



ORIGINAL ARTICLE

Relationship between Serum Levels of Body Iron Parameters and Insulin Resistance and Metabolic Syndrome in Korean Children

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Abstract

Objectives: An increase in serum ferritin and levels of the cleaved soluble form of transferrin receptor (sTfR) are related to several metabolic conditions. We evaluated the relationship between body iron status indicators, including ferritin and sTfR, and insulin resistance and metabolic syndrome (MetS) in Korean children.

Methods: A cross-sectional study was conducted on 1350 children in Korea. Anthropometrical parameters; lipid profiles; levels of glucose, insulin, and leptin; and iron status indicators, including sTfR, serum ferritin, serum iron, total iron-binding capacity (TIBC), and transferrin saturation (TS), were analyzed.

Results: Although serum sTfR levels were significantly higher in boys than in girls (2.20 vs. 2.06 mg/L, $p < 0.0001$), serum iron and TS were higher in girls than in boys (101.38 vs. 95.77 mg/L, $p = 0.027$ and 30.15 vs. 28.91%, $p = 0.04$, respectively). Waist circumference (WC) and leptin were most significantly associated with body iron indicators when adjusted for age and sex. After adjusting for age, sex, and WC, sTfR levels showed the strongest positive association with leptin levels ($p = 0.0001$). Children in the highest tertile for homeostasis model assessment-insulin resistance (HOMA-IR) had higher TIBC ($p = 0.0005$) and lower serum iron ($p = 0.0341$), and the lowest TS ($p < 0.0001$) after adjustment for confounders. Children with higher sTfR were most significantly associated with risk of MetS compared with those lower sTfR ($p = 0.0077$).

Conclusion: The associations of serum levels of iron metabolism markers with leptin levels, HOMA-IR, and MetS suggest that iron-related factors may involve insulin resistance and MetS.

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1. Introduction

Iron plays a key role in many biological processes such as erythrocyte production, DNA synthesis, and cellular respiration [1,2]. The liver acts as the central organ in the regulation of body iron stores, and it carries the main burden in situations of iron overload [3]. Clinical measurement of iron storage is assessed by serum ferritin levels, and low serum ferritin indicates depleted iron stores. The homeostatic iron system maintains transferrin saturation (TS) at physiological levels, and it responds to signals from pathways that consume iron and sends signals to cells that supply iron to the bloodstream [4]. Most iron is loaded to serum transferrin, which binds to transferrin receptors (TfR) on target cells. Soluble TfR (sTfR) is released from microsomal membranes and directly regulates the binding of its ligand ferritransferrin in response to iron availability [5]. Released sTfR concentrations reflect the cellular expression level of membrane TfR and cellular iron demands.

The development of metabolic syndrome (MetS) clustering obesity, hypertension, and insulin resistance increases body iron stores. Previous studies have reported higher ferritin levels in individuals with MetS [6–8]. A recent study used serum sTfR levels as a body iron indicator of iron sufficiency or iron depletion in obese European adolescents [9,10]. Also, insulin inducing iron transport and accumulation in hepatocytes stimulates iron uptake in fat cells and redistributes intracellular TfRs to the cell surface [11]. Moreover, TfRs and insulin-like growth factor 2 (IGF2) 2 receptors in vesicles from cultured adipocytes colocalize with intracellular glucose transporters [12]. Serum sTfRs concentrations had been reported to be influenced by insulin secretion and insulin sensitivity in individuals with normal glucose tolerance [13]. The relationship between body iron status indicators and MetS in the general pediatric population does, however, remain unclear.

We therefore conducted a population-based cross-sectional study including Korean elementary students to determine the relationships between indicator of iron status and pediatric overweight measurements, homeostasis model assessment-insulin resistance (HOMA-IR), and MetS. The objective was to investigate whether serum sTfR levels indicate body iron status and which indicators of iron status are related to childhood insulin resistance and MetS.

2. Materials and methods

2.1. Study population

This study was conducted as part of the Korean Pediatric Cohort Study, which was designed to follow a cohort of Korean students from their entry into

elementary school at age 7 years, to their graduation at age 13 years in Kyunggi Province and Seoul, Korea. The overall objective of the cohort study was to identify early risk factors for obesity and associated metabolic diseases in urban Korean children. The sole inclusion criterion was being enrolled in first grade in 2005 and 2008, and no exclusion criteria were applied. The children were to receive physical examinations annually and to provide blood samples for the measurement of levels of leptin, insulin, and indicators of body iron status. Children ($n = 1350$; 682 boys and 668 girls) aged 7 years and 10 years in 2008 were included in the present study. This study was approved by the Institutional Review Board of Inje University Seoul-Paik Hospital, Seoul, Korea and the Korean Center for Disease Control and Prevention. Written informed consent was obtained from the children's parents.

2.2. Anthropometric measurements

Height was measured using an automatic stadiometer (DS-102; Jenix, Seoul, Korea). Weight and percent body fat were measured via bioimpedance using a body composition analyzer (BC418; Tanita, Tokyo, Japan). Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. Waist circumference (WC) was measured at the midpoint between the lower border of the ribcage and the iliac crest using a nonelastic tape measure. Blood pressure was measured twice on the right arm using a mercury sphygmomanometer while the individual was resting in a seated position.

2.3. Biochemical analyses

After a 12 hour overnight fast, blood samples were collected from the antecubital vein into Vacutainer tubes (BD, Franklin Lakes, NJ USA). Triglyceride (TG) and high-density lipoprotein cholesterol (HDL) levels were measured via enzymatic assays and an autoanalyzer (model 7180; Hitachi, Tokyo, Japan). Fasting serum glucose levels were measured using the hexokinase method and a glucose analyzer (model 7180; Hitachi). Fasting serum insulin levels were measured using a radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles, CA, USA). Fasting serum leptin levels were determined using a kit from Linco Research (St. Charles, MO, USA). The HOMA-IR score, an estimate of insulin resistance, was calculated as [fasting serum insulin level ($\mu\text{IU/mL}$) \times fasting serum glucose level (mmol/L)]/22.5 [14]. Serum iron levels and total iron-binding capacity (TIBC) were measured using the FerroZine method and a Cobas Integra 800 analyzer (Roche, Mannheim, Germany). Ferritin levels were determined via chemiluminescence immunoassays (CLIA) and an autoanalyzer (model ADVIA CENTAUR; Bayer, USA). sTfR was measured using an enzyme immunoassay kit (Molecular Device, Sunnyvale, CA, California, USA). We defined MetS status in

7–10 year-old Korean children using modified the National Cholesterol Education Program Adult Treatment Panel III for adolescents by Cook ≥ 3 of the following: WC $\geq 90^{\text{th}}$ percentile (age, sex, ethnicity specific), TG ≥ 110 mg/dL, HDLC ≤ 40 mg/dL, $\geq 90^{\text{th}}$ percentile (age, sex, height specific), glucose ≥ 110 mg/dL; the cut off values for WC and blood pressure were based on the 2007 Korean Growth Charts [15,16].

2.4. Dietary intake

The children's questionnaire was brief, easy to read, self-explanatory, and thus age appropriate. Questionnaires that were completed by the children and their parents at home were used to determine dietary intake. The study protocol was approved by the regional ethical committees, and informed consent was obtained from the parents of the children and from adults prior to participation in the study. The typical dietary intake of each child was estimated based on food records that were maintained by each child with help from his or her parents for 3 consecutive days (2 weekdays, 1 weekend day). Parents were also asked to maintain 3-day food records for their children. Recipes of school meals (lunches) were provided to the parents. Dietary questionnaires, which were certified by Seoul-Paik Hospital, Inje University, were confirmed as eliciting sufficient dietary information. Prior to starting the study, guidelines of food records were provided for a meaningful reply to children and their parents. The guidelines were as follows: (1) record your typical diet; (2) include all beverages, meals, snacks, and tastes in total intake; (3) be as specific as possible about the foods and drinks – seasonings, ingredients, preparation methods, and other details; and (4) record portion size using kitchen utensils, nutrition facts label, and other measurements – volume (1 cup, 1 tablespoon, 2 cm \times 5 cm \times 1 cm), weight (5 g), size (small, medium, large), and count (2 pieces of chocolate). Food intake was analyzed for nutrient intake using the Computer Aided Nutritional Analysis version 3.0 for professional (CAN-pro 3.0) software program. The software was made for the purpose of easy and precise nutrition assessment and management by the Korean Nutrition Society (Seoul, Korea). The software included approximately 3500 commonly consumed Korean foods and was based on the Korean Nutrient Database. To obtain the information for various nutrients in food, we entered the food name, amount, and other details into the CAN-pro software and got results for vitamins and minerals.

2.5. Statistical analyses

Statistical analyses were performed with SAS software (version 9.1; SAS institute, Cary, NC, USA), and the values are presented as the mean \pm standard deviation (SD) for continuous variables or as raw numbers and percentages for categorical variables. The mean

values for each sex were compared using the Student *t* test. The Chi-square test was used to compare prevalence data, and associations among variables were expressed as Pearson's correlation coefficients. To evaluate HOMA-IR levels, individuals were classified into three tertiles according to their HOMA-IR levels. HT3 indicated the highest HOMA-IR tertile. Differences between the three tertiles were evaluated using a one-way analysis of variance test. When statistically significant effects were demonstrated, Duncan's *post hoc* test was used to identify group differences at $p < 0.05$. Differences between no MetS and MetS individuals were evaluated using a regression analyses at significance level of $p < 0.05$ after adjustments for age and sex.

3. Results

The general characteristics of the study participants are presented in Table 1. The mean age was 9.19 years, and no age difference existed between boys and girls. The sexes did differ in weight, BMI, BMI percentile, percent body fat, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), and levels of total cholesterol, TG, HDLC, glucose, insulin, sTfR, serum iron, and serum TS. sTfR levels were significantly higher in boys (2.20 mg/L) than in girls (2.06 mg/L) ($p < 0.0001$), and serum iron and TS were higher in girls than in boys (101.38 mg/L vs. 95.77 mg/L, $p = 0.027$ for iron; 30.15% vs. 28.91%, $p = 0.04$ for TS). TIBC and serum ferritin levels were slightly higher in girls than in boys. No differences in dietary iron or vitamin C intake were detected between boys and girls. The prevalence of MetS was 3.78% (3.08% in boys and 4.49% in girls) and did not differ between the sexes.

Anthropometric and biochemical variables closely correlated with iron status variables in children (Table 2). Iron status indicators also correlated significantly with each other (data not shown). WC was highly correlated with iron status variables when adjusted for age and sex. The correlation coefficients for the association between WC and serum ferritin, sTfR, sTfR/log ferritin ratio, serum iron, TIBC and TS were, respectively, 0.07 ($p = 0.008$), 0.21 ($p < 0.001$), 0.11 ($p < 0.001$), -0.13 ($p < 0.001$), 0.08 ($p = 0.003$), and -0.17 ($p < 0.001$). Leptin levels significantly correlated with iron status variables when adjusted for age and sex. The correlation coefficients for the association of leptin with sTfR, sTfR/log ferritin ratio, serum iron, TIBC, and TS were, respectively, 0.18 ($p < 0.001$), 0.10 ($p = 0.05$), -0.18 ($p < 0.001$), 0.20 ($p < 0.001$), and -0.25 ($p < 0.001$). sTfR was positively correlated with all anthropometric variables, total cholesterol, TG, and leptin. It was negatively correlated with HDLC although not significantly. TS was, however, negatively correlated with anthropometric variables, TG, HOMA-IR,

Table 1. General characteristics of the study participants.

Characteristic	Total (n = 1350)	Boys (n = 682)	Girls (n = 668)
Age (y)	9.19 ± 1.30	9.24 ± 1.29	9.15 ± 1.30
Height (cm)	135.41 ± 9.80	135.83 ± 8.61	134.98 ± 10.86
Weight (kg)	33.09 ± 8.70	34.01 ± 8.71	32.15 ± 8.59*
BMI (kg/m ²)	17.75 ± 3.00	18.17 ± 3.10	17.32 ± 2.83*
BMI percentile (%)	42.17 ± 30.84	44.08 ± 31.25	40.23 ± 30.31*
Body fat (%)	20.96 ± 7.82	20.32 ± 8.50	21.60 ± 7.03*
WC (cm)	61.42 ± 8.62	62.81 ± 8.65	60.01 ± 8.34*
SBP (mmHg)	103.66 ± 13.76	104.86 ± 13.36	102.44 ± 14.06*
DBP (mmHg)	68.09 ± 9.88	68.91 ± 9.62	67.25 ± 10.08*
Total cholesterol (mg/dL)	169.65 ± 25.92	167.64 ± 24.81	171.70 ± 26.87*
TG (mg/dL)	68.38 ± 39.91	63.40 ± 38.47	73.46 ± 40.73*
HDLC (mg/dL)	58.49 ± 11.34	59.74 ± 11.45	57.21 ± 11.09*
Glucose (mg/dL)	85.47 ± 7.28	86.20 ± 7.71	84.72 ± 6.75*
Insulin (uIU/mL)	5.25 ± 3.87	4.99 ± 3.64	5.51 ± 4.07*
HOMA-IR	1.13 ± 0.84	1.09 ± 0.80	1.17 ± 0.87
Leptin (ng/mL) ^a	5.45 ± 4.09	5.14 ± 4.05	5.78 ± 4.11
Hb (g/dL)	13.37 ± 0.85	13.36 ± 0.88	13.37 ± 0.82
Serum ferritin (ng/mL)	36.87 ± 19.53	36.68 ± 18.39	37.06 ± 20.64
sTfR (mg/L)	2.13 ± 0.63	2.20 ± 0.64	2.06 ± 0.61*
sTfR/log ferritin	0.64 ± 0.27	0.65 ± 0.26	0.63 ± 0.28*
Serum iron (μg/dL)	98.55 ± 35.85	95.77 ± 36.22	101.38 ± 35.28*
TIBC (μg/dL)	336.60 ± 59.88	335.51 ± 61.87	337.71 ± 57.81
TS (%)	29.52 ± 10.26	28.91 ± 10.57	30.15 ± 9.90*
Dietary iron (mg/d) ^b	11.91 ± 3.33	12.01 ± 3.48	11.81 ± 3.17
Dietary vitamin C (mg/d) ^b	81.83 ± 46.10	82.13 ± 49.74	81.54 ± 42.25
Prevalence of MetS ^c	51/(3.78)	21 (3.08)	30 (4.49)

^aLeptin (n = 426, boys n = 220, girls n = 206); ^bDietary iron and vitamin C (n = 1074, boys n = 533, girls n = 541); ^cMetS was defined as Modified NCEP-ATP III by Cook [≥ 3 of the following: WC $\geq 90^{\text{th}}$ percentile (age, sex, ethnicity specific), TG ≥ 110 mg/dL, HDLC ≤ 40 mg/dL, blood pressure $\geq 90^{\text{th}}$ percentile (age, sex, height specific), glucose ≥ 110 mg/dL; the cut off values for WC and blood pressure were based on the 2007 Korean Growth Charts]. Data are expressed as the mean \pm SD or n (%). *Significant difference ($p < 0.05$) between boys and girls by Student t test. BMI = body mass index; DBP = diastolic blood pressure; Hb = hemoglobin; HDLC = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment insulin resistance (n = 1215, boys n = 612, girls n = 603); MetS = metabolic syndrome; SBP = systolic blood pressure; sTfR = serum transferrin receptor; TG = triglyceride; TIBC = total iron-binding capacity; TS = transferrin saturation; WC = waist circumference.

and leptin, and TS was positively correlated with HDLC. When adjusted for age, sex, and WC, serum ferritin showed no association with leptin, and sTfR showed the strongest association with leptin ($r = 0.19$, $p = 0.0001$; Figure 1). Any iron indicators were not correlated with dietary iron or vitamin C intake except ferritin, but serum ferritin levels showed a negative correlation with dietary vitamin C intake ($r = -0.06$, $p = 0.04$; data not shown).

The iron status variables also were analyzed according to tertiles of HOMA-IR levels among study participants (Table 3). Several iron status parameters were significantly different among groups of individuals in each HOMA-IR tertile after adjustments for age, sex, and WC. The mean HOMA-IR level for each group was 0.50, 0.92, and 1.98 for HT1, HT2, and HT3, respectively and TIBC, serum iron, and TIBC levels were significantly different between groups of the HOMA-IR tertiles. Children in HT3 had significantly greater TIBC ($p = 0.03$) and lower serum iron ($p = 0.0005$) and TS ($p < 0.0001$) than did children in HT1. Hemoglobin (Hb), serum ferritin, sTfR and sTfR/

log ferritin ratio showed no association with HOMA-IR according to tertiles of HOMA-IR among study participants.

When children were separated by MetS status, sTfR, serum iron, and TS levels were significantly different between no MetS and MetS groups (Table 4). Children with MetS had greater sTfR ($p < 0.0077$), lower serum iron ($p = 0.0464$) and TS ($p = 0.0238$) levels than those without MetS. Serum ferritin levels tended to be greater in children with MetS than in those without MetS, but this was not statistically significant.

4. Discussion

Although the prevalence of pediatric MetS is increasing throughout the world [17,18], and iron is important in numerous biological processes [1–4], little information exists on the relationship between MetS clustering obesity, hypertension, and insulin resistance and body iron status indicators in the general pediatric population. Thus, in this study, we investigated the

Table 2. Pearson's correlation coefficients for the association between iron status indicators and biochemical/anthropometric variables adjusted by age and sex.

	Hb ^a	Serum ferritin	sTfR	sTfR/log ferritin	Serum iron	TIBC	TS (%)
Height (cm)	0.07*	0.00	0.09**	0.05	-0.04	0.04	-0.07*
Weight (kg)	0.03	0.07*	0.15**	0.06*	-0.08*	0.12**	-0.15**
BMI (kg/m ²)	0.03	0.09*	0.14**	0.06*	-0.08*	0.13**	-0.15**
BMI percentile (%)	0.04	0.09*	0.13**	0.04	-0.08*	0.14**	-0.14**
Body fat (%)	0.04	0.15**	0.14**	0.03	-0.10**	0.14**	-0.16**
WC (cm)	0.01	0.07*	0.21**	0.11**	-0.13**	0.08*	-0.17**
SBP (mmHg)	-0.07*	0.03	0.12**	0.07*	-0.06*	0.03	-0.08**
DBP (mmHg)	-0.02	0.04	0.04	0.01	-0.04	0.03	-0.07*
Total cholesterol (mg/dL)	0.06*	0.06*	0.07*	0.04	0.06*	0.07*	0.02
TG (mg/dL)	0.06*	0.03	0.07*	0.01	-0.03	0.12**	-0.09*
HDLC (mg/dL)	0.07*	-0.10*	-0.04	0.02	0.11**	0.02	0.09**
Glucose (mg/dL)	-0.02	-0.04	0.03	0.03	-0.09*	0.04	-0.12**
Insulin (uIU/mL) ^b	0.06	0.03	-0.02	-0.04	-0.09*	0.10**	-0.14**
HOMA-IR ^b	0.06*	0.03	-0.02	-0.03	-0.10**	0.11**	-0.15**
Leptin ^c	0.09	0.03	0.18**	0.10*	-0.18**	0.20**	-0.25**

^aHb ($n = 1276$); ^bInsulin and HOMA ($n = 1174$); ^cLeptin ($n = 417$). BMI = body mass index; DBP = diastolic blood pressure; Hb = hemoglobin; HDLC = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment insulin resistance; SBP = systolic blood pressure; sTfR = soluble transferrin receptor; TG = triglyceride; TIBC = total iron-binding capacity; TS = transferrin saturation; WC = waist circumference. * $p < 0.05$. ** $p < 0.01$.

association between serum iron status markers and anthropometric variables and obesity-related metabolic risk factors among children. Our study targeted a general pediatric population living in a typical Korean town. We found that iron status indicators were more closely associated with WC and leptin than with weight, BMI, plasma lipid levels, or HOMA-IR scores. Also, anthropometric/biochemical variables were more highly correlated with sTfR and TS than with serum iron, TIBC, serum ferritin, and sTfR/log ferritin ratio. When adjusted for age, sex, and WC, sTfR showed the strongest association with leptin and low TS was most significantly associated with insulin resistance. The

prevalence of MetS occurred in the higher level of serum sTfR.

sTfR is a determinant of a reduced iron supply at tissue levels. The concentration of sTfR starts to increase as the iron deficiency progresses beyond a depletion of iron stores and iron is not supplied in adequate amounts for erythropoiesis [19]. Higher sTfR levels were presented in children with abdominal obesity, a MetS component, as previously shown [7,20] and strongly associated with plasma leptin concentration, even when adjusted for abdominal obesity. The adipokine, leptin, is involved with iron metabolism through binding to signal transducer and activator of transcription 3 (STAT3) and the expression of hepatic hepcidin [21]. Because iron availability for erythropoiesis is reduced in children with abdominal obesity, sTfR indicates the imbalance between iron supply and iron requirement and leptin from adipose tissue positively activates circulating hepcidin increases.

In the present study, serum sTfR and ferritin levels did not show the relation with glucose metabolism components such as plasma glucose, insulin, and HOMA-IR. HOMA-IR levels were related to serum iron, TIBC, and TS. When our study participants were divided into three tertiles according to HOMA-IR levels, the effects of TIBC on HOMA-IR were positively noted. Children in the highest tertile for HOMA-IR showed higher TIBC and lower serum iron and TS when compared with children in the lower HOMA-IR tertiles. Serum sTfR concentrations influenced by insulin secretion and insulin sensitivity did not present the correlation with HOMA-IR in our children with normal glucose tolerance. The relationship between elevated

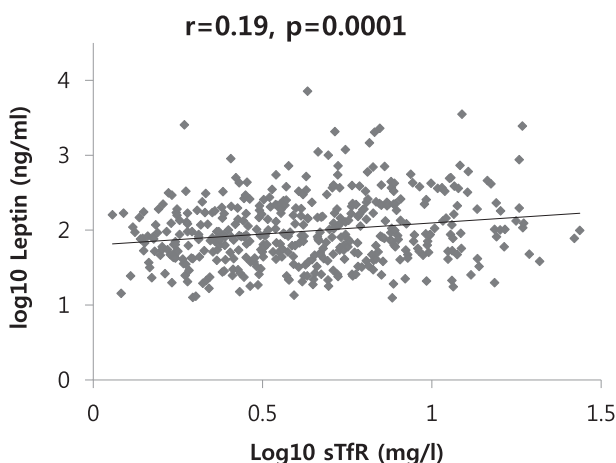


Figure 1. Pearson's correlation between soluble transferrin receptor (sTfR) and leptin. Correlation coefficient and p value adjusted by age, sex, and waist circumference (WC) are shown.

Table 3. Iron status indicators for the study participants grouped according to the homeostasis model assessment insulin resistance (HOMA-IR) tertile (HT).

	HT1 (0.14–0.7)	HT2 (0.71–1.14)	HT3 (1.15–7.48)	<i>p</i>
HOMA-IR level	0.50 ± 0.14 ^c	0.92 ± 0.1 ^b	1.98 ± 0.96 ^a	<0.0001
Hb	13.30 ± 0.81	13.43 ± 0.78	13.45 ± 0.88	0.0648
Serum ferritin (ng/mL)	34.94 ± 18.35	35.87 ± 19.58	38.04 ± 19.17	0.7579
sTfR (mg/L)	2.13 ± 0.61	2.16 ± 0.61	2.12 ± 0.64	0.0818
sTfR/log ferritin	0.65 ± 0.27	0.66 ± 0.30	0.63 ± 0.26	0.1874
Serum iron (µg/dL)	103.33 ± 35.84 ^a	96.48 ± 36.27 ^b	95.29 ± 34.44 ^b	0.0341
TIBC (µg/dL)	324.77 ± 55.97 ^c	336.48 ± 60.14 ^b	344.77 ± 60.63 ^a	0.0005
TS (%)	32.00 ± 10.13 ^a	28.80 ± 10.20 ^b	27.79 ± 9.67 ^c	<0.0001

a, b or c Means within a row with different superscripts (a, b, or c) are significantly different ($P < 0.05$) by Duncan's test after adjustments for age, sex and waist circumference. Data are expressed as the mean ± SD. sTfR = soluble transferrin receptor; TS = transferrin saturation.

body iron stores and insulin resistance or MetS is well illustrated in clinical manifestation and practice [6–10,13,14,16–18]. Of note, serum ferritin levels were associated with insulin resistance and fatty liver disease in patients without iron overload [22]. HOMA-IR levels were correlated with serum ferritin levels in a cohort of morbidly obese French children [23] and with sTfR/ferritin ratio in teenage females [24] regardless of liver transaminase activity. Recently, ferritin, transferrin, serum iron, and non-transferrin binding iron (NTBI) showed the association not only with HOMA-IR, but also with adipocyte insulin resistance after adjustment for a broad range of covariates including inflammatory markers [25]. In the high-fat/high-energy diet mouse model of insulin resistance, the mean values of transferrin concentration were higher and TS lower in the high-fat/high-energy diet group as compared to the normal diet group, although iron metabolism has not been assessed [26]. This study is in concordance with our current childhood observation that HOMA-IR had a significant association with TS but not serum ferritin. Furthermore, the National Health and Nutrition Examination Survey (NHANES) data most recently reported that lower TS showed a robust association with glycohemoglobin (HbA1C), fasting glucose, insulin, and

HOMA-IR in a US representative population with pre-diabetes [27]. These findings suggest that low TS, a measure of serum iron bound to transferrin, accounts for poor glycemic outcome.

Among body iron indicators, serum ferritin was recently well studied and found to have an association with MetS. A normal high level of ferritin is associated with MetS components such as high blood pressure and glucose, TGs, low HDLC, and abdominal adiposity. Recently, one Korean and two Chinese big population studies reported the association of serum ferritin and risk of MetS in Asia [6,8,28]. The participants with higher risks for MetS had the highest serum ferritin quartile compared with those with the lowest. However, the association study of body iron status and oxidative stress factors with MetS described that individuals with MetS presented low TfR, despite the increase of plasma ferritin [29]. Also, individuals with an abdominal adiposity component of MetS showed higher levels of sTfR, although sTfR presented no significant difference between participants with or without MetS in the population based case control study [7]. More importantly, plasma levels of sTfR in the MetS group children with low serum iron and TS were higher compared to the no MetS group children in this study.

Table 4. Iron status indicators of children by metabolic syndrome status (MetS).

Characteristic	No MetS ^a (<i>n</i> = 1299)	MetS (<i>n</i> = 51)	<i>p</i>
Hb (g/dL)	13.37 ± 0.84	13.35 ± 1.02	0.7629
Serum ferritin (ng/mL)	36.67 ± 19.58	41.94 ± 17.82	0.1544
sTfR (mg/L)	2.13 ± 0.64	2.34 ± 0.79	0.0077
sTfR/log ferritin	0.64 ± 0.27	0.65 ± 0.24	0.4872
Serum iron (µg/dL)	98.89 ± 35.63	89.88 ± 40.58	0.0464
TIBC (µg/dL)	336.41 ± 59.62	341.49 ± 66.70	0.8301
TS (%)	29.64 ± 10.20	26.40 ± 11.21	0.0238

^aMetS, was defined as Modified NCEP-ATP III by Cook [≥ 3 of the following: WC $\geq 90^{\text{th}}$ percentile (age, sex, ethnicity specific), TG ≥ 110 mg/dL, HDLC ≤ 40 mg/dL, blood pressure $\geq 90^{\text{th}}$ percentile (age, sex, height specific), glucose ≥ 110 mg/dL; the cut off values for WC and blood pressure were based on the 2007 Korean Growth Charts]. Data are expressed as the mean ± SD. Hb = hemoglobin; sTfR = soluble transferrin receptor; TIBC = total iron-binding capacity; TS = transferrin saturation.

In conclusion, serum levels of sTfR were increased in children with high levels of leptin and MetS. sTfR showed an inverse relationship with serum iron and TS as a sensitive indicator of decreased body iron status. Moreover, the decrease of TS in children associated with HOMA-IR reflects that iron metabolism and/or the iron stores in the body are involved in the development of glycemic outcome. These results suggest that changes in circulating iron metabolism-related factor levels among the general pediatric population might be a marker for insulin resistance and MetS.

Conflicts of interest

The authors declare that they have no competing interests.

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