Influence of thyroid function on the outcome of percutaneous coronary intervention in euthyroid patients with coronary artery disease

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Background
Thyroid hormonal disturbance plays an essential role in coronary artery disease (CAD) development and progress. Few studies have detected the relation between percutaneous coronary intervention (PCI), thyroid gland function, and morphology. We aimed to assess the influence of baseline thyroid function tests on the outcome of PCI in euthyroid patients with CAD, and to detect the effect of PCI on the thyroid function and ultrasound features.

Patients and methods
This study included 113 clinically euthyroid patients with stable CAD. Serum free T3, serum free T4, thyroid-stimulating hormone (TSH), thyroid-stimulating hormone index, free T3/T4 ratio, anti-thyroperoxidase (TPO), and high-sensitivity C-reactive protein had been measured before, and then 24 h and 3 months after PCI. The morphology of thyroid was evaluated through thyroid ultrasound before and 3 months after PCI.

Results
One day after PCI, there was a significant increase in serum FT3 and serum FT4 and no significant change in the serum TSH compared with just before PCI ($P < 0.001$, $P = 0.04$, $P = 0.97$, respectively). In addition, there was a significant increase in serum FT3/FT4 ratio compared with just before PCI ($P = 0.007$). Three months after PCI, there was a significant increase in serum FT4, decrease in serum FT3 returning to baseline, and a significant increase in serum TSH compared with just before PCI ($P = 0.42$, $P < 0.001$, $P < 0.001$, respectively). There was a significant decrease in the serum FT3/FT4 ratio and significant increase in serum thyroid-stimulating hormone index compared with just before PCI ($P \leq 0.001$, $P < 0.001$, respectively). Higher TSH and measured echogenicity index were independent pre-PCI predictors of unfavorable outcomes after 24 h with cutoff values greater than 0.95 mIU/ml and greater than 1.81, respectively. Lower FT3 and higher FT4 levels were independent pre-PCI predictors of unfavorable outcomes after 3 months with cutoff values less than or equal to 2.95 pg/ml and greater than 1.3 ng/dl, respectively.

Conclusion
A state of euthyroid hyperthyroxinemia was detected 24 h after PCI. A state of thyroid hormone resistance was detected 3 months after PCI. Higher TSH and measured echogenicity index independently predicted unfavorable outcome after 24 h. Lower FT3 and higher FT4 levels independently predicted unfavorable outcomes after 3 months.

Keywords:
coronary artery disease, echogenicity index, percutaneous coronary intervention, thyroid morphology, thyroid status

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Introduction

Thyroid hormones (TH) play critical roles in differentiation, growth, and metabolism; they have pleiotropic effects in many tissues [1]. Increased or reduced action of TH on certain molecular pathways in the heart and vasculature causes relevant cardiovascular derangements. Thyroid dysfunction is a common clinical problem that plays a key role in the regulation of the cardiovascular system and can contribute to the clinical course of coronary artery disease (CAD) [2].

In addition, subclinical thyroid dysfunction is associated with an increased incidence of death and other adverse events secondary to CAD. Coincidentally, a thyroid-stimulating hormone (TSH) value of 10 mUI/l emerged as an ideal cutoff to identify

patients at particularly high risk. In addition, patients with subclinical hyperthyroidism revealed that isolated reductions in TSH less than 0.1 mUI/l may lead to atrial fibrillation, as well as to an increased risk for total and CAD-related mortality [3]. T3 levels are inversely correlated to the presence and severity of CAD, and significantly predict adverse prognosis, even after adjusting for traditional coronary risk factors. In cardiac patients without a history of thyroid dysfunction, a low T3 syndrome (due to a reduced peripheral conversion of T4 into T3) is a frequent finding, particularly in patients with heart failure, acute myocardial infarction, and in patients following cardiac surgery [4].

Furthermore, iodinated contrast media used in coronary angiography (CA) is considered an important precaution in view of the potential interference of iodinated contrast media with thyroid metabolism. The average daily iodine requirement in adults is 95 mg/day, with a dietary allowance of 150 mg/day. A 200 ml dose of contrast medium containing 35 μg/ml provides 7000 μg free iodide, which is equivalent to 45 times the recommended daily intake. This amount can fill the iodine deposits in the thyroid gland for up to 2 months [5].

In the literature, there is a glaring lack of current data on the baseline thyroid function and the relation between ultrasonographic features and percutaneous coronary intervention (PCI) outcomes, as well as the effects on thyroid morphology and function after the administration of such a high single dose of iodine as part of PCI associated with average dose of radiation and intense manipulation.

Patients and methods

This prospective cohort study was carried out on 113 euthyroid patients with stable CAD who were referred to the Cardiac Catheter Lab in the Department of Cardiology of Alexandria Main University Hospital for elective PCI. Eligibility criteria included patients having stable CAD, with significant stenosis, and clinically euthyroid without a history of thyroid disease. The protocol of this study was approved by the ethical committee of Alexandria Faculty of Medicine. All patients signed an informed written consent prior to enrollment to the study.

Following were the exclusion criteria: patients with a history of thyroid disease; lab evidence of overt thyroid dysfunction with FT3 and FT4 being out of range (1.4–4.2 pg/ml and 0.8–2 ng/dl, respectively); patients taking drugs affecting the thyroid including amiodarone; patients who had been subjected to contrast agent over the last 3 months; patients with an acute coronary syndrome; patients in cardiogenic shock; heart failure (NYHA III, IV); liver failure or renal failure; and patients with underlying infectious, inflammatory, or malignant diseases.

At baseline, specific investigations included assessing serum FT3, FT4, TSH, serum anti-TPO, and serum high-sensitivity C-reactive protein (hsCRP) by using the enzyme-linked immunosorbent assay. In addition, FT3/FT4 ratio and thyroid-stimulating hormone index were calculated [6,7].

Thyroid ultrasonography was carried out before PCI using a Kontron device with a liner probe and a 7.5–10 MHz transducer to assess the volume of the gland, vascularity, nodules, and morphology. Morphology included echogenicity and heterogenicity. The echogenicity value of each lobe was measured by using the grey scale histogram analysis [8], and then the average of both lobes' echogenicity was measured to get the gland echogenicity [9]. Echogenicity index (EI) of each lobe was calculated as the ratio of the average histogram values of the gland lobe and the values for the adjacent muscles (using the same brightness gain for both), and then the average of both lobes' EIs was measured to get the gland EI [10]. The heterogeneity index (HI) of each lobe was calculated as a coefficient of variance (SD/mean) of each lobe, and then the average of coefficients of variance (SD/mean) for both lobes was measured to get the gland HI [11].

The recorded photographs were analyzed by using the Image J software (National Institutes of Health, USA) [12,13]. On the basis of image echogenicity, the histograms showed gray scales:

(a) Hyperechoic (close to 255),
(b) Hypoechoic (close to 0), and
(c) Isoechoic (similar to the tissue of comparison) [9,14].

Echocardiography using HD11XE echo machine (Philips, USA) was carried out before PCI. I-Transthoracic M-mode echocardiography was carried out for the assessment of left ventricle (LV) function by measuring ejection fraction (EF) and fractional shortening (FS), and for the assessment of left ventricular filling by using transmitral pulsed Doppler flow to detect E and A.

PCI was carried out in the standard fashion using Toshiba DFP-8000D Angio Lab, (Toshiba, Tokyo, Japan) [15,16]. The parameters assessed during the procedure were stenosis before and after and parameters affecting thyroid status (radiation dose measurement, dye injected, and manipulation difficulties).

Radiation exposure was assessed by using the cumulative Entrance Surface Air Kerma (mGy) and cumulative thyroid (mGy) [17], which were calculated by using a Windows-based computer program, CALDose_X 5.0 software (Recife, PE, Brazil) [18], and frames numbers, which were determined from a direct frame counter. Dye injection rate was assessed by using the dye injection duration and amount. PCI was carried out using different amounts of Ultravist(R) (370 mg iodine/ml; Schering AG, Berlin, Germany), with a total iodine load of 35 g. Manipulations were assessed by using stent (number, diameter, and length) as a surrogate for local inflammation induced by plaque disruption and magnitude of local plaque reduction. In addition, hsCRP level 24 h after PCI was an excellent surrogate marker for poststent inflammatory status, and its source might be the inflammation site of the plaque or the coronary arterial wall injured by stenting mechanical damage to the vessel wall, which has been shown to induce a systemic inflammatory response [19,20].

Serum FT4, FT3, TSH, anti-TPO, and hsCRP were measured 24 h and 3 months after PCI. Moreover, thyroid ultrasonography was re-evaluated 3 months after PCI. Cardiac echocardiography was carried out 24 h and 3 months after PCI. PCI outcome 24 h and 3months after PCI was assessed through the presence of contrast-induced nephropathy (an increase in serum creatinine ≥0.5 mg/dl over baseline), subacute stent thrombosis (symptoms suggestive of an acute coronary syndrome criteria and angiographic or pathologic confirmation of stent thrombosis), heart failure by deterioration of EF or EF less than 50%, arrhythmias, and major adverse cardiac events (deaths, nonfatal myocardial infarction, target vessel revascularisation (TVR), non target vessel revascularisation (NTVR), and cerebrovascular events).

Overt hyperthyroidism was diagnosed by a decrease in TSH less than 0.39 mIU/l, with a corresponding increase in FT3 greater than 4.2 pg/ml and in FT4 greater than 2 ng/dl. Subclinical hyperthyroid was diagnosed by a decrease in TSH less than 0.39 mIU/l, with a corresponding normal FT3 and FT4. Overt hypothyroid was diagnosed by a decrease in TSH greater than 6.16 mIU/l, with a corresponding increase in FT3 less than 1.4 pg/ml and in FT4 less than 0.8 ng/dl. Subclinical hypothyroid was diagnosed by a decrease in TSH greater than 6.16 mIU/l, with a corresponding normal FT3 and in FT4.

Statistical analysis was carried out by using the SPSS 20.0 (SPSS Inc., an IBM Company; Chicago, Illinois, USA) and MedCalc® 13.3.3.0 statistical software (MedCalc Software; Ostend, Belgium).

Table 1 Demographic data and risk factors for the coronary artery disease cases

Demographic data	Number of patients [*n* (%)]
Sex	
Male	93 (82.3)
Female	20 (17.7)
Age (years)	
<50	22 (19.5)
51–60	80 (70.8)
>60	11 (9.7)
CSA	
Grade 0	6 (5.3)
Grade I	11 (9.7)
Grade II	71 (62.8)
Grade III	24 (21.2)
Grade IV	1 (0.9)
DM	37 (32.7)
HTN	75 (66.4)
Family history of CAD	22 (19.5)
Smoking status	93 (82.3)
Drug history	
Aspirin	113 (100.0)
Clopidogrel	104 (92.0)
Statin	107 (94.7)
ACE	98 (86.7)
BB	104 (92.0)

ACE, angiotensin-converting enzyme; BB, b-blocker; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension.

Results

Table 1 shows the demographic data and clinical characteristics of 113 patients suffering from stable angina and who were enrolled for elective PCI in the present study.

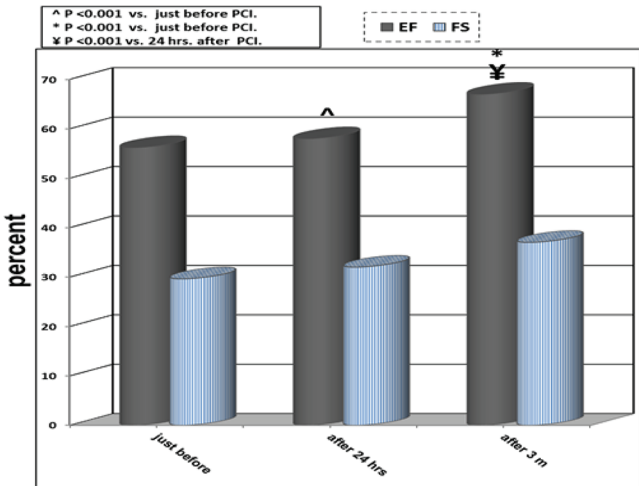
The follow-up results of echocardiography for the studied patients showed a significant increase in EF after 3 months compared with just before and 24 h after PCI (mean = 66.9 ± 7.5 vs. 56.5 ± 6.9% and 57.98 ± 5.99%, $P < 0.001$); in addition, there was a significant increase in EF after 24 h compared with just before PCI ($P < 0.001$). The FS (%) showed a significant increase in FS after 3 months compared with just before and 24 h after PCI (mean = 37.1 ± 6.7 vs. 30.0 ± 5.0% and 31.7 ± 6.3%, $P < 0.001$); in addition, there was a significant increase in FS after 24 h compared with just before PCI ($P < 0.001$) (Fig. 1).

Thyroid function tests for the studied patients revealed a significant increase in TSH after 3 months compared with just before PCI and after 24 h (mean = 3.2 ± 5 mIU/l vs. 1.5 ± 2.1% and 1.47 ± 1.82 mIU/l, $P < 0.001$), whereas there was no significant difference between TSH just before PCI and after 24 h (Fig. 2). There was a significant increase in serum FT3 after 24 h of PCI when compared with just before PCI (mean = 5.2 ± 0.5 vs. 3.3 ± 0.7 pg/ml, $P < 0.001$), whereas there was a significant decrease

in serum FT3 after 3 months compared with after 24 h (mean = 3.2 ± 1.3 vs. 5.2 ± 0.5 pg/ml, $P < 0.001$), whereas no significant difference was observed between just before PCI and after 3 months (Fig. 3). Serum FT4 (ng/dl) had a significant increase in serum FT4 after 3 months compared with just before and after 24 h of PCI (mean = 1.5 ± 0.3 vs. 1.2 ± 0.3 ng/dl and 1.3 ± 0.5 ng/dl, $P < 0.001$). In addition, there was a significant increase in serum FT4 after 24 h compared with just before PCI ($P = 0.043$) (Fig. 4). There was a significant increase in serum FT3/FT4 ratio after 24 h compared with just before PCI ($P = 0.007$); this was followed by a significant decrease in serum FT3/FT4 ratio after 3 months of PCI compared with after 24 h and just before PCI (mean = 2 ± 1.3 vs. 3 ± 0.9 and 2.1–70.9, $P < 0.001$) (Fig. 5). In our study, 24 h after PCI, 2.65% of the patients ($n = 3$) had overt hyperthyroidism, 0.9% ($n = 1$) had subclinical hyperthyroidism, 4.4% ($n = 5$) had subclinical hypothyroidism, and none of the patients had overt hypothyroidism. Three months after PCI, 2.65% of the patients ($n = 3$) had overt hyperthyroidism, 1.7% ($n = 2$) had subclinical hyperthyroidism, 2.65% ($n = 3$) had overt hypothyroidism, and 3.5% ($n = 4$) had subclinical hypothyroidism.

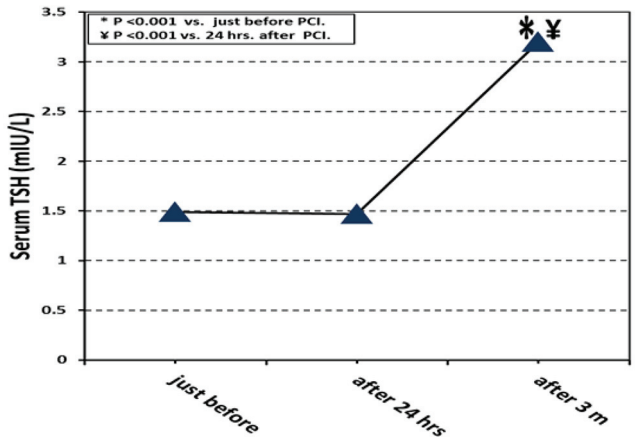
Serum anti-TPO (AU/ml) showed a significant decrease in anti-TPO 24 h after PCI compared with just before PCI (mean = 12.5 ± 12.4 vs. 15.7 ± 16.8 AU/ml, $P < 0.001$), followed by a significant increase

Figure 1



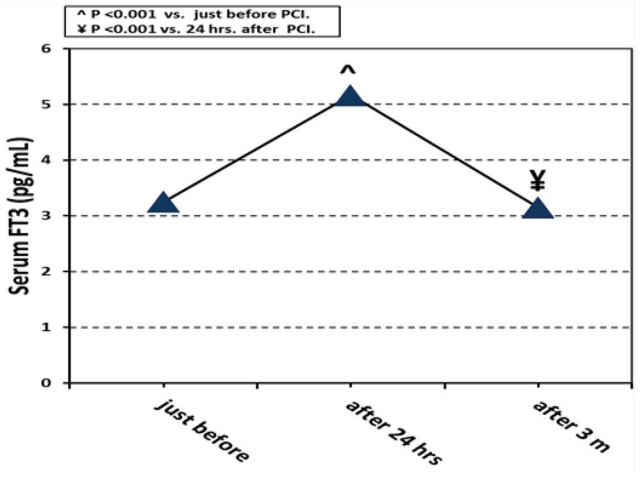
Comparison between ejection fraction (EF) and fraction shortening (FS) in coronary artery disease patients [before and after percutaneous coronary intervention (PCI)].

Figure 2



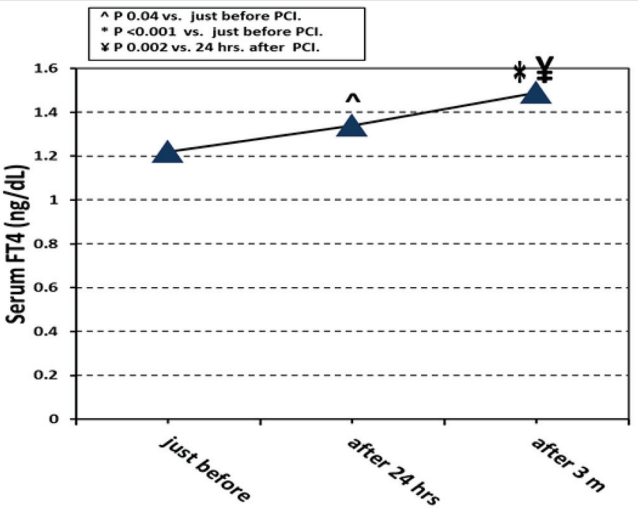
Comparison between mean serum thyroid-stimulating hormone (TSH) levels in coronary artery disease (CAD) patients [before and after percutaneous coronary intervention (PCI)].

Figure 3



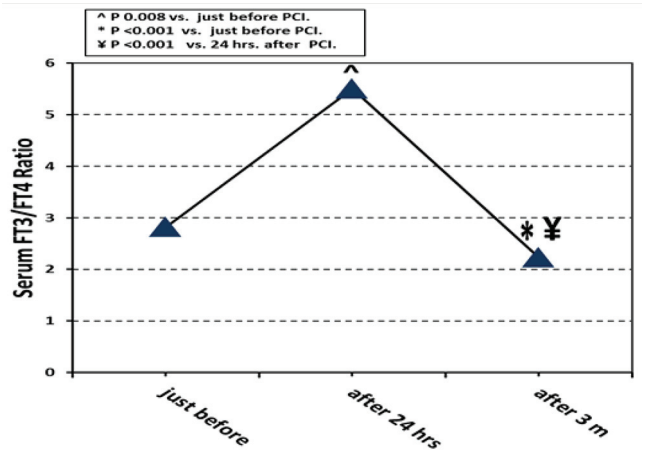
Comparison between mean serum FT3 levels in coronary artery disease (CAD) patients [before and after percutaneous coronary intervention (PCI)].

Figure 4



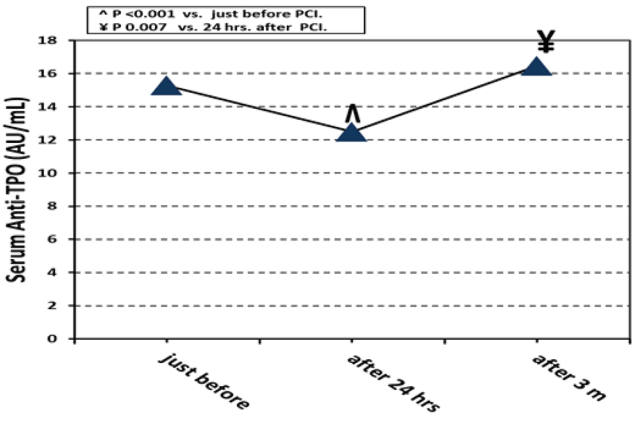
Comparison between mean serum FT4 levels in coronary artery disease (CAD) patients [before and after percutaneous coronary intervention (PCI)].

Figure 5



Comparison between mean serum FT3/FT4 in coronary artery disease (CAD) patients [before and after percutaneous coronary intervention (PCI)].

Figure 6



Comparison between mean serum anti-TPO in coronary artery disease (CAD) patients [before and after percutaneous coronary intervention (PCI)].

in anti-TPO after 3 months when compared with after 24 h post PCI (mean = 16.5 ± 17.8 vs. 12.5 ± 12.4 AU/ml, P = 0.007) (Fig. 6). There was no significant difference regarding serum hsCRP in between the three periods.

Thyroid ultrasonography results

As shown in Table 2, there was a significant increase in the volume of the thyroid gland 3 months after PCI compared with just before PCI (mean = 3.6 ± 3.9 vs. 13.1 ± 3.5 cm^3, P = 0.02). The measured echogenicity of the thyroid gland showed a significant decrease 3 months after PCI compared with just before PCI (mean = 67.1 ± 10.9 vs. 88.7 ± 25.66 GWE, P < 0.001). There was a significant decrease in measured EI in 3 months after PCI compared with just before PCI (mean = 1.5 ± 0.4 vs. 1.60 ± 0.5, P < 0.001). There was a significant decrease in measured HI in 3 months after PCI compared with just before PCI (mean = 40.8 ± 7.8 vs. 51.3 ± 9.5, P < 0.001).

Table 2 Comparison between the ultrasonographic morphological parameters of thyroid gland in coronary artery disease patients (before and after percutaneous coronary intervention)

Thyroid gland U/S	Before (mean ± SD)	After 3 months (mean ± SD)	Test of significance	*P*
Gland volume (ml)	13.05 ± 3.5	13.61 ± 3.9	*t* = 2.3*	0.02*
Echo gland (GWE)	88.7 ± 25.7	67.06 ± 10.9	*t* = 8.5*	<0.001*
EI	1.60 ± 0.5	1.45 ± 0.4	*Z* = 3.5*	<0.001*
HI	51.34 ± 9.5	40.75 ± 7.8	*t* = 11.1*	<0.001*

EI, echogenicity index; HI, heterogeneity index; *t*, paired *t*-test; U/S, ultrasound; *Z*, *Z* for Wilcoxon signed ranks test; *Statistically significant at $P \leq 0.05$.

Percutaneous coronary intervention

One-vessel CAD was found in 43.4% of the patients (n = 49) and multivessel CAD in 56.6% of the patients (n = 64) [two-vessel CAD in 46% (n = 52), three-vessel CAD in 8.8% (n = 10), four-vessel CAD in 0.9% (n = 1), and five-vessel CAD in 0.9% (n = 1)]. Right coronary artery (RCA) was found in 23% of the patients (n = 26), OM in 7.1% of the patients (n = 8), left anterior descending (LAD) in 54.9% of the patients (n = 62), and left circumflex (LCX) in 15.1% of the patients (n = 17). One stent was required in 73.5% of the patients (n = 83), two stents were required in 21.2% (n = 24), and three stents were required in 5.3% (n = 6). The mean stent length (mm) was 26.5 ± 6.1 mm and the mean stent diameter (mm) was 3.2 ± 0.5 mm.

The mean of Entrance Surface Air Kerma was 687.4 ± 325.4 mGy, whereas the calculated thyroid dose of radiation was 557.3 ± 446.6 mGy. The mean number of frames counted was 1117.4 ± 406.9 frames. The mean dye injection time was 57.1 ± 26.7 s, whereas the mean injected volume during PCI was 159 ± 74.9 ml.

Percutaneous coronary intervention outcomes

Clinical outcomes in hospital during the first 24 h and 3 months after PCI were analyzed, as shown in Table 3.

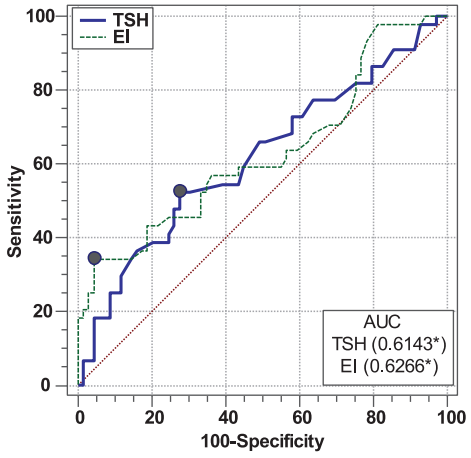
By using univariate analysis of variables, higher EI, higher gland echogenicity, higher TSH, higher hsCRP, smoking, lower FS, lower EF, and younger age appeared to be significant pre-PCI predictors of unfavorable outcomes 24 h after PCI. Multivariate logistic-regression analysis model found only smoking, higher EI, and higher serum TSH to be significant

independent factors predicting unfavorable outcomes (Table 4). The adjusted odds ratio (OR) for TSH level (OR = 1.3, P = 0.04) and EI (OR = 4.41, P = 0.04) indicated that patients with higher TSH had 1.3 times more risk for unfavorable outcomes and those with higher EI had 4.4 times more risk for unfavorable outcomes after adjusting for the effects of other factors.

As shown in Fig. 7, receiver operating characteristic curve was plotted for all thyroid measurements for the determination of the cutoff value for predicting unfavorable outcomes after 24 h. Basal TSH area under the curve was 0.614; the best cutoff value that could predict unfavorable outcomes after 24 h was greater than 0.95 mIU/ml with 52.3% sensitivity and 72.5% specificity. Basal ultrasonographic EI of the gland area under the curve was 0.627; the best cutoff value that could predict unfavorable outcomes after 24 h was greater than 1.81 with 35.8% sensitivity and 92.8% specificity.

Multivariate logistic-regression analysis model found only serum FT3, FT4, and age-significant independent factors that could predict unfavorable outcomes. The adjusted OR for serum FT3 level (OR = 0.4, P = 0.02) indicated that patients with 1 ng/dl decrease in serum FT3 level carried a 42% risk for unfavorable outcomes after adjusting for the effects of other factors. Adjusted OR for serum FT4 level (OR = 6.6, P = 0.04) indicated that patients with every 1 pg/ml increase in serum FT4 level carried 6.6 times the risk for unfavorable outcomes after adjusting for the effects of other factors. Furthermore, adjusted OR for age (OR = 0.914, P = 0.03) indicated that younger patients had a 91% risk for unfavorable outcomes after adjusting for the effects of other factors (Table 5).

Figure 7



Receiver operating characteristic (ROC) curve for echogenicity of thyroid; Echogenicity index (EI); and serum thyroid-stimulating hormone (TSH) before percutaneous coronary intervention (PCI) as predictors to 24 h post-PCI outcomes.

Table 3 Comparison between outcomes 24 h and 3 months after percutaneous coronary intervention

Unfavorable outcome	After 24 h (in hospital) [*n* (%)]	After 3 months [*n* (%)]	*P*
CIN	3 (2.7)	0 (0.0)	0.25
Vascular	0 (0)	—	—
Thrombosis	0 (0)	0 (0)	—
Instant restenosis	0 (0.0)	4 (3.6)	0.05
Arrhythmia	5 (4.4)	0 (0.0)	0.06
MACE	0 (0)	8 (7.1)	—
NTVR	0 (0)	3 (2.65)	
MI	0 (0)	4 (3.55)	—
Stroke	0 (0)	1 (0.9)	
Hospital readmission	—	11 (9.7)	—
Heart failure (DEF and EF <50)			
Not improved and <50	39 (34.51)	12 (10.62)	0.00

χ^2, χ^2 for McNemar test; CIN, contrast-induced nephropathy; EF, ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction; *Statistically significant at $P \leq 0.05$.

Table 4 Binary logistic regression for factors affecting unfavorable outcomes 24 h after percutaneous coronary intervention

Predictor	*B*	S.E	Adjusted *P*	OR	95% CI	
					LL	UL
EI	1.53	0.72	0.03	4.41	1.08	18.06
TSH	0.23	0.11	0.03	1.26	1.01	1.56
Smoking	2.35	0.76	0.002	10.45	2.34	46.57

B, unstandardized coefficients; CI, confidence interval; EI,echogenicity index; LL, lower limit; OR, odds ratio; TSH, thyroid-stimulating hormone; UL, upper limit.

Table 5 Binary logistic regression for factors affecting percutaneous coronary intervention outcomes after 3 months

Predictor	*B*	SE	*P*	OR	95% CI	
					LL	UL
Serum FT3	−0.87	0.38	0.02*	0.42	0.20	0.87
Serum FT4	1.88	0.89	0.04*	6.56	1.14	37.78
Age	−0.09	0.04	0.03*	0.91	0.85	0.99

B, unstandardized coefficient; CI, confidence interval; LL, lower limit; OR, odds ratio; UL, upper limit; *Statistically significant at $P \leq 0.05$.

The impact of percutaneous coronary intervention on thyroid parameters 24 h after percutaneous coronary intervention

Pearson's bivariate correlation coefficients were used to assess for the existence of any significant relationships between dose of radiation, iodinated contrast, and manipulations during PCI on the one hand and thyroid gland functions 24 h after PCI on the other (Table 6).

To assess the independent effects of the variables on serum TSH level after 24 h of PCI, a backward multiple linear regression analysis model was used. The model showed that stent diameter and length were the most important factors affecting serum TSH levels after 24 h of PCI [β = −1.245 (P < 0.001) and β = −0.077

(P = 0.003), respectively]; every 1 mm increase in stent diameter decreased the serum TSH level by 1.25 mIU/l, and every 1 mm increase in stent length decreased serum TSH levels by 0.08 mIU/l. The hsCRP, as a surrogate marker for manipulation, affects serum TSH levels after 24 h of PCI (β = 0.0008, P = 0.002); every 1 mg/l increase in hsCRP increases serum TSH levels by 0.83 mIU/l. Thus, the inflammatory state induced by manipulations and stents during PCI were the main regulators of serum TSH levels after 24 h of PCI.

Radiation had a negative effect on serum FT3, and a positive influence on serum FT3/FT4 ratio and anti-TPO. Dye injection time correlated positively with serum anti-TPO and negatively with serum FT4.

The impact of percutaneous coronary intervention on thyroid parameters 3 months after percutaneous coronary intervention

Thyroid radiation had a negative effect on serum TSH, anti-TPO, FT3, and FT3/FT4 ratio (Table 7). Dye injection time negatively correlated with serum anti-TPO and TSH.

Discussion

Twenty-four hours after PCI, we found a state of euthyroid hyperthyroxinemia in our patients, mostly because of increased peripheral conversion, which was not associated with autoimmune thyroiditis as

Table 6 Bivariate correlation between acute effects of different parameters during percutaneous coronary intervention with hormonal parameters 24 h after percutaneous coronary intervention in coronary artery disease patients

Parameters	Radiation effect			Dye	Manipulation			
	ESAK	Thyroid radiation dose	Frames no.	Dye injection time	CRP 24 h	Stent no.	St length	St diameter
TSH								
r	−0.08	0.05	−0.01	−0.03	0.27*	−0.16	−0.30*	−0.25*
P	0.37	0.56	0.89	0.74	0.003	0.08	0.001	0.006
Serum FT3								
r	−0.02	−0.10	−0.00	0.06	0.25*	0.08	0.19*	0.08
P	0.78	0.25	0.98	0.51	0.01	0.37	0.04	0.40
Serum FT4								
r	−0.53*	−0.42*	−0.37*	−0.35*	0.15	−0.09	−0.12	−0.01
P	<0.001	<0.001	<0.001	<0.001	0.09	0.34	0.17	0.83
Serum FT3/FT4								
r	0.37*	0.28*	0.17	0.12	−0.05	0.18*	0.15	−0.01
P	<0.001	<0.001	0.07	0.18	0.56	0.04	0.09	0.92
Serum anti-TPO								
r	0.20*	0.36*	0.23*	0.24*	0.06	−0.01	0.2*	0.01
P	0.03	<0.001	0.01	0.01	0.47	0.87	0.02	0.92

CRP, C-reactive protein; ESAK, Entrance Surface Air Kerma; *r*, Pearson coefficient; TSH, thyroid-stimulating hormone; *Statistically significant at $P \leq 0.05$.

Table 7 Bivariate correlation between long-term effect of different parameters during percutaneous coronary intervention with thyroid status 3 months after percutaneous coronary intervention

Parameters	Radiation effect			Dye	Manipulations			
	ESAK	Thyroid radiation dose	Frames no.	Dye injection time	CRP 24 h	Stent no.	Stent length	Stent diameter
Serum TSH								
r	−0.28	−0.10	−0.19	−0.25	−0.02	−0.05	−0.06	0.06
P	0.002*	0.26	0.04*	0.008*	0.85	0.58	0.51	0.50
Serum FT3								
r	−0.03	−0.26	−0.12	−0.12	−0.04	0.04	−0.05	0.05
P	0.74	0.005*	0.22	0.2	0.63	0.63	0.57	0.54
Serum FT4								
r	−0.00	−0.07	−0.02	0.04	0.06	0.32*	0.09	−0.12
P	0.97	0.41	0.85	0.68	0.52	<0.001	0.29	0.19
Serum FT3/FT4								
r	−0.02	−0.22	−0.09	−0.13	−0.06	−0.06	−0.10	0.10
P	0.79	0.02*	0.31	0.18	0.51	0.47	0.27	0.26
Serum anti-TPO								
r	−0.24	−0.10	−0.16	−0.21	0.07	0.007	0.001	0.01
P	0.01*	0.24	0.09	0.02*	0.76	0.74	0.62	0.7

CRP, C-reactive protein; ESAK, Entrance Surface Air Kerma; *r*, Pearson coefficient; TSH, thyroid-stimulating hormone; *Statistically significant at $P \leq 0.05$.

evidenced by no change in TSH, significant increase in serum FT3 above the normal limit, and a mild increase in serum FT4 associated with a mild decrease in serum anti-TPO. Three months after PCI, we found a state of TH resistance, mostly due to decreased peripheral conversion, and was associated with autoimmune thyroiditis 3 months after PCI as evidenced by significant increase in serum TSH, significant decrease in serum FT3 returning to the baseline level, and a continuous increase in serum FT4 associated with an increase in serum anti-TPO returning to baseline level, which was not affected by PCI parameters. Ultrasonographic examination of the thyroid gland 3 months after PCI revealed an increase in the volume of the thyroid gland associated with a significant decrease in the measured echogenicity, EI, and measured HI. Higher serum TSH and measured EI were independent pre-PCI predictors of unfavorable outcomes after 24 h with cutoff values greater than 0.95 mIU/ml and greater than 1.81, respectively. Lower serum FT3 and higher serum FT4 levels were independent pre-PCI predictors of unfavorable outcomes after 3 months with cut-off values less than or equal to 2.95 pg/ml and greater than 1.3 ng/dl, respectively.

A reduction in TSH and free T3, with an increase in free T4 after CA, was observed in a study by Marraccini *et al.* [21], who enrolled 1752 consecutive patients admitted for CA and measured their thyroid functions before CA and 24 h after it, and then the patients were followed up for an average duration of 63.5 months. Another study showed a significant decrease in TSH concentration with a corresponding increase in FT3 concentration 4 weeks after single iodine administration during CA. During the 3 months, FT3 concentration returned to its normal range, although the level of TSH took 6 more months to normalize [22]. A study by Özkan *et al.* [23] revealed significant decrease following CA in TSH levels, but no statistically significant changes were found in serum free T3 and serum free T4 levels at week 4 compared with baseline FT3 and FT4 levels. Moreover, in their study, Conn *et al.* [24] examined the thyroid function following the injection of nonionic contrast agent in 51 participants who had undergone CA; it showed that FT4 levels increased 8 weeks after CA, TSH values decreased, and no significant change occurred in T3 levels. On the other hand, Balbay and Cay in their study examined 50 euthyroid patients who underwent elective CA. Thyroid functions (TSH, FT3, and FT4) were examined before the study was initiated and 1 month after the procedure, and it decreased significantly within the normal range [25].

The main differences between previous studies and the current study were that most of the enrolled patients had CA, which is not comparable to PCI, absent ultrasonographic assessment, and a nonunified period of follow-up.

The early TH profile after PCI (normal TSH, high FT4, high FT3) was mostly accounted for by confounding effects of drugs (e.g. heparin including low molecular weight) and nonsteroidal anti-inflammatory agents, which are capable of displacing T4 and T3 from TH binding sites on thyroid binding globulin (TBG) leading to an increase in free TH plasma concentration [26]. In addition, it is not uncommon to find elevated FT4 levels with totally variable FT4 and FT3 levels in the early phase of thyroiditis [27]. Changes in TH (especially FT3) and TSH may be seen as early as 24 h after the onset of nonthyroidal illness syndrome (NTIS) [28]. The thyroid gland function in NTIS, determined according to the duration of the stressor action, is characterized by biphasic behavior [29]. First, an increase in T4 and T3 were observed, and then prolonged stress decreased the levels of TH (or T3 only) [30]. Reduced tissue/cellular uptake of T4 and T3 is mostly due to altered deiodinase (DIO) activity with reduced DIO1 but increased DIO2 and DIO3 [31] and altered TH receptor expression/signaling (e.g. reduced in skeletal muscle) [32]. Furthermore, acute stress may increase the brain T3 content in male and female rats by 12–19% [33].

Iodine administration to patients with underlying thyroid disease may lead to hypersecretion of THs, a phenomenon known as the Jod–Basedow effect, which develops over 2–12 weeks and persists for a longer period as the iodine is used as a substrate for new hormone formation [34]. But our patients developed hyperthyroxinemia of very rapid onset following exposure to iodinated contrast used during PCI. The rapidity and severity of hyperthyroxinemia suggested acute, destructive thyroiditis [35]. A necrotic effect of iodide excess has been demonstrated in vivo in various animal species and also in human thyroid follicles *in vitro* [36]. Difference between the two forms of iodine-induced increase in TH synthesis (Jod–Basedow hyperthyroidism) and iodine-induced cytotoxic damage of the thyroid gland (subacute destructive thyroiditis), with subsequent leakage of iodothyronines into the circulation, is detected mainly through electron microscopy characteristically [37]. The significant decrease in anti-TPO may be related to the observed decrease in TPO mRNA 24 h after acute iodide administration [38]. It seems reasonable to assume that the anti-inflammatory effect of iodide is based on its radical scavenging, with small contributions from other components in other stages of the inflammatory cascade [39].

C-reactive protein (CRP) did change significantly throughout the current study; however, it correlated positively with TSH and FT3. Importantly, PCI itself caused an acute vascular and systemic inflammatory response induced by stent implantation, plaque rupture, the endothelial damage, and barotrauma to the vessel wall [40,41]. This inflammation gets diminished by potent preprocedural antiplatelet (glycoprotein IIb/IIIa inhibitors, clopidogrel, and other P2Y12 inhibitors) and statin therapy, which might account for nonsignificant hsCRP changes in the current study [42]. CRP is known to be elevated in patients with hypothyroidism and hyperthyroidism. Several signs and symptoms in patients with thyroid dysfunction suggest a state of inflammation resulting from an interaction of interleukin-6 (IL-6) on tumor necrosis factor-a and IL-1 ending by elevated CRP [43,44]. IL-6 stimulates the production of CRP and other acute-phase proteins in the liver [45], which in turn suppress TSH — for example, IL-1 [46], and tumor necrosis factor [47].

The extreme radiosensitivity of the thyroid is evident. The ionizing radiation regulation recommends a dose limit of 300 mGy for thyroid gland for a year duration, which is lower than what we detected (557.3 ± 446.6 mGy) [48]. Many studies have reported acutely decreased TSH and increased T4 levels, the former occurring shortly after radiation therapy and the latter during treatment, which may indicate greater cell sensitivity, thus explaining negative correlation with serum FT4 with a dose of radiation. Patients may develop hyperthyroid or hypothyroid clinically and biochemically with a low radioiodine uptake [49,50]. A possible change mechanism of radiation-induced thyroid function is to direct cellular damage, exposing the immune system, and leading to the production of autoantibodies or overactivation of T-helper lymphocytes [51]. The negative correlation of radiation and anti-TPO can be attributed to the domination of male participants in the present study. Low frequency of increased anti-TPO levels in the male subpopulation was observed in a number of other studies [52,53].

The late TH profile after PCI (high TSH, high FT4, normal FT3) was mostly accounted by iodine effect, which leads to a state of acquired resistance to TH [54]. Short-lived rises in TSH are common during the first few months of iodine effect. The principal effect of some iodine-containing radiologic contrast media is the inhibition of T4 to T3 conversion by inhibiting both DIO1 and DIO2, which leads to persistent elevation of FT4, but normal FT3 with pituitary insensitivity to FT3 [55].

Recovery phase of NTIS results in discordant TSH/FT4 values for certain duration. During recovery from intercurrent illness, TH and TSH concentrations return to normal. However, it was reported for some patients that TSH may remain elevated for a short period of time, which precedes the elevation in T4 and T3 level, suggesting that it is required for the restoration of euthyroidism [26,56]. This elevation of TSH strongly suggests that the patients are recovering from a hypothyroid state, during which the ability of the pituitary to respond has been temporarily inhibited [57]. The simplest and probably the earliest method to exploit existing knowledge about thyroid homeostasis for diagnostic purposes is calculating the T3/T4 ratio [58]. It was shown that this parameter is reduced in nonthyroidal illness [59]. In addition, reduced T3/T4 ratio in central hypothyroidism is another hint for the stimulating role of TSH for deiodination [60].

Chronic radiation effect most commonly causes hypothyroidism [61]. The incidence of clinical and subclinical hypothyroidism varies substantially (4–49%), according to the techniques, doses, and frequency of radiation [62,63]. The development of thyroid autoantibodies may result from secretion of antigens after injury induced by thyroid radiation [64,65].

As regards the effect of PCI on ultrasonographic morphology of the thyroid gland 3 months after the procedure, the present study revealed an increase in the volume of the thyroid gland, associated with a decrease in measured echogenicity, EI, and HI. All of these may be accounted for; iodide-induced goiter (iodide goiter), without or with hypothyroidism (iodide myxedema), is encountered with a greater frequency in patients with Hashimoto's thyroiditis or previously treated Graves' disease [66]. A prospective study was conducted on 10 normal male volunteers to investigate the effect of excessive administration of iodide on the thyroid volume. The thyroid gland became significantly enlarged after 28 days of iodide intake. When iodide was discontinued, thyroid volume and function returned to baseline levels within 1 month for all participants [67].

Increased TSH affects gland morphology as hypoechogenicity of the thyroid gland is associated with increased TSH in patients with Hashimoto's thyroiditis [68]. In their study, Vejbjerg and colleagues found a strong negative association between TSH level and thyroid echogenicity (i.e. the higher the TSH level, the lower the thyroid echogenicity). Furthermore, they found that heterogeneous echotexture of thyroid gland was associated with an increased TSH level [69].

Pre-PCI thyroid gland parameters as predictors for PCI outcomes: The distinction between normal and abnormal thyroid function is not as clear-cut

as was once believed. Some studies have observed a relationship between FT4 and TSH levels and the presence or severity of coronary heart disease [70,71]. High serum TSH would predict all-cause and circulatory mortality in subjects with invasively treated coronary artery disease compared to euthyroid subjects [72]. Previous studies have demonstrated an increased risk for all-cause and circulatory mortality in patients with high serum TSH [73,74]. However, other studies showed similar [75] or decreased [76] mortality risk in patients with higher TSH level compared with reference participants.

Low T3 syndrome and hypothyroidism were associated with a higher prevalence of coronary heart disease, more serious coronary artery lesions, and poorer prognosis compared with euthyroidism, especially in cardiac patients undergoing CA [77]. A study by Marraccini *et al.* [21] indicated that hypothyroidism and low T3 syndrome had a significantly worse prognosis both for the over-all and cardiac death as compared with euthyroidism.

Moreover, high FT4 level was a significant independent factor predicting unfavorable outcomes. A study by Jung and colleagues showed that serum FT4 levels were associated with the presence and severity of CAD in Korean population. Another study evaluated 3885 men without thyroid disease, and then followed them up for 6.4 ± 1.5 years. The conclusion was that higher circulating FT4 levels, not TSH, could predict all-cause mortality in euthyroid elderly men [78].

Conclusion

A state of euthyroid hyperthyroxinemia was mostly due to an increased peripheral conversion and was not associated with autoimmune thyroiditis 24 h after PCI. There was a state of TH resistance in our patients, mostly due to a decreased peripheral conversion, and was associated with autoimmune thyroiditis 3 months after PCI. Increase in the volume of the thyroid gland was associated with significant decrease in measured echogenicity, EI, and measured HI, as well as a significant decrease in the number of nodules with an increase in echogenicity of nodules. Higher serum TSH and measured EI were independent pre-PCI predictors of unfavorable outcomes after 24 h with cutoff values greater than 0.95 mIU/ml and greater than 1.81, respectively. Lower serum FT3 and higher serum FT4 level were independent pre-PCI predictors of 3 months unfavorable outcomes with cut-off values less than or equal to 2.95 pg/ml and greater than 1.3 ng/dl, respectively.

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Conflicts of interest

There are no conflicts of interest.

References

1 Bernal J, Guadaño-Ferraz A, Morte B. Thyroid hormone transporters — functions and clinical implications. Nat Rev Endocrinol 2015; 11:406–417.

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

3 Collet TH, Gussekloo J, Bauer DC, *et al.* Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Intern Med 2012; 172:799–809.

4 Bai MF, Gao CY, Yang CK. Effects of thyroid dysfunction on the severity of coronary artery lesions and its prognosis. J Cardiol 2014; 64:496–500.

5 Jarvis C, Simcox K, Tamatea JA. A low incidence of iodine-induced hyperthyroidism following administration of iodinated contrast in an iodine-deficient region. Clin Endocrinol (Oxf) 2015; [Epub ahead of print]

6 Jostel A, Ryder WD, Shalet SM. The use of thyroid function tests in the diagnosis of hypopituitarism: definition and evaluation of the TSH Index. Clin Endocrinol (Oxf) 2009; 71:529–534.

7 Grunenwald S, Caron P. Central hypothyroidism in adults: better understanding for better care. Pituitary 2015; 18:169–175.

8 Höfling DB, Cerri GG, Juliano AG, *et al.* Echogenicity value of thyroid on the chronic autoimmune thyroiditis diagnosis. Radiol Bras 2009; 41:409–417.

9 Loy M, Cianchetti E, Cardia F. Correlation of computerized gray-scale sonographic findings with thyroid function and thyroid autoimmune activity in patients with Hashimoto's thyroiditis. J Clin Ultrasound 2004; 32:136–140.

10 Höfling DB, Chavantes MC, Juliano AG. Low-level laser in the treatment of patients with hypothyroidism induced by chronic autoimmune thyroiditis: a randomized, placebo-controlled clinical trial. Lasers Med Sci 2013; 28:743–753.

11 Wakita Y, Nagasaki T, Nagata Y, *et al.* Thyroid heterogeneity, as indicated by the CV of ultrasonographic intensities, correlates with anti-thyroid peroxidase antibodies in euthyroid Hashimoto's thyroiditis. Thyroid Res 2013; 6:5.

12 Rasband WS, Image J. U.S. National Institutes of Health, Bethesda, Maryland, USA. Available at: *http://rsb.Info.nih.gov/ij/* [Accessed 11 February 2015]

13 Ram HS, Ram S. Image J analysis of amniotic fluid echogenicity and labor. Int J Gynaecol Obstet 2013; 17:1–7. Available at: *https://ispub.com/IJGO/17/3/14517*. [Accessed 14 March 2015]

14 Mazziotti G, Sorvillo F, Iorio S, *et al.* Grey-scale analysis allows a quantitative evaluation of thyroid echogenicity in the patients with Hashimoto's thyroiditis. Clin Endocrinol (Oxf) 2003; 59:223–229.

15 Baim DS. Percutaneous balloon angioplasty and general coronary intervention. In: Baim DS *Grossman's cardiac catheterization, angiography and intervention*. Philadelphia: Lippincott Williams & Wilkins; 2005. 433–466.

16 Stone GW, Colombo A, Teirstein PS, *et al.* Percutaneous recanalization of chronically occluded coronary arteries: procedural techniques, devices, and results. Catheter Cardiovasc Interv 2005; 66:217–236.

17 Wang W, Zhang M, Zhang Y. Overall measurements of dose to patients in common interventional cardiology procedures. Radiat Prot Dosimetry 2013; 157:348–354.

18 Kramer R, Khoury HJ, Vieira JW. CALDose_X-a software tool for the assessment of organ and tissue absorbed doses, effective dose and cancer risks in diagnostic radiology. Phys Med Biol 2008; 53:6437–6459.

19 Roghani F, Mehrabi Koushki A, Nezarat N, *et al.* The correlation between early complications of percutaneous coronary intervention and high sensitive C-reactive protein. ARYA Atheroscler 2013; 9:263–267.

20 Toutouzas K, Karanasos A, Stefanadis C. Inflammatory mechanisms of adverse reactions to BMS. Curr Vasc Pharmacol 2013; 11:379–391.

21 Marraccini P, Bianchi M, Bottoni A, *et al.* Prevalence of thyroid dysfunction and effect of contrast medium on thyroid metabolism in cardiac patients undergoing coronary angiography. Acta Radiol 2012; 54:42–47.

22 Skórkowska-Telichowska K, Kosińska J, Szymczak R, *et al.* Comparison and assessment of thyroid morphology and function in inhabitants of Lower Silesia before and after administration of a single dose of iodine-containing contrast agent during cardiac intervention procedure. Endokrynol Pol 2012; 63:294–299.

23 Özkan S, Oysu AS, Kayataş K, *et al.* Thyroid functions after contrast agent administration for coronary angiography: a prospective observational study in euthyroid patients. Anadolu Kardiyol Derg 2013; 13:363–369.

24 Conn JJ, Sebastian MJ, Deam D, *et al.* A prospective study of the effect of nonionic contrast media on thyroid function. Thyroid 1996; 6:107–110.

25 Balbay Y, Cay S. Does coronary angiography induce clinically relevant changes in thyroid function parameters of euthyroid patients after one month? Health Med 2012; 6:259–262.

26 Koulouri O, Moran C, Halsall D, *et al.* Pitfalls in the measurement and interpretation of thyroid function tests. Best Pract Res Clin Endocrinol Metab 2013; 27:745–762.

27 Beckett GJ. Thyroid function and thyroid function tests in non-thyroidal illness. CPD Bulletin: Clin Biochem 2006; 7:107–116.

28 Warner MH, Beckett GJ. Mechanisms behind the non-thyroidal illness syndrome: an update. J Endocrinol 2010; 205:1–13.

29 Belyakova EI, Mendzheritskii AM, *et al.* Adrenocortical and thyroid systems of rats during the initial period of nociceptive influences. Neurosci Behav Physiol 2006; 36:561–564.

30 Helmreich DL, Tylee D. Thyroid hormone regulation by stress and behavioral differences in adult male rats. Horm Behav 2011; 60:284–291.

31 St Germain DL, Galton VA, Hernandez A. Minireview: defining the roles of the iodothyronine deiodinases: current concepts and challenges. Endocrinology 2009; 150:1097–1107.

32 Lado-Abeal J, Romero A, Castro-Piedras I, *et al.* Thyroid hormone receptors are down-regulated in skeletal muscle of patients with non-thyroidal illness syndrome secondary to non-septic shock. Eur J Endocrinol 2010; 163:765–773.

33 Friedman Y, Bacchus R, Raymond R, *et al.* Acute stress increases thyroid hormone levels in rat brain. Biol Psychiatry 1999; 45:234–237.

34 Leung AM, Braverman LE. Iodine-induced thyroid dysfunction. Curr Opin Endocrinol Diabetes Obes 2012; 19:414–419.

35 Rhee CM, Bhan I, Alexander EK, *et al.* Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism. Arch Intern Med 2012; 172:153–159.

36 Many MC, Mestdagh C, Van den Hove MF, *et al.* In vitro study of acute toxic effects of high iodide doses in human thyroid follicles. Endocrinology 1992; 131:621–630.

37 Cappiello E, Boldorini R, Tosoni A, *et al.* Ultrastructural evidence of thyroid damage in amiodarone-induced thyrotoxicosis. J Endocrinol Invest 1995; 18:862–868.

38 Eng PH, Cardona GR, Fang SL, *et al.* Escape from the acute Wolff-Chaikoff effect is associated with a decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein. Endocrinology 1999; 140:3404–3410.

39 Beukelman CJ, Van den Berg AJ, Hoekstra MJ, *et al.* Anti-inflammatory properties of a liposomal hydrogel with povidone-iodine (Repithel) for wound healing in vitro. Burns 2008; 34:845–855.

40 Saleh N, Tornvall P. Serum C-reactive protein response to percutaneous coronary intervention in patients with unstable or stable angina pectoris is associated with the risk of clinical restenosis. Atherosclerosis 2007; 195:374–378.

41 Munk PS, Breland UM, Aukrust P, *et al.* Inflammatory response to percutaneous coronary intervention in stable coronary artery disease. J Thromb Thrombolysis 2011; 31:92–98.

42 Yu XL, Zhang HJ, Ren SD, *et al.* Effects of loading dose of atorvastatin before percutaneous coronary intervention on periprocedural myocardial injury. Coron Artery Dis 2011; 22:87–91.

43 Czarnywojtek A, Owecki M, Zgorzalewicz-Stachowiak M, *et al.* The role of serum C-reactive protein measured by high-sensitive method in thyroid disease. Arch Immunol Ther Exp (Warsz) 2014; 62:501–509.

44 Pearce EN, Bogazzi F, Martino E, *et al.* The prevalence of elevated serum C-reactive protein levels in inflammatory and noninflammatory thyroid disease. Thyroid 2003; 13:643–648.

45 Azar RR, Badaoui G, Sarkis A, *et al.* Effects of tirofiban and statins on high-sensitivity C-reactive protein, interleukin-6, and soluble CD40 ligand following percutaneous coronary interventions in patients with stable coronary artery disease. Am J Cardiol 2005; 95:236–240.

46 Hermus RM, Sweep CG, van der Meer MJ, *et al.* Continuous infusion of interleukin-1 beta induces a non-thyroidal illness syndrome in the rat. Endocrinology 1992; 131:2139–2146.

47 Van der Poll T, Romijn JA, Wiersinga WM, *et al.* Tumor necrosis factor: a putative mediator of the sick euthyroid syndrome in man, J Clin Endocrinol Metab 1990; 71:1567–1572.

48 Devalia KL, Guha A, Devadoss VG. The need to protect the thyroid gland during image intensifier use in orthopaedic procedures. Acta Orthop Belg 2004; 70:474-477.

49 Mittra ES, Niederkohr RD, Rodriguez C, *et al.* Uncommon causes of thyrotoxicosis. J Nucl Med 2008; 49:265–278.

50 Bakhshandeh M, Hashemi B, Mahdavi SR, *et al.* Evaluation of thyroid disorders during head-and-neck radiotherapy by using functional analysis and ultrasonography. Int J Radiat Oncol Biol Phys 2012; 83:198–203.

51 Jereczek-Fossa BA, Alterio D, Jassem J, *et al.* Radiotherapy-induced thyroid disorders. Cancer Treat Rev 2004; 30:369–384.

52 Knudsen N, Jorgensen T, Rasmussen S, Christiansen E, Perrild H. The prevalence of thyroid dysfunction in a population with borderline iodine deficiency. Clin Endocrinol (Oxf) 1999; 51:361–367.

53 Völzke H, Werner A, Wallaschofski H, *et al.* Occupational exposure to ionizing radiation is associated with autoimmune thyroid disease. J Clin Endocrinol Metab 2005; 90:4587-4592.

54 Gurnell M, Halsall DJ, Chatterjee VK. What should be done when thyroid function tests do not make sense? Clin Endocrinol (Oxf) 2011; 74:673–678.

55 Gallagher AE, Panciera DL. Efficacy of iopanoic acid for treatment of spontaneous hyperthyroidism in cats. J Feline Med Surg 2011; 13:441–447.

56 Hamblin PS, Dyer SA, Mohr VS, *et al.* Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. J Clin Endocrinol Metab 1986; 62:717–722.

57 Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid 2014; 24:1456–1465.

58 Dietrich JW, Landgrafe G, Fotiadou EH. TSH and thyrotropic agonists: key actors in thyroid homeostasis. J Thyroid Res 2012; 2012:351864.

59 Gereben B, Zavacki AM, Ribich S, *et al.* Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. Endocr Rev 2008; 29:898-938.

60 Sesmilo G, Simó O, Choque L, *et al.* Serum free triiodothyronine (T3) to free thyroxine (T4) ratio in treated central hypothyroidism compared with primary hypothyroidism and euthyroidism. Endocrinol Nutr 2011; 58:9–15.

61 Bonato C, Severino RF, Elnecave RH. Reduced thyroid volume and hypothyroidism in survivors of childhood cancer treated with radiotherapy. J Pediatr Endocrinol Metab 2008; 21:943–949.

62 Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 1991; 325:599-605.

63 Demirkaya M, Sevinir B, Sağlam H, *et al.* Thyroid functions in long-term survivors of pediatric Hodgkin's lymphoma treated with chemotherapy and radiotherapy. J Clin Res Pediatr Endocrinol 2011; 3:89–94.

64 Sklar C, Whitton J, Mertens A, *et al.* Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2000; 85: 3227–3232.

65 Lin Z, Chen L, Fang Y, *et al.* Longitudinal study on the correlations of thyroid antibody and thyroid hormone levels after radiotherapy in patients with nasopharyngeal carcinoma with radiation-induced hypothyroidism. Head Neck 2014; 36:171–175.

66 Bürgi H. Iodine excess. Best Pract Res Clin Endocrinol Metab 2010; 24:107–115.

67 Namba H, Yamashita S, Kimura H, *et al.* Evidence of thyroid volume increase in normal subjects receiving excess iodide. J Clin Endocrinol Metab 1993; 76:605–608.

68 Schiemann U, Avenhaus W, Konturek J, *et al.* Relationship of clinical features and laboratory parameters to thyroid echogenicity measured by standardized grey scale ultrasonography in patients with Hashimoto's thyroiditis. Med Sci Monit 2003; 9:MT49.

69 Vejbjerg P, Knudsen N, Perrild H, *et al.* The association between hypoechogenicity or irregular echo pattern at thyroid ultrasonography and thyroid function in the general population. Eur J Endocrinol 2006; 155:547.

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

71 Jung CH, Rhee EJ, Shin HS, *et al.* Higher serum free thyroxine levels are associated with coronary artery disease. Endocr J 2008; 55:819–826.

72 Völzke H, Menzel D, Henzler J. Serum thyrotropin levels predict all-cause and circulatory mortality in patients with invasively treated coronary artery disease. Int J Cardiol 2009; 133: 407–410.

73 Imaizumi M, Akahoshi M, Ichimaru S, *et al.* Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. J Clin Endocrinol Metab 2004; 89:3365–3370.

74 Walsh JP, Bremner AP, Bulsara MK, *et al.* Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Intern Med 2005; 165:2467–2472.

75 Van den Beld AW, Visser TJ, Feelders RA, *et al.* Thyroid hormone concentrations, disease, physical function, and mortality in elderly men. J Clin Endocrinol Metab 2005; 90:6403–6409.

76 Gussekloo J, Van Exel E, De Craen AJ, *et al.* Thyroid status, disability and cognitive function, and survival in old age. JAMA 2004; 292:2591–2599.

77 Iervasi G, Pingitore A, Landi P. Low T3 syndrome a strong prognostic predictor of death in patients with heart disease. Circulation 2003; 107:708–713.

78 Yeap BB, Alfonso H, Hankey GJ, *et al.* Higher free thyroxine levels are associated with all-cause mortality in euthyroid older men: the Health In Men Study. Eur J Endocrinol 2013; 169: 401–408.