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Serum FGF21 Levels in Obese Korean Children and Adolescents

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Background: Serum fibroblast growth factor 21 (FGF21) has been suggested to be a possible biomarker for early detection of metabolic syndrome and type 2 diabetes in adults. However, few studies have investigated the correlation between FGF21 levels and metabolic parameters in children. This study sought to evaluate the relationship between FGF21 and metabolic parameters in obese Korean children and adolescents.

Methods: Fasting serum FGF21 and adiponectin levels as well as fasting insulin, glucose, transaminases, and lipid profiles were measured by enzyme-linked immunosorbent assays in 45 lean and 70 obese children aged 7-14 years. Independent *t*-test and multivariate correlation analysis were used to evaluate the relationship between FGF21 and metabolic parameters.

Results: Serum FGF21 was significantly higher in obese children than in lean children. Serum FGF21 levels were positively correlated with insulin resistance index homeostasis model assessment (HOMA-IR) ($r=0.355$, $P=0.004$) and triglycerides ($r=0.423$, $P<0.001$) and were negatively correlated with high-density lipoprotein (HDL) cholesterol ($r=-0.412$, $P<0.001$). After adjustment for body mass index, triglycerides, HDL cholesterol and adiponectin, FGF21 levels showed a significant correlation with only HOMA-IR on multivariate linear regression analysis.

Conclusion: Serum FGF21 levels were higher in obese children and significantly correlated with HOMA-IR. Therefore, FGF21 could be a biomarker for obesity-induced insulin resistance in children and adolescents as indicated in adults.

Key words: Fibroblast growth factor, Child, Obesity, Insulin resistance

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INTRODUCTION

The high prevalence of obesity and obesity-related metabolic abnormalities (e.g., type 2 diabetes, hypertension) in children and adolescents continues to increase worldwide.[1,2] This has attracted interest to the use of biomarkers to identify persons who are at risk for the development of metabolic abnormalities and for whom preventive measures could be tailored. One interesting finding is that fibroblast growth factor 21 (FGF21) plays a central role in the maintenance of glucose and lipid homeostasis.[3]

The FGF family consists of 22 members with several biological functions (FGF1 to FGF23, where FGF15 is the rodent ortholog of human FGF19).[4-7] FGFs are categorized according to their mechanism of action as intracrine, autocrine/paracrine, or endocrine types. FGF21 is a member of the diverse endocrine FGF subordinate group within the FGF subfamily that also includes FGF19 (FGF15 in the mouse) and FGF23.[8,9]

FGF21, a 210-amino-acid polypeptide hormone, is produced preferentially in the liver and regulates glucose and fat metabolism. Serum FGF21 is elevated in adults with obesity, steatohepatitis, hy-

perlipidemia, type 2 diabetes (T2DM), metabolic syndrome (MetS), and renal failure.[10-16] Serum FGF21 levels have also been suggested to be a potential biomarker for the early detection of MetS and T2DM in adults. Early detection of MetS using biomarkers, including FGF21, can be useful, because these patients may develop T2DM, coronary heart disease, and/or stroke.[17] The development of MetS risk factors at a young age is related to significantly increased risk of morbidity and mortality during adulthood.

Consequently, the use of biomarkers for the early detection of MetS in children and adolescents is of considerable value from a public health perspective. However, only a few studies have investigated the possible correlation between FGF21 levels and metabolic parameters in children, and the findings of these pediatric studies varied. The aim of the present study was to evaluate the relationship between serum FGF21 and metabolic parameters in children

METHODS

Subjects

Forty-five lean and 70 obese Korean children aged 7 to 14 years participated in this study. Children with obesity due to secondary causes (i.e., adrenal disorder, hypothyroidism, Prader-willi syndrome) and those taking medications for illness (i.e. diabetes, dyslipidemia, hypertension, and any other infectious or chronic disease that could interfere with metabolic data) were excluded. In this study, MetS in children aged 7-14 years of age was defined according to the modified NCEP-ATP III criteria.[18,19] MetS was identified when three or more of the following five components were present: (1) abdominal obesity: a waist circumference equal to or above the sex- and age-specific 90th percentile for Korean children; (2) elevated triglycerides: ≥ 110 mg/dL; (3) low high-density lipoprotein (HDL): ≤ 40 mg/dL; (4) elevated blood pressure (BP): an systolic BP and/or a diastolic BP ≥ 90th percentile for gender and age; and (5) elevated fasting glucose: a glucose ≥ 110 mg/dL. This study was approved by the Institutional Review Board of Korea University Hospital (IRB No. ED14096). Written informed consent was obtained from all children and their parents.

Measurement and laboratory evaluation

Height was measured using a Harpenden stadiometer (Holtain, UK), to the nearest 0.1 cm. Weight was measured using a TANITA BC-418 digital weighting machine (Tanita Corp., Tokyo, Japan), to the nearest 0.1 kg. BMI was calculated as body weight divided by body height squared, and is universally expressed in units of kg/m^2, resulting from mass in kilograms and height in meters. Reference data for the year 2007 Korean children were used.[20] Obese subjects were defined as having a BMI greater than or equal to the 95th percentile for their age and gender, or as a BMI over 25.0 kg/m^2. The Tanner stage in boys and girls was evaluated using the method of Marshall and Tanner.[21,22] BP was measured using a mercury sphygmomanometer (Baumanometer, Copiague, NY, USA).[23] Systolic and diastolic BP were measured twice in the right arm after a 10 minutes rest in the supine position with a calibrated sphygmomanometer, and the measurements were averaged.

Serum FGF21, adiponectin, and insulin resistance index homeostasis model assessment (HOMA-IR) were analyzed in all subjects. All blood samples were drawn by venipuncture after overnight fasting. We analyzed fasting glucose, insulin, transaminases, and lipid profiles using standard enzymatic methods. Serum insulin levels were measured using an immunoradiometric assay kit (DIAsource, Louvain-la-Neuve, Belgium). Human FGF21 enzyme-linked immunosorbent assay (ELISA) kits were obtained from R&D Laboratory Medicine, Minneapolis, USA. Adiponectin was measured with a commercial ELISA kit (BioVendor Laboratory Medicine, Modrice, Czech Republic). The insulin resistance index (HOMA-IR) was calculated using the formula: HOMA-IR = [glucose (mg/dL) × insulin (μIU/mL)/405], based on fasting glucose values.[24]

Statistical analyses

Statistical analyses were performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). All data were expressed as mean ± standard deviation or median (IQR). Mann-Whitney test was used for comparison between obese children and normal weight children. After adjusting for age and gender, FGF21 levels were analyzed for correlations with adiponectin, BMI, BP, lipid profiles, aspartate/alanine aminotransferase (AST/ALT), and HOMA-IR using Spearman's correlation analysis.

After multicollinearity checking among explanatory variables (BMI, triglycerides, HDL cholesterol, HOMA-IR, adiponectin), multivariate analysis with multiple linear regression analyses was also

conducted using FGF21 as a dependent variable and BMI, triglycerides, HDL-cholesterol, HOMA-IR, and adiponectin as independent variables. A P of < 0.05 was considered statistically significant.

RESULTS

Comparison of clinical parameters of lean and obese children

BMI(median) of lean and obese children was 17.3 kg/m^2 and 24.6 kg/m^2, respectively. No significant differences were noted in age distribution or fasting blood glucose between these groups. Serum FGF21 levels were significantly higher in obese than in lean children ($P = 0.009$). Obese children also showed significantly higher BMI, systolic and diastolic BP, triglycerides, total cholesterol, LDL cholesterol, insulin, HOMA-IR, and ALT. Serum adiponectin and HDL cholesterol were remarkably decreased in obese children (Table 1). No significant differences were found in serum FGF21 levels according to Tanner stage ($P = 0.070$) or gender ($P = 0.182$).

Correlation between serum FGF21 levels and other clinical and metabolic parameters

In obese children, univariate correlation analysis showed a significant association between serum FGF21 levels with HOMA-IR (r = 0.355, $P = 0.004$). Serum FGF21 levels were also significantly associated with triglycerides (r = 0.423, $P < 0.001$) and HDL cholesterol (r = -0.412, $P < 0.001$), but not with BP, total cholesterol, adiponectin, or ALT. Serum FGF21 was significantly associated with only triglycerides in lean children (Table 2). However, multivariate analysis in obese children adjusted for age and sex showed an independent significant correlation between serum FGF21 levels and HOMA-IR (adjusted $R^2 = 0.238$, Obese) (Table 3).

Comparison of FGF21 according to the presence or absence of metabolic syndrome

In obese children, we compared FGF21 levels according to the presence or absence of MetS. Serum FGF21 levels were signifi-

Table 1. Comparison of clinical parameters between lean and obese children

Parameters	Lean	Obese	*P*
Male/female (n)	17/28	33/37	0.061
Prepubertal/pubertal	13/32	20/50	0.978
Age (yr)	10.6 (2.1)	10.7 (2.7)	0.884
BMI (kg/m^2)	17.3 (4.1)	24.6 (3.4)	< 0.001
Systolic BP (mmHg)	107.0 (13.5)	114.0 (15.0)	0.002
Diastolic BP (mmHg)	58.0 (6.0)	63.0 (12.5)	0.012
Triglyceride (mg/dL)	84.0 (40.0)	108.0 (71.5)	0.002
Total cholesterol (mg/dL)	156.0 (39.2)	178.0 (40.0)	0.005
LDL cholesterol (mg/dL)	85.8 (35.1)	104.0 (38.0)	0.001
HDL cholesterol (mg/dL)	50.0 (13.7)	47.0 (13.0)	0.011
Fasting glucose (mg/dL)	94.0 (8.7)	94.0 (7.5)	0.447
Insulin (μIU/mL)	8.6 (5.3)	13.7 (13.8)	0.001
FGF21 (pg/mL)	67.8 (85.0)	113.8 (151.2)	0.009
HOMA-IR	2.0 (1.3)	3.2 (3.4)	< 0.001
Adiponectin (μg/mL)	9.9 (4.1)	8.4 (3.9)	0.005
AST (IU/L)	25.0 (6.5)	27.0 (8.5)	0.091
ALT (IU/L)	13.0 (6.0)	20.0 (17.0)	< 0.001

Parameter values are expressed as mean ± standard deviation or median (IQR).
The Mann-Whitney test was used for comparison between the two groups.
BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FGF, fibroblast growth factor; HOMA-IR, homeostatic model assessment-insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IQR, inter-quartile range = 75p-25p.

Table 2. Metabolic factors associated with serum FGF21 levels

	All subjects (n = 115)		Lean (n = 45)		Obese (n = 70)	
	r	*P*	r	*P*	r	*P*
BMI (kg/m^2)	0.299	0.001	0.168	0.275	0.185	0.134
Systolic BP (mmHg)	0.454	< 0.001	-0.027	0.861	-0.006	0.964
Triglyceride (mg/dL)	0.454	< 0.001	0.384	0.010	0.423	< 0.001
Total cholesterol (mg/dL)	0.156	0.101	0.146	0.344	0.016	0.901
HDL-cholesterol (mg/dL)	-0.371	< 0.001	-0.243	0.113	-0.412	< 0.001
HOMA-IR	0.309	0.001	0.123	0.426	0.355	0.004
Adiponectin (μg/mL)	-0.133	0.164	0.050	0.748	-0.164	0.186
ALT (IU/L)	0.154	0.130	0.012	0.938	0.158	0.248

Correlations were evaluated using Spearman's correlation and were adjusted for age and sex.
FGF, fibroblast growth factor; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; ALT, alanine aminotransferase.

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Table 3. Correlation between FGF21 and HOMA-IR, BMI, lipid profiles and adiponectin

	All subjects (n=115)		Obese (n=70)	
	Standardized β	*P*	Standardized β	*P*
BMI	0.123	0.301	-0.227	0.268
Triglyceride	0.165	0.138	0.153	0.315
HDL-cholesterol	-0.082	0.436	-0.084	0.579
HOMA-IR	0.247	0.038	0.404	0.012
Adiponectin	0.033	0.730	0.081	0.523

FGF, fibroblast growth factor; HOMA-IR, homeostatic model assessment-insulin resistance; BMI, body mass index; HDL, high-density lipoprotein.

Table 4. Comparison of FGF21 according to the presence or absence of metabolic syndrome

Variable	Obese children with MetS (n=24)	Obese children without MetS (n=43)	*P*
FGF21 (pg/mL)	153.1 (137.7)	102.1 (128.6)	0.034
HOMA-IR	5.4 (3.7)	2.7 (2.0)	<0.001
Adiponectin (μg/mL)	6.9 (2.8)	8.9 (3.9)	0.011

Data are expressed as median (IQR, interquartile range).
The Mann-Whitney test was used for comparison between two groups.
FGF, fibroblast growth factor; MetS, metabolic syndrome; HOMA-IR, homeostatic model assessment-insulin resistance.

cantly higher in children with MetS ($P=0.034$) (Table 4). This indicates that FGF21 is an indicator of MetS progression rather than simple obesity.

DISCUSSION

This study evaluated the correlation of serum FGF21 levels with metabolic parameters in Korean children. The results indicated that serum FGF21 levels were remarkably increased in obese children. Serum FGF21 levels were also higher in children with MetS than children without. Our study also showed that serum FGF21 levels were related to insulin resistance.

FGF21 originates in the liver, pancreas, adipose tissue, and muscle. FGF21 in fatty tissue is an important source of the higher serum FGF21 levels observed in obese individuals. Other studies in ob/ob and db/db obese mice and in diabetic monkeys showed that direct administration of recombinant FGF21 alleviated hyperglycemia, hyperinsulinemia, and dyslipidemia.[25,26] Therefore, metabolic changes in obese children may induce resistance to FGF21 action, leading to a compensatory up-regulation and elevation of serum FGF21 levels. Previous studies also showed that serum FGF21 levels were higher in obese than in lean children.[27,28]

FGF21 has been characterized as a favorable hormone that aids in regulating glucose and lipid metabolism. In adult studies, serum FGF21 levels were associated with BMI, non-alcoholic fatty liver disease, dyslipidemia, insulin resistance, T2DM, MetS, renal failure, and coronary heart disease. Serum FGF21 levels have been suggested to be a biomarker for the early detection of MetS and T2DM in adults, but the exact mechanisms by which FGF21 mediates its actions have not been elucidated.

Not all previous studies support a clear relationship between FGF21 and insulin resistance.[27,29] In our study, multivariate analyses revealed a significant independent correlation between serum FGF21 levels and HOMA-IR. On univariate analysis, FGF21 concentration was correlated with triglycerides ($r=0.423$, $P<0.001$) and HDL-C ($r=-0.412$, $P<0.001$). After adjustment for age and sex, FGF21 concentration showed no significant relationships with TG or HDL-C. This is probably because most subjects in our study had metabolic parameter levels within normal range.

In our study, HOMA-IR was significantly correlated with BMI, serum FGF21 and adiponectin levels, whereas serum FGF21 was not related with serum adiponectin. Therefore, adiponectin does not seem to mediate the effects of FGF21 on improvement of glucose homeostasis by reducing insulin resistance in children. Some previous studies showed similar results, without any correlation between serum FGF21 levels and serum adiponectin levels.[30,31] Other previous studies have indicated that adiponectin mediates the metabolic effects of FGF21 on energy exchange and insulin sensitivity in the liver and skeletal muscle.[32,33]

Weight loss in obese children led to a decrease in serum FGF21 levels when compared to levels before weight loss.[27] Therefore, the increase in FGF21 would appear to be a consequence, rather than a cause, of childhood obesity. The increase in FGF21 stimulates both adiponectin expression and secretion in adipocytes.[33] We suggest that increasing BMI causes elevated FGF21 levels and stimulates adiponectin secretion. However, previous studies showed a paradoxical decrease in serum adiponectin with increasing BMI.[34] This conflicting finding may explain why no correlation was found between serum FGF21 levels and serum adiponectin levels in the present study.

Previous studies showed that serum FGF21 levels are associated

with liver fat content, cytokeratin 18 (a marker of hepatic apoptosis), and ALT levels in children.[27,28] Our study indicated that serum FGF21 levels were not significantly correlated with ALT levels, most likely because the degree of obesity was relatively homogeneous in obese children.

This study used a cross-sectional design with potential selection bias, and causality cannot be proven based on these findings, which are limitations of this research.

In conclusion, our study indicated that serum FGF21 was remarkably higher in obese Korean children and was independently correlated with the insulin resistance index. Serum FGF21 levels might be a biomarker for metabolic disorders in children, but further longitudinal studies will be needed for confirmation.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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