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ASSESSMENT OF SERUM IRISIN HORMONE LEVEL IN NEWLY DIAGNOSED HYPOTHYROIDISM PATIENTS

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ABSTRACT

Introduction: Thyroid hormones control obligatory and facultative thermogenesis and affect cardiovascular health. Due to altered lipid metabolism and musculoskeletal system abnormalities, thyroid dysfunction increases cardiovascular risk. This study was designed to determine the relationship between irisin hormone and lipid profile parameter and body mass index in hypothyroidism patients. **Method:** Eighty-eight participants were studied. Forty-four were newly diagnosed with hypothyroidism over 18 years old, while forty-four were healthy volunteers (matching in age and sex). Electro-chemiluminescence immunoassay assessed blood TSH, FT4, Antithyroglobulin, and antithyroid peroxidase. ELISA measured serum irisin. Blood pressure, BMI, and homogeneous enzymatic colorimetric lipid profile were assessed. **Results:** The results showed significant differences between patients and control groups by increase in systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, low density lipoprotein, thyroid stimulating hormone, anti-thyroid peroxidase, and anti-thyroglobulin with p-value (0.00, 0.00, 0.002, 0.04, 0.03, 0.00, 0.00, 0.00) respectively, and significant difference by decrease in high density lipoprotein, free thyroglobulin, and Hypothyroidism patients had lower irisin levels than controls (p=0.000). Irisin is adversely linked with total cholesterol, triglycerides, and body mass index in obese hypothyroid patients (p-value 0.02). Irisin correlated positively with Anti-TPO and negatively with Anti-TG. Irisin was positively correlated with total cholesterol and Anti-TG in control group with p-value 0.04. **Conclusion:** Circulating irisin and a good lipid profile may lower the risk of non-communicable diseases. In hypothyroidism patients, irisin linked adversely with BMI (irisin hormone similar to thyroid hormone action). Chronic inflammation releases fibronectin type III domain-containing 5 genes, which increases irisin and anti-thyroid peroxidase in hypothyroidism patients.

KEYWORDS: Assessment, serum irisin hormone, newly diagnosed, hypothyroidism

INTRODUCTION

A lifelong endocrine disorder. Many academics take the thyroid gland's physiological significance seriously because thyroid hormones are essential for cell metabolism and energy equilibrium and because thyroid malfunction is linked to many disorders.[1] Subclinical and overt hypothyroidism exist. Subclinical hypothyroidism is characterised by increased thyroid-stimulating hormone (TSH), normal serum free thyroxine (fT4), and no clinical symptoms. Overt hypothyroidism is characterised by increased TSH and reduced fT4 levels and clinical symptoms. Some studies have linked overt and subclinical hypothyroidism to cardiovascular disease and death. Other studies have linked hypothyroidism to chronic renal disease, dementia, and fractures.[2] Primary and secondary (central) hypothyroidism are the main types. Primary hypothyroidism occurs when the thyroid gland cannot create enough thyroid hormone. When the thyroid gland is normal, secondary or central hypothyroidism is diagnosed. Iodine deficiency causes primary hypothyroidism globally. Autoimmune thyroid disorders cause most hypothyroidism in the US and iodine-sufficient locations. The most prevalent cause of lymphoma in the US is Hashimoto thyroiditis. Iodine fortification and new iodine-deficient locations might affect local etiology.[3] Is a thyroid-destroying autoimmune illness. It causes most hypothyroidism in developed nations. Iodine deficiency is the leading cause of hypothyroidism globally. Chronic lymphocytic thyroiditis and chronic autoimmune thyroiditis describe

this condition. Antithyroid antibodies target thyroid tissue, producing fibrosis. Diagnosis might be difficult and delayed until later in the disease. The most common test results are high TSH, low fT4, and high TPO antibodies. Early in the condition, individuals may have hyperthyroidism symptoms and normal test levels. Thyroid gland cells may die intermittently.[4] Mostly adipocytes—white in WAT and brown in BAT. WAT and BAT vary in structure and function. White adipocytes have a big lipid droplet and few mitochondria, dislocating the nucleus. Brown adipocytes are polygonal cells with a central nucleus, transparent cytoplasm, and plenty of mitochondria. They contain multiple tiny lipid droplets and are called multi-locular adipose tissue.[5] Recently discovered hormone irisin has 112 amino acids (12,587 kDa).[6] FNDC5 encodes type I membrane protein cleavage. A new exercise-induced myokine mediates process irisin.[7, 8] Skeletal muscle releases irisin in response to exercise. PGC-1α, the main regulator of irisin production, is up-regulated in skeletal muscle during and after exercise. FNDC5 transmembrane protein proteolytically cleaves irisin from skeletal muscle into circulation. Skeletal muscle intracellular ATP depletion may influence irisin secretion. Irisin from skeletal muscle causes white adipose tissue to brown by expressing uncoupling protein-1 (UCP-1).[9] Irisin may fight obesity. Aerobic activity raises irisin levels, activating genes that turn white fat into brown fat. This helps because brown adipose tissue burns more calories. This prevents obesity and maintains BMI.[7] Irisin regulates metabolism and cardiovascular function.[10] This study was designed to determine the relationship between irisin hormone and lipid profile parameter and body mass index in hypothyroidism patients.

METHOD

This case-control study was carried out at Biochemistry department, College of Medicine, University of Baghdad and at Medicine and Endocrine outpatient's clinic in Babylon city, from February 2021 to May 2021. It comprised of 88 persons; 44 persons suffered from hypothyroidism as patients group and 44 persons without any diseases as a control group. Both groups participants were aged from 18-65 years, number 33 males and 55 females. This group included 44 persons who were newly diagnosed with hypothyroidism by consultant physician, male was 15, female was 29, with age of 18-65 years. The exclusion criteria included: Hypertension, Pregnant women, Diabetes Mellitus, Acute –Chronic renal diseases, Coronary Heart Diseases, Heart Failure, Peripheral Artery Diseases, Cerebrovascular Events, Malignancy, Liver Diseases, Rheumatic Diseases, Alcohol Intake and smoking. This group involved 44 persons without any diseases depending on investigations, male 18, female 26, with age 18-65 years. The data that taken from each participant involved questions about name, age, sex, history of medical diseases and chronic diseases, taken drug or not. Systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) were assessed in the right upper arm using a calibrated sphygmomanometer with an appropriately sized cuff while the individual was in a seated position after having rested for at least 5 minutes. After obtaining a vocal informed consent, body weight and height of the study participants were measured. Body mass index (BMI) was calculated a weight (Kg)/square of height (m^2) and classified according to WHO classification. (5 ml) of fasting blood was taken from each participant's antecubital fossa veins using a disposable syringe and placed in a gel tube (serum separator tube) for 30 minutes at room temperature. Temperature in a standing posture until the blood clots, then centrifuge at 4000 rpm for 5 minutes to get serum. Aspirated serum was split into three eppendroff tube aliquots: Lipid test strips assess T-Ch, TG, HDL-C, and LDL-C immediately (STANDARD LIPIDO CARE), Aliquote(2):stored at (-80°C) until analysed for Thyroid stimulating hormone (TSH), free thyroxin (fT4), thyroid peroxidase antibody (Anti-TPO), and thyroglobulin antibody (Anti-TG) using automated technique (cobas e 411), Aliquote(3): kept at (-80°C) until serum irisin was tested by enzyme-linked immune-sorbent assay (ELISA). Statistical analysis done by SPSS 22, frequency and percentage used for categorical data, mean, median and SD for continuous data. Chi-square used for assessed association between variables, person correlation shows the correlation between continuous data. T test used for evaluation differences between mean and median of continues variables. ROC curve also used to show more specific and sensitive cutoff point. P-value less or equal to 0.05 is consider significant.

RESULTS

The study is a case control study, involved 88 participants (44 healthy control, 44 hypothyroidism patient), with age range (18-65) yrs. mean of age for all participant was 37.13 ± 0.95 years., 67.0% of them ≤ 40years old and 33.0% were > of 40 years old , 62.5% of all participant were females and 37.5% were males. As shown in table 1.

Table 1: frequency and percentage for the participant variables.

Variables		Frequency	Percent
group	Patient	44	50.0%
	Control	44	50.0%
gender	Female	55	62.5%
	Male	33	37.5%
Age group	≤ 40 yrs.	59	67.0%
	> 40 yrs.	29	33.0%
BMI Kg\m^2	Normal weight	20	22.7%
	over weight	63	71.6%
	Obese	5	5.7%
Total		88	100%

Independent t-test was calculated for each measured biomarkers for both group as presented in table (2). The Mean ±SE of age of patient was 42.23 ± 1.32yrs that is statically non- significant from the mean ±SE of control group 40.02 ± 0.85yrs (p- value 0.56). The Mean ±SE of systolic blood pressure of patient was 142.23 ± 15.32 mmHg that is statistically higher than mean ±SE of control group 118.40 ± 6.53 mmHg, p-value 0.0001. The Mean ±SE of diastolic blood pressure of patient was 94.23 ± 6.71 mmHg that is statistically higher than mean ±SE of control group 78.29 ± 5.98 mmHg, p-value 0.001. The lipid profile markers (TCH, TG, and LDL) mean ±SE in patient group (174.91 ±4.57, 126.11 ± 9.66 and 101.10 ± 4.48 mg\dl) which are statistically higher than markers mean ± SE in control group (157.48 ± 2.74, 95.27 ± 3.77 and 90.13 ± 2.46mg\dl), p-value 0.002, 0.004 and 0.03 respectively. However, the mean ±SE serum level of HDL in patient group. (40.61 ± 1.89mg\dl) which statistically significant difference from the mean±SE (48.16 ± 0.95mg\dl) in control group with p-value 0.04. The Mean±SE serum level of TSH in patient group (42.16 ± 3.36 µIU/l) is statistically higher than mean ±SE serum level (2.74 ± 0.11µIU/l) in control group, p-value< 0.001, in contrast, the mean±SE level of T4 in patient group (7.59 ± 0.23 pmol/l) is statistically lowered than mean±SE level in control group (16.49 ± 0.32pmol/l), p-value <0.001. Both antithyroid peroxidase (Anti-TPO) and antithyroglobulin (Anti-TG) show a statistical higher mean±SE level in patient group (135.59 ± 20.68, 137.25 ± 16.38U/ml) than mean ± SE in control group (11.45 ± 0.94, 14.89 ± 2.06U/ml), with p-value< 0.001, <0.001, respectively. Irisin mean ± SE level in patient group (73.37 ± 2.32 pg/ml) is statistically lowered than control group (95.49 ± 3.21pg/ml), p-value < 0.001.

Table 2: mean difference between the two groups, patient and control regarding: age, SBP,DBP, TCH, TG, HDL, LDL, TSH, FT4, ATPO, ATG and IRISIN.

	group	Mean ± Std. Error	p-value
AGE years	patient	42.23 ± 1.32	0.56
	control	40.02 ± 0.85	
SBP mmhg	Patient	142.23±15.32	0.000*
	control	118.40±6.35	
DBP mmhg	Patient	94.23±6.71	0.00*
	control	78.29±5.98	
TCH mg/dl	patient	174.91 ±4.57	0.002*
	control	157.48 ± 2.74	
TG mg/dl	patient	126.11 ± 9.66	0.004*
	control	95.27 ± 3.77	
HDL mg/dl	patient	40.61 ± 1.89	0.04*
	control	48.16 ± 0.95	
LDL mg/dl	patient	101.10 ± 4.48	0.03*
	control	90.13 ± 2.46	
TSH µIU/L	patient	42.16 ± 3.36	0.000*
	control	2.74 ± 0.11	
FT4 pmol/l	patient	7.59 ± 0.23	0.000*
	control	16.49 ± 0.32	
ATPO u/ml	patient	135.59 ± 20.68	0.000*
	control	11.45 ± 0.94	
ATG u/ml	patient	137.25 ± 16.38	0.000*
	control	14.89 ± 2.06	
IRISIN pg/ml	patient	73.37 ± 2.32	0.000*
	control	95.49 ± 3.21	

p-value is statically significant if ≤ 0.05

SBP=systolic blood pressure, DBP=diastolic blood pressure, TCH=total cholesterol, TG=triglyceride, HDL=high density lipoprotein, LDL= low density lipoprotein, TSH=thyroid stimulating hormone, FT4=thyroxin, ATPO=antithyroid peroxidase, ATG=antithyroglobulin.

However, results show no statistical significance, weak positive correlation with LDL, FT4 and ATPO in patient group r= 0.07, 0.18, 0.09, p- value 0.62, 0.22 and 0.53 respectively. No statistical significance, weak positive correlation with TG, HDL and LDL in control group, r= 0.01, 0.14 and 0.27, p-value= 0.91, 0.33 and 0.06, respectively. No statistical significance, weak negative correlation found between irisin with, TCH, TG, HDL, TSH and ATG, r= -0.11, -0.12,-0.19,-0.08,-0.16 p-value 0.46,0.42,0.2, 0.57 and 0.29 in patient group. A non-statistical significance, weak positive correlation between irisin with TG, HDL and LDL r= 0.01, 0.14 and 0.27, p-value 0.91, 0.33 and 0.06 in control group. A non-statistical significance, weak negative correlation between irisin with TSH, and ATPO in control group, r= -0.11, and -0.05, p-value 0.46, and 0.74.

Table 3: correlation between Irisin and other biomarkers.

Biomarkers	patient		control	
	r	p-value	r	p-vale
TCH	-0.11	0.46	0.3	0.04*
TG	-0.12	0.42	0.01	0.91
HDL	-0.19	0.2	0.14	0.33
LDL	0.07	0.62	0.27	0.06
TSH	-0.08	0.57	-0.11	0.46
FT4	0.18	0.22	0.005	0.97
ATPO	0.09	0.53	-0.05	0.74
ATG	-0.16	0.29	0.29	0.05*

*** P-value is statically significant if ≤ 0.05.**

The correlation between each BMI subgroup and irisin level in each group is presented in table 3-8. Result showed non included patients has normal BMI, and 20 of included control (44) have normal BMI, the correlation coefficient of normal BMI and irisin level in control group was 0.09 and p-value 0.69 indicated non-statistical significant, very weak positive correlation between normal BMI and irisin level in control group. Forty-one of included patients were over weighted BMI, and 22 of included control were over weighted BMI, the correlation coefficient of over weighted BMI and irisin level in patient group was -0.05 and p-value 0.73 indicated non-statistical significance, very weak negative correlation between over weighted BMI and irisin level in patient group. In control group r 0.06 and p-value 0.78 indicate indicated non-statistical significance, very weak positive correlation between over weighted BMI and irisin level in control group.

Table 4: the correlation between each BMI subgroup and irisin level in each group is presented.

Irisin BMI subgroups	Patient			control		
	N	r	p- value	N	r	p-value
Normal	0	/	/	20	0.09	0.69
Overweight	41	- 0.05	0.73	22	0.06	0.78
Obese	3	- 0.99	0.02*	2	-1.0	o.oo
Total	44	/	/	44	/	/

*** P-value is statically significant if ≤ 0.05.**

DISCUSSION

This study examined the link between irisin hormone, lipid profile, and BMI in hypothyroidism patients. 62.5% of hypothyroidism patients in this research were female. 37.5% were male, which supports Mahenta A et al (2017) and Bauer M et al (2014), who observed that hypothyroidism is more common in women due to autoimmune illness.[11, 12] To reduce biological variability and avoid ageing effects, we sampled patients and controls approximately 40 years old. Patients and controls differ in body mass index statistically (BMI) This conclusion agrees with Song.R H et al (2019) because thyroid hormone regulates metabolic rate, and hypothyroidism lowers metabolic rate, energy expenditure, and hunger, causing weight gain.[13] Ates I et al. found that patient blood pressure was statistically higher than control group (2016).[14] Hypothyroidism causes secondary hypertension. Hypothyroidism is associated with high blood pressure. Cardiac electrophysiology may regulate potassium channels, Na/K and Na/Ca ATPases, endothelial function, peripheral vascular resistance, and atherosclerosis. Hypothyroidism may cause diastolic hypertension due to poor cardiac output and carotid intima media thickness

with hypercoagulability. Hypothyroids have large volume alterations. (Cappola AR, et al., 2019).[15] This study revealed that patients had significantly higher blood T-CH, TG, and LDL-C levels than controls, comparable to Alamdari S et al. (2016) and AL-Sharifi Z. R & Kadom S M. (2021).[16, 17] Thyroid hormones increase cholesterol ester transfer protein (CETP) activity, which exchanges cholesterol esters from HDL2 to VLDL, stimulate lipoprotein lipase (LPL), which catabolizes TG-rich lipoproteins, and hydrolyze HDL2 to HDL3 and contribute to the conversion of intermediate-density lipoproteins (IDL) to LDL and LDL to small d. (sdLDL). Thyroid hormone also upregulates TG-regulating Apo lipoprotein. Hypothyroidism increases total cholesterol, LDL, and HDL and decreases HDL through decreasing LDL-C receptor activation and catabolism (Ghosh Amrita et al., 2018).[18] Hypothyroidism causes TSH to rise owing to thyroid follicle destruction and decreased negative feedback. Thyroid peroxidase antibody (Anti-TPO) and thyroglobulin antibody (Anti-TG) were significantly higher in patients than controls, confirming Unnikrishnan A.G et al.[19] Thyroid peroxidase, an enzyme in the thyroid gland that helps produce T3 and T4, uses iodine to produce thyroid hormones. Autoantibodies stop thyroid peroxidase from using iodine, causing hypothyroidism and inflammatory reactions that can destroy the thyroid gland. Anti-thyroglobulin (Anti-TG) attacks thyroglobulin, causing hypothyroidism. Shoman M.[20] Irisin exhibits statistically significant positive connection with T-CH in control group, comparable to earlier research. In previous investigations, Elbert T et al. and Liu JJ et al. demonstrated an inverse connection between irisin and total cholesterol.[21,22] The muscle fibronectin domain type III containing 5 gene was favourably related with total cholesterol and triglycerides and negatively associated with HDL cholesterol in previous research.[23] There was no statistical significant, positive correlation between irisin and free T4 this result agreed with study of Yang N. *et al*.[24], and disagreed with Ates I *et al*.[14] that found no statistical significant, negative correlation between free T4 and irisin in patients group. There is no statistically significant, negative correlation between TSH and irisin, this result agree with the study of Halawa M.R *et al.* that found no statistical significant, negative correlation between TSH and irisin, and no statistical significant, positive correlation with freeT4 and irisin in patients group.[25] Thyroid hormones regulate energy expenditure and glucose–lipid metabolism, both of which are also regulated by irisin. Irisin levels were significantly lower in patients with hypothyroidism than in normal persons. Additionally, irisin levels were positively associated with FT4 levels, and negatively associated with TSH levels. There was negative correlation between irisin and T-CH, TG, and HDL-C this result similar to study Yang N *et al*.[24], while this study disagreed with our result in correlation between irisin and LDL-C we found positive correlation between irisin and LDL-C, this result agreed with Ates I *et al*.[14] In patient with hypothyroidism found abnormal blood lipid profile and negative correlation between irisin and T-CH and TG, the mechanism by which irisin improves lipid metabolism may be its suppression of CHOL and TG synthesis in hepatocytes. These findings suggest that irisin is one of the factors of dyslipidemia in patients with hypothyroidism.[26] The study showed that there was no statistical significant, negative correlation between over-Wight and irisin in patient group which agree with Liu BW *et al* [22]. there is statistically significant, negative correlation between obese and irisin in patient and control group and that result agree with Barja-Femandez S *et al*.[27]

CONCLUSION

There is a link between circulating irisin and a good lipid profile, and an increase in irisin concentration may reduce the risk of noncommunicable illnesses. Irisin had a negative correlation with hypothyroidism patients' body mass index (irisin hormone similar to thyroid hormone action). Irisin was positively connected with Anti-thyroid peroxidase in hypothyroidism patients because chronic inflammation caused an increase in the release of the fibronectin type III domain-containing gene.

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