

# Association of thyroid hormones with obesity and metabolic syndrome in Japanese children

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**Obesity is associated with health consequences, and thyroid dysfunction may be an adaption to the increased energy expenditure in obesity. With the rising prevalence of obesity in childhood, the prevalence of metabolic syndrome may also increase. In the current study, we have shown gender differences in the association of thyroid hormones with obesity, and attempted to elucidate the relationship between thyroid hormones and anthropometric parameters and biochemical data in obese Japanese children. We analyzed anthropometric measurements, blood pressure, body composition, thyroid hormones, and lipid profiles in 283 obese children. The association between thyroid hormones and several parameters differed by gender. The free T3 to free T4 ratio (fT3/fT4) in boys was negatively associated with the quantitative insulin sensitivity check index, whereas in girls, thyroid-stimulating hormone levels were positively correlated with levels of glucose, diastolic blood pressure, and non-high density lipoprotein-cholesterol, and fT3/fT4 was positively correlated with uric acid levels. fT3/fT4 in boys with metabolic syndrome was relatively higher than in those without metabolic syndrome. The cause of gender differences is unknown. Therefore, further studies with larger sample sizes and a long-term follow-up period are needed to address the influence of thyroid hormones on various parameters.**

**Key Words:** thyroid hormone, obesity, metabolic syndrome, children

The prevalence of obesity and overweight in children and adolescents has been increasing in recent decades around the world.<sup>(1)</sup> Obesity in children is associated with negative health consequences including hypertension, dyslipidemia, insulin resistance, and cardiovascular disease. Moreover, obesity is a social problem, in that treating obesity-related diseases raises medical cost.<sup>(1)</sup> Thus, preventing overweight and obesity is becoming increasingly important.<sup>(2)</sup> Notably, lifestyle intervention is recommended as the initial therapy for obesity in children.<sup>(3)</sup>

Metabolic syndrome in adulthood consists of metabolic risk factors including obesity, hypertension, dyslipidemia, and insulin resistance, accompanied with the development of cardiovascular disease caused by atherosclerosis and type 2 diabetes. Diagnostic criteria for pediatric metabolic syndrome have been proposed by several groups around the world,<sup>(4)</sup> however a uniform standard has not been set. The uncertainty in the diagnosis of metabolic syndrome in children and adolescents may affect how well children are screened for metabolic syndrome. With the rising prevalence of obesity in childhood and adolescence, the prevalence of metabolic syndrome may be increasing. Early-childhood interventions are needed to reduce the incidence of metabolic syndrome.<sup>(5)</sup>

Thyroid hormones regulate basal metabolic rate and affect lipid

metabolism thermogenesis. Thyroid functions are exerted by signal transduction from the thyroid hormone receptor, a member of the nuclear superfamily of hormone receptors.<sup>(6)</sup> The mechanisms underlying the alteration of thyroid function in obesity have yet to be determined. Thyroid dysfunction may be an adaptation to the increased energy expenditure in obesity.<sup>(7)</sup> Thyroid-stimulating hormone (TSH) may be elevated for several reasons, including subclinical hypothyroidism caused by iodine deficiency, autoimmune thyroiditis, or non-synonymous mutations of the TSH gene. Moreover, increased production of pro-thyrotropin mediated by leptin, thyroid hormone resistance, or mitochondrial dysfunction have been observed in obesity.<sup>(7)</sup>

A number of studies regarding the association of thyroid function with obesity and metabolic syndrome have been reported in children and adults.<sup>(6,7)</sup> However, to the best of our knowledge, there are very few reports on the role of gender in the association of thyroid function with obesity in Asian children. The purpose of the current study is to identify gender differences in the association between thyroid function and obesity, and to elucidate the relationship between thyroid hormones and anthropometric parameters and biochemical data in obese Japanese children. In addition, we attempted to evaluate the association of thyroid hormones with metabolic syndrome in children.

## Subjects and Methods

**Subjects.** A total of 283 obese Japanese children, including 161 boys and 122 girls, were enrolled in this study from 2009 to 2012. They attended the clinic for obese children at the Department of Pediatrics of Osaka Medical College Hospital (Osaka, Japan) in the morning after an overnight fast and no strenuous exercise during the previous day. Blood samples were taken and anthropometric measurements were obtained, including height, weight, and waist circumference. The age of the children ranged from 6 to 15 years. They had no endocrine, metabolic, or renal diseases and no conditions other than obesity. Obesity was defined as a body weight exceeding 120% of the standard body weight, which was defined as the mean body weight for height and age based on national statistics for Japanese school children in 2000.<sup>(8)</sup> The Japanese Ministry of Health, Labor and Welfare has adopted this percentage of weight (POW) criterion based on the age- and sex-specific standard body weight for height. This study was approved by the ethics committee of Osaka Medical College (approval code; 1473) and informed consent was obtained from the parents of all the subjects for participation.

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**Measurement of anthropometric data and blood pressure.** Anthropometric measurements were always performed by the same medical staff at the clinic of the Department of Pediatrics of Osaka Medical College Hospital, as described previously.<sup>(9)</sup> Waist circumference (WC) was measured at the level of the umbilicus to the nearest millimeter using a plastic measuring tape. The blood pressure (BP) was measured in the right arm three times consecutively using an automated sphygmomanometer and the third measurement was used for analysis. Obesity was defined using POW, and the comparison of obesity was evaluated using body mass index–standard deviation score (BMI-SDS). BMI-SDS and height-SDS were calculated as each divided by the BMI or height at the 50th percentile for age and sex, respectively.<sup>(10)</sup> Body composition was estimated by determining the body fat percentage, which is calculated using a biochemical impedance analyzer SS-103 (Sekisui Chemical Co., LTD., Tokyo, Japan) as previously described.<sup>(11)</sup>

**Biochemical data.** Blood samples were obtained from children after an overnight fast, and the serum levels of total cholesterol, triglycerides, alanine aminotransferase (ALT), glucose, and uric acid were measured with the AU5800 automated analyzer (Beckman Coulter, CA). High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were quantified using an enzymatic method. Non HDL-C was calculated by subtracting LDL-C from total cholesterol. Insulin, TSH, free thyroxine (fT4), and free triiodothyronine (fT3) were quantified using an electrochemiluminescence immunoassay. The reference ranges for TSH, fT4, and fT3 are 0.5–5.0  $\mu$ IU/ml, 0.9–1.7 ng/dl, and 2.3–4.3 pg/ml, respectively. The degree of insulin resistance was quantified using the homeostatic model assessment ratio (HOMA-R), [insulin (mU/L)  $\times$  glucose (mg/dl)/405]. The quantitative insulin sensitivity check index (QUICKI) was calculated as previously described.<sup>(12)</sup>

**Definition of metabolic syndrome.** We used the definition of metabolic syndrome established by a task force that was

supported by Health and Labour Science Research Grants in Japan, which investigated metabolic syndrome in children aged 6–15 years.<sup>(13)</sup> Metabolic syndrome in children aged 6–15 years was defined as WC  $\geq$ 75 cm (<13 years old) or WC  $\geq$ 80 cm ( $\geq$ 13 years old) or waist-to-height ratio  $\geq$ 0.5; triglycerides  $\geq$ 120 mg/dl, and/or HDL  $\leq$ 40 mg/dl; systolic BP  $\geq$ 125 mmHg and/or diastolic BP  $\geq$ 70 mmHg; and/or fasting plasma glucose  $\geq$ 100 mg/dl. Metabolic syndrome was defined as two or three positive risk factors (dyslipidemia, hyperglycemia, and hypertension) in addition to a high WC in obese children.

**Statistical analysis.** All analyses were performed with the SPSS program (SPSS Inc., Chicago, IL). All values are expressed as the mean  $\pm$  SD. Histograms were used to evaluate the normal distribution of the variables. Group differences between boys and girls were calculated using the unpaired *t* test. A multiple stepwise linear regression analysis was performed in order to investigate the possible association between each thyroid hormone and other variables. Each thyroid hormone was used as the dependent variable, and age, height-SDS, BMI-SDS, total body fat, systolic/diastolic blood pressure, glucose, insulin, QUICKI, HOMA-R, total cholesterol, triglycerides, non-HDL-C, LDL-C cholesterol, ALT, and uric acid were set as independent variables. The prevalence of metabolic syndrome was analyzed using the unpaired *t* test. A *p* value of less than 0.05 indicated statistical significance.

## Results

**Subject characteristics.** The clinical and biochemical characteristics of the 283 children are shown in Table 1. Height-SDS, WC, and body fat percentage were higher in boys than in girls. Triglycerides levels were higher in girls than in boys, whereas ALT and fT4 levels were higher in boys than in girls.

**Subject characteristics according to serum TSH.** Histograms of serum TSH of obese boys and girls, respectively, are shown in Fig. 1. The obese boys and girls were divided into two

**Table 1.** Characteristics of all obese boys and girls

	Boys (n = 161)	Girls (n = 122)	<i>p</i> value
Age (years)	9.51 $\pm$ 1.91	9.54 $\pm$ 2.24	0.898
Physical Data			
Height-SDS	0.69 $\pm$ 1.02	0.20 $\pm$ 0.92	<.001
BMI-SDS	1.86 $\pm$ 0.36	1.81 $\pm$ 0.43	0.276
WC (cm)	79.01 $\pm$ 10.56	74.63 $\pm$ 9.77	<.001
Body fat percentage (%)	34.19 $\pm$ 10.32	30.31 $\pm$ 6.45	<.001
S-BP (mmHg)	112.27 $\pm$ 15.20	109.74 $\pm$ 12.42	0.125
D-BP (mmHg)	70.54 $\pm$ 11.98	68.66 $\pm$ 12.16	0.196
Biochemical Data			
Glucose (mg/dl)	91.0 $\pm$ 5.60	89.9 $\pm$ 6.29	0.116
Insulin ( $\mu$ U/ml)	12.92 $\pm$ 8.42	14.38 $\pm$ 10.33	0.19
QUICKI	0.34 $\pm$ 0.03	0.33 $\pm$ 0.02	0.19
HOMA-R	3.06 $\pm$ 2.24	3.20 $\pm$ 2.25	0.59
Triglycerides (mg/dl)	59.0 $\pm$ 35.8	78.4 $\pm$ 43.9	<.001
Non HDL-C (mg/dl)	125.9 $\pm$ 30.0	133.9 $\pm$ 27.0	0.106
LDL-C (mg/dl)	99.32 $\pm$ 33.01	110.78 $\pm$ 32.18	0.005
ALT (IU/L)	23.47 $\pm$ 13.85	18.40 $\pm$ 13.22	0.002
UA (mg/dl)	5.15 $\pm$ 1.13	4.96 $\pm$ 0.89	0.127
TSH ( $\mu$ U/ml)	3.13 $\pm$ 1.37	2.87 $\pm$ 1.25	0.096
Free T3 (pg/ml)	4.26 $\pm$ 0.66	4.18 $\pm$ 0.49	0.247
Free T4 (ng/dl)	1.41 $\pm$ 0.53	1.30 $\pm$ 0.17	0.019
Free T3/freeT4	3.25 $\pm$ 0.67	3.25 $\pm$ 0.48	0.956

Data are expressed as mean  $\pm$  SD, and abbreviations are referred following. BMI-SDS, body mass index-SDS; WC, waist circumference; S-BP/D-BP, systolic/diastolic blood pressure; QUICKI, quantitative insulin sensitivity check index; HOMA-R, homeostatic model assessment ratio; Non-HDL-C, non-HDL-cholesterol; LDL-C, LDL-cholesterol; ALT, alanine aminotransferase; UA, Uric Acid; freeT3/free T4, free T3 to free T4 ratio.

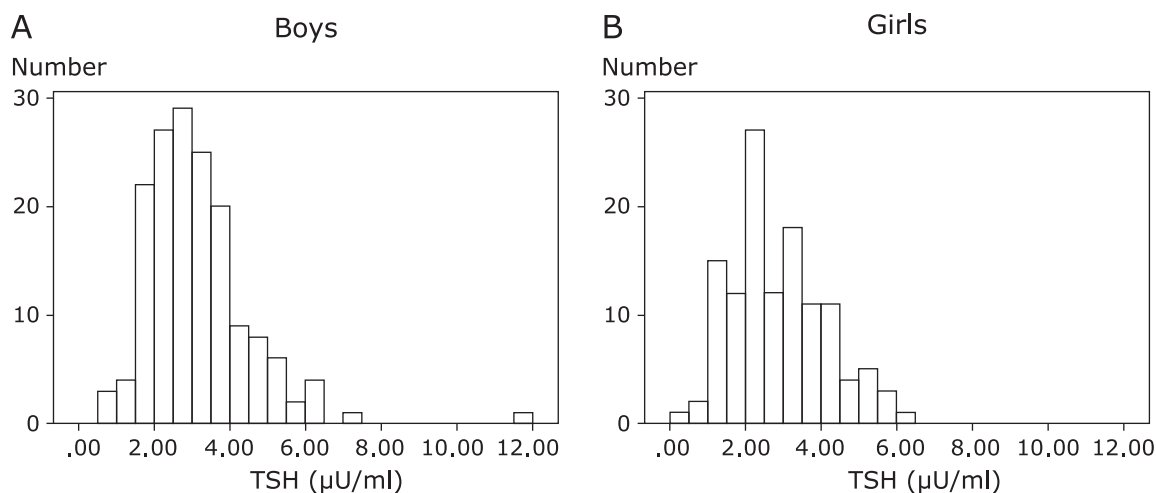


Fig. 1. Frequency distribution of thyroid-stimulating hormone levels in obese boys and girls.

Table 2. Comparison of demographic and biochemical parameters of obese boys according to serum TSH level

	TSH <4.0 μU/ml	TSH ≥4.0 μU/ml	p value
Number	130	31	
Age (years)	9.57 ± 2.04	9.28 ± 1.26	0.285
Height-SDS	0.65 ± 1.03	0.65 ± 0.94	0.316
BMI-SDS	1.85 ± 0.36	1.92 ± 0.34	0.306
WC (cm)	78.74 ± 10.60	80.13 ± 10.53	0.511
Body fat percentage (%)	34.23 ± 9.70	34.03 ± 12.80	0.921
S-BP (mmHg)	112.72 ± 15.46	110.39 ± 14.11	0.445
D-BP (mmHg)	70.75 ± 12.23	69.65 ± 11.02	0.645
Glucose (mg/dl)	90.68 ± 5.48	92.29 ± 6.00	0.15
Insulin (μU/ml)	12.41 ± 7.92	15.05 ± 10.12	0.116
QUICKI	0.34 ± 0.03	0.33 ± 0.02	0.046
HOMA-R	2.80 ± 1.85	3.49 ± 2.53	0.086
Triglycerides (mg/dl)	58.36 ± 31.40	61.90 ± 50.87	0.622
Non HDL-C (mg/dl)	124.28 ± 30.48	132.48 ± 27.31	0.172
LDL-C (mg/dl)	98.55 ± 35.32	102.55 ± 34.10	0.569
ALT (IU/L)	22.60 ± 13.67	27.13 ± 14.30	0.102
UA (mg/dl)	5.18 ± 1.18	5.00 ± 0.88	0.414
Free T3 (pg/ml)	4.26 ± 0.66	4.25 ± 0.63	0.902
Free T4 (ng/dl)	1.40 ± 0.50	1.43 ± 0.69	0.834
Free T3/free T4	3.25 ± 0.67	3.25 ± 0.67	0.978

Data are expressed as mean ± SD, and abbreviations are listed in Table 1.

groups (TSH ≥4 μU/ml and <4 μU/ml), respectively, previously described.<sup>(7)</sup> An elevated serum TSH level (≥4 μU/ml) was found in 31 (19.2%) boys and 24 (19.6%) girls, respectively. One boy had an extremely high TSH level (11.6 μU/ml) (Fig. 1); however, his thyroid hormone levels were within the normal range (fT3, 4.26 pg/ml; fT4, 1.21 ng/ml). The obese boys with TSH ≥4 μU/ml differed from those with TSH <4 μU/ml with respect to QUICKI (Table 2). Alternatively, the obese girls with TSH ≥4 μU/ml showed higher non-HDL-C and LDL-C and younger age compared to those with TSH <4 μU/ml (Table 3).

#### Multiple linear regression analysis of thyroid hormones with anthropometric, metabolic, and hormonal variables.

The multiple linear regression analysis was performed to examine the association between each thyroid hormone and other variables. In obese boys, TSH, fT3, or fT4 levels were not correlated with any variables, and fT3/fT4 was negatively correlated with

QUICKI (Table 4). On the contrary, in obese girls, all of the thyroid hormones levels, including TSH, fT3, and fT4, and free T3 to free T4 ratio (fT3/fT4), were negatively correlated with age. TSH levels in obese girls were positively correlated with levels of glucose, D-BP, and non-HDL-C. fT3/fT4 in the girls was positively correlated with uric acid.

#### Comparison of demographic and biochemical parameters between subjects with and without metabolic syndrome.

Age and values of height-SDS, WC, S-BP, D-BP, glucose, insulin, QUICKI, and uric acid were higher in obese boys with metabolic syndrome than in those without metabolic syndrome (Table 5). fT3/fT4 tended to be higher in obese boys with metabolic syndrome than in those without metabolic syndrome. On the contrary, BMI-SDS, WC, S-BP, D-BP, insulin, QUICKI, non HDL-C, and uric acid were higher in obese girls with metabolic syndrome than in those without metabolic syndrome (Table 6).

**Table 3.** Comparison of demographic and biochemical parameters of obese girls according to serum TSH level

	TSH <4.0 $\mu$ U/ml	TSH $\geq$ 4.0 $\mu$ U/ml	<i>p</i> value
Number	98	24	
Age (years)	9.77 $\pm$ 2.23	8.63 $\pm$ 1.89	0.025
Height-SDS	0.24 $\pm$ 0.95	0.01 $\pm$ 0.78	0.278
BMI-SDS	1.80 $\pm$ 0.44	1.84 $\pm$ 0.42	0.688
WC (cm)	75.39 $\pm$ 10.23	71.49 $\pm$ 6.91	0.079
Body fat percentage (%)	30.23 $\pm$ 6.63	30.64 $\pm$ 5.78	0.781
S-BP (mmHg)	109.67 $\pm$ 12.83	110.00 $\pm$ 10.82	0.908
D-BP (mmHg)	68.12 $\pm$ 12.30	70.83 $\pm$ 11.55	0.33
Glucose (mg/dl)	89.64 $\pm$ 6.35	90.79 $\pm$ 6.04	0.425
Insulin ( $\mu$ U/ml)	14.07 $\pm$ 8.13	15.66 $\pm$ 16.75	0.655
QUICKI	0.33 $\pm$ 0.02	0.33 $\pm$ 0.03	0.607
HOMA-R	3.14 $\pm$ 1.89	3.45 $\pm$ 3.42	0.554
Triglycerides (mg/dl)	77.20 $\pm$ 40.81	83.13 $\pm$ 55.48	0.556
Non HDL-C (mg/dl)	130.70 $\pm$ 25.44	146.88 $\pm$ 29.71	0.008
LDL-C (mg/dl)	107.14 $\pm$ 29.68	125.63 $\pm$ 37.92	0.011
ALT (IU/L)	18.63 $\pm$ 14.13	17.21 $\pm$ 8.70	0.624
UA (mg/dl)	4.95 $\pm$ 0.93	5.01 $\pm$ 0.70	0.779
Free T3 (pg/ml)	4.17 $\pm$ 0.50	4.18 $\pm$ 0.49	0.975
Free T4 (ng/dl)	1.29 $\pm$ 0.16	1.33 $\pm$ 0.20	0.32
Free T3/free T4	3.27 $\pm$ 0.49	3.18 $\pm$ 0.42	0.406

Data are expressed as mean  $\pm$  SD, and abbreviations are listed in Table 1.

**Table 4.** Significant determinants of thyroid hormones in multiple linear regression analysis

Dependent variables	Independent variables	Beta coefficient	SE of beta coefficient	<i>r</i> <sup>2</sup>	<i>p</i>
Boys					
ft3/ft4	QUICKI	-4.282	-0.185	0.034	0.019
Girls					
TSH	Age	-0.182	-0.327	0.207	<0.001
	Glucose	0.44	0.223		0.009
	D-BP	0.021	0.201		0.019
	Non HDL-C	0.008	0.181		0.032
ft3	Age	-0.118	-0.541	0.293	<0.001
ft4	Age	-0.016	-0.217	0.047	0.017
ft3/ft4	Age	-0.07	-0.331	0.107	<0.001
	UA	0.121	0.222		0.018

## Discussion

In the present study, we demonstrated gender differences in the association between thyroid hormones and obesity, and attempted to elucidate the correlation between thyroid hormones and various parameters including anthropometry and biochemical data in obese Japanese children. TSH levels in obese individuals are slightly higher than those in normal weight subjects, and TSH levels are positively associated with BMI and weight change.<sup>(6,14)</sup> In clinical studies of children, 7–23% of obese children exhibit elevated TSH levels, and obese children have moderately higher ft3 levels within the normal range compared with controls.<sup>(7)</sup> There are conflicting findings regarding the relationship between thyroid functions and anthropometry.<sup>(7)</sup> We showed that there was no correlation between thyroid hormone levels and anthropometric parameters including WC, BMI-SDS, and body fat percentage in obese boys and girls. The reason is unclear, however the differences in race and diagnostic criteria can affect the relationship between thyroid hormone levels and anthropometric parameters. The sample size in this study was small, and a larger study is needed to verify these results.

Reference ranges of thyroid hormones in children and adolescents have been reported in several studies, and they vary with age and gender. Thyroid hormones levels, including TSH, ft3, and ft4, are higher in the neonatal period than the rest of childhood and adolescence.<sup>(15,16)</sup> In a population of healthy Indian children, TSH, ft3, and ft4 levels in girls declined with age whereas TSH and ft3 levels in boys decreased with age, indicating a gender difference in thyroid hormones alteration.<sup>(17)</sup> In studies of healthy children in America, Canada, and the Netherlands, TSH and ft3 levels decreased with age, but there was no gender difference.<sup>(16,18,19)</sup> In the current study, thyroid hormone levels including TSH, ft3, ft4, and ft3/ft4 in obese girls were negatively associated with age, whereas there was no correlation between any of those measures and age in obese boys. The finding regarding age-dependent alteration of thyroid hormones in obese girls is in agreement with previous reports. However, gender differences may vary by racial or regional characteristics.

There are a number of reports on the association between thyroid function and lipid profiles in obese and overweight children, but the results are conflicting.<sup>(7)</sup> TSH levels in obese children were not associated with total cholesterol, LDL-C, or HDL-C,

**Table 5.** Comparison of demographic and biochemical parameters of boys with and without metabolic syndrome

	Mets (-) n = 128	Mets (+) n = 33	p value
Age (years)	9.09 ± 1.67	11.12 ± 1.94	<.001
Height-SDS	0.60 ± 1.02	1.04 ± 0.94	0.024
BMI-SDS	1.82 ± 0.33	1.97 ± 0.45	0.076
WC (cm)	76.50 ± 8.00	88.72 ± 13.48	<.001
Body fat percentage (%)	33.65 ± 9.78	36.31 ± 12.14	0.187
S-BP (mmHg)	108.5 ± 13.60	127 ± 11.8	<.001
D-BP (mmHg)	68.3 ± 11.07	79.2 ± 11.6	<.001
Glucose (mg/dl)	89.9 ± 5.10	95.18 ± 5.57	<.001
Insulin (μU/ml)	10.9 ± 6.0	20.6 ± 11.47	<.001
QUICKI	0.34 ± 0.027	0.31 ± 0.021	<.001
HOMA-R	2.43 ± 1.33	4.91 ± 2.86	<.001
Triglycerides (mg/dl)	51.18 ± 23.94	89.55 ± 54.11	<.001
HDL-C (mg/dl)	60.30 ± 16.40	49.48 ± 14.89	0.001
Non HDL-C (mg/dl)	125.4 ± 30.1	127.9 ± 29.88	0.671
UA (mg/dl)	4.91 ± 0.93	6.01 ± 1.33	<.001
TSH (μU/ml)	3.11 ± 1.42	3.22 ± 1.19	0.677
freeT3 (pg/ml)	4.26 ± 0.66	4.28 ± 0.65	0.87
freeT4 (ng/dl)	1.43 ± 0.55	1.33 ± 0.48	0.336
freeT3/freeT4	3.20 ± 0.65	3.45 ± 0.73	0.05

Data are expressed as mean ± SD, and abbreviations are listed in Table 1.

**Table 6.** Comparison of demographic and biochemical parameters of girls with and without metabolic syndrome

	Mets (-) n = 101	Mets (+) n = 21	p value
Age (years)	9.38 ± 2.21	10.33 ± 2.24	0.075
Height-SDS	0.19 ± 0.94	0.21 ± 0.81	0.95
BMI-SDS	1.76 ± 0.40	2.02 ± 0.51	0.012
WC (cm)	73.11 ± 8.63	82.0 ± 11.68	<.001
Body fat percentage (%)	29.87 ± 6.62	32.42 ± 5.15	0.099
S-BP (mmHg)	107.6 ± 11.6	119.8 ± 11.42	<.001
D-BP (mmHg)	67.0 ± 11.83	76.6 ± 10.66	<.001
Glucose (mg/dl)	89.9 ± 5.10	95.8 ± 5.50	<.001
Insulin (μU/ml)	10.90 ± 0.93	20.76 ± 11.47	<.001
QUICKI	0.33 ± 0.02	0.31 ± 0.02	<.001
HOMA-R	2.95 ± 2.24	4.42 ± 1.93	<.001
Triglycerides (mg/dl)	67.42 ± 29.98	131.05 ± 60.29	<.001
HDL-C (mg/dl)	59.69 ± 14.32	45.71 ± 17.00	<.001
Non HDL-C (mg/dl)	130.47 ± 26.4	150.3 ± 24.12	0.002
UA (mg/dl)	4.91 ± 0.93	6.01 ± 1.33	<.001
TSH (μU/ml)	2.90 ± 1.27	2.77 ± 1.13	0.676
freeT3 (pg/ml)	4.19 ± 0.51	4.13 ± 0.39	0.646
freeT4 (ng/dl)	1.30 ± 0.17	1.32 ± 0.16	0.513
freeT3/freeT4	3.27 ± 0.50	3.15 ± 0.34	0.291

Data are expressed as mean ± SD, and abbreviations are listed in Table 1.

but positively related to triglycerides.<sup>(20,21)</sup> Grandone *et al.*<sup>(22)</sup> revealed that TSH levels had no relation to HDL-C and triglycerides. Alternatively, Aeberli *et al.*<sup>(23)</sup> demonstrated that TSH levels in obese children had a markedly positive correlation with total cholesterol and LDL-C. In the current study, TSH levels within the normal range in obese girls were positively associated with non-HDL-C, which was in agreement with Aeberli's report. In a cross-sectional study of adults, TSH levels within the normal range were significantly associated with lipids including total cholesterol, non-HDL-C, and LDL-C and negatively with triglycerides.<sup>(24)</sup> Although TSH levels in obese children are within the normal range, obese children may be still potentially at risk for

cardiovascular disease in the future because of abnormalities in their lipid profiles.

Thyroid hormones have a critical role in cardiovascular hemodynamics including systemic vascular resistance, blood pressure, cardiac contractility, heart rate, thermogenesis, and cardiac output.<sup>(25)</sup> Several studies of adults demonstrated that individuals with hypothyroidism exhibited increased systolic and diastolic blood pressure.<sup>(26)</sup> There have been very few studies on the relationship between thyroid function and blood pressure in children, and the results are conflicting. Ittermann *et al.*<sup>(27)</sup> demonstrated that TSH levels in children and adolescents were significantly correlated with hypertension. Normal TSH and fT3 levels range

were associated with blood pressure in school-aged children.<sup>(28)</sup> In contrast, Cerbone *et al.*<sup>(29)</sup> reported that TSH levels had no relation to blood pressure in a study comparing children with subclinical hypothyroidism to controls. In the current study, TSH levels in obese girls were markedly associated with systolic blood pressure, but not in obese boys in Table 4. In a cross-sectional study of Chinese adults, hypertension was significantly more common in women with subclinical hypothyroidism than in women with normal thyroid gland function.<sup>(30)</sup> Alternatively, Chen *et al.*<sup>(28)</sup> demonstrated that the relationship between TSH levels and blood pressure was more pronounced in boys than in girls. The role of gender in this relationship may vary by age, nationality, and body constitution.

Insulin resistance is an essential mechanism responsible for metabolic syndrome and the development of type 2 diabetes.<sup>(31,32)</sup> Dysregulation of thyroid hormones may lead to insulin resistance. Hyperthyroidism and hypothyroidism may cause impaired glucose tolerance of the liver, muscles and adipose tissues, respectively.<sup>(33)</sup> Several studies have examined the relationship between thyroid function and insulin resistance in children and adults, but there are conflicting findings regarding the association of insulin resistance with hypothyroidism or hyperthyroidism. Levels of thyroid hormones within the normal range were positively associated with insulin resistance.<sup>(34)</sup> Maratou *et al.*<sup>(35)</sup> determined that insulin resistance was comparable in patients with both hyperthyroidism and subclinical hyperthyroidism. However, there are several reports of adult patients with hypothyroidism associated with insulin resistance, which later progressed to metabolic syndrome.<sup>(31,36)</sup> Brufani *et al.*<sup>(37)</sup> revealed that QUICKI was negatively correlated with TSH levels in obese prepubertal children and suggest that QUICKI was the only predictor of elevated TSH levels. Nader *et al.*<sup>(38)</sup> demonstrated that elevated TSH levels were associated with elevated levels of both insulin and HOMA. The obese children had relatively elevated TSH levels and significantly elevated fT3 levels compared with controls.<sup>(20,39)</sup> There are very few reports on gender differences in the relationship between thyroid function and insulin resistance. Prats-Puig *et al.*<sup>(40)</sup> reported that fT4 levels in healthy euthyroid prepubertal girls had a significant association with insulin resistance. Low-normal fT4 levels were associated with relatively increased HOMA levels. Gender differences in maturation rate or insulin sensitivity may lead to this observed gender distribution between thyroid functions and insulin resistance.<sup>(40)</sup> In the current study, fT3/fT4 was negatively associated with QUICKI in obese boys but not girls. Normal TSH levels in obese girls were positively associated with glucose levels. There was a gender difference in the association between thyroid hormone levels and insulin sensitivity. Thyroid hormones and insulin resistance including QUICKI and HOMA-R were not different between obese boys and girls. The reason for these findings remains to be determined, therefore further studies are required to clarify the mechanism linking thyroid function to insulin sensitivity in obese children.

Uric acid is the final product of purine catabolism, and uric acid levels are affected by uric acid synthesis, excretion, and the combination of these mechanisms.<sup>(41)</sup> Hyperuricemia is associated with several disorders including metabolic syndrome, diabetes, hypertension, renal disease, and cardiovascular diseases, and may be a predictor of the development of these disorders in adults.<sup>(42)</sup> Elevated uric acid levels are associated with metabolic syndrome, and predict cardiovascular risk in children.<sup>(9,43)</sup> The current study demonstrates an association of fT3/fT4 with uric acid in obese girls. To our knowledge, this is the first report regarding the relationship between thyroid functions and uric acid in a population of children. Erickson *et al.*<sup>(44)</sup> reported that the prevalence of hypothyroidism was higher in patients with gout than in control subjects. Free T4 levels were negatively associated with uric acid levels in euthyroid Chinese subjects with nonalcoholic fatty liver disease.<sup>(45)</sup> The association between thyroid function and hyper-

uricemia is unclear. TSH levels were significantly correlated or had no relation with uric acid levels in patients with subclinical hypothyroidism.<sup>(46)</sup> Alternatively, among patients with thyroid diseases, uric acid levels were significantly higher in patients with hyperthyroidism than in euthyroid patients.<sup>(47)</sup> The mechanism of the association between thyroid function and uric acid levels remains to be determined. There is a possibility that the presence or absence of complications including liver disease or obesity might affect the association between thyroid functions and uric acid levels. Further investigations are required to clarify this issue.

Thyroid dysfunction and subclinical hypothyroidism may affect the prevalence and development of metabolic syndrome. Imbalances between the hypothalamus, pituitary gland, thyroid, and adipose tissue are considered an essential part of the pathophysiological mechanism.<sup>(48)</sup> A number of investigators have attempted to evaluate the association of thyroid function with the prevalence of metabolic syndrome, but the studies examining this relation have shown conflicting results.<sup>(49-52)</sup> These discrepancies among studies of adults may arise from differences in the age, gender, and races of the participants. To the best of our knowledge, there are few reports regarding the association between thyroid hormones and metabolic syndrome in Asian children. Survivors of childhood cancer may develop metabolic syndrome due to endocrine dysfunction, endothelial cell injury, osteoblastic inactivity, or adipocyte dysfunction.<sup>(53)</sup> Among children treated with allogeneic stem cell transplantation, metabolic syndrome associated with other endocrine dysfunction was evaluated.<sup>(54)</sup> There was no significant difference between the rate of hypothyroidism in patients with metabolic syndrome and those without. In the current study, TSH levels of obese children did not differ within each gender by presence or absence of metabolic syndrome. However, fT3/fT4 in obese boys with metabolic syndrome tended to be higher than in those without metabolic syndrome. This finding is different from the above-mentioned studies of adults, which is difficult to explain. We hypothesize that the extent of the involvement of thyroid function in the development of metabolic syndrome might differ between children and adults. Further studies with large numbers of obese children are needed to clarify this issue.

There are some limitations to the present study. First, this study lacks the age- and sex-matched control group of children with normal weight. Second, the sample size is too small to properly evaluate the relationship between obesity and thyroid function in obese children. Third, the authors did not evaluate the antibodies of thyroid peroxidase or thyroglobulin, and did not consider the family history of thyroid disease. In conclusion, we demonstrated gender differences in the relationship between thyroid hormones and several parameters. The cause of these gender differences remains to be determined, but sex hormones might affect the relationship between thyroid hormones and various parameters, which may differ across races, nationality, and regional characteristics. Therefore, further evaluation of thyroid functions with larger sample sizes and long-term follow-up will be needed to address the influence of thyroid hormones on various parameters including anthropometric measurements, lipid profiles, insulin sensitivity, and blood pressure in obese children. Moreover, a better understanding of the relationship between thyroid function and these parameters is important in order to develop strategies to prevent or treat childhood obesity.

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## Abbreviations

ALT alanine aminotransferase

BMI	body mass index
D-BP	diastolic blood pressure
ft4	free thyroxine
ft3	free triiodothyronine
HDL-C	high-density lipoprotein cholesterol
HOMA-R	homeostatic model assessment ratio
LDL-C	low-density lipoprotein cholesterol
QUICKI	quantitative insulin sensitivity check index

S-BP	systolic blood pressure
TSH	thyroid-stimulating hormone
UA	uric acid
WC	waist circumference

## Conflict of interest

No potential conflicts of interest were disclosed.

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