Association of the serum irisin level with obstructive sleep apnea: a body mass index- and physical activity-matched study

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Abstract. Obesity is strongly correlated with the pathogenesis of obstructive sleep apnea (OSA); myokines may play important roles in this condition. We performed a body mass index- (BMI) and physical activity- (PA) matched study to explore the relationship between the irisin level and OSA. Ninety-six consecutive participants were recruited. After matching in terms of BMI and PA, 28 OSA patients and 28 healthy controls were finally included. Whole-night laboratory-based polysomnography was used to identify OSA. The Recent Physical Activity Questionnaire and Epworth Sleepiness Scale Questionnaire were employed to assess PA over the past 4 weeks, and daytime sleepiness. We measured serum irisin, fasting blood glucose, and insulin levels in blood samples. The serum irisin concentrations differed significantly between the control, mild OSA, moderate OSA, and severe OSA groups (p < 0.001) and correlated significantly with the apnea/hypopnea index (AHI) (r = –0.787, p < 0.001). All of age, BMI, neck, waist and hip circumferences, fasting blood glucose level, and the Epworth Sleepiness Scale and PA scores were associated with irisin levels (p < 0.05). After adjustment for these factors, the serum irisin level was independently correlated with the AHI (r = –0.428, p = 0.002). On forward logistic regression analysis, the association remained significant in the final multiple regression model (β = –0.107, p < 0.001). The serum irisin concentration was significantly correlated with OSA severity, independently of BMI and PA. Further studies are needed to determine the molecular mechanisms in play.

Key words: Obstructive sleep apnea, Irisin, Obesity, Physical activity
skeletal muscle is an endocrine organ secreting hormones termed myokines [9]. Any possible association between myokine levels and OSA has remained unexplored. If myokines were involved in OSA pathophysiology, this would provide a new insight for OSA diagnosis and prognosis.

Irisin is a myogenic factor discovered in 2012 and processed from the product of the FNDC5 gen [10]. Irisin induces the browning of subcutaneous adipocytes and increases energy expenditure. Irisin reverses diet-induced obesity and diabetes by inducing such browning and upregulating the expression of genes involved in heat production [11]. Many studies underline the positive role of irisin in metabolic processes; however, the association between this molecule and OSA is temporarily questioned. Until now, few studies have explored the relationship between irisin levels and OSA, and each exhibited limitation. Li [12] and Luo [13] found that lower serum irisin concentrations were associated with more severe OSA. However, the serum irisin concentration is associated with the body mass index (BMI) [14], physical activity (PA) [15], and glucose homeostasis [16], neither the BMI nor PA was considered in the present studies. Therefore, we used BMI- and PA-matched controls to explore the relationship between irisin levels and OSA.

Methods

Participants and measurements

Ninety-six consecutive participants evaluated in our sleep center were recruited from March 2018 to July 2018. OSA was diagnosed via overnight polysomnography (PSG); healthy controls who did not snore were recruited from a clinical study in our center. All subjects were asked to complete a questionnaire exploring prior illnesses and medical treatments. The Epworth Sleepiness Scale (ESS) was completed prior to PSG to assess daytime sleepiness. The Recent Physical Activity Questionnaire was used to assess PA over the past 4 weeks, allowing total energy expenditure (TEE) to be estimated as the PA score [17]. Body habitus was measured with subjects in light clothing and barefoot, using standard anthropometric methods. Waist (WC), hip (HC) and neck circumferences (NC) were the means of two measurements. BMI was the weight divided by the height squared (kg/m^2). Controls who had been diagnosed with or treated for OSA were excluded. We also excluded subjects with mental illness, a history of alcohol and/or drug abuse, and/or systemic cardiovascular, cerebrovascular, lung, or neuromuscular disease. Patients with sleep disorders other than OSA (upper airway resistance syndrome, restless leg syndrome, or narcolepsy) were also excluded. Subjects for whom data were incomplete were excluded. Finally, when matched for BMI and PA, we studied 28 OSA patients and 28 healthy controls. The study adhered to the ethics guidelines of the Helsinki Declaration and was approved by the Institutional Research Ethics Board of our hospital. All subjects provided written informed consent.

PSG

All OSA patients and controls underwent laboratory-based PSG (Alice 4; Respironics Inc., Pittsburgh, PA) in our sleep center. All PSG records were manually evaluated (using standard criteria) by a single skilled technician. The AHI is the number of apnea and hypopnea events/h of sleep. Subjects were divided into OSA (AHI ≥5/h) and control groups (AHI <5/h). We measured mean oxygen saturation (SaO_2), the minimum SaO_2, the percentage of time at SaO_2 <90% (CT90%), and the oxygen desaturation index (ODI).

Blood measurements

After overnight PSG, fasting blood samples were taken in the morning. Serum lipids and fasting serum glucose levels were measured in our hospital laboratory using an autoanalyzer (H-7600; Hitachi, Tokyo, Japan). The serum lipids assayed included total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL). Fasting serum insulin levels were measured immunoradiologically. Serum irisin levels were assayed using an AMEKO human irisin enzyme-linked immunosorbent assay kit (Shanghai Lianshuo Biological Technology Co. Ltd., Shanghai, China).

Statistical analysis

Continuous variables are presented as means ± standard deviations unless they were skewed; the latter variables are presented as means with 95% confidence intervals (CIs). Categorical variables are expressed as percentages. Differences between the OSA and control groups were examined using the independent Student’s t-test, Wilcoxon’s signed-rank test, Kruskal-Wallis H test or the χ² test, as appropriate. Correlations between variables and PSG parameters were sought using the Spearman or Pearson correlation test. A two-sided p-value < 0.05 was taken to indicate statistical significance. All statistical analyses were performed with the aid of SPSS software ver. 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

We finally included 28 OSA patients and 28 BMI-
PA-matched healthy controls. The demographic and clinical characteristics of all subjects are shown in Table 1. None of gender ratio, BMI, or TEE differed between the groups (all \(p > 0.05\)). None of the homeostasis model assessment of insulin resistance (HOMA-IR) score, or the WC, HC, ESS score, TC level, TG level, or LDL level differed significantly between the groups (all \(p > 0.05\)). All of age, NC, the HDL level, AHI, mean \(\text{SaO}_2\), minimum \(\text{SaO}_2\), ODI, CT90%, and irisin levels differed between the groups (all \(p < 0.05\)). The serum irisin level differed significantly between the control, mild OSA (5 ≤ AHI ≤ 15 events/h), moderate OSA (15 < AHI ≤ 30 events/h), and severe OSA groups (AHI >30 events/h) (\(p < 0.001\), Fig. 1).

**Table 1** Clinical characteristics of the OSA group and the control group.

| Indicators            | OSA group | Control group | \(p\)-Value |
|-----------------------|-----------|---------------|-------------|
| Sex (Female, %)       | 13 (46.4%)| 7 (25%)       | 0.163       |
| Age (years)           | 39.0 ± 9.1| 32.8 ± 7.5    | 0.007       |
| BMI (kg/m\(^2\))      | 23.7 ± 1.9| 22.7 ± 2.1    | 0.062       |
| NC (cm)               | 38.9 (36.1–41.8)| 35.4 (34.3–36.5)| 0.001      |
| WC (cm)               | 88.5 (83.1–94.0)| 87.3 (81.9–92.6)| 0.08        |
| HC (cm)               | 98.9 (97.1–100.8)| 95.9 (93.1–98.7)| 0.09        |
| FPG (mmol/L)          | 5.23 (4.97–5.50)| 4.98 (4.81–5.15)| 0.195       |
| Fasting insulin (mU/L)| 10.4 (8.02–12.69)| 9.27 (7.45–11.09)| 0.566       |
| HOMA-IR               | 2.48 (1.85–3.11)| 2.10 (1.63–2.56)| 0.432       |
| TEE (kcal/d)          | 2,327 ± 501| 2,520 ± 248   | 0.072       |
| ESS                   | 7.8 (5.8–9.8)| 5.8 (3.9–7.7)  | 0.158       |
| TC (mmol/L)           | 4.72 ± 0.92| 4.56 ± 0.85   | 0.495       |
| TG (mmol/L)           | 1.54 (1.20–1.89)| 1.31 (0.97–1.66)| 0.310       |
| HDL (mmol/L)          | 1.11 (1.04–1.19)| 1.32 (1.18–1.46)| 0.015       |
| LDL (mmol/L)          | 2.93 ± 0.76| 2.75 ± 0.68   | 0.393       |
| AHI (events/h)        | 26.4 (19.0–33.7)| 1.7 (1.2–2.2)  | <0.001      |
| Mean \(\text{SaO}_2\) (%) | 95.2 (94.8–95.7)| 96.4 (96.1–96.8)| <0.001      |
| Minimum \(\text{SaO}_2\) (%) | 83.4 (79.7–87.0)| 93.4 (92.8–95.1)| <0.001      |
| ODI                   | 22.7 (15.3–30.1)| 1.7 (1.2–2.3)  | <0.001      |
| CT90% (%)             | 4.6 (2.4–6.9)| 0.03 (0.01–0.06)| <0.001      |
| Irisin (ng/mL)        | 21.3 (11.8–30.7)| 61.7 (47.8–75.7)| <0.001      |

Data are expressed as the mean ± SD or means with 95% confidence intervals. Abbreviations: BMI, body mass index; NC, neck circumference; WC, waist circumference; HC, hip circumference; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TEE, total energy expenditure; ESS, Epworth sleepiness scale; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AHI, apnea hypopnea index; \(\text{SaO}_2\), oxygen saturation; ODI, oxygen desaturation index; CT90%, percentage of time spent at \(\text{SaO}_2\) <90%

**Correlation between serum irisin level and the severity of OSA**

The serum irisin level correlated significantly with the AHI (\(r = -0.787, p < 0.001\)) (Table 2) and also with the mean \(\text{SaO}_2\), minimum \(\text{SaO}_2\), ODI, and CT90% (all \(p < 0.001\)). All of age, BMI, NC, WC, HC, fasting blood glucose, ESS score, and TEE were associated with the irisin level (all \(p < 0.05\), Table 3). When adjusted for these factors, the serum irisin level correlated independently with the AHI (\(r = -0.428, p = 0.002\)). Using a PSG AHI cutoff ≥5, all participants were divided into the control and OSA groups. On forward logistic regression analysis, the irisin level was strongly associated with the AHI in the final multiple regression model (\(\beta = -0.107, p < 0.001\), Table 4).
Discussion

We found that the serum irisin level correlated significantly with the AHI, mean \( \text{SaO}_2 \), minimum \( \text{SaO}_2 \), the ODI, and the CT90%. After adjusting for age, BMI, the fasting blood glucose level, and the ESS and PA scores, the irisin level remained independently correlated with the AHI.

Many factors affect OSA pathogenesis; obesity is a key risk factor for OSA development and progression [18]. OSA is almost twice as common in obese than in normal-weight adults. A 10% weight gain predicts a 32% increase in the AHI; a 10% reduction yields a 26% improvement in OSA severity [19]. However, the mechanisms connecting obesity and OSA remain unclear. Recent studies have focused on the roles of respiratory muscles in this context. Obesity may impair skeletal muscle mitochondrial function and inspiratory muscle strength [20]; mitochondrial function recovers after weight loss [21]. However, the underlying mechanism remains unclear. In humans, irisin, a novel myokine, may play a role in abnormal metabolism and obesity development [10]. Irisin may protect against OSA pathogenesis by inhibiting the development of obesity. A few studies have reported correlations between irisin levels and OSA [12]. However, irisin levels are increased in individuals engaged in exercise-induced activities and progressively reduced in those less active [22], and may also be affected by BMI [23]; these factors were not considered in earlier studies. Therefore, we enrolled BMI- and PA-matched controls and found that irisin levels correlated significantly with OSA, independently of age, BMI, fasting blood glucose level, and ESS and PA scores.

Irisin acts on both adipose tissue and skeletal muscle [24], increasing energy expenditure and oxidative metabolism by inducing anabolic genes [25]. Irisin stimulates the expression of uncoupling protein 1 in white adipose cells [10] and promotes the browning of white adipose tissue, thereby increasing energy expenditure and promoting insulin secretion and islet \( \beta \)-cell restruction [26, 27]. Irisin reportedly exerts autocrine regulatory effects on muscle cells. In vivo, irisin injection promoted the synthesis of FNDC5 by muscle fiber cells in mice [28]. In vitro, C2C12 myofbroblasts were stimulated by irisin;
the expression of peroxisome proliferator-activated receptor γ coactivator 1α was increased, accompanied by increased mitochondrial concentration and oxygen consumption [29]. Therefore, irisin is regarded as a transmitter, sending signals that modulate the functions of adipocytes and skeletal muscle cells [30]. Levels of irisin are positively correlated with muscle mass [31] and strength [22]. Moreover, irisin is presumed to be the molecular link between muscle and brain, because it influences hippocampal neurogenesis and neural differentiation of embryonic stem cells in mice; moreover, it is considered to be a messenger between exercise and brain function. Because irisin is also regarded a messenger within the muscle–fat–bone–brain axis [32], it may be involved in OSA pathogenesis, which is characterized by dysfunctional metabolism and chronic neuromuscular injury. Our results suggest a potential connection between irisin and OSA; however, no molecular mechanism has yet been reported. Therefore, further work is necessary to elucidate the underlying processes in detail.

Our work had certain limitations including a small sample size and measurement of only a few parameters. Larger studies are required. Second, our work was cross-sectional in nature, so we cannot define causal relationships; these must be sought in future cohort studies featuring long-term follow-up. Finally, the molecular mechanism involved remains unclear.

### Conclusion

The serum irisin concentration correlated significantly with OSA severity, independently of BMI and PA. However, further studies are needed to determine the molecular mechanisms of irisin acting on OSA.

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### Conflict of Interest

The authors have no conflicts of interest to declare.

### Statement of Human Rights

This study was approved by the Ethics Committee of the Shanghai Jiao Tong University Affiliated Sixth People’s Hospital and complied with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

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