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The Possible Association between Thyroid Dysfunction in Male Rat Model and Serum Irisin Level and Glycemic Status

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Abstract:

Introduction: Insulin resistance, energy balance, and pancreatic beta cell function are some of the processes via which thyroid dysfunctions are strongly linked to glucose intolerance.

Aim of the study: To assess the correlation between serum irisin and thyroid dysfunction (hypo- and hyperthyroidism), as well as the relationship between these parameters and glycemic status.

Subjects and Methods: 45 mature male albino strain rats weighing between 200 and 250 grams were used in this experimental investigation. Three equal groups were formed: The hypothyroid cohort was administered 50 mg of propylthiouracil (PTU) per kilogram of body weight per day for four weeks. the hyperthyroid group got increasing doses of levothyroxine sodium (starting at 50 µg and reaching up to 200 µg/Kg body weight daily), and the control group stayed without medication.

Results: The hypothyroid group demonstrated a notable reduction in serum fT3, fT4, HOMA B, and BMI, alongside a noteworthy increase in serum TSH, irisin, fasting insulin, fasting glucose, and HOMA IR when compared to the control group. Nevertheless, HOMA B, TSH, BMI, and irisin levels were significantly lower in the hyperthyroid group, accompanied by a significant rise in serum fT3, fT4, fasting insulin, fasting glucose and HOMA IR. Furthermore, serum irisin correlated positively with TSH levels but negatively with fT3 and fT4 levels.

Conclusions: The study supports the hypothesised relationship between irisin and thyroid hormones (THs) and shows that THs may be in vivo regulators of irisin secretion.

Keywords: Thyroid hormones; Thyroid dysfunction; Irisin; Glycemic status; Rat model.

1. Introduction

The growing incidence of metabolic disorders, such as diabetes, obesity and hyperlipidemia has brought attention to the significance of thyroid hormone once again since it can improve the body's energy metabolism [1].

One of the most prevalent endocrine illnesses worldwide, thyroid dysfunctions (hypothyroidism and hyperthyroidism) are characterized by a metabolic imbalance, poor energy homeostasis, oxidative stress, and abnormalities in the muscles [2].

Thyroid problems have been associated with difficulty processing glucose due to several pathways, such as insulin resistance, pancreatic beta cell function, and energy balance [3].

Skeletal muscle releases myokines, a type of protein, that enable interaction with different tissues, including bone, liver, and fat [4]. Irisin, a thermogenic adipomyokine that Bostrom and his colleagues discovered in 2012, is the extracellular breakdown of a type I transmembrane glycoprotein FNDC5 (Fibronectin type III domain-containing protein 5), the precursor of irisin, that is encoded by the FNDC5 gene, a gene that encodes a prohormone, a single-pass type 1 membrane protein (human, 212 amino acids; mouse and rat,209 amino acids) and is regulated by the Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC1alpha). It is believed that irisin is essential for body metabolism and thermogenesis in addition to the beneficial effects of exercise on metabolism [5].

Since being found, irisin has garnered much interest due to its important physiological effects in various metabolic disorders such as obesity, osteoporosis, diabetes, nonalcoholic fatty liver disease, and even cancer [6-7].

Numerous investigations have been carried out to examine changes in irisin levels in individuals with hypothyroidism and hyperthyroidism based on the similarities between THs and irisin; nevertheless, the link between them is not entirely understood, and the findings are inconsistent [8]. So, this research aimed to examine how inducing thyroid dysfunction experimentally in a rat model affected their levels of circulating irisin and to assess how this was linked to their glycemic status.

2. Subjects and Methods

2.1 Chemicals

Thyrocil® from Amoun Pharmaceutical Co. in Egypt offers PTU as white, disc-shaped tablets that contain 50 mg of propyl thiouracil as the active constituent. The levothyroxine sodium B.P. was purchased as 100 µg T4 sodium Eltroxin pills from GlaxoWellcome, Germany.

2.2 Animals

45 mature male albino strain rats, weighing between 200 and 250 grams, were used in this experimental investigation. The Institute of Ophthalmic Disease Research in Cairo, Egypt, is where they were purchased. Animals had been kept in wire-mesh cages with 24-hour light/dark cycles and a comfortable ambient temperature ranging from 23 to 25 ºC. The rats were provided with free access to water and their regular rat food diet for a week as they adjusted to their new environment. Three equal groups of fifteen rats were created. Each cage had five individuals in each group.

2.3 Experimental design

Following a week of initial acclimation, three equal groups were created out of the rats randomly:

Group I (normal control group): Rats were fed on a standard diet and kept without medication.

Group II (the hypothyroid group): administered propylthiouracil (PTU) at a daily rate of 50 mg per kilogram of BW via oral gavage for four weeks [9].

Group III (hyperthyroid group): received Levothyroxine sodium in increasing doses through oral gavage for four weeks [10].

Induction of hypothyroidism

Rats in this group received an oral dose of PTU at a rate of 50 mg kg−1 body weight daily over four weeks via gavage. To create this dosage, one PTU tablet (50 mg) was ground and dissolved in 5 ml of purified water. The medication was given to rats according to their weight as 5 ml/ kg body weight [9]. Development of a hypothyroid state was confirmed 48h before decapitation of rats by detecting a significantly elevated serum TSH in comparison to control rats.

Induction of hyperthyroidism

Levothyroxine sodium B.P. was given orally to this group by administering a suspension in distilled water for four weeks, beginning at 50µg and increasing to 200µg/kg/day. hyperthyroidism was induced. The rats received 50µg/kg body weight of Eltroxin in the initial week after the tablets were crushed and mixed in 5 ml of distilled water. The amount was raised to 100µg/kg body weight in week two, 150µg/kg body weight in week three, and 200µg/kg body weight in week four [10]. Measurements of a much lower serum TSH in comparison to control rats 48 hours before the rats' beheading, indicated the development of a hyperthyroid condition.

Measurement of body weight and length

During the experiment, the rats' weights and lengths were measured at day 0 and day 28. As instructed by Nascimento et al. (2008) [11], weight was measured in grams with a digital scale. According to Novelli et al. (2007), the length from "nose to anus" was measured in centimeters [12]. After that, the body mass index was determined.

Blood Collection

Rats that had been fasted overnight had their blood drawn through the retro-orbital sinus after the trial. The sera were kept at −80 °C until biochemical analysis was carried out.

Biochemical Analysis

TSH, free T4, free T3, irisin, and insulin concentrations were assessed in serum by Rat ELISA kits that were acquired from The SUNLONGbiotech.com. The country of China.

The blood glucose levels were assayed biochemically.

Insulin sensitivity was evaluated by Homeostatic Model Assessment for Insulin Resistance (HOMA IR), while Homeostatic Model Assessment of β-cell function (HOMA β) assessed β-cell function, using specific equations:

HOMA IR = (Fasting glucose (mg/dl) × Fasting insulin (µU/ml))/405 [13].

HOMA β = (20× Fasting insulin (µU/ml))/ (fasting glucose(mg/dl) -63) [14].

2.4 Statistical analysis

IBM Corp., a US-based company located in Armonk, NY, coded and imported the data into SPSS 28. Data was condensed using the standard deviation and mean [15].

3. Results

The hypothyroid group showed that serum TSH levels significantly increased and fT3 and fT4 levels significantly decreased compared to those of the normal control group (p <0.05). Whereas, the hyperthyroid group had a notable drop in TSH levels and a marked rise in fT3 and fT4 levels relative to the normal control group (p <0.05) (**Table 1**).

The BW of the three groups under investigation did not differ significantly when the study first started. Rats in the hyperthyroid group had considerably lower ultimate body weights and BMIs than rats in the normal control group (p <0.05). Additionally, the hypothyroid group's end BW and BMI significantly declined (p <0.05) (**Table 1**).

Table 1: Comparison between serum TSH, fT3, fT4, initial BW, final BW and BMI in the three studied groups.

	Control group	Hypothyroid group	Hyperthyroid group
TSH (ng/ml)	0.93 ±0.28	3.83 ±0.47 *	0.38 ±0.07 *#
fT3 (pg/ml)	23.14 ±3.44	12.93 ±2.39 *	55.98 ±4.9 *#
fT4 (ng/ml)	24.28 ±6.54	15.19 ±4.05 *	38.08 ±6 *#
Initial BW (g)	222.93 ±7.66	222.92 ±11.13	222.25 ±15.6
Final BW (g)	227.4 ±8.09	181.17 ±13.10*	179.83 ±19.46 *
BMI (g/cm^2)	0.51 ±0.02	0.43 ±0.02*	0.42 ±0.03 *

*Values are presented as mean ±SD. *: statistically significant compared to the corresponding value in the control group (p <0.05). #: statistically significant compared to the corresponding value in the Hypothyroidism group (p <0.05).*

Table 2 showed that the hypothyroid group's serum irisin level, insulin, fasting glucose, and HOMA-insulin resistance were noticeably greater compared to those of the typical control group (p <0.05). Nonetheless, the hyperthyroid group showed a notable drop in serum irisin levels along with notable increases in fasting insulin, glucose and HOMA-IR in relation to the normal control group. When comparing both groups to the normal control group, HOMA B revealed a substantial reduction (p <0.05). Although the hyperthyroid group's fasting insulin, glucose and HOMA-IR values were greater than those of the hypothyroid group, their irisin levels decreased noticeably (p <0.05) (**Table 2**).

Table 2: Comparison between serum irisin, fasting insulin, glucose, HOMA-B and HOMA IR in the three studied groups.

	Control group	Hypothyroid group	Hyperthyroid group
Serum Irisin (pg/ml)	15.01±6.51	30.28 ±9.2 *	7.18 ±1.82 *#
Fasting glucose mg/dl	90.17±6.61	138.85 ±14.34 *	159.38 ±9.47 *#
Fasting insulin (mU/l)	5.54±0.36	8.04 ±1.03 *	9.94 ±1.3 *#
HOMA IR	1.24±0.16	2.79 ±0.62 *	3.93 ±0.69 *#
HOMA-B	4.27±0.92	2.15 ±0.24 *	2.07 ±0.21 *

*Values are presented as mean ±SD. *: statistically significant compared to the corresponding value in the control group (p <0.05). #: statistically significant compared to the corresponding value in the Hypothyroidism group (p <0.05).*

Table 3 illustrates that the mean TSH levels and mean blood irisin levels were significantly positively correlated (r =0.839 and p <0.001). whereas the mean level of serum irisin was shown to be strongly inversely correlated with the mean concentrations of fT3 and fT4 (r =-0.694 and -0.804, p < 0.001). However, there is no strong connection between the mean serum irisin level and the mean levels of blood insulin, glucose, HOMA-B, HOMA-IR and BMI.

Table 3: Correlation between irisin and thyroid parameters, BMI and glycemic status parameters.

		TSH (ng/ml)	fT3 (pg/ml)	fT4 (ng/ml)	Fasting glucose (mg/dl)	Fasting insulin (mU/l)	HOMA IR	HOMA -β	BMI (g/cm^2)
Serum Irisin (pg/ml)	**R**	0.839	-0.694-	-0.804-	-0.080-	-0.174-	-0.173-	-0.102-	-0.049-
	P	<0.001*	<0.001*	<0.001*	0.641	0.311	0.313	0.553	0.777

4. Discussion

In the present study, the hypothyroid group experienced a notable rise in serum irisin concentrations relative to the control group. These results were consistent with those of Leustean and associates, who reported that increased TSH levels in primary thyroid insufficiency cause fat cells to develop and produce hormones that control body fat distribution, including ghrelin, irisin, and leptin [16]. As a result, higher TSH levels have been linked to elevated irisin levels in hypothyroidism.

In addition, the hypothyroid group's end body weights and BMI were considerably less than the control group's; these results aligned with the findings of Avci et al. (2022), who reported that this reduction could be attributed to reduced food intake [17], that occurs as a result of the higher levels of leptin hormone [18], taste dysfunction that occurs in hypothyroidism [19] and the bitter taste of PTU [20]. Furthermore, the reduced body weight increase seen in this research could be related to the elevated irisin levels in this cohort, a hormone that prompts White-to-brown fat cell transformation and boosts thermogenesis, ultimately enhancing body weight and body composition [21].

Moreover, the hypothyroid group showed significantly higher serum levels of fasting insulin and glucose, as well as lower HOMA B and higher HOMA IR relative to the control group. These results were in line with what Saleh and his associates had discovered [22].

Reduced GLUT-4 expression and the disruption of its translocation in the cell membrane may be the cause of the elevated fasting blood glucose levels [22]. While reduced renal clearance of insulin [23] and elevated prohormone processing enzyme activity in hypothyroidism result in slower insulin breakdown, which may be the cause of the elevation in serum insulin in the

hypothyroid group [24]. And the persistently elevated levels of serum insulin can lead to the downregulation of insulin receptors on the target tissues and desensitization of the post-receptor pathways [25].

According to a recent study by Krishnamurthy et al. (2023), the hypothyroid group's higher HOMA-IR levels in our research validate the existence of insulin resistance in the hypothyroid model [26]. Elevated TSH levels in hypothyroid individuals may directly bind to hepatic TSHR, leading to increased ER stress, and the development of insulin resistance and abnormal glucose metabolism may be significantly influenced by this stress. [27].

Conversely, our study's hyperthyroid group reported a significantly lower serum level of irisin than the control group. This reduced level of irisin production may be directly caused by hyperthyroidism-associated hyperglycemia and increased circulating FFA from lipolysis of adipose tissue [28] or indirectly via insulin resistance [29]. Insulin resistance has been postulated to be the cause of the decline in PGC-1 activity [30].

In this study, we revealed that irisin levels were directly correlated with TSH levels but showed an inverse relationship with fT3 and fT4 levels. Thus, it is plausible that THs are in vivo regulators of irisin secretion.

In the present investigation, we found that the final body weight and BMI of hyperthyroid rats were significantly lower than those of the controls. These results agreed with Zhao et al. [31]. This was explained by adrenergic hyperstimulation in hyperthyroidism is linked to enhanced basal metabolism and thermogenesis, as well as higher total expenditure of energy; therefore, the likelihood of weight loss [32].

The current study shows that the hyperthyroid group's serum fasting insulin, glucose, and HOMA-IR readings were consistently greater than those of the control group. These outcomes were consistent with the findings of Fasciolo and colleagues (2023) [33].

Increased glucose absorption from the GIT is one of the mechanisms that have been proposed to explain hyperthyroidism-mediated hyperglycemia and insulin resistance [34], and higher levels of thyroid hormones increase the concentrations of the liver's main glucose transporter, glucose transporter 2, which raises hepatic glucose output [35]. FFA-induced lipotoxicity has a

major effect on the pathogenesis of IR, β-cell dysfunction, and inflammatory response [36].

In this study, compared to the hypothyroid group, the hyperthyroid group's fasting insulin, glucose, and HOMA IR levels were significantly higher, suggesting that the elevated irisin in the hypothyroid group acted as a mediator in the reduction of the aforementioned indices, as noted by Stratigou et al. [37].

5. Conclusion

Increased irisin concentration in the hypothyroid group and its decrease in the hyperthyroid one support the speculated interaction between irisin and THs and suggest that THs could be in vivo regulators of irisin secretion. Irisin may act as a mediator to protect against obesity and diabetes, as evidenced by its possible functions in controlling insulin sensitivity and body weight in hypothyroidism.

Ethical committee approval: The study was approved by the Institutional Ethics Committee: code M 539, 2021

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