Impact and predictors of thyroid dysfunction among patients with stenotic coronary artery lesion during late postacute coronary syndrome

Sahar H. Elhini[a], Ragaa A. Matta[a], Nossa N. Eledawi[a], Lamia Hamdi[b]

[a]Departments of Internal Medicine, [b]Clinical Pathology, School of Medicine, Minia University Hospital, Minia, Egypt

Correspondence to Ragaa A. Matta, MD, Department of Internal Medicine, School of Medicine, Minia University Hospital, Minia, 61111, Egypt; Tel: +20 100 879 2833; fax: 20 86 2156052; e-mail: mattaragaa@yahoo.com

Received 19 November 2016
Accepted 26 January 2017

Egyptian Journal of Obesity, Diabetes and Endocrinology 2017, 3:1–9

Objective
Thyroid dysfunction (TD) is a risk factor for coronary heart disease (CHD) events. We study the prevalence and predictors of TD and its impact on characteristics, cardiac function, and ischemic severity of patients with manifest CHD.
Patients and methods
A total of 200 patients 6–12 months after acute coronary syndrome had at least one vessel – significant stenotic coronary artery lesion. Before elective angiography, patients underwent anthropometric measurement, routine biochemical assay, thyroid hormones, and thyroid peroxidase antibody.
Results
The prevalence of TD was 17.5%: 12% for hypothyroidism (9.5% subclinical, 2.5% overt) and 5.5% for hyperthyroidism (2.5% subclinical, 3% overt). Compared with the euthyroid group, the hypothyroid group had a significantly higher age, BMI, diastolic blood pressure (BP), atherogic lipid profile, and impaired cardiac functions and higher pulmonary artery systolic pressure (PASP), and the hyperthyroid group had significantly higher systolic BP, ejection fraction (EF), and PASP and significantly lower diastolic BP and lipid profile. Independent predictors for hypothyroidism were age, bradycardia, increased BMI, lower EF, diastolic dysfunction, and atherogenic lipid profile, whereas increased PASP was an independent predictor for hyperthyroidism. Thyroid-stimulating hormone (TSH) was positively correlated and both free triiodothyronine and free thyroxine were negatively correlated to BP, BMI, lipid profile, impaired EF, and coronary atherosclerosis severity. TSH and free thyroxine were positively correlated to PASP, which increased significantly through hypothyroidism to hyperthyroidism. TSH and free triiodothyronine were independent predictors of severity of CHD.
Conclusion
Age, obesity, impaired cardiac function, and atherogenic lipid profile are predictors of hypothyroidism, and PASP is the predictor of hyperthyroidism among manifest CHD. Thyroid hormones are predictors of severity of coronary atherosclerosis and correlated to cardiac functions and PASP.

Keywords:
late postacute coronary syndrome, severity of coronary atherosclerosis, thyroid dysfunction

Egypt J Obes Diabetes Endocrinol 3:1–9

2356-8062

Introduction

Thyroid hormones have many effects on the cardiovascular system [1]. The relationship between abnormal thyroid function and coronary heart disease (CHD) has been recognized for a long time, especially in hypothyroidism status [2]. Even subclinical hypothyroidism and subclinical hyperthyroidism [3,4] have been related to increased risk of CHD events and mortality, although still controversial [5,6]. Similar to severe systemic conditions, myocardial infarction or severe heart failure may affect thyroid hormone secretion and their peripheral conversion, leading to low T3 syndrome. Although the recovery stage of altered thyroid hormone concentration takes place as the illness resolves and is characterized by elevated thyroid-stimulating hormone (TSH) levels, full recovery may be prolonged to several months [7,8]. Previous studied to detect primary thyroid disorders during acute coronary syndrome (ACS) may be biased. Others were retrospective and rare in our locality [9–12].

In animal studies, thyroid hormones, particularly free triiodothyronine (FT3), influence cardiomyocyte phenotype and morphology, and they have cardio-protective effects: they inhibit inflammation, apoptosis, and pathological cardiac remodeling after myocardial infarction [13]. Clinical trials have highlighted on influences of low T3 syndrome rather than primary thyroid disorder on cardiac functions and prognosis [14,15].

Cross-sectional studies among patients undergoing coronary angiography showed conflicting data about the relation of thyroid hormones with severity of coronary atherosclerosis [16–19]. However, all these studies were conducted in euthyroid patients with small samples and without previous ACS. From a clinical point of view, the effect of thyroid dysfunction (TD) on prevalent CHD may be more important than the effect of the thyroid function in the reference range.

Little data about thyroid autoimmunity are available among CHD patients despite its association with many coronary risk factors namely hyperlipidemia, abdominal obesity, and endothelium-dependent arterial dilation in euthyroid patients [20,21].

Our study aimed to identify the prevalence and predictors of primary thyroid disorders, and their interplay with conventional coronary risk factors, cardiac function, and severity of coronary atherosclerosis among patients with manifest CHD with significant stenotic coronary lesion in late post-ACS.

Patients and methods

This prospective observational cross-sectional study, among 200 manifest CHD patients, was carried out in Internal Medicine Department, Minia University Hospital, between December 2012 and December 2014. Patients were selected from consecutive adults aged older than 30 years undergoing coronary angiography for diagnostic and revascularization purposes in Cardiac Catheterization Unit, Minia University Hospital. Patients were recruited into the study if they fulfilled two criteria: (i) clinically stable at the time of the study with minimum 6 months and maximum 12 months after hospitalization for acute coronary events to allow full recovery of altered thyroid hormones during acute illness (sick euthyroid syndrome), and (ii) significant coronary artery stenosis more than 70 obstruction of the lumen in one vessel or more. Patients having any one of the following criteria were excluded: (a) euthyroid sick syndrome (excluding critically ill patients, acute cardiac injury, or severe heart failure) or low serum T3 syndrome; (b) recent acute myocardial infarction, previous revascularization, or rheumatic valvular heart disease; (c) hypothalamus and/or pituitary gland diseases; (d) intake of drugs that influence thyroid function within the past 3 months including amiodarone; (e) recent infections, a malignant tumor, serious liver dysfunction, renal dysfunctions, or chest disease; and (f) pregnancy.

Ethical aspects

The study protocol was approved by the Institutional Ethics Committee, and all patients gave informed consents to participate in this study. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice.

Patients were first evaluated for CHD at the outpatient department. All patients answered a standardized questionnaire and underwent thorough clinical examination, blood sampling, ECG, and echocardiography before coronary angiography. Personal history, demographic characteristics, conventional risk factors for CHD, and current pharmacotherapy were obtained at interview. Anthropometric measurements were taken in a standardized manner. Height and weight were measured to calculate BMI by dividing body weight (kg) by square of height (m^2) [22]. Systemic arterial blood pressure (BP) was measured after 15 min of rest. Systemic arterial hypertension was defined by diagnosis of hypertension made previously by a physician or systolic BP more than or equal to 140 mmHg or diastolic BP more than or equal to 90 mmHg or treatment with antihypertensive medications according to European Society of Hypertension and the European Society of Cardiology guidelines [23]. Diabetes mellitus (DM) was defined by diagnosis of diabetes made previously by a physician, fasting plasma glucose (FPG) more than or equal to 126, either 2-h postprandial glucose or random blood glucose more than or equal to 200 mg/dl, classic symptoms in previously untreated patients, or use of insulin or oral hypoglycemic agents according to the American Diabetes Association guidelines [24].

Laboratory analysis

Before coronary angiography, venous blood samples were collected from all patients between 8:00 and 10:00 a.m. after an overnight fast for at least 12 h. All samples were collected and processed according to standard biochemistry assay in the clinical laboratory at Minia University hospital. FPG, 2-h postprandial glucose, serum creatinine, triglyceride (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) were determined by enzymatic methods using automated chemistry analyzer system Konelab 201 (Thermo Electron Corporation, Vantaa, Finland). Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald formula [25]. Estimated glomerular filtration rate was calculated using the Cockcroft–Gault formula [26]:

$$\text{Creatinine clearance} = \left[\frac{(140 - \text{age}) \times \text{weight})}{(\text{serum creatinine} \times 72)}\right] \times 0.85 \text{ in females.}$$

Assessment of thyroid hormones

Stored serum at −20°C was used to assess thyroid function. Automated chemiluminescent procedures (Mini-VIDAS; BioMérieux, Marcy-l'Étoile, France) were used for quantitative measurement of TSH, FT3, and free thyroxin (FT4) by available kits from Biomerieux Deutschland GmbH (Nürtingen, Germany). The laboratory reference ranges were 0.3–4.5 μIU/ml for TSH, 1.4–4.2 pg/ml for FT3, and 0.65–1.97 ng/dl for FT4.

Patients were classified according to thyroid function into three groups:

(1) Group I: the euthyroid group included patients with FT3, FT4, and TSH levels within the reference ranges.
(2) Group II: the hypothyroid group included patients with TSH levels above 4.5 μIU/ml and subdivided into subclinical or overt hypothyroidism when both FT3and FT4 levels were within or less than the reference ranges, respectively.
(3) Group III: the hyperthyroid group included patients with TSH levels below 0.3 μIU/ml and subdivided into subclinical or overt hyperthyroidism when both FT3 and FT4 levels were within or more than the reference ranges, respectively.

Anti-thyroid peroxidase (TPO): The architect anti-TPO assay is a two-step immunoassay for the quantitative measurement of anti-TPO using Chemiflex technology (Accubind ELISA micro wells; Monobind Inc., Lake Forest, California, USA). Normal value ranges up to 5.6 IU/ml [27].

Imaging studies

After undergoing routine ECG to detect ischemic changes or old myocardial infarction [28], echocardiography was performed by using Vivid-3 echocardiography device (General Electric Inc., USA) with probe frequency of 7.5 MHz. According to recommendations of the American Society of Cardiology, ejection fraction (EF), a marker of systolic function, was assessed using M-mode by parasternal long axis while the patient in the left lateral position. Resting wall motion abnormalities were assessed using calculative method by e-ball assessment. Diastolic dysfunction was assessed by tracing of mitral flow Doppler. Pulmonary artery systolic pressure (PASP) was assessed using the modified Bernoulli equation [29].

Coronary angiography

All patients were subjected to coronary angiography, which was performed using standard Judkins technique [30]. Angiographic findings were reviewed by two experienced cardiologists who were blinded to the study protocol. CHD was defined as a greater than 50% stenosis by visual assessment in at least one major vessel or principal side branch (Judkins technique). The affected artery was determined from angiographic characteristics of occlusion (occlusion due to thrombus formation or ulceration with decreased contrast density). Coronary artery stenosis of more than 70% is defined as significant or obstructive. Multivessel coronary artery disease is defined as having two or more coronary arteries with obstructive lesions [31].

Thyroid ultrasound

It was performed and evaluated by radiology specialists using TOSHIBA SSA-340 machine (Toshiba Co., Tokyo, Japan), with superficial probe of 7 MHz frequency following standard ultrasonography techniques [32].

Results

In the present study, 17.5% of CHD patients had primary thyroid disorders (35/200). Group I, the euthyroid group, represented 82.5% (165/200), with a mean age±SD of 58.76±8.98 years and male/female ratio of 109 : 56. Group II, the hypothyroid group, corresponded to 12% (24/200), with a mean age of 64.70±5.74 years and a male/female ratio of 15 : 9, of which 9.5% (19/200) and 2.5% (5/200) had subclinical and overt hypothyroidism, respectively. Group III, the hyperthyroid group, corresponded to 5.5% (11/200), with a mean age of 56.90±7.73 years and a male/female ratio of 5 : 6, of which 2.5% (5/200) and 3% (6/200) had subclinical and overt hyperthyroidism. Owing to the small number of subgroups, the statistical study involved the three main groups.

Thyroid studied parameters among different coronary heart disease groups

In Table 1, as expected compared with group I, TSH levels and positive anti-TPO were statistically significantly higher but FT3 and FT4 were statistically significantly lower in group II. Group III had statistically significant higher FT3, FT4, positive anti-TPO, and thyroid gland morphological changes (diffuse enlargement, thyroid nodule, multinodular goiter) and significantly lower TSH level than group I.

Comparison of studied conventional cardiovascular risk factors by thyroid status among coronary heart disease patients

As shown in Table 2, groups II and III were comparable to group I as regards sex, smoking, presence of DM and

Table 1 Thyroid parameters among different groups

	Group I: euthyroidism (*n*=165)	Group II: hypothyroidism (*n*=24)	Group III: hyperthyroidism (*n*=11)	A	B	C	D
TSH (μIU/ml)	01.26±0.88	10.53±6.65	0.131±0.09	<0.001*	<0.001*	0.124	<0.001*
FT3 (pg/ml)	2.66±1.07	1.92±1.06	3.26±1.	<0.001*	0.001*	0.005*	<0.001*
FT4 (ng/dl)	0.84±0.52	1.26±0.73	2.06±2.04	<0.001*	0.011*	<0.001*	0.002*
Positive anti-TPO [*n* (%)] (IU/ml)	0 (0)	9 (37.5)	1 (9.1)	<0.001*	<0.001*	<0.001*	0.084
Thyroid ultrasound [*n* (%)]							
Normal	130 (78.8)	17 (70.9)	5 (45.5)	<0.001*	0.289	<0.001**	0.122
Diffuse enlargement	1(0.6)	0 (0)	2 (18.2)				
Multinodular goiter	14 (8.5)	3 (12.5)	2 (18.2)				
Thyroid nodule	20 (12.1)	4 (16.6)	2 (18.2)				

Quantitative data compared by analysis of variance test followed by post-hoc correction for normally distributed data, and Kruskal–Wallis test and Mann–Whitney for nonparametric quantitative data, whereas qualitative variables were compared by χ^2-test. A, B, C, and D are *P* values between three groups: group I vs. group II, group I vs. group III, and group II vs. group III, respectively. FT3, free triiodothyronine; FT4, free thyroxine; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone. *$P<0.05$, significant difference.

Table 2 Comparative study of conventional cardiovascular risk factors among different coronary heart disease groups

Variables	Group I: euthyroidism (*n*=165)	Group II: hypothyroidism (*n*=24)	Group III: hyperthyroidism (*n*=11)	A	B	C	D
Age (years)	58.76±8.98	64.70±5.74	56.90±7.73	0.006*	0.002*	0.490	0.016*
Sex: male/female [*n* (%)]	109/56 (66.1/33.9)	15/9 (62.5/37.5)	5/6 (45.5/54.5)	0.375	0.732	0.167	0.344
DM [*n* (%)]	88 (53.3)	10 (41.7)	6 (54.5)	0.56	0.28	0.93	0.47
Hypertension [*n* (%)]	74 (44.8)	13 (54.1)	8(72.7)	0.15	0.39	0.07	0.29
Smoking [*n* (%)]	63(38.2)	5 (20.8)	5 (45.5)	0.21	0.09	0.63	0.13
BMI (kg/m^2)	31.21±6.23	35.81±4.24	22.79±4.38	0.009*	0.003*	0.36	0.27
Systolic BP (mmHg)	126.97±15.61	128.87±18.61	140.42±14.76	0.14	0.634	0.035*	0.129
Diastolic BP (mmHg)	82.43±13.33	93.33±10.18	71.45±10.33	<0.001*	<0.001*	0.009*	0.001*
FPG (mg/dl)	108.11±25.7	91.06±15.8	103.00±17.86	0.070	0.028*	0.376	0.176
2-h pp PG	161.28±34.25	157.71±25.22	156.71±25.06	0.749	0.506	0.673	0.969
Total cholesterol (mg/dl)	183.06±41.56	218.31±28.67	150.28±23.65	<0.001*	<0.001*	0.008*	<0.001*
LDL-C (mg/dl)	110.41±0.91	138.37±34.33	77.05±23.30	0.06	0.001*	0.006*	<0.001*
Triglycerides (mg/dl)	161.06±53.76	195.75±43.8	131.42±32.98	0.001*	0.003*	0.06	0.001*
HDL-C (mg/dl)	41.36±5.23	34.18±4.87	37.14±4.97	0.06	0.003*	0.089	0.134
Estimated GFR	103.69±29.5	110.63±30.21	104.94±30.71	0.545	0.281	0.750	0.708

BP, blood pressure; DM, diabetes mellitus; GFR, glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; 2-h pp PG, 2-h postprandial plasma glucose. Statistical analysis and comparison between group as Table 1.

hypertension, 2-h pp blood glucose level, and estimated glomerular filtration rate. Group II had a significantly higher age, BMI, diastolic BP, TC and LDL-C, and TG, and significantly lower HDL-C and FPG than group 1 (*P*=0.002, 0.003, <0.001, <0.001, 0.001, 0.003, 0.003, 0.028, respectively). Group III had significantly higher systolic BP and significantly lower diastolic BP, TC, and LDL-C than group I (*P*=0.035, 0.009, 0.008, 0.006, respectively), but no significant difference as regards age, BMI, TG, and HDL-C between both groups was detected.

Comparison of studied cardiac parameters among different coronary heart disease patient groups

As shown in Table 3, groups II and III were comparable to group I as regards the presence of dyspnea and ECG ischemic changes. Group II had significantly impaired systolic and diastolic functions and higher PASP pressure than group I (*P*=0.03, 0.04, <0.001, respectively), with no significant difference of SWMA between the two groups. Group III had significantly higher EF and PASP and lower SWMA than Group (*P*<0.001, <0.001, 0.015, respectively).

Correlation of thyroid hormones levels and studied conventional cardiovascular risk factors

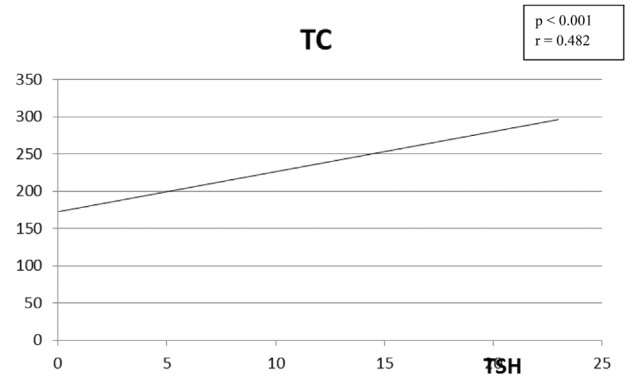
On one hand, TSH level had significant positive but FT3 and FT4 had significant negative correlations with diastolic BP, BMI, TC (Fig. 1), LDL-C (Fig. 2), and TG (Fig. 3) (*P*<0.001 for all except for correlation of FT3 with diastolic BP and LDL-C, *P*=0.02 for both). In addition, TSH had significant positive correlation with age and negative correlations

Table 3 Comparison of studied cardiac parameters among different coronary heart disease patients groups

	Group I: euthyroidism (*n*=165)	Group II: hypothyroidism (*n*=24)	Group III: hyperthyroidism (*n*=11)	A	B	C	D
Dyspnea [*n* (%)]	126 (76.4)	19 (79.2)	9 (81.8)	0.88	0.761	0.999	0.858
Orthopnea[*n* (%)]	45 (27.3)	17 (70.8)	3 (27.3)	0.001*	0.001*	0.999	0.016*
ECG							
Heart rate (beats/min)	84.45±15.84	69.77±8.62	96.09±10.64	0.006*	0.11	0.008*	0.001*
Arrhythmias (%)	13 (7.9)	2 (12.5)	4 (36.36)	0.037*	0.895	0.005*	0.041*
No ischemia	13 (7.9)	4 (16.7)	0 (0)	–	–	–	–
Ischemia	88 (53.3)	8 (33.3)	5 (45.5)	0.217	0.128	0.442	0.339
Infarction	64 (38.8)	12 (50)	6 (54.5)	–	–	–	–
Echocardiography							
EF (%)	50.76 ±11.7	45.62 ±8.88	67.14±4.50	<0.001*	<0.001*	0.001*	0.039*
PASP (mmHg)	31.26±8.81	35.12±11.33	47.18±8.23	<0.001*	<0.001*	0.001*	0.045*
RWMA [*n* (%)]	121 (73.3)	16 (73.3)	6 (54.5)	0.028*	0.308	0.015*	0.011*
Diastolic dysfunction [*n* (%)]							
No	67 (40.6)	0 (0)	5 (45.5)	<0.001*	0.081	<0.001*	<0.001*
Grade I	43 (26.1)	6 (25)	6 (54.5)				
Grade II	54 (32.7)	10 (41.7)	0 (0)				
Grade III	1 (0.6)	8 (33.3)	0 (0)				
Angiography [*n* (%)]							
One vessel	79 (47.9)	8 (33.3)	6 (54.5)	0.353	0.182	0.866	0.243
Multivessels	86 (52.1)	16 (66.7)	5 (45.5)				

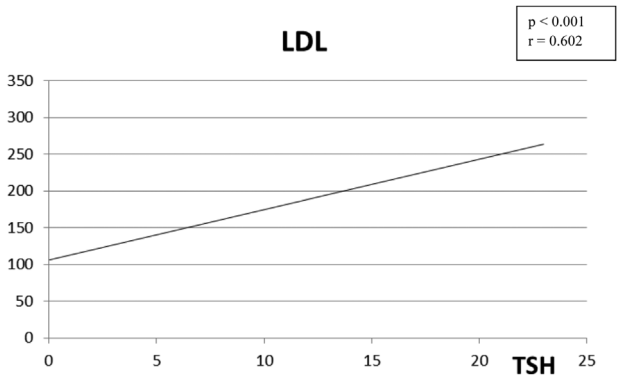
EF, ejection fraction; PASP, pulmonary artery systolic pressure; RWMA, resting wall motion abnormality. Statistical analysis and comparison between group as Table 1.

Figure 1



Correlation of TSH with TC among patients with CHD. CHD, coronary heart disease; TC, total cholesterol; TSH, thyroid-stimulating hormone

Figure 2



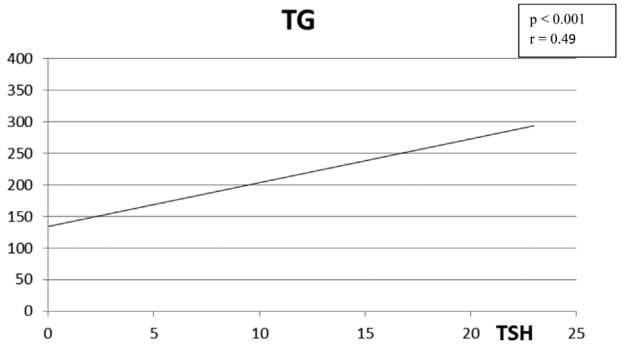
Correlation of TSH with LDL among patients with CHD. CHD, coronary heart disease; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone

with HDL-C ($P<0.001$ for both, Fig. 4), and FT4 had a significant positive correlation with systolic BP ($P<0.001$). No significant correlation was found between TSHs levels and DM, hypertension, smoking, and plasma glucose level (Fig. 1).

Correlation of thyroid hormones levels previously mentioned cardiac parameters (clinically, by ECG, echocardiography, and angiography)

TSH had significant positive and FT3 had significant negative correlations with the presence of orthopnea, right-side heart failure, diastolic dysfunction, and number of coronary vessel occluded angiographic assessed ($P<0.001$ for all except for correlation of FT3 with angiographic data and diastolic dysfunction;

Figure 3



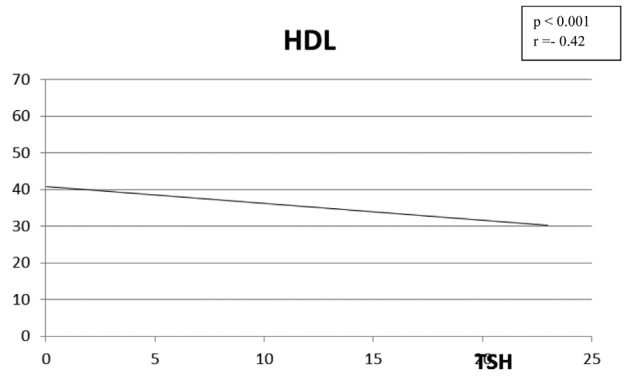
Correlation of TSH with serum TG among patients with CHD. CHD, coronary heart disease; TG, triglyceride; TSH, thyroid-stimulating hormone

P=0.002 for both). As regards other echocardiographic data, EF had a significant negative correlation with TSH level and positive correlations with FT3 and FT4 (*P*=0.001 for all); PASP had a significant positive correlation with TSH level and FT4 (*P*=0.02, <0.001, respectively); and resting wall motion abnormalities had a significant negative correlation with TSH level and FT3 (*P*=0.02, 0.03, respectively). FT4 had a significant negative correlation with angiographic data (*P*=0.001).

To evaluate the independent role of studied conventional risk factors and cardiac parameters in addition to thyroid hormones for prediction of hypothyroidism and hyperthyroidism among CHD patients, multiple logistic regression analyses were performed using all parameters that were significant in the university analyses as independent factors in Table 4; as expected, TSH levels were predictors for both disorders. Older age, higher pulse and BMI, the presence of orthopnea, impaired EF, diastolic dysfunction, and elevated LDL-C and TG levels were independent predictors for hypothyroidism (*P*=0.040, 0.037, 0.021, 0.026, 0.008, 0.044, 0.013, respectively); higher PASP was an independent predictor for hyperthyroidism (*P*<0.001, respectively).

When the following risk factors – hypertension, DM, smoking, dyspnea, orthopnea, diastolic BP, BMI, EF, LDL-C, TC, TG, TSH, and FT3–were subjected to multiple logistic regression analysis as independent factors for prediction of severe ischemia hypertension, DM, smoking, dyspnea, orthopnea, BMI, EF, LDL-C, TC, and TSH were positive independent predictors of severe ischemia (*P*=0.042, 0.009, 0.008, 0.002, 0.029, 0.0388, 0.042, 0,001, 0.034, 0.004, respectively). Only free T3 was a negative predictor (*P*=0.001).

Figure 4



Correlation of TSH with HDL cholesterol among patients with CHD. CHD, coronary heart disease; HDL, high-density lipoprotein; TSH, thyroid-stimulating hormone

Discussion

To ensure that our study had considerable strength, we included the large study sample (200 CHD patients) and used coronary angiography to evaluate coronary atherosclerosis. We used more stringent exclusion criteria and the impact of potential confounders was

Table 4 Multiple logistic regression analysis of some risk factors for prediction of hypothyroidism and hyperthyroidism in ischemic patients

	Predictors of hyperthyroidism		Predictors of hypothyroidism	
	β	*P*	*β*	*P*
Age (years)	–0.092	0.082	0.242	0.040*
Diastolic BP (mmHg)	–0.026	0.696	0.082	0.112
Pulse (beats/min)	0.048	0.911	–0.148	0.048*
BMI (kg/m^2)	–0.024	0.708	0.546	0.037*
Orthopnea (yes/no)	–0.095	0.204	0.221	0.021*
RTHF (yes/no)	0.097	0.194	–0.012	0.856
Vessel occlusion (angiography)	0.080	0.150	–0.056	0.387
RWMA (yes/no)	–0.144	0.065	0.028	0.575
Ejection fraction (%)	0.064	0.305	0.181	0.026*
Diastolic dysfunction	–0.041	0.459	0.176	0.008*
PASP (mmHg)	0.212	<0.001*	–0.067	0.161
HDL-C (mg/dl)	0.003	0.962	–0.013	0.780
LDL-C (mg/dl)	–0.093	0.207	0.104	0.044*
Total cholesterol (mg/dl)	–0.060	0.372	0.088	0.094
Triglyceride (mg/dl)	–0.019	0.755	0.163	0.013*
TSH (μIU/ml)	–0.654	<0.001*	0.739	<0.001*
FT3 (pg/ml)	0.063	0.049*	–0.236	0.004*
FT4 (ng/dl)	0.607	<0.001**	–0.135	0.011*

BP, blood pressure; FT3, free triiodothyronine; FT4, free thyroxine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PASP, pulmonary artery systolic pressure; RTHF, right-side heart failure; RWMA, resting wall motion abnormality; TSH, thyroid-stimulating hormone. All is *=<0.05.

minimized. First, we ruled out the individuals with euthyroid sick syndrome, which has a higher prevalence up to 25% in CHD patients [10]. Second, the patients enrolled in our study were clinically stable. Acute myocardial infarction and any other acute or serious diseases were not included. Third, individuals using drugs that influence thyroid function were excluded.

Studies on the prevalence and distribution of TD have primarily been carried out in the general population and to a lesser extent in ACS [9,12,33]. Studies have rarely investigated clinically stable CHD patients with obstructive coronary lesion –to our knowledge, one small study among 81 elderly Egyptian and another large retrospective study among 568 CHD patients in China [10,11]. Among CHD patients in our study, the prevalence of TD was 17.5 versus 23.5 and 18.5% in the previous two studies, respectively. Interestingly, the prevalence of hypothyroidism in our study was 12%, of which the prevalence was 2.5% for overt and 9.5% for subclinical forms versus 17.3, 14.8, and 2.5% among elderly Egyptians and 15.3, 5.28, and 10.05% among Chinese with CHD, respectively. In our study, the prevalence of hyperthyroidism was 5.5%, of which the prevalence was 2.5% for overt and 3% for subclinical forms versus 6.2, 2.5, and 3.7% among elderly Egyptians, respectively, and 3.3% for hyperthyroidism (overt and subclinical) among Chinese with CHD. These studies were partly matched to our result. The difference may be explained by different study design and races, and the cutoff value of TSH level may be different to identify subclinical hypothyroidism.

Despite lower prevalence of autoimmune thyroid disorder in our study (5%, 10/200) compared with the general population (8.4–11.35%) [33,34], its prevalence was about 37.5% of hypothyroidism and 9.1% of hyperthyroidism groups versus 0% in euthyroid. Anti TPO antibody level was positively correlated to TSH, but not to FT3 or FT4. Therefore, the presence of anti-TPO was necessitating a compensatory increase in levels of TSH and the presence of TD in CHD patients. This was supported by the study of Roos and colleagues. In contrast, it was not a predictor of severity of ischemia or of TD in our study among CHD patients. Supporting our results, positive anti-TPO was neither associated with cardiovascular risk factor nor with severity of coronary ischemia in previous studies among CHD patients [10,35].

Thyroid hormones affect lipid metabolism and BP [36]. Population-based studies reported association of thyroid function even within normal range with cardiovascular risk factors [10,37–41]. Similarly in CHD, we found an inverse association of both T3 and T4, and a positive association of TSH with BP, BMI, and lipid profile levels (TC, LDL-C, and TG levels); TSH was positively associated with age and inversely with HDL-C. Moreover, we studied the association of some coronary risk factors by thyroid status. In comparison with euthyroid, older age, higher diastolic BP, obesity, and atherogenic lipid profile were associated with hypothyroidism, whereas inverse lipid profile level was associated with hyperthyroidism. However, similar to Ling *et al.* [41], among patients undergoing coronary angiography, we found no association of thyroid status with the presence of DM, hypertension, smoking, and sex. The lipid abnormalities of hypothyiod and hyperthyiod groups were matched with Peppa *et al.* [42].

Some authors consider increased TSH with advanced age a normal process and consider different TSH reference ranges for different age groups [43]. Association of obesity with hypothyroid state is explained by abolishing catabolic effect of thyroid hormones on body fats. Both T3 and T4 are vasodilators. Contributors to dystolicdysfunction in hypothyroidism even in subclinical hypothyroidism are increased peripheral vascular resistance, increased arterial stiffness and endothelial dysfunction. Thyroid hormones modulate lipid metabolism including enzyme activity, receptor expression, lipid breakdown, and clearance, thereby contributing to the expression of the lipid phenotype. Thyroid hormone deficiency and subclinical hypothyroidism were accompanied by a reduced number and activity of hepatic LDL receptor [36]. TSH has direct action on lipid metabolism, endothelial function, and adipose tissues via binding to its own receptor. It could upregulate 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, and it may reduce hepatic LDL receptor [44,45]. It attenuates endothelial nitric oxide and prostaglandin production and enhances adipogenesis [46,47].

As expected, we noticed increased prevalence of arrhythmias, especially atrial fibrillation, in hyperthyroid patients. Increased sensitivity toward circulating catecholamines, direct action of thyroid hormones on atrial ion channels, and atrial enlargement as a result of the expanded blood volume are the underlying causes [36].

Previous studies have reported an impaired left ventricular function among patients with overt and subclinical hypothyroidism [48,49], but the impact of thyroid hormone pattern on cardiac function in late post-ACS is not clear. Low thyroid hormone level is associated with increased oxidative stress, which in turn induces apoptosis

[50]. Low FT3 levels change the expression of cardiac genes and cause pathological cardiac remodeling after myocardial infarction. These lead to decreased contractility, impaired diastolic function, and reperfusion injury [13]. In accordance with aforementioned data, a novel finding in the present study, clinical (orthopnea and right-sided heart failure) and echocardiographic (impaired EF and diastolic dysfunction) parameters of heart failure among CHD patients are more pronounced in the hypothyroid group compared with both euthyriod and hyperthyroid groups. Interestingly, these parameters were inversely correlated mainly with FT3 and to a lesser extent with FT4 (only with EF). Moreover, impaired left ventricular function was an independent predictor of hypothyroidism among CHD patients – an aspect not evaluated before. Previous studies focus on the impact of low T3 level or syndrome among patients with ACS. It was an indicator of severe cardiac injury and left ventricular functions, and a strong predictor of short-term and long-term poor prognoses. Moreover, 6-month echocardiographic left ventricular mechanics were specific and sensitive for prediction of low FT3 levels [14,15,51,52].

TD, but primarily with hyperthyroidism, may be associated with pulmonary hypertension because of increased pulmonary vascular resistance, endothelial dysfunction, endothelial and smooth muscle cell proliferation, and autoimmunity. These changes are reversible with treatment of underlying thyroid disorder [53]. In accordance, novel findings in our study were higher PASP among CHD patients with TD predominantly among those with hyperthyroidism; also, PASP was positively correlated with TSH level and FT4 not FT3, and it was an independent predictor of hyperthyroidism among CHD patients – an aspect not mentioned before.

Association of thyroid hormones and subclinical hypothyroidism with carotid atherosclerosis is still under debate [54,55]. We found that FT3 and FT4 levels were inversely associated and TSH concentration was positively associated with the severity of coronary atherosclerosis angiography assessed. In addition, both FT3 and TSH were independent predictors to it. Results of previous cross-sectional studies among patients undergoing coronary angiography were conflicting. Although Erta *et al.* [18], reported FT3 (neither FT4 nor TSH) was both inversely correlated with and independent predictor for severity of coronary atherosclerosis in euthyroid CHD, Linga *et al.* [41], reported that FT4 was inversely and TSH was positively, on one hand, correlated to severity of coronary atherosclerosis in the entire wide spectrum range of thyroid hormones not in the euthyroid range. In contrast, Jung *et al.* [17], reported positive associations of FT4 and coronary atherosclerosis.

The proportion of TD among patients with late post-ACS in our study was higher than the prevalence reported in the epidemiological survey (3.8–6.7%) [55,56].

Conclusion

The proportion of TD among patients with late post-ACS is 17.5%. Age, obesity, impaired cardiac function, and atherogenic lipid profile are predictors of hypothyroidism, and PASP is a predictor of hyperthyroidism among manifest CHD. Thyroid hormones are predictors to severity of coronary atherosclerosis and correlated to cardiac functions and PASP. These findings suggested that thyroid function screening may facilitate risk stratification in individuals with symptoms of CHD and could provide additional information for selecting the individuals who would benefit from coronary angiography.

Limitations of our study

This study has a cross-sectional design, and it is impossible to consider the causality of TD in CHD. Despite the large sample size, the small number of participants with subclinical and overt hyperthyroidism precluded precise estimates for those subgroups.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001; 344:501–509.

2 Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. J Clin Endocrinol Metab; 88:2438–2444.

3 Rodondi N, Den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP *et al.* Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010; 304:1365–1374.

4 Collet TH, Gussekloo J, Bauer DC, Den Elzen WP, Cappola AR, Balmer P, *et al.* Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Intern Med 2012; 172:799–809.

5 Hyland KA, Arnold AM, Lee JS, Cappola AR. Persistent subclinical hypothyroidism and cardiovascular risk in the elderly: the cardio-vascular health study. J Clin Endocrinol Met 2013; 98:533–540.

6 Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GH, *et al.* Thyroid status, cardiovascular risk, and mortality in older adults. JAMA 2006; 295:1033–1041.

7 Thompson MJ. Chapter VII: endocrine problems in the intensive care unit. In: Irwin RS, Rippe JM, editors. Manual of intensive care medicine. 5th ed. Philadelphia, PA:Lippincott Williams & Wilkins; 2010:515–562.

8 Economidou F, Douka E, Tzanela M, Nanas S, Kotanidou A. Thyroid function during critical illness. Hormones 2011; 10:117–124

9 Pimentel RC, Cardoso GP, Escosteguy CC, Abreu LM. Thyroid hormone profile in acute coronary syndromes. Arq Bras Cardiol 2006; 87: 688–694.

10 Nammas W, Mostafa M, Sabry I, Abdel-Aziz M, Kabil H. Thyroid hormone patterns in elderly patients undergoing elective coronary procedures. Eur Rev Med Pharmacol Sci 2011; 15:175–180.

11 Xu C, Yang X, Liu W, Yuan H, Yu C, Gao L, Zhao J. Thyroid stimulating hormone, independent of thyroid hormone, can elevate the serum total cholesterol level in patients with coronary heart disease: a cross-sectional design. Nutr Metab (Lond) 2012; 9:44.

12 Qari FA. Thyroid hormone profile in patients with acute coronary syndrome. Iran Red Crescent Med J 2015; 17:e26919.

13 Frączek MM, Gackowski A, Przybylik-Mazurek E, Nessler J. The relation between the low T3 syndrome in the clinical course of myocardial infarction and heart failure. Pol Merkur Lekarski 2016; 40:380–383.

14 Jankauskienė E, Orda P, Rumbinaitė E, Žaliaduonytė-Pekšienė D, Steponavičiutė R, Krasauskienė A. Left ventricular function by speckle-tracking echocardiography in patients with low-T3 syndrome and acute myocardial infarction. Medicina (B Aires) 2015; 51:209–216.

15 Jankauskienė E, Orda P, Barauskienė G, Mickuvienė N, Brožaitienė J, Vaškelytė JJ, *et al.* Relationship between left ventricular mechanics and low free triiodothyronine levels after myocardial infarction: a prospective study. Intern Emerg Med 2016; 11:391–398.

16 Yun KH, Jeong MH, Oh SK, Lee EM, Lee J, Rhee SJ, *et al.* Relationship of thyroid stimulating hormone with coronary atherosclerosis in angina patients. Int J Cardiol 2007; 122:56–60.

17 Jung CH, Rhee EJ, Shin HS, Jo SK, Won JC, Park CY, *et al.* Higher serum free thyroxine levels are associated with coronary artery disease. Endocr J 2008; 55:819–826.

18 Ertas F, Kaya H, Soydince MS. Low serum free triiodothyronine levels are associated with the presence and severity of coronary artery disease in the euthyroid patients: an observational study. Anadolu Kardiyol Derg 2012; 12:591–596.

19 Yang L, Zou J, Zhang M, Xu H, Qi W, Gao L, Zhao J The relationship between thyroid stimulating hormone within the reference range and coronary artery disease: impact of age. Endocr J 2013; 60:773–779.

20 Xiang GD, He YS, Zhao LS, Hou J, Yue L, Xiang HJ. Impairment of endothelium-dependent arterial dilation in Hashimoto's thyroiditis patients with euthyroidism. Clin Endocrinol (Oxf) 2006; 64:698–702.

21 Tamer G, Mert M, Tamer I, Mesci B, Kilic D, Arik S. Effects of thyroid autoimmunity on abdominal obesity and hyperlipidaemia. Endokrynol Pol 2011; 62:421–428.

22 World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva, Switzerland: WHO; 2000.

23 Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, *et al.* 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013; 31:1281–1357.

24 American Diabetes Association. Standards of medical care in diabetes – 2014. Diabetes Care 2014; 37:S15.

25 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18:499–502.

26 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41.

27 Rasmussen U. Analytical and clinical performance goals for testing autoantibodies to thyroperoxidase, thyroglobulin, and thyrotropin receptor. Clin Chem 1996; 42:160–163.

28 Goldberger AL. Myocardial infarction and ischemia. In: Goldberger AL, editor. Clinical electrocardiography. a simplified approach. 7th ed. Philadelphia, PA: Mobsy Elsevier; 2006: 87–123.

29 Spencer KT, Kimura BJ, Korcarz CE, Pellikka PA, Rahko PS, Siegel RJ. Focused cardiac ultrasound: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2013; 26:567–581.

30 Judkins MP. Selective coronary arteriography. A percutaneous transfemoral technique. Radiology 1967; 89:815–824.

31 Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA *et al.* ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. Circulation 1999; 99:2345–2357.

32 Chaudhary V, Bano S. Thyroid ultrasound. Indian J Endocrinol Metab 2013; 17:219–227.

33 Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, *et al.* Serum TSH, T4, and thyroid antibodies in the United States population(1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002; 87:489–499.

34 Roos A, Links TP, Gans RO, Wolffenbuttel BH, Bakker SJ. Thyroid peroxidase antibodies,levels of thyroid stimulating hormone and development of hypothyroidism in euthyroid subjects. Eur J Intern Med 2010; 21:555–559.

35 Mayer Jr O, Šimon J, Filipovský J, Plášková M, Pikner R. Hypothyroidism in coronary heart disease and its relation to selected risk factors. Vasc Health Risk Manag 2006; 2:499–506.

36 Klein I, Danzi S. Thyroid disease and the heart. Circulation 2007; 116:1725–1735.

37 Asvold BO, Bjøro T, Nilsen TI, Vatten LJ. Association between blood pressure and serum TSH concentration within the reference range: a population-based study. J Clin Endocrinol Metab 2007; 92:841–845.

38 Lai Y, Wang J, Jiang F, Wang B, Chen Y, Li M, *et al.* The relationship between serum thyrotropin and components of metabolic syndrome. Endocr J 2011; 58:23–30.

39 Mehran L, Amouzegar A, Tohidi M, Moayedi M, Azizi F. Serum free thyroxine concentration is associated with metabolic syndrome in euthyroid subjects. Thyroid 2014; 24:1566–1574.

40 Roef GL, Rietzschel ER, van Daele CM, Taes YE, de Buyzere ML, Gillebert TC, *et al.* Triiodothyronine and free thyroxine levels are differentially associated with metabolic profile and adiposity-related cardiovascular risk markers in euthyroid middle-aged subjects. Thyroid 2014; 24:223–231.

41 Ling Y, Jiang J, Gui M, Liu L, Aleteng Q, Wu B, *et al.* Thyroid function, prevalent coronary heart disease, and severity of coronary atherosclerosis in patients undergoing coronary angiography. Int J Endocrinol 2105:708272.

42 Peppa M, Betsi G, Dimitriadis G. Lipid abnormalities and cardio-metabolic risk in patients with overt and subclinical thyroid disease. J Lipids 2011; 2011:575840.

43 Kahapola-Arachchige KM, Hadlow N, Wardrop R, Lim EM, Walsh JP. Age-specific TSH reference ranges have minimal impact on the diagnosis of thyroid dysfunction. Clin Endocrinol 2012; 77:773–775.

44 Tian L, Song Y, Xing M, Zhang W, Ning G, Li X, *et al.* A novel role for thyroid stimulating hormone: up regulation of hepatic 3 hydroxy-3-methyl-glutarylcoenzyme A reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein pathway. Hepatology 2010; 52:1401–1409.

45 Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med 2012; 367:1891–1900.

46 Tian L, Zhang L, Liu J, Guo T, Gao C, Ni J. Effects of TSH on the function of human umbilical vein endothelial cells. J Mol Endocrinol 2014; 52:215–222.

47 Muscogiuri G, Sorice GP, Mezza T, Prioletta A, Lassandro AP, Pirronti T *et al.* High-normal TSH values in obesity: is it insulin resistance or adipose tissue's guilt? Obesity (Silver Spring) 2013; 21:101–107.

48 Tiryakioglu SK, Tiryakioglu O, Ari H, Basel MC, Ozkan H, Bozat T. Left ventricular longitudinal myocardial function in overt hypothyroidism: a tissue Doppler echocardiographic study. Echocardiography 2010; 27:505–511.

49 Ilic S, Tadic M, Ivanovic B, Caparevic Z, Trbojevic B, Celic V. Left and right ventricular structure and function in subclinical hypothyroidism: the effects of one-year levothyroxine treatment. Med Sci Monit 2013; 19:960–968.

50 Belló-Klein A, Khaper N, Llesuy S, *et al.* Oxidative stress and antioxidant strategies in cardiovascular disease. Oxid Med Cell Longev; 2014; 2014:678741.

50 Zhang B, Peng W, Wang C, Li W, Xu Y. A low fT3 level as a prognostic marker in patients with acute myocardial infarctions. Intern Med 2012; 51:3009–3015.

52 Wang WY, Tang YD, Yang M, Cui C, Mu M, Qian J, *et al.* Free triiodothyronine level indicates the degree of myocardial injury in patients with acute ST-elevation myocardial infarction. Chin Med J 2013; 126:3926–3929.

53 Scicchitano P, Dentamaro I, Tunzi F, Ricci G, Carbonara S, Devito F, *et al.* Pulmonary hypertension in thyroid diseases. Endocrine 2016; 54:578–587.

54 Gao N, Zhang W, Zhang YZ, Yang Q, Chen SH. Carotid intima-media thickness in patients with subclinical hypothyroidism: a meta-analysis. Atherosclerosis 2013; 227:18–25.

55 Delitala AP, Filigheddu F, Orrù M, AlGhatrif M, Steri M, Pilia MG, *et al.* No evidence of association between subclinical thyroid disorders and common carotid intima medial thickness or atherosclerotic plaque. Nutr Metab Cardiovasc Dis 2015; 25:1104–1110.

56 Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab 2014; 99:923–931.