Current Medical Science
DOI https://doi.org/10.1007/s11596-018-1955-5
38(5):868-874,2018

Characterization of Wnt1-inducible Signaling Pathway Protein-1 in Obese Children and Adolescents*

An-ru WANG[1, 2], Xue-qin YAN[3], Cai ZHANG[1], Cai-qi DU[1], Wen-jun LONG[1], Di ZHAN[1], Jie REN[1], Xiao-ping LUO[1#]
[1]*Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*
[2]*Department of Pediatrics, the Second Affiliated Hospital of Nanjing Medical University, Nanjing 210003, China*
[3]*Department of Pediatrics, Boai Hospital of Zhongshan, Zhongshan 528400, China*

Summary: Wnt1-inducible signaling pathway protein-1 (WISP1), a member of the CCN family, is increasingly being recognized as a potential target for obesity and type 2 diabetes mellitus. Recent studies have shown that WISP1 can regulate low-grade inflammation in obese mice, and circulating WISP1 levels are associated with obesity and type 2 diabetes mellitus in adults. Herein, we measured serum WISP1 levels in obese youth and explored its relationships with pro-inflammatory cytokine interleukin 18 (IL-18) and other metabolic indexes. Totally, 44 normal-weight and 44 obese children and adolescents were enrolled. Physical and laboratory data were recorded, and then serum levels of WISP1 and IL-18 were determined by enzyme-linked immunosorbent assays. Results showed that serum levels of WISP1 were significantly higher in obese children and adolescents than in normal-weight healthy controls (1735.44±15.29 *vs*. 1364.08±18.69 pg/mL). WISP1 levels were significantly positively correlated with body mass index (BMI) and BMI z-score (r=0.392, P=0.008; r=0.474, P=0.001, respectively) in obese group; circulating IL-18 was increased in obese individuals (1229.06±29.42 *vs*. 295.87±13.30 pg/mL). Circulating WISP1 levels were significantly correlated with IL-18 (r=0.542, P<0.001), adiponectin (r=0.585, P<0.001) and leptin (r=0.592, P<0.001). The multivariate stepwise regression analysis showed that higher IL-18 levels represented the main determinant of increased WISP1 levels after adjusting for BMI, waist circumference, fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR) and HbA1c in obese individuals (β=0.542, P=0.000). WISP1 can be involved in glucose/lipid metabolism in obese youth, which may be modulated by IL-18. Increased WISP1 levels may be a risk factor of obesity and insulin resistance, and WISP1 has a potential therapeutic effect on insulin resistance in obese children and adolescents.
Key words: Wnt1-inducible signaling pathway protein-1; interleukin 18; children and adolescents; insulin resistance, obesity

The worldwide prevalence of obesity among children and adolescents has been increased during the past 40 years[1]. Obesity is associated with insulin resistance, type 2 diabetes mellitus (T2DM) and long-term cardiovascular complications. Recent clinical and animal studies reported that Wingless-type MMTV integration site family member 1 (Wnt1)-inducible signaling pathway protein-1 (WISP1) was associated with obesity and T2DM[2]. WISP1 is a member of the cysterine-rich protein 61 (Cyr61)/connective tissue growth factor (CTGF)/nephroblastoma overexpressed (NOV) (CCN) family of matricellular proteins[3]. As a downstream target gene of the canonical Wnt signaling pathway, it was found to participate in a variety of pathologic processes, such as myocardial

An-ru WANG, E-mail: anruwang@aliyun.com
#Corresponding author, E-mail: xpluo@tjh.tjmu.edu.cn
*This study was supported by the National Natural Science Foundation of China (No. 81670781) and program for Changjiang Scholars and Innovative Research Team in University (No. PCSIRT1131).

cell proliferation and remodeling, cancer formation and progression, neuronal cells apoptosis.

Rudovich *et al*[4] firstly found that WISP1 expression was upregulated during human adipocyte differentiation. Further analysis showed that WISP1 was involved in adipogenesis and low-grade inflammation in obesity. Adipocyte may be a major source of circulating WISP1. In adults, circulating WISP1 has been found significantly increased in obese individuals[5]. Tacke *et al*[6] reported that circulating WISP1 was apparently correlated with body mass index (BMI), hip circumference, and leptin level. WISP1 was also associated with metabolic parameters in gestational diabetes mellitus[7]. Hence, WISP1 was identified as a potential human adipokine. However, features of WISP1 in obese children and adolescents remain unclear.

Interleukin-18 (IL-18), a pro-inflammatory cytokine, was increased in adults with obesity and T2DM[8, 9]. IL-18 could induce human saphenous vein smooth muscle cell (VSMC) proliferation mediated by WISP1[10]. The relationship between WISP1 and IL-18 has not been reported yet. Therefore, to explore the putative role of WISP1 in youth, we measured circulating serum WISP1 levels in obese children and adolescents, and identified a possible relationship between WISP1 and IL-18.

1 MATERIALS AND METHODS

1.1 Subjects and Baseline Data

Forty-four obese children and adolescents (5–15 years of age) were recruited from Boai Hospital of Zhongshan. Forty-four normal-weight healthy children and adolescents from the child health care department were also enrolled as controls. Obesity was defined as having an age- and sex-specific body mass index (BMI) of greater than or equal to 95th percentile according to the growth charts for children in China[11, 12]. Insulin resistance was evaluated by the homeostatic model assessment of insulin resistance (HOMA-IR) index, calculated as follows: fasting plasma insulin (mIU/L)×fasting plasma glucose (mmol/L)/22.5[13, 14]. Insulin resistance was defined as the values equal to or greater than the 75th percentile of HOMA-IR for sex and age according to the China Health and Nutrition Surveys (CHNS), as described previously[15]. Obese individuals were further classified into two groups: insulin-resistant (IR) group (n=18) and non-IR group (n=26). Individuals in the obese group who had specific medical diagnoses (e.g. hypothyroidism, Cushing's syndrome, or polycystic ovary syndrome) and/or received medications that might affect body composition or lipid and glucose metabolism (e.g. the use of thyroid medication, thiazolinediones, or metformin) were excluded. Written informed consent was obtained from the parents or other guardians. The Ethics Committee of Boai Hospital of Zhongshan approved the study protocol.

1.2 Physical and Laboratory Parameters

BMI values were converted to standard deviation scores (SDS) in children and adolescents using the lambda-mu-sigma method, as follows: Z=([BMI/M] L–1)/(L×S), where M is the median, S is the coefficient of variation, and L is the skewness[11, 16]. Waist circumference (WC), an indicator of central obesity, was measured at a level midway between the lowest rib and the top of the iliac crest with the individuals standing in the upright position[15].

Fasting glucose (FG) was detected using the glucose oxidase-phenol and aminophenazone (GOD-PAP) method (Biosino Bio-Technology and Science, Beijing, China). Insulin levels were determined using a chemiluminescent immunoassay (Roche Diagnostic, Germany). Serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A (Apo-A), and apolipoprotein B (Apo-B) levels were measured using enzymatic colorimetric methods (Cobas 6000 biochemistry analyzer, Roche Diagnostics, USA). Hemoglobin A1c (HbA1c) levels were detected using high-performance liquid chromatography (HPLC) (ADAMS A1c, HA-8180 analyzer, Arkray, Japan). Non-alcoholic fatty liver disease (NAFLD) was determined by abdomen ultrasound[11].

1.3 WISP1 and Other Biomarkers

Fasting blood samples were collected from all participants after fasting for 8 h. Serum WISP1 levels were determined through enzyme-linked immunosorbent assays (ELISA; Cloud-Clone Corp., China). Circulating IL-18, adiponectin and leptin levels were determined through ELISA (Cusabio, China). All samples were analyzed in duplicate, and samples with a coefficient of variation of more than 15% were excluded.

1.4 Statistical Analysis

SPSS version 18.0 for Windows (SPSS Inc, USA) was used for statistical analysis of the data. The variables were tested for normality with the Shapiro-Wilk test. Normally distributed data are shown as the mean±standard error of the mean (SEM). Non-normally distributed data are shown as median (interquartile range). Comparisons of continuous variables between two groups were carried out using independent sample t-tests. Categorical variables were analyzed using the chi-square test. Pearson correlation analysis was performed to assess the relationships between WISP1 and other normally distributed data. Spearman correlation analysis was performed to assess the relationships between WISP1 and other non-normally distributed data. The multivariate regression

model included variables significantly associated with serum WISP1 levels at the bivariate correlation analyses. Two-tailed *P*-values of less than 0.05 were considered significant.

2 RESULTS

2.1 Baseline Characterization of Individuals in Different Groups

The anthropometric and biochemical characteristics of all the participants are shown in table 1. There were no significant differences in age, sex or height among the different groups. Obese children and adolescents had higher levels of obesity descriptors, such as BMI, BMI z-score, and WC. Serum LDL-C levels were higher in the obese individuals than that in normal-weight controls (P=0.008). Fasting insulin, HOMA-IR and HbA1c were higher in the obese group than in healthy controls. FG showed no difference between the obese and control group. No significant differences in anthropometric, FG, HbA1c, HDL-C and LDL-C levels were observed between the IR and non-IR obese groups. Apo-A and ALT were higher in the IR obese individuals than in the non-IR groups.

Table 1 Descriptive clinical data for the obese children and adolescents and the normal-weight healthy controls

Variable	Total			Obesity		
	Controls (n=44)	Obesity (n=44)	P	Non-IR (n=26)	IR (n=18)	P
Age (years)	9.45±0.33	9.51±0.34	0.906	9.83±0.50	9.05±0.38	0.259
Sex (male:female)	24:20	21:23	NS	13:13	8:10	NS
Height (cm)	134.86±1.78	139.72±1.91	0.066	140.85±2.96	138.07±1.89	0.479
Weight (kg)	30.83±1.10	46.04±1.95	0.000	47.70±2.98	43.63±2.04	0.265
BMI (kg/m^2)	16.57±0.17	23.07±0.39	0.000	23.35±0.54	22.67±0.53	0.389
BMI z-score	0.10±0.04	2.42±0.08	0.000	2.37±0.09	2.47±0.13	0.516
WC (cm)	59.95±1.17	77.69±1.89	0.000	77.89±2.69	77.40±2.60	0.901
FG (mmol/L)	4.78±0.08	4.99±0.06	0.510	4.92±0.09	5.08±0.08	0.200
Fasting insulin (mIU/L)	6.70 (5.42–8.18)[a]	11.49 (7.46–16.84)[a]	0.000	8.00 (6.21–11.09)[a]	18.22 (13.60–22.78)[a]	0.000
HOMA-IR	1.42 (1.03–1.90)[a]	2.35 (1.66–3.76)[a]	0.000	1.83 (1.45–2.21)[a]	4.09 (3.13–5.06)[a]	0.000
HbA1c (%)	4.99±0.06	5.29±0.04	0.000	5.29±0.05	5.29±0.06	0.996
TC (mmol/L)	4.19±0.09	4.27±0.10	0.548	4.36±0.14	4.14±0.16	0.320
TG (mmol/L)	1.08±0.05	0.97±0.05	0.101	0.90±0.06	1.07±0.07	0.078
HDL-C (mmol/L)	1.56±0.05	1.50±0.05	0.361	1.57±0.06	1.40±0.06	0.061
LDL-C (mmol/L)	2.26±0.04	2.48±0.07	0.008	2.50±0.10	2.46±0.10	0.819
Apo-A (g/L)	1.27±0.04	1.21±0.03	0.278	1.27±0.05	1.12±0.04	0.031
Apo-B (g/L)	0.80±0.02	0.78±0.02	0.375	0.79±0.03	0.75±0.03	0.360
ALT (IU/L)	16.86±0.75	22.75±2.03	0.000	18.12±1.50	29.44±4.04	0.000
NAFLD	0	13 (30%)		1 (0.04%)	12 (66.6%)	0.000[b]

IR: insulin resistant; BMI: body mass index; FG: fasting glucose; WC: waist circumferences; HOMA-IR: homeostasis model assessment of insulin resistance; HbA1c: hemoglobin A1c; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; Apo-A: apolipoprotein A; Apo-B: apolipoprotein B; ALT: alanine aminotransferase; NAFLD: non-alcoholic fatty liver disease; NS: not significant.
Normally distributed data are given as mean±SEM. a: Non-normally distributed data are shown as medians (interquartile range). b: Pearson chi-square.

2.2 WISP1, IL-18, Adiponectin and Leptin

Serum WISP1 levels were increased in obese children and adolescents, meanwhile circulating WISP1 levels were higher in the IR obese group than in the non-IR obese group (table 2, fig. 1B). Furthermore, we analyzed the correlation between serum WISP1 levels and other variables (table 3). WISP1 levels were significantly positively correlated with BMI and BMI z-score in the obese children and adolescents (r=0.392, P=0.008; r=0.474, P=0.001, respectively; fig. 1C and 1D). In the obese group, WISP1 concentration was significantly correlated with WC (r=0.308, P=0.042; fig. 1E). WISP1 concentration was not correlated with FG and LDL-C in the obese group. Spearman correlation analysis revealed that circulating WISP1 levels were significantly correlated with fasting insulin (r=0.571, P<0.001) and HOMA-IR in the obese individuals (r=0.541, P<0.001; fig. 1F). Serum WISP1 levels were significantly correlated with IL-18 in the obese group (r=0.542, P<0.001; fig. 2A), not in the control group. Furthermore, circulating WISP1 levels were significantly correlated with adiponectin in obese individuals (r=0.585, P<0.001; fig. 2B). In obese children and adolescents, serum WISP1 levels were significantly correlated with leptin (r=0.592, P<0.001; fig. 2C). The multivariate stepwise linear regression analysis showed that IL-18 was associated with WISP1 in obese individuals after adjusting for BMI, WC, fasting insulin, HOMA-IR and HbA1c, with the standardized and unstandardized coefficients being 0.542 and 0.282 respectively (both P<0.001).

Table 2 Comparison of serum WISP1, IL-18, adiponectin and leptin levels in different conditions (mean±SEM)

Variable	Total			Obesity		
	Normal-weight (*n*=44)	Obesity (*n*=44)	*P*	Non-IR (*n*=26)	IR (*n*=18)	*P*
WISP1 (pg/mL)	1364.08±18.69	1735.44±15.29	0.000	1690.02±14.82	1801.05±23.47	0.000
IL-18 (pg/mL)	295.87±13.30	1229.06±29.42	0.000	1222.00±32.67	1239.26±55.43	0.220
Adiponectin (μg/mL)	8.81±0.29	29.77±1.75	0.000	25.81±2.24	35.48±2.26	0.005
Leptin (ng/mL)	4.38±0.33	19.26±1.15	0.000	16.97±1.44	22.46±1.63	0.017

WISP1: Wnt1-inducible signaling pathway protein-1; IL-18: interleukin 18; IR: insulin resistant

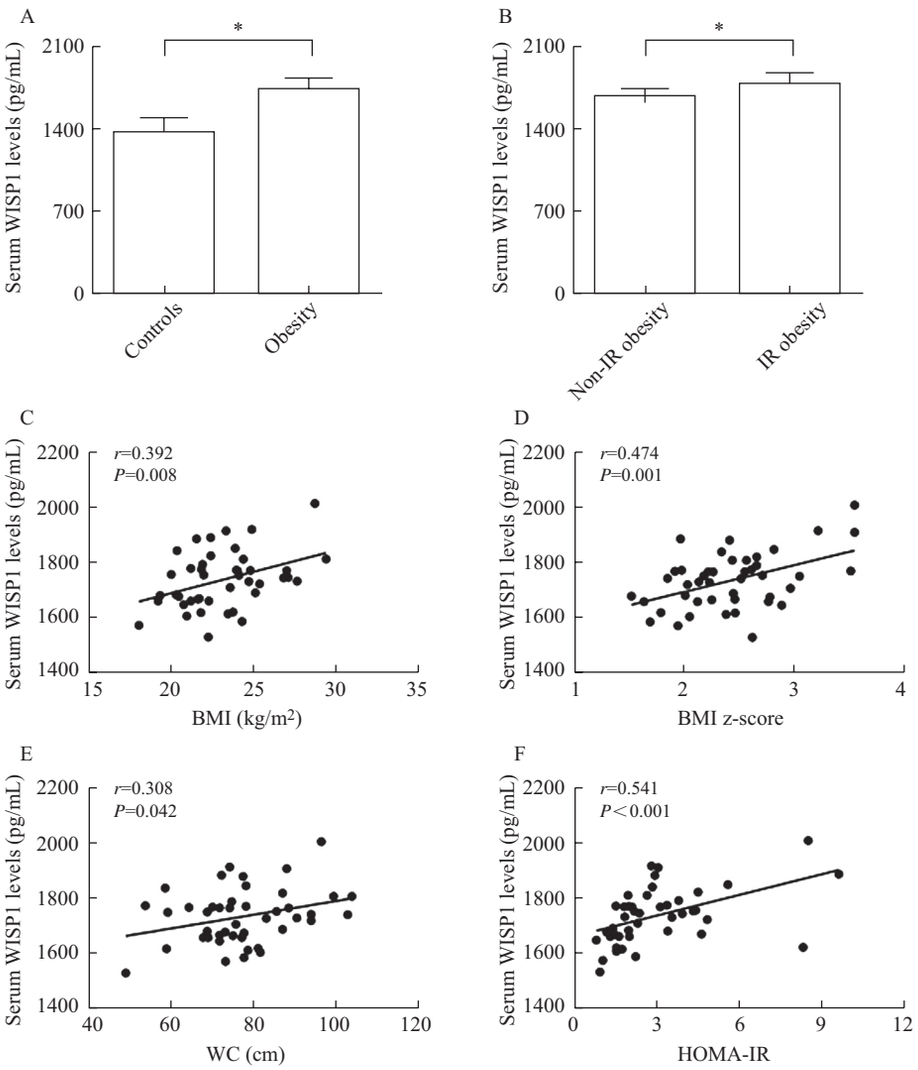

Fig. 1 Comparison of Wnt1-inducible signaling pathway protein-1 (WISP1) in different conditions
A: Comparison serum WISP1 levels between the obese children and adolescents (*n*=44) and the normal-weight healthy controls (*n*=44); B: Comparison of circulating WISP1 levels between the insulin resistant (IR) group (*n*=18) and the non-IR obese (*n*=26) group; C: Serum WISP1 levels were significantly correlated with body mass index (BMI) in the obese group; D: Serum WISP1 levels were significantly correlated with BMI z-score in the obese group; E: Circulating WISP1 levels were significantly correlated with waist circumference (WC) in the obese group; F: Serum WISP1 levels were significantly correlated with homeostatic model assessment of insulin resistance (HOMA-IR) in the obese group. Normally distrubted data are shown as mean±SEM. $^{*}P<0.05$

Circulating IL-18 levels were increased in the obese children and adolescents (table 2, fig. 3A). There were no significant differences at all for IL-18 levels between the IR group and non-IR obese group. In obese individuals, IL-18 levels were significantly correlated with BMI and BMI z-score (r=0.457, P=0.002; r=0.510, P<0.001, respectively; fig. 3B and 3C). In the obese group, circulating IL-18 concentration was significantly correlated with WC (r=0.332, P=0.028). Serum IL-18 was not correlated with fasting insulin (r=0.282, P=0.064) and HOMA-IR (r=0.258, P=0.090) in obese individuals.

Table 3 Correlation coefficients among WISP1 and other variables in obese children and adolescents and normal-weight healthy controls

WISP1	Variable	Control (n=44)		Obesity (n=44)	
		r	P	r	P
Pearson coefficients	BMI (kg/m^2)	0.432	0.003	0.392	0.008
	BMI z-score	0.123	0.426	0.474	0.001
	WC (cm)	0.035	0.823	0.308	0.042
	FG (mmol/L)	0.258	0.090	0.157	0.307
	HbA1c (%)	0.214	0.162	0.542	0.000
	LDL-C (mmol/L)	0.227	0.138	0.115	0.457
	IL-18 (pg/mL)	0.192	0.212	0.542	0.000
	Adiponectin (μg/mL)	0.258	0.091	0.585	0.000
	Leptin (ng/mL)	0.018	0.907	0.592	0.000
Spearman coefficients	Fasting insulin (mIU/L)	0.008	0.957	0.571	0.000
	HOMA-IR	0.046	0.765	0.541	0.000

Pearson correlation coefficients for normally distributed data; Partial correlation coefficients adjusted for BMI; Spearman correlation coefficients for not normally distributed data; BMI: body mass index; FG: fasting glucose; WC: waist circumferences; HOMA-IR: homeostasis model assessment of insulin resistance; WISP1: Wnt1-inducible signaling pathway protein-1; IL-18: interleukin 18

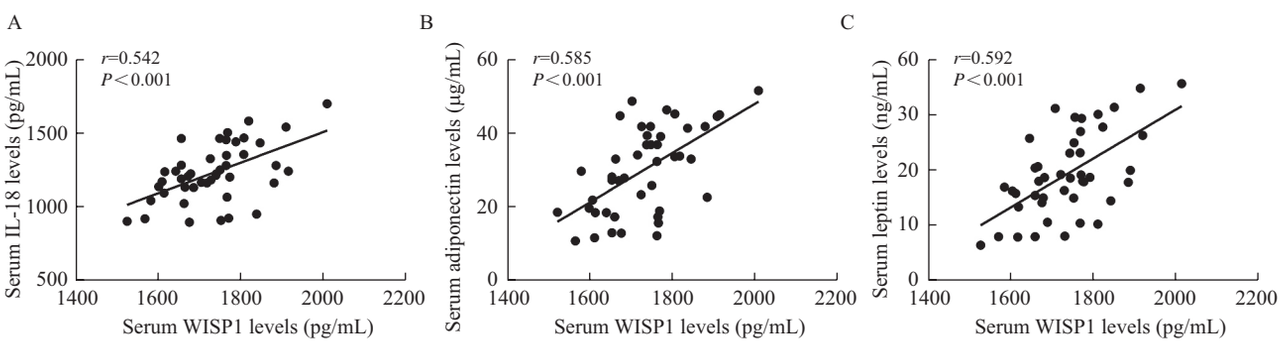

Fig. 2 Correlation among Wnt1-inducible signaling pathway protein-1 (WISP1) and other biomarkers in obese children and adolescents
A: Serum WISP1 levels were significantly correlated with interleukin 18 (IL-18) levels in the obese group; B: Circulating WISP1 levels were significantly correlated with adiponectin levels in the obese group; C: Serum WISP1 levels were significantly correlated with leptin in the obese group.

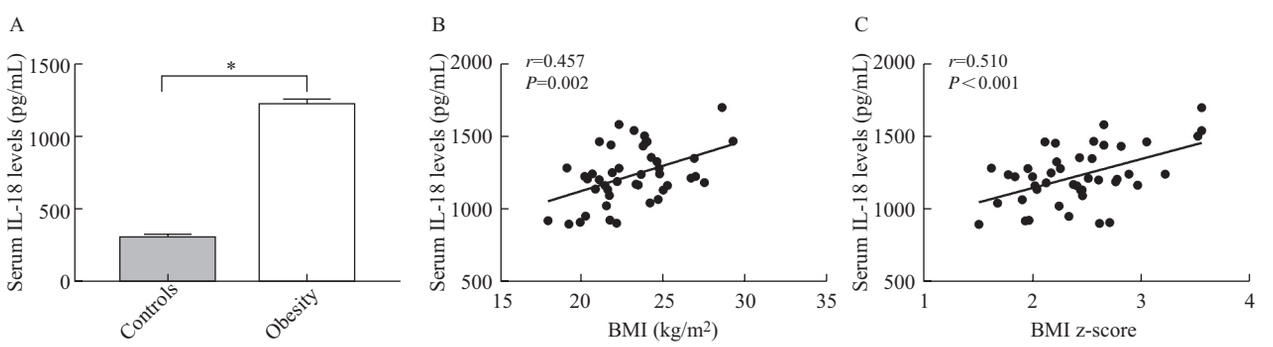

Fig. 3 Comparison of circulating interleukin 18 (IL-18) in different conditions
A: Comparison of serum IL-18 levels between the obese children and adolescents (n=44) and the normal-weight healthy controls (n=44); B: Circulating IL-18 levels were significantly correlated with body mass index (BMI) in the obese group; C: Serum IL-18 levels were significantly correlated with BMI z-score in the obese group. $^*P$<0.05

Serum adiponectin and leptin levels were significantly higher in the obese children and adolescents than in the normal-weight controls, meanwhile they were higher in the IR obese group than in the non-IR obese group (table 2). Serum leptin levels were significantly correlated with BMI and BMI z-score in obese individuals (r=0.319, P=0.035; r=0.585, P=0.000, respectively). In the obese group, circulating leptin concentration was significantly correlated with fasting insulin and HOMA-IR

(r=0.344, P=0.022; r=0.328, P=0.030, respectively). In obese individuals, serum adiponectin levels were significantly correlated with BMI and BMI z-score (r=0.432, P=0.003; r=0.372, P=0.013, respectively).

3 DISCUSSION

We analyzed serum levels of WISP1, IL-18, adiponectin and leptin in obese children and adolescents and compared them with those in normal-weight healthy youth in the present study. We reported that the levels of WISP1, IL-18, adiponectin, and leptin were significantly higher in the obese individuals than in the healthy controls. Furthermore, circulating levels of WISP1, adiponectin and leptin were significantly higher in IR obese children and adolescents than in the non-IR group. Circulating levels of WISP1, IL-18, adiponectin and leptin were positively correlated with BMI and BMI z-score. Serum WISP1 levels were significantly correlated with WC, fasting insulin and HOMA-IR in the obese children and adolescents. Circulating levels of leptin were positively correlated with HOMA-IR and fasting insulin in the obese individuals. Serum WISP1 levels were significantly correlated with IL-18 in the obese group after adjusting for BMI, WC, fasting insulin, HOMA-IR and HbA1c. To the best of our knowledge, the present study is the first to analyze WISP1 levels and their relationship with IL-18 and other glucose/lipid metabolic variables in obese children and adolescents.

The CCN family consists of six extracellular matrix associated proteins, including CYR61/CCN1, CTGF/CCN2, NOV/CCN3, WISP1/CCN4, WISP2/CCN5 and WISP3/CCN6[17]. All members are characterized by an N-terminal secretory peptide followed by four conserved cysteine-rich domains[3]. Human WISP1 gene, located on 8q24.1-24.3, encodes 367 amino acids, including 38 conserved cysteine residues and four potential N-linked glycosylation sites. As a matricellular protein, WISP1 is present in multiple sites throughout the body. WISP1 was primarily identified as one of the genes expressed at high levels in Wnt1-transformed C57MG cell[18]. Wnt signaling family members regulate cell proliferation, differentiation and organism development through autocrine and paracrine pattern. Early work highlighted WISP1 effects on cellular growth, differentiation, tumorigenesis and fibrotic disorders. Recently, WISP1 was found to act on insulin target tissues, such as fat. Rudovich *et al*[4] suggested that WISP1 was an adipokine released by fully differentiated human adipocyte. WISP1 mRNA expression in epididymal fat tissue was increased in high-fat diet mice. Plasma WISP1 was significantly increased in obese individuals, thus WISP1 concentration was a suitable biomarker of adult obesity[5, 6]. Furthermore, a prospective cross-sectional study in pregnant women also found that serum WISP1 levels significantly elevated in gestational diabetes mellitus[7]. Nevertheless, there are very limited data on the role of WISP1 in metabolic disturbances in youth. In the current study, we found that serum WISP1 levels were higher in obese children and adolescents than in normal-weight healthy individuals and WISP1 may be a biomarker in obese youth.

We next found circulating WISP1 levels were positively correlated with BMI and WC in children and adolescents. Notably, as an indicator of central obesity, WC plays an important role in metabolic syndrome[15]. The relationship with WC suggests WISP1 may be a biomarker of metabolic syndrome.

Rudovich *et al*[4] then found that insulin upregulated WISP1 mRNA expression in human adipocyte and adipose, and WISP1 mRNA expression was significantly correlated with plasma fasting insulin levels and adiponectin levels in normal-weight adults. Serum WISP1 levels were significantly correlated with fasting insulin and HOMA-IR in obese women with polycystic ovary syndrome (PCOS)[19]. We found that WISP1 levels were higher in the IR obese group and significantly correlated with adiponectin, leptin, fasting insulin and HOMA-IR in obese children and adolescents. These results indicated that WISP1 may be correlated with metabolic disorders in obese youth.

IL-18 is a member of the IL-1 family and synthesized by T-lymphocytes and adipocytes[20, 21]. IL-18 induces differentiation of T-lymphocytes and NK cells, stimulates production and secretion of other cytokines[22]. Obesity is characterized by low-grade underlying inflammation. As a strong pro-inflammatory cytokine, IL-18 is tightly associated with obesity and metabolic syndrome. Circulating IL-18 levels were increased in adults with obesity or metabolism syndrome[8, 9]. Increased IL-18 levels caused by a polymorphism of IL-18 gene was reportedly associated with insulin resistance[23]. Our study showed that IL-18 levels were increased in obese children and adolescents and IL-18 levels were significantly correlated with BMI and BMI z-scores in the obese individuals, suggesting IL-18 may play an important role in the pathogenesis of obese youth.

Reddy *et al*[10] reported that IL-18 could stimulate rapid and significant proliferation of VSMC. They further demonstrated that this proliferation effects were partly mediated by WISP1. IL-18 induced WISP1 expression via Akt/glycogen synthase kinase-3β/β-catenin/T-cell factor-lymphoid enhancer binding factor signaling. Adipose WISP1 mRNA expression was significantly correlated with macrophage infiltration and treatment of human macrophages with WISP1 caused a pro-inflammatory response[4]. Barchetta *et al* identified WISP1 was a marker of systemic and adipose tissue inflammation in

T2DM[5]. These studies focus on the relationship between WISP1 and adipose tissue inflammation. Action mechanisms of WISP1 in obesity-related slight inflammation and relationship between WISP1 and IL-18 in human remain unclear. We found that WISP1 was significantly correlated with IL-18 after adjusting for BMI in obese children and adolescents. Inflammation mediated by WISP1 in obesity may be correlated with IL-18.

There are some limitations in our study. This is a pilot study with a small number of patients and controls, especially for IR and non-IR obese subjects. Prospective cohort studies are needed. Despite these preliminary characters, this study shows that serum WISP1 levels are higher in obese children and adolescents. WISP1 might be used as a biomarker in obese youth. The positive relationship between WISP1 and IL-18 suggests that the role of WISP1 in obese children and adolescents may be related to IL-18.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

REFERENCES

1 NCD Risk Factor Collaboration (NCD-RisC). World trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measured studies in 1289 million children, adolescents, and adults. Lancet, 2017,390(10113):2627-2642

2 Kaplanski G. Interleukin-18: biological properties and role in disease pathogenesis. Immunol Rev, 2018,281(1):138-153

3 Maiese K. Programming apoptosis and autophagy with novel approaches for diabetes mellitus. Curr Neurovasc Res, 2015,12(2):173-188

4 Blüher M, Pfeiffer AF, Rudovich N. WISP1 is a novel adipokine linked to inflammation in obesity. Diabetes, 2015,64(3):856-866

5 Barchetta I, Cimini FA, Capoccia D, *et al*. WISP1 is a marker of systemic and adipose tissue inflammation in dysmetabolic subjects with or without type 2 diabetes. J Endocr Soc, 2017,1(6):660-670

6 Tacke C, Aleksandrova K, Rehfeldt M, *et al*. Assessment of circulating Wnt1 inducible signalling pathway protein 1 (WISP1)/CCN4 as a novel biomarker of obesity. J Cell Commun Signal, 2018,12(3):539-548

7 Sahin Ersoy G, AltunEnsari T, Subas S, *et al*. WISP1 is a novel adipokine linked to metabolic parameters in gestational diabetes mellitus. J Matern Fetal Neonatal Med, 2017,30(8):942-946

8 Bruun JM, Stallknecht B, Helge JW, *et al*. Interleukin-18 in plasma and adipose tissue: effects of obesity, insulin resistance, and weight loss. Eur J Endocrinol, 2007,157(4):465-471

9 Zaharieva E, Kamenov Z, Velikova T, *et al*. Interleukin-18 serum level is elevated in type 2 diabetes and latent autoimmune diabetes. Endocr Connect, 2018,7(1):179-185

10 Reddy VS, Valente AJ, Delafontaine P, *et al*. Interleukin-18/WNT1-inducible signaling pathway protein-1 signaling mediates human saphenous vein smooth muscle cell proliferation. J Cell Physiol, 2011,226(12):3303-3315

11 Barlow SE, Dietz WH. Obesity evaluation and treatment: Expert Committee recommendations. the maternal and child health bureau, health resources and services administration and department of health and human services. Pediatrics, 1998,102(3):E29

12 Li H, Ji CY, Zong XN, *et al*. Body mass index growth curves for Chinese children and adolescents aged 0 to 18 years. Zhonghua Er Ke Za Zhi (Chinese), 2009,47(7):493-498

13 Brown RJ, Yanovski JA. Estimation of insulin sensitivity in children: methods, measures and controversies. Pediatr Diabetes, 2014,15(3):151-161

14 Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care, 2004,27(6):1487-1495.

15 Song P, Yu J, Chang X, *et al*. Prevalence and correlates of metabolic syndrome in Chinese children: the China health and nutrition survey. Nutrients, 2017,9(1).pii: E79

16 Wu S, Gao H, Ma Y, *et al*. Characterisation of betatrophin concentrations in childhood and adolescent obesity and insulin resistance. Pediatr Diabetes, 2016,17(1):53-60

17 Brigstock DR. The CCN family: a new stimulus package. J Endocrinol, 2003,178(2):169-175

18 Pennica D, Swanson TA, Welsh JW, *et al*. WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors. Proc Natl Acad Sci USA, 1998,95(25):14717-14722

19 Sahin Ersoy G, Altun Ensari T, Vatansever D, *et al*. Novel adipokines WISP1 and betatrophin in PCOS: relationship to AMH levels, atherogenic and metabolic profile. Gynecol Endocrinol, 2017,33(2):119-123

20 Okamura H, Tsutsi H, Komatsu T, *et al*. Cloning of a new cytokine that induces IFN-gamma production by T cells. Nature, 1995,378(6552):88-91

21 Skurk T, Kolb H, Müller-Scholze S, *et al*. The proatherogenic cytokine interleukin-18 is secreted by human adipocytes. Eur J Endocrinol, 2005, 152(6):863-868

22 García VE, Uyemura K, Sieling PA, *et al*. IL-18 promotes type 1 cytokine production from NK cells and T cells in human intracellular infection. J Immunol, 1999,162(10):6114-6121

23 Presta I, Andreozzi F, Succurro E, *et al*. IL-18 gene polymorphism and metabolic syndrome. Nutr Metab Cardiovasc Dis, 2009,19(2):e5-6

(Received Apr. 12, 2018; revised Aug. 6, 2018)