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Relation of subclinical hypothyroidism with Coronary Artery Calcium Score

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Abstract

Subclinical hypothyroidism (SCH) is a minor form of hypothyroidism disorder that has no obvious clinical symptoms. SCH is linked to premature atherosclerosis and a higher prevalence of coronary artery disease - a leading killer. Our aim is to investigate the relation of SCH and coronary artery disease (CAD) by measuring the coronary artery calcium score (CACS) detected by multi-slice CT coronary angiography in apparently healthy subjects Patients and Methods: A total of asymptomatic 100 (50 SCH and 50 euthyroid (EU)), without known coronary artery disease and meet our inclusion criteria from December 2018 to November 2019 at Mustafa Kamel Military Hospital outpatient clinic were enrolled in this study. Detailed history, laboratory investigations as: thyroid, lipid profile, renal function test, and HA1C were recorded. Framingham Risk Score (FRS) was calculated, CACS analysis by cardiac CT scan was performed on all subjects. SCH and EU groups were comparable when it came to age, gender, BMI, prevalence of diabetes, systemic hypertension, hypercholesterolemia, and smoking. There were no differences between the two groups in terms of mean Ca score, type of affected coronary arteries, or the number of affected coronary arteries, and the frequency of Ca score > 100 was not higher in the SCH group. The mean Ca score and the probability of a Ca score > 100 were higher in the SCH group when just the intermediate and high FRS were evaluated (P = 0.00). Serum TSH was positively correlated with CACS in intermediate/high FRS group (rs=0.86, P=0.001*). In conclusion, our findings highlight the importance of SCH and TSH level as predictive risk factors for coronary artery disease particularly in the intermediate/high FRS subgroups.

Keywords: Subclinical Hypothyroidism, Coronary Artery Disease, Calcium Score.

1. Introduction

Subclinical hypothyroidism (SCH), an early form of thyroid insufficiency, is characterized by a mild lack of thyroid hormones. It's defined by the isolated increase in serum TSH > 4mU/L accompanied by normal levels of FT4 and T3, and it's graded as mild (serum TSH 4-10 mU/L) or moderate/severe (serum TSH > 10 mU/L).[1] Thyroid hormones have a significant impact on a variety of metabolic processes. Each tissue in the body has been demonstrated to be affected by thyroid

hormone to one extent or another, but the cardiovascular system has been identified as a crucial target by thyroid hormones, as changes in thyroid function contribute to altered cardiovascular hemodynamics .[2]
Coronary atherosclerosis is more frequently connected with overt hypothyroidism (OVH), and OVH is known to accelerate coronary atherosclerosis [3]. Elevated LDL-C levels increased total cholesterol and serum triglyceride values, coagulation abnormalities, and other cardiovascular risk factors are among the suggested processes by which OVH causes cardiovascular disease (CVD). Because SCH is a preclinical stage of OVH, a similar CVD pathophysiology is expected .[4]
Coronary angiography is the gold standard approach for diagnosing CAD however, it has certain limitations due to its invasive nature, which limits it to a narrow group. It is now possible to explore coronary artery anatomy and pathophysiology in detail because of the progress of noninvasive multidetector computed tomography (CT) technology.[5]
Noninvasive CT scanning can be used to quantify the calcium content of atherosclerotic plaques in coronary arteries. CACS (coronary artery calcium score) is a new developing CAD risk factor that has already been established as an approved predictive indicator of CAD independent of traditional cardiovascular risk factors.[6] .
This study aims to investigate the relation of SCH and CAD by measuring the CACS detected by multi-slice CT coronary angiography in apparently healthy subjects.

2. Patients and Methods

This is a cross-sectional study that was carried out between December 2018 to November 2019. We studied 50 SCH patients from the endocrine outpatient clinics (in Mostafa Kamel Armed Force Outpatient Clinic) and 50 EU participants with the following inclusion criteria: all participants with SCH, EU thyroid (based on thyroid function test analysis) were aged between 35 and 65 years old in both genders, without known CAD.
The exclusion criteria in our study included: symptomatic CAD, history of percutaneous coronary intervention, coronary artery bypass graft, regional wall motion abnormalities, congenital, rheumatic heart or significant valvular heart disease by conventional echocardiography, pregnant female, systemic illness, or using drugs such as statin which is known to interfere with circulating thyroid hormone level.
All participants gave their informed consent before being subjected to a full history taking that included myocardial infarction or angina, hypertension, diabetes mellitus, dyslipidemia, a family history of premature CAD, a current drug profile, and smoking status. Height (cm) and body weight (kg) were measured. Body mass index was calculated by dividing weight by the height squared (kg/m2). Systolic and diastolic blood pressure were recorded by mercury sphygmomanometer evaluation. Laboratory Investigation including thyroid function test, lipid profile, HbAIc, renal function tests were measured. ECG analysis and transthoracic echo-Doppler screening were done to exclude ischemia and any significant echo Doppler findings.
Framingham Risk Score which estimates an individual's 10-year cardiovascular risk based on scoring characteristics such as age, sex, total cholesterol, HDL cholesterol, blood pressure (and whether the patient is being treated for hypertension), diabetes, and smoking was calculated according to the NCEP (National Cholesterol Education Program) guidelines [7], and Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult [8]. All participants were grouped into two groups: group (I): SCH and Group (II): EU. We then used FRS to categorize all participants into two categories: low

risk, intermediate/high risk. Additionally, intermediate and high FRS risk were subclassified into group (A) SCH intermediate and high FRS, group (B) EU intermediate and high FRS.

Multi-slices CT coronary angiography to measure the CACS coronary calcium score was performed using Siemens Somatom Definition Flash which is a second-generation dual-source 128-slice CT scanner with the following characteristics: Acquisition (2x128), Rotation speed (0.28 sec), Generator power (200 KW), Table load (300Kg/660Ib), Scan range (200 cm), Detector collimation was 64x0.6 mm. CACS was measured using a scoring system previously described by Agatston et al. [9]. Based on the CACS, participants were categorized in the following manner: 0 no identifiable calcification, 1 - 99 mild, 100-399 moderate, and 400 or higher - severe affection [9].

2.1 Statistical analysis of the data:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. Kolmogorov-Smirnov test was used to verify the normality of distribution. The student's t-test was used to test for differences in normally distributed continuous variables and Mann–Whitney U test was used for comparisons involving variables that were not normally distributed. Categorical variables were compared with the $\chi 2$ test or Fisher's exact test as appropriate. Analysis of the correlation between two variables was performed using Spearman's correlation coefficient (rs). A P value <0.05 was considered to be statistically significant.

3. Results

In our study SCH group included more females (64.0%) vs. (44 %) of the EU group, which is statistically significant (P = 0.04*). Both groups were similar in the frequencies of smoking, DM, HTN, and obesity. There is a statistically significant difference in both groups as regard: lower HDL (P =<0.001*), higher TG (P = 0.04*) in the SCH group. Mean serum TSH was significantly higher (P =<0.001*) and Mean serum FT4 was significantly lower (P =<0.006*) in SCH. FRS assessed the absolute risk of cardiovascular CV event in 10 years (AR10y) and divided the results into three categories: low, moderate, and high, with no significant difference between SCH, EU groups. Mean FRS was 9.2±8.4 in the SCH group vs. 6.6±4.6 in the EU group. This had a statistically significant difference (P= 0.01*) (Table 1). Because the FRS findings differed significantly across the SCH and EU groups, we utilized a stratified analysis to examine more homogeneous groups. Based on their FRS, participants in SCH and EU groups were divided into two groups: low risk (AR10y< 10%) and intermediate/high risk (AR10y≥ 10%). This analysis between SCH and EU participants in the two categories of FRS (low risk and intermediate/high risk) revealed that in terms of risk factor, all participants were comparable as shown in Table 2. All subjects were comparable in regard to thyroid profile and as expected TSH was significantly higher and FT4 was significantly lower in SCH groups (low risk and intermediate/high risk) (Table 3). Comparison of Ca score in the SCH (Group I) versus EU (Group II) regardless of FRS, revealed no statistically significant differences in the mean Ca score between the SCH and EU groups, Likewise, the frequency of Ca scores more than 100 was not higher in the SCH group. When only the intermediate/high FRS were considered, the SCH group had a higher mean Ca score and a higher frequency of Ca score >100 compared to EU group.

Table 1: Comparison between the two studied groups according to demographic data.

	SCH (n = 50)	**EU (n = 50)**	**Test of Sig.**	**p**
Age (years)				
Min. – Max.	35 – 65	39 – 65	t= 1.175	0.243
Mean ± SD.	53.2 ± 8.2	51.4 ± 7.6		
Sex				
Male	18 (36%)	28 (56%)	$\chi2$= 4.026*	0.045*
Female	32 (64%)	22 (44%)		
Smoking	22 (44%)	25 (50%)	$\chi2$= 0.361	0.548
DM	4 (8%)	2 (4%)	FE = 0.709	=0.678
HTN	28 (56%)	23 (46%)	$\chi2$= 1.000	0.317
BMI (kg/m2)				
Min. – Max.	22.5 – 41.1	20.9 – 36.6	t=1.296	0.198
Mean ± SD.	30 ± 5	28.8 ± 4.3		
Obesity (≥30)	23 (46%)	18 (36%)	$\chi2$= 1.033	0.309
Total cholesterol	226 ± 46	211.8 ± 30.6	$\chi2$= 0.162	0.687
HDL (mg/dl)	47± 5.1	52± 4.3	t= 1.900*	<0.001*
TG (mg/dl)	173 ± 37.1	158.4 ± 37	t= 2.045*	0.044*
TSH (mu/ml)	6.2 ± 2.1	2.4 ± 0.9	U= 0.0*	<0.001*
FT4 (ng/dl)	1 ± 0.26	1.2 ± 0.34	U= 875.0*	0.006*
FT3 (pg/ml)	3.094 ± 0.59	2.99 ± 0.614	U= 0.789	0.429
FRS	9.2 ± 8.4	6.6 ± 4.6	U= 898.50*	0.015*
Absolute risk of cardiovascular events in 10 years (AR_{10y}%)				
• **Low** (AR_{10y} <10)	43 (86%)	44 (88%)	$\chi2$= 0.866	^{MC}p= 0.817
• **Intermediate** (AR_{10y} 10 –20)	3 (6%)	4 (8%)		
• **High** (AR_{10y} >20)	4 (8%)	2 (4%)		

$\chi2$: Chi square test. t: Student t-test. U: Mann Whitney test. FE: Fisher exact. MC: Monte Carlo. p: p value for comparing between the studied groups. *: Statistically significant at $p \leq 0.05$. i

Table 2 Comparison between low, intermediate, and high FRS group according to lipid profile.

	Low risk		**Test of Sig.**	**p**	**Intermediate/ High risk**		**Test of Sig.**	**p**
	SCH (n = 43)	**EU (n = 44)**			**SCH (n = 7)**	**EU (n = 6)**		
Hypercholesterolemia	22(51.2%)	22(50.0%)	$\chi2$=0.012	1.000	7(100.0%)	5(83.3%)	$\chi2$=1.264	^{FE}p= 0.462
Total Cholesterol								
Min. – Max.	180 – 312	175 – 286	t= 1.337	0.185	204 – 387	187– 295	t= 1.546	0.150
Mean ± SD.	216.6 ± 34	207.8±26.6			288.6±63.1	241.2± 43.7		
HDL (mg/dl)								
Min. – Max	34 – 55	47 – 59	t=6.511*	<0.001*	35 – 48	36 – 52	t= 1.586	0.141
Mean ± SD.	47.9 ± 4.6	53.3 ± 3.1			41.1 ± 4.1	45.3 ± 5.4		
TG (mg/dl)								
Min. – Max.	100 – 238	102 – 230	t= 1.864	0.066	140 – 265	117– 265	t= 0.789	0.447
Mean ± SD	168.6 ± 34.4	155 ± 33.9			204 ± 41.8	183.7 ± 51.2		

χ^2: Chi square test. t: Student t-test. U: Mann Whitney test. p: p value for comparing between the studied groups. *: Statistically significant at $p \leq 0.05$.

Table 3: Comparison between low, intermediate /high FRS group according to thyroid profile and HBA1C.

	Low risk		Test of Sig.	p	Intermediate/High risk		Test of Sig.	p
	SCH (n = 43)	EU (n = 44)			SCH (n = 7)	EU (n = 6)		
TSH (mU/ml)								
Min. – Max.	4 – 9	0.9 – 3.8			7 – 12	1.8 – 3.7		
Mean ± SD.	5.5 ± 1.3	2.4 ± 0.9	U= 0.0*	<0.001*	9.9 ± 1.4	2.3 ± 0.7	U= 0.0*	0.003*
FT4 (ng/dl)								
Min. – Max.	0.7 – 1.8	0.7 – 1.8			0.7 – 1.7	0.8– 1.8		
Mean ± SD.	1.009±0.25	1.2 ± 0.34	U= 676	0.01*	1.004 ± 0.34	1.3 ± 0.37	U= 5.5	0.03*
FT3 (pg/ml)								
Min. – Max.	2.3 – 4.2	2.2 – 4.3			2.8 – 4	2.6– 4.1		
Mean ± SD.	3.03 ± 0.59	2.95 ± 0.61	U= 0.447	0.652	3.47 ± 0.45	3.2 ± 0.52	U= 0.447	0.652

t: Student t-test. U: Mann Whitney test. p: p value for comparing between the studied groups. *: Statistically significant at $p \leq 0.05$.

Table 4: Comparison between Total, low, Intermediate and High FRS group groups according to Ca Score.

	Total		Low risk		Intermediate/High risk	
	GI SCH (n = 50)	GII EU (n = 50)	SCH (n = 43)	EU (n = 44)	GA SCH (n = 7)	GB EU (n = 6)
Min. – Max.	0 – 920.0	0 – 541.0	0.0 – 623.0	0 – 316.0	76.0 – 920.0	0 – 541.0
Mean ± SD.	87.8±215.1	49.2±119.0	24.4±97.8	30.8±74.2	477.3±324.3	184.0±258.3
Median (IQR)	0 (0 – 23.0)	0 (0 – 10.0)	0 (0 – 0)	0 (0 – 0.5)	641 (183.5–668.5)	36.5 (0 – 490)
U(p)	1189.0(0.612)		913.0(0.709)		6.0*(0.035*)	
>100 agatston	9(18.0%)	7(14.0%)	3(7.0%)	5(11.4%)	6(85.7%)	2(33.3%)
χ2(p)	0.298(0.585)		0.501(^{FE}p=0.713)		3.745* (^{FE}p=0.000*)	

U: Mann-Whitney *U* test χ^2: Chi square test *: Statistically significant at $p \leq 0.05$

Table5: Multivariate analysis for the parameters affecting MVD

MVD variables	Multivariate	
	F	P
Age	9.581*	0.003*
Sex	3.513	0.064
DM	24.827*	0.001*
HTN	4.520*	0.036*
Smoking	0.017	0.897
BMI	1.499	0.224
HbA1C	10.119*	0.002*
S.Cholesterol	19.529*	0.000*
HDL	-12.477*	0.001*
TG	3.925	0.050
TSH	6.283*	0.014*
FT4	1.263	0.264
Ca. Score	81.885*	0.000*

MVD: multivessel diseases. F:f F ratio: *: Statistically significant at $p \leq 0.05$

ROC curve between serum TSH and CACS (a predictor for CAD probability) was plotted to show graphically the connection between clinical sensitivity and specificity for every cut-off point of the serum TSH. The most appropriate TSH cut–off point for CAD prediction was 6.25 with 77.8% sensitivity and 99.93% specificity. Also, the area under the curve was (0.930 with P =0.000*) which gives a clue about the accuracy of using serum TSH level as a tool for prediction of CAD by using Ca score and prove that serum TSH has a very good discriminative ability (Figure 1). Serum TSH was positively correlated with coronary Ca score in the intermediate/high FRS subgroup but not in all participants (Table 6). Serum TSH was positively correlated with serum cholesterol, systolic blood pressure and a significant negative correlation with HDL level in the intermediate/high FRS subgroup. Also positively correlated with serum cholesterol, systolic blood pressure, and age in all participants (Table 7).

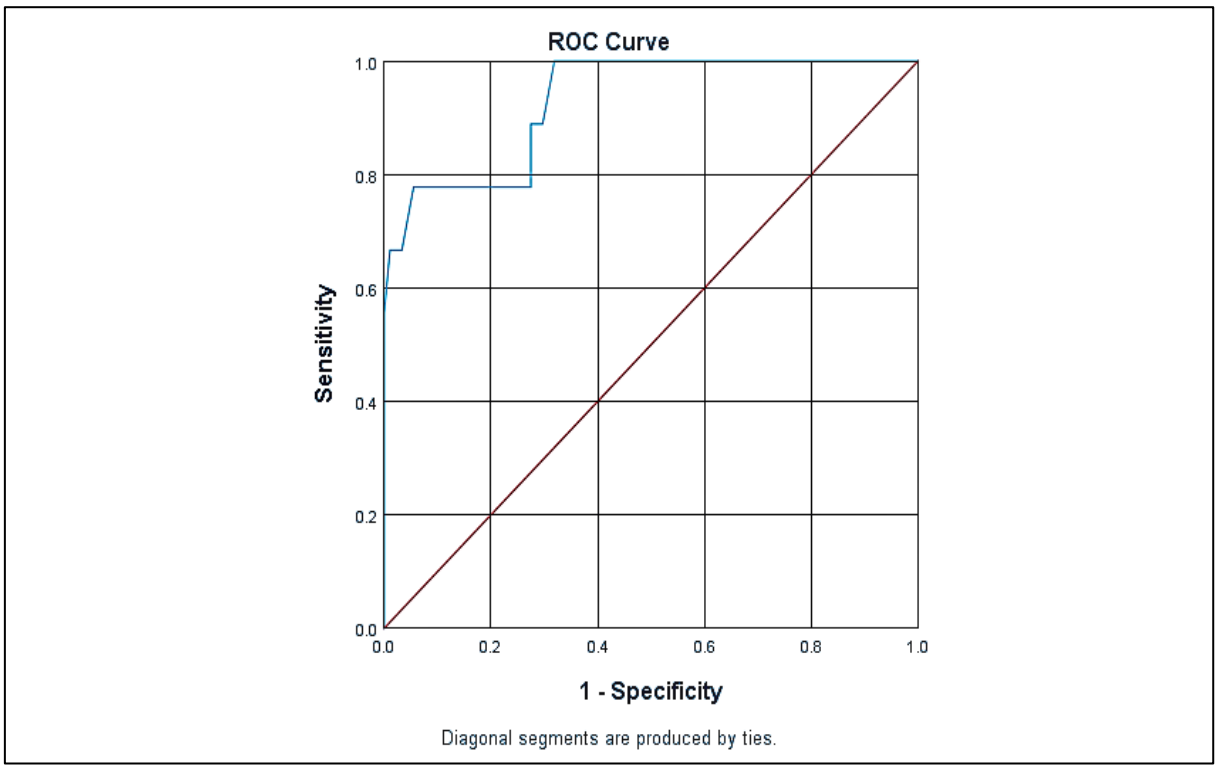

Figure 1: ROC curve between TSH and Ca score in all participant's (SCH and EU) n= 100.

Table 6: Correlation between TSH with Ca score in in all participant's SCH and EU groups.

	TSH (mU/ml)			
	Total (n = 100)		**Intermediate/High risk (n = 13)**	
	r_s	**p**	**r_s**	**p**
Ca Score	0.111	0.269	0.860*	0.0015*

r_s: Spearman coefficient
*: Statistically significant at $p \leq 0.0.5$

Table7: Correlation between TSH with total cholesterol, systolic BP, BMI, TG, Age, HDL in all participants SCH, EU groups.

	TSH (mU/ml)			
	Total (n = 100)		Intermediate/High-risk (n = 13)	
	r_s	p	r_s	p
Total Cholesterol	**0.324***	**0.001***	**0.722***	**0.005***
Systolic BP	**0.197***	**0.0494***	**0.648***	**0.016***
TG	**1.965**	**0.0521**	**0.526**	**0.064**
BMI	**1.741**	**0.084**	**0.3581**	**0.229**
Age	**0.256***	**0.009***	**0.259**	**0.392**
HDL	**-0.573**	**4.624**	**-0.566***	**0.0436***

4. Discussion

This study was designed to evaluate the association between SCH and CAD by measuring CACS detected by cardiac CT. In our age-matched study the SCH group is predominantly female gender which is consistent with the higher prevalence of SCH among females in general.[1]

We noticed that, when there was an intermediate/high risk of CV disease progression (AR10y≥ 10%), the CACS was higher and more severe in SCH patients. This result is in accordance with Silva et al [10], They reported significant differences in mean CACS when only intermediate / high risk was evaluated, and the frequency of Ca score >100 was higher in the SCH intermediate/high FRS.

The results of our study were also consistent with Park et al [11], they only looked at people with a moderate to high CV risk with the majority of whom were men, expressing that Male SCH patients have a higher CACS. And reported that SCH cases were much more likely than euthyroid cases to have occult CAD. They found significant differences in mean Ca score and the frequency of Ca score >100 in both groups confirming that SCH contributes to the development of CAD independently.

Our results regarding the correlation between TSH and CACS are consistent with the findings of Silva et al [10] who reported a positive correlation in the SCH group between serum TSH and CACS in the intermediate/ high FRS subgroup, but not in the entire group. Also similar to Park et al [11], they included only subjects with intermediate/high FRS and reported a significant correlation in the SCH group between serum TSH and CACS.

The previous findings in our study support the theory that SCH contributes to atherosclerosis by amplifying not only traditional CV risk factors such as dyslipidemia, hypertriglyceridemia, and systemic hypertension but also a newly emerging risk factor as CACS.[4]

A favorable association between serum TSH and cardiovascular risk factors as shown in our study has been found in several studies. According to [12, 13, 14], a positive correlation between serum TSH and blood pressure has been established. Wang et al [15], showed a positive correlation between serum TSH and serum cholesterol. Also, many studies have

examined the link between serum TSH levels and SCH [16, 17]. SCH patients with a serum TSH level > 10mU/L have a higher risk of CAD events and mortality [18]. Cho et al. [19] found that SCH with a serum TSH level > 10 mU/L is linked to CACS. In our study, we found 3 subjects with TSH levels> 10 mU/L. Therefore, we could not compare the group with higher TSH levels with the remaining participants.

The Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated the usefulness of the CACS as a CAD screening test [20]. Russot al. [21] noted that CACS is a predictor of a coronary event. The fact that even after controlling CVD risk factors SCH was still significantly associated with the presence of CAD suggests that SCH can be a useful marker to predict future major adverse cardiovascular events.

SCH has been demonstrated to be an independent risk factor for both CAD and radiologically evident aortic atherosclerosis, according to a recent Dutch study [22], which supports our findings. Also, the Busselton health study reported that SCH itself is an independent risk factor for coronary heart disease .[23]

Hulten et al. [24] showed that major cardiovascular events were rarely present in patients with normal coronary CT results, and future events increased progressively with increasing CAD in patients with aberrant coronary CT findings. As a result, the presence of CAD on coronary CT could be a highly sensitive and effective marker for predicting acute cardiovascular events in an asymptomatic individual.

5. Conclusion

In conclusion, our findings highlight the importance of SCH and TSH level as predictive risk factors for coronary artery disease particularly in the intermediate/high FRS subgroups.

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