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The correlation between serum adipokines levels and metabolic indicators in girls with Turner syndrome

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ABSTRACT

Objective: The following study investigated the serum adiponectin, chemerin and vaspin levels and their relationship with body mass index (BMI), glucose and lipid metabolism in girls with Turner Syndrome (TS).

Methods: A total of 64 girls with TS (mean age, 12.22 ± 3.98 years; mean BMI, 18.90 ± 3.45 kg/m^2) were ascertained by chromosome analysis. Height, weight, waist circumference, hip circumference and blood pressure were measured, as well as the levels of fasting plasma glucose (FPG), fasting plasma insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG). The BMI, BMI standard deviation score (SDS), waist to hip ratio, waist to height ratio and insulin resistance index (HOMA-IR) were calculated. The TS group and the control group were subdivided into non-puberty or puberty subgroup.

Results: The TS group had higher waist to hip ratio and waist to height ratio compared to the control group. There was no significant difference in FPG, fasting plasma insulin, HOMA-IR, blood lipid and blood pressure between the two groups. Significantly higher serum levels of adioponectin (12.51 ± 4.58 μg/ml) and chemerin (173.71 ± 37.88 ng/ml) and significantly lower levels of vaspin (0.67 ± 0.47 ng/ml) were found in the TS group compared to the control group (9.30 ± 3.17 μg/ml, 159.43 ± 23.19 ng/ml and 1.06 ± 0.49 ng/ml, respectively) (all $P < 0.05$). In the TS group, adiponectin levels were negatively correlated with age, BMI and TG (r = −0.251, −0.247, −0.294, $P < 0.05$ for all). In the control group, adiponectin levels were negatively correlated with BMI and BMI SDS (r = −0.416 and −0.315, $P < 0.05$ for both), while vaspin levels were positively correlated with age, fasting plasma insulin and HOMA-IR (r = 0.257, 0.273 and 0.282, $P < 0.05$ for all). In addition, significantly higher levels of adiponectin were found in the non-puberty subgroup (13.88 ± 4.49) μg/ml compared to puberty subgroup (9.72 ± 3.39) μg/ml ($P < 0.05$), while no significant differences in chemerin and vaspin were found between the two TS subgroups.

Conclusions: Elevated adiponectin and chemerin levels and significantly reduced vaspin were found in girls with TS. Puberty or estrogen replacement therapy may reduce adiponectin in girls with TS.

1. Introduction

Turner syndrome (TS) is a chromosomal disorder which occurs in about 25–50 cases per 100,000 live-born females. TS is associated with loss of an entire sex chromosome or a portion of the X chromosome containing the tip of its short arm [1]. TS can involve multiple organs, and patients may have an increased risk of metabolic abnormalities, including abdominal obesity, hypertension, insulin resistance/glucose intolerance and dyslipidaemia [2].

Nowadays, adipose tissue is regarded as an active endocrine organ which secretes many bioactive adipokines, such as adiponectin, chemerin and vaspin. Despite its better-known role in regulating fat mass and nutrient homeostasis, adipokines have been shown to influence the adipocyte function through numerous mechanisms, and to affect multiple metabolic and endocrine processes. Adipokines participate in the regulation of multiple biological processes, such as feeding behavior, glucose and lipid metabolism, energy balance, as well as playing a role in neuroendocrine and cardiovascular systems [3]. Because central obesity, hypertension, dyslipidemia, and impaired glucose homeostasis are common in TS [1], we opined that dysregulation of adipokines may contribute to the pathogenesis of metabolic abnormalities in girls with TS. Therefore, we measured the adipokines levels in

Abbreviations: BMI, body mass index; BMI SDS, body mass index standard deviation score; ELISA, enzyme linked immunosorbent assay; FPG, Fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, insulin resistance index; TC, total cholesterol; TG, triglyceride; TS, Turner Syndrome

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girls with TS and controls, and analyzed the relationship between the three adipokines and body mass index (BMI), glucose and lipid metabolism.

2. Subjects and methods

2.1. Study participants

The study included 64 girls with TS diagnosed by routine G-band karyotyping that included minimally 40 cells (while 100 cells were performed whenever possible), and 61 healthy girls with normal karyotype. Age ranged from 5 to 18 years. The exclusion criteria were: (1) patients with untreated hypothyroidism or hyperthyroidism; (2) patients with history of malignant diseases or clinical liver disease or those treated with drugs interfering with glucose homeostasis or fat metabolism. All subjects and their parents or legal guardians signed a written informed consent. The participants' medical history, family history, and current medications were collected. Anthropometric measurements (height, weight, waist circumference and hip circumference), pubertal staging according to the method of Tanner [4], vital signs (blood pressure and pulse), fasting plasma glucose (FPG), and serum lipids were also analyzed. BMI was calculated by dividing weight (kg) with squared height (m^2); BMI standard deviation score (SDS) was calculated using data for Chinese children and adolescents [5].

Both groups were additionally divided into non-puberty and puberty subgroup based on clinical exam (Tanner breast stage > B1) or estrogen replacement therapy.

The definitions for metabolic abnormalities were based on the 2012 Chinese guideline [6]: (1) Obesity if the BMI was equal or greater than 95th centile for age and sex, and overweight if BMI was between the 85th and 95th centile for age and sex. (2) Hypertension if systolic pressure or diastolic pressure ≥95th percentile for age and sex. (3) Dyslipidaemia if low high-density lipoprotein cholesterol (HDL-C) < 1.03 mmol/L or non-HDL-C ≥3.76 mmol/L or triglyceride (TG) ≥1.47 mmol/L; (4) Hyperglycemia if FPG ≥5.6 mmol/Lor the 2-hour glucose measurement following oral glucose tolerance test (OGTT) ≥7.8 mmol/L.

2.2. Biochemical assays

Fasting total serum adiponectin, chemerin, vaspin (BioVendor, Laboratorni medicina a.s. Czech Republic) were measured using commercially available enzyme linked immunosorbent assay (ELISA). The lower limit of sensitivity of the adiponectin assay was 0.47 ng/mL. Serum was diluted 1:300 in dilution buffer before analysis, and coefficients of variation were: intra-assay, 3.3–4.4% and inter-assay, 5.8–6.2%. The lower limit of sensitivity of the chemerin assay was 0.1 ng/mL. Serum was diluted 1:100 in dilution buffer before analysis, and coefficients of variation were: intra-assay, 5.1–7.0% and inter-assay, 6.9–8.3%. The lower limit of sensitivity of the vaspin assay was 0.01 ng/mL. Serum was diluted 1:3 in dilution buffer before analysis, and coefficients of variation were: intra-assay, 6.5–8.7% and inter-assay, 5.8–9.5%. Fasting plasma insulin concentrations were measured by Dissociation-Enhanced Lanthanide Fluorescent Immunoassay (Siemens; Siemens Healthcare Diagnostics Products Ltd). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following equation: HOMA-IR = FPG (mmol/L) × fasting plasma insulin (mIU/L)/22.5.

2.3. Statistical analysis

All statistical calculations were conducted out using SPSS for Windows version 21.0 (SPSS Inc., USA). Results were expressed as mean ± SD, or median and range when data were not parametrically distributed. Data were examined by Student two-tailed unpaired *t*-test or the Mann-Whitney *U* test, where appropriate. Pearson correlation was used to examine relations between the three adipokines and BMI, glucose and lipid metabolism. Backward multiple linear regression was used to examine the principal determinants of estimates of adipokines, where independent variables were omitted from the model when $P > 0.1$. *P* values less than 5% were considered to be significant.

Table 1
Characteristics comparison between the TS group and the control group.

	TS group	Control group	t	P
Age (yr)	12.25 ± 3.95	12.38 ± 1.86	−0.284	0.815
BMI (kg/m^2)	18.90 ± 3.45	19.42 ± 2.95	−0.863	0.390
BMI SDS	0.39 ± 1.29	0.52 ± 1.32	−0.539	0.591
Systolic pressure (mmHg)	105.91 ± 13.13	103.80 ± 13.40	0.804	0.423
Diastolic pressure (mmHg)	69.07 ± 10.36	66.37 ± 9.27	1.395	0.166
Waist circumference (cm)	62.96 ± 11.00	65.45 ± 6.83	−1.398	0.166
Waist/hip ratio	0.85 ± 0.07	0.79 ± 0.08	4.601	< 0.001
Waist/height ratio	0.47 ± 0.05	0.43 ± 0.04	4.883	< 0.001
FPG (mmol/L)	4.89 ± 0.49	5.01 ± 0.45	−1.626	0.110
Fasting insulin (mIU/L)	12.10 ± 6.65	13.2 ± 4.47	−1.004	0.317
HOMA-IR	2.66 ± 1.60	2.95 ± 1.05	−1.170	0.245
TC (mmol/L)	4.65 ± 0.73	4.52 ± 0.71	0.975	0.332
HDL-C (mmol/L)	1.65 ± 0.38	1.57 ± 0.28	1.206	0.230
LDL-C (mmol/L)	2.66 ± 0.59	2.69 ± 0.54	−0.284	0.777
Non-HDL-C (mmol/L)	3.00 ± 0.67	2.94 ± 0.61	0.475	0.636
TG (mmol/L)	1.00 ± 0.44	0.95 ± 0.37	0.730	0.467

BMI: body mass index; BMI SDS: body mass index standard deviation score; FPG: fasting plasma glucose; HOMA-IR: homeostasis model assessment of insulin resistance; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride.

3. Results

3.1. Clinical characteristics

TS karyotypes were distributed as following: 45, X (23/64, 35.9%), chimera (25/64, 39.1%), structural abnormality (16/64, 25%). The mean age was 12.22 ± 3.98 yr, mean BMI was 18.90 ± 3.45 kg/m^2, and mean BMI SDS was 0.39 ± 1.29. Four children (4/64, 6.3%) were obese, while 11 were overweight (15.6%). The control group was matched in age, BMI, and BMI SDS with the TS group. The waist to hip ratio in the two groups were (0.85 ± 0.07) and (0.79 ± 0.08) ($P < 0.001$), respectively, whereas waist to height ratio was (0.47 ± 0.05) and (0.43 ± 0.04) ($P < 0.001$), respectively. Comparisons of anthropometric characteristics between the two groups are shown in Table 1.

In the TS group, FPG in 4 girls were over 5.6 mmol/L, the maximum was 6.38 mmol/L, and the 2-hour glucose in OGTT in these 4 girls were normal. HDL-C in 3 girls were low, non-HDL-C in 6 girls were high, and TG in 7 girls were high. Four girls were diagnosed with hypertension. In addition, no significant differences in FPG, fasting plasma insulin, HOMA-IR, blood lipid and blood pressure were found between the TS group and the control group (see Table 1).

3.2. Adipokines

Significantly higher levels of adioponectin (12.51 ± 4.58 μg/ml) and chemerin (173.71 ± 37.88 ng/ml) and significantly lower levels of vaspin (0.67 ± 0.47 ng/ml) were found in the TS group compared to the control group (9.30 ± 3.17 μg/ml, 159.43 ± 23.19 ng/ml and 1.06 ± 0.49 ng/ml, respectively) (Fig. 1).

3.3. Relationship of adipokines, BMI and metabolic index

In the TS group, serum adiponectin concentration was negatively correlated with age, BMI and TG (r = −0.251, −0.247, −0.294, $P < 0.05$ for all). In the control group, adiponectin levels were negatively correlated with BMI and BMI SDS (r = −0.416 and −0.315,

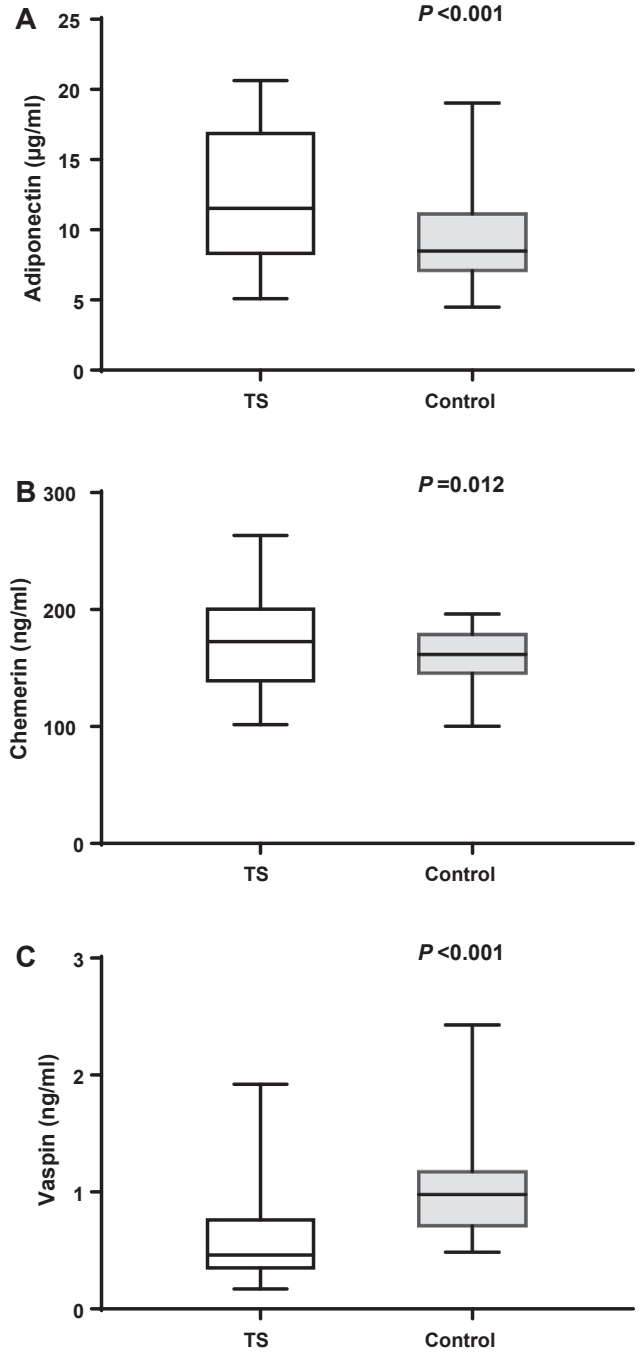

Fig. 1. Comparison of adiponectin (A), chemerin (B) and vaspin (C) between the TS group and the control group. Significance levels are indicated in each graph.

$P < 0.05$ for both), while vaspin levels were positively correlated with age, fasting plasma insulin and HOMA-IR (r = 0.257, 0.273 and 0.282, $P < 0.05$ for all) (see Table 2).

The principal determinants of adipokines were evaluated by backward multiple linear regression with measures of adipokines as dependent and independent variables. The significant variables were taken from the Pearson correlation analyses above.

In a multivariate model (r = 0.337, $P = 0.011$) with adiponectin in the TS group as the dependent variable, TG ($P = 0.026$) was the explanatory variable. Studying the same model in the control group (r = 0.392, $P = 0.005$), BMI was a significant explanatory variable. In a multivariate model (r = 0.489, $P = 0.014$) with vaspin in the control group, only age was a significant explanatory variable.

3.4. Relationship of adipokines and puberty

The two groups were divided into the non-puberty subgroup and puberty subgroup, respectively. Briefly, significantly higher levels of adiponectin were found in the non-puberty subgroup (13.88 ± 4.49) μg/ml compared to the puberty subgroup (9.72 ± 3.39) μg/ml ($P < 0.05$), while no significant differences between the puberty TS subgroup, the non-puberty control subgroup and the puberty control subgroup were found (Fig. 2). In addition, no statistically significant differences in chemerin and vaspin between non-puberty and puberty subgroups were found in both groups (Table 3).

4. Discussion

The present data confirmed disproportionate anthropometries in TS vs controls, as well as difference in serum adipokines concentrations. A range of metabolic indicators were analyzed for possible determinants of the adipokines.

Fat mass and BMI are higher in adult patients with TS compared with age- matched controls, the distribution of fat and muscle has also shown to be discordant with accumulation of both the trunk (a mixture of subcutaneous and visceral fat mass) and visceral fat mass determined by dual energy X-ray absorptiometry [7,8]. In our study, BMI SDS was 0.39 ± 1.29 in girls with TS, and 6.3% were obese, 15.6% were overweight, which were consistent with previous reports [5,9]. Further, waist to hip ratio and waist to height ratio in girls with TS were elevated compared to age- and BMI-matched controls. Therefore, TS is a syndrome of disproportionate anthropometry and body composition, prone to cause metabolic syndrome in children and adolescents [10].

Adipose tissue synthesizes a large number of bioactive adipokines, which affect glucose, lipid metabolism and energy balance and have a direct regulatory role on the cardiovascular system. Hence, we speculated that the dysregulation of adipokines may contribute to the pathogenesis of metabolic abnormalities in girls with TS.

Adiponectin protein is secreted by adipocytes and widely recognized for its antidiabetic, anti-inflammatory, antiatherogenic, and cardioprotective effects [11,12]. Adiponectin concentrations have shown to be lower in obese subjects compared with non-obese [13,14]. In this study, adiponectin levels were negatively associated with BMI in the control group, but not so in the TS group. Also, the adiponectin concentration was higher compared to the control group and higher in the non-puberty subgroup. In adult TS patients, similar comparisons have been reported, Høst et al. [15] reported that short time hormone replace treatment suppressed adiponectin levels in TS patients and withdrawing treatment for 2 months, increased the adiponectin levels. Consistent with our observation, estrogen suppressed adiponectin in mice and 3T3-L1 adipocytes [16]. The mechanism behind this phenomenon is still not clear, Høst and his team [15] suggested the estrogen may exert a direct effect on adiponectin secretion or clearance in TS patients, or can affect other mechanisms such as changes in fat distribution.

Chemerin, which is produced in visceral adipose tissue, placenta and liver, confers its biological function through binding to and activating the G protein-coupled receptor chemokine receptor-like 1 [17,18]. Furthermore, it regulates adipocyte differentiation and modulates the expression of adipocyte specific genes involved in glucose and lipid metabolism, and has a role in adaptive and innate immunity [19]. Chemerin concentrations are significantly higher in obese compared to lean children, and correlated with obesity-related parameters such as BMI SDS, leptin, and skinfold thickness [20]. Moreover, plasma chemerin levels have reported to be significantly associated with metabolic syndrome-related parameters, including BMI, fasting plasma

Table 2
The relationship between adipokines, BMI and metabolic index.

	Age	BMI	BMI SDS	FPG	Fasting insulin	HOMA-IR	TG	HDL-C	Non-HDL-C	Adiponectin	Chemerin	Vaspin
TS group												
Adiponectin	−0.247*	−0.251*	−0.034	−0.034	−0.047	−0.043	−0.294*	0.113	−0.054	–	−0.08	0.043
Chemerin	0.228	−0.105	−0.062	0.150	−0.088	−0.079	0.089	0.035	−0.220	−0.08	–	−0.194
Vaspin	−0.056	−0.070	−0.020	0.150	−0.088	−0.068	0.059	0.102	0.218	0.043	−0.194	–
Control group												
Adiponectin	−0.126	−0.416*	−0.315*	0.184	−0.065	−0.024	−0.196	0.049	0.219	–	0.036	0.02
Chemerin	−0.193	0.221	0.239	0.023	0.150	0.132	−0.004	0.070	0.037	0.036	–	−0.125
Vaspin	0.257*	−0.073	−0.113	0.085	0.273*	0.282*	0.142	0.025	0.125	0.02	−0.125	–

BMI: body mass index; BMI SDS: body mass index standard deviation score; FPG: fasting plasma glucose; HOMA-IR: homeostasis model assessment of insulin resistance; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride. *$P < 0.05$

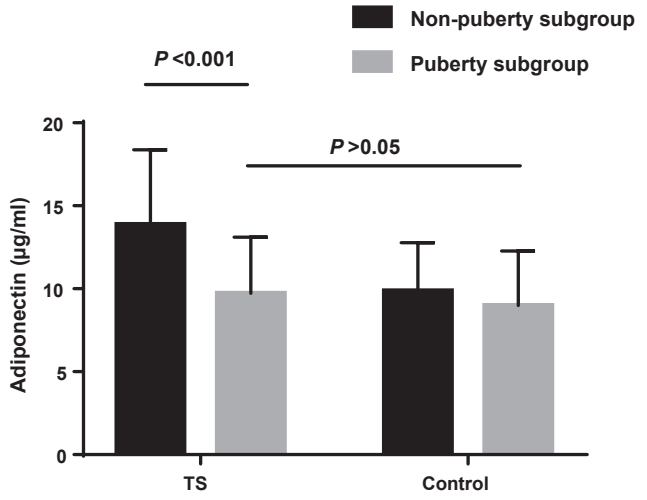

Fig. 2. Comparisons of adiponectin between the non-puberty subgroup and puberty subgroup. Significance levels are indicated in the graph.

Table 3
The relationship between adipokines and puberty.

	Non-puberty subgroup	Puberty subgroup	t	*P*
TS group				
N	43	21		
Adiponectin (μg/ml)	13.88 ± 4.49	9.72 ± 3.39	4.125	< 0.001
Chemerin (ng/ml)	168.41 ± 38.08	184.54 ± 35.94	−1.620	0.110
Vaspin (ng/ml)	0.71 ± 0.50	0.59 ± 0.40	0.993	0.325
Control group				
N	21	40		
Adiponectin (μg/ml)	9.87 ± 2.90	8.99 ± 3.29	1.207	0.309
Chemerin (ng/ml)	165.64 ± 35.94	156.17 ± 22.60	1.533	0.131
Vaspin (ng/ml)	0.98 ± 0.40	1.10 ± 0.53	−0.946	0.348

insulin, TG, and HDL-C, independent of age and sex in nondiabetic subjects [21]. Landgraf et al. [20] found an association of serum chemerin with obesity, as well as inflammatory and endothelial activation markers, thus implicating chemerin as a molecular link between fat mass accretion and an early atherogenic risk profile in obese children. In our study, chemerin levels were higher in Turner patients compared with BMI- matched controls, independent of BMI, perhaps contribute to the TS metabolic disturbances.

Vaspin, a member of the serine protease inhibitor family of serpins, has been recently proposed as a biomarker of human obesity which may contributes to related metabolic alterations [22,23]. A meta-analysis [24] found that serum vaspin levels were significantly higher in obese subjects or type 2 diabetes patients compared to non-obese healthy controls. Exogenous vaspin treatment results in reduced cytokine-induced activation of the intracellular and pro-inflammatory NF-κB signaling cascades in 3T3-L1 cells, moreover, vaspin increases insulin signaling [25]. Based on these observations, it has been suggested that an increase in vaspin could act as a compensatory mechanism against insulin resistance [26]. In this study, vaspin levels were significantly associated with insulin and HOMA-IR in the control group, while there was no correlation in the TS group, suggesting these children lack the vaspin related compensatory response.

In summary, compared to controls, girls with TS had higher waist to hip ratio and waist to height ratio. The serum adiponectin and chemerin levels in girls with TS were elevated, vaspin levels were significantly reduced, and puberty or estrogen replacement therapy may reduce adiponectin in girls with TS. Yet, in this study, there were no obvious changes in glucose and lipid metabolism in girls with TS. Further studies should elucidate whether there is additional relationship between adipokines and metabolic disorders in adult patients with TS.

5. Conflict of interest

The authors declare no conflict of interest.

6. Formatting of funding sources

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