

Irisin and Insulin Interplay in Thyroid Disorders: A Pilot Study

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ABSTRACT

Background: This research was performed to evaluate Irisin and Insulin concentrations in Thyroid patients.

Material and methods: This investigation was performed as a cross-sectional study within the Biochemistry Department at KMC, Mangalore, and the Central Lab at KMCH-AT, Mangalore. Participants were classified into two cohorts: those having regular thyroid function as well as those having thyroid disorder, including both hypothyroid and hyperthyroid patients, with 28 individuals (n = 28) in each category based on thyroid stimulating hormone (TSH) levels obtained during thyroid dysfunction screenings. Socio-demographic variables like height, weight, and body mass index were calculated, along with the assessment of hypertensive or hypotensive conditions. Insulin levels were quantified using an automated analyzer system. Statistical analyses were performed utilizing Easy-R (EZR) version 1.55, developed by Jichi Medical University in Saitama, Japan. The normal distribution of the parameters was evaluated through normality tests, with t-tests and Kruskal-Wallis tests applied as appropriate.

Results: Irisin levels significantly declined in hypothyroid individuals while showing an insignificant rise in hyperthyroidism. Insulin levels significantly increased in hyperthyroid patients compared to normal and hypothyroid groups. A positive correlation between insulin and irisin was found in hypothyroidism, while a negative correlation was observed in hyperthyroidism.

Conclusion: Preliminary findings of this study indicate a potential interdependence between Irisin and thyroid levels. Investigating the interaction between the thyroid profile and irisin can pave the way for considering irisin as a biomarker for novel treatment strategies in thyroid disorders and metabolic conditions.

Keywords: Adipose tissue, Irisin, Metabolic changes, Thyroid disorders

Introduction

Sedentary behavior is related to a greater likelihood of various health disorders like obesity, diabetes, cardiac disorder, certain cancers, as well as neurological disorders. Irisin, a hormone produced during exercise, is derived from the proteolysis of FNDC5, a cell membrane protein, and plays a crucial role in connecting muscles with other tissues. Recent research has highlighted the numerous beneficial effects of irisin, including the browning of adipocytes, modulation of metabolic processes, and regulation of bone metabolism. White adipocytes, which are associated with endocrine

functions, can impact various metabolic processes. The uncoupling protein 1 (UCP1), also called thermogenin, is responsible for distinguishing cellular respiration from heat production and is found in the mitochondrial membranes of brown adipose tissue. Beige or brown fat cells produce thermogenic cells, which can help prevent obesity (1).

Thyroid hormones appear to function as natural thermogenins by disrupting the process of mitochondrial ATP synthesis, thereby generating heat instead of producing ATP. These hormones significantly influence lipid profiles and insulin sensitivity, with one potential outcome being obesity (2,3). The incidence of hyperthyroidism is notably higher in Asian populations compared to European populations. Both hyperthyroidism and hypothyroidism are common medical conditions, with spontaneous hypothyroidism occurring in approximately 1% to 2% of the population. Individuals exhibiting clinically or subclinically impaired thyroid function are at an increased risk for cardiovascular issues, complications associated with abnormal lipid metabolism, and disorders of the musculoskeletal system (4).

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Brown adipocytes and skeletal muscle cells, which are derived from myf5-expression, are under the regulation of transcriptional regulators such as PRDM16, PGC1a, and others. A recent animal model study demonstrated that chronic rosiglitazone, a PPAR γ agonist, activation of mouse preadipocytes from epididymal white adipose tissue revealed that UCP1-expressing adipocytes have the ability for thermogenesis but lack the expression of BAT transcription factors like ZIC1 and PRDM16. These cells are known as “brute” (brown-in-white) adipocytes. The transition from PGC1 overexpression in mouse skeletal muscle, as well as exercise-induced expression of the FNDC5 gene, has been previously overlooked despite the initial reports of the mouse sequence of FNDC5 in 2002 by two distinct groups. FNDC5 is highly expressed in adult murine tissues but to a lesser extent in skeletal muscle. The protein FNDC5 is a precursor peptide, which, upon proteolytic cleavage, gives rise to irisin. Previous studies have shown that the FNDC5 gene is also associated with the development of myoblasts and neurons (5).

Recent research has shown that irisin has the capacity to impact the functionality of pancreatic islets. More specifically, irisin has been proven to boost insulin production as well as hasten glucose-stimulated insulin release in pancreatic cells by means of a process that relies on protein kinase A (PKA). In situations marked by elevated levels of glucose or fat, irisin has displayed the capability to enlarge cell size while decreasing cell death within pancreatic islets. Additionally, it promotes cell growth, enhances insulin production and secretion, and has the ability to affect insulin signaling. For example, in mouse C2C12 myoblasts, the overexpression of irisin led to heightened glucose absorption, glycogen synthesis, and activation of AMPK/insulin receptor subunit/ERK1/2 following insulin administration. Another recent investigation demonstrated that irisin counteracts the inhibition of insulin signaling caused by palmitic acid in rat cardiomyocytes, underscoring its potential to amplify insulin-triggered glucose absorption through activation (6).

Material and methods

Inclusion criteria

Age group 18-35 years, both male and female, non-alcoholic, non-smoking individuals. Newly diagnosed thyroid disorder patients were included in the study.

Exclusion criteria

Known diabetics, known malignancies, patients with cancer therapy, women with pregnancy, lactation, menopause or on oral contraceptives were excluded.

This investigation was performed as a cross-sectional study within the patients who were referred for thyroid stimulating hormone (TSH) investigations to the Biochemistry laboratory section at the Central Lab at KMCH-AT, Mangaluru. Participants were classified into two groups based on their TSH levels: those with normal thyroid function and those with thyroid disorders, both hypothyroid and hyperthyroid patients, constituting 28 individuals (n = 28) in each group.

Socio-demographic variables like height and weight were recorded, and Body Mass Index was calculated, along with the

assessment of hypertensive or hypotensive conditions using medical records. Insulin levels were quantified using ELISA kits obtained from DRG diagnostics. Irisin levels were measured using ELISA kits procured from Origin Labs. (The detection range was 15.63-1000 pg/ml, and sensitivity was 6.9 pg/ml) TSH levels were analyzed by ECLIA using Roche-COBAS Pro Immunomodule autoanalyzer at KMC hospital Attavar. Statistical analysis was performed using EZR (Easy-R) version 1.55, developed by Jichi Medical University in Saitama, Japan. The normal distribution of the parameters was evaluated through normality tests, with t-tests and Kruskal-Wallis tests applied as appropriate.

Results

TABLE 1 - Descriptive statistics of study groups with parameters expressed as Mean \pm SD for normal data and median with (Q1, Q3) for skewed data

Parameters	Normal	Hypothyroid	Hyperthyroid
Age	25.89 \pm 6.2	26.8 \pm 5.09	28.5 \pm 4.71
Weight	66.0 \pm 13.4	73.0 \pm 14.01	62.3 \pm 11.33
BMI	23.9 \pm 5.17	27.2 \pm 4.68	22.6 \pm 4.11
Irisin	1.01 (0.44, 1.26)	1.57 (1.27, 1.86)	0.98 (0.5, 1.22)
TSH	2.23 (1.51, 3.08)	6.94 (5.41, 14.4)	0.24 (0.03, 0.40)
Insulin	29.39 (15.35, 67.57)	9.54 (3.72, 33.03)	32.79 (14.43, 87.06)

TABLE 2 - Inter-group comparisons showing p-values (only)

Statistical Analysis	Hyperthyroid vs Hypothyroid	Normal vs Hyperthyroids	Normal vs Hypothyroids	Hyper-Hypo-Normal
TSH	<0.001	<0.001	<0.001	<0.001
Insulin	0.0287	0.954	0.0047	<0.001
Irisin	<0.001	1	<0.001	<0.001
BMI	<0.001	0.307	0.0156	0.00138

The above table shows the level of significance obtained between the three groups ($p < 0.01$). Parametric Independent sample t-test and non-parametric Mann-Whitney U test were done to analyze the data between the two groups. One-way ANOVA and Kruskal-Wallis were done to find the significant change between all three groups.

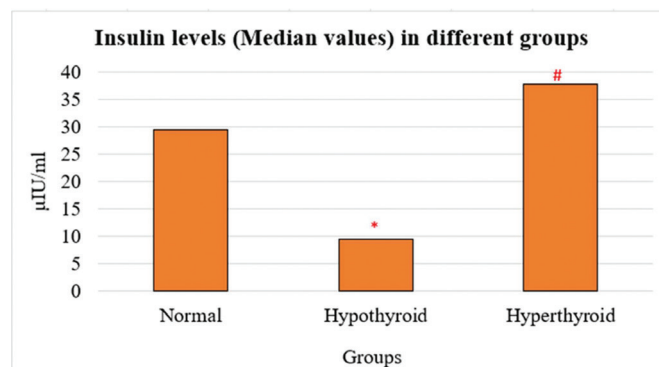


FIGURE 1 - Median values for insulin levels. * denotes $p < 0.005$ in comparison with the normal group. # denotes $p < 0.005$ in comparison with the hyperthyroid group.

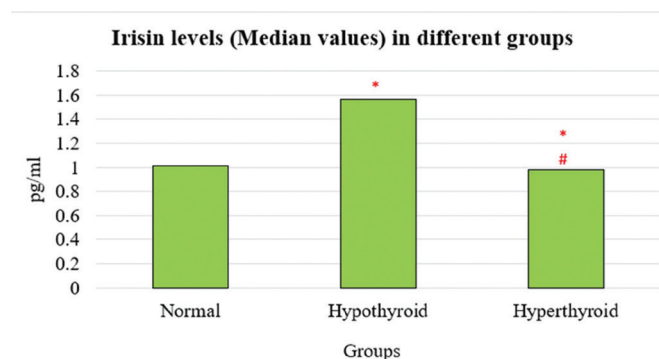


FIGURE 2 - Median values for Irisin levels. * denotes $p < 0.005$ in comparison with the normal group. # denotes $p < 0.005$ in comparison with the hyperthyroid group.

There had been a marked decline in irisin concentrations in individuals with hypothyroidism, while there was a statistically insignificant rise in irisin concentrations in those having hyperthyroidism. The difference in irisin levels among the three groups was deemed significant. On the other hand, the insulin levels exhibited a highly significant increase in the hyperthyroid group when compared to both the normal and hypothyroid groups. Additionally, there had been a positive association between insulin as well as irisin concentrations in individuals with hypothyroidism, whereas a negative correlation was noted in those with hyperthyroidism.

Discussion

Thyroid disorders represent chronic endocrine conditions that impact individuals globally. These disorders typically necessitate lifelong management and are linked to greater fatality rates as well as morbidity, especially among older populations. Balance in the circulating thyroid hormones is disturbed, leading to alterations in metabolic parameters and subsequent metabolic dysfunction. The irisin molecule has emerged as a potential agent for the prevention, monitoring, and management of significant metabolic disorders, including polycystic ovarian syndrome (PCOS), obesity, diabetes, chronic renal disorder, ischemic heart disease, as well as high blood pressure (6).

Despite the prevalence of thyroid diseases, the parameters utilized for monitoring treatment remain insufficient. In 2012, researchers identified irisin as a promising myokine released from its precursor protein FNDC5 in response to physical activity, which facilitates the transformation of white adipose tissue (WAT) into brown adipose tissue (BAT). A variety of studies have highlighted the role of irisin in physiological adaptations, particularly concerning exercise. For example, research conducted on murine models examined the role of irisin in promoting the browning of WAT as a result of exercise (7). There is limited or no proof that physical activity has an impact on WAT browning in humans. This investigation examines the connection between “irisin,” insulin, and TSH in hypothyroid and hyperthyroid individuals (8,9).

Irisin has the potential to impact the functioning of the thyroid gland. The communication of thyroid hormones occurs through both central and peripheral pathways,

affecting energy expenditure. The central pathway involves the hypothalamus, which secretes “thyrotropin-releasing hormone (TRH)” in response to various stimuli like low levels of thyroid hormones or exposure to cold temperatures. Once released into the bloodstream, T4 is transformed into the more active form, T3, in peripheral tissues like the liver, kidneys, and skeletal muscles. T3 then adheres to particular receptors in target tissues, including adipose tissue, muscle, and the central nervous system, activating genes related to metabolism and leading to increased energy consumption. Irisin influences metabolism by promoting the browning of subcutaneous white adipocytes, resulting in increased expression of UCP1 and subsequent enhancements in oxygen consumption and thermogenesis (9).

It is highly likely that fluctuations in irisin levels are influenced by metabolic status due to the intricate interplay between irisin and thyroid hormones. Undoubtedly, further investigation into the physiology of irisin and its regulatory mechanisms will be imperative in the foreseeable future. Recent studies have indicated a correlation between thyroid function and irisin levels. Specifically, thyroid hormones, particularly T3, have been demonstrated to impact the production and release of irisin in skeletal muscle tissue. Animal research has shown that hypothyroidism is linked to reduced irisin expression, while hyperthyroidism is associated with elevated irisin levels. These results align with our own study, raising intriguing questions about the complex relationship between the thyroid gland and the irisin hormone (10).

Insulin and thyroid disorders have been connected, with interactions between the two systems influencing metabolic equilibrium. Thyroid hormones, such as thyroxine (T4) and triiodothyronine (T3), play a crucial role in energy metabolism and glucose utilization. These hormones affect insulin sensitivity and glucose metabolism in various organs, including the liver, muscle, and adipose tissue. Thyroid dysfunction, such as hypothyroidism (reduced thyroid activity) or hyperthyroidism (excessive thyroid activity), can disrupt insulin signaling and glucose metabolism (11).

Conclusion

In our study, we saw an inverse relationship between TSH levels and irisin. In hypothyroid subjects, irisin levels have significantly decreased, and in hyperthyroid subjects, there is a rise, though insignificant. Evaluation of T3, T4, intermediates and enzymes of the thyroid metabolic pathway would provide more insights into the role of Irisin in the regulation of thyroid profile parameters.

Limitations: Among thyroid profiles, Only TSH was estimated, Detailed thyroid function was not considered, and subjects were selected randomly and not classified based on gender. Correlation with lifestyle parameters and other demographic parameters were not evaluated.

Disclosures

Conflict of interest: The authors declare no conflict of interest.

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Data Availability statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Authors Contribution: AM, SA: Data collection and benchwork; VC: Protocol preparation; GMR: Manuscript preparation; AM: Statistical analysis and data entry.

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