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Serum Irisin Level Among Patients with Subclinical Hypothyroidism in Relation with Plasma Atherogenic Indices

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Abstract

Background and objectives: Subclinical hypothyroidism, impacting 3-8% of the general population with a higher incidence in women and older individuals, is linked to cardiovascular and atherosclerosis. This study evaluated the serum irisin levels in individuals with newly diagnosed subclinical hypothyroidism compared to a control group, explored its association with atherogenic plasma indices.

Methods: A case-control study, enrolled 160 participants, including 80 with newly diagnosed subclinical hypothyroidism and 80 euthyroid individuals as controls. The study was conducted at the Endocrine Department of Rzgary Teaching Hospital in Erbil City, Iraq. The study was conducted between September 2022 - September 2023. Blood samples were collected for measurement of serum irisin levels, thyroid hormones, lipid profile, anti- thyroid peroxidase antibodies, and atherogenic indices.

Results: Notably, 76.3% of Subclinical Hypothyroidism cases were young females (<40, p<0.001) with higher rates of overweight/obesity (73.8%) compared to controls (p<0.001). Waist circumference and thyroid hormone levels were significantly higher in subclinical hypothyroidism cases (p<0.001). The prevalence of high atherogenic coefficient was higher in cases (83.7% vs. 63.8%, p=0.004). Thyroid stimulating hormone levels were elevated in subclinical hypothyroidism cases (7.37µ-IU/mL) compared to controls (2.67µ-IU/mL) (p < 0.001). Anti- thyroid peroxidase antibodies titer was significantly higher in cases (54.37 IU/mL) than controls (16.55 IU/mL) (p < 0.001).

Conclusions: Subclinical hypothyroidism is prevalent among young obese females. Serum irisin levels remain steady in subclinical hypothyroidism compared to healthy controls but positively correlate with atherogenic indices in these patients.

Keywords: Atherogenic indices, Irisin, Overweight/obesity, Subclinical hypothyroidism

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Introduction

Subclinical hypothyroidism (SCH), characterized by normal serum free thyroxine (T4) alongside elevated serum thyroid-stimulating hormone (TSH), presents a diagnostic challenge due to the absence of distinctive clinical symptoms.[1,2] Its prevalence ranges from 3% to 8% in the general population, displaying a higher occurrence in women and increases with age. [3] This condition has garnered attention for its association with cardiovascular risk factors, dyslipidemia, and heightened atherosclerosis, particularly when TSH levels surpass 10 mU/L.[4] Irisin, a recently identified adipomyokine derived from fibronectin type III domain-containing 5 (FNDC5) which undergoes regulation by peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1 alpha (PGC1α).[5] Studies suggested that increased expression of FNDC5/irisin prompts browning and boosts thermogenesis within white adipose tissue, thereby aiding in the regulation of glucose levels and mitigating insulin resistance.[5] Fibronectin type III domain-containing 5, the precursor of irisin, is present in various tissues, including the thyroid.[5-7] The role of irisin has been explored in diverse conditions such as type 2 diabetes mellitus, metabolic syndrome, insulin resistance, obesity, chronic renal disease, anorexia nervosa, and hypothyroidism.[8] Moreover, irisin has been associated with increased cardio metabolic risk, suggesting its involvement in proinflammatory and atherogenic pathways.[9] The plasma's atherogenic indices, encompassing the atherogenic index of plasma (AIP), Castelli's risk indices I and II, as well as the atherogenic coefficient (AC), serve as crucial predictive measures in cardiovascular disease (CVD).[10-12] Monitoring SCH patients for dyslipidemia is essential, and studies propose AIP as a superior parameter for assessing cardiovascular risk in these patients compared to conventional lipid profiles.[13,14] The main objective of this research was to assess the concentration of serum irisin in individuals with SCH in comparison to a group of individuals with normal thyroid function. Additionally, the study aimed to investigate the potential association between irisin levels and atherogenic markers in the plasma of these patients aiming at improving our understanding of the pathophysiology of this condition.

Patients and methods

This is a case-control study that involved 160 participants. Among them, 80 individuals were newly diagnosed with SCH, while the remaining 80 served as control subjects, matched for gender and age. The study was conducted at the Endocrine Department of Rzgary Teaching Hospital in Erbil City, Iraq. The study was conducted between September 2022 - September 2023.Inclusion criteria included individuals with newly diagnosed SCH, while exclusion criteria included participants with chronic inflammation, diabetes mellitus, and neoplasm. Data collection involved face-to-face interviews utilizing a structured questionnaire. The questionnaire covered personal details such as name, age, date of birth, gender, and family history of certain diseases. Anthropometric data, including height, weight, and waist circumference, were collected and the Body Mass Index (BMI). All subjects' participants in the study were classified according to BMI as follow: Underweight; BMI<18.5 kg/m^2, Normal weight, BMI 18.5 – 24.9 kg/m^2, Overweight BMI 24.9–29.0 kg/m^2 and Obese BMI ≥ 30 kg/m^2. [15] In the morning and after an overnight fasting at Mazi laboratory, a 5ml venous blood sample was taken into a Gel tube and centrifuged for 20 minutes at 3000 revolutions per minute. All parameters were measured by Cobas 6000 (Roche-HITACHI) based upon different principles. Hormones such as (TSH, T4, T3, Insulin, TPO) were

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depended upon electrochemiluminescence (ÈCL) immunoassay, whereas the serum glucose was depended upon enzymatic colorimetric method, serum visfatin were measured by ELISA that is done in sandwich enzyme immunoassay form depending on antigen -antibody reaction and enzymatic reaction. The cutoff used for serum glucose (74-109 mg/dl), insulin (less than 25 mIU/L). thyroid stimulating hormonc (0.2-4.2 microIU/mL), free T4(12-22 pmol/L), and free T3 (3.1-6.8 pmol/L). TPO (up to 34IU/L). Homcostatic Model Assessment of Insulin Resistance HOMA-IR was measured from fasting glucosc and insulin as follows: HAMA-IR = Glucose(mg/dl) x_ insulin(hU/) / 405 (HOMA-IR>3.0) was regarded as insulin resistance ' Ethical permission was gained from the Rescarch Committee of the Directorate. The Enzyme-Linked Immunosorbent Assay (ELISA) was utilized to measure the level of serum-soluble gp91phox/NOX2, relying on antigen-antibody reactions and enzymatic processes. All other parameters were assessed using the cobas 6000 system (Hitachi, Roche) based on manufacturer's instructions. Hormones, including TSH, free T4(FT4), free T3(FT4), and Anti-thyroid peroxidase antibodies (Anti-TPO), were determined using electrochemiluminescence immunoassay, while lipid profiles were assessed using an enzymatic colorimetric method. The cutoff values applied for serum-soluble gp91phox (NADPH oxidase 2) were (6.1 ± 0.5 ng/mL), serum TSH (0.2 - 4.2μIU/mL), FT4 level (12–22 pmol/ml), and FT3 (3.1–6.8 pmol/ml), Anti-TPO (below 30 IU/mL).[16,17] The lipid profile cutoff values were determined based on the national cholesterol education program.[18,19] The atherogenic lipid indices assessed in this study were as follows: Atherogenic Index of Plasma (AIP) = log (TG/HDL-C), where values less than 0.11 are associated with a low risk of cardiovascular disease (CVD), values between 0.11 to 0.21 indicate moderate risk, and values greater than 0.21 indicate high risk. Castelli's Risk Index I (CRI-I) was calculated as TC/HDL-C, with a risky CRI-I value defined as ≥5.0. Castelli's Risk Index II (CRI-II) was determined as LDL-C/HDL-C, and a risky CRI-II value was ≥3.0. In addition, the atherogenic Coefficient (AC) was computed as (TC – HDL-C)/HDL-C, where a risky AC value was defined as >2.1. These indices were employed based on established criteria.[20–23] The study received ethical approval from the Medical Ethics Committee of Duhok Directorate of Health and the Kurdistan Higher Council of Medical Specialties. All subjects provided written informed consent before enrollment in the study. Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). Chi square test of association was used to compare proportions of the two study groups. Fisher's exact test was used when the expected frequency (value) was less than 5 of more than 20% of the cells of the table. Student's t test for two independent samples (unpaired t test) was used to compare means of the two study groups. A p value of less than 0.05 was considered as statistically significant.

Results

In this study, a total of 160 participants were included, with a mean age (SD) of 33.1± (8.7) years. The participants were divided into two groups: 80 patients with (SCH) and 80 individuals serving as healthy controls. A significant proportion (76.3%) of the patients were under the age of 40. Furthermore, the majority (75.0%) of the patients were females. Regarding the body weight, approximately one-third (33.8%) of the SCH cases were classified as overweight, and 40% were categorized as obese. Notably, none of the individuals in the control group fell into the overweight or obese categories, and this difference was statistically significant ($p < 0.001$). Analysis of waist circumference

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revealed that 51.3% of the SCH cases exhibited large waist circumference, while only 6.3% of the control group had a similar characteristic ($p < 0.001$), Table (1).

Table (1): Basic characteristics of study participants

Variables	Cases of SCH (n=80)	Controls (n=80)	Total (n=160)	p
Age (years)				
< 40	61 (76.2)	63 (78.7)	124 (77.5)	0.705*
≥ 40	19 (23.8)	17 (21.3)	36 (22.5)	
Mean (SD)	33.4 (8.9)	32.8 (8.6)		0.705†
Gender				
Male	20 (25.0)	19 (23.8)	39 (24.4)	0.854*
Female	60 (75.0)	61 (76.2)	121 (75.6)	
BMI (Kg/m^2)				
Normal	21 (26.2)	80 (100.0)	101 (63.1)	< 0.001**
Over-weight	27 (33.8)	0 (0.0)	27 (16.9)	
Obese	32 (40.0)	0 (0.0)	32 (20.0)	
Mean (SD) Kg/m^2	29.0 (6.2)	23.5 (1.1)		< 0.001†
Waist circumference(cm)				
Normal	39 (48.7)	75 (93.7)	114 (71.2)	< 0.001*
Large	41 (51.3)	5 (6.3)	46 (28.8)	
Mean (SD)	91.5 (14.4)	79.5 (7.6)		< 0.001†

*Chi square test. **Fisher's exact test. †Unpaired t test.

The mean TSH level among cases with SCH was 7.37µ-IU/mL, which represented a statistically significant elevation compared to the control group with a mean TSH of 2.67µ-IU/mL ($p < 0.001$). On the contrary, there were no notable differences in the mean levels of FT3 ($p = 0.865$) and FT4 ($p = 0.658$) between the cases and controls. The mean Anti-TPO titer in cases (54.37 IU/mL) exhibited a significant increase in comparison to that of controls (16.55 IU/mL) with a $p < 0.001$. Moreover, the prevalence of elevated Anti-TPO titer in cases was 36.3%, contrasting with 8.8% in the control group. The lipid profile analysis revealed that the means of all lipid's parameters, except cholesterol, in the cases were significantly elevated from those in the control group, with p less than 0.05. Furthermore, there was no significant difference in the mean serum Irisin levels between the cases and controls ($p = 0.521$), as summarized in Table (2).

Table (2): Biochemical parameters in Cases and Controls

Parameters	Cases with SCH (n=80)		Controls (n=80)		p
	Mean	(SD)	Mean	(SD)	
TSH (**µ**IU/mL)	7.37	(2.98)	2.67	(0.88)	< 0.001
FT3 (pmol/ml)	4.21	(0.82)	4.13	(3.84)	0.865
FT4 (pmol/ml)	15.97	(1.71)	15.85	(1.67)	0.658

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Anti-TPO (IU/mL)	54.37	(82.93)	16.55	(14.70)	< 0.001
Anti-TPO categories (N%)					
< 30 (IU/mL)	51	(63.80)	73	(91.30)	< 0.001*
≥ 30 (IU/mL)	29	(36.30)	7	(8.80)	
Cholesterol (mg/dl)	155.85	(30.34)	155.26	(20.63)	0.886
Triglycerides (mg/dl)	119.31	(84.09)	98.44	(39.69)	0.047
HDL (mg/dl)	40.74	(7.08)	44.06	(9.36)	0.012
LDL (mg/dl)	96.33	(21.38)	86.45	(19.19)	0.002
Irisin (ng / ml)	20.10	(14.36)	21.53	(13.81)	0.521

*Chi square test. The other p values were calculated by the Unpaired t-test.

In the comparative analysis between the two groups, no statistically significant differences were observed in relation to various atherogenic indices, including AIP (p = 0.307), CRI-I (p = 0.358), and CRI-II (p = 1.000). However, a notable difference emerged concerning the prevalence of high AC, with 83.7% of cases exhibiting elevated AC compared to 63.8% of controls (p = 0.004). Despite the slightly higher mean AC in cases (2.93) compared to controls (2.7), this difference did not attain statistical significance (p = 0.177), Table (3).

Table (3): Comparative Analysis of Atherogenic Indices between Cases and Controls

Indices	Case	Control	Total	p
	No. (%)	No. (%)	No. (%)	
AIP				
Low risk	16 (20.0)	14 (17.5)	30 (18.8)	0.307*
Intermediate risk	14 (17.5)	8 (10.0)	22 (13.8)	
High risk	50 (62.5)	58 (72.5)	108 (67.4)	
Mean (SD)	0.36 (0.32)	0.34 (0.23)		0.678†
CRI-I				
< 5	71 (88.8)	67 (83.8)	138 (86.3)	0.358*
≥ 5	9 (11.3)	13 (16.3)	22 (13.8)	
Mean (SD)	3.71 (1.16)	3.93 (0.89)		0.177†
CRI-II				
< 3	70 (87.5)	70 (87.5)	140 (87.5)	1.000*
≥ 3	10 (12.5)	10 (12.5)	20 (12.5)	
Mean (SD)	2.29 (0.72)	2.20 (0.68)		0.459†
AC				
< 2.1	13 (16.3)	29 (36.3)	42 (26.3)	0.004*
≥ 2.1	67 (83.7)	51 (63.8)	118 (73.7)	
Mean (SD)	2.93 (1.16)	2.71 (0.89)		0.177†

*Chi square test. †Unpaired t-test.

In analyzing patients diagnosed with SCH, a comparative assessment was conducted on atherogenic indices based on their TSH levels, distinguishing between low TSH (< 10μ-IU/mL) and high TSH (≥ 10μ-IU/mL). Statistical analysis revealed no statistically significant differences in the examined indices between the two subgroups. Furthermore, the investigation of Irisin levels exhibited a mean of 19.05(±13.11) ng/ml in the lower TSH subgroup and 22.84(±17.26) ng/ml in the higher TSH subgroup, with no statistically significant difference identified (p = 0.295), Table (4).

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Table (4): Atherogenic indices and Irisin by TSH levels among patients with subclinical hypothyroidism

Indices	TSH (micro-IU/mL)		Total	p
	(n%)	(n%)	(n%)	
	< 10	≥ 10		
AIP				
`Low risk	13 (22.4)	3 (13.6)	16 (20.0)	0.127**
Intermediate risk	7 (12.1)	7 (31.8)	14 (17.5)	
High risk	38 (65.5)	12 (54.6)	50 (62.5)	
Mean (SD)	0.35 (0.32)	0.36 (0.32)		0.917†
CRI-I				
< 5	51 (87.9)	20 (90.9)	71 (88.8)	1.000**
≥ 5	7 (12.1)	2 (9.1)	9 (11.2)	
Mean (SD)	3.65 (1.18)	3.85 (1.10)		0.493†
CRI-II				
< 3	50 (86.2)	20 (90.9)	70 (87.5)	0.719**
≥ 3	8 (13.8)	2 (9.1)	10 (12.5)	
Mean (SD)	2.24 (0.61)	2.30 (0.76)		0.726†
AC				
< 2.1	24 (41.4)	5 (22.7)	29 (36.3)	0.121*
≥ 2.1	34 (58.6)	17 (77.3)	51 (63.8)	
Mean (SD)	2.65 (1.18)	2.85 (1.10)		0.493†
Irisin				
Mean (SD)	19.05 (13.11)	22.84 (17.26)		0.295†
Total	58 (100.0)	22 (100.0)	80 (100.0)	

*Chi square test. **Fisher's exact test. †Unpaired t-test.

Discussion

This study aimed to evaluate serum irisin levels in SCH patients compared to an euthyroid control group. In this case-control study, the majority of patients with SCH were obese females younger than 40 years old, with approximately one-third testing positive for TPO antibodies. The association between SCH and obesity was primarily related to elevated serum TSH levels, adipocyte-secreted leptin, the presence of thyroid autoantibodies, and an adaptive response to increased resting energy expenditure. TSH directly stimulates preadipocyte differentiation, leading to adipogenesis. Our findings align with previous studies, demonstrating a higher prevalence of SCH among young obese females with positive TPO antibodies.[24,25] The exact explanation remains elusive, but estrogen and a potential link between SCH and autoimmune thyroid disease (Hashimoto's disease) have been suggested. Although the association between SCH and dyslipidemia is well known , there is limited researches examining the connection between SCH and atherogenic indices.[18,26] Atherogenic Index of Plasma AIP is more predictive of cardiovascular diseases than individual lipids, and CRI-II is a more accurate predictor of heart disease risk than LDL alone.[18,27,28] Our study demonstrated significantly higher mean levels of AIP and CRI-II, with non-significantly higher mean levels of CRI-I and AC compared to healthy participants. These abnormalities can be explained by the essential role of thyroid hormones in

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regulating lipid metabolism.[19,31–33] The findings indicated that there was no notable difference in serum irisin levels among cases of SCH when compared to the control group. Additionally, irisin levels were positively correlated with the low TSH level group but were not significantly associated with AIP, CRI-I, or CRI-II levels. Elevated irisin levels appear to be associated with an increased risk of atherogenic indices positivity with or without SCH.[29,30] Irisin, first identified in 2012 by Bostrom et al., is produced and released by skeletal muscle cells to communicate with other endocrine glands. Irisin induces "browning and_beiging" of white adipose tissue, increasing energy expenditure via upregulated UCP1 expression.[34] Thyroid hormones, endogenous regulators of brown adipose tissue, influence heat regulation. [35] Both T3 and irisin can improve UCP1 production, and T3 can suppress Fibronectin type III domain-containing protein 5 (FNDC5) synthesis in human subcutaneous adipocytes.[36] The similarities between thyroid hormone and irisin effects on metabolism suggest that thyroid hormones' functions might be mediated by and/or attributable to changes in irisin levels. This investigation unveiled that serum irisin levels exhibited no significant variation between the healthy euthyroid controls and SCH groups, and were not linked to TSH or FT4 levels, which is consistent with previous studies by Panagiotou et al.[37] and Zhengyi Chen et al.[37,38] Nevertheless, these findings contradict those of Stratigou et al., who discovered a notable increase in serum irisin levels in individuals diagnosed with SCH compared to healthy subjects.[39] Irisin levels were positively associated with TSH levels. This discrepancy may be attributed to the inclusion of thyroid antithyroglobulin antibody (TAA)-positive patients in the SCH group in Stratigou et al. study.[39] In contrast, only patients who had undergone thyroidectomy were included in Panigiotou et al., excluding the influence of autoimmune thyroiditis.[37] In addition, isolated SCH might not be sufficient enough to cause any changes in serum irisin levels due to the presence of TSH receptors across various tissues such as adipose tissue, liver, and bone cells; besides there being limited data on the direct impact of TSH on human skeletal muscle cells concerning mediating irisin release.

Conclusions

The current study provides conclusive evidence that serum Irisin level in patients with SCH remain unaltered when compared to a healthy control group. Additionally, among patients with SCH, a positive association was observed between serum Irisin levels and atherogenic indices. This study illuminates the prevalence of SCH, particularly among young, obese females. The findings contribute towards comprehending the intricate relationship between serum Irisin levels, SCH, and associated cardiovascular risk factors. These results, when considered collectively, underscore the importance of exploring the multifaceted aspects of thyroid function and associated biomarkers in diverse patient populations.

Conflict of interest

No conflicts of interest exist.

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