(21.7-31.1)	0.014

*Creatinine; **Mann-Whitney test; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TG, triglyceride; HDL, high-density lipoprotein; UACR, urine albumin-to-creatinine ratio; FGF-21, fibroblast growth factor 21.

Table 4. Cutoff points of urinary adiponectin and fibroblast growth factor 21 (FGF-21) as biomarkers for obesity and metabolic syndrome screening

Sex	Biomarker	Metabolic syndrome					Obesity				
		Cutoff	*P*-value	Sensitivity	Specificity	AUC value	Cutoff	*P*-value	Sensitivity	Specificity	AUC value
All	UAd (ng/dL)	3.31	0.164	63.3%	55.8%	0.581	2.54	0.012	66.7%	53.9%	0.605
	UFGF-21 (ng/dL)	81.14	0.057	40.0%	81.7%	0.610	49.7	0.005	62.0%	60.4%	0.617
	UAd/Cr* (mg/g)	3.34	0.029	53.3%	75.3%	0.624	2.68	< 0.001	51.6%	78.0%	0.665
	UFGF-21/Cr* (mg/g)	39.7	0.011	60.0%	69.3%	0.641	35.7	< 0.001	55.4%	75.8%	0.678
Male	UAd (ng/dL)	3.31	0.404	73.7%	46.9%	0.565	2.40	0.033	81.1%	46.8%	0.622
	UFGF-21 (ng/dL)	81.0	0.046	52.6%	82.5%	0.652	46.0	0.003	75.0%	55.3%	0.666
	UAd/Cr* (mg/g)	3.05	0.183	68.4%	60.5%	0.605	2.61	0.002	64.2%	72.3%	0.671
	UFGF-21/Cr* (mg/g)	39.7	0.013	68.4%	68.7%	0.676	35.7	< 0.001	61.5%	76.6%	0.699
Female	UAd (ng/dL)	0.93	0.305	90.9%	38.4%	0.585	0.76	0.202	82.5%	43.2%	0.581
	UFGF-21 (ng/dL)	31.6	0.584	81.8%	41.1%	0.548	48.9	0.344	52.5%	61.4%	0.560
	UAd/Cr* (mg/g)	0.69	0.081	90.9%	46.6%	0.649	0.44	0.008	85.0%	45.5%	0.660
	UFGF-21/Cr* (mg/g)	29.2	0.352	63.6%	58.9%	0.585	24.9	0.012	60.0%	65.9%	0.650

*Creatinine; AUC, area under the curve; UAd, urinary adiponectin; UFGF-21, urinary FGF-21; UAD/Cr, creatinine-adjusted urinary adiponectin; UFGF-21/Cr, creatinine-adjusted urinary FGF-21.

Table 5. Univariate and multivariate logistic regression of urinary biomarkers

Sex	Biomarkers	Metabolic syndrome vs. non-metabolic syndrome				Obesity vs. normal			
		Univariate (crude)		Multivariate (adjusted)		Univariate (crude)		Multivariate (adjusted)	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
All	UACR (mg/g)	1.0007 (0.9989-1.0026)	0.4205	1.0012 (0.9992-1.0031)	0.2370	0.9994 (0.9974-1.0013)	0.5138	1.0004 (0.9985-1.0024)	0.6734
	UAd (ng/dL)	0.9981 (0.9777-1.0188)	0.8533	0.9243 (0.8204-1.0413)	0.1954	0.9958 (0.9812-1.0106)	0.5746	0.7982 (0.6740-0.9453)	0.0090†
	UFGF-21 (ng/dL)	1.0079 (1.0001-1.0159)	0.0485†	1.0002 (0.9852-1.0155)	0.9748	1.0085 (1.0012-1.0159)	0.0228†	0.9916 (0.9729-1.0108)	0.3894
	UAd/Cr* (mg/g)	1.0091 (0.9773-1.0419)	0.5788	1.1887 (0.9166-1.5417)	0.1924	1.0049 (0.9744-1.0365)	0.7547	1.7222 (1.1445-2.5917)	0.0091†
	UFGF-21/Cr* (mg/g)	1.0113 (1.0025-1.0201)	0.0113	1.0075 (0.9927-1.0224)	0.3230	1.0203 (1.0096-1.0311)	0.0002	1.0201 (0.9928-1.0482)	0.1504
Male	UACR (mg/g)	1.0021 (0.9988-1.0055)	0.2086	1.0077 (0.9956-1.0199)	0.2122	1.0003 (0.9975-1.0031)	0.8570	1.0030 (0.9990-1.0071)	0.1450
	UAd (ng/dL)	0.9965 (0.9738-1.0197)	0.7647	0.7409 (0.5206-1.0545)	0.0959	0.9946 (0.9788-1.0106)	0.4543	0.7635 (0.6190-0.9419)	0.0118†
	UFGF-21 (ng/dL)	1.0083 (0.9987-1.0180)	0.0908	1.0232 (0.9916-1.0558)	0.1519	1.0107 (1.0004-1.0211)	0.0262†	1.0100 (0.9886-1.0320)	0.3626
	UAd/Cr* (mg/g)	1.0054 (0.9720-1.0400)	0.7533	1.5766 (0.8783-2.8300)	0.1272	0.9985 (0.9684-1.0294)	0.9211	1.8815 (1.1407-3.1036)	0.0133†
	UFGF-21/Cr* (mg/g)	1.0147 (1.0026-1.0268)	0.0166†	0.9857 (0.9470-1.0259)	0.4796	1.0231 (1.0079-1.0385)	0.0004†	1.0014 (0.9690-1.0349)	0.9345
Female	UACR (mg/g)	0.9986 (0.9894-1.0080)	0.7753	0.9993 (0.9904-1.0083)	0.8840	0.9866 (0.9548-1.0194)	0.4187	0.9988 (0.9838-1.014)	0.8719
	UAd (ng/dL)	0.9963 (0.8528-1.1578)	0.9348	0.9355 (0.5968-1.4665)	0.7713	1.0096 (0.9130-1.1166)	0.8517	0.4605 (0.1913-1.1087)	0.0837
	UFGF-21 (ng/dL)	1.0058 (0.9911-1.0207)	0.4427	0.9839 (0.9531-1.0157)	0.3176	1.0055 (0.9946-1.0166)	0.3250	0.9643 (0.9270-1.0030)	0.0700
	UAd/Cr* (mg/g)	1.0654 (0.8238-1.3779)	0.6292	1.1869 (0.5299-2.6582)	0.6771	1.2297 (0.9797-1.5435)	0.0745	5.2803 (0.9983-27.9283)	0.0502
	UFGF-21/Cr* (mg/g)	1.0078 (0.9979-1.0177)	0.1237	1.0153 (0.9927-1.0384)	0.1853	1.0167 (1.0015-1.0322)	0.0314†	1.0352 (0.9810-1.0924)	0.2078

*Creatinine; †P-value < 0.05; OR, odds ratio; CI, confidence interval; UACR, urine albumin-to-creatinine ratio; UAd, urinary adiponectin; UFGF-21, urinary fibroblast growth factor 21.

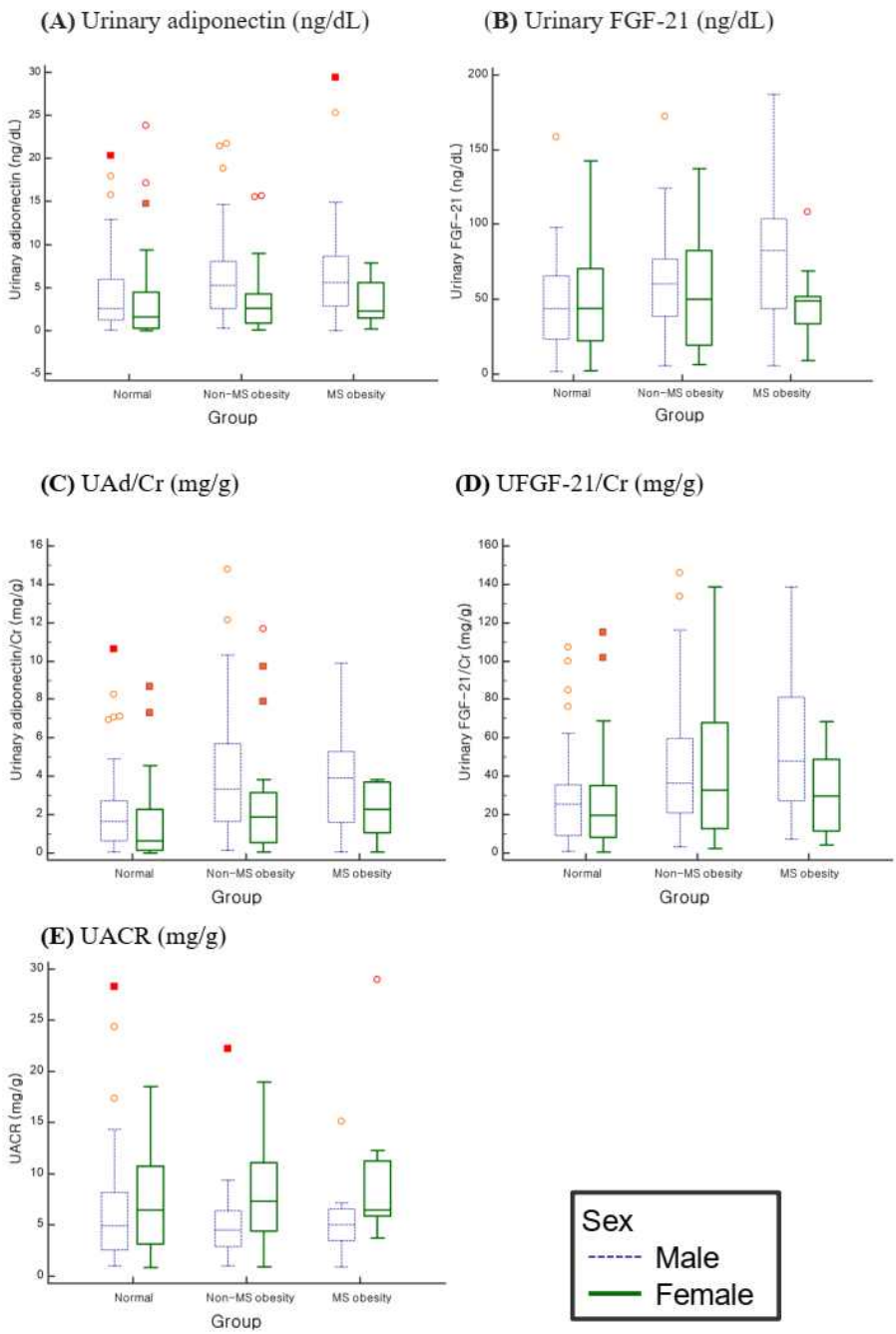
(A) Urinary adiponectin (ng/dL)
Urinary adiponectin (ng/dL)
Normal
Non-MS obesity
MS obesity
Group
(B) Urinary FGF-21 (ng/dL)
Urinary FGF-21 (ng/dL)
Normal
Non-MS obesity
MS obesity
Group
(C) UAd/Cr (mg/g)
Urinary adiponectin/Cr (mg/g)
Normal
Non-MS obesity
MS obesity
Group
(D) UFGF-21/Cr (mg/g)
Urinary FGF-21/Cr (mg/g)
Normal
Non-MS obesity
MS obesity
Group
(E) UACR (mg/g)
UACR (mg/g)
Normal
Non-MS obesity
MS obesity
Group
Sex
Male
Female

Figure 1. Differential expression of (A) urinary adiponectin, (B) fibroblast growth factor 21 (FGF-21, non-adjusted), (C) creatinine-adjusted urinary adiponectin (UAd/Cr), and (D) creatinine-adjusted urinary FGF-21 (UFGF-21/Cr) between the metabolic syndrome obesity (MS obesity), non-metabolic syndrome obesity (non-MS obesity), and normal groups (95% confidence interval) by sex. All biomarkers were higher in the MS obesity group than in the normal group. UAd/Cr ($P < 0.001$) was also significantly higher in the male group than in the female group, regardless of obesity status, whereas UFGF-21/Cr ($P = 0.063$) showed no significant difference between the male and female groups. (E) Urinary albumin-to-creatinine ratio (UACR) showed no significant difference between the MS obesity and normal groups ($P = 0.546$), but was higher in the female group than in the male group ($P = 0.019$).

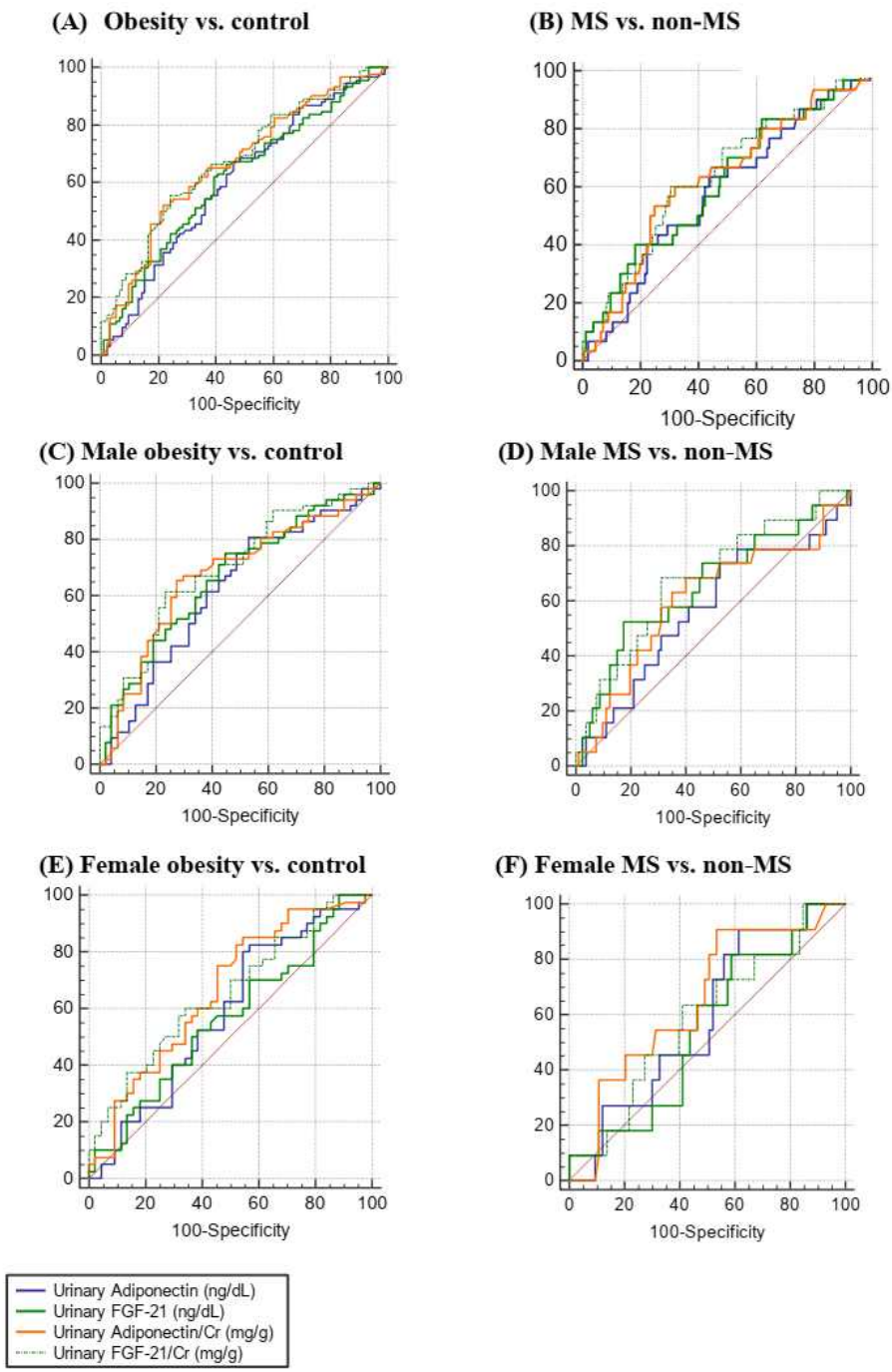
(A) Obesity vs. control
(B) MS vs. non-MS
(C) Male obesity vs. control
(D) Male MS vs. non-MS
(E) Female obesity vs. control
(F) Female MS vs. non-MS
100-Specificity
Urinary Adiponectin (ng/dL)
Urinary FGF-21 (ng/dL)
Urinary Adiponectin/Cr (mg/g)
Urinary FGF-21/Cr (mg/g)

Figure 2. Receiver operating characteristic (ROC) curve analysis of urinary biomarkers in the (A) obesity and control groups, (B) metabolic syndrome (MS) and non-MS groups (including non-MS obesity and normal), (C, D) male group, and (E, F) female group. In the ROC curve analysis between the obesity and control groups, the highest area under the curve (AUC) was identified for creatinine-adjusted urinary fibroblast growth factor 21 (FGF-21) (0.678 and 0.641 in the obesity and MS groups, respectively). In the male group, creatinine-adjusted urinary FGF-21 showed higher AUC values than creatinine-adjusted urinary adiponectin (0.699 vs. 0.673 in the obesity group, 0.603 vs. 0.676 in the MS group), whereas creatinine-adjusted urinary adiponectin showed higher AUC values in the female group (0.660 vs. 0.650 in the obesity group, 0.649 vs. 0.585 in the MS group).

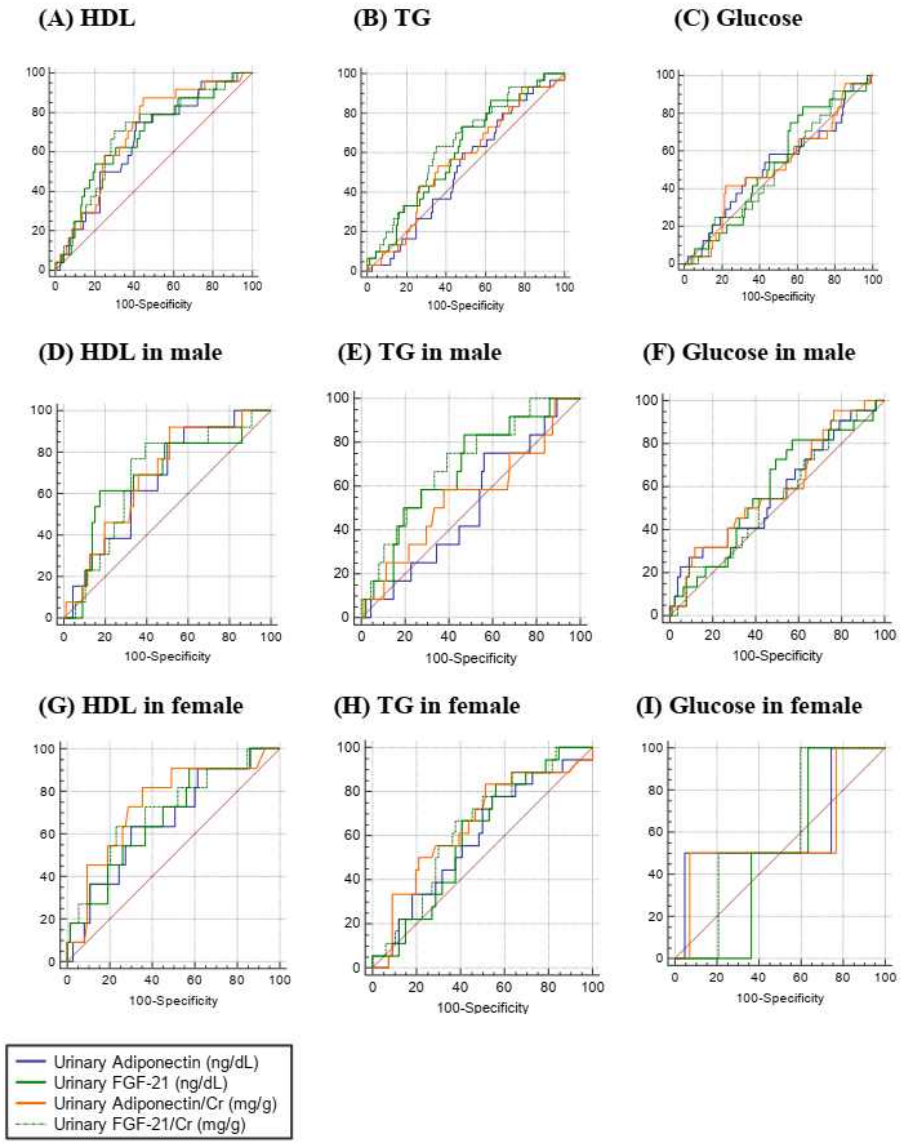

Figure 3. Receiver operating characteristic (ROC) curve analysis of urinary biomarkers as alternatives to invasive blood biomarkers – (A) serum high-density lipoprotein (HDL), (B) triglyceride (TG), and (C) glucose – for the diagnosis of pediatric metabolic syndrome based on the International Diabetes Federation definition. The highest area under

the curve (AUC) values of each graph were (A) 0.700 (urinary adiponectin/creatinine [Cr], mg/g), (B) 0.644 (urinary fibroblast growth factor 21 [FGF-21]/Cr, mg/g), and (C) 0.534 (urinary FGF-21, ng/dL). In the analysis of urinary adiponectin/Cr alternative to HDL, the female group showed higher AUC: (D) male, 0.685 vs. (G) female, 0.739. In the analysis of urinary FGF-21/Cr as an alternative to TG, the male group showed higher AUC: (E) male, 0.700 vs. (H) female, 0.638.

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요약(국문초록)

소아의 대사증후군을 선별검사하는 것은 비만 아동의 다양한 질병을 관리하고 삶의 질을 높이기 위해 중요한 과정이다. 소아의 대사증후군을 진단하기 위해서는 몇 가지의 침습적인 혈액 바이오마커가 필요하다. 혈청 아디포넥틴과 섬유모세포 성장인자 21(FGF-21)는 비만 및 대사증후군과 관련된 것으로 알려져 있으나, 비침습적 소변 바이오마커로서의 유용성은 아직 제한된 데이터만 보고되어 있다. 따라서, 우리는 소변 아디포넥틴과 FGF-21의 소아 대사증후군 진단에서의 유용성에 대해 조사하였다.

한국 질병관리본부에 보관되어 있는 13-15세 사이의 아동과 청소년의 소변 검체를 이용하였다. 체질량지수(BMI)가 99백분위를 넘어가는 93명의 비만 아동들과 체질량지수 백분위가 25-75 사이에 있는 정상 아동 대조군 92명이 선택되었다. 모든 비만 및 정상 아동은 성별과 연령에 따라 맞추어졌다. 키, 체중, 허리 둘레, 수축기 및 이완기 혈압을 비롯한 신체 데이터를 수집하였다. 소변 크레아티닌과 알부민, 그리고 혈청 공복혈당, 고밀도지단백 콜레스테롤(HDL), 중성지방이 각각 측정되었다. 소변 아디포넥틴과 FGF-21 농도는 효소결합면역흡착측정법을 이용하여 측정하였다. 대사증후군 진단기준은 국제당뇨협회의 소아 대사증후군 진단기준 및 2007년 소아청소년 성장도표를 활용하였다.

소아 대사증후군은 93명의 비만 아동들 중 30명에서 진단되었고, 정상 아동 대조군에서는 진단되지 않았다. 대사증후군 환자에서 체질량지수의 허리 둘레의 중간값은 각각 34.35 kg/m^2와 106.0 cm였고, 정상 아동 대조군에서는 각각 20.6 kg/m^2와 69.4 cm였다. 크레아티닌 보정 소변 아디포넥틴과 FGF-21 농도는 비만 아동에서 유의하게 높았다(소변 아디포넥틴/크레아티닌: 중간값 3.5 vs 1.3 mg/g, $P < 0.001$; 소변 FGF-21/크레아티닌; 중간값 68.7 vs 31.7 mg/g, $P < 0.001$). 로지스틱 선형 분석에서, 크레아티닌 보정 소변 아디포넥틴은

통계적으로 유의하지 않으나 대사증후군에 대해 양성 효과를 보였으나 (소변 아디포넥틴/크레아티닌: 교차비 1.1189, P = 0.192), 비만에는 통계적으로 유의한 양성 효과를 보였다 (교차비 = 1.722, P = 0.009). 크레아티닌 보정 소변 아디포넥틴을 고밀도지단백 콜레스테롤 대체 바이오마커로 사용하여 대사증후군 진단에 사용하였을 경우, 곡선하면적(AUC) 값은 0.700였으며 크레아티닌 보정 소변 FGF-21을 중성지방 대체 바이오마커로 사용하였을 경우에는 0.644였다.

따라서 소변 아디포넥틴과 FGF-21 검사는 소아의 대사증후군 선별검사에 있어 침습적인 혈액검사를 대체할 수 있을 가능성이 있으나 추가적인 연구가 필요하다.

주요어: 소아 대사증후군, 바이오마커, 아디포넥틴, FGF-21
학번: 2015-22019