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Association of serum irisin concentration with thyroid autoantibody positivity and subclinical hypothyroidism

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Abstract

Objective: This study evaluated the association of serum irisin level with thyroid autoantibody (TAA) positivity and subclinical hypothyroidism (SH).

Methods: In this cross-sectional study, 334 participants were assigned to one of the following four age- and sex-matched groups: TAA plus SH (84 patients), isolated TAA (83 patients), isolated SH (83 patients), or healthy controls (84 individuals). Irisin and creatine kinase (CK) were measured in serum samples.

Results: Patients with TAA plus SH, isolated TAA, and isolated SH had higher irisin levels compared with the controls. There was a significant increase in the irisin level in the TAA plus SH group compared with the control group. Among all participants, the irisin levels were positively associated with thyroglobulin and thyroid peroxidase antibody titers and high-density lipoprotein cholesterol levels, but negatively associated with waist circumference, glycated hemoglobin levels, and fasting plasma glucose levels. The irisin level was not associated with the thyroid-stimulating hormone, free thyroxine, or CK levels. Irisin levels were independently associated with TAA, with or without SH, but they were not associated with SH alone.

Conclusions: Irisin level may help to predict the risk of developing TAA with or without SH.

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Introduction

Hashimoto thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is the most common autoimmune thyroid disease.[1,2] Thyroid autoantibodies (TAAs) are a key serum marker in patients with HT, and a recent Chinese study showed a prevalence of 14.2% for TAA, 10.9% for thyroid peroxidase antibodies (TPOAb), and 9.7% for thyroglobulin antibodies (TgAb).[3] A large proportion of the Chinese population are susceptible to developing HT, and approximately 20% to 30% of patients with HT have concurrent thyroid dysfunction, which generally manifests as subclinical hypothyroidism (SH) or clinical hypothyroidism.[4] Moreover, HT is the most common cause of SH and clinical hypothyroidism in iodine-sufficient areas, and it is associated with various metabolic diseases, including cardiovascular disease, hypertension, dyslipidemia, and insulin resistance.[5–7] Therefore, it is useful to identify individuals who have a high risk of developing TAA positivity or HT to guide the monitoring of thyroid function and treatment.

Irisin is a recently discovered adipomyokine that is the extracellular cleavage product of the membrane protein fibronectin type III domain containing 5 (FNDC5).[8] It can induce "browning and beiging" of white adipose tissue by increasing uncoupling protein-1 (UCP1) expression, increasing energy expenditure, and enhancing systemic metabolism.[9] Thus, irisin has attracted attention for its potential role in metabolic diseases. Moreover, it has been proposed that FNDC5 expression can be observed in the thyroid gland,[10] and that activation of thyroid hormone receptors can promote UCP-1 gene expression to induce "browning and beiging" of white adipose tissue.[11] Therefore, some recent studies have focused on the relationship between serum irisin level and thyroid function.

There are conflicting data regarding the possible relationships and regulatory mechanisms that are responsible for the association between irisin levels and clinical hypothyroidism or SH. For example, Zybek-Kocik et al.[12] reported that patients with clinical hypothyroidism that was caused by autoimmune thyroiditis had lower serum irisin levels than those of healthy controls, and that patients with hypothyroid condition also had elevated creatine kinase (CK) levels. The authors hypothesized that this might reflect a regulatory mechanism that involves muscle injury. However, other studies have revealed that the serum irisin levels are elevated among patients with clinical hypothyroidism that is caused by HT[13] and among patients with SH,[14] which might reflect a regulatory mechanism that is related to autoimmune thyroid inflammation. In addition, Samy et al.[15] and Atici et al.[16] observed elevated serum and heart tissue irisin levels[17] in rat models of hypothyroidism (vs. euthyroid rats), and they claimed that these elevated levels might be

associated with oxidative stress and muscle injury on the basis of their response to exercise. Moreover, serum irisin levels were positively associated with serum CK levels and with markers of oxidative stress in the muscle and liver, but they were not associated with thyroid-stimulating hormone (TSH) levels.[15] Panagiotou et al.[18] reported that serum irisin levels did not differ significantly between euthyroid individuals and individuals with iatrogenic hypothyroidism (due to thyroidectomy for thyroid cancer and withdrawal of thyroxin replacement treatment before radio-iodine ablation). Moreover, that study revealed that serum irisin levels were not associated with TSH, free thyroxine (FT4), free triiodothyronine (FT3), or CK levels. The influence of autoimmune thyroid inflammation could be excluded because the study included patients who had undergone thyroidectomy. Thus, there is a lack of clarity regarding the relationship between irisin levels and clinical hypothyroidism or SH in the context of autoimmune thyroid inflammation. Moreover, to the best of our knowledge, no previous study has evaluated the relationship between the irisin level and thyroid autoantibodies.[19] Therefore, we performed a cross-sectional study to evaluate serum irisin and CK levels among patients with isolated SH, isolated TAA positivity, TAA positivity plus SH, and healthy controls.

Methods

Design and patients

This cross-sectional study evaluated data from Guiyang (an iodine-sufficient area), which is one of 31 Chinese cities that participated in an epidemiological investigation of thyroid diseases in China.[3] The inclusion criteria were as follows: (i) $\geq$18 years old; and (ii) lived in the selected community for $\geq$5 years. The exclusion criteria were as follows: (i) pregnancy within the previous year; (ii) taking contraceptive drugs or estrogen; (iii) taking glucocorticoids or dobutamines; (iv) taking anticonvulsant drugs, such as phenytoin sodium; (v) any chronic degenerative or severe systemic disease, such as adrenal insufficiency and renal failure; and (vi) a history of receiving oral iodine-containing drugs or iodine-containing contrast agents during the previous 6 months. On the basis of these criteria, participants were recruited using stratified cluster sampling between October 2014 and March 2015. The participants completed a self-assessment questionnaire, a physical examination, and had overnight fasting blood samples collected, which were stored at -80°C until testing. The study protocol was approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University (approval date: 12 October 2014; approval number: 2014-86). All participants provided written informed consent upon enrollment. The study protocol was designed in accordance with the STROBE guidelines.[20]

Questionnaires and anthropometric measurements

The self-assessment questionnaires were administered by trained endocrinologists, who guided the participants in completing the standardized questionnaire, which included information on the following: (i) demographic characteristics (name, sex, date of birth, marital status); (ii) lifestyle factors (smoking, drinking, and coffee consumption); (iii) medical treatment (medication use, medical or surgical treatment); (iv) family history of disease; and (v) personal disease history. Physical examinations were also performed by trained endocrinologists, who measured height, weight, waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Body mass index (BMI) values were calculated as follows: weight/height^2 (kg/m^2).

Biochemical and hormone measurements

Venous blood samples were collected after a 12-hour fast. The laboratory tests included TSH, TPOAb, TgAb, fasting plasma glucose (FPG), plasma glucose 2 hours after an oral glucose tolerance test (2hPG), glycated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Abnormal results for the serum TSH level prompted additional testing to determine the FT4 level. The TSH, TPOAb, TgAb, and FT4 levels were determined using an automated immunoluminescence analyzer (Roche Cobas601; Roche Diagnostic, Basel, Switzerland). Lipid, FPG, and 2hPG levels were measured using an automated biochemical immunoanalyzer (OLYMPUS AU5400; Roche Diagnostic). CK levels were determined using a Roche Cobas c702 system (Roche Diagnostic). Serum irisin levels were determined using an enzyme-linked immunosorbent assay kit (detection range: 0.1–1000 ng/mL; EK-067-29, Phoenix Pharmaceuticals Inc., Burlingame, CA, USA), which is considered to be the best kit for measuring irisin levels and it has a $<10\%$ inter-assay coefficient of variation and a $<15\%$ intra-assay coefficient of variation.[21]

Statistical analyses

All statistical analyses were performed using IBM SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). The normality of data distribution was evaluated using the Shapiro–Wilk test and homogeneity of variance was evaluated using Levene's test. Normally distributed continuous variables were reported as the mean $\pm$ standard deviation, and non-normally distributed continuous variables were reported as the median and interquartile range. One-way analysis of variance was used for multiple comparisons of normally distributed variables, and significant differences were examined via post-hoc pairwise comparisons using the least significant difference test. Multiple comparisons of non-normally distributed variables were performed using the Kruskal–Wallis test. Categorical variables were reported as the frequency and percentage, and were compared using the chi-squared test. Correlations between the irisin level and the continuous variables were evaluated using Pearson or Spearman correlation coefficients. Binary logistic regression was used to evaluate the association between irisin level and isolated SH, isolated TAA positivity, and TAA positivity plus SH. Two-sided *P*-values of <0.05 were considered to be statistically significant.

Results

Clinical and biochemical characteristics

After excluding individuals with diabetes or hypertension and those using lipid-lowering drugs or other drugs that may affect thyroid function, there were 2245 eligible participants. Using the laboratory reference ranges, SH was defined on the basis of a TSH level of $>4.2\,\mu$IU/mL and a normal FT4 level. Positivity for TPOAb was defined as a TPOAb level of >34 IU/mL, and TgAb positivity was defined as a TgAb level of >115 IU/mL. TAA positivity was defined as a positive result for TPOAb and/or TgAb. Among the eligible patients, we performed matching according to sex and age (± 2 years), which resulted in matched groups with TAA positivity plus SH (84 patients), isolated SH (83 patients), isolated TAA positivity (83 patients), and healthy controls (84 patients; Figure 1). None of the 334 participants regularly engaged in strenuous exercise and the male-to-female ratio was 0.4:1.0.

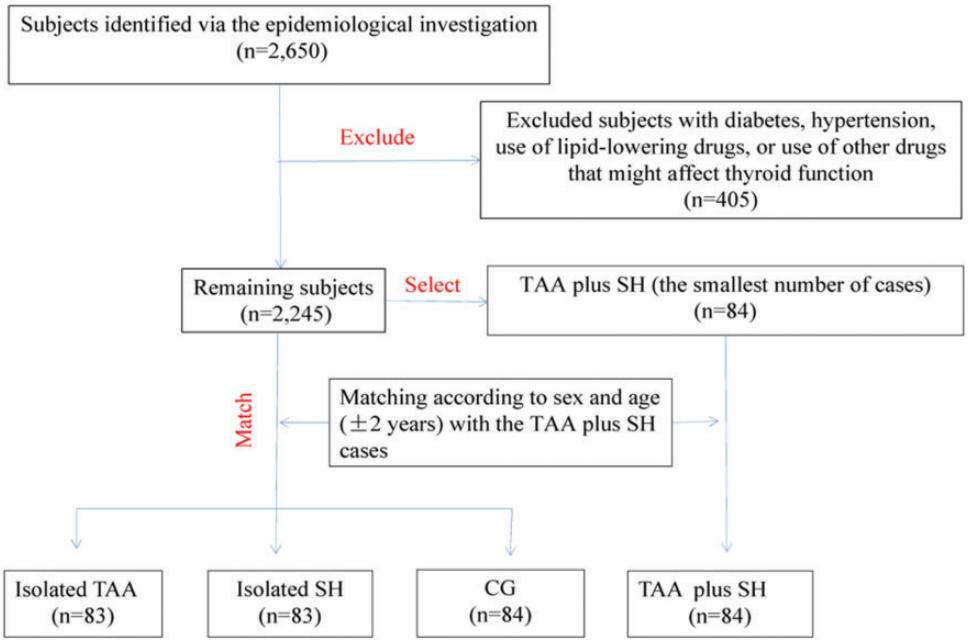

Figure 1. Study flowchart.

There were 24, 23, 24, and 24 men in the TAA plus SH, isolated TAA, isolated SH, and control groups, respectively. The participants were 44.8 ± 13.4, 44.1 ± 12.9, 44.4 ± 13.5, and 45.0 ± 13.3 years old in the four study groups, respectively. No significant differences were observed between the four groups for sex or for smoking history, coffee consumption, and alcohol consumption. The participants' characteristics are shown in Table 1. As expected, the two groups with SH had significantly elevated TSH levels ($P < 0.001$), while the two groups with TAA positivity had significantly elevated TPOAb and TgAb levels ($P < 0.001$) compared with the other two groups. The TAA plus SH group had significantly higher SBP than the isolated SH group ($P < 0.05$), TC levels were significantly higher in the control group than in the isolated TAA group ($P = 0.01$), and HbA1c levels were significantly higher in the control group than in the isolated SH group ($P < 0.001$). However, no significant intergroup differences were observed for age, height, weight, BMI, WC, or DBP, or for HDL-C, LDL-C, TG, FPG, 2hPG, or CK levels. There was also no significant difference in FT4 levels between the two groups with SH. As shown in Figure 2, the irisin levels were significantly higher in the TAA plus SH group than in the control group ($P = 0.006$), and the serum irisin levels in the control group tended to be lower than in the isolated TAA group and the isolated SH group, but these differences were not significant.

Correlations of irisin levels with the anthropometric, metabolic, and thyroid indicators

The correlations between irisin levels and the various indicators are summarized in Table 2. Among all participants, irisin levels were positively correlated with TgAb ($r = 0.122$, $P = 0.025$) and HDL-C levels ($r = 0.154$, $P = 0.005$), marginally

Table 1. Clinical and biochemical characteristics of the study subjects.

	TAA plus SH (n = 84)	Isolated TAA (n = 83)	Isolated SH (n = 83)	CG (n = 84)	*P*-value
Sex (male, %)	24 (28.57)	23 (27.71)	24 (28.92)	24 (28.57)	0.998
Coffee consumption (n, %)					0.434
Yes	9 (10.59)	15 (18.07)	15 (18.07)	16 (18.82)	
No	75 (89.41)	68 (81.93)	68 (81.93)	68 (81.18)	
Smoking history (n, %)					0.819
Smoker	16 (18.82)	16 (19.28)	13 (15.66)	18 (22.35)	
Non-smoker	68 (81.18)	67 (80.72)	70 (84.34)	66 (77.65)	
Alcohol consumption (n, %)					0.562
Yes	26 (30.95)	20 (24.10)	18 (21.69)	21 (25.00)	
No	58 (69.05)	63 (75.90)	65 (78.31)	63 (75.00)	
Age (years)	44.8 ± 13.4	44.1 ± 12.9	44.4 ± 13.5	45.0 ± 13.3	0.958
Height (cm)	158.0 ± 7.7	157 (153–164)	159.5 (155–165)	160.4 ± 9.4	0.185
Weight (kg)	59.0 ± 10.7	56.5 (50–61.4)	59 (52–64)	56 (49–62.9)	0.64
BMI (kg/m^2)	23.5 ± 3.3	22.3 (20.5–25.2)	22.6 ± 3.1	22.5 (20.0–24.6)	0.166
WC (cm)	84.4 ± 9.3	82.1 ± 9.1	83.4 ± 9.1	83.6 (75.9–91.1)	0.438
SBP (mmHg)[a]	122 (112–135)	117 (108–130)	114 (105–126)	119 (107–132)	0.03
DBP (mmHg)	78 (72–88)	79.4 ± 10.5	79 ± 9.7	79 (73–86)	0.965
HDL-C (mmol/L)	1.40 ± 0.31	1.37 ± 0.33	1.36 (1.13–1.57)	1.46 ± 0.34	0.302
LDL-C (mmol/L)	2.92 ± 0.71	2.77 (2.52–3.31)	3.06 ± 0.73	3.05 ± 0.83	0.21
TC (mmol/L)[b]	4.87 ± 0.95	4.66 (4.13–5.24)	4.91 ± 1.11	5.16 ± 1.07	0.015
TG (mmol/L)	1.36 (0.87–2.05)	1.2 (0.84–1.8)	1.34 (0.92–1.97)	1.37 (0.97–1.91)	0.692
HbA1c (%)[c]	5.4 (5.1–5.7)	5.4 (5.2–5.6)	5.3 (5.1–5.6)	5.56 ± 0.43	0.006
FPG (mmol/L)	5.33 (4.91–5.74)	5.27 (4.99–5.58)	5.44 (5.08–5.80)	5.33 (5.06–5.67)	0.353
2hPG (mmol/L)	5.62 (4.68–6.76)	5.64 (4.75–6.86)	5.54 (4.87–6.47)	5.77 (5.13–7.02)	0.444
TSH (μIU/mL)[c,d,e,f]	6.03 (4.71–7.93)	2.73 ± 0.79	5.38 (4.78–6.48)	2.58 ± 0.85	< 0.001
TPOAb (IU/mL)[a,b,e,f]	91.1 (41.06–279.3)	87.29 (34.09–264.8)	7.26 (5.14–10.52)	6.54 (5-9.82)	< 0.001
TgAb (IU/mL)[a,b,e,f]	195.7 (49.55–430.05)	128.4 (33.8–330.1)	12.33 (10.57–15.10)	12.56 (10.2–15.46)	< 0.001
Irisin (ng/mL)[e]	8.89 ± 1.70	8.57 ± 1.95	8.37 ± 1.68	8.14 ± 1.72	0.044

(continued)

Table 1. Continued.

	TAA plus SH (n = 84)	Isolated TAA (n = 83)	Isolated SH (n = 83)	CG (n = 84)	*P*-value
CK (U/L)	72 (56–100.8)	75 (60–104)	80 (59–116)	76.5 (66.3–91.8)	0.727
Free T4 (mmol/L)	15.42 (14.02–16.74)	–	15.1 (13.63–16.46)	–	0.371

Normally distributed variables are reported as the mean ± SD and non-normally distributed variables were reported as median (interquartile range).
[a]a significant difference ($P < 0.05$) between the TAA plus SH group and the isolated SH group.
[b]a significant difference ($P < 0.05$) between the isolated TAA group and the CG group.
[c]a significant difference ($P < 0.05$) between the isolated SH group and the CG group.
[d]a significant difference ($P < 0.05$) between the TAA plus SH group and the isolated TAA group.
[e]a significant difference ($P < 0.05$) between the TAA plus SH group and the CG group.
[f]a significant difference ($P < 0.05$) between isolated SH group and isolated TAA group.
TAA, thyroid autoantibody positivity; SH, subclinical hypothyroidism; CG, control group; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; HbA1c, glycated hemoglobin A1; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose after the OGTT; OGTT, oral glucose tolerance test; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; TPO, thyroid peroxidase; Ab, antibody; CK, creatine kinase; T4, thyroxine; SD, standard deviation.

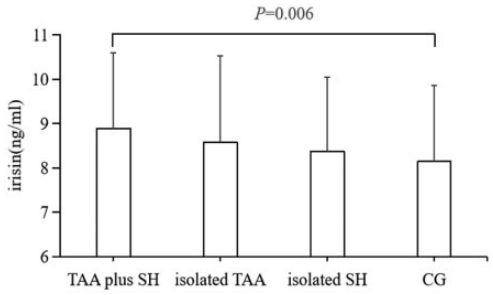

Figure 2. Box plots for circulating irisin concentrations in the four groups.

correlated with TPOAb levels ($r = 0.105$, $P = 0.05$), and negatively correlated with WC ($r = -0.127$, $P = 0.02$), FPG levels ($r = -0.111$, $P = 0.042$), and HbA1c levels ($r = -0.127$, $P = 0.02$). In the TAA plus SH group, irisin levels were positively correlated with age ($r = 0.238$, $P = 0.03$). In the isolated TAA group, irisin levels were negatively correlated with HbA1c levels ($r = -0.232$, $P = 0.035$). However, irisin levels were not significantly correlated with any of the indicators in the isolated SH group or the control group. Moreover, irisin levels were not significantly correlated with the overall TSH, FT4, or CK levels or among the participants in any of the four groups.

Association between the irisin level and TAA positivity

Before and after adjustment for associated confounders, a high irisin level was significantly associated with isolated TAA (odds ratio [OR] 1.167, 95% CI 1.030–1.321, $P = 0.015$; and OR 1.151 95% CI 1.008–1.315, $P = 0.038$, respectively; Table 3) and TAA plus SH (OR 1.184 95% CI 1.027–1.364, $P = 0.020$; and OR 1.178, 95% CI 1.014–1.369, $P = 0.033$, respectively; Table 4) but was not significantly associated with isolated SH (OR 1.093, 95% CI 0.967–1.235; OR 1.116, 95% CI 0.980–1.272, respectively; Table 5).

Table 2. Correlations between the various indicators and circulating irisin concentrations.

Variables	TAA plus SH (n = 84)		Isolated TAA (n = 83)		Isolated SH (n = 83)		CG (n = 84)		All subjects (n = 334)	
	r	*P*	*r*	*P*	*r*	*p*	*r*	*P*	*r*	*P*
Age	0.238	0.03*	−0.102	0.360	0.008	0.942	−0.008	0.942	0.051	0.355
BMI	−0.206	0.06	0.033	0.764	−0.118	0.286	−0.08	0.467	−0.092	0.094
TSH	−0.101	0.359	0.024	0.831	−0.089	0.421	0.121	0.274	0.05	0.367
TgAb	−0.031	0.780	0.016	0.888	−0.069	0.538	−0.072	0.518	0.122	0.025*
TPOAb	−0.063	0.569	−0.004	0.968	0.036	0.746	0.005	0.963	0.105	0.05
CK	0.191	0.082	−0.002	0.985	−0.067	0.545	0.063	0.570	0.061	0.268
WC	−0.134	0.225	−0.056	0.614	−0.167	0.131	−0.121	0.275	−0.127	0.02*
SBP	0.096	0.387	−0.007	0.953	−0.164	0.139	−0.024	0.826	−0.009	0.867
DBP	−0.072	0.513	0.034	0.763	−0.115	0.300	−0.075	0.500	−0.087	0.112
HDL-C	0.123	0.267	0.172	0.119	0.020	0.859	0.006	0.960	0.154	0.005**
LDL-C	−0.001	0.995	−0.105	0.344	−0.126	0.256	−0.011	0.919	−0.089	0.103
TC	0.054	0.627	0.050	0.652	−0.104	0.348	0.005	0.966	−0.019	0.730
TG	−0.018	0.868	−0.132	0.236	−0.035	0.753	−0.007	0.948	−0.093	0.09
HbA1c	−0.173	0.116	−0.232	0.035*	0.111	0.317	−0.069	0.535	−0.127	0.02*
FPG	−0.03	0.788	−0.119	0.284	−0.193	0.081	−0.028	0.802	−0.111	0.042*
2hPG	−0.033	0.763	0.097	0.385	0.019	0.867	−0.071	0.519	−0.018	0.743
Free T4	−0.012	0.913	–	–	−0.008	0.944	–	–	0.011	0.889

*$p < 0.05$, **$p < 0.01$.

TAA, thyroid autoantibody positivity; SH, subclinical hypothyroidism; CG, control group; BMI, body mass index; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; TPO, thyroid peroxidase; Ab, antibody; CK, creatine kinase; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; HbA1c, glycated hemoglobin A1; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose after the OGTT; OGTT, oral glucose tolerance test; T4, thyroxine.

Table 3. Odd ratios and 95% confidence intervals for risk of isolated TAA positivity according to serum irisin concentrations.

	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)[a]	*P*-value
Irisin	1.167 (1.030–1.321)	0.015	1.151 (1.008–1.315)	0.038

[a]OR adjusted for sex, age, fasting plasma glucose, 2-hour plasma glucose after the OGTT, glycated hemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, triglycerides, height, weight, waist circumference, and body mass index.

OR, odds ratio; 95% CI, 95% confidence interval; TAA, thyroid autoantibody positivity; OGTT, oral glucose tolerance test.

Table 4. Odd ratios and 95% confidence intervals for risk of TAA plus SH according to serum irisin concentrations.

	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)[a]	*P*-value
Irisin	1.184 (1.027–1.364)	0.020	1.178 (1.014–1.369)	0.033

[a]OR adjusted for sex, age, fasting plasma glucose, 2-hour plasma glucose after the OGTT, glycated hemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, triglycerides, height, weight, waist circumference, and body mass index.

OR, odds ratio; 95% CI, 95% confidence interval; TAA, thyroid autoantibody positivity; SH, subclinical hypothyroidism; OGTT, oral glucose tolerance test.

Table 5. Odd ratios and 95% confidence intervals for risk of isolated SH according to serum irisin concentrations.

	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)[a]	*P*-value
Irisin	1.093 (0.967–1.235)	0.153	1.116 (0.980–1.272)	0.097

[a]OR adjusted for sex, age, thyroid peroxidase antibodies, thyroglobulin antibodies, fasting plasma glucose, 2-hour plasma glucose after the OGTT, glycated hemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, triglycerides, height, weight, waist circumference, and body mass index.
OR, odds ratio; 95% CI, 95% confidence interval; SH, subclinical hypothyroidism; OGTT, oral glucose tolerance test.

Discussion

This study evaluated the relationships between serum irisin levels and isolated SH, isolated TAA positivity, and TAA positivity plus SH. The results revealed that, compared with the control group, elevated serum irisin levels were only observed in the TAA plus SH group. In addition, irisin levels were positively correlated with TgAb and TPOAb levels, but were not significantly associated with TSH, FT4, or CK levels. Thus, elevated irisin levels seem to be associated with an increased risk of TAA positivity with or without SH.

Irisin is a cytokine that was discovered in 2012 by Bostrom et al.,[9] and it is mainly synthesized and secreted by skeletal muscle to transmit information to other endocrine organs. Irisin reportedly induces "browning and beiging" of white adipose tissue and increases energy expenditure via upregulated UCP1 expression. Notably, thyroid hormones are endogenous regulators of brown adipose tissue,[22] which influences heat regulation. In addition, both triiodothyronine (T3) and irisin can improve UCP1 production, and T3 can suppress FNDC5 synthesis in human subcutaneous adipocytes.[23] There are similarities between the effects of thyroid hormone and irisin on metabolism. Therefore, it is plausible that these functions of thyroid hormones might be mediated by and/or attributable to changes in irisin levels.

This study revealed that serum irisin levels did not differ significantly between the control and isolated SH groups, and were not associated with TSH or FT4 levels, which is consistent with the results reported by Panagiotou et al.[18] However, these results conflict with the findings of Stratigou et al.,[14] who reported that serum irisin levels were significantly elevated in individuals with SH compared with healthy controls, and that irisin levels were positively correlated with the TSH levels. This discrepancy may be because some patients who were TAA-positive were included in the SH group in the study by Stratigou et al.,[14] while only patients who had undergone thyroidectomy were included in the study by Panigiotou et al.,[18] which would exclude the influence of autoimmune thyroiditis. Therefore, isolated SH may not be sufficient to cause changes in serum irisin levels. This may be related to the presence of TSH receptors in numerous tissues including the liver, adipose tissue, and bone, although there are limited data regarding TSH receptors in human skeletal muscle cells.[18] Thus, TSH may not be able to act directly on skeletal muscle cells to mediate the release of irisin.

Notably, serum irisin levels were significantly higher in the TAA plus SH group than in the control group, and irisin levels were positively correlated with TPOAb and TgAb levels. These results are consistent with previous reports.[13,14] Moreover, binary logistic regression revealed that elevated serum irisin levels were significantly associated with having TAA plus SH, which suggests that elevated serum irisin

levels in patients with clinical hypothyroidism or SH may be related to autoimmune thyroid inflammation. In this context, a previous study found that thyroid follicular cells were destroyed by chronic inflammation, which increased FNDC5 release and led to an increase in the serum irisin level.[13] In addition, irisin could have an anti-inflammatory effect by decreasing the levels of some proinflammatory cytokines (e.g., interleukin 6 and tumor necrosis factor alpha),[24] which participate in the autoimmune thyroid inflammation process. Therefore, the elevated serum irisin levels in participants in the TAA plus SH group may be related to the anti-inflammatory effects of irisin. However, other researchers have found that serum irisin levels were lower in patients with chronic autoimmune thyroiditis and hypothyroidism compared with the control group.[25,26] These conflicting results may reflect differences in the inclusion of patients with or without severe and sustained clinical hypothyroidism. Furthermore, a state of "irisin resistance" has been described, which involves the compensatory secretion of irisin immediately after thyroid injury, with a subsequent decrease in irisin levels over time as the thyroid injury worsens.[14] Moreover, this study revealed that the isolated TAA group had non-significantly higher irisin levels compared with the control group, which could be related to the small sample size. However, the binary logistic regression analysis revealed that elevated irisin levels may reflect an increased risk of TAA positivity. However, the TPOAb and TgAb levels were lower in the isolated TAA group than in the TAA plus SH group, but this decrease was not significant. These results suggest that less severe and a shorter duration of thyroid gland damage may not be sufficient to induce changes in serum irisin levels.[12]

We also compared the serum CK levels between the four groups to determine whether muscle injury explained the relationship between irisin levels and thyroid dysfunction. We found that CK levels were not significantly different between the four groups, and that CK levels were not significantly related to irisin levels. These results conflict with the findings from previous studies.[25,27] This inconsistency may be related to our selection of participants with newly diagnosed TAA positivity and SH. These participants had minimal muscle injury, which would be consistent with a lack of significant inter-group differences in the serum lipid indexes. However, our results are consistent with the findings from some studies,[18,28,29] and the lack of an association between the irisin levels and the CK levels could be explained because CK and irisin have different circadian secretion rhythms.[30]

To the best of our knowledge, this is the first study to identify an independent relationship between irisin levels and TAA positivity. However, the cross-sectional study design precludes a conclusion regarding the causality of this relationship. Moreover, we did not perform a sample size calculation because we were not aware of the likely effect size when planning the study, so the limited number of samples may have affected the statistical significance of the results. Thus, large prospective studies are needed to validate our findings and to determine whether there is a causal relationship between irisin levels and TAA positivity.

Conclusions

Our results suggest that serum irisin levels were not significantly associated with isolated SH or CK levels, but that they were closely associated with TAA positivity. Thus, irisin levels may help to predict the risk of TAA positivity, with or without SH. This may help physicians to identify and initiate early treatment in these patients.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Supplemental Material

Supplemental material for this article is available online.

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