MEDICAL RESEARCH REPORTS

Med Res Rep 2022;5(1):1-9
https://doi.org/10.55517/mrr.1065047

*ORIGINAL ARTICLE*

# The Relationship Between Thyroid Diseases and Irisin Hormone

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**ÖZET**

**Amaç:** Bu çalışmanın amacı, enerji metabolizması ve termogenez üzerine benzer etkileri bulunan, yeni bir test olan irisin ile tiroid hormonları arasındaki ilişkiyi araştırmaktır. **Yöntem:** 86 kişi çalışmaya dahil edildi. Çalışmaya alınanlar, TSH ve sT4 düzeyleri değerlendirilerek ötiroid, hipotiroidi ve hipertiroidi grubu olarak üç gruba ayrıldı. Tüm olgularda cinsiyet, yaş, tıbbi öykü ve kan testi sonuçları incelendi. Tüm grupların irisin seviyeleri ölçüldü. Elde edilen verilerle istatistiksel analiz yapıldı. **Bulgular**: Yeni tanı almış 30 hipotiroidi hastası, 28 hipertiroidi hastası ve kontrol grubu olarak 28 ötiroid birey olmak üzere toplam 86 kişi çalışmaya alındı. Ortalama irisin düzeyi hipertiroidi grubunda en yüksek, hipotiroidi grubunda en düşüktü. Ortalama irisin düzeyi hipertiroidi grubunda, hipotiroidi ve kontrol grubuna göre anlamlı olarak daha yüksek bulundu ($p<0.01$).İrisin düzeyi, kontrol grubunda hipotiroidi grubuna göre anlamlı olarak daha yüksek bulundu ($p<0.01$). İrisin düzeyleri ile TSH düzeyleri arasında istatistiksel olarak anlamlı negatif korelasyon bulundu ($p<0.01$). İrisin seviyeleri ile fT4, fT3 seviyeleri arasında istatistiksel olarak anlamlı pozitif korelasyon bulundu ($p<0.01$). **Sonuç:** TSH, fT3, fT4 ve irisin arasında anlamlı bir korelasyon bulunmuştur. TSH düzeyi arttıkça irisin düzeyinin düştüğü ve fT3, fT4 düzeyi arttıkça irisin düzeyinin arttığı saptanmıştır. İrisinin, gelecekte yapılacak daha kapsamlı ve uzun süreli takipli çalışmalarla tiroid hastalıklarının takibinde ve tanısında yeni bir test olarak kullanılabileceğini düşünmekteyiz.
**Anahtar kelimeler:** İrisin hormonu, Hipotiroidi, Hipertiroidi, Ötiroidi, Tiroid hastalıkları, Tiroid fonksiyon testi

**ABSTRACT**

**Introduction:** The aim of this study is to investigate the relationship between irisin, a new test with similar effects on energy metabolism and thermogenesis, and thyroid hormones. **Material and Methods:** 86 subjects included in the study. The subjects were divided into three groups as euthyroid, hypothyroid and hyperthyroid group by evaluating their TSH and fT4 levels. For all subjects, gender, age, medical history and blood test results were examined. Irisin levels of all groups were measured. Statistical analysis was performed with the obtained data. **Results:** A total of 86 people; 30 patients with newly diagnosed hypothyroidism, 28 patients with newly diagnosed hyperthyroidism and 28 euthyroid individuals as the control group were included in the study.The mean irisin level was highest in the hyperthyroid group and lowest in the hypothyroid group. The mean irisin level was found to be significantly higher in the hyperthyroid group than in the hypothyroid and control group ($p<0.01$).The irisin level was found to be significantly higher in the control group than in the hypothyroid group ($p<0.01$). A statistically significant negative correlation was found between the irisin levels and TSH levels ($p<0.01$). A statistically significant positive correlation was found between the irisin levels and fT4,fT3 levels ($p<0.01$). **Conclusion:** A significant correlation has been found between the TSH,fT3,fT4 and irisin.It was found that as TSH levels increase, irisin levels decreased and that as fT3, fT4 levels increase, irisin levels increased.We believe that irisin can be used as a new test in the follow-up and diagnosis of thyroid diseases, with studies with larger sample size and long-term follow-up in future.
**Keywords:** Irisin hormone, Hypothyroidism, Hyperthyroidism, Euthyroidism Thyroid diseases, Thyroid function test

**Cite this article as: Ozge E, Arslan K, Ozge H, Altunoğlu EG. The Relationship Between Thyroid Diseases and Irisin Hormone. Medical Research Reports 2022; 5(1):1-9**

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## INTRODUCTION

Thyroid dysfunction is one of the important endocrine disorders that are common in the population and can be associated with morbidity and mortality, particularly in elderly populations (1). Thyroid hormones have a regulating effect on the functions of almost every cell and tissue in the human body and are known to affect metabolic states, basal metabolic rate, and energy balance and to have important effects on them. Low thyroid hormone secretion causes the body functions to slow down whereas high amounts of secretion cause the body functions to speed up. Hyperthyroidism is a condition caused by the effects of excessive amounts of thyroid hormones on body tissues. Hyperthyroidism is a hypermetabolic condition accompanied by increased oxygen use, leading to changes in anti-oxidative factors as a result of the production of reactive oxygen species (ROS). Basal metabolic rate increases as the mechanism of heat production and energy metabolism are stimulated more than normal (2). Hypothyroidism is associated with a general metabolic slowdown. The slowdown in energy metabolism causes a decrease in oxygen consumption, a decrease in basal metabolic rate, and thus metabolic suppression (3).

Irisin is a novel hormone secreted by myocytes which mediates the beneficial effects of exercise on metabolism. It is a glycoprotein hormone that is 12 kDa in size and consists of 112 amino acids. It was first isolated from muscle tissue (4,5). Irisin is a proteolytic product of the fibronectin type III domain-containing protein 5 (FNDC5) molecule, a type I transmembrane protein. Recent studies have shown that irisin is synthesized in many tissues, but its main source is skeletal muscle and adipose tissue. Irisin has been shown to act through many metabolic pathways such as energy and glucose metabolism and mediates the beneficial effects of exercise. Irisin is a protein that causes the white adipose tissue to turn into brown adipose tissue and is effective in energy and glucose metabolism (4). It is a molecule released from muscle tissue through the activation of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) and has a messenger role between muscle and adipose tissue. Exercise has been reported to regulate energy metabolism and numerous related biological processes via PGC-1α, a transcription cofactor (6). The FNDC5 gene has been shown to be activated by increasing PGC-1α expression in the muscle cell as a result of exercise, and the resulting FNDC5 protein is released from the muscle cell as a hormone into the blood. Irisin increases the expression of uncoupling protein 1 (UCP1), which is a mitochondria pump, in white adipose tissue cells. Increased UCP1 expression increases heat production in the cell, providing thermogenesis and glucose homeostasis (7). Irisin decreases body weight by increasing the total energy expenditure of the metabolism and decreases the diet-related insulin resistance, consequently leading to a reduction in the incidence of obesity and insulin resistance (4,8). In light of these data, the concentration of irisin is thought to be able to better reflect the metabolic status of patients suffering from metabolic disorders. In recent years, promising

studies have been conducted on the use of newly discovered myokines, such as irisin, in the early diagnosis, prevention, and treatment follow-up of metabolic diseases such as thyroid diseases, obesity, diabetes mellitus (DM), non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD). Studies to be conducted will have significant contributions to public health.

This study investigated the correlation between thyroid hormones affecting almost all systems and the irisin molecule. The aim of this study was to quantitatively reveal the correlation between thyroid hormone affecting energy metabolism and body metabolic rate in the organism and the irisin molecule, which was shown to be effective on similar systems in recent studies, and to contribute to the demonstration of this quantitative correlation with similar studies to be conducted in the future and to the introduction of new molecules that could be used in the diagnosis, follow-up, and treatment of thyroid diseases and metabolic diseases.

## MATERİALS AND METHODS

A total of 86 people who applied to the Internal Medicine and Endocrinology Outpatient Clinic were included in this study. In all subjects, gender, age, medical history, smoking and alcohol use and blood test results were examined. Those who were using pharmacological agents for thyroid diseases, those who had a history of thyroid cancer, pituitary disease, CKD, DM, obesity, metabolic syndrome, chronic liver disease, congestive heart failure, chronic obstructive pulmonary disease, malabsorption, inflammatory bowel disease, hypo-hyperparathyroidism, and malignancy were excluded from the study. Thyroid-stimulating hormone (TSH), free T4 (fT4), free T3 (fT3), anti-thyroglobulin antibody (Anti-TG), anti-thyroid peroxidase antibody (Anti-TPO), urea, creatinine, transaminases, and creatine kinase values in the last three months were obtained and recorded by examining the patient files from the hospital information management system. The patients were divided into three groups as euthyroid group (control group), hypothyroid group and hyperthyroid group by evaluating their TSH and fT4 levels. And the serum irisin level was measured from the blood samples taken from the subjects.

For this study, approval was obtained from local ethics committee on 23/02/2018 with the decision number 1191. Written consent was obtained from all participants.

Statistical Analysis: The IBM SPSS (Statistical Package for Social Sciences; version 25.0 for windows, Chicago, USA) was used for statistical analyses. The Kolmogorov–Smirnov test was used to measure the distribution of variables. Kruskal-Wallis and Mann-Whitney U test was used for the analysis of quantitative independent data whereas qualitative independent data were analyzed using the chi-square test. Spearman's correlation coefficient was used for correlation analysis. $p<0.05$ was considered significant for all statistical analyses.

## RESULTS

A total of 86 people (61 females, 25 males) were included in the study. The mean

age of all group was 48.5±18.8 years. 28 people (32.6%) were in the hyperthyroid group, 30 people (34.8%) were in the hypothyroid group and 28 people (32.6%) were in the control group. When we compared the groups, there was no significant difference between the groups in terms of age and gender. The mean irisin level was highest in the hyperthyroid group and lowest in the hypothyroid group. The mean irisin level was found to be significantly higher in the hyperthyroid group than in the hypothyroid and control group ($p<0.01$). And the mean irisin level was found to be significantly higher in the control group than in the hypothyroid group ($p<0.01$).(Table 1).

**Table 1. Comparison of irisin level and metabolic parameters of patient groups**

| | Hyperthyroid Group | Hypothyroidi Group | Control Group | p |
|---|---|---|---|---|
| Gender(n%)<br>Female<br>Male | 17 (60.7%)<br>11 (39.3%) | 23 (76.7%)<br>7 (23.3%) | 21 (75.0)<br>7 (25.0%) | 0.346 $^{X^2}$ |
| | Mean±SD - Med | | | |
| Age (year) | 51.2±19.1 - 49.0 | 50.3±20.1 - 47.0 | 44.0±16.8 - 45.5 | 0.290$^{K}$ |
| Irisin | 15.8±1.7 – 15.9 | 7.6±2.1 - 7.9 | 9.6±3.4 - 10.0 | **<0.001$^{K}$** |
| TSH | 0.14±0.24 – 0.05 | 13.4±9.6 – 9.3 | 1.8±1.0 - 1.6 | **<0.001$^{K}$** |
| fT4 | 1.4±0.8 – 1.1 | 0.6±0.2- 0.6 | 0.8±0.2 - 0.8 | **<0.001$^{K}$** |
| fT3 | 4.1±3.2 – 3.3 | 2.8±0.8 – 3.0 | 3.4±0.5 – 3.3 | **0.012$^{K}$** |
| Anti-TG | 54.5±141.9 – 0.9 | 47.1±127.9 – 2.4 | 9.7±42.2 – 0.5 | **0.002$^{K}$** |
| Anti-TPO | 87.2±233.8 – 1.4 | 200.1±342.5 – 8.7 | 45.4±229.1 – 0.3 | **<0.001$^{K}$** |
| CK | 67.1±38.2 – 60.0 | 101.3±103.8 – 66.5 | 94.7±66.8 – 75.5 | 0.217$^{K}$ |
| ALT | 21.1±16.0 – 19.5 | 17.8±8.4 – 16.0 | 26.8±33.2 – 19.0 | 0.580$^{K}$ |
| Creatinine | 0.70±0.28 – 0.66 | 0.66±0.16 – 0.60 | 0.70±0.15 – 0.69 | 0.538$^{K}$ |

$^{K}$ Kruskal-Wallis (Mann-Whitney U test) , $^{X^2}$ Chi-square test, SD:Standard deviation, TSH: **Thyroid stimulating hormone, TG:** T**hyroglobulin, TPO: Thyroid peroxidase, CK: Creatine kinase, ALT: A lanine aminotransferase**

It was found that as TSH levels increased, irisin levels decreased. A statistically significant negative correlation was found between the irisin levels and TSH levels ($p<0.01$).(Figure 1) On the other hand, it was found that as fT3, fT4 levels increased, irisin levels increased. A statistically significant positive correlation was found between the irisin levels and fT4, fT3 levels ($p<0.01$,$p<0.01$).(Figures 2,3) There was no significant correlation between the irisin levels and anti-TG, Anti-TPO, CK, ALT, creatinine levels. (Table 2)

**Figure 1. Correlation between serum irisin level and TSH**

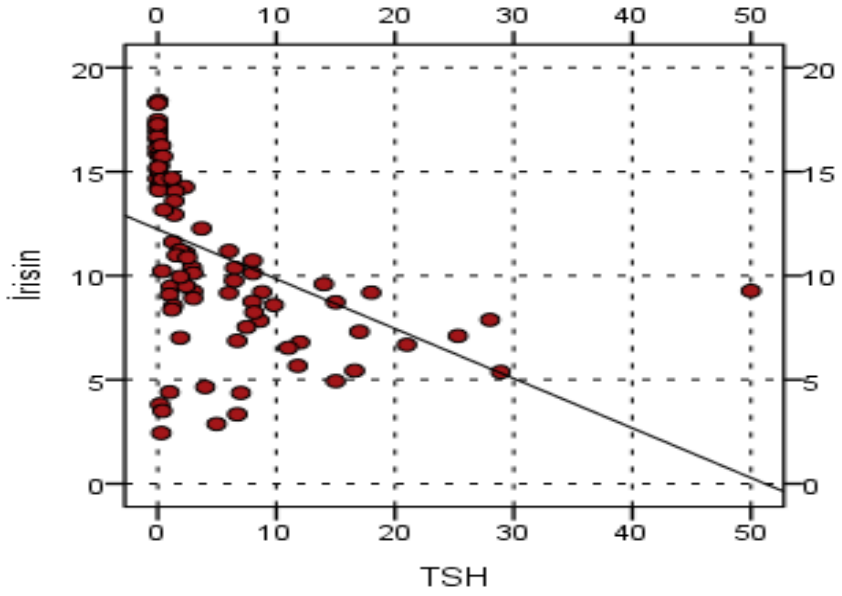


**Figure 2. Correlation between serum irisin level and T4**

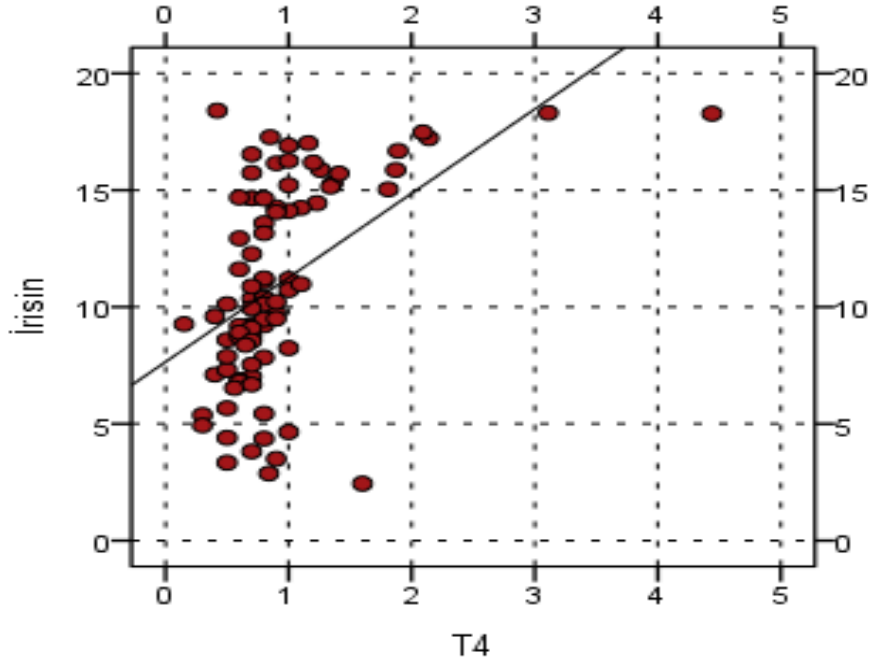

**Figure 3 Correlation between serum irisin level and T3**

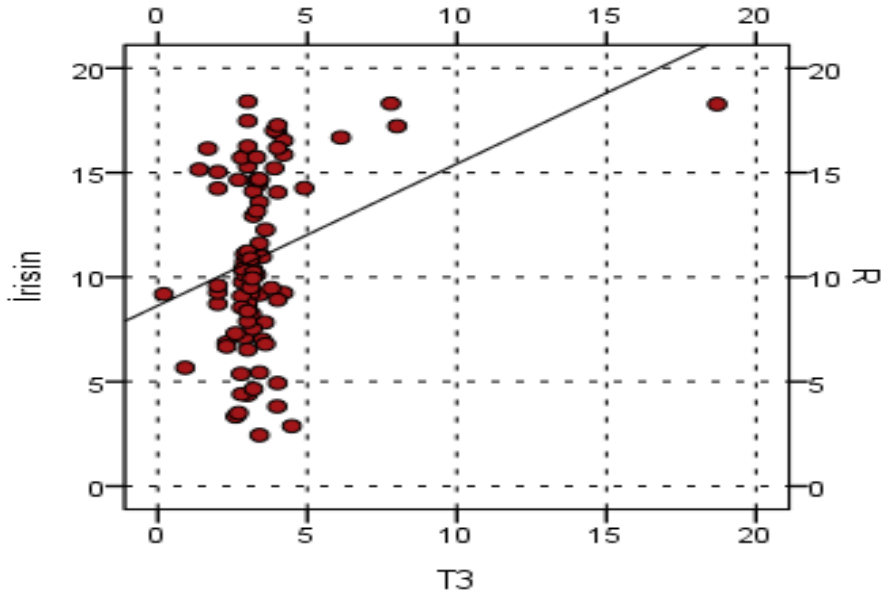


**Table 2.** Correlation between irisin level and other parameters

| | | TSH | fT4 | fT3 | Anti-TG | Anti-TPO | CK | ALT | Creatinine |
|---|---|---|---|---|---|---|---|---|---|
| Irisin | r | -0.742 | 0.536 | 0.271 | -0.135 | 0.018 | -0.081 | 0.130 | 0.083 |
| | p | **<0.001** | **<0.001** | **0.012** | 0.215 | 0.867 | 0.458 | 0.234 | 0.446 |

Spearman Correlation
TSH: **Thyroid stimulating hormone, TG: Thyroglobulin, TPO: Thyroid peroxidase, CK: Creatine kinase, ALT: A lanine aminotransferase**



## DISCUSSION

Thyroid dysfunctions are important chronic endocrine disorders that are common throughout the world. They often require lifelong treatment and may be associated with mortality and morbidity, particularly in the elderly population. These disorders cause a change in the concentrations of circulating thyroid hormones and this change deteriorates metabolic values, leading to the patients presenting to the hospital with a wide range of mild to severe complaints and complications. Therefore, researchers are trying to discover new agents that prevent and treat chronic and metabolic diseases, including thyroid diseases, DM, CKD, and obesity, and conduct various studies in this regard. Although thyroid diseases are a common medical condition, the parameters used for treatment follow-up have been observed to be limited. Irisin molecule is one of the agents predicted to be used in the prevention, follow-up, and treatment of common metabolic diseases such as polycystic ovary syndrome (PCOS), obesity, DM, CKD, ischemic heart disease, and hypertension.

Thyroid hormone causes thermogenesis and energy consumption by increasing the energy consumption of tissues through different mechanisms.(9) The effect of thyroid hormones on thermogenesis is mainly due to its relationship with the sympathetic nervous system at various levels. Furthermore, many studies have shown that thyroid hormones regulate some genes that affect metabolism in adipose tissue (10,11). The UCP-1 is an anion transporter expressed from brown adipose tissue and has important effects on thermogenesis. They are expressed in the inner membrane of mitochondria and cause oxygen consumption in the respiratory chain (12). The UCP-1 causes the proton to pass through the mitochondrial inner membrane, resulting in heat generation without ATP synthesis (13). Thyroid and irisin hormones increase UCP-1 expression (14,15). Irisin increases total energy consumption, lowers body weight, reduces diet-related insulin resistance, and may result in weight loss (4,5). This study has investigated the correlation between these two hormones, which have similar effects on energy consumption and thermogenesis and have been shown to act through similar physiological pathways.

In the study by Ruchala M et al., a negative correlation was demonstrated to be present between CK level and irisin, fT4 and fT3 levels.(16) The authors reported a significant increase in CK levels in patients with decreased serum T3 levels and suggested that it might have been useful for scanning in patients with hypothyroidism. In the present study, no statistically significant correlation was observed between irisin hormone and CK although there was a statistically significant correlation between irisin hormone and fT3 in patients with thyroid dysfunction Unlike other studies, the present study examined CK, fT3, and irisin hormones together for the first time in three different thyroid patient groups. Therefore, it is of great importance in terms of drawing attention to new questions and new issues that need to be investigated.

In a study by Ates I et al, the mean irisin levels of male individuals were shown to be significantly higher than those of female individuals (17). In the present study, no significant difference was found between male and female participants in terms of irisin hormone levels. The inclusion of heterogeneous patient groups may be one of the reasons why no significant relationship could have been revealed. Furthermore, whereas Ateş İ et al. reported a negative correlation between irisin level and age, no significant correlation was observed between the age of the subjects and the irisin hormone level in the present study (13).

Most of the studies investigating irisin hormone reported that irisin affects the exercise-induced 'browning' of adipose tissues and accordingly, causes an increase in thermogenesis. Therefore, irisin contributes more to understand the underlying mechanisms in the regulation of body weight. Thyroid hormone causes thermogenesis and energy consumption by increasing the energy consumption of tissues through different mechanisms. The effect of thyroid hormones on thermogenesis is mainly due to its relationship with the sympathetic nervous system at various

levels. Furthermore, many studies have shown that thyroid hormones regulate some genes that affect metabolism in adipose tissue (7,8). The present study investigated the relationship between two different hormones that affect energy consumption and thermogenesis.

There is a need for further studies involving larger patient groups with different clinical conditions to clearly demonstrate the correlation between the serum irisin hormone and parameters used directly and indirectly in the diagnosis and follow-up of thyroid diseases and to reveal the quantitative value range.

## CONCLUSION

In our study, the mean irisin level was higher in the hyperthyroid group than the hypothyroid and control group. And we found a significant correlation between the TSH, fT3, fT4 levels and irisin levels. It was found that as TSH levels increased, irisin levels decreased and hat as fT3, fT4 levels increased, irisin levels increased. We believe that irisin hormone can be used as a new test in the follow-up and diagnosis of thyroid diseases, with studies with larger sample size and long-term follow-up in future.

## Ethical Approval

For this study, approval was obtained from Istanbul Training and Research Hospital Clinical Research Ethics Committee on 23/02/2018 with the decision number 1191.

## Conflict Of Interest Statement

The authors have no conflicts of interest to declare.

## Funding Sources

There are no funding sources to declare.



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