Original Article

Negative association between free triiodothyronine level and international normalized ratio in euthyroid subjects with acute myocardial infarction

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Aim: To investigate the relationship between free triiodothyronine (FT3) and the international normalized ratio (the ratio of the prothrombin time of a patient to the normal sample, INR) in Chinese euthyroid subjects with acute ST-segment elevation myocardial infarction (STEMI).

Methods: A total of 231 consecutive patients (177 males, 54 females) with STEMI were enrolled. Anthropometric and laboratory measurements, including heart rate, respiratory rate, blood pressure, body temperature, platelet count, INR, prothrombin time, activated partial thromboplastin time, FT3, free thyroxine (FT4), and thyroid-stimulating hormone, were collected from all the patients. The levels of FT3 and FT4 were measured with a full-automatic immune analyzer. The INR was determined using a coagulation analyzer. **Results:** Patients were classified into 4 groups according to their quartile FT3 and FT4 levels: 0.40-3.09 (n=52), 3.10-3.69 (n=56), 3.70-4.29 (n=64) and 4.30-7.10 (n=59) for FT3; 4.9-14.8 (n=57), 14.9-16.8 (n=58), 16.9-18.7 (n=57) and 18.8-29.0 (n=59) for FT4. Subjects with a high FT3 level had significantly lower values of INR than those with a low FT3 level (P=0.01). Multiple linear regression analysis revealed decreased serum FT3 as an independent risk factor for elevated INR values ($\beta=-0.139$, P=0.025). The value of INR was similar among the 4 groups according to the quartile FT4 levels (P=0.36).

Conclusion: Free triiodothyronine was negatively associated with INR in the patients with acute STEMI and normal thyroid function.

Keywords: free triiodothyronine; free thyroxine; prothrombin time; international normalized ratio; acute ST elevation myocardial infarction; Chinese euthyroid subject

Acta Pharmacologica Sinica (2011) 32: 1351-1356; doi: 10.1038/aps.2011.118; published online 3 Oct 2011

Introduction

In 1878, Greenfield found diffuse atherosclerosis in a 58-yearold woman with myxedema at autopsy^[1, 2]. Soon after, Kocher reported that arteriosclerosis commonly occurs after thyroid extirpation and raised the hypothesis of a causal relationship between hypothyroidism and atherosclerosis^[3]. This link between the hemostatic system and thyroid disease was finally described in 1913, when an episode of cerebral vein thrombosis in a hyperthyroid patient was reported^[4].

It is now well-known that thyroid dysfunction and autoimmunity may modify the physiological processes of primary and secondary hemostasis and lead to bleeding or thrombosis^[5]. Following levothyroxine treatment, patients with overt

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Received 2011-04-08 Accepted 2011-08-02

hypothyroidism display decreased bleeding time, prothrombin time (PT), activated partial thromboplastin time (APTT), and clotting time as well as increased factor VIII activity, von Willebrand factor, and platelet count^[6]. The occurrence of myocardial infarction (MI) shortly after the initiation of thyroid hormone substitution treatment could reflect an acutely increased risk of thrombosis^[7, 8].

The association between the thyroid hormone level and the coagulation system in subjects with acute ST-segment elevation myocardial infarction (STEMI) and normal thyroid function has not been definitely elucidated. In the present study, we prospectively explored this association in Chinese euthyroid subjects with STEMI.

Materials and methods Study subjects

From 27 July 2010 to 21 March 2011, 231 consecutive euthyroid patients (177 males), aged 30 to 94 years (mean, 63 years) with

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acute STEMI at the First Affiliated Hospital of Nanjing Medical University, Nanjing, China, were enrolled in the study. The current guidelines for the ECG diagnosis of the ST segment elevation type of acute myocardial infarction require at least 1 mm (0.1 mV) of ST segment elevation in the limb leads, and at least 2 mm elevation in the precordial leads^[9]. Because anticoagulation is an integral part of both fibrinolytic therapy and percutaneous intervention (PCI) in the reperfusion treatment of STEMI^[10], all patients were given antiplatelet therapy with aspirin and clopidogrel. Exclusion criteria were cardiac shock, severe liver and/or renal dysfunction, hyperthyroidism, hypothyroidism, severe hypovolemia, thyroid disease, and concurrent treatment with diuretics or amiodarone. Complete medical histories, including history of bleeding and smoking habits, were recorded.

Among the 231 patients with STEMI, the types of MI were anteroseptal MI in 35 cases, anterior wall MI in 72 cases, extensive anterior wall MI in 20 cases, inferior wall MI in 98 cases, and lateral wall MI in 6 cases. Patients were divided into 4 groups according to their levels of free triiodothyronine (FT3) and free thyroxine (FT4). The median (quartile range) for FT3 and FT4 were 3.7 pmol/L (3.1-4.3 pmol/L) and 16.9 pmol/L (14.9–18.8 pmol/L), respectively.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University, and informed consent was obtained from each patient.

Clinical characteristics

At admission to the coronary care unit, the patients were immediately examined by the attending physician, who performed a complete physical examination, including blood pressure, heart rate, respiratory rate, and body temperature, and recorded demographic and historical data.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the right arm with the participant seated and the arm bared. Three readings were recorded for each individual, and the average was recorded. After a rest of at least 5 min, the heart rate was measured by pulse palpation over a 30-s period and was multiplied by 2 to evaluate the heart rate per minute. The respiratory rate was measured by observing the frequency of thoracic ups and downs over a 60-s interval. The axillary body temperature was measured by placing a thermometer under the armpit, with the arm skin tightening the thermometer. The thermometer was removed and read after 5–10 min.

Thyroid level measurements

The 12-h fasting blood samples were collected from every patient upon admission to the coronary unit. All samples were collected in serum separator tubes and immediately centrifuged (at 3000 r/min for 20 min at room temperature) and analyzed. Thyroid-stimulating hormone (TSH), FT3, and FT4 levels were measured with full-automatic immune analyzer (cobas e601, Roche, Berlin, Germany), with normal reference ranges of 0.3–4.2 mIU/L, 3.10–6.8 pmol/L, and 12.0–22.0 pmol/L, respectively.

Blood coagulation measurements

Two common coagulation tests, PT and APTT, were performed with a computerized blood coagulation analyzer (CA 7000, Sysmex, Kobe, Japan). The reference ranges for PT and APTT were 11.0±3 s and 24.5±10 s, respectively. The international normalized ratio (INR) is the ratio of the PT of the patient to a normal (control) sample. The INR was measured by the coagulation analyzer (CA 7000, Sysmex, Kobe, Japan), with a reference range of 0.8–1.2. The platelet count was obtained with an automated blood analyzer (XE-2100; Sysmex, Kobe, Japan).

Statistical analysis

Significance was defined as a P value of <0.05. Data were analyzed with Statistics Package for Social Sciences (version 16.0; SPSS Inc, Chicago). All variables were checked by the Kolmogorov-Smirnov test.

Patients were classified into 4 groups according to their quartile FT3 and FT4 levels, respectively: 0.40-3.09 (n=52 patients), 3.10-3.69 (n=56), 3.70-4.29 (n=64), and 4.30-7.10 (n=59) for FT3; 4.9-14.8 (n=57 patients), 14.9-16.8 (n=58), 16.9-18.7 (n=57), and 18.8-29.0 (n=59) for FT4. In every group, the DBP, body temperature, heart rate, respiratory rate, PT, APTT, platelet count, and TSH were expressed as median (quartile range), and comparisons between the 4 groups were analyzed by Kruskal-Wallis test (for non-normal distribution). Age, SBP, FT4, FT3, and INR were expressed as the mean±SD, and comparisons were analyzed by analysis of variance (ANOVA)-Sheffe's *F* test. Categorical variables, including sex, were compared among the groups of patients by chi-squared analysis.

The independent relationship between FT3 or FT4 and other variables was assessed by stepwise or enter multiple regression analysis, respectively. Differences were considered to be significant if the null hypothesis could be rejected with >95% confidence. All reported *P* values are two-tailed.

Results

Demographic and clinical characteristics and coagulation parameters in patients according to the level of FT3 and FT4

Of the 231 patients with STEMI, 177 (76.6%) were male and 54 (23.4%) were female. Table 1 shows the baseline demographic and clinical characteristics and biochemical and coagulation parameters of the 4 groups. The frequency distribution of sex (P=0.04) differed significantly among the groups. Age (P=0.00), SBP (P=0.02), DBP (P=0.01), INR (P=0.01), PT (P=0.00), and APTT (P=0.00) differed significantly among the groups. However, platelet count (P=0.21), body temperature (P=0.55), heart rate (P=0.21), respiratory rate (P=0.53), FT4 (P=0.23), and TSH (P=0.88) were similar among the 4 groups.

Patients were classified into 4 groups according to their quartile FT4 levels. Sex (P=0.67), age (P=0.85), SBP (P=0.58), DBP (P=0.83), platelet count (P=0.24), INR (P=0.36), body temperature (P=0.86), heart rate (P=0.25), respiratory rate (P=0.12), PT (P=0.39), APTT (P=0.17), and TSH (P=0.26) were similar among the 4 groups (Table 2). FT3 (P=0.04) differed significantly among the groups.

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	Free triiodothyronine (quartile range)					
Variable	0.40-3.09	3.10-3.69	3.70-4.29	4.30-7.10	or F	Р
	(<i>n</i> =52)	(<i>n</i> =56)	(<i>n</i> =64)	(<i>n</i> =59)		
Age (year)	66.9 (54.5-79.5)	69.1 (57.3-81.0)	64.5 (51.9-77.0)	53.5 (43.1-63.8)	20.01	0.00
Male/Female	34/18	41/15	50/14	52/7	8.42	0.04
SBP (mmHg)	123 (99-147)	120 (101-139)	131 (110-152)	124 (106-142)	3.28	0.02
DBP (mmHg)	74 (65-80)	70 (65-79)	78 (70-90)	80 (70-85)	16.9	0.01
Platelet count (10 ⁹ /L)	196 (117-275)	187 (131-244)	206 (110-301)	218 (137-299)	1.52	0.21
INR	1.05 (0.88-1.22)	1.00 (0.88-1.12)	0.97 (0.86-1.08)	0.96 (0.78-1.14)	3.84	0.01
BT (°C)	36.8 (36.5-37.0)	36.6 (36.5-36.8)	36.6 (36.5-36.8)	36.7 (36.5-36.8)	2.09	0.55
HR (beat/min)	81.5 (69.5-91.7)	72.0 (64.0-88.5)	74.0 (66.0-80.8)	75.5 (64.3-84.0)	4.53	0.21
RR (time/min)	18.0 (18.0-20.0)	18.0 (17.8-20.0)	18.0 (18.0-20.0)	18.0 (17.0-20.0)	2.19	0.53
PT (s)	11.4 (10.4-14.0)	11.1 (10.2-12.5)	10.6 (9.8-12.7)	10.1 (9.6-11.8)	13.5	0.00
APTT (s)	33.0 (27.0-42.3)	27.7 (24.1-32.9)	28.9 (24.9-37.5)	27.4 (24.7-34.5)	14.5	0.00
FT4 (pmol/L)	16.0 (14.0-18.4)	16.9 (14.5-19.3)	17.1 (15.2–18.3)	17.4 (15.7–19.5)	4.27	0.23
TSH (mIU/L)	1.03 (0.54-2.64)	1.46 (0.83-2.29)	1.30 (0.72-2.51)	1.43 (0.93-2.24)	0.69	0.88

Table 1. Clinical characteristics and biochemical and coagulation parameters in patients according to the level of free triiodothyronine.

SBP, systolic blood pressure; DBP, diastolic blood pressure; INR, international normalized ratio; BT, body temperature; HR, heart rate; RR, respiratory rate; PT, prothrombin time; APTT, activated partial thromboplastin time; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

Table 2. Clinical characteristics and biochemical and coagulation parameters in patients according to the level of free thyroxine.

	Free thyroxine (quartile range)					
Variable	4.9-14.8 (<i>n</i> =57)	14.9–16.8 (n=58)	16.9–18.7 (<i>n</i> =57)	18.8-29.0 (<i>n</i> =59)	or F	Р
Age (vear)	63 4 (50 6-76 2)	621(469-773)	63 8 (52 0-75 4)	64 2(50 9-77 4)	0.27	0.85
Male/Female	45/12	47/11	42/15	43/16	1.54	0.67
SBP (mmHg)	123 (108-137)	123 (95-151)	127 (106-148)	126 (107-146)	0.66	0.58
DBP (mmHg)	75 (70-80)	74 (64-80)	75 (68-89)	74 (70-85)	0.88	0.83
Platelet count (10 ⁹ /L)	177 (147-222)	180 (143-247)	200 (167-235)	199 (152-237)	4.19	0.24
INR	1.00 (0.87-1.13)	0.98 (0.85-1.10)	0.97 (0.83-1.11)	1.02 (0.81-1.22)	1.08	0.36
BT (°C)	36.6 (36.5-37.1)	36.6 (36.5-36.8)	36.6 (36.5-36.8)	36.7 (36.5-36.8)	0.74	0.86
HR (beat/min)	71.5 (64.0-82.5)	74.0 (64.0-85.0)	78.0 (65.5-84.5)	78.0 (70.0-95.0)	4.08	0.25
RR (time/min)	18.0 (18.0-20.0)	18.0 (18.0-20.0)	18.0 (16.5-19.5)	18.0 (18.0-20.0)	5.76	0.12
PT (s)	11.1 (10.4-12.5)	10.6 (9.8-12.8)	10.5 (9.6-12.9)	11.0 (9.8-13.1)	2.99	0.39
APTT (s)	30.2 (25.9-36.5)	27.8 (24.7-33.7)	27.7 (24.2-34.2)	31.1 (25.1-38.5)	5.08	0.17
FT3 (pmol/L)	3.38 (2.34-4.42)	3.69 (2.92-4.46)	3.83 (3.14-4.52)	3.72 (2.81-4.63)	2.87	0.04
TSH (mIU/L)	1.19 (0.58-2.06)	1.15 (0.89-2.19)	1.62 (0.75-3.59)	1.62 (0.91-2.49)	4.04	0.26

SBP, systolic blood pressure; DBP, diastolic blood pressure; INR, international normalized ratio; BT, body temperature; HR, heart rate; RR, respiratory rate; PT, prothrombin time; APTT, activated partial thromboplastin time; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone.

Multiple linear regression analysis with FT3 and FT4 as the dependent variable

Multiple linear regression analysis was used to examine the independent association between FT3 or FT4 and INR in patients with STEMI. In this model, FT3 or FT4 was employed as the dependent variable, and other variables were considered as the independent variables. Table 3 shows that INR (β =-0.139, *P*=0.025), age (β =-0.344, *P*=0.000), and DBP (β =0.144, *P*=0.020) were significant independent factors associated with the level of FT3 after adjustment. Figure 1 presents the partial regression and shows the relationship between FT3 and INR.

Sex (β =0.063, *P*=0.377), age (β =0.120, *P*=0.097), body temperature (β =-0.020, *P*=0.763), heart rate (β =0.065, *P*=0.336), respiratory rate (β =-0.056, *P*=0.413), SBP (β =-0.028, *P*=0.784), DBP (β =0.126, *P*=0.215), platelet count (β =0.086, *P*=0.218), and INR (β =0.024, *P*=0.725) were not significantly associated with the FT4 levels (Table 4).

Discussion

In the present study, we investigated the association between thyroid hormones and the coagulation system in patients with STEMI and normal thyroid function. Subjects with high FT3

Variable	Unstandardized coefficients B	Std. Error	Standardized coefficients (Beta)	Т	Ρ
Constant	5.199	0.532 -		9.776	0.000
Age (year)	-0.023	0.004	-0.344	-5.596	0.000
DBP (mmHg)	0.009	0.004	0.144	2.352	0.020
INR	-0.973	0.351	-0.139	-2.261	0.025

Table 3. Multiple linear regression analysis to identify independent variables associated with serum free triiodothyronine levels.

DBP, diastolic blood pressure; INR, international normalized ratio. Stepwise multiple linear regression analysis was performed.



Figure 1. The relationship between free triiodothyronine (FT3) and the international normalized ratio (INR) in Chinese euthyroid subjects.

levels had lower INR values than those with low FT3 (P=0.01). To our knowledge, this is the first study to report that an increased INR is associated with a decreased FT3 level in euthyroid patients.

The strong relationship between thyroid hormones and the coagulation system has been appreciated since the beginning of the past century^[11]. For instance, hyperthyroid patients are known to have an increased prevalence of shortened APTT and higher fibrinogen levels than those with normal thyroid function. Because prolonged APTT and PT results indicate a

reduced coagulation response and a bleeding tendency, these findings indicate that hyperthyroidism might be associated with hypercoagulability^[12]. Previous studies largely have explored patients with clinically overt hypo- or hyperthyroidism who appeared to have an increased risk of bleeding or thrombosis^[13].

In contrast, conflicting results have been reported concerning the association between subclinical hyperthyroidism and coagulation. Bucerius et al reported that subclinical hyperthyroidism has no significant impact on coagulation metabolism^[14], whereas Smallridge reported that subclinical hyperthyroidism is associated with various cardiac effects, particularly atrial fibrillation that increases the thromboembolism risk^[15]. Recently, a correlation between thyroid hormone levels and atherosclerosis was suggested in euthyroid patients, in whom the thyroid hormone levels were found to affect the presence and severity of coronary atherosclerosis^[11]. Similarly, logistic regression analysis in the present study revealed decreased serum FT3 as an independent risk factor for elevated INR in patients with STEMI and normal thyroid function, after adjustment for confounders. Age was also observed to be an independent risk factor for elevated FT3, consistent with a previous study showing that the FT3 level in old subjects is negatively associated with age^[16].

Female gender by itself had a negative and independent

Table 4.	Multiple linear regres	ssion analysis to id	entify independent v	ariables associated	with serum free thyroxine levels.
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	Unstandardized		Standardized		
Variable	coefficients		coefficients	Т	Р
	В	Std. Error	(Beta)		
Constant	18.171	21.557 -		0.843	0.400
Sex	0.489	0.552	0.063	0.885	0.377
Age (year)	0.030	0.018	0.120	1.667	0.097
BT (°C)	-0.175	0.581	-0.020	-0.301	0.763
HR (beat/min)	0.003	0.003	0.065	0.964	0.336
Respiratory rate (time/min)	-0.031	0.037	-0.056	-0.821	0.413
SBP (mmHg)	-0.004	0.016	-0.028	-0.275	0.784
DBP (mmHg)	0.032	0.025	0.126	1.245	0.215
Platelet count (10 ⁹ /L)	0.004	0.003	0.086	1.235	0.218
INR	0.528	1.498	0.024	0.353	0.725

BT, body temperature; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; INR, international normalized ratio.



influence on mortality in STEMI patients^[17]. However, of the 231 patients with STEMI in our study, 177 (76.6%) were male and 54 (23.4%) were female. Among the subjects with a high serum FT3 level, there were significantly more males than females (*P*=0.04). A typical pattern of altered thyroid hormone metabolism called nonthyroid illness syndrome (NTI) occurs after acute MI. This syndrome is characterized by low serum and free T3 levels, increased serum reverse T3 levels, and, in the most severe condition, by decreased serum T4 and TSH levels^[18]. In present study, among of 231 patients, 23% were lower than the normal reference of FT3 (3.1 pmol/L).

Thyroid hormones exert various effects on the coagulation system^[19]. Modulation of the levels of T3 in hyper- and hypothyroidism is extremely important for the capability to increase or decrease the concentrations of fibrinogen and numerous blood clotting factors^[20]. In particular, a decrease in active hormone T3 leads to further impairment in cardiac function^[21]. Recently, Lymvaios et al reported that T3 levels are closely correlated with the cardiac function after AMI^[22]. Everts et al also reported that T3, and not T4, is transported into the myocyte^[23]. However, the exact mechanisms underlying the association between FT3 and cardiac function require further study. Regardless, these previous findings, combined with those of the present study, indicate the importance of assessing the FT3 level of patients. Acute myocardial infarction was the consequence of the acutely increased coronary thrombogenesis and the deficient blood. Whether or not substitution of thyroid hormone should be (routinely) considered as a treatment in patients with STEMI undergoing surgery should be considered.

The findings of the present study are consistent with previous observations that a rise in thyroxine level is associated with increased levels of factors VIII and IX, von Willebrand factor, and fibrinogen^[24]. Several biological mechanisms have been proposed to explain this intriguing association, including the effects of thyroid hormones on the synthesis of coagulation factors and the thyroid-related autoimmune processes^[13, 19]. However, the exact mechanism underlying the relationship between FT3 and INR remains unclear. Deficiency or excess of thyroid hormone may disturb the production and/or clearance of coagulation factors, such that a patient will bleed or develop thrombosis^[20].

Limitations of the present study include a small sample size and the patient selection. Future large clinical and intervention studies are needed to obtain more definitive information on the clinical relevance and the effects of pharmacologic treatment with acute MI. Prophylactic examination of FT3 might be proposed in cases of older people with cardiovascular disease.

In conclusion, free T3 is negatively associated with INR in patients with acute STEMI and normal thyroid function.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (No 30400173 and 30971257).

Author contribution

En-zhi JIA designed research; Li LI and Chang-yan GUO performed research; Tie-bing ZHU, Lian-sheng WANG, Ke-jiang CAO contributed new analytical tools and reagents; Wenzhu MA, Zhi-jian YANG, and Jing YANG analyzed data; Li LI wrote the paper.

References

- 1 Greenfield WS. Autopsy findings in a 58 year old woman with myxoedema public hed as an appendix. Ord WM Med Chir Trans 1878; 61: 57
- 2 Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. J Clin Endocr Metab 2003; 88: 2438–44.
- 3 Kocher T. Ueber Kropfexstirpation und ihre Folgen. Arch Klein Cir 1883; 29: 254–337.
- 4 Squizzato A, Gerdes VE, Brandjes DP, Büller HR, Stam J. Thyroid diseases and cerebrovascular disease. Stroke 2005; 36: 2302–10.
- 5 Marongiu F, Cauli C, Mariotti S. Thyroid, hemostasis and thrombosis. J Endocrinol Invest 2004; 27: 1065–71.
- 6 Gullu S, Sav H, Kamel N. Effects of levothyroxine treatment on biochemical and hemostasis parameters in patients with hypothyroidism. Eur J Endocrinol 2005; 152: 355–61.
- 7 Smyth CJ. Angina pectoris and myocardial infarction as complications of myxedema. Am Heart J 1938: 15: 652–60.
- 8 Wayne EJ. Clinical and metabolic studies in thyroid disease. Br Med J 1960: 1:78–90.
- 9 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care – Part 8: Stabilization of the Patient With Acute Coronary Syndromes. Circulation 2005; 112: IV-89-IV-110.
- 10 Wong CK, White HD. Antithrombotic therapy in ST-segment elevation myocardial infarction. Expert Opin Pharmacother 2011; 12: 213–23.
- 11 Squizzato A, Romualdi E, Büller HR, Gerdes VE. Thyroid dysfunction and effects on coagulation and fibrinolysis: a systematic review. J Clin Endocrinol Metab 2007; 92: 2415–20.
- 12 Lippi G, Franchini M, Targher G, Montagnana M, Salvagno GL, Guidi GC, et al. Hyperthyroidism is associated with shortened APTT and increased fibrinogen values in a general population of unselected outpatients. J Thromb Thrombolysis 2009; 28: 362–5.
- 13 Franchini, M, Lippi G, Manzato F, Vescovi PP, Target G. Hemostatic abnormalities in endocrine and metabolic disorders. Eur J Endocrinol 2010; 162: 439–51.
- 14 Bucerius J, Naubereit A, Joe AY, Ezziddin S, Biermann K, Risse J, et al. Subclinical hyperthyroidism seems not to have a significant impact on systemic anticoagulation in patients with coumarin therapy. Thromb Haemost 2008; 100: 803–9.
- 15 Smallridge RC. Disclosing subclinical thyroid disease. An approach to mild laboratory abnormalities and vague or absent symptoms. Postqrad Med 2000; 107: 143–6, 149–52.
- 16 Corsonello A, Montesanto A, Berardelli M, De Rango F, Dato S, Mari V Mazzei B, et al. A cross-section analysis of FT3 age-related changes in a group of old and oldest-old subjects, including centenarians' relatives, shows that a down-regulated thyroid function has a familiar component and is related to longevity. Age Ageing 2010; 39: 723–7.
- 17 Trigo J, Mimoso J, Gago P, Marques N, Faria R, Santos W, et al. Female gender: an independent factor in ST-elevation myocardial infarction. Rev Port Cardiol 2010; 29: 1383–94.
- 18 Adler SM, Wartofsky L. The non-thyroidal illness syndrome. Endocrinol Metab Clin North Am 2007; 36: 657–72.
- 19 Franchini M, Montagnana M, Manzato F, Vescovi PP. Thyroid

dysfunction and hemostasis: an issue still unresolved. Semin Thromb Hemost 2009; 35: 288–94.

- 20 Shih CH, Chen SL, Yen CC, Huang YH, Chen CD, Lee YS, *et al.* Thyroid hormone receptor-dependent transcriptional regulation of fibrinogen and coagulation proteins. Endocrinology 2004; 145: 2804–14.
- 21 Iervasi G, Pingitore A, Landi P, Ripoli A, Scarlattini M, L'Abbate A, *et al.* Low T3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation 2003; 107: 708–13.
- 22 Lymvaios I, Mourouzis I, Cokkinos DV, Dimopoulos MA, Toumanidis ST, Pantos C. Thyroid hormone and recovery of cardiac function in

patients with acute myocardial infarction: A strong association? Eur J Endocrinol 2011; 165: 107–14.

- 23 Everts ME, Verhoeven FA, Bezstarosti K, Moerings EP, Hennemann G, Visser TJ, et al. Uptake of thyroid hormones in neonatal rat cardiac myocytes. Endocrinology 1996; 137: 4235–42.
- 24 Debeij J, Cannegieter SC, VAN Zaane B, Smit JW, Corssmit EP, Rosendaal FR, *et al.* The effect of changes in thyroxine and thyroidstimulating hormone levels on the coagulation system. J Thromb Haemost 2010; 8: 2823–6.