



Assessment of Cardiovascular Risk Factors and Insulin Resistance in Patients with Subclinical Hypothyroidism

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Authors' contributions

This work was carried out in collaboration among all authors. Authors ZS, LEA, IK and AES done the conceptualization. Authors ZS, AES, NA and LEA managed the data curation. Author IK done the formal analysis. Authors ZS, AES and LEA managed the investigations. Authors ZS, AES and IK managed the methodology. Authors LEA, NA and AES supervised the work. Authors ZS, IK and AES wrote the original draft of the manuscript. Authors ZS, AES, NA and LEA wrote reviewed & edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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ABSTRACT

Background: Overt hypothyroidism is associated with Insulin resistance (IR), accelerated arteriosclerosis and cardiovascular disease (CVD). Although SCH (SCH) is also associated with CVD risk remains controversial.

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Objective: The present research aimed to assess risk factors for CVD and IR in SCH cases.
Methods: Case control study was carried out on 90 participants. The research included two groups; group one included 45 SCH cases and group two (controls) included 45 healthy volunteers. We assessed common lipid variables, fasting blood glucose, fasting insulin, HOMA IR, thyroid profile for all participants.
Results: There was highly significant rise in anthropometric measures including body weight, BMI and waist circumference in SCH than controls (**P value = <0.001**). There was significant rise in systolic and diastolic blood pressure (BP) in SCH than controls (**P value = <0.001, 0.001**). There was significant rise in triglyceride level, total cholesterol and LDL-C in SCH in comparison to controls (**P value = 0.019, <0.001, <0.001**) and significant decline in HDL-C in SCH in comparison to controls (**P value = 0.011**). There was significant positive correlation between TSH level and anthropometric measures, BP, indices of IR, total cholesterol, triglycerides and LDL-C, but significant negative correlation with HDL-C.
Conclusion: Our findings suggest that SCH might increase the risk for CVD which explain the needs for early detection and treatment of such individuals.

Keywords: Hypothyroidism; insulin resistance; cardiovascular diseases; HOMA IR.

1. INTRODUCTION

Thyroid hormones triiodothyronine (T3) and tetraiodothyronine (T4) maintain a fine balance of glucose homeostasis. Hypothyroidism can break this equilibrium and alter glucose metabolism, which can lead to IR [1]. Based on severity of symptoms, clinical signs, and thyroid function test, hypothyroidism is classified as overt hypothyroidism (OH) and subclinical hypothyroidism (SCH) [2].

Previous studies have established overt hypothyroidism as a risk factor for IR through complex mechanisms of biochemical, genetic, and secretory malfunctions [3-4]. It was observed that serum TSH concentrations in SCH cases were positively associated with Homeostatic Model Assessment for IR (HOMA-IR) index or insulin levels and other components of metabolic syndrome [5].

Insulin resistance (IR) may contribute to the formation of atherosclerosis via mechanisms involving elevated glucose and insulin levels, dyslipidemia, hypertension, and inflammation, thereby increasing the likelihood of cardiovascular disease (CVD) [6].

In hypothyroidism, the main CV alterations include a decrease in cardiac output, a decrease in heart rate, and a rise in peripheral vascular resistance. Greater alterations in modifiable atherosclerotic risk factors have been identified [7]. The present research aimed to assess risk factors for CVD and IR in SCH cases.

2. PATIENTS AND METHODS

Case control study was carried out on 90 participants over 1 year duration at Clinics of Diabetes, Metabolism and Endocrinology Unit, Tanta University Hospital (TUH) and Clinic of Internal Medicine Department, Kafr El-Sheikh University Hospital (KUH) in the period from March 2020 to March 2021. Exclusion criteria included: cases with treatments that could potentially cause thyroid malfunction, such as surgery, radioactive iodine, radiation to the neck, or any drugs (such as amiodarone, lithium, interferon alpha), cases diagnosed with diabetes mellitus, cases with active malignancy based on history, cases with acute or chronic inflammatory conditions based on history, cases with known cardiovascular disease and pregnant females.

The research included two groups; **Group I** included 45 subclinical hypothyroid cases, SCH can be defined as a serum thyroid stimulating hormone (TSH) above the upper limit of the standard reference level in the presence of normal serum free T3 and free T4 levels.

Group II (controls) included 45 healthy volunteers, age and gender matched, having TSH, free T3 and free T4 levels in the standard reference level.

All cases went through to a questionnaire for gathering data, which included the following:

- a- **Thorough history taking:** Including age, gender, and history of receiving any medications for chronic diseases.

b- **Full clinical examination:**

- Blood pressure was measured after at least 10 minutes of repose for each participant.
- The body mass index (BMI), height, and body weight were measured. The BMI was computed by dividing body weight in kilograms by height in meters squared (kg/m²)
- The waist circumference (WC) was calculated as the lowest circumference at the umbilical level.
- Thyroid examination.
- Chest, cardiac and abdominal examination to exclude subjects with any abnormal findings.

c- **Investigations:** Include Thyroid function tests (TSH, Free T₃ and Free T₄), Anti-Thyroglobulin antibody (Anti-Tg), Anti-Thyroid peroxidase antibody (Anti-TPO), Oral glucose tolerance test (OGTT) to exclude cases with diabetes mellitus, HbA_{1c}, Lipid profile (Total cholesterol (TC), Triglycerides (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C)), Fasting plasma insulin, HOMA-IR was calculated, and thyroid ultrasonography (US) was done. Blood samples were taken into heparinized tubes.

2.1 Statistical Analysis

Using IBM's SPSS version 19 (Statistical Package for Social Studies), the collected data were organized, tabulated, and statistically analyzed. The range mean and standard deviations were calculated for numerical values. Using the student's t test, the differences between two mean values were determined. For categorical variables, the number and percentage were calculated, and the chi-square test was used to examine differences between subcategories. We calculated odds ratio (OR) and 95% confidence interval (CI) for the estimated risk. The correlation between variables was determined using Pearson's correlation coefficient (r). The significance level was set at p<0.05.

3. RESULTS

This research was carried out on 90 participants who were recruited at the clinic of Diabetes, Metabolism and Endocrinology Unit, Tanta University Hospital (TUH) and Clinic of Internal

Medicine Department, Kafr El-Sheikh University Hospital (KUH).

The mean age was 34.98±13.16 years in SCH, 35.51±13.38 years in controls. There were 11.1% male cases 88.9% female cases in SCH, 20% male cases and 80% female cases in controls. There was no statistical significant difference regarding age and sex.

Regarding the anthropometric measures among the studied subjects, the mean of BW was 84.73±15.41 in SCH and 69.58±13.84 in controls. The mean of BMI was 32.45±6.14 in SCH and 25.90±5.03 in controls and the mean of WC was 102.93±14.19 in SCH and 85.56±9.58 in controls. The BW, BMI and WC showed statistically highly significant rise in SCH than controls (P value = <0.001) (Table 1).

Regarding the BP measures among the studied subjects, the mean of systolic BP (SBP) was 123.56±12.95 in SCH (SCH) and 114.00±11.76 in controls with statistically highly significant rise in SBP in SCH than controls (P value = <0.001). The mean of diastolic BP (DBP) was 81.00±8.30 in SCH (SCH) and 75.27±7.42 in controls with statistically significant rise in DBP in SCH than controls (P value = 0.001) (Table 1).

Regarding the indices of IR among studied subjects as regard fasting blood glucose, fasting insulin and HOMA IR there was statistically highly significant rise in SCH than controls. (P value = <0.001) (Table 2).

The lipid profile among the studied subjects revealed that there was statistically significant rise in SCH than controls as regard TG, Cholesterol and LDL-C. (P value =0.019, <0.001 and <0.001, respectively) and statistically significant decline in SCH than controls as regard HDL-C (P value = 0.011) (Table 3).

As regard the relation between TPO antibodies and severity of SCH, the percentage of cases with severe SCH (TSH ≥10 µU/mL) was higher in those with positive TPO antibodies (27.3%) than negative TPO antibodies (4.3%). The percentage of cases with mild SCH (TSH<10) was higher in those with negative TPO antibodies (95.7%) than those with positive TPO antibodies (72.7%) with statistical significant difference (P value=0.047) (Table 4).

Regarding the relation between thyroglobulin antibodies and severity of SCH, the percentage

Table 1. Comparison of anthropometric measures, systolic and diastolic BP among studied subjects

Anthropometric measures	SCH	Controls	T	P
Body weight				
Range	45-109	50-100	4.908	<0.001*
Mean \pm SD	84.73 \pm 15.41	69.58 \pm 13.84		
BMI:				
Range	18-42	19-39	5.546	<0.001*
Mean \pm SD	32.45 \pm 6.14	25.90 \pm 5.03		
Waist circumference				
Range	74-125	75-110	6.810	<0.001*
Mean \pm SD	102.93 \pm 14.19	85.56 \pm 9.58		
SBP				
Range	100-145	100-140	3.665	<0.001*
Mean \pm SD	123.56 \pm 12.95	114.00 \pm 11.76		
DBP			3.455	0.001*
Range	70-100	60-90		
Mean \pm SD	81.00 \pm 8.30	75.27 \pm 7.42		

Table 2. Comparison of fasting plasma glucose, fasting insulin and HOMA-IR among studied subjects

Variables	SCH	Controls	T	P
Fasting glucose				
Range	70-100	72-90	5.843	<0.001*
Mean \pm SD	88.09 \pm 7.80	80.35 \pm 4.18		
Fasting insulin				
Range	3.2-30.5	3.6-16.4	3.859	<0.001*
Mean \pm SD	11.29 \pm 5.87	7.32 \pm 3.61		
HOMA-IR				
Range	0.5-6.9	0.7-3.3	4.236	<0.001*
Mean \pm SD	2.49 \pm 1.38	1.47 \pm 0.75		

of cases with severe SCH (TSH \geq 10 μ U/mL) was higher in those with positive thyroglobulin antibodies (28.6%) than negative thyroglobulin antibodies (9.7%). The percentage of cases with mild SCH (TSH<10) was higher in those with negative thyroglobulin antibodies (90.3%) than those with positive thyroglobulin antibodies (71.4%) with no statistical significant difference (P value=0.18) (Table 4).

As regard the ultrasonography in SCH cases, cases with diffuse thyroid disease (DT) on ultrasonography, 65% had TSH<10 and 35% had TSH \geq 10. All SCH cases with normal ultrasound had TSH <10. There was statistical significant difference (P value=0.002) (Table 4).

Regarding the relation between anti-TPO and other studied parameters in SCH cases, the research showed that there was statistically significant rise in BMI and WC in anti TPO positive than anti TPO negative (P value= 0.005 and 0.002 respectively), but no statistical

significant difference as regard DBP, HOMA IR, fasting insulin, TC/HDL and LDL/HDL (Table 5).

Regarding correlation between TSH and other studied variables, there was significant and good positive correlation between TSH and BW, BMI, WC, SBP, DBP, Fasting glucose, Fasting insulin, HOMA IR, Cholesterol, TG and LDL-C but weak negative correlation between TSH and HDL-C (Table 6).

4. DISCUSSION

Glucose homeostasis is kept in a delicate balance by thyroid hormones (TH). This equilibrium can be disrupted and glucose metabolism altered by hypothyroidism, leading to Insulin resistance (IR) [1]. The progression of IR can result in metabolic syndrome, a noticeable CV risk factor, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes mellitus [8].

Due to its increasing prevalence and potential adverse effects, SCH is becoming a global health problem. The effects of SCH are varied and could rely on the duration and level of serum TSH elevation. Consequently, a number of essential concerns regarding SCH arise, such as whether it increases CV risk and, consequently, mortality, whether it adversely affects metabolic parameters, and whether it should be treated with L-thyroxin [9].

In our research, there was statistically highly significant rise in the anthropometric measures including body weight, BMI and WC in SCH than controls. Also there was significant and good positive correlation between TSH level and these measures. In our research, there was statistically significant rise in the BMI and abdominal obesity, indicated by waist circumference in anti TPO positive than anti TPO negative cases with SCH. In Hashimoto thyroiditis (HT), it is possible that

Table 3. Comparison of plasma lipid profile tests among studied subjects

Lipid profile tests	SCH	Controls	T	P
Triglycerides				
Range	50-203	79-155	2.385	0.019*
Mean \pm SD	123.09 \pm 38.40	107.73 \pm 19.79		
Total cholesterol				
Range	135-280	125-235	5.553	<0.001*
Mean \pm SD	203.97 \pm 35.33	167.42 \pm 26.47		
HDL				
Range	25-73	39-60	2.601	0.011*
Mean \pm SD	47.51 \pm 7.74	50.93 \pm 4.24		
LDL				
Range	67-180	66-142	6.141	<0.001*
Mean \pm SD	126.14 \pm 29.41	94.11 \pm 18.97		
TC/HDL				
Range	2.8-5.6	2.4-5.9	5.769	<0.001*
Mean \pm SD	4.26 \pm 0.86	3.28 \pm 0.74		
LDL/HDL				
Range	1.4-3.9	1.2-3.5	6.171	<0.001*
Mean \pm SD	2.63 \pm 0.69	1.83 \pm 0.51		

Table 4. The relation between TPO antibodies, thyroglobulin antibodies, ultrasonography and severity of SCH

		TSH		P
		TSH <10	TSH \geq 10	
Anti TPO	Positive (n = 22)	16 (72.7%)	6 (27.3%)	0.047*
	Negative (n = 23)	22 (95.7%)	1(4.3%)	
Anti-thyroglobulin	Positive (n = 14)	10 (71.4%)	4 (28.6%)	0.18
	Negative (n = 31)	28 (90.3%)	3 (9.7%)	
Ultrasonography	Abnormal (DT) (n=20)	13 (65%)	7 (35%)	0.002*
	Normal (n=25)	25 (100%)	0 (0%)	

Table 5. Comparison of studied parameters in relation to anti-TPO among cases with SCH

Variables	Anti-TPO		p
	Positive (n=22)	Negative (n= 23)	
BMI	34.61 \pm 6.65	30.39 \pm 4.90	0.005*
Waist circumference	108.91 \pm 14.38	97.22 \pm 11.63	0.002*
Diastolic BP	82.04 \pm 9.08	80.00 \pm 7.54	0.411
HOMA-IR	2.63 \pm 1.52	2.35 \pm 1.25	0.625
Fasting insulin	11.77 \pm 6.60	10.83 \pm 5.19	0.883
TC/HDL	4.32 \pm 0.86	4.20 \pm 0.88	0.439
LDL/HDL	2.67 \pm 0.68	2.59 \pm 0.73	0.601

increased IFN- γ and TNF-a may cause obesity independent on TSH levels. This was in agreement with a research assessed the interconnection between obesity, thyroid function, IR, and CV risk factors in cases with SCH and found that waist circumference was significantly higher in SCH cases than euthyroid individuals [10], also this was in line with research assessed the relation between SCH and metabolic syndrome and found that BMI was statistically significant higher in the studied SCH cases [11].

Table 6. Correlation between thyroid stimulating hormone (TSH) and other studied variables

Variables	TSH	
	r	P
Body Weight	0.379	<0.001
BMI	0.449	<0.001
Waist Circumference	0.523	<0.001
Systolic BP	0.237	0.024
Diastolic BP	0.263	0.012
Fasting glucose	0.481	<0.001
Fasting insulin	0.426	<0.001
HOMA-IR	0.457	<0.001
Triglycerides	0.293	0.005
Total Cholesterol	0.526	<0.001
HDL	-0.299	0.004
LDL	0.595	<0.001
TC/HDL	0.579	<0.001
LDL/HDL	0.611	<0.001

Several metabolic pathways, including appetite, lipid and glucose breakdown, and energy expenditure from fat depots, are influenced by TH. Inversely, adipocytokines mediate the impact of abdominal obesity on thyroid function. Increased TSH levels in obese cases may be a result of leptin, peripheral hormone resistance, or adaptation to increased energy expenditure. Obesity as a cause or a result of elevated TSH is a matter of controversy [12].

We suggest that obesity is a consequence to elevated TSH in our research as about 53% of the studied cases had underlying autoimmune disease represented by positive autoimmune antibodies (anti TPO, anti TG). The mean BMI and WC were noticeably higher in cases with positive TPO antibodies in comparison to anti TPO negative SCH cases. It seems reasonable to suggest that the relation between obesity and thyroid disease is bidirectional. More research is needed to develop a new standard reference level for TSH in obese non pregnant adults.

In our research, both systolic BP and diastolic BP were statistically significant higher in SCH than controls. Diastolic BP was higher in anti-TPO positive cases than anti-TPO negative cases, however not statistically significant. Significant and positive correlation between TSH level and diastolic BP was found. This was in consonance a research reported that SCH cases had significantly higher values of both systolic and diastolic BP versus the control in the study of atherosclerosis among SCH cases [13]. Another research found that the systolic BP measurements of all participants were not substantially different, whereas the diastolic BP of SCH cases was noticeably higher than that of the controls ($p < 0.001$) [11]. In contrast, an observational research assessing BP characteristics of SCH in conjunction with office BP and 24-h ambulatory BP found no statistical difference between the SCH and the euthyroid in terms of office SBP and DBP ($P > 0.05$). On the other hand, the daytime SBP, nighttime SBP, 24-h SBP, and diastolic BP in the SCH were substantially higher than those in the euthyroid group [14]. The SCH cases had substantially higher levels of mean diastolic BP, daytime diastolic BP, nocturnal diastolic BP, and nighttime systolic BP [15].

All these results suggest that SCH is a neglected cause of arterial hypertension. A number of studies have suggested that the risk of hypertensive CV complications correlates more closely with 24-hour, daytime, or nighttime ambulatory BP monitor than with the BP measured in the office [14-15]. Therefore, we propose that the BP in SCH can be better understood by integrating office and ambulatory BP measurements.

In our research, the percentage of cases having severe SCH (cutoff point TSH ≥ 10) are greater in anti TPO positive than anti TPO negative SCH cases with statistical significant difference. Severe SCH was greater among cases with thyroglobulin antibodies than negative thyroglobulin antibodies, however not statistically significant. Another research of the prevalence of elevated TPO antibodies in SCH revealed that the prevalence of TPO-Ab was noticeably higher with TSH ≥ 8 [16]. These findings could potentially suggest that anti-TPO positivity is associated with higher rate of progression to overt hypothyroidism. Regular follow up of those cases is recommended for detection of disease progression.

In our research, association between ultrasonographic abnormalities and severity of SCH was found. 35% of SCH cases with diffuse thyroid disease on US had severe SCH in comparison to none of those with normal US. There was statistical significant difference. The association between hypoechogenicity, heterogeneity degree and severity of thyroid dysfunction in adolescents with autoimmune thyroid disease was found in a research assessed the relation between ultrasound findings and thyroid function in children and adolescent autoimmune diffuse thyroid diseases [17] Another research evaluated the prognostic value of ultrasound and found that and hypoechographic US patterns increases the risk of progression to overt hypothyroidism from SCH [18].

Thyroid US combined with the TPO Ab assay throughout the initial diagnostic work up of a case with SCH seems to be more useful than TPO Ab alone in predicting the clinical progression and establishing a treatment plan, particularly in cases with mildly elevated serum TSH levels ($<10\mu\text{IU/mL}$) [18].

In our research, the mean fasting blood glucose level, fasting insulin and HOMA-IR were significantly higher in SCH in comparison to controls. Fasting insulin and HOMA-IR were higher in anti-TPO positive than anti-TPO negative cases however, not statistically significant. Higher central fat as observed by greater waist circumference in SCH cases might explain the high prevalence of IR among participants; we also observed a positive correlation between TSH level and fasting glucose, fasting insulin and HOMA-IR suggesting a lower sensitivity of tissues to insulin with increasing TSH. This was in agreement with a research showed statistical significant difference of fasting blood glucose, and indices of IR including, fasting insulin and HOMA-IR between the SCH and euthyroid controls [19]. Another research reported statistical significant rise in fasting insulin and HOM-IR formula ($p < 0.05$), but no statistical significant difference in fasting blood glucose in cases with SCH compared to healthy controls [20]. Research assessed the IR and glucose levels in subjects with SCH and demonstrated that measures of IR including serum fasting insulin and HOMA-IR rise from euthyroidism to subjects having SCH [21].

In our research, there was a statistically significant rise in (TG, Cholesterol and LDL) and

statistically significant decline in HDL in SCH compared to controls. Also significant positive correlation was present between TSH level and TC, TG, LDL, TC/HDL and LDH/HDL but significant negative correlation with HDL. In accordance with our results a research evaluated the effect of SCH on serum lipid profile and reported significant rise in LDL, total cholesterol, and TG levels in SCH than in controls. HDL levels were substantially lower in SCH than in the controls. Comparing two groups, the VLDL levels were low in the controls and high in the SCH [22]. In another research comparing the lipid profiles of cases with and without SCH, TC and LDL were found to be noticeably higher in cases with SCH than in cases without SCH [23]. In addition, the research of dyslipidemia in SCH and the effect of thyroxin on lipid profile revealed that the mean levels of total cholesterol and LDL were noticeably higher in SCH than in controls. After treatment with thyroxin, mean total cholesterol, mean LDL, mean VLDL, and mean triglyceride levels decreased significantly [24].

In our research, TC/HDL and LDL/HDL were higher in anti-TPO positive cases than anti-TPO negative cases, however not statistically significant. This was in agreement with research showed that there was a noticeable positive correlation between Anti-TPO and LDL ($p < 0.001$), triglyceride ($p = 0.005$) and total cholesterol ($p = 0.001$) [25], Therefore it may be beneficial to determine the lipid profile of all cases with Hashimoto thyroiditis, even if they are euthyroid.

Every step of lipid metabolism, including synthesis, mobilization, and degradation, are influenced by TH. The impact of TH on the rate of lipid breakdown is regarded as predominating. The possible explanations of dyslipidemia found in our research and other studies could be that thyroxin is necessary for gene expression and synthesis of LDL receptors. The susceptibility of SCH cases to atherosclerosis has been noticed and may be partially explained by the presence of dyslipidemia and IR in SCH cases. Immune system involvement in atherosclerosis is supported by the presence of activated T cells in atherosclerotic lesions and circulating antibodies to plaque components.

Numerous studies provide contradictory findings regarding the clinical significance of SCH in cardiovascular disease and mortality. This is due to the selection of heterogeneous case groups,

arbitrary TSH reference limits when defining SCH, the absence of stratification based on elevated TSH levels, and the use of diverse research designs.

According to our results and other above mentioned results, SCH increase the risk of IR and CV disease risk. Therefore, early diagnosis of SCH and assessment of measures of CV risk is essential for early prevention of complication.

5. CONCLUSION

SCH cases have higher risk of developing metabolic syndrome and type 2 diabetes. Our findings suggest that the high incidence of hypertension and unfavorable lipid profiles in SCH cases may raise the risk of increased atherosclerosis and early coronary artery disease. TPO Ab, Thyroglobulin Ab positivity and diffuse thyroid disease on ultrasound (decreased echogenicity) were associated with severe SCH.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

CONSENT

As per international standard or university standard, Participants' written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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