Assessment of serum irisin level in thyroid disorder

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Background
Irisin is a newly discovered myokin secreted by myocytes responsible for transmission of signals from muscles to other body tissues. Irisin improves systemic metabolism by increasing the energy expenditure. Owing to numerous similarities in action between irisin and thyroid hormones it seems imperative to explore these substances' potential mutual influence on the body.
Objective
To estimate serum irisin concentration in patients with hypothyroid and hyperthyroid diseases, and to detect the relation of serum irisin in patients with thyroid disorders with creatine kinase (CK), a serum marker of muscle damage.
Patients and methods
The study comprised 30 hyperthyroid patients (group 1), 30 hypothyroid patients (group 2), and 30 normal persons (group 3). Irisin was measured using enzyme-linked immunosorbent assay. Thyroid-stimulating hormone, triiodothyronine, and free thyroxine levels were measured using chemiluminescent microparticle immunoassay technology.
Results
Irisin hormone level significantly decreased in hypothyroid patients in comparison with hyperthyroid patients. Irisin hormone level increased in hyperthyroid patients in comparison with normal persons, whereas it decreased in hypothyroid patients in comparison with normal persons. CK level significantly decreased in hyperthyroid patients in comparison with hypothyroid patients. CK level significantly increased in hypothyroid patients in comparison with normal persons, whereas it significantly decreased in hyperthyroid patients in comparison with normal persons.
Conclusion
Obtained results suggest the influence of thermometabolic state on irisin level.

Keywords:
hyperthyroidism, hypothyroidism, irisin

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Introduction

Myokines are specifically defined as cytokines or other peptides that are produced, expressed, and released by muscle fibers and that exert endocrine effects [1].

Irisin is a hormone induced with exercise from the skeletal muscles in mice and humans, and mildly increased irisin levels in the blood cause an increase in energy expenditure with no changes in the movement or food intake. This results in improvements in obesity and glucose homeostasis [1].

Irisin improves systemic metabolism by increasing the energy expenditure. Irisin have a significant influence on the body metabolism and thermogensis by acting on adipose tissue and promoting a phenomenon called white adipose tissue browning. Whereas, white adipose tissue is the primary site of triglycerides storage, brown adipose tissue is specialized in energy expenditure to maintain body temperature in a cold environment. Brown adipose tissue oxidizes fatty acids and generates heat by the mitochondrial uncoupling protein [2].

Irisin has also potential antiobesity effects. When irisin levels rise through aerobic exercise the hormone switches on genes that convert white fat into good brown fat. This is beneficial because brown adipose tissue continues to burn off more calories. This helps people to maintain a healthy BMI and avoid obesity [3].

There are other recognized factors that also influence metabolic state, such as thyroid hormones [thyroxine (free T4) and metabolically active triiodothyronine (free T3)] that increase heat production and control the energy balance by stimulating numerous metabolic pathways including the increase on brown adipose

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tissue mass. Also thyroid hormones increase oxidative phosphorylation and oxygen consumption [4].

Owing to numerous similarities in action between irisin and thyroid hormones it seems imperative to explore these substances' potential mutual influences on the body.

Aim

Detect relation between serum irisin and thyroid disorders with serum creatine kinase (CK) as a marker of muscle damage.

Patients and methods

Type of study

Case control study.

Patients

This study was conducted on 90 Egyptian patients. They were selected from the outpatient's clinic of Ain Shams University Hospital. The patients were classified into the following.

Group 1 included 30 hyperthyroid patients; nine males and 21 females. Group 2 included 30 hypothyroid patients; seven males and 23 females. Group 3 included 30 healthy volunteers; 13 males and 17 females.

Methods

Both patients and controls were subjected to the following. Full medical history with emphasis in taking (age, duration of the disease, drug intake, and physical exercise); thorough medical examination (height, weight, and BMI); complete evaluation of thyroid functional state [thyroid-stimulating hormone (TSH), free T3, free T4, and thyroid ultrasound examination]; measurement of fasting serum irisin hormone and measurement of serum CK; and lactate dehydrogenase (LDH).

Measurement of fasting serum irisin

Name

Human Irisin ELIZA Kit (2015; SunLong Biotech, China).

Sample preparation

In our study we collected blood after overnight fasting (6–8 h) and allowed samples to clot for 30 min before centrifuging for 15 min at ~1000*g*, then samples were stored at −20°C for a month till the time of assay.

Principle of irisin assay

This assay is a competitive enzyme-linked immunosorbent assay for quantitative determination of irisin in human biological fluids (plasma, serum, cell culture supernatant). A polyclonal antibody recognizing native irisin reacts with a series of predetermined recombinant irisin standard proteins or samples under competition in the irisin-coated plate. Their relative reactivity is plotted with that of the standard proteins (normal values, 0.50–30 ng/ml).

Measurement of creatine kinase

Name

Sigma-Aldrich, India (Ref.: MAK116).

Sample preparation

In our study we used blood samples and assayed them directly.

Priniciple of assay

This reaction can be carried out at either room temperature or 37°C. Bring all components to room temperature or 37°C before use. Prepare enough of the Reconstituted Reagent for each sample to be tested. Each sample requires 100 ml of Reconstituted Reagent. Transfer 10 ml of samples into separate wells. Add 100 ml of the Reconstituted Reagent to each sample well and tap plate to mix. Incubate the samples at either room temperature or 37°C. After 20 min, take the initial absorbance measurement at 340 nm (A340) initial. Note: CK is fully activated within 20 min by the glutathione present in the substrate solution. Continue to incubate the plate at either room temperature or 37°C for 20 additional minutes (normal value, 0–171 U/l).

Results

Ninety persons participated in the study. All are age and sex matched. They were divided into three groups: group 1: includes 30 hyperthyroid patients, nine (30%) males and 21 (70%) females (Table 1). Their mean age was 40.6±12.5 years. Their mean height was 165.8 ±7.7 cm. Their mean weight was 76.3±10.8 kg and their mean BMI was 27.7±3.4 kg/m^2 (Table 2). Group 2: includes 30 hypothyroid patients, seven (23.3%) males and 23 (76.7%) females (Table 1). Their mean age was 40.5±12.7 years. Their mean height was 164.8±7.3 cm. Their mean weight was 95.8±9.3 kg and their mean BMI was 35.2±3.01 kg/m^2 (Table 2). Group 3: includes 30 persons as control group, 13 (43.3%) males and 17 (56.7%) females

(Table 1). Their mean age was 41.5±15.5 years. Their mean height was 166.7±8.7 cm. Their mean weight was 75.4±12.4 kg and their mean BMI was 27.2 ±3.2 kg/m^2 (Table 2).

There was a highly significant difference between the studied groups with respect to TSH, free T3, and free T4 ($P<0.01$). Post-hoc test reveals that there was a highly significant difference between normal and hyperthyroid groups, hyperthyroid and hypothyroid groups with respect to TSH, free T3, and free T4 ($P<0.01$) and a highly significant difference between normal and hypothyroid groups with respect to TSH ($P<0.01$) (Table 3).

There is a high significant difference between the studied groups with respect to thyroid ultrasound findings ($P<0.01$); in hyperthyroid patients (46.7%), show multinodular goiter, whereas 33.3% show generalized enlargement, and 20.0% show normal gland finding; in hypothyroid patients, 26.7% show multinodular goiter; whereas the majority (73.3%) show normal gland finding, and 100.0% of controls show normal gland by thyroid ultrasound (Table 4).

There was a high significant difference between the studied groups with respect to CK, LDH, and irisin ($P<0.01$). Post-hoc test reveals that there was a highly significant difference between normal and hypothyroid groups, hyperthyroid and hypothyroid groups, and normal and hyperthyroid groups with respect to CK ($P<0.01$). In addition to that; there was a high significant difference between normal and hyperthyroid groups and normal and hypothyroid groups with respect to LDH ($P<0.01$). Moreover, there was a high significant difference between normal and hypothyroid groups and hyperthyroid and hypothyroid groups with respect to irisin ($P<0.01$) (Table 5).

Comparing all of the studied parameters between hyperthyroidism and normal, there was a high significant difference of TSH, free T3, free T4, CK, and LDH between hyperthyroid group and normal group ($P<0.01$) (Table 6).

Comparing all of the studied parameters between hypothyroidism and normal. There was a high significant difference of TSH, CK, and LDH between hypothyroid group and normal group ($P<0.01$) (Table 7).

Table 1 Comparison of Gender between studied groups (using chi-square test)

Patient characteristics	Diagnosis			χ^2	*P* value
	Hyperthyroid [*n* (%)]	Hypothyroid [*n* (%)]	Normal [*n* (%)]		
Sex					
Male	9 (30.0)	7 (23.3)	13 (43.3)	2.849	0.241
Female	21 (70.0)	23 (76.7)	17 (56.7)		

This table shows comparison of sex between the studied groups (using χ^2 test).

Table 2 Comparison of demographic and Anthropometric Measurements between studied groups (using ANOVA and Post Hoc test)

Parameters	Hyperthyroid (*N*=30) (mean±SD)	Hypothyroid (*N*=30) (mean±SD)	Normal (*N*=30) (mean±SD)	ANOVA	*P* value	Post-hoc test
Age	40.6±12.5	40.5±12.7	41.5±15.5	0.05	0.95	
Weight	76.3±10.8	95.8±9.3	75.4±12.4	33.56	0.00**	2 vs. 3**, 1 vs. 2**
Height	165.8±7.7	164.8±7.3	166.7±8.7	0.40	0.67	
BMI	27.7±3.4	35.2±3.0	27.2±3.2	58.93	0.00**	2 vs. 3**, 1 vs. 2**

This table shows comparison of demographic and anthropometric measurements between the studied groups (using ANOVA and post-hoc test). ANOVA, analysis of variance. ***P* value less than 0.01, highly significant.

Table 3 Comparison of TSH, Free T3 and Free T4 between studied groups using ANOVA and Post Hoc test)

Parameters	Hyperthyroid (*N*=30) (mean±SD)	Hypothyroid (*N*=30) (mean±SD)	Normal (*N*=30) (mean±SD)	ANOVA	*P* value	Post-hoc test
TSH (μIU/ml)	0.026±0.002	9.50±3.41	2.56±1.02	170.43	000**	2 vs. 3**, 1 vs. 2**, 1 vs. 3**
Free T3 (pmol/l)	4.57±0.64	2.88±0.73	2.74±0.5	14.53	0.00**	1 vs. 3**, 1 vs. 2**
Free T4 (pmol/l)	1.69±0.75	0.7±0.26	1.14±0.46	10.55	0.00**	1 vs. 3**, 1 vs. 2**

This table shows comparison of TSH, free T3, and free T4 between the studied groups (using ANOVA and post-hoc test). ANOVA, analysis of variance; Free T3, triiodothyronine; free T4, thyroxine; TSH, thyroid-stimulating hormone. * *P* value less than 0.05, significant. ***P* value less than 0.01, highly significant.

Table 4 Comparison of thyroid Ultrasound between studied groups (using Chi-square test).

Thyroid ultrasound	Hyperthyroid (*N*=30) [*n* (%)]	Hypothyroid (*N*=30) [*n* (%)]	Normal (*N*=30) [*n* (%)]	χ^2	*P* value
Normal gland	6 (20)	22 (73.3)	30 (100.0)	48.903	0.000**
Multinodular goiter/thyroid nodule	14 (46.7)	8 (26.7)	0 (0.0)		
Generalized enlargement	10 (33.3)	0 (0.0)	0 (0.0)		

This table shows comparison of thyroid ultrasound between the studied groups (using χ^2 test). **P value less than 0.01, highly significant.

Table 5 Comparison of CK, LDH and Irisin between studied groups (using ANOVA and Post Hoc test)

Parameters	Hyperthyroid (*N*=30) (mean ±SD)	Hypothyroid (*N*=30) (mean ±SD)	Normal (*N*=30) (mean±SD)	ANOVA	*P* value	Post-hoc test
CK (μ/l)	33.80±1.49	196.26±4.53	62.86±1.63	265.096	0.00**	1 vs. 2**, 1 vs. 3**, 2 vs. 3**
LDH (μ/l)	252.40±7.03	245.60±9.64	183.73±2.36	8.702	0.00**	1 vs. 3**, 2 vs. 3**
Irisin (pg/ml)	26.83±7.95	16.60±4.07	25.70±5.29	26.227	0.00**	2 vs. 3**, 1 vs. 2**

This table shows comparison of CK, LDH, and irisin between the studied groups (using ANOVA and post-hoc test). ANOVA, analysis of variance; CK, creatine kinase; LDH, lactate dehydrogenase. *P value less than 0.05, significant. **P value less than 0.01, highly significant.

Table 6 Comparison of all studied parameters between hyperthyroidism and normal (student-test)

Parameters	Hyperthyroid (mean±SD)	Normal (mean±SD)	Independent sample *t* test	*P* value
TSH	0.026±0.002	2.561±1.025	13.531	0.000**
Free T3	4.577±0.642	2.745±0.514	–5.531	0.000**
Free T4	1.698±0.755	1.143±0.462	–3.437	0.001**
CK	33.800±1.499	62.866±1.633	7.181	0.000**
LDH	252.400±7.035	183.733±2.360	–5.068	0.000**
Irisin	26.833±7.957	25.700±5.298	–0.649	0.519

This table shows comparison of all the studied parameters between hyperthyroidism and normal (Student's *t* test). CK, creatine kinase; free T3, triiodothyronine; free T4, thyroxine; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone. *P value less than 0.05, significant. **P value less than 0.01, highly significant.

Table 7 Comparison of all studied parameters between hypothyroidism and normal (student-test)

Parameters	Hypothyroid (mean±SD)	Normal (mean±SD)	Independent sample *t* test	*P* value
TSH	9.506±3.415	2.561±1.025	–10.666	0.000**
Free T3	2.889±0.738	2.745±0.514	–0.872	0.387
Free T4	0.72±0.267	1.143±0.462	0.586	0.560
CK	196.266±4.535	62.866±1.633	–15.158	0.000**
LDH	245.600±9.642	183.733±2.360	–3.413	0.002**
Irisin	16.600±4.073	25.700±5.298	7.457	0.000**

This table shows comparison of all the studied parameters between hypothyroidism and normal (Student's *t* test). CK, creatine kinase; free T3, triiodothyronine; free T4, thyroxine; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone. *P value less than 0.05, significant. **P value less than 0.01, highly significant.

Our correlation study with irisin in hyperthyroid group found a high significant negative correlation with TSH, weight, BMI, and CK ($P<0.01$), whereas there is a high significant positive correlation with free T3 and free T4 (Table 8).

Our correlation study with irisin in hypothyroid group found a significant positive correlation with LDH ($P<0.05$) (Table 9), whereas there was insignificant correlation between irisin and other studied variables in the control group ($P>0.05$) (Table 10).

With respect to the multiple linear regression analysis, it displays that CK are independent predictor of serum irisin in patients (hyperthyroid and hypothyroid) (Table 11).

Discussion

Irisin is a newly discovered myokin secreted by myocytes responsible for transmission of signals from muscles to other body tissues [5].

Irisin improves systemic metabolism by increasing energy expenditure. Irisin have a significant influence on the body metabolism and thermogensis by acting on adipose tissue and promoting a phenomenon called white adipose tissue browning.

Table 8 Shows Correlation between (TSH, Free T3, Free T4, CK, LDH, Age, Weight, Height and BMI) and Irisin in Patients with Hyperthyroidism (Using Pearson Correlation Coefficient)

Variables	Irisin (pg/ml)	
	Pearson's correlation (*r*)	Significance (2-tailed) *P* value
TSH (μIU/ml)	–0.570	0.000**
Free T3 (pmol/l)	0.354	0.005**
Free T4 (pmol/l)	0.487	0.000**
CK (μ/l)	–0.651	0.000**
LDH (μ/l)	–0.010	0.940
Age (years)	–0.156	0.233
Weight (kg)	–0.424	0.001**
Height (cm)	0.107	0.415
BMI (kg/m^2)	–0.493	0.000**

This table shows correlation between TSH, free T3, free T4, CK, LDH, age, weight, height, and BMI and irisin in patients with hyperthyroidism (using Pearson's correlation coefficient). CK, creatine kinase; free T3, triiodothyronine; free T4, thyroxine; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.

Table 9 Correlation between Irisin and (TSH, Free T3, Free T4, CK, LDH, Age, Weight, Height and BMI) in Patients with Hypothyroidism (Using Pearson Correlation Coefficient)

Variables	Irisin (pg/ml)	
	Pearson's correlation (*r*)	Significance (2-tailed) *P* value
TSH (μIU/ml)	–0.015	0.937
Free T3 (pmol/l)	0.187	0.323
Free T4 (pmol/l)	0.176	0.351
CK (μ/l)	–0.171	0.368
LDH (μ/l)	0.363	0.048*
Age (years)	–0.357	0.053
Weight (kg)	–0.284	0.128
Height (cm)	–0.145	0.444
BMI (kg/m^2)	–0.178	0.348

This table shows correlation between irisin and TSH, Free T3, Free T4, CK, LDH, age, weight, height, and BMI in patients with hypothyroidism (using Pearson's correlation coefficient). CK, creatine kinase; free T3, triiodothyronine; free T4, thyroxine; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.

Whereas, white adipose tissue is the primary site of triglycerides storage, brown adipose tissue is specialized in energy expenditure to maintain the body temperature in a cold environment. Brown adipose tissue oxidizes fatty acids and generates heat by the mitochondrial uncoupling protein [2].

Irisin has also a potential antiobesity effect. When irisin levels rise through aerobic exercise the hormone switches on genes that convert white fat into good brown fat. This is beneficial because brown adipose tissue continues to burn off more calories. This helps people to maintain a healthy BMI and avoid obesity [3].

Table 10 Correlation between Irisin and (TSH, Free T3, Free T4, CK, LDH, Age, Weight, Height and BMI) in controls (Using Pearson Correlation Coefficient)

Variables	Irisin (pg/ml)	
	Pearson's correlation (*r*)	Significance (2-tailed) *P* value
TSH (μIU/ml)	–0.031	0.873
Free T3 (pmol/l)	–0.019	0.919
Free T4 (pmol/l)	–0.254	0.175
CK (μ/l)	–0.119	0.530
LDH (μ/l)	–0.262	0.162
Age (years)	0.311	0.095
Weight (kg)	–0.001	0.996
Height (cm)	0.134	0.480
BMI (kg/m^2)	–0.184	0.332

This table shows correlation between irisin and TSH, Free T3, Free T4, CK, LDH, age, weight, height, and BMI in controls (using Pearson's correlation coefficient). CK, creatine kinase; free T3, triiodothyronine; free T4, thyroxine; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.

There are other recognized factors that also influence metabolic state, such as thyroid hormones (free T4 and metabolically active free T3), which increase heat production and control the energy balance by stimulating numerous metabolic pathways including the increase on brown adipose tissue mass [4]. Also thyroid hormones increase oxidative phosphorylation and oxygen consumption [6].

The aim of this study is the evaluation of serum irisin concentration in patients with thyroid dysfunction and its correlation with CK levels as a serum marker of muscle damage.

Our study showed that hyperthyroid patients had higher irisin level (26.83±7.95 pg/ml) than hypothyroid patient (16.60±4.07 pg/ml) with a high significant difference ($P<0.01$).

These results are in agreement with those reported by Ruchala *et al.* [7] who studied 10 patients with hypothyroidism and 10 patients with hyperthyroidism, and found that irisin is lower in hypothyroid patients compared with hyperthyroid patients with a bordering statistical significance of $P=0.0725$. Lower irisin hormone level found in patients with

Table 11 Regression analysis showing independent predictors for Serum Irisin in patients (Hyper and Hypothyroid) (Using Multiple Linear Regression analysis)

	Unstandardized coefficients		Standardized coefficients		
Model	*B*	SE	Beta	*t*	Significance (*P* value)
1					
Constant	20.897	9.660	0.030	2.163	0.035
Age	–0.058	0.073	–0.089	–0.796	0.430
BMI	0.169	0.278	0.104	0.609	0.545
TSH	–0.169	0.288	–0.111	–0.588	0.559
Free T3	0.212	1.315	0.020	0.161	0.873
Free T4	2.731	1.397	0.235	1.955	0.056
CK	–0.049	0.017	–0.531	–2.840	0.006
LDH	–0.001	0.011	–0.009	–0.081	0.936
a. Dependent Variable: irisin					

This table shows regression analysis showing independent predictors for serum irisin in patients (hyper and hypothyroid) (using multiple linear regression analysis). CK, creatine kinase; free T3, triiodothyronine; free T4, thyroxine; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.

hypothyroidism might be explained with muscles destruction, however the higher level of irisin in hyperthyroidism might be explained by hypermetabolic state.

In our results we found CK level were significantly higher in hypothyroid patients (196.26±4.53 μ/l) when compared with hyperthyroid patients (33.80±1.49 μ/l) with a high statistical significance ($P<0.01$).

High CK found in hypothyroidism may be explained by muscle destruction characteristic of hypothyroidism and therefore irisin is low in hypothyroid patient.

These results agreed with McGrowder *et al.* [8] who studied serum CK and LDH in 68 hypothyroid patient and 92 hyperthyroid patient and found that CK level were significantly higher in hypothyroid patients when compared with hyperthyroid patients ($P=0.0004$) as hypometabolic state of hypothyroidism, which can cause a reduction in glycolysis and oxidative phosphorylations and thus reduce ATP concentrations beyond a critical limit. The alteration in sarcolemmal membranes can cause increased cell permeability and the leakage of CK from cells. Another possibility is reduced turnover of CK because of hypothyroidism allowing serum activities to rise generating a marked release of CK through the altered sarcolemmal membranes. Hypermetabolic state in hyperthyroidism increased enzyme degradation, which may have contributed to these low CK activity, so muscle cell is less permeable than normal to efflux of CK. Also agreed with Prakash *et al.* [9] who studied 30 hypothyroid and 20 hyperthyroid and found CK levels in hyperthyroid patients (54.80±22.30 IU/l) are significantly lower as compared with hypothyroid patients (186.53±34.79 IU/l) Hypothyroid patients have increased concentration of CK, which is mostly due to increased CK-MM.

In our study, LDH increased in both hypothyroid group (245.60±9.64 μ//l) and hyperthyroid group (252.40±7.03 μ/l) with no significant difference ($P>0.05$). This agreed with McGrowder and colleagues who found that LDH activity was increased in the hypothyroid and hyperthyroid states. This elevations of LDH levels could reflect increased release and/or decreased clearance from the liver.

Our study showed high significant positive correlation between irisin, free T3, and free T4, highly significant negative correlation between irisin, TSH, weight, BMI, and CK ($P<0.01$), in hyperthyroid patients.

These results agreed with Ruchala *et al.* [7] who found positive correlation between irisin and free T4 ($P=0.036$), negative correlation between irisin and CK ($P=0.014$), this indicate the profound influence of disturbed thyroid function on irisin levels.

Multivariate regression analysis found that CK are independent predictors of serum irisin in hyperthyroid and hypothyroid patients.

Conclusion

Obtained results suggest the influence of thermometabolic state on irisin concentration. Lower irisin hormone level found in patients with hypothyroidism might be explained with muscles destruction demonstrating with high CK levels.

However, the higher level of irisin in hyperthyroidism might be explained by hypermetabolic state.

Recommendations

Further in depth studies are needed to study the relationship of irisin with thyroid disorders. Studies needed to demonstrate if treating thyroid diseases and restorating euthyroid state reversed changes in irisin and CK levels. Patients who participated in further studies should be deprived from the treatment for long a period.

Financial support and sponsorship

Nil.

Ethical approval

The study was registered and approved by the local institutional ethical committee and all procedures were in accordance with the standards of 1964 Helsinki Declaration and its later amendments ethical standards. Informed consent was obtained from each participant who were included in the study.

Conflicts of interest

There are no conflicts of interest.

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