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CARDIOVASCULAR BIOMARKERS, TYG INDEX AND TG/HDL-C RATIO IN SUBCLINICAL HYPOTHYROIDISM PATIENTS

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ABSTRACT:

Subclinical hypothyroidism (SCH) is characterized by exhibiting a normal value of free thyroxine (T4) and excessive blood thyroid-stimulating hormone (TSH) concentration. SCH may be regarded as a prevalent concern of the emergence of overt hypothyroidism and cardiovascular disease (CVD). Disturbance in irisin, visfatin, NADPH oxidase, triglyceride/high-density lipoprotein-cholesterol (TG/HDL-c) ratio, and triglyceride glucose (TyG) index are associated with an increased cardiometabolic risk. The present study aimed to investigate serum levels of visfatin, irisin, NADPH oxidase ($gp91^{phox}$), TyG index, TG/HDL-c ratio, and anti-TPO in patients with SCH in comparison to apparently healthy individuals. A study of the case-control method was carried out at Vin Specialist Laboratory, Kurdistan Region, Iraq, involving 146 subjects, including 73 newly diagnosed subclinical hypothyroid patients and 73 healthy controls. Biochemical tests such as glucose, TSH, FT4, FT3, Anti-Thyroid Peroxidase (anti-TPO), TG, and HDL-C were analyzed using Cobas6000 (Roche), whereas, enzyme-linked immunosorbent assay was conducted to estimate the value of serum visfatin, NADPH oxidase ($gp91^{phox}$) and irisin. There was significantly a higher mean serum level of NADPH oxidase in 73 patients with SCH compared to that of 73 healthy individuals (8.73±2.89 ng/mL, 6.41±1.23 ng/mL, P=0.004). Mean serum levels of visfatin (41.29±8.16 ng/ml) and NADPH oxidase (8.73±2.89 ng/ml) were elevated in subclinical hypothyroid patients in comparison with healthy individuals with significant differences ($p<0.001$ and $p=0.001$), whereas, the mean serum level of irisin (15.78±2.64 ng/ml) was reduced in the SCH patients compared to healthy individuals ($p=<0.001$). The study found that, in contrast to healthy control individuals, patients with subclinical hypothyroidism had lower levels of serum irisin and higher mean values of TG/HDL-C, visfatin, TyG index, and NADPH oxidase.

KEYWORDS: Irisin, NADPH Oxidase, Subclinical Hypothyroidism, TYG Index, TG/HDL-c, Visfatin.

1. INTRODUCTION

Subclinical hypothyroidism (SCH) is a status in which free thyroxine (FT4) and free triiodothyronine (FT3) values remain normal despite high thyroid stimulating hormone (TSH). SCH has often aroused significant controversy, as this manifests in individuals without any noticeable symptoms, as well as frequently detected during health screenings with a frequency rate between 5% and 15% (Biondi*, et al,* 2019; Hami, *et al*., 2022). The two most typical reasons for SCH all over the world are iodine deficiency and autoimmune thyroiditis (Boelaert & Zimmermann, 2015; Hasan & Raziq, 2019). SCH can be regarded as a common risk condition for the progress of overt hypothyroidism and cardiovascular disorders (CVD), as it is related to the progression of atherosclerosis, disturbance of blood pressure, dyslipidemia, hypercoagulability, and endothelial failure (Bhardwaj *et al*., 2013; Razvi, *et al*., 2010).

Irisin, an adipocytokine, is released into the bloodstream by cleavage of the fibronectin type III domain-containing5 (FNDC5), which can be controlled with the Gamma coactivator-1 alpha's function in peroxisome proliferator-activated receptors (PGC1α) (Walczak & Sieminska, 2021). Thyroid tissue contains the irisin precursor FNDC5, which is released into the bloodstream. This offers an additional reason for the elevated irisin levels linked to chronic inflammation of the thyroid (Leustean, *et al*., 2021). Irisin synthesis and secretion disruption is linked to insulin resistance, abnormal glucose homeostasis, and increased cardiometabolic risk development because it is involved in pro-inflammatory and atherogenic processes (Aroda & Ratner, 2008).

Oxidative stress is characterized by an imbalance in the production of free radicals and antioxidants. Research has shown mixed findings on the relationship between SCH and oxidative stress markers (Ma *et al*., 2020; Özturk *et al.,* 2012). A recently identified oxidase that produces reactive oxygen species (ROS) in the cardiovascular system is nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) (Gp91phox) (Zhang, *et al*., 2020). Its activation promotes the emergence of heart-related conditions as it enhances in the progress of the atherosclerotic process (Sedeek *et al*., 2012). Thyroid hormone production is an367 oxidative process that requires hydrogen peroxide (H2O2) as a substrate that is generated through NADPH oxidases (Szanto *et al*., 2019). Visfatin (pre-B cell colony boosting element or Nicotinamide phosphoribosyl transferase), a visceral fat adipokine, was discovered in 2005 along with a molecular weight of 52 kilodaltons as well as 491 amino acids (Luok *et al*., 2008). Leukocytes (particularly granulocytes), fat tissue, macrophages, and monocytes are responsible for visfatin secretion (Mayi *et al*., 2010). Visfatin rises in inflammatory situations because it accelerates upward the products of cytokines that promote inflammation involving tumour necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β), interleukin-1 receptor antagonist (IL-1Ra), interleukin 6 (IL-6), and interleukin 10 (IL-10) (Wu *et al*., 2018). Visfatin can be considered as a biomarker of the development of CVD as its level is changed in a similar pattern to cardiac marker in acute myocardial infarction (Erten 2021).

The triglyceride glucose (TyG) index is a novel diagnostic that has demonstrated exceptional specificity and sensitivity in identifying metabolic disorders. It is also linked to the

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development of CVD risk since it increases coronary artery calcification and carotid atherosclerosis (Irace 2013). In overweight and obese people, the triglyceride to high-density-lipoprotein-cholesterol (TG/HDL-c) ratio remained a valid indicator for insulin resistance that is positively correlation with the occurrence of diabetics with type 2 and metabolic syndrome. Moreover; Cardiovascular incidents including elevated blood pressure, coronary heart disease, newly diagnosed heart failure, in addition to myocardial infarction can be associated with TG/HDL-c (Jawzal *et al*., 2022 ; Marotta 2010;).

The main aim of the study was to evaluate values of different promising cardiovascular biomarkers (irisin, visfatin and NADPH), TyG index, and TG/HDL-c ratio in patients of SCH in comparison to apparently healthy subjects. Moreover, this study aimed to evaluate serum levels of different promising cardiovascular biomarkers (irisin, visfatin, and NADPH), TyG index, and TG/HDL-c ratio in SCH patients with positive Anti-Thyroid Peroxidase (anti-TPO) comparing with those SCH patients with negative anti-TPO. Finally, Additionally, the current study attempted to examine the amounts of promising cardiovascular biomarkers with high TyG index as well as high TG/HDL-c ratio in patients with SCH compared to patients with SCH with normal TyG index and normal TG/HDL-c ratio.

2. MATERIALS AND METHODS

Study Sample :

A study was executed at Vin Specialist Laboratory, Duhok City, Kurdistan Region - Iraq, covering a period of 1-year interval from October 2023 to July 2024. The current case-control study recruited a total of 146 participants of males and females with ages ranging between 18 to 54 years; seventy-three patients were newly diagnosed with subclinical hypothyroidism and the remaining seventy-three were healthy volunteers that were regarded as a control group. The latter group had been chosen from family, friends, and relatives with similar age and gender distribution of patients. Patients were diagnosed with new subclinical hypothyroidism depending on a serum level of TSH equal to or above 4.20 µIU/mL with the regular value of FT4 12 until 22 (pmol/l) and FT3 3.1 until 6.8 (pmol/l) (Salih 2022). Exclusion criteria were those patients who suffered from the following conditions; chronic inflammation, diabetes mellitus, neoplasm, smoking, alcohol, medications, recent severe illness, and pregnancy as all these disorders and conditions were associated with abnormality of the studied biomarkers.

An interview was held to collect data by completing a questionnaire form. The study permission and ethical clearance were obtained from the Ethics Committee of the General Directorate of Health of Duhok Governorate with reference number (30102024-9-49). The questionnaire comprised items regarding the respondent's name, age, date of birth, and gender. The study collected anthropometric data encompassing height (in centimeters), body weight (in kilograms), and waist circumference, and the body mass index (BMI) is calculated by dividing the weight in (kg) of weight by the square of the height in (m) (Suleiman *et al*., 2023).

Biomarker Analysis :

All subjects were informed to attend Vin Specialist Laboratory, in the morning, and follow an overnight fast. Five ml of blood were extracted from all individuals and gathered inside gel vacutainer tubes and centrifuged for 15 min at 4000 rpm.

The levels of serum irisin, visfatin, and NADPH oxidase (gp91*phox*) were tested by an enzyme-linked immunosorbent assay, depending on the antigen-antibody reaction and the enzymatic reaction. The Cobas 6000 (Hitachi, Roche) was used to measure all other parameters, employing various principles. Hormones such as TSH, FT4, FT3, and anti-TPO had to depend upon electrochemiluminescence immunoassay, whereas the TG, HDL-C, and glucose depended upon the enzymatic colorimetric methods. The instruments used were the Cobas 6000 and ELISA, which were calibrated daily at the start of the project using a calibration curve and standard controls given by the device's supplier. The following equation determines the TyG index: Ln [FBS (mg/dl) multiplied by TG (mg/dl), divided by 2] (normal index between 4 and 8). TG/HDL-c ratio was figured out using Fasting TG divided by fasting HDL-c (normal ratio less than 3), anti-TPO ≥ 34.0 regarded as positive anti-TPO and < 34.0 regarded as negative anti-TPO values (Alhubaish *et al*., 2023).

Statistical Analysis :

The SPSS 26 program was used to analyze data. The research groups' demographic characteristics and thyroid function parameters (control and patients) were shown as a percentage or as a mean (SD). The data were normally distributed and the study's groups were compared utilizing Pearson Chi-Square and independent t-tests. Independent-sample Ttests were used to examine cardiovascular biomarkers, the TyG index, in addition to the TG/HDL-C ratio in patients of SCH with positive and negative anti-TPO results. A value of p was deemed statistically significant if it was 0.05 or less.

3. RESULTS

The mean serum levels of TSH and anti-TPO in SCH patients were 7.22 µIU/mL and 59.07 IU/mL correspondingly, which had significant differences and were higher than that of apparently healthy individuals, 2.59 µIU/mL and 12.59 IU/mL separately, with p of lower than 0.001. Moreover, the mean and SD of BMI and WC of subclinical hypothyroid patients was higher in comparison with apparently healthy participants with p-value of <0.001, as shown in Table 1

Table: Basic features and thyroid function parameters of study participants

Characters	SCH N (73)	Controls N (73)	*p-value*
	Mean± Std	Mean± Std	
Age (years)	33.96±9.04	32.89±8.77	0.470 [i]
Gender Male Female	 18 (24.7%) 55 (75.3%)	 18 (24.7%) 55 (75.3%)	1.000 [p]
BMI (Kg/m^2)	29.30±6.26	23.51±1.05	<0.001 [i *]
W.C (cm)	92.33±14.42	79.33±7.65	<0.001 [i*]
TSH (µIU/mL)	7.22±2.89	2.59±0.87	<0.001 [i*]
FT3 (pmol/l)	3.84±0.64	3.71±0.24	0.086 [i]
FT4 (pmol/l)	15.94±1.73	15.84±1.64	0.714 [i]
Anti-TPO (IU/mL)	59.07±85.37	12.59±5.32	<0.001 [i*]

statistical analysis was performed by [i] independent T-test and [p] Pearson Chi-Square.
N=number of cases; SCH= subclinical hypothyroidism; BMI= body mass index; W.C= waist circumferences; TSH= thyroid-stimulating hormone; FT4= free thyroxine; FT3= free triiodothyronine; anti-TPO= Anti-thyroid peroxidase.
* A p-value of <0.05 is considered statistically significant

The mean levels of serum NADPH oxidase were significantly higher in SCH patients compared to healthy participants (8.73±2.89 ng/mL, 6.41±1.23 ng/mL, separately) (P less than 0.001). the levels of serum Visfatin were significantly higher within SCH patients compared to control participants (p=0.001). Furthermore, the concentration of serum TyG index and TG/HDL-C ratio were insignificantly higher in subclinical hypothyroidism in comparison with those of control subjects (p=0.081 and p=0.112), whereas, the mean serum level of irisin was significantly decreased in the SCH in contrast to that of control individuals (p<0.001) as presented in Table (2).

Table 2: Cardiovascular biomarkers, TyG index, and TG/HDL-C ratio of study participants

Parameters	SCH N (73)	Controls N (73)	*p-value*
	Mean± Std	Mean± Std	
Irisin (ng/mL)	15.78±2.64	25.58±4.95	<0.001*
Visfatin (ng/mL)	41.29±8.16	37.09±7.01	0.001*
NADPH oxidase (ng/mL)	8.73±2.89	6.41±1.23	<0.001*
TyG index	8.46±0.62	8.29±0.49	0.081
TG/HDL-C	3.09±2.94	2.49±1.34	0.112

statistical analysis was conducted utilizing an independent T-test.
N=number of cases; SCH= subclinical hypothyroidism; NADPH oxidase= nicotinamide adenine dinucleotide phosphate; anti-TPO= Anti-thyroid peroxidase; TG/HDL-c= triglyceride/high-density lipoprotein-cholesterol ratio; TyG= index triglyceride glucose index.
* A p-value of <0.05 is considered statistically significant

The mean levels of cardiovascular biomarkers, TyG index, and TG/HDL-c ratio in SCH subjects of positive and negative Anti-TPO were shown in Table 3. The mean conc. of irisin was significantly lesser in SCH with positive anti-TPO (14.86±1.69 ng/ml) compared with those patients with negative anti-TPO (16.35±2.96 ng/mL) (p=0.018). Furthermore, the levels of visfatin, NADPH oxidase, TyG index, and TG/HDL-C ratio were insignificantly greater in the subclinical hypothyroid patients in comparison with negative anti-TPO of subclinical hypothyroid patients, (in turn, p = 0.522, p = 0.444, p = 0.500, & p = 0.689).

Table 3: Cardiovascular biomarkers, TyG index, and TG/HDL-C ratio in SCH patients with positive and negative anti-TPO.

Biomarkers	SCH N=73		
	Negative Anti-TPO < 34.00 IU/mL, N=45 Mean± SD	Positive Anti-TPO ≥ 34.00 IU/mL, N=28 Mean± SD	*p-value*
Irisin (ng/mL)	16.35±2.96	14.86±1.69	0.018*
Visfatin (ng/mL)	40.76±8.89	42.03±6.91	0.522
NADPH oxidase (ng/mL)	8.53±2.26	9.07±3.70	0.444
TyG index	8.42±0.65	8.52±0.58	0.500
TG/HDL-C	2.98±1.23	3.28±1.88	0.689

statistical analysis was computed by an independent T-test.
N=number of cases; SCH= subclinical hypothyroidism; NADPH oxidase= nicotinamide adenine dinucleotide phosphate; anti-TPO= Anti-thyroid peroxidase; TG/HDL-c= triglyceride/high-density lipoprotein-cholesterol ratio; TyG= index triglyceride glucose index.
* A p-value of <0.05 is considered statistically significant

The mean serum levels of irisin, visfatin, and NADPH oxidase in cases with SCH with abnormally high TyG index and TG/HDL-C ratio have been shown in Table 4. Serum irisin had non-significant and lower levels in SCG with TyG index more than 8 (15.56±2.52 ng/ml) and TG/HDL-C ratio more than 3 (15.43±2.11 ng/ml) comparing to those patients with normal TyG index (16.59±2.97 ng/ml) and TG/HDL-C ratio (15.94±2.87 ng/ml). Moreover, the mean serum level of visfatin and NADPH oxidase were insignificantly higher in patients with SCH with abnormally high TyG index and TG/HDL-C ratio compared to those with normal TyG index and TG/HDL-C ratio, (correspondingly, p = 0.289 and p = 0.689).

Table 4: Mean level of cardiovascular biomarkers in subclinical hypothyroid patients with abnormal TyG index and abnormal TG/HDL-C ratio

Biomarkers	TG/HDL-c in SCH (N=73)			TyG index in SCH (N=73)		
	< 3.0 N=49	≥ 3.0 N=24	*p-value*	< 8.0 N=22	≥ 8.0 N=51	*p-value*
	Mean± Std	Mean± Std		Mean± Std	Mean± Std	
Irisin (ng/mL)	15.94±2.87	15.43±2.11	0.441	16.59±2.97	15.56±2.52	0.169
Visfatin (ng/mL)	40.41±7.40	42.96±9.49	0.211	39.32±5.83	41.78±8.67	0.289
NADPH oxidase (ng/mL)	8.35±2.21	8.92±3.17	0.434	8.47±3.11	8.81±2.84	0.689

The statistical analysis has been done using an independent samples t-test.
N= number of cases; SCH= subclinical hypothyroidism; NADPH oxidase= nicotinamide adenine dinucleotide phosphate oxidase; TG/HDL-c= triglyceride/high-density lipoprotein-cholesterol ratio; TyG= index triglyceride glucose index.

4. DISCUSSION

The results indicate that SCH patients have an increased mean level of BMI and WC, as well as, three-quarters of patients with SCH were females compared to one-quarter were males. These results are in agreement with other studies results (Al-Mousawi *et al*, 2024 ; Bashir *et al*, 2013;). The higher majority of SCH in the females was not clearly defined, but the distinct impact of sexual hormones on thyroid function, such as estrogen's influence over women's TSH is linked to sex discrepancy, as well as, related to the high predominance of autoimmune thyroid diseases in women (Kweon *et al*. 2013). The obesity of patients with SCH may be related to adipocyte-secreted leptin, the presence of thyroid autoantibodies, and an evolutionary reaction to raise energy consumption at rest (Closs *et al*., 2023). Moreover, TSH directly stimulates preadipocyte differentiation, causing adipogenesis (Solanki *et al*., 2013).

The current results showed that the serum irisin levels have been significantly reduced in the subclinical hypothyroid cases compared to the healthy individuals, as this aligned with research conducted by Yang and his associates in China (Yang *et al*., 2019). This can be explained by individuals having chronic myopathy, which may affect how well muscle tissue functions, or by increased muscle damage as an organ that secretes hormones, which causes a progressive reduction in serum irisin levels (Zybek *et al*., 2016). Furthermore, decreases in irisin levels in patients with SCH put them at risk for cardiovascular disease development (Aronis *et al*., 2015). The significance of thyroid hormones in managing blood visfatin concentrations is controversial (Alshaikh *et al*., 2019; Özturk *et al*, 2012). However, this study indicated that the values of mean serum visfatin were significantly greater in patients of SCH in comparison with healthy control participants as this was consistent with a past study (Dakroub *et al*., 2021; Farghaly *et al*, 2017). In the current study, the mean level of NADPH oxidase was developed in patients of SCH than in healthy participants with statistically significant differences, this observation can be clarified by the cause that the serum TSH increase in patients with SCH will enhance the oxidative process along with inflammatory reaction as it is linked with increasing TNF-α and IL-6 production, that could potentially perform an active part in the modulation of vascular function through the elevation of nitric oxide metabolites (Mancini *et al*., 2016). The present results were at the same line with another research, which found increased oxidative stress and levels of serum NADPH oxidase among patients with SCH (Ma *et al* 2020). This study also indicated that average levels of TyG index were developed within the subclinical hypothyroid individuals, which was consistent with an earlier study that indicated greater TyG index and the TSH level and the TyG index have a positive relationship (Onur *et et*., 2022). Evidently could be an association between subclinical hypothyroidism and atherosclerosis since TSH straightly promotes gluconeogenesis of hepatic, cholesterol production, and leptin release in adipocytes (Mahat *et al*., 2023). The present research observed a higher mean level of TG/HDL-C ratio in cases with SCH in comparison to healthy control participants. This can be explained by a combination of factors that occur in SCH such as decreased synthesis and increased metabolism of HDL-C, impaired lipoprotein lipase activity which is essential for triglyceride breakdown, and induction of insulin resistance that further disrupts lipid metabolism, as a consequence of these abnormalities and disruption in lipid metabolism, the patients with SCH are more prone to the hazards of cardiovascular diseases development (Sabharwal *et al*., 2017).

The current investigation discovered that one-third of patients with SCH were of autoimmune process as evidenced by higher levels of anti-TPO antibodies. The mean of serum Irisin was significantly lower in those autoimmune patients of SCH as consistent with others and mostly due to a combined effect of thyroid dysfunction and chronic inflammatory process that exists in those patients (Bocale *et al.,* 2021). Furthermore, the levels of serum visfatin were enhanced in subclinical hypothyroid individuals with positive anti-TPO, which were comparable with a prior study conducted by Nadia and her colleagues (Abdullah *et al*., 2012). The incidence of anti-TPO antibodies indicates chronic low-grade inflammation associated with autoimmune thyroiditis, which can stimulate visfatin production as part of the inflammatory response. Immune system activation and cellular stress from ongoing autoimmune activity further contribute to elevated visfatin levels (Fröhlich & Wahl 2017). Furthermore; There were higher mean levels of NADPH oxidase among subclinical hypothyroid patients with positive Anti-TPO, which could be explained the presence of dual oxidase that performs an important function in joining iodine-binding thyroid peroxidase to thyroglobulin. This matched with the research conducted by Ginabreda and his associates (Ginabreda *et al*., 2008).

Moreover, in the current study, two-thirds and one-third of patients with SCH showed a higher level and riskier level of TyG index and TG to HDL-C ratio, respectively. The mean of serum irisin had insignificant with lower correlation in those patients with SCH with high TyG index and TG/HDL-C ratio that had been approved by Sagana and his teammates, which may be due association of subclinical hypothyroid patients with insulin resistance (Nilofer *et al*., 2024). The study found that the mean level of visfatin was increased with higher levels of TG/HDL-C ratio and TyG index. This might be because visfatin can block NO2 synthase action, which results in endothelial dysfunction, and it interacts with certain inflammatory mediators including TNF-α and interleukin-8, which increases endothelium permeability and smooth muscle cell reproduction (Kong *et al*., 2014). The relationship between visfatin and TyG index

highlights the objective of visfatin as an alternative factor in the altered metabolic profile seen in subclinical hypothyroidism (Dakroub *et al*., 2021). A study done by Ugur and his colleagues supports this relationship, demonstrating that visfatin levels were insignificantly linked with the TyG index in individuals of subclinical hypothyroidism, indicating its potential role in exacerbating insulin resistance in this population (Ugur *et al*., 2022). Furthermore; the current study showed insignificant high mean level of NADPH oxidase in patients with SCH with higher TG/HDL ratio and TyG index indicating a high-risk level with those patients to the development of cardiovascular diseases, that is consistent with study done by Ma *et al* (2020). This can be linked to that; an abnormal thyroid hormone metabolism was correlated with both oxidative stress and insulin resistance (Choi *et al*, 2021).

CONCLUSION

The levels of serum NADPH oxidase were significantly developed in the patients with subclinical hypothyroidism. NADPH oxidase, visfatin, TyG index and TG/HDL-C levels were insignificantly greater in autoimmune SCH (positive anti-TPO) and serum irisin level was insignificantly lower in positive anti-TPO patients. Moreover, two thirds and one third of patients with SCH showed higher level of TyG index and TG/HDL-C ratio, respectively. Furthermore, the mean level of serum irisin was insignificantly lower in those patients with SCH with high TyG index and TG/HDL-C ratio.

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Author Contributions:

All authors reviewed the final version of the manuscript to be published and agreed to be accountable for all aspects of the work. S.F.S., was responsible for the concept and design of the study. B.I.A., handled the data analysis and interpretation. The drafting of the manuscript was performed by B.I.A., and S.F.S.,

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