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Original Article

Fetuin-A as an Alternative Marker for Insulin Resistance and Cardiovascular Risk in Prepubertal Children

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***Aim*: Fetuin-A plays a role in insulin resistance and cardiovascular disease. This study aims to determine the relationship between fetuin-A levels and cardiometabolic risk factors, as well as to investigate the effect of serum fetuin-A on insulin resistance indices to determine whether fetuin-A is an additional marker for insulin resistance in prepubertal children.**

***Methods*: A total of 99 prepubertal Korean children (59 males) aged from 6.0 to 10.0 years was included in this study. Subjects were divided into underweight/normal-weight and overweight/obese groups. Serum fetuin-A levels were measured using an enzyme-linked immunosorbent assay and were natural logarithm (ln)-transformed.**

***Results*: Serum fetuin-A concentrations were significantly elevated in overweight/obese children as compared with underweight/normal-weight children ($P=0.029$). Ln serum fetuin-A was significantly positively correlated with body mass index (BMI) standard deviation scores (SDSs) ($r=0.239$, $P=0.017$), triglyceride levels ($r=0.285$, $P=0.004$), ln insulin ($r=0.377$, $P<0.001$), systolic blood pressure (BP) ($r=0.274$, $P=0.006$), and diastolic BP ($r=0.304$, $P=0.006$) and was significantly inversely correlated with high-density lipoprotein cholesterol (HDL-C) levels ($r=-0.236$, $P=0.019$). In univariate linear regression analysis, ln fetuin-A was significantly positively associated with the homeostasis model assessment of insulin resistance (HOMA-IR) ($r=0.356$, $P<0.001$) and significantly inversely associated with the quantitative insulin sensitivity check index (QUICKI) ($r=-0.309$, $P=0.002$). Following adjustment for age, gender, BMI, and lipid profiles in multivariate linear regression analysis, fetuin-A was significantly positively associated with HOMA-IR ($P=0.048$) and marginally inversely associated with QUICKI ($P=0.054$).**

***Conclusions*: Our results suggest that fetuin-A can be an alternative marker for insulin resistance and cardiovascular risk in prepubertal children.**

Key words: Fetuin-A, Insulin resistance, Cardiovascular risk, Children, Obesity

Introduction

Childhood obesity is recognized as a major medical and public health problem in many countries, including Korea[1]. Obesity in adulthood is related to adverse consequences that lead to morbidity. Obese children have a high risk of adult obesity. Moreover, childhood obesity is an independent factor for adult morbidity development[2]. There is an association between being overweight and developing insulin resistance in childhood and early development of atheromas in young adulthood[3]. Children with insulin resistance are likely to grow up as adults with insulin resistance[4]. It has been discovered that overweight children and adolescents are at a risk of insulin resistance and metabolic syndrome as well[5]. Moreover, insulin resistance is an independent risk factor for cardiovascular and metabolic diseases[6].

Fetuin-A, known as α2-Heremans-Schmid glycoprotein (AHSG) in humans, is an abundant protein produced predominantly in the liver[7]. In animal studies, fetuin-A acts as a natural inhibitor of insulin receptor tyrosine kinase activity in the muscle and the liver[8]. Fetuin-A is related to insulin resistance and non-alcoholic fatty liver disease (NAFLD) in adults[9]. It has been reported that higher fetuin-A levels are associated with insulin resistance and cardiometabolic

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risk factors, including systolic blood pressure (BP), diastolic BP, dyslipidemia, and waist circumference, in obese children and adults[10-12].

In this study, we aimed to evaluate the differences in serum fetuin-A levels between overweight and obese prepubertal children and underweight and normal-weight prepubertal children, as well as to determine the relationships between fetuin-A levels and metabolic and cardiovascular risk factors. We also investigated the impact of serum fetuin-A on insulin resistance indices to determine whether fetuin-A is an alternative marker for insulin resistance in children.

Materials and Methods

Subjects

A total of 99 prepubertal children (59 males and 40 females) aged from 6.0 to 10.0 years was included in this study. All subjects underwent a health examination at Kangdong Sacred Heart Hospital between 2007 and 2014. Children with obesity-related diseases, such as hypothyroidism, Cushing syndrome, Prader–Willi syndrome, and type 2 diabetes mellitus (T2DM), were excluded from the study. Participants were divided into an underweight/normal-weight group and an overweight/obese group according to their body mass index (BMI). The underweight group was defined as having a BMI less than the 3rd percentile for age and gender. The normal-weight group was defined as having a BMI between the 3rd and 85th percentile for age and gender. The overweight group was defined as having a BMI between the 85th and 95th percentile and the obesity group was defined as a having a BMI greater than or equal to the 95th percentile for age and gender. The BMI percentiles were determined using the 2007 Korean National Growth Charts[13]. The study protocols were approved by the Institutional Review Board of Hallym University Kangdong Sacred Heart Hospital. Informed Consent was obtained from all subjects and their parents.

Anthropometric Measurements

Height was recorded to the nearest 0.1 cm using a Harpenden stadiometer. Weight was measured using an electronic scale, which was accurate to the nearest 0.1 kg. Pubertal stage was determined by experienced pediatric endocrinologists according to Marshall and Tanner[14]. The prepubertal stage was defined as a testicular size <4 mL and no pubic hair in boys and as a lack of breast development (Tanner stage I) and no pubic hair in girls. BMI was determined as follows: Weight (kg)/(height (m))^2. Height, weight, BMI, and waist circumference (WC) standard deviation scores (SDSs) were used because height, weight, and BMI were not evenly distributed among the various child age groups. Height SDSs, weight SDSs, BMI SDSs, and WC SDSs were calculated via the LMS method using the 2007 Korean National Growth Charts[13]. Before their BPs were measured, all participants rested in a sitting position for 10 minutes. Systolic and diastolic BP (mmHg) were measured twice in the right upper arm using a calibrated sphygmomanometer with an appropriate cuff size. Thereafter, the means of the two measured values for each parameter were used for analysis. Bone age was determined according to the Greulich and Pyle method[15].

Laboratory Measurement

Blood samples were obtained from all subjects in the morning after overnight fasting. The collected specimens were kept frozen at −80℃ after centrifugation. The samples were transported to and analyzed at one central laboratory on the same day. Serum fetuin-A, insulin, fasting plasma glucose, total cholesterol (T-C), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) concentrations were measured.

Serum fetuin-A levels were measured by an enzyme-linked immunosorbent assay (BioVendor Laboratory Medicine, Brno, Czech Republic). Intra-assay and inter-assay coefficients of variation (CVs) ranged from 3.9% to 4.9% and from 7.3% to 8.4%, respectively. Serum insulin concentrations were determined using immunoradiometric assay (Biosource, Nevelles, Belguim). A Hitachi-747 automatic analyzer (Hitachi, Tokyo, Japan) was used to estimate biochemical parameters, such as fasting plasma glucose and serum T-C, TG, LDL cholesterol (LDL-C), HDL-C, aspartate aminotransferase (AST), and alanine transaminase (ALT) concentrations.

Determination of Insulin Resistance Index

Insulin resistance was determined based on basal fating plasma glucose and insulin levels using the homeostasis model assessment for insulin resistance (HOMA-IR)[16] and the quantitative insulin sensitivity check index (QUICKI)[17]. HOMA-IR and QUICKI were determined using the following equations:

HOMA-IR = [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5

QUICKI = 1/[log(fasting glucose (mg/dL)) + log(fasting insulin (μU/mL))

Statistical Analyses

All analyses were performed using SPSS for Windows, version 21 (IBM SPSS Inc., Chicago, IL, USA). The results are presented as the mean ± SD. Groups were compared using independent sample *t*-tests and

Table 1. Clinical Characteristics of the study children ($n=99$)

	Underweight/Normal-weight	Overweight/Obesity	*P*
Number	52	47	
Age (year)	8.02 ± 1.14	8.36 ± 1.08	0.132
Male (%)	29 (56%)	30 (64%)	0.539
Height SDS	0.28 ± 1.39	0.96 ± 0.0.89	0.005
Weight SDS	−0.06 ± 1.0	1.64 ± 0.51	<0.001
BMI SDS	−0.29 ± 0.83	1.66 ± 0.47	<0.001
WC SDS	−0.54 ± 1.10	1.29 ± 0.67	<0.001
Systolic BP (mmHg)	99.00 ± 9.37	101.64 ± 9.78	0.174
Diastolic BP (mmHg)	62.79 ± 4.89	65.45 ± 6.89	0.031
Bone age (year)	7.34 ± 1.76	8.82 ± 1.76	<0.001
Glucose (mg/dL)	103.35 ± 15.78	100.72 ± 9.48	0.314
T-C (mg/dL)	168.19 ± 25.13	170.96 ± 25.02	0.585
TG (mg/dL)	64.46 ± 25.69	80.64 ± 32.00	0.006
LDL-C (mg/dL)	96.33 ± 20.51	101.84 ± 22.73	0.157
HDL-C (mg/dL)	63.73 ± 12.83	56.79 ± 10.98	0.005
AST (IU/L)	25.96 ± 6.70	25.57 ± 6.66	0.774
ALT (IU/L)	14.79 ± 9.54	20.60 ± 11.66	0.008
Insulin (μU/mL)	4.72 ± 2.18	7.42 ± 3.55	<0.001
Ln insulin	1.45 ± 0.47	1.88 ± 0.54	<0.001
HOMA-IR	1.22 ± 0.63	1.83 ± 0.87	<0.001
QUICKI	0.38 ± 0.03	0.36 ± 0.04	0.001
Fetuin-A (ng/mL)	119.89 ± 86.54	203.21 ± 254.54	0.029
Ln fetuin-A	4.66 ± 0.52	4.97 ± 0.71	0.013

Values are mean ± SD. SDS, standard deviation score; BMI, body mass index; BP, blood pressure; WC, waist circumference; T-C, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

chi-square tests. Because the distributions of serum fetuin-A and insulin concentrations were skewed, they were transformed by natural logarithms (lns). To investigate the association among fetuin-A, clinical parameters, and insulin resistance indices, Pearson correlation coefficients were determined by single linear univariate correlations. Stepwise multivariate regression analyses were conducted with insulin resistance indices as a dependent variable. Results of the analyses are presented as *P*-values, correlation coefficients (rs), and β-coefficients. Statistical significance was defined as $P<0.05$.

Results

Clinical Characteristics of the Study Population

The clinical characteristics of subjects are shown in **Table 1**. A total of 52 children were underweight/normal-weight and 47 children were overweight and obese. Overweight/obese children had a significantly higher mean height SDS (0.96 vs 0.28, $P=0.005$), weight SDS (1.64 vs −0.06, $P<0.001$), BMI SDS (1.66 vs −0.29, $P<0.001$), and WC SDS (1.29 vs −0.54, $P<0.001$) and a significantly higher diastolic BP (65.45 mmHg vs 62.79 mmHg, $P=0.031$), bone age (8.82 years vs 7.34 years, $P<0.001$), ALT (20.60 IU/L vs 14.79 IU/L, $P=0.008$), TG level (80.64 mg/dL vs 64.46 mg/dL, $P=0.006$), insulin level (7.42 μU/mL vs 4.72 μU/mL, $P<0.001$), HOMA-IR (1.83 vs 1.22, $P<0.001$), and fetuin-A level than underweight/normal-weight children (203.21 ng/mL vs 119.89 ng/mL, $P=0.029$). Overweight/obese children had significantly lower mean HDL-cholesterol concentrations (56.79 mg/dL vs 63.73 mg/dL, $P=0.005$) and QUICKIs than underweight/normal-weight children (0.36 vs 0.38, $P=0.001$).

Correlations Between Ln Fetuin-A and Clinical Parameters in Prepubertal Children

Ln fetuin-A levels were significantly positively correlated with BMI SDS ($r=0.239$, $P=0.017$), systolic BP ($r=0.274$, $P=0.006$), diastolic BP ($r=0.304$, $P=0.002$), and TG levels ($r=0.285$, $P=0.004$) and were significantly inversely correlated with T-C ($r=-0.264$,

Table 2. Correlations between ln fetuin-A and clinical parameters in prepubertal children ($n=99$)

Variable	Ln fetuin-A	
	r	*P*
Age	0.192	0.057
Gender (male)	0.086	0.400
BMI SDS	0.239	0.017
WC SDS	0.154	0.127
Systolic BP (mmHg)	0.274	0.006
Diastolic BP (mmHg)	0.304	0.002
Glucose (mg/dL)	−0.170	0.093
T-C (mg/dL)	−0.264	0.008
TG (mg/dL)	0.285	0.004
LDL-C (mg/dL)	−0.378	<0.001
HDL-C (mg/dL)	−0.236	0.019
Ln insulin	0.377	<0.001

BMI, body mass index; SDS, standard deviation score; WC, waist circumference, BP, blood pressure; T-C, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

$P=0.008$), LDL-C ($r=-0.378$, $P<0.017$), and HDL-C levels ($r=-0.236$, $P=0.019$) (**Table 2**).

Associations Between Insulin Resistance and Clinical Parameters

Univariate linear regression analysis results for insulin resistance indices (HOMA-IR, QUICKI) are presented in **Table 3**. In univariate analysis, HOMA-IR was significantly positively associated with age ($r=0.263$, $P=0.009$), BMI SDS ($r=0.439$, $P<0.001$), WC SDS ($r=0.387$, $P<0.001$), glucose levels ($r=0.200$, $P=0.047$), TG levels ($r=0.395$, $P<0.001$), ln insulin ($r=0.915$, $P<0.001$), and ln fetuin-A ($r=0.356$, $P<0.001$). HOMA-IR was inversely correlated with HDL-C levels ($r=-0.274$, $P=0.006$). QUICKI was significantly inversely associated with BMI SDS ($r=-0.384$, $P<0.001$), WC SDS ($r=-0.358$, $P<0.001$), glucose levels ($r=-0.225$, P = 0.025), TG levels ($r=-0.341$, $P=0.001$), ln insulin ($r=-0.964$, $P<0.006$), and ln fetuin-A ($r=-0.309$, $P=0.002$). QUICKI was positively correlated with HDL-C levels ($r=0.288$, $P=0.004$). Systolic BP, diastolic BP, and T-C and LDL-cholesterol levels were not significantly associated with either HOMA-IR or QUICKI. Ln fetuin-A was significantly positively correlated with HOMA-IR and significantly inversely correlated with QUICKI.

Stepwise multivariate linear regression analysis was conducted with HOMA-IR and QUICKI as dependent variables. Independent variables, such as age, gender, BMI SDS, T-C, TG, LDL-C, HLD-C, and ln fetuin-A, were included in the analysis. Ln fetuin-A was a significant independent predictor of HOMA-IR ($P=0.048$) and a marginal independent predictor of QUICKI ($P=0.054$) (**Table 4**). In addition, BMI SDS and TG levels were significant independent predictors of insulin resistance indices ($P=0.001$ and $P=0.012$ for HOMA-IR and $P=0.005$ and $P=0.041$ for QUICKI, respectively).

Discussion

This study showed that fetuin-A levels were significantly higher in overweight and obese prepubertal children than in underweight/normal-weight children. Higher fetuin-A concentrations were significant positive predictors of insulin resistance, as determined by HOMA-IR, and were marginal negative predictors of insulin resistance, as determined by QUICKI, in 99 Korean prepubertal children following adjustment for age, gender, BMI SDS and T-C, TG, LDL-C and HDL-C levels.

The association between fetuin-A levels and BMI is controversial. In our study, fetuin-A concentrations were higher in overweight/obese children than in normal-weight children. Furthermore, BMI SDS was significantly positively associated with fetuin-A levels. Adults with elevated fetuin-A concentrations had a higher BMI than those with lower fetuin-A concentrations[18]. Serum fetuin-A concentrations were significantly higher in obese children than in children in the control group[19]. Ismail *et al.*[11] reported that fetuin-A levels were correlated with BMI in obese children. However, other studies demonstrated that fetuin-A concentrations are not related to body fat mass percentages and BMI[20] and are not associated with BMI[21] in adults. In the study by Reinehr *et al.*[10], serum fetuin-A levels were not significantly higher in normal-weight children than in obese children without NAFLD. However, there are a few studies whose results support the hypothesis that a positive correlation exists between fetuin-A levels and BMI. Elevated fetuin-A concentrations decreased after weight reduction in adults[22] as well as in children and adolescents[10]. In addition, fetuin-A concentrations were independent predictors of abdominal adiposity[23]. Our results support the above hypothesis. One of the advantages of this study was that all the children enrolled in this study were of the same ethnicity and at the same pubertal stage.

Insulin resistance is defined as the impaired ability of plasma insulin to adequately promote peripheral glucose disposal, suppress hepatic glucose production, and inhibit very low density lipoprotein (VLDL) out-

Table 3. Univariate linear regression analyses of HOMA-IR, and QUICKI in prepubertal children (n=99)

Variable	HOMA-IR		QUICKI	
	r	P	r	P
Age	0.263	0.009	−0.192	0.057
Gender (male)	0.079	0.439	−0.043	0.669
BMI SDS	0.439	<0.001	−0.384	<0.001
WC SDS	0.387	<0.001	−0.358	<0.001
Systolic BP (mmHg)	−0.034	0.738	0.075	0.460
Diastolic BP (mmHg)	0.194	0.055	−0.099	0.331
Glucose (mg/dL)	0.200	0.047	−0.225	0.025
T-C (mg/dL)	−0.081	0.428	0.074	0.469
TG (mg/dL)	0.395	<0.001	−0.341	0.001
LDL-C (mg/dL)	−0.048	0.638	0.009	0.933
HDL-C (mg/dL)	−0.274	0.006	0.288	0.004
Ln insulin	0.915	<0.001	−0.964	<0.001
Ln fetuin-A.	0.356	<0.001	−0.309	0.002

HOMA–IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; BMI, body mass index; SDS, standard deviation score; BP, blood pressure; T-C, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

Table 4. Stepwise multivariate regression analyses of homeostasis model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index QUICKI in prepubertal children (n=99)

Variable	HOMA-IR			QUICKI		
	β	SE	P	β	SE	P
Age	0.134	0.062	0.032	−0.004	0.003	0.177
BMI SDS	0.209	0.061	0.001	−0.008	0.003	0.005
TG	0.006	0.002	0.012	0.000	0.000	0.041
Ln fetuin-A	0.229	0.114	0.048	−0.010	0.005	0.054

HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; BMI, body mass index; SDS, standard deviation score; TG, triglyceride.

put at normal concentrations[24]. Insulin resistance is related to numerous physical health conditions that have serious health consequences, such as obesity, hyperlipidemia, hypertension, cardiovascular disease, and T2DM[25]. The pathogenesis of insulin resistance is related to nutritional overloads, genetic factors, birth weight, physical activity, puberty, ethnicity, and hormones, such as leptin, adiponectin, and ghrelin[24]. Higher fetuin-A concentrations are associated with the development of insulin resistance. In an animal study, administration of purified human fetuin-A induced inhibition of insulin-stimulated phosphorylation of insulin receptors and insulin receptor substrate-1[26]. It has been demonstrated that fetuin-A was correlated with insulin resistance in adults[27]. Furthermore, the association between fetuin-A and insulin resistance was investigated in children and adolescents[10, 19]. We evaluated the relationship between serum fetuin-A concentrations and insulin resistance in prepubertal children. Fetuin-A was associated with insulin resistance indices. Fetuin-A concentrations were significantly positively correlated with HOMA-IR and significantly inversely correlated with QUICKI. Fetuin-A remained a significant independent predictor of HOMA-IR when we adjusted for age, gender, BMI SDS, and lipid profiles. However, fetuin-A was a marginal independent predictor of QUICKI.

In this study, fetuin-A concentrations were associated with cardiometabolic risk factors in prepubertal children. Based on the modified criteria for metabolic syndrome developed by the National Cholesterol Education Program Adult Treatment Panel Ⅲ(NCEP-ATP

Ⅲ)[28] and the International Diabetes Federation (IDF)[29], TGs, HDL-C, and BP were significantly correlated with fetuin-A concentrations. Fetuin-A concentrations were significantly positively associated with TGs and systolic and diastolic BP and significantly inversely associated with HDL-C in prepubertal subjects. A significant association between fetuin-A concentrations and cardiometabolic risk factors has been demonstrated in adults[30]. In children and adolescents, it has been consistently demonstrated that elevated fetuin-A concentrations are a risk factor for cardiovascular and metabolic diseases[31]. Because fetuin-A is a hepatokine produced predominantly in the liver[7], the risk factors for cardiometabolic diseases that are related to fetuin-A are associated with increased insulin resistance rather than obesity or overweight. However, there is evidence that fetuin-A plays an independent role in cardiovascular and metabolic disease risk. In humans, the fetuin-A gene is located on chromosome 3q27, which is strongly linked to MetS[32] and T2DM[33]. Fetuin-A induces low-grade inflammation[34], which is linked to MetS and atherogenic lipid profiles[30].

Overweight and obesity in children are positively associated with insulin resistance, cardiovascular disease, and atherosclerosis in adults[35, 36]. Early recognition of insulin resistance is necessary to avoid these conditions. The hyperinsulinemic–euglycemic clamp test and oral glucose intolerance test, which are frequently conducted, are accurate and correlated with pancreatic β-cell function and insulin resistance. However, these methods require frequent sampling, are expensive and invasive, and may be complicated in children. Fasting insulin concentrations as well as HOMA-IR and QUICKI, which are based on fasting glucose and fasting insulin levels, are accurate and easily measurable but are also influenced by age, gender, and pubertal stage. Fetuin-A is a relatively stable protein and its concentrations are not influenced by age, gender, or pubertal stage[37, 38]. Therefore, fetuin-A can be clinically utilized as an additional marker for insulin resistance and cardiovascular risk in children.

There were limitations to this study. Neither did we evaluate the association between fetuin-A and metabolic syndrome in overweight/obese children, nor did we evaluate the effect of weight loss on changes in serum fetuin-A concentrations. We could not find positive correlations between fetuin-A levels and T-C and LDL-C levels in this study. In studies on adults, serum fetuin-A concentrations were significantly positively correlated with T-C and LDL-C[12, 39]. However, there were discrepancies with regard to the association between fetuin-A and lipid profile parameters in children. A study on Polish children with nephrotic syndrome demonstrated that fetuin-A was significantly positively correlated with T-C. However, serum fetuin-A was significantly positively correlated with HDL-C in children and was not correlated with LDL-C and TGs[11]. The discrepancies with regard to correlations between fetuin-A and lipid profile parameters may be associated with variations in age, gender, ethnicity, and comorbid diseases. Cholesterol value distributions varied with age, gender, and ethnicity[40]. Furthermore, the relationship between fetuin-A and lipid profiles is mediated by insulin resistance. Insulin resistance influences changes in lipid profiles. Elevations in TG levels and decreases in HDL-C levels are mainly related to insulin resistance, although T-C and LDL-C levels are affected. A recent study demonstrated that the TG-to-HDL-C ratio, which was proposed as a marker for insulin resistance, can be an approach for identifying overweight individuals who are insulin resistant[41]. In our study, fetuin-A was significantly positively correlated with TG and inversely correlated with HDL-C but was not significantly associated with T-C or LDL-C. It may be associated with cholesterol distributions, which are affected by age, gender, and ethnicity as well as insulin resistance.

Conclusion

Fetuin-A concentrations were higher in overweight/obese prepubertal children than in underweight/normal-weighted prepubertal children and were positively correlated with BMI SDS. Higher fetuin-A levels were a risk factor for insulin resistance, dyslipidemia, and hypertension. Furthermore, fetuin-A was an independent risk factor for insulin resistance, as determined by HOMA-IR, after adjustment for age, gender, BMI SDS, and TG, LDL-C, HDL-C, and LDL-C levels. Therefore, fetuin-A can be an alternative marker for insulin resistance and cardiometabolic risk in prepubertal children.

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Conflict of Interest

The authors declare no conflicts of interest.

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