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The Subclinical Hypothyroidism and Cardiovascular System

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ABSTRACT

Background: Because of its high prevalence, subclinical hypothyroidism (SCH) has clinical significance as it is associated with many of the risks of atherosclerotic cardiovascular disease (CVD) due to its direct and indirect effect on lipid profile, diastolic function, and endothelial dysfunction. However, the link between SCH and CVD is still unknown.

Objectives: This study aimed to evaluate the carotid intima media thickness (CIMT) and the lipid profile as evidence of endothelial dysfunction and atherosclerosis on patients with SCH.

Patients and methods: The current study was a cross-section study carried out on 50 patients with SCH who were enrolled from the Outpatient Clinics of Diabetes and Internal Medicine Department, Assiut University Hospitals, Assiut, Egypt in the period from the 1st of September 2019 up to the end of December 2021. Also, 50 healthy matched participants who served as control group. All participants underwent full history taking, a thorough clinical examination, and routine lab investigation, in addition to thyroid function tests, lipid profile, echocardiography, and estimation of CIMT.

Results: Patients with SCH had significantly higher waist to hip ratio (W/H), higher triglycerides, cholesterol, low-density lipoprotein cholesterol (LDL-c), and increase in CIMT. Seven patients (14%) in the study group had diastolic dysfunction versus no one in the control group. In addition, SCH patients showed that significant positive correlations were founded between CIMT and thyroid-stimulating hormone (TSH), cholesterol and LDL levels.

Conclusions: The study found that various cardiovascular risk factors were prevalent in patients with SCH and should be considered.

Keywords: Subclinical hypothyroidism, Cardiovascular system.

INTRODUCTION

Subclinical hypothyroidism is a biochemical disorder marked by elevated serum level of TSH while the thyroid hormone concentrations still within their normal reference values[1]. The prevalence rate ranges from 12 to 18%, being more common with increased age and among women[2].

Autoimmune thyroiditis is one of the main causes of SCH, but it can also be caused by other factors [3]. Subclinical hypothyroidism is accompanied by cardiovascular hazards such as hyperlipemia, diastolic hypertension, increase arterial stiffness, an elevated C- reactive protein, and endothelial dysfunction[4, 5].

Hyperlipidemia is a significant risk factor for atherosclerosis; elevated TSH is linked to higher LDL, higher serum triglycerides (TGs), and reduced breakdown of cholesterol. This could contribute to the dyslipidemia observed with SCH[4, 5].

Endothelial dysfunction is the centerpiece in the onset and progression of atherosclerotic CVD, which leads to increase carotid artery intima media thickness (CIMT) [4, 5].

The association between SCH, atherosclerosis and CIMT has been reported but the exact mechanisms have not entirely cleared[6].

The main goal of this study was to estimate the correlation between SCH and cardiovascular risk factors by assessment of lipid profile and CIMT as evidence of atherosclerosis and endothelial dysfunction.

MATERIALS AND METHODS

Study participants:

The current study was a cross-sectional hospital-based study at one of major Tertiary Health Care Hospitals, Assiut University Hospital, Assiut, Egypt through the period from the 1st of September 2019 to the end of December 2021. Fifteen patients with SCH were recruited from the Outpatient Clinics of Diabetes and Internal Medicine Department of Assiut University Hospitals, in addition to 50 healthy matched individuals with normal thyroid function who serve as control group. All patients had a thorough medical history taking, including their body mass index (BMI) and W/H ratio, presence of other comorbidities (as hypertension, diabetes mellitus), and current use of medications. Assessment of vital signs was done for all studied participants. 3 ml of venous blood samples were collected from all studied participants to assess the thyroid stimulation hormone (TSH), lipid profile, blood glucose, and CRP. All participants were subjected to ECG, Echocardiography, and measurement of CIMT.

Exclusion criteria:

Patients aged less than 18 years old, those with thyroid dysfunction (either hypo or hyperthyroidism), diabetics, hypertensives, pregnant or lactating women, smokers, those who received antithyroid medications or any drug that had an effect on thyroid functions, patients with a history of receiving

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radiotherapy or underwent thyroid surgery, and those who refused to be included in the present study.

Ethical approval:

The study adhered to the regulations of Assiut University's Ethical Committee (IRB No. 17101049). The study protocol was also registered at clinicaltrials.gov (ID: NCT04236232). An official written consent was provided by each studied subjects before enrollment in the current study.

Statistical analysis

Data was analyzed using SPSS (Statistical Package for the Social Sciences, version 22, IBM, and Armonk, New York). Qualitative data were statistically described as mean ± SD and compared by the student t test, while categorical data were statistically described as frequency (percentage) and compared by the Chi^2-test. The correlation between various variables was examined using the Pearson correlation test. $P \leq 0.05$ was used to determine significance.

RESULTS

Demographic data of the studied groups:

Both studied groups were comparable regarding to age, sex and BMI with no significant difference between them (P=0.50, and 0.34 respectively).

However, the studied cases had significantly higher waist/hip ratio as compared to control group (82.52 ± 5.87 vs. 79.44 ± 3.45; p= 0.004), as shown in table (1).

Table 1: Demographic data of the studied groups (n=100)

Variables	Study group (n= 50)	Control group (n= 50)	P value
Age (years), mean ± SD	35.64 ± 8.87	32.68 ± 10.08	0.50
Sex, n (%)			0.34
Male	15 (30.0)	21 (42.0)	
Female	35 (70.0)	29 (58.0)	
BMI (kg/m^2), mean ± SD	25.07 ± 2.28	25.20 ± 2.06	0.74
WHR, mean ± SD	82.52 ± 5.87	79.44 ± 3.45	**0.004**

BMI: body mass index, WHR: waist hip ratio. Quantitative data are presented as mean ± SD, qualitative data are presented as number (percentage), Significance defined by p < 0.05.

Blood pressure and laboratory data among the studied groups: No significant difference was observed between both studied groups regarding to the vital signs, FBG, and CRP (P>0.05, for all). Meanwhile the studied cases had significantly higher triglycerides level (183.28 ± 18.22 vs. 153.74 ± 18.25, P< 0.001), cholesterol level (202.50 ± 26.03 vs. 162.50 ± 26.03, P< 0.001), and LDL level (162.64 ± 26.09 vs. 102.70 ± 21.75, P< 0.001) in both studied groups respectively, while HDL showed no significant difference between both studied groups (Table 2).

Table 2: Blood pressure and laboratory data among the studied groups

Variables	Study group (n= 50)	Control group (n= 50)	P value
Systolic BP (mmHg)	118.98 ± 6.37	117.52 ± 6.28	0.26
Diastolic BP (mmHg)	79.24 ± 5.86	78.33 ± 5.72	0.38
FBG (mg/dl)	90.42 ± 5.44	89.62 ± 6.32	0.49
CRP (mg/dl)	6.98 ± 2.95	6.86 ± 2.42	0.0.82
Triglycerides (mg/dl)	183.28 ± 18.22	153.74 ± 18.25	**< 0.001**
Cholesterol (mg/dl)	202.50 ± 26.03	162.50 ± 26.03	**< 0.001**
LDL (mg/dl)	162.64 ± 26.09	102.70 ± 21.75	**< 0.001**
HDL (mg/dl)	41.76 ± 10.57	43.45 ± 8.98	0.19
TSH (mU/ll)	7.42 ± 1.32	2.93 ± 0.76	**< 0.001**

BP: blood pressure; FBG: fasting blood glucose; CRP: C-reactive protein; LDL: low density lipoproteins; HDL: high density lipoproteins; TSH: thyroid stimulating hormones. Quantitative data are presented as mean ± SD. Significance defined by p < 0.05.

Echocardiography and carotid duplex among the studied groups:

The ejection fracti on (%) was comparable between both studied groups with no significant difference between them (P=0.12). Seven SCH cases (14.0%) had abnormal E/A ratio <1, seven SCH cases had diastolic dysfunction compared to no one in the control group (P< 0.001). Also, the SCH had higher CIMT (mm) compared to the control group (0.70 ± 0.17 vs. 0.56 ± 0.06, P< 0.001) as shown in table (3).

Table 3: Echocardiography and carotid duplex among the studied groups:

Variables	Study group (n= 50)	Control group (n= 50)	P value
EF (%), mean ± SD	64.40 ± 3.49	65.09 ± 2.22	0.12
E/A ratio, n (%)			
Normal (> 1)	7 (14.0)	50 (100.0)	**< 0.001**
Abnormal (< 1)	43 (86.0)	0 (0.0)	
Diastolic dysfunction, n (%)	7 (14.0)	0 (0.0)	**< 0.001**
CIMT (mm), mean ± SD	0.70 ± 0.17	0.56 ± 0.06	**< 0.001**

EF: ejection fraction; E: left ventricular relaxation in early diastole; A: peak velocity flow in late diastole caused by atrial contraction; CIMT: carotid intima media thickness. Quantitative data are presented as mean ± SD. Quantitative data are presented as mean ± SD, qualitative data are presented as number (percentage), Significance defined by p < 0.05.

Correlation of CIMT with other data variables: Among patients with SCH, significant positive correlations were observed between CIMT and TGs level (r=0.38, p=0.01), cholesterol (r=0.45, P<0.001), LDL (r=0.43, P<0.001), and TSH level (r=0.61, P<0.001). Other variables showed no significant correlation with CIMT (P>0.05, for all), as shown in table (3).

Table 4: Correlation of CIMT with other data variables:

Variables	r value	P value
Age (years)	0.12	0.22
BMI (kg/m^2)	-0.10	0.63
WC (cm)	-0.08	0.43
Systolic BP (mmHg)	0.14	0.16
Diastolic BP (mmHg)	0.01	0.86
FBG (mg/dl)	0.04	0.63
CRP (mg/dl)	0.01	0.63
Triglycerides (mg/dl)	**0.38**	**0.01**
Cholesterol (mg/dl)	**0.45**	**< 0.001**
LDL (mg/dl)	**0.43**	**< 0.001**
HDL (mg/dl)	-0.08	0.38
TSH (mU/ll)	**0.61**	**< 0.001**
Ejection fraction (%)	0.17	0.08

BMI: body mass index; WC: waist circumference; BP: blood pressure; FBG: fasting blood glucose; CRP: C-reactive protein; LDL: low density lipoproteins; HDL: high density lipoproteins; TSH: thyroid stimulating hormones. Date expressed as r value (strength of correlation), P value (significance of correlation). P value was significant if < 0.05.

DISCUSSION

With the progression of laboratory techniques, subclinical hypothyroidism has become more prevalent, thereby gaining attention recently. The term "SCH" refers to an increase in serum thyrotropin (TSH) concentrations with normal serum free thyroxin levels (T4) [7].

The current study was conducted at the Outpatients Clinics of Diabetes and Internal Medicine Department to assess the correlation between SCH and cardiovascular system by evaluation of lipid profile and CIMT, as evidence of atherosclerosis, and endothelial dysfunction. The study enrolled 50 patients with SCH and another 50 healthy subjects as control group. The mean age of the studied SCH cases was 35.64 ± 8.87 vs. 32.68 ± 10.08 years in the control group (P=0.50). also, no significant difference was observed between both studied groups as regards BMI, and waist circumference. In agreement with the current study, **Deshmukh *et al.*** [8] observed that 74% of people with SCH were between the ages of 35 and 54, and that the prevalence increased with age.

Also we observed that the majority of the studied SCH were females. In line with current study In agreement with the present study **Dey *et al.*** [9] stated that 80% of the studied patients with SCH were females. However the reasons for this female predominance are poorly understood [10].

In the current study we found that SCH diseased patients had a significantly higher WHR in comparison to control group. Our findings agreed with those of **Jung *et al***.[11] who discovered that the W/H ratio was significantly higher in SCH patients compared to control group.

In the current study we observed that both groups were comparable regarding to the blood pressure measurements. Similar finding was reported by the previous study of **Harada *et al.*** [10].

In the current study, we found that the studied cases had significantly higher cholesterol, triglycerides, and LDL levels (P< 0.001, for all), Other clinical and laboratory data namely (CRP, and HDL) were comparable between both studied groups. This finding could be explained by the fact that thyroid hormone regulates cholesterol synthesis via multiple mechanisms. As a result, the increase in total cholesterol and LDL-C that can occur in hypothyroidism contributed to a variety of changes in lipid synthesis, mobilisation, and metabolism. The thyroid hormone stimulates the liver's production of hydroxymethylglutaryl coenzyme A reductase (HMG-CoA) and the expression of the LDL receptor (LDL-R) gene [12]. According to the same author, HDL levels decrease SCH and contribute to the risk of CVD [12].

Similarly, **Efstathiadou *et al.***[13] observed that SCH diseased patients had significantly higher cholesterol and LDL-C levels, while TGs and HDL-C levels didn't differ significantly as compared to control group. Also **Iqbal *et al.***[14] showed higher LDL-C levels in SCH patients.

Both groups had no significant differences regarding ejection fraction, but seven patients (14%) in the studied patients with SCH had diastolic dysfunction versus no one in the control group. Subclinical hypothyroidism had clinical importance, potential for future development into clinical hypothyroidism, and relationships with both direct and indirect risk factors of CVD. Additionally, studies have linked SCH to an increased risk of coronary heart disease, demonstrating the critical necessity of disease prevention [9].

In the current study, we observed that SCH patients had significant higher CIMT in comparison with the healthy group (0.70 ± 0.17 vs. 0.56 ± 0.06 mm; P < 0.001). According to earlier research, the mean C-IMT levels were 0.503±0.090 mm in the control group, 0.836±0.267 mm in the overt group, and 0.825±0.272 mm in the SCH group. Overt hypothyroidism and SCH groups did not differ significantly from one another (p=0.979), although there were significant differences between the control and overt hypothyroidism group and between the control and SCH group [15].

It was found that CIMT showed no significant correlation with all continuous variables in the current study, with exception of significant positive correlation with TSH (r= 0.61, p< 0.001), cholesterol (r= 0.45, p< 0.001), LDL-C (r= 0.43, p< 0.001) and TGs (r= 0.38, p= 0.01).

This is consistent with previous study found that CIMT was correlated positively with LDL-C (r=0.24, P<0.0005) and TGs (r=0.21, P<0.001). But in contrast to the current finding authors reported significant negative correlations between CIMT and HDL-C (r=−0.19, P<0.001) [16].

There have been reports of the detrimental effects of high blood TSH levels on lipid metabolism, and further research has revealed an elevated risk of atherosclerosis and cardiovascular symptoms in SCH people with high normal TSH levels. Lipid abnormalities were common in SCH individuals [17]. This highlights the need for further larger studies to confirm the role of SCH in the development of CVD among those patients. In order to identify high risk group for earlier intervention and better outcome.

Limitation:

Our study had some limitations as it was single centered study, and carried out on small sample size, this was the main obstacle in the current study. Also, we didn't evaluate the effect and benefit of thyroid hormone replacement therapy on the lipid profile, CIMT, and diastolic dysfunction in SCH studied patients. However, up to our knowledge, this study was the first study to discuss such an association in our locality.

CONCLUSIONS

Our study supports and confirms the role of SCH in the acceleration and progression of CVD in SCH patients by increasing LDL, total cholesterol, and TGs levels in those patients.

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