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# EFFECT OF EXERCISE ON SERUM IRISIN LEVELS IN HYPOTHYROID SPRAGUE DAWLEY RATS

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## ABSTRACT

**Background:** Irisin, a newly discovered exercise-induced myokine, is responsible for mediating beneficial effects such as weight loss and thermoregulation.

**Objectives:** The objective of the study was to determine serum irisin levels in hypothyroid rats with and without exercise, and to correlate irisin levels with TFTs.

**Study Design:** It was an experimental, randomized control trial (RCT).

**Setting of the Study:** The study was carried out in the Department of Physiology, Islamic International Medical College (IIMC) Rawalpindi, in collaboration with National Institute of Health (NIH) Islamabad from September 2020 to September 2021.

**Material and Methods:** A total number of 30 male Sprague Dawley rats were randomly divided into three groups. Each comprising of 10 rats. Group I was control group, group II was hypothyroid group and group III was exercise group.

**Results:** Significant changes were observed in the mean serum Irisin levels at 0 weeks and 12 weeks in all groups. The mean differences in serum irisin levels were found to be statistically significant between control, hypothyroid and exercise groups**.**The mean change in TSH levels for the hypothyroid group was significantly greater than that for control group ($p < 0.001$) and exercise group ($p < 0.001$). The mean change in T4 levels for the hypothyroid group was significantly greater than that for control group ($p < 0.001$) as well as the exercise group ($p < 0.001$).

**Conclusion:** Irisin is an exercise induced myokine that greatly affects energy expenditure and systemic metabolism. In our study irisin levels are decreased in association with decreased thyroid hormone levels. Moreover thyroid hormone levels are restored to normal following exercise-induced irisin.

**KEYWORDS:** Irisin, Hypothyroidism, Thyroid-stimulating hormone, cholesterol, triglycerides, exercise, swimming.

## INTRODUCTION

Exercise is any regular physical activity that enhances and maintains overall health and wellness of a person.[1] Different health care associations worldwide have suggested regular physical activity for the prevention of obesity, type 2 diabetes and cardiovascular disease. [2]Physical inactivity and a low degree of physical training has been identified as a major risk factor for premature death alongside smoking, high cholesterol levels, and arterial hypertension. Regular physical activity caused by the contraction of skeletal muscles resulting in secretion of Myokines. Because of this reason the skeletal muscles have been recognized as an endocrine organ playing a functional role in metabolic homeostasis by its capacity to correspond with multiple tissue including adipose tissue liver and brain.[3] Among those myokines, irisin, is an exercise induced polypeptide, secreted mainly by skeletal muscles and adipose tissue[4]. Irisin is also secreted in small amounts from cardiac muscle, pancreas and sebaceous glands[5]. It is cleaved and secreted from fibronectin type III domain-containing protein 5 (FNDC5 gene) and is regulated by the peroxisome proliferator-activated receptor-γ co activator 1-α (PGC1-α) [6].

The most important function of Irisin is thermogenesis, by inducing the browning of white adipose tissue, thereby increasing energy consumption, encouraging weight loss and decreasing dietary insulin resistance. Examining the irisin-obesity relationship it is observed that following exercise, there is up regulation of a thermogenin ,an uncoupling protein UCP1.[7]

Thyroid hormone also plays an important role in glucose–lipid metabolism and energy homeostasis. Patients with thyroid dysfunction of either clinical or subclinical type suffer from cardiovascular diseases obesity and musculoskeletal disorders.[8] It has been found that thyroid hormone is also involved in thermogenesis by inducing

browning of white adipose tissue, through thyroid hormone receptors .[9] FNDC5 (Fibronectin type III domain-containing protein 5), which is the precursor of irisin, is a protein that is encoded by the FNDC5 gene, is present in many tissues, including the thyroid tissue and therefore effects thyroid hormone .[10] Thus adipogenesis of white adipose tissue and brown adipose tissue is both regulated by and dependent on the actions of the irisin and the thyroid hormone.[11]

Hypothyroidism is a disorder of endocrine system and is characterized by low production of thyroid hormone. This leads to an increased levels of thyroid stimulating hormone (TSH) .It causes adipogenesis by stimulating preadiposite differentiation directly through the receptors in the adipose tissue[10]. Fatty tissue is increased by adipocyte hypertrophy as a consequence of previous adipogenesis, and newly formed adipocyte[10], resulting in clinical obesity.[12]

Therefore dysregulation of both Thyroid and Irisin hormones result in metabolic syndrome. The metabolic syndrome is a common metabolic disorder that has been linked to the increasing prevalence of obesity[12]. By regulating thyroid hormone levels, irisin has a powerful impact on metabolism and thermogenesis.[13]

**Objectives**

The objective of the study was to determine serum irisin levels in hypothyroid rats with and without exercise and to correlate irisin levels with TFTs in hypothyroid rats.

## METHODOLOGY

This experimental randomized controlled study was conducted in the Department of Physiology, Islamic International Medical College, Rawalpindi, in collaboration with the National Institute of Health, Islamabad. The study was carried out over one year, from September 2020 to September 2021, after approval of the research synopsis. Ethical approval was obtained from the Ethics Review Committee of Islamic International Medical College, and all procedures were performed in accordance with national guidelines for animal experimentation. A total of 30 healthy adult male Sprague Dawley rats were included. Eligible animals were 6–8 weeks of age and weighed approximately 250–300 g. Female rats, animals younger than 6 weeks or older than 8 weeks, and rats weighing less than 200 g or more than 300 g were excluded.

**Sampling and Randomization**

The animals were selected through convenience sampling and were subsequently randomly allocated into three equal groups, with 10 rats in each group. The rats were housed in steel wire cages under hygienic laboratory conditions in the NIH Animal House. They were acclimatized at a temperature of 24 ± 2°C, relative humidity of 50–70%, and a 12-hour light/dark cycle. A standard pellet diet and water were provided ad libitum throughout the study period. The animals were divided into the following groups:

**Group I: Euthyroid Control Group**

Ten rats received normal saline and were maintained on a standard pellet diet.

**Group II: Hypothyroid Group**

Ten rats received carbimazole at a dose of 5 mg/100 g body weight for six weeks to induce hypothyroidism. Half of the calculated dose was administered through drinking water and the remaining half through medicated pellets.

**Group III: Hypothyroid Exercise Group**

Ten rats received the same carbimazole regimen for induction of hypothyroidism and subsequently underwent a structured swimming exercise program.


**Figure 1: The normal diet for Sprague Dawley rats in pellet form (a) that was formulated at the Animal house of NIH, Islamabad**

**Induction and Confirmation of Hypothyroidism**

Experimental hypothyroidism was induced in Groups II and III by administering carbimazole for six weeks. Thyroid function was assessed during the study, and hypothyroidism was confirmed by measuring serum thyroid-stimulating hormone, triiodothyronine, and thyroxine concentrations. Rats in Group III were acclimatized to swimming for three consecutive days in a circular water tank measuring 70 × 70 cm, with water maintained at 28 ± 2°C. The acclimatization duration ranged from 10 to 45 minutes/day. After acclimatization, the animals performed swimming exercise for 45 minutes/day during the first two weeks and 60 minutes/day during the following four weeks. Exercise sessions were conducted daily at approximately 10:00 a.m.

**Blood Sampling and Serum Preparation**

At the end of the intervention period, the rats were anesthetized and sacrificed. Intracardiac blood sampling was performed using a sterile syringe, and approximately 2 mL of blood was collected into labelled gel tubes. Samples were transported in an ice box and centrifuged at 3000 rpm for 15 minutes. The separated serum was stored at 2–8°C until biochemical analysis. Serum irisin was measured using a commercially available sandwich enzyme-linked immunosorbent assay kit designed for rat FNDC5/irisin. Serum T3, T4, and TSH concentrations were also measured using ELISA-based assays. The lipid profile, including total cholesterol, triglycerides, and high-density lipoprotein cholesterol, was assessed by enzymatic methods. Low-density lipoprotein cholesterol was calculated using the Friedewald equation. The main study variables included serum irisin, T3, T4, TSH, total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol.

**Statistical Analysis**

Data were analyzed using SPSS version 26.0. Continuous variables were presented as mean ± standard deviation. Comparisons among the three groups were performed using one-way analysis of variance, followed by Tukey's post hoc test where appropriate. A p-value of <0.05 was considered statistically significant.

**Figure 2: Anesthetized male Sprague Dawley rat (a), placed ventrally on dissection board (b), for intra-cardiac sampling, using a 5 mL disposable syringe (c).**

**RESULTS**

At baseline, serum irisin and thyroid hormone levels were broadly comparable across the three groups. By week 12, serum irisin remained unchanged in the control group at 3.14 ± 0.40 ng/mL, decreased markedly to 0.55 ± 0.52 ng/mL in the hypothyroid group, and increased substantially to 12.60 ± 3.32 ng/mL in the hypothyroid exercise group, with a significant overall difference ($p<0.001$). Serum TSH increased from 1.07 ± 0.11 to 13.51 ± 2.92 mIU/L in the hypothyroid group, whereas it remained stable in controls and increased only slightly to 1.93 ± 1.38 mIU/L in the exercise group ($p<0.001$). Similarly, T3 fell to 1.34 ± 0.74 pg/mL and T4 to 1.79 ± 0.78 ng/dL in hypothyroid rats, while both remained near baseline or increased slightly in the exercise group, with significant differences across groups (both $p<0.001$).

**Table 1. Comparison of serum irisin and thyroid profile among study groups (n=10 per group)**

| Parameter | Time point | Control group | Hypothyroid group | Hypothyroid exercise group | p-value |
|---|---|---|---|---|---|
| Serum irisin (ng/mL) | Week 0 | 3.14 ± 0.40 | 3.56 ± 0.90 | 3.14 ± 0.40 | |
| | Week 12 | 3.14 ± 0.40 | 0.55 ± 0.52 | 12.60 ± 3.32 | <0.001 |
| | Mean change | 0.00 ± 0.00 | −3.01 ± 0.88 | 9.46 ± 3.31 | |
| Serum TSH (mIU/L) | Week 0 | 1.09 ± 0.15 | 1.07 ± 0.11 | 1.03 ± 0.03 | |

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|---|---|---|---|---|---|
| | Week 12 | 1.09 ± 0.15 | 13.51 ± 2.92 | 1.93 ± 1.38 | <0.001 |
| | Mean change | 0.00 ± 0.00 | 12.44 ± 2.87 | 0.89 ± 1.37 | |
| Serum T3 (pg/mL) | Week 0 | 3.80 ± 1.03 | 3.90 ± 1.00 | 3.90 ± 0.99 | |
| | Week 12 | 3.80 ± 1.03 | 1.34 ± 0.74 | 4.26 ± 1.02 | <0.001 |
| | Mean change | 0.00 ± 0.00 | −2.56 ± 1.05 | 0.36 ± 0.86 | |
| Serum T4 (ng/dL) | Week 0 | 7.92 ± 0.88 | 8.02 ± 1.06 | 7.92 ± 0.88 | |
| | Week 12 | 7.83 ± 0.79 | 1.79 ± 0.78 | 8.42 ± 1.35 | <0.001 |
| | Mean change | −0.09 ± 0.31 | −6.23 ± 1.25 | 0.50 ± 1.43 | |

At week 12, the hypothyroid group showed marked deterioration in the lipid profile. Total cholesterol increased to 248.50 ± 27.76 mg/dL, triglycerides to 220.50 ± 18.57 mg/dL, and LDL cholesterol to 161.30 ± 8.84 mg/dL. In contrast, the exercise group showed only a modest increase in total cholesterol to 106.10 ± 7.74 mg/dL, while triglycerides decreased to 116.70 ± 9.78 mg/dL and LDL cholesterol to 27.10 ± 7.37 mg/dL.

**Table 2. Comparison of serum lipid profile among study groups (n=10 per group)**

| Parameter | Time point | Control group | Hypothyroid group | Hypothyroid exercise group | p-value |
|---|---|---|---|---|---|
| Total cholesterol (mg/dL) | Week 0 | 84.50 ± 8.42 | 83.20 ± 8.13 | 87.60 ± 12.16 | |
| | Week 12 | 84.50 ± 8.42 | 248.50 ± 27.76 | 106.10 ± 7.74 | <0.001 |
| | Mean change | 0.00 ± 0.00 | 165.30 ± 26.45 | 18.50 ± 10.81 | |
| Triglycerides (mg/dL) | Week 0 | 115.70 ± 8.72 | 116.50 ± 8.71 | 123.30 ± 18.83 | |
| | Week 12 | 116.60 ± 8.63 | 220.50 ± 18.57 | 116.70 ± 9.78 | <0.001 |
| | Mean change | 0.90 ± 2.51 | 104.00 ± 21.14 | −6.60 ± 22.71 | |
| LDL cholesterol (mg/dL) | Week 0 | 25.90 ± 7.64 | 28.00 ± 8.34 | 30.60 ± 9.85 | |
| | Week 12 | 25.90 ± 7.64 | 161.30 ± 8.84 | 27.10 ± 7.37 | <0.001 |
| | Mean change | 0.00 ± 0.00 | 133.30 ± 12.01 | −3.50 ± 13.55 | |
| HDL cholesterol (mg/dL) | Week 0 | 36.70 ± 16.41 | 36.70 ± 16.41 | 36.70 ± 16.41 | |
| | Week 12 | 36.70 ± 16.41 | 58.90 ± 19.60 | 27.10 ± 7.37 | <0.001 |
| | Mean change | 0.00 ± 0.00 | 22.20 ± 13.64 | −9.60 ± 17.52 | |

Post hoc analysis showed that serum irisin differed significantly between the control and hypothyroid groups (mean difference 3.01 ± 0.88, p=0.006), control and exercise groups (−9.46 ± 0.88, p<0.001), and hypothyroid and exercise groups (−12.48 ± 0.88, p<0.001). TSH differed significantly between the control and hypothyroid groups and between the hypothyroid and exercise groups (both p<0.001), while the control and exercise groups did not differ significantly (p=0.532). All pairwise comparisons for T3 were significant (all p<0.001).

**Table 3. Post hoc comparison of changes in serum irisin and thyroid profile**

| Parameter | Group comparison | Mean difference | p-value |
|---|---|---|---|
| Serum irisin | Control vs hypothyroid | 3.01 ± 0.88 | 0.006 |
| | Control vs exercise | −9.46 ± 0.88 | <0.001 |
| | Hypothyroid vs exercise | −12.48 ± 0.88 | <0.001 |
| Serum TSH | Control vs hypothyroid | −12.43 ± 0.82 | <0.001 |
| | Control vs exercise | −0.89 ± 0.82 | 0.532 |
| | Hypothyroid vs exercise | 11.54 ± 0.82 | <0.001 |
| Serum T3 | Control vs hypothyroid | 2.56 ± 0.35 | <0.001 |
| | Control vs exercise | −0.36 ± 0.35 | <0.001 |

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|---|---|---|---|
| | Hypothyroid vs exercise | −2.92 ± 0.35 | <0.001 |
| Serum T4 | Control vs hypothyroid | 6.13 ± 0.50 | <0.001 |
| | Control vs exercise | −0.59 ± 0.50 | 0.468 |
| | Hypothyroid vs exercise | −6.72 ± 0.50 | <0.001 |

Post hoc comparison of lipid changes showed that total cholesterol differed significantly between all groups, including control versus hypothyroid ($p<0.001$), control versus exercise ($p=0.047$), and hypothyroid versus exercise ($p<0.001$). Triglyceride levels differed significantly between the control and hypothyroid groups and between the hypothyroid and exercise groups (both $p<0.001$), but not between the control and exercise groups ($p=0.624$).

**Table 4. Post hoc comparison of changes in serum lipid profile**

| Parameter | Group comparison | Mean difference | p-value |
|---|---|---|---|
| Total cholesterol | Control vs hypothyroid | −165.30 ± 7.38 | <0.001 |
| | Control vs exercise | −18.50 ± 7.38 | 0.047 |
| | Hypothyroid vs exercise | 146.80 ± 7.38 | <0.001 |
| Triglycerides | Control vs hypothyroid | −103.10 ± 8.03 | <0.001 |
| | Control vs exercise | 7.50 ± 8.03 | 0.624 |
| | Hypothyroid vs exercise | 110.60 ± 8.03 | <0.001 |
| LDL cholesterol | Control vs hypothyroid | −133.30 ± 4.68 | <0.001 |
| | Control vs exercise | 3.50 ± 4.68 | 0.737 |
| | Hypothyroid vs exercise | 136.80 ± 4.68 | <0.001 |

Serum irisin showed a moderate positive correlation with serum T3 at week 12 ($r=0.574$, $p=0.001$) and a stronger positive correlation with serum T4 ($r=0.691$, $p<0.001$). In contrast, serum irisin was moderately and negatively correlated with serum TSH ($r=-0.559$, $p=0.001$).

**Table 5. Correlation of serum irisin with thyroid profile at week 12**

| Reference variable | Correlated variable | Pearson correlation coefficient (r) | p-value |
|---|---|---|---|
| Serum irisin | Serum T3 | 0.574 | 0.001 |
| Serum irisin | Serum T4 | 0.691 | <0.001 |

## DISCUSSION

Skeletal muscle is increasingly recognized as an endocrine organ that influences glucose and lipid metabolism through the release of myokines. Irisin is produced by cleavage of fibronectin type III domain-containing protein 5 and is regulated through the PGC-1α pathway. It promotes the browning of white adipose tissue, increases uncoupling protein-1 expression, enhances thermogenesis, and contributes to improved energy expenditure and metabolic regulation. Because thyroid hormones also play a central role in energy homeostasis and lipid metabolism, alterations in thyroid function may influence circulating irisin concentrations.

In the present study, serum irisin levels were markedly reduced in hypothyroid rats compared with controls. At week 12, mean serum irisin was 0.55 ± 0.52 ng/mL in the hypothyroid group compared with 3.14 ± 0.40 ng/mL in the control group. In contrast, rats exposed to swimming exercise showed a substantial increase in serum irisin to 12.60 ± 3.32 ng/mL. The differences between the control and hypothyroid groups ($p=0.006$), control and exercise groups ($p<0.001$), and hypothyroid and exercise groups ($p<0.001$) were statistically significant. These findings suggest that hypothyroidism suppresses irisin secretion, while regular exercise strongly stimulates its release.[13]

The lower irisin levels observed in hypothyroid rats were consistent with previous research reporting reduced circulating irisin in individuals with thyroid hormone deficiency. Reduced skeletal muscle metabolism, impaired mitochondrial activity, and decreased energy expenditure in hypothyroidism may contribute to lower irisin production.[14] However, findings in the literature remain inconsistent, as some studies have reported increased or unchanged irisin levels in hypothyroidism. Higher irisin concentrations reported in some patients may reflect muscle injury, inflammatory changes in thyroid tissue, disease duration, or compensatory metabolic responses. These differences indicate that circulating irisin may vary according to the severity, duration, and underlying cause of thyroid dysfunction.[15]

The marked increase in irisin following chronic swimming exercise was an important finding. Exercise activates skeletal muscle PGC-1α expression and increases FNDC5 cleavage, thereby promoting irisin release. Although previous experimental research has reported variable effects of chronic exercise on irisin levels in hypothyroid animals, the present findings demonstrated a clear exercise-induced increase. This may indicate that sustained swimming restored skeletal muscle endocrine activity despite the presence of experimentally induced hypothyroidism.[16] Serum irisin was positively correlated with T3 ($r=0.574$, $p=0.001$) and T4 ($r=0.691$, $p<0.001$), while a moderate negative correlation was observed with TSH ($r=-0.559$, $p=0.001$). These relationships support a close interaction between thyroid status and irisin regulation. Higher thyroid hormone concentrations were

associated with higher irisin levels, whereas increasing TSH, reflecting greater thyroid hormone deficiency, was associated with lower irisin concentrations.[17]

The hypothyroid group showed a marked increase in serum TSH from 1.07 ± 0.11 to 13.51 ± 2.92 mIU/L, while T3 decreased to 1.34 ± 0.74 pg/mL and T4 to 1.79 ± 0.78 ng/dL. In comparison, the exercise group maintained T3 and T4 concentrations near control levels, with week-12 values of 4.26 ± 1.02 pg/mL and 8.42 ± 1.35 ng/dL, respectively. TSH in the exercise group was also substantially lower than in the untreated hypothyroid group.[18] These results suggest that exercise may have attenuated the hormonal disturbances associated with experimentally induced hypothyroidism.[19]

Exercise also appeared to improve the lipid abnormalities associated with hypothyroidism. The untreated hypothyroid group developed marked elevations in total cholesterol, triglycerides, and LDL cholesterol, whereas these parameters remained considerably lower in the exercise group. This improvement may partly be related to increased irisin secretion, enhanced energy expenditure, improved fatty acid oxidation, and better regulation of lipid metabolism. However, because irisin was measured as an associated biomarker rather than experimentally manipulated, a direct causal role cannot be established from the present study.[20] Overall, the findings indicate that experimental hypothyroidism was associated with reduced serum irisin, impaired thyroid function, and adverse lipid changes. Chronic swimming exercise significantly increased circulating irisin and was accompanied by improvement in thyroid and lipid parameters. These results support the potential role of exercise-induced irisin in the metabolic adaptation to hypothyroidism.

## CONCLUSION

It is concluded that experimentally induced hypothyroidism significantly reduced serum irisin levels and was accompanied by lower T3 and T4 levels, increased TSH, and an adverse lipid profile. Chronic swimming exercise markedly increased serum irisin and improved thyroid hormone and lipid parameters. Serum irisin showed positive correlations with T3 and T4 and a negative correlation with TSH, suggesting a close association between irisin secretion and thyroid status. However, further mechanistic studies are required to determine whether irisin directly contributes to the restoration of thyroid and metabolic function.

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