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

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

Laboratory Measurement
Blood samples were obtained from all subjects in the morning after overnight fasting. The collected specimens were kept frozen at −80°C 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, Belgium). 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 fasting plasma glucose and insulin levels using the homeostasis model assessment for insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI). HOMA-IR and QUICKI were determined using the following equations:

\[
\text{HOMA-IR} = \frac{\text{fasting insulin (μU/mL)} \times \text{fasting glucose (mmol/L))}}{22.5}
\]

\[
\text{QUICKI} = \frac{1}{\log(\text{fasting glucose (mg/dL))} + \log(\text{fasting insulin (μU/mL))}}
\]

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
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 (r_s), 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 (1.66 vs −0.06, P<0.001), BMI SDS (1.29 vs −0.54, 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, P=0.001).

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

| Parameter                  | 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±0.89          | 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.
Table 2. Correlations between ln fetuin-A and clinical parameters in prepubertal children (n=99)

| Variable         | Ln fetuin-A |
|------------------|-------------|
| Age              | 0.192       |
| Gender (male)    | 0.086       |
| BMI SDS          | 0.239       |
| WC SDS           | 0.154       |
| Systolic BP (mmHg) | 0.274     |
| Diastolic BP (mmHg) | 0.304     |
| Glucose (mg/dL)  | -0.170      |
| T-C (mg/dL)      | -0.264      |
| TG (mg/dL)       | 0.285       |
| LDL-C (mg/dL)    | -0.378      |
| HDL-C (mg/dL)    | -0.236      |
| Ln insulin       | 0.377       |

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 \( (r = 0.393, P < 0.001) \), 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 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, HDL-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\(^{19}\). 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-
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

### 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  | 0.733  | 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 |
|-------------|---------|--------|
|             | \(\beta\) | SE | \(P\) | \(\beta\) | 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.

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 loads, genetic factors, birth weight, physical activity, puberty, ethnicity, and hormones, such as leptin, adiponectin, and ghrelin \(^{26}\). 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
drome 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\(^1\). 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\(^4\). 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\(^4\). 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.

**Acknowledgements**

None.

**Conflict of Interest**

The authors declare no conflicts of interest.

**Funding**

Supported by a grant no.2014-04 from the Kangdong Sacred Heart Hospital Fund.
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