RESEARCH ARTICLE

Association of serum irisin concentrations with the presence and severity of obstructive sleep apnea syndrome

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Objective: Obesity is involved in the pathogenesis of obstructive sleep apnea syndrome (OSAS). Irisin, a recently discovered myokine, protects the mice from obesity. This study aims to determine the association of serum irisin concentrations with the presence and severity of OSAS.

Methods: This cross-sectional investigation was performed in 165 male OSAS patients and 98 healthy male subjects. Serum irisin concentrations were assessed using an enzyme-linked immunosorbent assay kit.

Results: The serum irisin concentrations of OSAS patients significantly decreased compared with the healthy controls ($P < .001$). Multivariable logistic regression analysis indicated that serum irisin concentrations were an independent determinant of OSAS (OR .971, 95% CI .960 to .981; $P < .001$). Serum irisin concentrations were significantly reduced among patients with severe OSAS compared with patients with mild and moderate OSAS ($P < .001$ and $P = .010$, respectively). Spearman correlation analysis revealed that serum irisin concentrations were inversely correlated with OSAS severity ($r = -.327$, $P < .001$).

Conclusion: Decreased serum irisin concentrations are associated with the presence and severity of OSAS.

KEYWORDS

inflammation, irisin, obesity, obstructive sleep apnea syndrome

1 | INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by the cessation of respiration during sleep due to the obstruction of the upper airways.¹ OSAS is a highly prevalent disease affecting approximately 4% of males and 2% of females in the adult population.² OSAS contributes to increased morbidity and mortality of humans, particularly from cardiovascular diseases.³ The exact mechanism of OSAS is unclear. Recent investigations focused on the importance of obesity in the pathogenesis of OSAS. Furthermore, obesity is considered as the most important risk factor of OSAS.⁴ At least two out of every three OSAS patients are estimated to be obese.⁵ Subjects with a body mass

index (BMI) of more than 29 kg/m² exhibited a 10-fold increased risk for OSAS.⁵ Inflammation is also involved in the mechanism of OSAS.⁶ Lots of inflammatory molecules were demonstrated to be correlated with OSAS.⁶

Irisin, an exercise-induced myokine, is secreted into the circulation. Recently, irisin is secreted not only by muscle but also by adipose tissues. Therefore, irisin is also considered as an adipokine.^{7,8} Elevated irisin levels in the circulation increased the energy expenditure in mice with no changes in movement or food intake.⁹ Irisin reverses diet-induced obesity and diabetes by stimulating thermogenesis in mice by promoting the proliferation of brown adipocyte-like cells.¹⁰ In humans, serum irisin levels were found to be negatively correlated with BMI.⁷ Serum irisin concentrations were significantly lower in obese subjects than lean ones.¹¹ In addition, irisin restored ox-LDL-induced human umbilical vein endothelial cell dysfunction by reducing the levels of inflammatory

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genes.¹² Therefore, irisin is speculated to mediate the pathogenesis of OSAS through its anti-obesity and anti-inflammation effects.

This study aims to determine whether serum irisin concentrations are correlated with the presence and severity of OSAS.

2 | MATERIALS AND METHODS

2.1 | Patients

This study consisted of 165 male patients newly diagnosed with OSAS through polysomnography (PSG). The exclusion criteria included psychiatric disorders, history of alcohol and drug abuse, and systemic illnesses, such as cardiovascular, cerebrovascular, pulmonary, or neuromuscular disease. Ninety-eight male healthy subjects who went on a medical check-up in our hospital were recruited for the control group. The controls were matched with OSAS patients in age and BMI, and diagnosed without OSAS using PSG. Subjects with systemic illnesses such as heart failure, chronic renal failure, and chronic obstructive pulmonary disease were excluded from the control group. The study was designed according to the ethics guidelines of the Helsinki Declaration and was approved by the Institutional Research Ethics Board of our hospital. All patients provided a written informed consent for their participation in this study.

2.2 | Sleep study

Full PSG monitoring was performed by the Compumedics E-series Sleep System (Compumedics Sleep; Melbourne, Australia). Apnea was defined as the cessation of breathing for at least 10 seconds, whereas hypopnea referred to the 50% decrease in nasal airflow with at least 4% decrease in oxygen saturation. The apnea-hypopnea index (AHI) was the average frequency of apnea and hypopnea in 1 hour.¹³ Subjects with AHI <5 were included in the control group. The diagnosis of OSAS was based on AHI ≥ 5 events/h which was further subdivided into mild ($5 \leq \text{AHI} < 15$ events/h), moderate ($15 \leq \text{AHI} < 30$ events/h), and severe (≥ 30 events/h).¹³

2.3 | Measurements

During the initial examinations, the height, weight, and blood pressure of the subjects were measured. Venous blood was collected after at least a 10-hour fasting. The blood specimen was then centrifuged and stored at -80°C until examination. Serum irisin concentrations were measured using an enzyme-linked immunosorbent assay (#EK-067-29, Phoenix Pharmaceuticals, Inc., Belmont, CA, USA) [coefficient of variations (CVs) of intra assay: 5%-7%; CVs of inter assay: 12%-15%; detecting range: 0.1-1000 ng/mL; linear range: 1.29-27.5 ng/mL]. The serum was diluted to a suitable concentration to match the best linear range of the kit.

2.4 | Statistical analysis

Power and sample size calculators was utilized to calculate the sample size (α of .05 and power of 90%). A minimum of 21 subjects in

the OSAS and control groups are necessary to obtain the difference in serum irisin concentrations. Data are presented as means $\pm$ SD or median (interquartile range). Data normality was analyzed using the Kolmogorov-Smirnov test. The characteristics of OSAS patients were compared with healthy controls through unpaired *t*-test (normally distributed data) or Mann-Whitney *U*-test (not normally distributed data). Univariate analysis was performed and the variables with a $P < .10$ were then entered into a backward stepwise multivariate logistic regression model to calculate the odds ratio values (OR) and 95% confidence intervals (CI) for the presence of OSAS. Kruskal-Wallis test was used to compare the differences in serum irisin concentrations among patients with mild, moderate, and severe OSAS. Afterwards, Mann-Whitney *U*-test was performed to compare the subgroup differences in serum irisin concentrations among patients with mild, moderate, and severe OSAS. The correlation of serum irisin concentrations with the severity of OSAS and the correlation between serum irisin and other parameters were analyzed using Spearman correlation analysis. Statistical significance was accepted at a *P*-value of $< .05$.

3 | RESULTS

3.1 | Baseline clinical characteristics

Patients with OSAS demonstrated elevated levels of homeostasis model assessment-insulin resistance (HOMA-IR), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and AHI compared with healthy controls (Table 1).

3.2 | Serum irisin concentrations in OSAS patients

Serum irisin concentrations were significantly decreased in OSAS patients compared with healthy controls ($P < .001$; Table 1). Simple logistic regression analysis indicated that HOMA-IR (OR 2.844, 95% CI 1.915 to 4.223; $P < .001$), TC (OR 1.323, 95% CI 1.044 to 1.676; $P = .020$), LDL-C (OR 1.523, 95% CI 1.092 to 2.213; $P = .013$), and serum irisin (OR .973, 95% CI .964 to .983; $P < .001$) showed a trend toward an association with the presence of OSAS (Table 2). All these parameters were then entered into a multivariate logistic regression model. The adverse association of serum irisin concentrations with the presence of OSAS persisted (OR .971, 95% CI .960 to .981; $P < .001$) (Table 2).

3.3 | Serum irisin concentrations with the severity of OSAS

Patients with severe OSAS reported significantly lower serum irisin concentrations compared with those with mild and moderate OSAS ($P < .001$ and $P = .010$, respectively) (Figure 1). Furthermore, decreased serum irisin concentrations were observed among moderate patients compared with mild patients ($P = .014$; Figure 1). Spearman correlation analysis suggested the negative correlation of serum irisin concentrations with OSAS severity ($r = -.327$, $P < .001$).

TABLE 1 Clinical and biochemical characteristics of OSAS patients and healthy controls

	OSAS patients	Control	P-value
N	165	98	
Age (y)	54.36±6.94	54.72±5.99	.669
BMI (kg/m ²)	27.25±3.22	26.79±3.95	.299
SBP (mm Hg)	144.07±17.35	142.33±12.36	.385
DBP (mm Hg)	88.73±9.73	88.21±7.50	.654
HOMA-IR	3.30±0.81	2.70±0.80	<.001
TC (mmol/L)	5.50±1.10	5.16±1.16	.019
TG (mmol/L)	2.06±0.57	1.85±0.62	.133
LDL-C (mmol/L)	3.55±0.77	3.30±0.86	.012
HDL-C (mmol/L)	1.15±0.21	1.16±0.24	.765
AHI	17.00 (14.00-30.00)	2.00 (1.00-3.00)	<.001
Irisin (ng/mL)	117.00 (93.60-133.25)	135.70 (105.51-168.19)	<.001

OSAS, obstructive sleep apnea syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AHI, apnea-hypopnea index.

TABLE 2 Logistic regression Analysis for the presence of OSAS

	Simple regression		Multiple regression	
	OR (95%CI)	P	OR (95%CI)	P
Age (y)	0.992 (0.955-1.030)	.667		
BMI (kg/m ²)	1.040 (0.966-1.119)	.298		
SBP (mm Hg)	1.007 (0.991-1.024)	.384		
DBP (mm Hg)	1.006 (0.979-1.035)	.653		
HOMA-IR	2.844 (1.915-4.223)	<.001	3.288 (2.105-5.136)	<.001
TC (mmol/L)	1.323 (1.044-1.676)	.020	1.441 (1.098-1.890)	.008
TG (mmol/L)	1.213 (0.941-1.565)	.137		
LDL-C (mmol/L)	1.523 (1.092-2.213)	.013	1.548 (1.059-2.261)	
HDL-C (mmol/L)	1.242 (0.461-3.351)	.668		.024
Irisin (ng/mL)	0.973 (0.964-0.983)	<.001	0.971 (0.960-0.981)	<.001

Abbreviations as Table 1.

3.4 | The correlation of serum irisin with other parameters

Table 3 shows the Spearman correlation analysis results indicating the correlation of serum irisin with BMI ($r=-.230$, $P=.003$), LDL-C ($r=-.245$, $P=.001$), and AHI ($r=-.302$, $P<.001$).

4 | DISCUSSION

Obesity is considered a key risk factor for the development and progression of OSAS.¹⁴ Obese or severely obese patients showed approximately twice the prevalence of OSAS compared with normal-weight adults. In addition, mild OSAS patients experienced a 10% weight gain demonstrated a sixfold increased risk of progressing OSAS severity, whereas a 10% weight loss contributed to over 20% improvement

of OSAS severity.¹⁵ The exact mechanism of obesity leading to the development and progression of OSAS remains unclear. Obesity possibly results in and worsens OSAS by fat deposition at specific sites.¹⁶ Increased fat tissues in the neck may have additional effects on the collapsibility of the upper airway and increase OSAS susceptibility.¹⁷ In addition, many genetic polymorphisms may positively affect obesity and OSAS, and may be interrelated in the development of these conditions.¹⁸

Irisin stimulates the uncoupling protein 1 expression in white adipose cells in culture and in vivo.⁹ Irisin production is induced by exercise in mice and humans.⁹ In addition, elevated serum irisin concentrations help increase energy expenditure and weight loss in mice.⁹ Huh et al.¹⁹ reported that irisin caused the uncoupling protein 1 up-expression and consequently increased adipocyte energy expenditure and reduced lipid accumulation in human adipocytes. In addition, irisin inhibits preadipocyte differentiation, suggesting its additional role in

FIGURE 1 Serum irisin concentrations in mild, moderate, and severe obstructive sleep apnea syndrome (OSAS) patients. Severe OSAS patients showed significantly lower serum irisin concentrations compared with mild and moderate OSAS patients. Furthermore, there are decreased serum irisin concentrations in moderate patients compared with mild patients. ^a $P < .05$ vs patients with mild OSAS; ^b $P < .05$ vs. patients with moderate OSAS

TABLE 3 The correlation between irisin and other clinical parameters

Parameters	<i>r</i>	<i>P</i> -value
Age (y)	-.099	.206
BMI (kg/m ²)	-.230	.003
SBP (mm Hg)	-.047	.545
DBP (mm Hg)	-.033	.677
HOMA-IR	.104	.112
TC (mmol/L)	.018	.823
TG (mmol/L)	.047	.552
LDL-C (mmol/L)	-.245	.001
HDL-C (mmol/L)	.072	.359
AHI	-.302	<.001

Abbreviations as Table 1.

suppressing fat mass.¹⁹ Obese children showed increased circulating irisin levels after 1 year of exercise and lifestyle intervention.²⁰ All these findings demonstrated the important role of irisin in obesity. Obesity is a clear risk factor for OSAS. Therefore, irisin is hypothesized to have a protective role in the pathogenesis of OSAS by inhibiting obesity development. However, other studies reported contradicting results. In humans, serum irisin levels were found to be negatively correlated with BMI,^{7,21} whereas other investigators reported that circulating irisin levels were positively correlated with BMI.^{22–24} These inconsistent data may be caused by the different conditions or diseases among the subjects, as well as the differences in the populations, or the assays applied in the studies.

The OSAS mechanism involves inflammation. Irisin is demonstrated to have an anti-inflammatory role. The FNDC4 is a secreted

factor sharing high homology with FNDC5. The FNDC4 administration in bone marrow-derived macrophages helped reduce phagocytosis, increase cell survival, and reduce proinflammatory chemokine expression.²⁵ Irisin can provide protection against diabetic retinopathy through the potential effects on anti-interleukin-17A.²⁶ Irisin restored ox-LDL-induced human umbilical vein endothelial cell dysfunction by reducing the levels of inflammatory genes including interleukin-6 (IL-6), macrophage chemoattractant protein-1 (MCP-1), intercellular cell adhesion molecule-1 (ICAM-1), and vascular cell adhesion protein 1 (VCAM-1).¹² These findings indicated the anti-inflammatory role of irisin. Thus, irisin may be involved in the mechanism of OSAS development and progression through its anti-inflammatory effects.

Skeletal muscles are considered as an endocrine organ that secretes a number of myokines, including follistatin, myostatin, activin A, and irisin.²⁷ The present study demonstrated the decreased serum irisin in OSAS patients. However, no investigations have yet focused on the association of OSAS with other myokines. Thus, further studies are necessary to determine the role of other myokines in OSAS.

Serum irisin concentrations were found to be higher in numerous conditions or diseases. Increased circulating irisin was observed in patients with metabolic syndrome,²² polycystic ovary syndrome,²⁸ and non-alcoholic fatty liver disease.²⁹ The increased irisin levels may be attributed to either the increased secretion by adipose/muscle tissue and/or the compensatory irisin increase to overcome an underlying irisin resistance in these subjects.

This study has several potential limitations. First, the sample size was not sufficiently large to arrive at definitive conclusions. Thus, further studies with larger samples are warranted. Second, the cross-sectional design of our study requires its causative relation to be confirmed by future longitudinal studies. Third, we enrolled only male subjects in our study. There are significant gender differences in serum irisin concentrations. Irisin levels were lower in males than females.^{30,31} Therefore, this condition may lead to biased results. We intend to conduct a further study using a population of both male and female subjects.

In conclusion, serum irisin concentrations were negatively correlated with the presence and severity of OSAS.

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