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Difference in Circulating Irisin Levels before and after Treatment of Overt Hypothyroidism in Newly Diagnosed Autoimmune Hashimoto's Thyroiditis

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ABSTRACT

Background: Thyroid hormones have critical roles in regulating metabolism, muscle function, and thermogenesis. Autoimmune Hashimoto's thyroiditis is the leading etiology of overt hypothyroidism and is often associated with metabolic alterations.

Objective: This study aimed to assess differences in circulating irisin concentrations prior to and following management of overt hypothyroidism in newly identified patients with Hashimoto's thyroiditis and to explore associations between irisin concentrations and thyroid function indicators.

Methods: This case-control research, performed at the Internal Medicine Clinic in both Benha and Zagazig Universities. It included 12 healthy participants and 12 cases with overt hypothyroidism from Hashimoto thyroiditis. Serum levels of irisin, free thyroxine (fT4), anti-thyroid peroxidase (anti-TPO), TSH, free triiodothyronine (fT3), anti-thyroglobulin (anti-TG) and creatine kinase (CK) have been determined. Measurements were repeated after achieving euthyroid status following individualized levothyroxine therapy.

Results: At baseline, hypothyroid patients showed significantly greater anti-TPO, anti-TG, TSH, and CK concentrations and lower fT4, fT3, and irisin levels in comparison with controls (all p-values were below 0.001). After treatment, irisin concentrations significantly increased in the patients. Irisin was negatively related to anti-TPO, TSH, CK and anti-TG, and positively related to free thyroxine.

Conclusion: Cases with overt hypothyroidism from Hashimoto's thyroiditis had reduced circulating irisin levels, which significantly increased after restoring euthyroidism. The findings suggest that irisin level reflects thyroid hormone status and may serve as a metabolic biomarker in hypothyroid patients. Larger investigations are warranted to validate these results and clarify underlying mechanisms.

Keywords: Hypothyroidism, Hashimoto's thyroiditis, Irisin, Metabolism.

INTRODUCTION

The human body is greatly impacted by thyroid hormones, which are essential for the metabolism of proteins, fats, and carbohydrates. Additionally, they have significant impacts on the circulatory system and can control basal metabolic rate as well as facultative and obligatory thermogenesis [1, 2].

Thyroid hormones have an essential role in the regulation of numerous physiological processes, involving metabolism, growth, thermogenesis and neuromuscular function. Hypothyroidism is a condition that characterized by insufficient thyroid hormone production and it is a common endocrine disorder affecting individuals globally, with autoimmune Hashimoto's thyroiditis being the leading etiology in iodine-sufficient regions [3]. Hashimoto's thyroiditis is an autoimmune condition characterized by antibodies targeting the thyroid gland, causing chronic inflammation that progressively impairs the gland's capability to release thyroid hormones, resulting in a progressive loss of function and ultimately leading to hypothyroidism**,** or an underactive thyroid [4]. Skeletal muscle is a primary target of thyroid hormone signaling. Irisin was newly recognized as a myokine generated through exercise and released through skeletal muscle. The mediation of exercise is a useful influence on metabolism was suggested. Regulated via peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1-alpha (PG1-α) [5]. This myokine is proteolytically derived from the product of the fibronectin type III domain-containing protein 5 (FNDC5) gene before it is produced into the circulation. Fibronectin type III domain-containing protein 5 serves as the precursor to irisin and is found in different tissues, involving the thyroid gland. Nonetheless, irisin therapy wasn't related to alterations in cell proliferation or possible tumors in thyroid cell lines [6]. Overt hypothyroidism is clinically defined by increased concentrations of thyroid-stimulating hormone (TSH) and decreased concentrations of free thyroxine, often accompanied by various nonspecific symptoms such as fatigue, cold intolerance, weight gain and cognitive slowing. In autoimmune thyroiditis, elevated serum concentrations of thyroid peroxidase antibodies and thyroglobulin antibodies serve as serological hallmarks, reinforcing the autoimmune nature of the disease [7, 8].

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This research aimed to assess the variance in circulating irisin concentrations prior to and following management of overt hypothyroidism in recently identified autoimmune Hashimoto's thyroiditis.

PATIENTS AND METHODS

This case-control research, performed at the Internal Medicine Clinics in both Benha and Zagazig Universities. It included 12 healthy participants and 12 cases with overt hypothyroidism from Hashimoto's thyroiditis.

Inclusion criteria for patient group: Adults (>18 years), newly diagnosed overt hypothyroidism (thyroid-stimulating hormone > 4.78 mIU/mL and free thyroxine < 0.85 nanograms per deciliter), positive anti-thyroid peroxidase and/or anti-thyroglobulin antibodies, and ultrasound evidence of heterogeneous echogenicity in the thyroid gland.

Exclusion criteria (for all participants): Previous hormone replacement therapy, presence of chronic systemic illnesses (e.g., diabetes mellitus, hepatic, renal and cardiac disease), neurological or psychiatric disorders, known muscular disorders, pregnancy, obesity (BMI >30 kg/m²), as it significantly affects irisin concentration, regular engagement in strenuous physical activity or professional sports and use of daily medications affecting thyroid or muscle metabolism.

All patients were subjected to the following:

Clinical and laboratory assessment: All participants underwent a detailed history and full clinical examination, measurement of weight and height to estimate body mass index (BMI) and body composition assessment using a Tanita BC 418 MA analyzer.

Blood sampling: Venous blood samples have been collected in the morning (eight to ten AM) following an overnight fast (8–10 hours). In the hypothyroid group, baseline samples were taken before starting treatment; follow-up samples were collected after reaching euthyroid state (confirmed by normalization of TSH and fT4 after levothyroxine therapy).

Laboratory measurements: All collected blood samples have been centrifuged immediately, and serum aliquots have been stored at –80 °C until analysis.

Serum irisin levels was determined through enzyme-linked immunosorbent assay (ELISA) kit (Phoenix Pharmaceuticals, USA) detecting range from 0 to 100 nanograms per milliliter.

Thyroid function tests: Free triiodothyronine, thyroid-stimulating hormone and free thyroxine determined by electrochemiluminescence immunoassay (ECLIA) (Advia Centaur XP, Siemens, United States of America).

Autoantibodies: Anti-TG and Anti-TPO also determined by ECLIA.

Creatine kinase (CK) was assessed as an indicator of muscle injury using the photometric method (Architect C8000, Abbott Diagnostics, USA). All assays were performed in duplicate for reliability. Quality control measures, including intra- and inter-assay coefficients of variation, have been documented and found acceptable.

Intervention and follow-up: Patients in the hypothyroid group were treated with individualized doses of levothyroxine, adjusted based on initial TSH values and follow-up laboratory tests, to achieve euthyroidism. Duration to achieve euthyroid status was typically around 3 months.

STUDY VARIABLES

Primary outcome: Change in serum irisin concentrations prior to and following achieving euthyroidism. **Secondary outcomes:** Correlations between irisin levels and thyroid function parameters (fT3, fT4 & TSH), anti-thyroid antibodies (anti-thyroglobulin, anti-thyroid peroxidase), BMI and creatine kinase levels.

Ethical consideration: The study based on the principles stated in the Declaration of Helsinki for medical ethics for every research including human subjects. The study was performed after informed written consents from the patients after approval from the Ethical Committee of Faculty of Medicine, Banha University, Banha, Egypt (approval code: RC 19-7-2025).

Statistical Analysis

Information was examined applying IBM SPSS version 25. Continuous parameters were tested for normality utilizing the Kolmogorov–Smirnov test. Normally distributed parameters were represented as mean ± standard deviation (SD). Non-normally distributed data were represented as median (min–max). Between-group comparisons, independent t-test (parametric information) or Mann–Whitney U test (non-parametric) were used. Within-patient comparisons prior to and following management, paired t-test or Wilcoxon signed-rank test were used. Categorical parameters were described as percentages and frequencies and compared utilizing Fisher's exact test or Chi-square test. Correlations were evaluated utilizing Pearson or Spearman correlation coefficients as appropriate. A two-tailed p-value ≤ 0.05 has been deemed statistically significant.

RESULTS

An insignificant variance was observed among control and hypothyroid groups in BMI, age and sex distribution (all p-values above 0.05) (Table 1).

Table (1): Distribution of baseline characteristics among examined groups

Variable	Control group (number=12)	Hypothyroid group (number=12)	Test statistic	p-value
Age (years) mean ±SD	32.0 ± 3.8	35.2 ± 7.5	t = -1.32	0.205
BMI (kg/m²) mean ± SD	24.9 ± 3.1	27.5 ± 3.8	t = -1.84	0.08
Gender				
Male, n (%)	3 (25.0)	2 (16.7)	χ^2 = 0.252	0.615
Female, n (%)	9 (75.0)	10 (83.3)		

P-value above 0.05: Not significant, P-value below 0.05 is statistically significant, p-value below 0.001 is greatly significant, SD: Standard Deviation. BMI: body math index. X^2: Chi square test. T: independent t test.

A significant variance was observed among groups. The hypothyroid group had greater thyroid-stimulating hormone, anti-thyroid peroxidase, anti-thyroglobulin and creatine kinase concentrations, while it had lower fT4 and fT3 levels in comparison with controls (all p-values below 0.001) (Table 2).

Table (2): Distribution of laboratory findings among examined groups

Variable	Control group (number=12)	Hypothyroid group (number=12)	Test statistic	p-value
TSH (mIU/mL) Median (min-max)	2.2 (1.0–3.7)	14.8 (9.0–95.0)	MWU=4.12	< 0.001*
FT4 (ng/dL) Median (min-max)	1.25 (1.0–1.5)	0.68 (0.4–0.85)	MWU=-4.32	< 0.001*
FT3 (pg/mL) mean ±SD	3.31 ± 0.12	2.72 ± 0.37	t = 5.27	< 0.001
Anti-TG (U/mL) Median (min-max)	16.0 (15–36)	210 (20–480)	MWU=3.92	< 0.001*
Anti-TPO (U/mL) Median (min-max)	59 (13–104)	1270 (120–1300)	—	< 0.001*
CK (U/L) Median (min-max)	59 (13–104)	108 (80–159)	MWU=3.95	< 0.001

Irisin concentrations were significantly reduced in the hypothyroid group (56.3 ± 12.4 nanograms per milliliter) in comparison with the control group (79.5 ± 11.5 ng/mL) with a highly significant difference (t = 4.75, p-value below 0.001) (Table 3).

Table (3): Distribution of irisin levels among examined groups

Variable	Control group (number=12)	Hypothyroid group (number=12)	Test statistic	p-value
Irisin (ng/mL) mean ±SD	79.5 ± 11.5	56.3 ± 12.4	t = 4.75	< 0.001

There were significant correlations between irisin levels and several clinical variables. Irisin was negatively related to TSH (r = -0.58, p-value equal to 0.001), anti-TG (r = -0.53, p-value equal to 0.001), anti-thyroid peroxidase (r = -0.47, p-value equal to 0.002) and CK (r = -0.33, p-value equal to 0.030). Positive correlation was observed with fT4 (r = 0.61, p-value below 0.001). No significant association was found with age, BMI and fT3 (Table 4).

Table (4): Correlation between irisin and clinical variables

	Irisin	
	R	**p-value**
Age (years)	-0.120	0.420
BMI (kg/m²)	-0.220	0.150
TSH (mIU/mL)	-0.580	0.001
fT4 (ng/dL)	0.610	<0.001
fT3 (pg/mL)	0.190	0.230
Anti-TG (U/mL)	-0.530	0.001
Anti-TPO (U/mL)	-0.470	0.002
CK (U/L)	-0.330	0.030

DISCUSSION

Our findings showed that there were insignificant variances among control and hypothyroid groups in BMI, age and sex distribution (all p > 0.05).

This is in accordance with **Uc *et al.*** [9], who investigated the potential alterations in serum irisin levels prior to and following management in hypothyroid individuals, their research was performed on twenty-six cases with overt hypothyroidism because of Hashimoto's thyroiditis and nineteen healthy individuals. They showed insignificant variances among the two groups concerning age, sex, and body mass index with a p-value above 0.05.

Also, **Halawa *et al.*** [10] estimated serum irisin level in 30 cases with hypothyroidism compared to thirty normal individuals. There were insignificant variances that were observed among control and hypothyroid groups in gender and age distribution with a p-value above 0.05. However, a significant variance was observed among the two groups as regards BMI. In contrast with our result, **Malhotra *et al.*** [11] evaluated irisin in thyroid patients and reported that there were significant variances among the two groups (normal and hypothyroid) as regards BMI with a p-value of 0.0156. BMI may have influenced their assessment of irisin levels. This discrepancy might be clarified by variances in research design, population features, or sample size.

The current research demonstrated that the hypothyroid group had greater anti-TG, anti-TPO, TSH and CK concentrations and lower fT4 and fT3 levels in comparison with controls (all p-values below 0.001). This is consistent with ***Uc et al.*** [9] who found that cases with hypothyroidism had significantly reduced free thyroxine and greater anti-TG, anti-TPO, CK and TSH concentrations in comparison with the control group (p-value below 0.001).

Also, **Halawa *et al.*** [10] found that CK concentration was significantly elevated in hypothyroid cases compared to normal individuals, a greatly significant variance among hypothyroid and normal groups regarding thyroid-stimulating hormone (p-value below 0.01), and lower fT4 and fT3 levels.

Regarding irisin levels, this study demonstrated that irisin concentrations were significantly decreased in the hypothyroid group (56.3 ± 12.4 nanograms per milliliter) in comparison with the control group (79.5 ± 11.5 ng/mL), with a greatly significant variance (t = 4.75, p-value below 0.001). This is consistent with **Ateş *et al.*** [12] who determined the association between the irisin hormone, which has an influence comparable to thyroid hormones on the metabolism and adipose tissue and the thyroid functions. They found that irisin concentrations were reduced in cases with newly identified Hashimoto's thyroiditis-dependent hypothyroidism. As well, **Halawa *et al.*** [10] found that irisin hormone concentration significantly reduced in hypothyroid cases because thyroid hormones regulate metabolism and muscle function. In hypothyroidism, reduced thyroid hormones lead to slower metabolism and impaired muscle activity, resulting in less irisin production. Since irisin is mainly released by muscles during physical activity, muscle weakness and reduced energy expenditure in hypothyroid patients cause a significant drop in irisin levels. Also, **Uc *et al.*** [9] revealed that serum irisin concentrations were significantly reduced in cases with hypothyroidism in comparison with the control group, at 58.8±13.8 and 80.1±12.1 nanograms per milliliter, respectively, with a p-value <0.001.

Concerning correlations between irisin and clinical variables, the current study showed that irisin was negatively related to TSH (r = -0.58, p-value equal to 0.001), anti-thyroglobulin (r = -0.53, p-value equal to 0.001), anti-thyroid peroxidase (r = -0.47, p-value equal to 0.002), and CK (r = -0.33, p-value equal to 0.030). Positive association has been observed with fT4 (r = 0.61, p-value below 0.001). No significant association was found with age, BMI, or fT3.

Consistent with our results, **Uc *et al.*** [9] reported that significant negative association has been found among TSH and irisin, anti-thyroid peroxidase and irisin, anti-thyroglobulin and irisin and creatine kinase and irisin concentrations (r=−0.623, p-value below 0.001; r=−0.508, p-value below 0.001; r=−0.566, p-value below 0.001 & r=−0.389, p: 0.008 correspondingly). Whereas, a significant positive association among irisin and fT4 concentrations has been observed (r=0.570, p-value below 0.001) across the entire study population. No

correlation has been detected among irisin concentrations and other laboratory variables in the hypothyroid group. Also, **Zybek *et al.*** [13] assessed serum irisin levels in cases with thyroid dysfunction and its association with creatine kinase (CK) concentrations. They performed their study on twenty cases recently identified with thyroid dysfunction. They found a positive association among irisin and free T4 (p-value equal to 0.036) and a negative association among irisin and creatine kinase (p-value equal to 0.014) indicating the profound effect of impaired thyroid function on irisin concentrations.

Similarly, **Yang *et al.*** [14] showed that irisin concentrations had a positive association with FT4 and FT3 concentrations, while a negative correlation with thyroid-stimulating hormone concentrations. Free thyroxine was a significant predictor of serum irisin concentration.

CONCLUSION

Circulating irisin concentrations were significantly reduced in cases with overt hypothyroidism because of autoimmune Hashimoto's thyroiditis compared to healthy controls. The findings indicated a strong inverse association among irisin concentrations and markers of hypothyroidism severity, such as TSH, anti-thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulin) and creatine kinase levels, while a positive correlation existed with fT4 levels. These results suggest that irisin may be influenced by thyroid hormone status and might possibly act as a biomarker for metabolic alterations associated with hypothyroidism. Additional study with larger sample sizes is recommended to confirm these results and discover the mechanistic link between thyroid function and irisin regulation.

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Conflict of Interest: Nil.

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