Does subclinical hypothyroidism confer an increased risk of coronary heart disease in the elderly?

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Received 15 August 2017
Accepted 9 September 2017

Egyptian Journal of Obesity, Diabetes and Endocrinology 2018, 4:58–71

Background
Subclinical hypothyroidism (SCH) is defined as an isolated elevation of thyroid stimulating hormone (TSH) levels in conjugation with normal circulating levels of free triiodothyronine and free thyroxine. It is a highly prevalent disease especially in the elderly population. Thyroid hormones affect the heart and vasculature by both genomic and nongenomic pathways. However, the impact of SCH on the cardiovascular system is a matter of debate. Researches have been conducted to study the effect of SCH on cardiovascular system, yielding conflicting results. Although some studies support increased risk of cardiovascular events in patients with SCH, others show no significant increased risk.

Aim
This study was conducted to evaluate if SCH is associated with higher risk of coronary heart diseases in the elderly and if dyslipidemia, endothelial dysfunction as measured by flow-mediated dilatation (FMD) and carotid artery intima-media thickness were associated with SCH.

Patients and methods
Fifty elderly individuals aged 65 years and older were enrolled in this study and were divided into two groups, group I: 30 patients with SCH and group II comprised 20 age-matched and sex-matched euthyroid elderly serving as a control group. In all participants we performed serum TSH, free thyroxine, and antithyroperoxidase antibodies. SCH was defined as an elevated thyrotropin (TSH) (>4.5 mU/l) and normal free thyroxine level. Complete lipid profile, thyroid ultrasound, echocardiography to assess cardiac function and markers of endothelial dysfunction namely carotid artery intima-media thickness and FMD of the brachial artery (BA) after occlusion were done to all cases.

Results
The mean age of group I was 69.2±3.1 years and the mean age of group II was 68.6 ±3.2 years. Overall, 50% of the elderly patients with SCH (group I) were suffering from hypertension, whereas 35% in the elderly euthyroid group (group II) were hypertensive. The systolic and diastolic blood pressures are higher in group I as compared with group II (140±20 and 86±12, respectively vs. group II were 131±19 and 82±12, respectively), but the differences were statistically insignificant (P=0.12 and 0.21, respectively). No significant statistical difference was observed when the elderly SCH patients were compared with a euthyroid control group as regards the mean cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein levels (P=0.69, 0.79, 0.77, 0.42, respectively). For the elderly SCH group I the mean BA diameter before dilation was 3.12±0.44 versus 3.44 ±0.68 mm for euthyroid group II. However, the mean BA diameter after dilation was 3.64±0.60 mm compared with 4.05±0.73 mm for the euthyroid group. The mean percentage of FMD% of BA after occlusion was 16.2±5.7 in group I versus 17.9±5.5 in group II. There was no statistically significant difference between the two groups as regards flow-mediated vasodilatation% of the BA after occlusion (P=0.29).

Conclusion
This study did not find a significant association between thyroid function, lipid profile, and vascular parameters in patients who were similar with respect to age, BMI, smoking and menopausal status, and endothelial function modifiers.

Keywords:
atherosclerosis, elderly, flow mediated dilation, subclinical hypothyroidism, thyroid,

Egypt J Obes Diabetes Endocrinol 4:58–71

2356-8062

Introduction

Subclinical hypothyroidism (SCH) is a relatively common disorder in clinical practice. It is essentially a laboratory diagnosis as patients have no or few

symptoms. It is defined as serum thyroid stimulating hormone (TSH) concentration above the upper limit of the reference range in the face of normal circulating concentrations of free triiodothyronine (FT4) and free thyroxine (FT3) [1,2]. SCH is more prevalent in the elderly as compared with young or adult patients [1]. It has been agreed by most of the experts that this biochemical condition represents early thyroid failure with a rate of progression to overt hypothyroidism, ~2–5% annually [3], which is proportionate to the degree of TSH elevation and the presence of positive antithyroid antibodies [4].

It has been shown by previous studies that Subclinical hypothyroidism (SCH) is associated with various negative clinical outcomes such as increased risk of cardiovascular diseases, cognitive impairment, and dyslipidemia [5,6]. However, it remains controversial whether to treat or not to treat subclinical hypothyroidism (SCH), especially in elderly patients. This may be attributed to lack of consensus of cutoff levels for TSH to define SCH in the elderly. Moreover, mild elevation of thyroid function tests in the elderly population may merely represent a normal physiological aging process [7], due to the downregulation of the hypothalamic–pituitary axis rather than true occult thyroid disease making it challenging to reach a correct diagnosis of SCH in the elderly [2].

Whether SCH confers high risk of developing coronary heart disease (CHD) in the elderly population has been an area of extensive investigations with various and even controversial results. Although some studies have shown that patients with SCH have increased risk of developing CHD, others concluded no increased CHD risk except in patients with TSH exceeding 10 mIU/ml and yet others have shown that SCH is not associated with an increased risk for CHD [8]. Contrary to the results of all these studies, one study showed a decreased cardiovascular and all-cause mortality in elderly people with SCH [9].

The increased cardiovascular risk that is primarily observed with elevated TSH levels especially when it exceeds 10 mIU/ml can be explained by several mechanisms. SCH has been associated with elevated total cholesterol (TC) and low-density lipoprotein, increased blood pressure, and metabolic syndrome in some studies. Other possible explanations for the increased cardiovascular risk in persons with SCH include increased carotid artery intima-media thickness (CIMT), hypercoagulability, insulin resistance, oxidative stress, and endothelial dysfunction [7], supporting a biologically plausible role for mild hypothyroidism in the development of early atherosclerosis.

This study was conducted aiming to evaluate if SCH is associated with higher risk of CHD in elderly individuals and to figure out if dyslipidemia and endothelial dysfunction assessed by CIMT and flow-mediated dilatation (FMD) of the brachial artery (BA) induced by occlusion are associated with SCH.

Aim

The aim of this study was to evaluate if SCH is associated with higher risk of CHD in elderly individuals.

Patients and methods

A cross-sectional comparative study was conducted on 50 elderly individuals aged 65 years and older. The cases were recruited from the outpatient clinic or from those admitted to Internal Medicine Department, Faculty of Medicine, Alexandria University Main Hospital. The study was conducted between January 2016 and January 2017.

The enrolled cases were divided into two groups. Group I: 30 patients with SCH and group II comprised 20 age-matched and sex-matched euthyroid elderly serving as a control group. SCH was defined as a TSH level greater than 4.5 mU/l in the presence of a normal FT4 level (0.8–1.7 ng/dl). Euthyroidism was defined as a normal TSH level (0.4–4.5 mU/l). Group I was further stratified based on TSH levels into: TSH>4.5 to <10 and TSH>10 mIU/ml.

Individuals were excluded from the study if they were suffering from any known atherosclerotic cardiovascular disease (myocardial infarction, angina pectoris, or stroke) or its signs, had a history of other chronic diseases that could affect endothelial function such as diabetes, chronic renal failure, and liver diseases. Patients who were receiving thyroid medications whether antithyroid drugs or thyroxine replacement therapy and those taking drugs which can cause hypothyroidism (e.g. lithium, interferon α), hyperthyroidism (e.g. amiodarone) or having abnormal thyroid function tests without a direct effect on thyroid function by affecting the thyroxine-binding globulin status (e.g. glucocorticoids, etc.) were excluded from the study.

The two groups were matched for age, sex, smoking habits, hypertension, and family history of cardiovascular disease, regarding the well-known risk factors for atherosclerosis.

The study was approved by the Ethics Committee (Faculty of Medicine, University of Alexandria), and all study participants provided written informed consent.

Methods

All patients were subjected to the following:

(1) Thorough history taking, focusing on the history of thyroid disorders, suggestive features of thyroid dysfunction, hypertension, diabetes mellitus, smoking habits, ischemic chest pain, ischemic heart attacks, and family history of cardiovascular disease. Detailed drug history was taken focusing on drugs known to cause thyroid dysfunction, for example, iodine-containing drugs such as amiodarone, lithium, interferon α, etc.
(2) Complete physical examination with emphasis on signs of thyroid dysfunction (hypothyroidism which is mostly presented by weight gain, easy fatigability, lethargy, cold intolerance, hair fall, depression, constipation) followed by detailed thyroid gland examination.
(3) Laboratory investigations: Venipuncture was performed, and fasting blood samples of 3–5 ml blood were collected after a 12-h overnight fast; patients were subjected to the following laboratory investigations. Complete lipid profile including serum TC, triglycerides (TGs), high-density lipoproteins (HDLs), and low-density lipoproteins.
    (a) Hormonal assay using the enzyme-linked immunosorbent assay technique: Serum TSH [10], serum FT4 [11].
    (b) Thyroid autoantibodies using one sandwich enzyme-linked immunosorbent assay technique: serum antithyroid peroxidase (TPO) antibodies [12].
    (c) Anti-TPO titer less than 36 IU/ml was considered as negative.
(4) Ultrasonographic examination of the thyroid gland: Ultrasound evaluation of the thyroid gland was carried out using a commercially available real-time instrument (Kontron – imagic Agile, SHT: Esaote Medical Company, France) using a 7.5 MHz linear transducer in cross transverse and longitudinal planes. The patients were made to lie supine with their neck slightly hyperextended by placing a pillow underneath their shoulders, with full comment on the following: the volume of the thyroid gland, by using the prolate ellipsoid method (volume=length×breadth×depth×π/6).
Echogenicity of the gland/vascularity of the gland by the color Doppler/the presence of nodules which are further examined by their size, shape, echogenicity, border, margin, halo, vascularity, and calcification and cervical lymph nodes.
(5) Doppler ultrasound of brachial and carotid arteries: The patients were investigated by high-resolution color-Doppler ultrasound imaging (14-mHz linear probe; Hitachi Aloka, Tokyo, Japan) of the BA to assess endothelial responses in the dominant arm [13] The study was performed with patients resting in the supine position. The blood pressure and heart rate were recorded on the opposite arm every 3 min using an automatic sphygmomanometer [14].
(6) The patients' dominant arm was comfortably immobilized in the extended position to allow consistent access to the BA. Doppler ultrasound measurements were performed before (at rest) and 60 s after reactive hyperemia. To avoid interobserver variability, all measurements were performed by the same examiner, who was blinded to the patients' clinical status. BA vasodilatation in response to reactive hyperemia was determined by a previously validated technique. The intraclass correlation coefficient of this technique has been reported previously by some laboratory and ranges from *R* equal to 0.7001–0.8420 (*P*=0.05). The scans were recorded on an S-VHS videotape. The internal diameter of the BA was assessed at the end of the diastole (timed by the QRS complex), and the arterial flow was measured using the pulse Doppler sample volume at an angle of 60° or less in the center of the artery. For each patient, optimal BA images were obtained ~5 cm above the antecubital fossa. Arm pressure was generated by inflating a pneumatic arm band above the elbow cuff to a pressure of 30 mmHg higher than the patient's systolic arterial pressure for 5 min. The cuff was then deflated, the arterial flow was immediately recorded, and the diameter was measured 60 s after deflation. For both diameters, one measurement was recorded. FMD was calculated according to the following formula [14]:

$$\text{FMD} = (\text{Postocclusion diameter} - \text{baseline diameter}) \times 100 / \text{baseline diameter}.$$

(7) The carotid images were obtained with the patient in the supine position with the neck mildly extended and the head rotated contralaterally to the side. The intima-media thickness (IMT) of the common carotid artery was calculated by the same examiner with high-resolution ultrasound imaging (10 mH linear probe; Acuson Aspen Advanced model, Minnesota, United States). The common carotid arteries were scanned at the level of the bifurcation on both the right and left sides. The bulb dilation served as a landmark to indicate the border between the distal common carotid artery and the carotid bulb [13]. Subsequently, the IMT was measured in the far wall of the arteries at sites of most advanced atherosclerotic lesions, identified as diffuse and continuous projections with the greatest distance between the lumen-intimal interface and the media-adventitial interface, but without atherosclerotic plaques. Localized lesions of at least 2.0 mm thickness were considered to be atherosclerotic plaques. Three measurements were made for each patient and the mean value was used for the analysis. The scans were recorded on an S-VHS videotape. Reproducibility of the IMT measurement was acceptable, as demonstrated by coefficients of variation of 7.7±4.3% [14].

Statistical analysis [15]

(1) Analyses were performed for the entire group with SCH and stratified by the degree of TSH elevation (4.45–9.9 and 10.0–19.9 mU/l) and the euthyroid control group.
(2) Data were fed to the computer and analyzed using IBM SPSS software package, version 20.0 (IBM Corp., Armonk, New York, USA) [16]. Qualitative data were described using number and percentage. The Kolmogorov–Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, SD, and median. Significance of the obtained results was judged at the 5% level.
(3) The used tests were:
   (a) χ^2-test: For categorical variables, to compare between different groups.
   (b) Fisher's exact: Correction for χ^2 when more than 20% of the cells have an expected count of less than 5.
   (c) Student's *t*-test: For normally distributed quantitative variables, to compare between two studied groups.
   (d) Paired *t*-test: For normally distributed quantitative variables, to compare between two periods.
   (e) Pearson's coefficient: To correlate between two normally distributed quantitative variables.
   (f) Mann–Whitney test: For abnormally distributed quantitative variables, to compare between two studied groups.
   (g) Spearman's coefficient: To correlate between two distributed abnormally quantitative variables.
   (h) Receiver operating characteristic (ROC) curve: It is generated by plotting sensitivity (true positive) on the *y*-axis versus 1–specificity (false positive) on the *x*-axis at different cutoff values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test. The ROC curve allows also a comparison of performance between two tests.
   (i) Sensitivity: The capacity of the test to correctly identify diseased individuals in a population 'true positives'. The greater the sensitivity, the smaller the number of unidentified cases 'false negatives'.
   (j) Specificity: The capacity of the test to correctly exclude individuals who are free of the disease 'true negatives'. The greater the specificity, the fewer 'false positives' will be included.
   (k) Positive predictive value: The probability of the disease being present, among those with positive diagnostic test results.
   (l) Negative predictive value: The probability that the disease was absent, among those whose diagnostic test results were negative.

Results

Clinical and laboratory characteristics, Doppler findings, and echocardiography parameters of elderly patients with subclinical hypothyroidism patients (group I) as compared with to the control group with euthyroidism (group II)

(1) The two studied groups were age-matched and sex-matched, with the majority of cases being women in both groups; 90% in group I versus 85% in group II (Table 1).
(2) Hypertension was found in 50% of patients in group I as compared with 35% of patients in group II (Table 1).
(3) No significant statistical difference was observed between the two groups as regards mean SBP and DBP levels (Table 1).
(4) No significant statistical difference was observed among the two studied groups as regards mean

Table 1 Clinical, laboratory, Doppler, and echocardiography findings of elderly subclinical hypothyroidism patients (group I) compared to elderly euthyroid controls (group II)

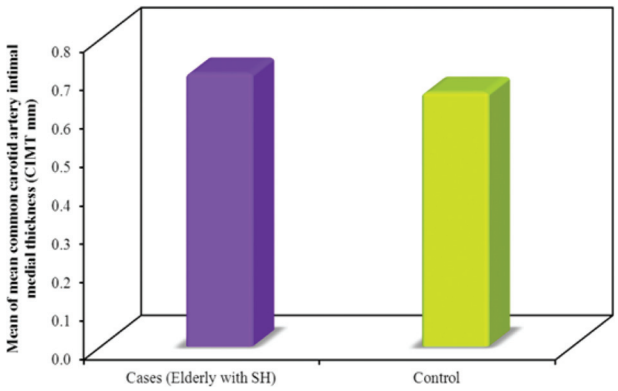
	Group I (*N*=30)	Group II (*N*=20)	*P* value
Age	69.20 ±3.06	68.65±3.27	0.55
Sex (female/male) (%)	90/10	85/15	0.67
SBP (mmHg)	140.07 ±20.11	131.15 ±19.29	0.125
DBP (mmHg)	86.33 ±11.96	81.90 ±11.99	0.206
TC (mg/dl)	219.40 ±69.77	212.05 ±52.16	0.690
Serum TG (mg/dl)	137.50 ±37.45	140.25 ±33.92	0.793
Serum LDL-C (mg/dl)	134.23 ±45.52	144.15 ±37.37	0.423
Serum HDL-C (mg/dl)	47.80 ±11.76	48.75 ±11.49	0.779
TSH (mIU/ml)	8.56±2.96	1.49±0.67	<0.001*
FT4 (μg/dl)	1.31±0.19	1.22±0.19	0.086
Anti-TPO (IU/ml)	481.12 ±260.64	18.36±5.44	<0. 001*
CIMT (mm)	0.71±0.16	0.66±0.18	0.293
BA diameter before occlusion (mm)	3.12±0.44	3.44±0.68	0.076
FMD after occlusion (mm)	3.64±0.60	4.05±0.73	0.038
FMD% dilation after induced occlusion	16.20 ±5.68	17.93±5.47	0.290
LA (mm)	41.53 ±5.69	43.0±4.53	0.339
IVS (mm)	9.57±0.82	9.50±0.69	0.765
LVESD (mm)	34.97 ±6.31	36.70±7.20	0.373
LVEDD (mm)	52.10 ±7.23	48.60±9.18	0.139
PWT (mm)	9.57±0.82	9.50±0.69	0.765
EF%	9.57±0.82	9.50±0.69	0.189

BA, brachial artery; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; EF, ejection fraction; FMD, flow-mediated dilatation; FT4, free thyroxine; HDL-C, high-density lipoprotein cholesterol; IVS, interventricular septum; LA, left atria; LDL-C, low-density lipoprotein cholesterol; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; PWT, posterior wall thickness; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone. *Significant.

serum TC, TG, LDL-C, and high-density lipoprotein cholesterol (HDL-C) (Table 1).

(5) A significant statistical difference was observed between the studied groups as regards mean serum TSH, and anti-TPO, being higher in group I as compared with group II (Table 1).
(6) No significant statistical difference was observed between the two groups as regards mean serum FT4 (Table 1).
(7) CIMT was higher in group I as compared with group II; however, the difference is not statistically significant (Table 1 and Fig. 1).

Figure 1



Comparison between the two studied groups according to mean common CIMT. CIMT, carotid artery intima-medial thickness; SH, subclinical hypothyroidism.

(8) FMD% after occlusion was lower in group I as compared with group II; however, the difference is not statistically significant (Table 1 and Fig. 2).
(9) Echocardiographic parameters are shown in Table 1 with no statistically significant difference between the two studied groups.

Severity of subclinical hypothyroidism in the elderly subclinical hypothyroid group

It has been observed that 17% of group I were suffering from severe SCH with their serum TSH levels of at least 10 mIU/ml, whereas 83% of cases had their serum TSH level between 4.5 and less than 10 mIU/ml (Fig. 3).

In group I, 50% (15/30) of the patients were seropositive for anti-TPO antibodies.

Thyroid ultrasound findings

Thyroid ultrasound showed that most of the cases had a picture of thyroiditis (27/30) constituting 90%. Two cases showed no residual thyroid tissue post-thyroidectomy and one case had evidence of multinodular goiter on top of thyroiditis.

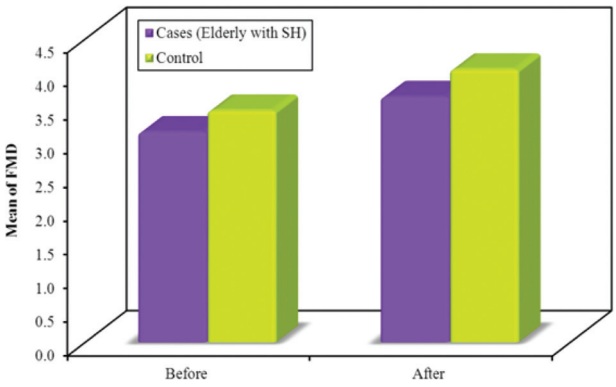
Correlation of the studied vascular parameters

There was a statistically significant inverse correlation between studied vascular parameters namely carotid intimal thickness and flow-mediated BA vasodilatation after occlusion (r=-0.69, P<0.001) (Table 2 and Fig. 4).

Echocardiography findings

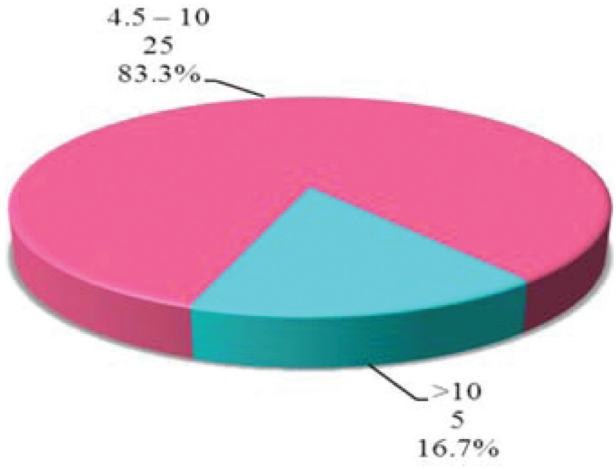
Overall, 53% of the elderly patients with SCH (group I) had normal study of echocardiography versus 65% of elderly patients with euthyroidism (group II), whereas 36.7% of cases in group I had evidence of diastolic dysfunction versus 35% of cases in group II. Only three

Figure 2



Comparison between the two studied groups according to brachial artery dilatation before and after occlusion. FMD, flow-mediated dilatation; SH, subclinical hypothyroidism.

Figure 3



A figure representing severity of subclinical hypothyroidism in group I.

Table 2 Correlation between flow-mediated vasodilatation% dilatation and mean common carotid artery intima-medial thickness in cases group

	r_s	FMD of BA% after induced dilation *P*
CIMT	**–0.692**	<0.001*

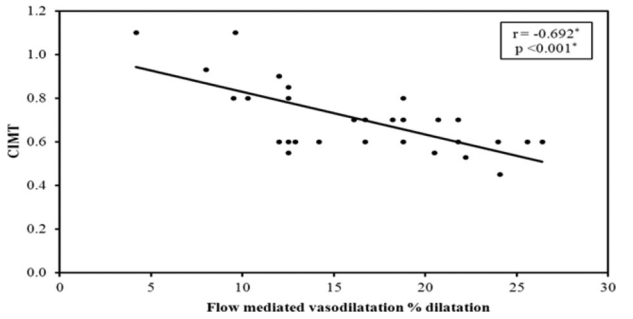
BA, brachial artery; CIMT, carotid artery media thickness; FMD, flow-mediated dilatation; r_s, Spearman's coefficient. *Significant.

cases in group I had evidence of ischemic heart disease (IHD) based on echocardiography findings; in contrast, none of the cases in group II had evidence of IHD.

Framingham 10-year Coronary Heart Disease Risk Score

In a trial to match atherosclerotic risk factors, we assessed the Framingham 10-year Coronary Heart Disease Risk Score. No significant difference was detected between the two groups, with the majority of cases in both groups had a risk score of less than 10%.

Figure 4



Correlation between flow-mediated vasodilatation% dilatation and mean common carotid artery intima-medial thickness (CIMT) in cases of group I. *Significant negative correlation.

The Framingham 10-year Coronary Heart Disease Risk Score was found to be positively correlated with CIMT (r=–0.54, P=0.002), and negatively correlated with FMD% of BA after occlusion (r=–0.73, P<0.001) (Table 3).

Correlation between thyroid stimulating hormone and different parameters in group I

There was a statistically significant positive correlation between TSH and mean CIMT (r=0.5, P=0.005), systolic blood pressure (SBP) (r=0.34, P=0.039), diastolic blood pressure (DBP) (r=0.41, P=0.025), TC (r=0.61, P<0.001), and low-density lipoprotein cholesterol (LDL-C) (r=0.6, P<0.001), whereas there was a statistically significant negative correlation between TSH and BA diameter before dilation and after dilation (r=–0.378, P=0.039 and r=–0.474, P=0.008) (Table 4, Figs 5 and 6).

There was no statistically significant negative correlation between TSH and mean HDL-C and mean serum TG.

Correlation between free thyroxine and different parameters in group I

There was a statistically significant negative correlation between FT4 and SBP (r=–0.44, P=0.014), DBP (r=–0.52, P=0.003), TC (r=–0.41, P=0.024), and LDL-C (r=–0.5, P=0.004) (Table 5 and Fig. 7).

There was no statistically significant negative correlation between FT4 and mean CIMT.

Receiver operating characteristic curve for the prediction of diastolic dysfunction with subclinical hypothyroidism

In elderly cases with SCH (group I), the ROC curve for the prediction of diastolic dysfunction associated with

Table 3 Framingham risk score in patients versus controls

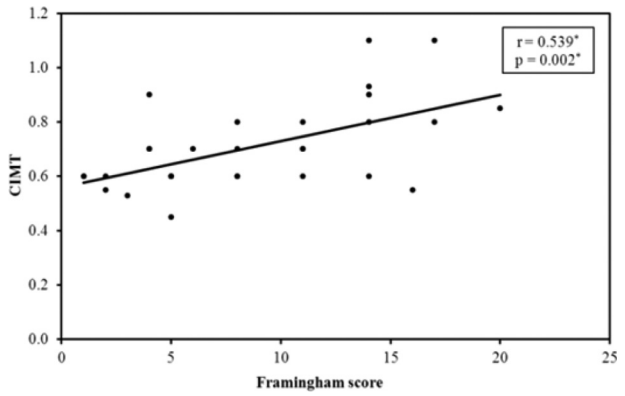
Framingham Risk Score	Cases (*n*=30) [*n* (%)]	Controls (*n*=20) [*n* (%)]	Test of significance	*P*
<10	17 (56.7)	16 (80)		
10–20	12 (40)	4 (20)	χ^2=3.021	0.173
20–30	1 (3.3)	0 (0)		
Minimum–maximum	1.0–20.0	1.0–16.0	Mann–Whitney *U*-test=230.0	0.091
Mean±SD	8.77±5.42	6.10±4.45		

Table 4 Correlation between mean thyroid stimulating hormone and different parameters in group I

	TSH	
	r_s	*P*
CIMT	0.500*	0.005*
FMD% of BA after occlusion	–0.539*	0.002*
BA diameter after occlusion	–0.474*	0.008*
SBP	0.379*	0.039*
DBP	0.407*	0.025*
TC	0.600*	<0.001*
LDL	**–0.692**	<0.001*

BA, brachial artery; CIMT, carotid artery media thickness; DBP, diastolic blood pressure; FMD, flow-mediated dilatation; LDL, low-density lipoprotein; r_s, Spearman's coefficient; SBP, systolic blood pressure; TC, total cholesterol; TSH, thyroid stimulating hormone. *Significant. The value showing an asterisk (*) is significant.

Figure 5



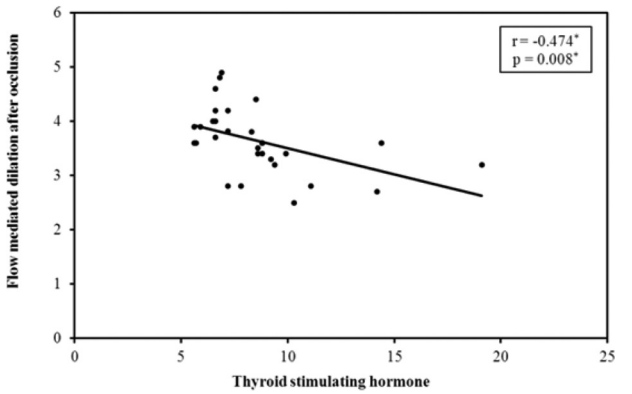
Correlation between flow-mediated vasodilatation% dilatation after occlusion, mean common carotid artery intima-medial thickness (CIMT) in the studied cases.

SCH showed that the cutoff point was more than 9.4 with a sensitivity of 11.1% and specificity of 71.4%, with 95% confidence interval (CI) (lower limit–upper limit): 0.32–0.76 (Fig. 8).

Receiver operating characteristic curve for the prediction of significant increase in carotid artery intima-media thickness with subclinical hypothyroidism

In elderly cases with SCH (group I), the ROC curve for the prediction of CIMT more than 0.9 mm associated with SCH showed that the cutoff point was more than 9.4 with a sensitivity of 100% and specificity of 88.9% with 95% CI (lower limit–upper limit): 0.79–1.01 (Fig. 9).

Figure 6



Correlation between TSH and flow-mediated dilatation after occlusion in cases of group I. AUC, area under the curve; CI, confidence interval; LL, lower limit; TSH, thyroid stimulating hormone; UL, upper limit.

Discussion

SCH is defined as an isolated elevation of TSH levels in conjunction with normal circulating levels of FT3 and FT4. It is a highly prevalent disease especially in the elderly population.

Thyroid hormones affect the heart and vasculature by both genomic and nongenomic pathways [17]. However, the impact of SCH on the cardiovascular system is a matter of debate. Researches have been conducted to study the effect of SCH on cardiovascular system yielding conflicting results. Although some studies support increased risk of cardiovascular events in patients with SCH, others show no significant increases risk.

This study was conducted to evaluate if SCH is associated with higher risk of CHD in the elderly and if dyslipidemia, endothelial dysfunction as measured by FMD, and CIMT were associated with SCH.

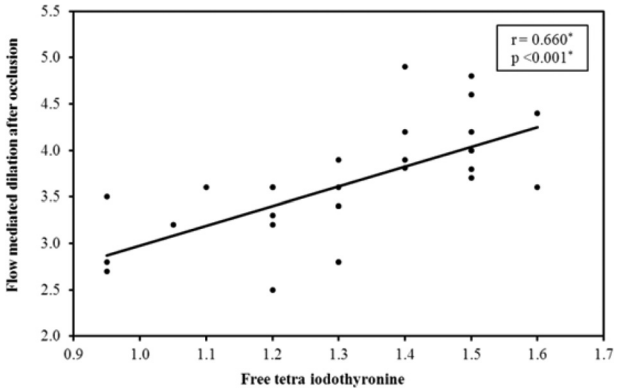
Fifty elderly individuals aged 65 years and older were enrolled in this study and were divided into two groups. Group I: 30 patients with SCH and group II comprised 20 age-matched and sex-matched euthyroid elderly serving as a control group. Complete lipid profile, thyroid ultrasound, echocardiography to assess

Table 5 Correlation between mean free thyroxine and different parameters in group I

	TSH	
	r_s	*P*
Mean common carotid artery intima-media thickness	–0.332	0.073
BA diameter before occlusion	0.599*	<0.001*
BA diameter after occlusion	0.660*	<0.001*
Systolic blood pressure	–0.444*	0.014*
Diastolic blood pressure	–0.525*	0.003*
Total cholesterol	–0.412*	0.024*
LDL	**–0.692**	<0.001*

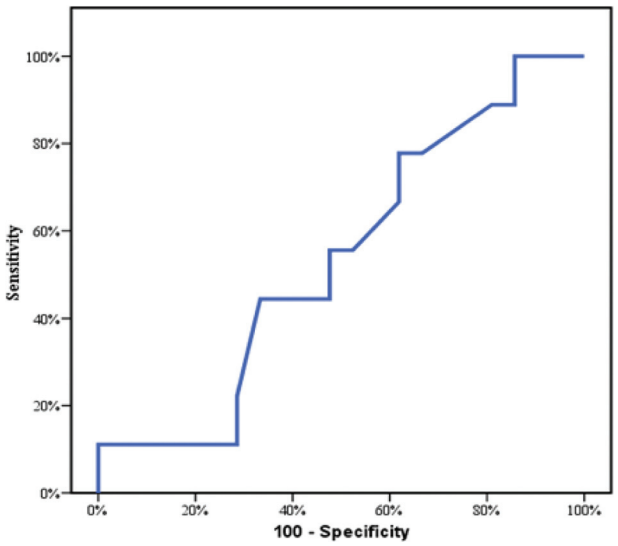
BA, brachial artery; LDL, low-density lipoprotein; r_s, Spearman's coefficient; TSH, thyroid stimulating hormone. *Significant. The value showing an asterisk (*) is significant.

Figure 7



Correlation between free tetra iodothyronine and flow-mediated dilatation after occlusion in cases of group I. *Significant negative correlation.

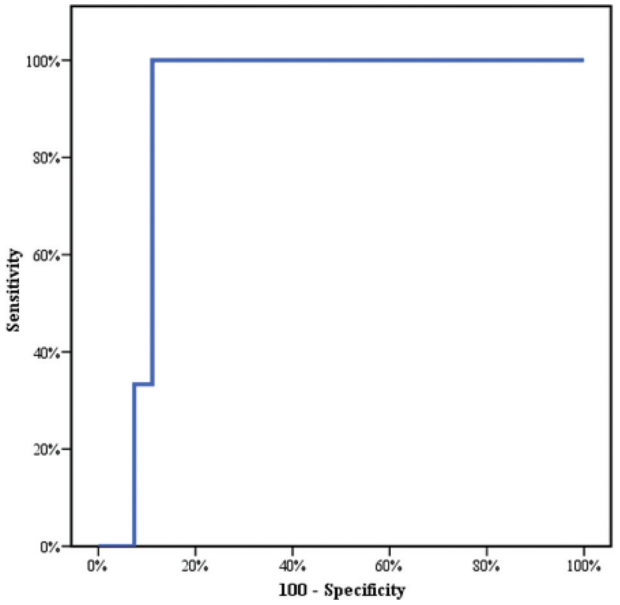
Figure 8



Receiver operating characteristic curve for thyroid stimulating hormone to predict diastolic dysfunction cases.

cardiac function and markers of endothelial dysfunction namely CIMT and FMD of the BA after occlusion were done to all cases.

Figure 9



Receiver operating characteristic curve for TSH to predict carotid artery intima-medial thickness more than 0.9 cases. AUC, area under the curve; CI, confidence interval; LL, lower limit; TSH, thyroid stimulating hormone; UL, upper limit. Is a ROC curve to show the sensitivity and specificity only.

Old age, male sex, diabetes mellitus, hypertension, hypercholesterolemia, and smoking are known risks for CHD [18]. The two groups were matched regarding age and sex in accordance with the designed protocol. The majority of cases were women. Men were 10% of the SCH and 15% of the euthyroid. None of the individuals were diabetic and the smoking status was similar.

Overall, 50% (15/30) of elderly patients with SCH (group I) were suffering from hypertension, whereas 35% (7/20) in the elderly euthyroid group (group II) were hypertensive. Despite that SBP and DBP were higher in group I as compared with group II, both SBP and DBP differences were statistically insignificant (*P*=0.12 and 0.21, respectively).

However, it was shown in our study in agreement with the previous studies that TSH is positively correlated with SBP and DBP and that FT4 was negatively correlated with these parameters.

In India, Singhai and Gupta [19] studied the relationship between hypertension and TSH at different levels of both SCH and euthyroidism, where TSH and FT4 were measured. Results of his study suggested an association between SCH and increased blood pressure. Furthermore, an interventional study held by Adrees *et al.* [20], including 56 women with SCH found elevated SBP and DBP, serum cholesterol and homocysteine levels compared with healthy controls, with normalization of these factors after 18 months of levothyroxine therapy [20].

Several mechanisms have been proposed to explain why SCH has an impact on blood pressure. One of these mechanisms is attributed to increased systemic vascular resistance in thyroid failure. Moreover, the study by Hak *et al.* (Rotterdam study) [21] showed that SCH was an independent risk factor for atherosclerosis and myocardial infarction. In addition, blood hypercoagulability, blood viscosity, and lipid abnormalities presenting in SCH patients could increase the risk for atherosclerosis with subsequent hypertension [21].

Thyroid hormones exert multiple effects on the regulation, absorption, and metabolism of lipid synthesis [17]. It was found in our study that the mean serum TC, TGs, and LDL-C and HDL-C levels were not statistically significantly different between elderly patients with SCH and elderly patients with euthyroidism. In this study, serum TC level ranged from 108 to 342 mg/dl with a mean of 219.4±69.7, whereas the TGs level ranged from 52 to 196 mg/dl with a mean of 137.5±37.4, the HDL-C level ranged from 33 to 77 mg/dl with a mean of 47.8 ±11.8, and the LDL-C ranged from 49 to 212 mg/dl with a mean of 134.2±45.5. No significant statistical difference was observed when the elderly SCH patients were compared with a euthyroid control group as regards the mean cholesterol, TGs, and LDL-C and HDL levels (P=0.69, 0.79, 0.77, 0.42, respectively). In spite of the nonsignificant differences between the two elderly groups studied in our study, we found that TSH is positively correlated with TC, LDL-C but not with serum TGs and is negatively correlated with HDL-C. In addition, it was shown that FT4 is negatively correlated with TC and LDL-C.

Canaris *et al.* [22], in contrast, in the Colorado Thyroid Disease Prevalence Study found a significant statistical difference between patients with mild thyroid failure versus euthyroid individuals as regards lipid parameters even in cases with mild SCH, which is more pronounced in those having TSH more than 10 mIU/ml. However, these findings were not demonstrated in our study and this may can be attributed to two reasons; first, the majority of our cases had their TSH less than 10 mIU/ml, the second explanation is that we were studying elderly patients of at least 65 years, where dyslipidemia is more prevalent apart from its link to SCH.

The relationship between elevated serum cholesterol concentration and atherosclerotic vascular disease has been well established. Despite various assessments of the literature, the relationship between mild thyroid failure and serum lipid levels is still ambiguous [23], whereas some cross-sectional studies suggest that serum cholesterol levels are significantly higher in individuals with mild thyroid failure as compared with euthyroid individuals [24,25]. Other cross-sectional studies show that lipid parameters between mild hypothyroidism and euthyroidism are not significantly statistically different [26,27]. Zhang *et al.* [28] performed a meta-analysis to investigate the association between SCH and alteration in lipid parameters; 16 observational studies were included in the meta-analysis. They suggested that the serum TC, LDL-C, and total TG levels were significantly increased in patients with SCH compared with euthyroidism individuals. No significant difference was observed for serum HDL-C [28]. Accordingly, an important question was raised in the literature concerning the beneficial effect of treatment of mild thyroid failure with levothyroxine in terms of reduction of TC and LDL-C. A quantitative review of the literature and analysis was conducted by Danese *et al.* [23], addressing this point investigating 13 studies on 250 patients in this context. It was concluded based on this meta-analysis that T4 therapy in individuals with mild thyroid failure lowers mean serum total and LDL-C concentrations. The reduction in serum TC may be larger in individuals with higher pretreatment cholesterol levels and in those receiving suboptimal T4 doses. It does not seem that thyroxine replacement therapy has significant effects on serum HDL or TG concentrations [23].

It has been suggested that SCH may be further classified into a milder condition with TSH levels between 4.5 and 10 mIU/ml (mild SCH) and a severe form with TSH more than 10.0 mIU/ml (severe SCH) [17]. The majority of our cases in group I in this study accounting for 83% of the total cases had their mean serum TSH between 4.5 and less than 10 mIU/ml and only 17% of cases had a TSH of at least 10 mIU/ml.

The most common endogenous cause of SCH is considered to be chronic autoimmune thyroiditis (Hashimoto's thyroiditis) associated with anti-TPO antibodies [7]. Overall, 50% of patients in our study were seropositive to anti-TPO antibodies; two cases had a history of total thyroidectomy. Thyroid ultrasound showed that most of the cases had a picture of thyroiditis (27/30) constituting 90% of cases in group I. Two cases showed no residual thyroid tissue post-thyroidectomy and one case had evidence of multinodular goiter on top of thyroiditis. It has been shown that positivity to anti-TPO antibodies increases the risk of progression to overt hypothyroidism with all its consequences to 38%. Thus, it is prudent to assess the antibodies to thyroperoxidase in elderly patients with SCH [3].

In trial to match known atherosclerotic risk factors for CHD between elderly groups, we assessed The Framingham Coronary Heart Disease Risk Score for estimating the risk of heart attack in 10 years. We found that more of than 50% of patients in group I and 80% of cases in group II are having a Framingham Risk Score of less than 10% with no significant difference between mean Framingham Score in group I versus II (P=0.173).

In this study, we evaluated the CIMT. The B-mode ultrasound measurement of IMT in the common carotid artery permits easy evaluation of atherosclerosis [14]. In this study, the common CIMT ranged from 0.45 to 1.1 mm, with a mean of 0.76±0.16 for the elderly SCH group. The common CIMT ranged from 0.3 to 0.94 mm, with a mean of 0.66±0.18 for the elderly hypothyroid group. Though the mean CIMT was higher in the SCH patients (0.71 ±0.16) compared with the euthyroid group (0.66 ±0.18), the difference was not statistically significant (P=0.29). In contrast, CIMT was shown to be positively correlated with mean TSH levels with a P value of 0.005. Despite being negatively correlated with FT4 the correction was not statistically significant (P=0.07).

In addition, in this work, we examined the endothelial function using a simple noninvasive, harmless method that enables accurate and reproducible assessment of vascular response to flow increase. BA FMD, a validated surrogate marker of coronary artery endothelial function, is emerging as an independent predictor of future cardiac events. FMD is currently the main method used to assess endothelial function and is convenient for clinical practice [14]. For the elderly SCH group, the mean BA diameter before dilation was 3.12±0.44 mm versus 3.44±0.68 mm for the euthyroid group. However, the mean BA diameter after dilation was 3.64±0.60 mm compared with 4.05±0.73 mm for the euthyroid group. The mean percentage of FMD% of BA after occlusion was 16.2±5.7 in group I versus 17.9±5.5 in group II. There was a no statistically significant difference between the two groups as regards flow-mediated vasodilatation% of the BA after occlusion (P=0.29).

Lekakis *et al.* [29] was the first to describe the negative association between borderline and mild hypothyroidism and FMD. In their study, cholesterol did not differ significantly among groups, but tended to be higher in the hypothyroidism and SCH groups. On the basis of the results, the authors concluded that higher cholesterol levels may be associated with endothelial dysfunction. In this study, the cholesterol did not differ significantly among groups, and we did not find altered FMD compared with the euthyroid group [29].

Cikim *et al.* [13] compared 25 subclinical hypothyroid patients (mean age: 32.28±9.67 years) and 23 euthyroid patients (mean age: 35.87±9.67 years) strictly matched for atherosclerotic risk factors and demonstrated that the subclinical hypothyroid group had significantly lower FMD values (10.68±3.71% for the SCH group as compared with 15.92±7.92% for the euthyroid group; $P<0.05$). No significant differences were observed between groups with respect to other vascular parameters, including CIMT. Since the lipid profile was comparable between groups, the authors suggested that endothelial function could deteriorate before the emergence of hypothyroidism-induced metabolic changes. Cholesterol levels were lower in their study compared with our present study (181.04 ±36.71 mg/dl for the euthyroid group and 179.56 ±30.21 mg/dl for the SCH group). This study found similar TSH levels (8.56±2.96 compared with our study (8.85±6.86 mIU/ml), but thyroid antibodies levels were elevated in their SCH patients (mean: 496.71±677.09 IU/ml compared with 56.74±56.65 in this study), reflecting the autoimmune nature of hypothyroidism. They evaluated the association of thyroid autoantibodies and the FMD/IMT ratio and found no significant correlation. This study also could not find any significant association between anti-TPO concentrations and FMD or CIMT.

Monzani *et al.* [30] did a double-blind, placebo-controlled study of individuals below 55 years of age. The mean IMT of their SCH patients was significantly higher (0.75±0.13) than that of euthyroid controls

(0.63±0.07) in the subgroup older than 35 years. Levothyroxine replacement therapy reduced both LDL-C and mean IMT, suggesting that lipid infiltration of the arterial wall may represent the main mechanism underlying the increase in IMT in SCH [30].

In agreement to our results, Cabral *et al*. [14] compared 21 subclinical hypothyroid patients (mean age: 42.4 ±10.8 years) and 21 euthyroid patients (mean age: 44.2 ±8.5 years) matched for atherosclerotic risk factors and observed no significant differences with respect to FMD or IMT between the SCH and control groups. Their FMD% was 20.6±11.2% for the SCH and 16.1±8.8%for the euthyroid compared with 16.20 ±5.68 for the SCH and 17.93±5.47 for euthyroid control in this study. When the SCH group in their study was subdivided into low (≥4 but >8 μIU/ml) or high (≥8 but <12 μIU/ml) TSH levels, no differences were observed in metabolic or vascular parameters. Lipid parameters, FMD, and IMT values in the common carotid artery and carotid bifurcation were higher in SCH patients with positive serum TPO antibodies (0.62±0.2 and 0.62±0.16 mm, for common carotid artery and carotid bifurcation, respectively) compared with the negative TPO antibodies group (0.55±0.24 and 0.58±0.13 mm, for common carotid and carotid bifurcation, respectively) although the difference was not statistically significant [14].

More recently, Niknam *et al*. [31] in a quasi-experimental study involving 25 SCH and 25 euthyroid controls observed that the patients and the controls were similar in IMT (0.56±0.09 vs. 0.58 ±0.08 mm, *P*=0.481), but FMD was lower in patients than in controls (4.95±2.02 vs. 6.50±2.57%) but this difference was not statistically significant. A significant increase was observed in FMD (4.11 ±2.37%, *P*=0.001), but not in IMT (−0.004 ±0.020 mm, *P*=0.327), after levothyroxine therapy among the patients [31].

The causative agent of endothelial damage in thyroid dysfunction conditions is unclear, but seems to be associated with decreased endothelial nitric oxide synthesis due to the low hormone levels or inflammation induced by thyroid autoantibodies [14].

It has been demonstrated in our study that cardiac function as assessed by echocardiography shows no significant difference between the two studied groups. Also, it has been observed that 36.7% of the elderly subclinical hypothyroid group versus 35% of elderly euthyroid group had evidence of mild diastolic dysfunction by echocardiography with no significant difference demonstrated between the two studied groups. Three cases in group I had evidence of IHD and the rest of the patient show unremarkable study by echocardiography.

Rodondi *et al*. [32], in the famous cardiovascular health study, the risk of heart failure (HF) and cardiac function in subclinical thyroid dysfunction were assessed, where 3044 adults older than 65 years initially free of HF were studied. They compared HF events over a mean 12-year follow-up and changes in cardiac function over 5 years among euthyroid participants, those with SCH (stratified by TSH levels: 4.5–9.9, ≥10.0 mU/l) and those with subclinical hyperthyroidism. Baseline echocardiographic parameters addressing SBP and DBP functions did not differ significantly from the elderly subclinical hypothyroid group versus the elderly euthyroid group in agreement with our study. Compared with the euthyroid older adults, those with a TSH of at least 10.0 mU/l have a moderately elevated risk of HF and alterations in cardiac function, but not elderly adults with mild SCH; TSH less than 10. The rate of CHD events, stroke, peripheral arterial disease, and mortality did not significantly differ by different TSH levels [8]. Hence, they recommended conducting well-designed clinical trials aiming to assess whether the risk of HF might be ameliorated by thyroxine replacement in individuals with TSH of at least 10.0 mU/l [32].

An interesting meta-analysis investigated by Razvi *et al*. [33] where the individuals were divided into two groups below and above the age of 65 years. They found that the incidence and prevalence of IHD and cardiovascular mortality was higher in the younger age group but not in the group above 65 years of age [34]. The striking effect of age on vascular risk observed by Razvi *et al*. [33] in patients with SCH was explained in a variety of ways as proposed by them. First, it is possible that at a younger age, SCH has a more severe pathophysiological effect, resulting in accelerated vascular disease, perhaps through dyslipidemia, endothelial dysfunction, or a direct effect on the myocardium in a proportion of susceptible individuals. As populations age, patients that are relatively resistant to the adverse vascular effects of SCH may survive, leading to an attenuation of this effect in older age. Differential effects of other vascular risk factors during aging are well recognized, for example, being overweight does not appear to carry the same health implications in

advanced age. An alternative explanation is that SCH is contributing equally to vascular risk at all ages, but in the more elderly cohorts, there is a relatively larger component from conventional, non-SCH, vascular risk factors and that the effects of SCH are relatively masked by the larger contribution from other risk factors.

Other studies have shown that SCH is associated with increased risk for CHD. The first study regarding the associated cardiovascular risk in patients with SCH was the long-time large cross-sectional study conducted in Rotterdam in The Netherlands [21]. It showed an increased risk for atherosclerosis (defined as aortic calcification on lateral radiograph) [odds ratio (OR)=1.7; 95% CI: 1.1–2.6] and prevalence of myocardial infarction (OR=2.3; 95% CI: 1.3–4.0) among female patients with SCH aged older than 55 years [21]. However, in their study they did not stratify their results based on TSH values to mild and severe SCH. Another cross-sectional analysis conducted in Australia by Roddini *et al.* [32], further revealed SCH to be an independent risk factor for CHD, parallel to hypercholesterolemia, hypertension, smoking, and diabetes [35].

Park *et al.* [18] in a cross-sectional study of apparently healthy SCH individuals evaluated by coronary computed tomography angiography and measurement of coronary artery calcium score (CACS) found higher CACS [mean (range)] in the SCH group [45.3 (0–2836.7) vs. 141.5 (0–4582), P=0.015]. The incidences of CAD and CACS more than 100 were also higher in men with SCH [CAD vs. SCH, 948 (40.6%) vs. 31 (63.3%), P<0.005; CACS>100, 232 (10.3%) vs. 10 (20.4%), P=0.031]. The differences in CAD incidences remained after adjusting for age (whole group, OR=1.935, 95% CI: 1.021–3.668, P=0.021; male, OR=1.086, 95% CI: 1.075–1.097, P=0.024). They concluded that SCH is an independent risk factor for coronary artery disease (CAD) in apparently healthy individuals and that the risk of occult CAD is increased in SCH patients who have an increased clinical CAD risk. This study included only one individual with TSH levels more than 10 mU/l, and there were only four patients with TSH levels more than 7 mU/l. Therefore, they could not compare the group with higher TSH levels with the others because of the small number in that category [14].

Several other studies supported that SCH is considered as an independent risk factor for CHD. The association between SCH and IHD and the associated mortality was also confirmed by the unselected community-based, 20-year follow-up of the Whickham survey in the UK [36] and a Japanese–Brazilian thyroid study [37]. The 12-year follow-up of the HUNT Study in Norway [38] showed that SCH was associated with increased mortality from CHD [hazard ratio (HR)=1.76; 95% CI: 1.21–2.56], but there was no association of thyroid function with the risk of being hospitalized with myocardial infarction [35].

One study, in contrast, showed a decreased cardiovascular and all-cause mortality [9]. In this Leiden 4-year cohort study of those aged more than 85 years in which 599 people were followed up from the age of 85 years through the age of 89 years (mean follow-up: 3.7 years) showed that the increasing levels of TSH and decreasing levels of FT4 were associated with a decreased risk of both cardiovascular and noncardiovascular mortality (HR=0.66, 95% CI: 0.48–0.98 and HR=0.84, 95% CI: 0.66–1.07, respectively) mainly due to reduced IHD events. These findings might suggest an interaction of age on the effects of thyroid hormones, which could not be demonstrated in the individual participant data analysis that assessed the outcomes in people of all ages [7] Furthermore, it is recommended to consider age-specific ranges for TSH in individuals older than 80 years based on the assumption that TSH elevation in the very old, that is those older than 80 years is considered as a physiological adaptation to aging [39].

This study did not find a significant association between thyroid function and vascular parameters in patients who were similar with respect to age, BMI, smoking and menopausal status, and endothelial function modifiers, but who differed in thyroid function. The exclusion of participants with concomitant endocrinologic, renal, or hepatic diseases allowed us to control for confounding variables and yielded a homogenous population. The small sample size for this study (50 patients) may be the reason it did not detect a difference between SCH and euthyroid controls in vasodilatation parameters.

On the basis of our data, we concluded that minimal thyroid dysfunction (SCH) had no adverse effects on endothelial function in patients with SCH in our cohort. Current evidence is insufficient to support the association between minimal thyroid disease and endothelial dysfunction, especially that most of the studies acknowledging increased risk of CHD in patients with SCH link these associations to severe

SCH with a TSH of more than 10 mIU/ml. Hence, it is recommended that more studies are necessary to identify if there is any beneficial effect of levothyroxine treatment on endothelial function in patients with SCH, stratified according to the level of TSH into mild and severe SCH.

The main limitation of this study is the cross-sectional nature of the design and a small number of study patients, which necessitates careful interpretation of the results. This study did not find association of SCH with CHD even with those patients with TSH above 10 but the sample in this category was too small (five patients) to draw any conclusions. Other limitations include the lack of information about the duration of the thyroid dysfunction, and because patients were self-referred for management, selection bias may limit the generalization of the clinical characteristics of this cohort to the overall SCH population. To eliminate nonthyroidal illness as a cause of elevated TSH levels in our study, the SCH patients did not differ from the euthyroid ones in levels of total protein, albumin, and creatinine. Therefore, it is highly unlikely that nonthyroidal illness affected the validity of our results.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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