Journal of Clinical & Experimental Cardiology

Helmy, et al., J Clin Exp Cardiolog 2016, 7:5
DOI: 10.4172/2155-9880.1000445

Research Article Open Access

Prevalence of Subclinical Hypothyroidism among Patients with Acute Coronary Syndrome

Mohammed Mansour Helmy[1*], Hamza Mohamed Kabil[2], Ali Ibrahim Atia[2] and Mohammed Mahrous Ali[2]

[1]*Cardiology Department, Matarya Teaching Hospital, Egypt*

[2]*Cardiology Department, Faculty of medicine, Benha University, Egypt*

[*]**Corresponding author:** Mohammed Mansour Helmy, Cardiology Department, Matarya Teaching Hospital, Cairo, 11752, Egypt, Tel: 0021111699944; E-mail: dr.moh.mansour@gmail.com

Received date: April 19, 2016; **Accepted date:** May 12, 2016; **Published date:** May 22, 2016

Abstract

Objectives: to detect prevalence of subclinical hypothyroidism (SCH) among acute coronary syndrome patients and to assess its association with both inhospital morbidity and mortality.

Methods: The study included 300 patients admitted with the diagnosis of acute coronary syndrome (either STEMI or NSTEMI or UA) with close follow up during the inhospital stay to detect any morbidity or mortality. All subjects underwent complete lipid profile (TC-TG-LDL-C-HDL-C-VLDL-C) and thyroid profile (free T3-free T4-TSH).

Results: SCH was associated with hypercholesterolemia (in 83.1% of patients), hypertriglyceridemia (in 80% of patients), increased LDL-C (in 83.3% of patients), decreased HDL-C (in 85.7% of patients) and increased VLDL-C (in 86.6% of patients). The prevalence of SCH among ACS patients was 5%. Morbidity was 34.6% in ACS patients with normal thyroid profile (euthyroid) *vs*. 20% in those with SCH (p value 0.7). Mortality was 2.5% in ACS patients with normal thyroid profile (euthyroid) *vs*. 0% in those with SCH (p value more than 0.05).

Conclusion: Prevalence of SCH is 5% in ACS patients and it has no association with inhospital morbidity and mortality.

Keywords: Acute coronary syndrome; Mortality; Morbidity; Subclinical hypothyroidism; Prevalence

Introduction

Subclinical hypothyroidism, also referred to as mild thyroid failure, is diagnosed when serum free thyroid hormone levels are within the normal range, but thyroid stimulating hormone (TSH) is mildly elevated [1]. It is a common problem, occurring in 3% to 8% in the population without known thyroid disorders and carries a risk of development to overt hypothyroidism of 2-5% per year [2,3]. There is growing evidence that subclinical hypothyroidism is associated with increased risk of cardiovascular morbidities mainly due to dyslipidemia, particularly in older women [4,5]. It is known that overt hypothyroidism is associated with increased prevalence of coronary heart disease which is at least partly due to the lipid metabolism abnormalities leading to premature atherosclerosis [6,7]. The link between hypothyroidism and atherosclerosis can be explained by possible mechanisms other than dyslipidemia which include disturbances in coagulation system, homocysteine metabolism and parasympathetic function [4,8]. Coronary artery disease (CAD), its acute form, and acute coronary syndrome (ACS) are the major cause of death all over the world [9]. ACS is the umbrella term of clinical signs and symptoms of myocardial ischemia including unstable angina (UA), ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) [10]. Several prospective, population-based cohort studies found that subclinical hypothyroidism was associated with increased risks of atherosclerotic coronary heart diseases and cardiovascular mortality, whereas other studies showed no correlation. Because of these conflicting reports and the large numbers of populations afflicted by this condition, there is an urgent need for settling the controversy.

Aim: The aim of the study is to detect the prevalence of subclinical hypothyroidism among patients with acute coronary syndrome and its association with both in-hospital morbidity and mortality.

Patients and Methods

Study design

This is a prospective, randomized study that involved 300 patients from the attendants of the cardiology department at Matarya Teaching hospital, admitted with the diagnosis of acute coronary syndrome, including ST-segment elevation Myocardial infarction (STEMI)/Non ST-segment elevation Myocardial infarction (NSTEMI)/Unstable Angina (UA) irrespective of age, gender, race and clinical severity, during the period from March 2015 to March 2016 and followed up during the inhospital stay.

Exclusion criteria: Patients were excluded from the study if they were using amiodarone, corticosteroids or received any iodinated contrast agent within the previous two weeks or those with diseases that are known to affect thyroid function tests, such as neoplasia, chronic renal failure, liver cirrhosis, active infection, chronic obstructive pulmonary disease requiring antibiotic therapy and diabetic ketoacidosis. Approval from institutional medical research

committee was obtained and an informed consent from all patients was obtained.

Methods

The following data were collected:

Complete and detailed medical history: With attention to the risk factors for developing CAD (smoking status, hypertension, diabetes mellitus, and family history of premature CAD in first degree relatives).

Full clinical examination: Including heart rate & rhythm, systolic & diastolic blood pressure and heart & chest auscultation.

Electrocardiography: Resting standard 12 leads electrocardiogram was done for each patient to detect any findings consistent with CAD either ST elevation or ST depression or T wave inversion or pathological Q waves or new onset LBBB.

Echocardiography: Two-dimensional echocardiography and Doppler examination were performed for all patients in the left decubitus position during normal respiration using a GE Vivid 5 Ultrasound Machine (Echo Pac; GE Vingmed, Horten, Norway) to detect any wall motion abnormalities or ischemic complications.

Laboratory tests: Venous blood samples were obtained from all patients on arrival for serum cardiac markers (including cardiac troponin (cTn) and creatine kinase MB isoenzyme (CK-MB), liver and kidney functions , lipid profile (including Total cholesterol (TC),high density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein Cholesterol (LDL-C), very low density lipoprotein-Cholesterol (VLDL-C) and triglycerides (TG) and thyroid profile (including free T3,free T4 and TSH). We defined high serum levels as TC ≥ 200 mg/dl, LDL-C ≥130 mg/dl, VLDL-C ≥ 40 mg/dl and TG ≥ 150 mg/dl; a low serum level of HDL-C was defined as ≤ 40 mg/dl. FreeT3, FreeT4, TSH were measured using electrochemiluminescent method (cobas-e411-Roche). Measured hormones and their respective reference values were: free T3 (1.3-5 pg/ml), free T4 (0.8-2 ng/dl) and TSH (0.4-4 mIU/l). All the patients were followed up during the inhospital stay for any morbidity and mortality.

Statistical analysis

Data management and analysis were performed using SPSS program; version 17. The numerical data were statistically presented in terms of mean and standard deviation. Categorical data were summarized as percentages. Comparisons between numerical variables were done by unpaired Student's t-test. Comparing categorical variables were done by Chi-square test or Fisher exact test for small sample size. A probability value $p<0.05$ was considered statistically significant, a P value <0.001 was considered highly significant and P value >0.05 was considered non-significant.

Results

Baseline clinical characteristics

This study included 300 patients in the period from March 2015 to March 2016. The Mean age was 55.7 ± 10 years (range from 32 -83 years). 198 (66%) were males, 150 (50%) were diabetic, 186 (62%) were hypertensive, 174 (58%) were current smokers, 42 (14%) had family history of premature CAD, 108 (26%) presented by STEMI, 84 (28%) presented by NSTEMI and 108 (36%) presented by UA. These data are showed in (Table 1).

Variable		All patients (300)	
		No	%
Age (years)	**Mean ± SD**	55.7 ± 10	
Sex	Male	198	66%
Hypertension		186	62%
DM		150	50%
Smoking (current)		174	58%
Family history of premature CAD		42	14%
Presentation	STEMI	108	36%
	NSTEMI	84	28%
	UA	108	36%

Table 1: Baseline clinical characteristics and presentation of the study population: DM: Diabetes Mellitus; CHD: Coronary Heart Disease; STEMI: ST Segment Elevation Myocardial Infarction; NSTEMI: Non-St Segment Elevation Myocardial Infarction; UA: Unstable Angina.

Thyroid status and lipid profile abnormalities

This study showed that euthyroid status was the most prevalent among the whole study population (81%) while subclinical hypothyroidism represents only 5% (Table 2). Each thyroid status is associated with different lipid profile abnormalities. Hypercholesterolemia and hypertriglyceridemia are present in all thyroid status (Table 3) (Figure 1).

Thyroid state	No. (percent)	Male gender (No.)
1- Euthyroid	243 (81%)	159 Males
2- Subclinical hypothyroidism	15 (5%)	15 Males
3- Overt hypothyroidism	6 (2%)	6 Males
4- Subclinical hyperthyroidism	21 (7%)	18 Males
5- Overt hyperthyroidism	15 (5%)	6 Males

Table 2: Distribution of different thyroid abnormalities.

Thyroid state	Euthyroid	Subclinical hypothyroidism	Overt hypothyroidism	Subclinical hyperthyroidism	Overt hyperthyroidism	p value
1-Hyper TC	150 (61.7%)	202 (83.1%)	99 (40.7%)	182 (74.8%)	175 (72%)	p<0.05
2-Hyper TG	10 (66.6%)	12 (80%)	9 (60%)	11 (73.3%)	10 (66.6%)	p<0.05
3-Increased LDL-C	5 (83.3%)	5 (83.3%)	4 (66.6%)	2 (33.3%)	3 (50%)	p<0.05
4-Decreased HDL-C	14 (66.6%)	18 (85.7%)	10 (47.6%)	13 (61.9%)	17 (80.9%)	p<0.05
5-Increased VLDL-C	9 (60%)	13 (86.6%)	8 (53.3%)	12 (80%)	12 (80%)	p<0.05

Table 3: Association between thyroid status and lipid profile abnormalities among the whole study population. TC: Total Cholesterol; TG: Triglycerides; LDL-C: Low Density Lipoprotein-Cholesterol; HDL-C: High Density Lipoprotein–Cholesterol; VLDL-C: Very Low Density Lipoprotein–Cholesterol.

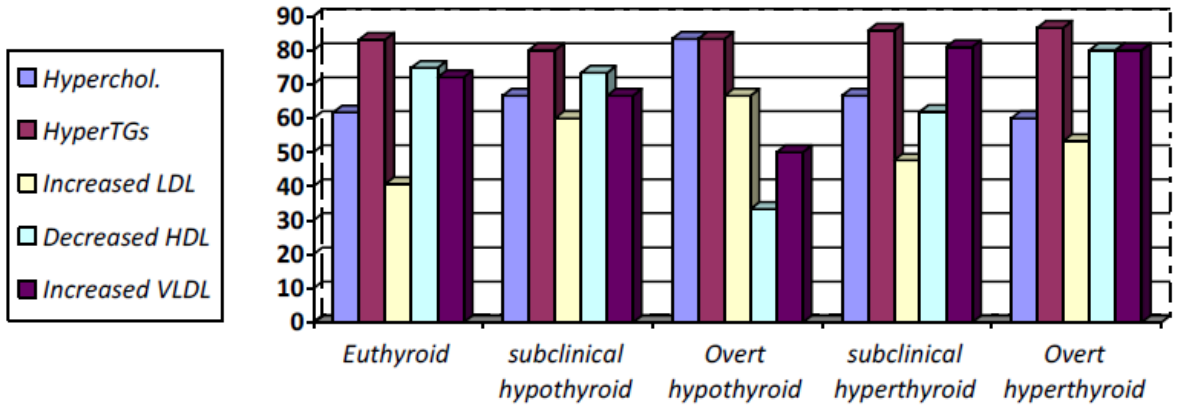

Figure 1: Association between thyroid status and lipid profile abnormalities among the whole study population.

Morbidity and mortality among patients in the study population

This study showed that the total morbidity among patients in the study population was 36% distributed as shown in (Table 4) taking in consideration that one patient may have more than one morbidity while the total mortality among patients in the study population was 4 % due to different causes as shown in (Table 5).

Cardiac complication	No. of patients (%)
1- Post MI angina	57 (19%)
2- Cardiogenic shock	15 (5%)
3- Heart failure	57 (19%)
4- Mechanical complication (mitral regurge)	3 (1%)
5- Pericarditis	3 (1%)
6- Arrhythmias	36 (12%)
1- Atrial fibrillation (AF)	9 (3%)
2- Supraventricular tachycardia	3 (1%)
3- Ventricular tachycardia	12 (4%)
4- Ventricular fibrillation	3 (1%)
5- Second degree heart bock	3 (1%)
6- Complete heart block (CHB)	6 (2%)

Table 4: Morbidity among patients in the study population

Mortality	No. of patients	(%)
1- Cardiogenic shock	7	-2.30%
2- Congestive Heart failure	4	-1.60%
3- Complete heart block (CHB)	1	-0.33%

Table 5: Mortality among patients in the study population

Subclinical hypothyroidism and its association with inhospital morbidity and mortality

This study showed that the prevalence of SCH among the whole study population was 5% (15 patients). According to age, prevalence of SCH was 5.6% in patients who are sixty or older *vs.* 4.7% in patients who are below age of sixty , and according to gender, prevalence of SCH was 4.5% in males *vs.*5.9% in females while according to the type of ACS, prevalence of SCH was 8.3% in patients presented by UA *vs.* 3.1% in those presented by MI and it was 2.8% in patients presented by ST elevation ACS *vs.* 6.2% in those presented by Non-ST elevation ACS (Table 6).

There is also no statistically significant difference between both morbidity and mortality in both patients who had normal thyroid profile (euthyroid) *vs.* who had subclinical hypothyroidism (P value for both morbidity and mortality was not significant). Morbidity was 34.6% in ACS patients with normal thyroid profile (euthyroid) *vs.* 20% in those SCH (P value 0.7). Mortality was 2.5% in ACS patients with normal thyroid profile (euthyroid) *vs.* 0% in those with SCH with non-significant P value (Table 7).

Variable		No	%	P value
Age	60 or older	6	5.60%	NS
	Below 60	9	4.70%	
Gender	Male	9	4.50%	NS
	Female	6	5.90%	
Type of ACS	UA	9	8.30%	0.3
	MI	6	3.10%	
	ST elevation ACS	3	2.80%	0.6
	Non-ST elevation ACS	12	6.20%	

Table 6: Prevalence of SCH among the whole study population. ACS: Acute Coronary Syndrome; UA: Unstable Angina; MI: Myocardial Infarction; NS: Non-Significant.

	Euthyroid	SCH	P value
Morbidity	84(34.6%)	3(20%)	0.7
Mortality	6(2.5%)	0(0%)	NS

Table 7: Comparison between euthyroid patients *vs.* patients with SCH as regard inhospital morbidity and mortality.

Discussion

Subclinical hypothyroidism is a common clinical problem, diagnosed mainly by laboratory methods. Screening is needed to detect SCH in most cases since most patients with this disorder are asymptomatic. It is recognized by abnormally high serum TSH value with normal FT4 and FT3 concentrations. Although it was recently reported that SCH is associated with elevated risks of cardiovascular events, cardiac dysfunction, lipid metabolism abnormalities and neuropsychiatric disorders, it is still debated whether long-term subclinical hypothyroidism is associated with systemic complications.

Regarding association between lipid profile and thyroid status, our study showed that in euthyroid status, the prevalence of hypercholesterolemia was 61.7%, hypertriglyceridemia was 83.1%, LDL-C level was increased in 40.7%, HDL-C level was decreased in 74.8% and VLDL-C was increased in 72% while in the subclinical hypothyroid status, Hypercholesterolemia occurred in 66.6%, hypertriglyceridemia occurred in 80%, LDL-C level was increased in 60%, HDL-C level was decreased in 73.3% and VLDL-C level was increased in 72%. Our results were consistent with Duntas and Wartofsky study in which SCH was associated with lipid profile abnormalities, especially increases in the concentrations of serum total and LDL cholesterol, but its effects on serum HDL-C and triglycerides concentrations were unclear [11,12]. It is also consistent with the results of Colorado study in which patients with SCH had higher serum total cholesterol concentrations than euthyroid individuals [13]. However, our results were disconcordant with NHANES III cohort study which showed higher total cholesterol and triglycerides concentrations in subclinical hypothyroid patients than in euthyroid subjects, but these changes were no longer observed after adjustment of different variables such as age, sex, race, and management with lipid lowering drugs [2]. The inconsistency between these studies may be due to the differences of the populations studied, including selection criteria based on sex, age, race, smoking history, and insulin resistance as well as variations in serum TSH concentrations used to define SCH.

Regarding prevalence of SCH, this study showed that the prevalence of SCH was 5% among the whole ACS patients (UA, STEMI, and NSTEMI). These results are supported by Cooper and Biondi study which showed that the prevalence of SCH in adults has been reported to range from 4% to 20%. This wide range can be explained explained by differences in age, gender, race, body mass index, and dietary iodine intake in the studied populations as well as differences in serum TSH evaluation methods [14]. Our results are also concordant with the results of the Colorado study in which the prevalence of SCH ranged from 4 to 21% in women and 3 to 16% in men [13]. However, our results are disconcordant with the results of Whickham Survey [15] and NHANES III [2] which showed higher prevalence of SCH in older population and obese individuals. In fact, in people who are in their 70 s-90 s, the 95 percentile for TSH may go as high as 6-9 mU/l [16]. Thus, an 80 year old woman with a serum TSH of 6.3 mU/l and a normal free T4 level may be a normal healthy individual, rather than a person with subclinical hypothyroidism. Higher serum TSH concentrations are also reported in overweight and obese subjects, which may result in a false diagnosis of subclinical hypothyroidism [17]. Mild increases in serum TSH concentration in obese individuals are usually associated with serum T3 values at the upper limit of the normal range. Therefore, the frequently cited high prevalence of SCH in the general population, especially in the elderly and obese needs to be re-examined in light of these new data.

Regarding prevalence of subclinical hypothyroidism according to age, gender and type of ACS at presentation, this study showed no statistically significant difference in the prevalence of SCH between both males and females. It was 4.5% in males' *vs.*5.9% in females. Also this study showed no statistically significant difference in the prevalence of subclinical hypothyroidism between persons (who are sixty or older) when compared to persons (who are below age of sixty). It was 5.6% in patients who are sixty or older *vs.*4.7% in patients who are below age of sixty.

Our results were inconsistent with results of NHANES III cohort study in which the prevalence increases with increasing age and is

higher in the female population [2] and Colorado study which showed that the percentage of women with elevated serum TSH concentration was higher than that of men in each decade of life, ranging from 4 to 21% in women and 3 to 16% in men [13] while in Ertugrul et al. study, prevalence of SCH was higher among men with AMI with more prominence of severe SCH among women with AMI [18]. This disconcordance can be explained by the high prevalence of elevated serum TSH in the elderly, with about 10% of individuals above the age of sixty having serum TSH levels above the reference range [19] and also by antithyroid peroxidase antibodies which were more prevalent in women than in men and in whites than in blacks leading to more prevalence of SCH in these groups [2]. This study showed no statistically significant difference in prevalence of SCH between patients presented by UA (8.3%) *vs.* those presented by myocardial infarction (MI) (3.1%) (P value 0.3). Up to our knowledge no previous study assessed the difference in the Prevalence of subclinical hypothyroidism between patients presented by UA *vs.* those presented by myocardial infarction (MI). This study also showed no statistically significant difference in prevalence of SCH between patients presented by ST elevation ACS (2.8%) *vs.* those presented by Non-ST elevation ACS (6.2%) (P value 0.6). Up to our knowledge no previous study assessed the difference in the prevalence of subclinical hypothyroidism between patients presented by ST elevation ACS *vs.* those presented by Non-ST elevation ACS.

Regarding association between SCH and in-Hospital morbidity and mortality in ACS patients, we have compared both morbidity and mortality in both patients who had normal thyroid profile (euthyroid) *vs.* who have subclinical hypothyroidism and we did not find a statistically significant difference between both (p value for both morbidity and mortality was not significant). Morbidity was 34.6% in ACS patients with normal thyroid profile (euthyroid) *vs.* 20% in those with SCH (p value 0.7). Mortality was 2.5% in ACS patients with normal thyroid profile (euthyroid) *vs.* 0% in those with SCH (p value not significant).

Our results were consistent with the results of the study conducted by Rodondi et al. in which SCH was not related to increase overall CHD events and cardiovascular mortality risk in elderly individuals [20]. It was also consistent with the results of Gussekloo study which showed that despite higher serum total cholesterol levels in individuals with subclinical hypothyroidism, they had lower cardiovascular events and mortality than euthyroid controls and it also showed decreased mortality in subclinical hypothyroid individuals older than 85 years which might be attributed to the associated lower metabolic rate [21]. However, our results were inconsistent with Razvi study which showed higher ischemic heart disease events and cardiovascular mortality rate only in subclinical hypothyroid patients younger than 65 years [22] and it was also inconsistent with the results of the study conducted by Ochs et al. which showed mild increased risk for CHD and mortality in subclinical hypothyroidism and hyperthyroidism [23]. This discrepancy can be explained by the elevated diastolic blood pressures and elevated serum total cholesterol levels in subclinical hypothyroid patients than in euthyroid controls [24] and that SCH is considered a potent risk factor for atherosclerosis and myocardial infarction in postmenopausal women [25].

Conclusion

Prevalence of SCH is 5% among patients with ACS. There is no association between SCH and inhospital morbidity and mortality in ACS patients. Longitudinal prospective study of larger groups of subclinical hypothyroid patients, after exclusion of other baseline confounding factors is needed.

References

1. Cooper DS (2001) Clinical practice. Subclinical hypothyroidism. N Engl J Med 345: 260-265.
2. Hallowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, et al. (2009) "Serum TSH, T4, and thyroid antibodies in the United States population(1988 to 1994): national health and nutrition examination survey (NHANES III)," Journal of Clinical Endocrinology and Metabolism 87: 489-499.
3. Karmisholt J, Andersen S, Laurberg P (2008) "Variation in thyroid function tests in patients with stable untreated subclinical hypothyroidism," Thyroid 18: 303-308.
4. Kahaly GJ (2000) Cardiovascular and atherogenic aspects of subclinical hypothyroidism. Thyroid 10: 665-679.
5. Efstathiadou Z, Bitsis S, Milionis HJ, Kukuvitis A, Bairaktari ET, et al. (2001) "Lipid profile in subclinical hypothyroidism: is L-thyroxine substitution beneficial?" European Journal of Endocrinology 6: 705-710.
6. Bastenie PA, Vanhaelst L, Neve P (1967) Coronary-artery disease in hypothyroidism. Lancet 2: 1221-1222.
7. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, et al. (1977) Lipid profiles and cardiovascular disease in the Whickham area with particular reference to thyroid failure. Clin Endocrinol (Oxf) 7: 495-508.
8. Johnson JL, Duick DS (2002) "Diabetes and thyroid disease: a likely combination," Diabetes Spectrum 15: 140-114.
9. Kumar A, Sivakanesam R, Gumasekera S (2006) Ischemia modified albumin: a potential marker in acute myocardial infarction in normo-lipidemia. Pak J Medsci 24:364-367.
10. Overbaugh KJ (2009) Acute coronary syndrome. Am J Nurs 109: 42-52.
11. Cappola AR, Ladenson PW (2003) Hypothyroidism and atherosclerosis. J Clin Endocrinol Metab.
12. Duntas LH, Wartofsky L (2007) Cardiovascular risk and subclinical hypothyroidism: focus on lipids and new emerging risk factors. What is the evidence? Thyroid 17: 1075-1084.
13. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC (2000) The Colorado thyroid disease prevalence study. Arch Intern Med 160: 526-534.
14. Cooper DS, Biondi B (2012) Subclinical thyroid disease. Lancet 379: 1142-1154.
15. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, et al. (1977) The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf) 7: 481-493.
16. Surks MI, Hollowell JG (2007) Age-specific distribution of serum thyrotrophin and anti-thyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab 92: 4575-4582.
17. Biondi B (2012) Natural history, diagnosis and management of subclinical thyroid dysfunction. Best Pract Res Clin Endocrinol Metab 26: 431-446.
18. Ertugrul O, Ahmet U, Asim E, Gulcin HE, Burak A, et al. (2011) Prevalence of Subclinical Hypothyroidism among Patients with Acute Myocardial Infarction. ISRN Endocrinol 2011: 810251.
19. Parle JV, Franklyn JA, Cross KW (1993) Thyroxine prescription in the community: serum thyroid stimulating hormone level assays as an indicator of under treatment or overtreatment. Br J Gen Pract.
20. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, et al. (2010) Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 304: 1365-1374.
21. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, et al. (2004) Thyroid status, disability and cognitive function, and survival in old age. JAMA 292: 2591-2599.
22. Razvi S, Shakoor A, Vanderpump M, Weaver JU, Pearce SH (2008) The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. J Clin Endocrinol Metab 93: 2998-3007.

23. Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, et al. (2008) Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med 148: 832-845.

24. Razvi S, Weaver JU, Vanderpump MP, Pearce SH (2010) The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. J Clin Endocrinol Metab 95: 1734-1740.

25. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, et al. (2000) Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med 132: 270-278.