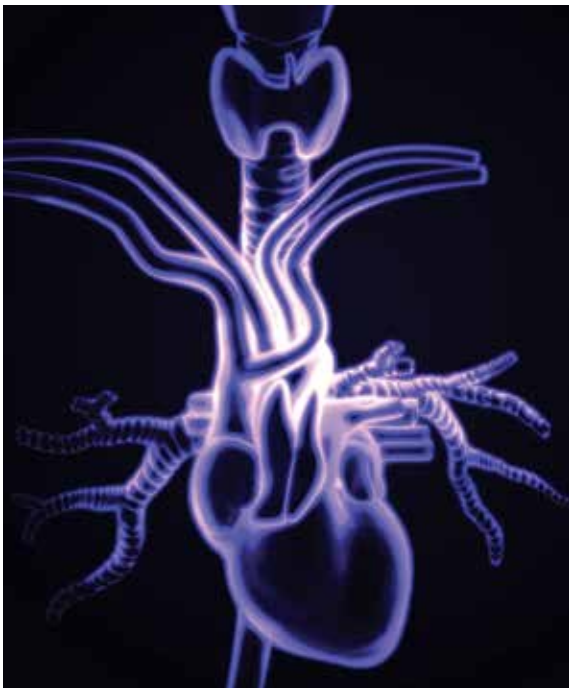

Cardiac effects of thyroid disease

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Thyroid hormone has important actions on the heart, and thyroid dysfunction can cause significant adverse cardiovascular effects. Thyroid dysfunction occurs on a spectrum ranging from subclinical disease to overt thyrotoxicosis or hypothyroidism. This article addresses the cardiovascular manifestations of both subclinical and overt thyroid dysfunction, and suggests potential indications for treatment to improve cardiac outcomes.

Key points

- **Overt thyrotoxicosis can cause marked cardiovascular abnormalities, including tachyarrhythmias, heart failure and pulmonary hypertension.**
- **Subclinical hyperthyroidism is associated with adverse cardiac effects, including increased cardiovascular mortality. These risks are most pronounced in older patients.**
- **Overt hypothyroidism has cardiovascular effects that are, in many ways, opposite to those seen in thyrotoxicosis.**
- **Mild elevations in serum thyroid-stimulating hormone levels (<10 mIU/L) can occur with normal ageing. Subclinical hypothyroidism perhaps poses a greater cardiac risk to younger patients with underlying coronary heart disease or other cardiovascular risk factors.**
- **The decision of whether or not to treat a patient with subclinical thyroid dysfunction needs to be individualised. Factors such as age, underlying cardiac status and degree of subclinical dysfunction are all important considerations.**

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Thyroid hormone has important actions on the heart, and thyroid dysfunction can cause significant adverse cardiovascular effects. The specific effects and their importance differ with the type and severity of thyroid dysfunction. Thyroid dysfunction occurs on a spectrum ranging from subclinical disease to overt thyrotoxicosis or hypothyroidism. Overt thyroid dysfunction (either thyrotoxicosis or hypothyroidism) is usually symptomatic whereas mild forms of thyroid disease are generally (but not always) asymptomatic. Subclinical thyroid disease is defined biochemically as an abnormal level of serum thyroid-stimulating hormone (TSH) in the presence of normal thyroxine (T4) and tri-iodothyronine (T3) levels. Thus, in patients with subclinical hyperthyroidism the TSH level is suppressed with normal T4 and T3 levels, and conversely in those with subclinical hypothyroidism the serum TSH level is elevated.

Thyroid hormone physiology: cardiac effects

The thyroid gland predominantly secretes T4, a prohormone with intrinsic activity, which is converted peripherally in the liver, kidney and skeletal muscle to active T3. The free T3 serum concentration determines the cardiac effects of thyroid hormones because cardiac myocytes cannot convert T4 to T3.[1] Within the nucleus, T3 binds to thyroid hormone receptors to positively or negatively regulate the transcription of a number of key genes. T3 also has nongenomic cardiac effects by directly affecting the function of several membrane ion channels.[2]

Haemodynamically, the overall effect of T3 on cardiac myocytes is an increase in ventricular contractility and resting heart rate. Peripherally, T3 lowers systemic vascular resistance through relaxation of vascular smooth muscle leading to an increase in circulating blood volume via activation of the renin-angiotensin system. In patients with thyrotoxicosis, these haemodynamic changes can increase cardiac output by as much as 300%.[1]

Overt thyrotoxicosis

Rhythm disturbances

An increase in heart rate occurs in almost all cases of overt thyrotoxicosis. Sinus tachycardia is the most common dysrhythmia, but atrial fibrillation

(AF) poses the greater clinical challenge (note: in this article AF also denotes the closely related condition of atrial flutter). The prevalence of AF in patients with thyrotoxicosis is estimated to be between 2 and 20%.[1] In a large population-based study, 8.3% of 40,628 patients with thyrotoxicosis were diagnosed with AF within 30 days of their diagnosis of thyrotoxicosis.[3] Factors associated with an increased risk of AF included male sex, older age, ischaemic or valvular heart disease, and congestive cardiac failure.[3]

Restoration of euthyroidism is fundamental to the management of patients with AF in the setting of thyrotoxicosis. Approximately 60 to 70% of patients will revert to sinus rhythm within two to three months of achieving euthyroidism.[4] Thyroid function testing is therefore recommended in all patients with new-onset AF.[2] Rate control for AF in patients with thyrotoxicosis is best achieved with use of beta blockers.[1] Digoxin is less effective in the thyrotoxic state due to both increased drug clearance and increased expression of the sodium–potassium ATPase necessitating higher than usual digoxin doses.[5] For patients with persistent AF, the decision of whether or not to anticoagulate is based on weighing the risks of thromboembolism (CHA_2DS_2-VASc score) versus bleeding, as for other cases of AF. Some caution should be applied if initially anticoagulating with warfarin, because lower doses than usual may be needed in patients with thyrotoxicosis.[6] In patients who become euthyroid and revert to sinus rhythm, and whose AF was clearly provoked by the thyrotoxicosis, the decision regarding continuation of anticoagulation is beyond the scope of this article, but would often be discussed with a cardiologist.

Heart failure

In a study of 591 consecutive patients with thyrotoxicosis, 5.8% had heart failure at the initial presentation.[7] The mechanism of thyrotoxicosis-induced heart failure involves a tachycardia-induced left ventricular dysfunction.[1] Elderly patients and those with underlying heart disease are more likely to develop heart failure from thyrotoxicosis.

Pulmonary hypertension

Several studies have shown an association between thyrotoxicosis and pulmonary hypertension. In a study of 114 patients with hyperthyroidism, 43% had an elevated pulmonary artery systolic pressure on transthoracic echocardiogram.[8] It has been postulated that thyrotoxicosis is associated with pulmonary endothelial cell dysfunction, which leads to elevated pulmonary pressures.[9]

Subclinical hyperthyroidism

Subclinical hyperthyroidism is defined as a suppressed serum TSH level with normal circulating levels of T4 and T3. Transient suppression of TSH levels can occur in certain circumstances (e.g. thyroiditis, nonthyroidal illness, pregnancy) and so the diagnosis of subclinical hyperthyroidism requires demonstration of persistently suppressed TSH levels on repeat testing at least two to three months apart.[10]

Atrial fibrillation

Several large studies have shown an association between subclinical hyperthyroidism and an increased risk of AF. A large retrospective case-control study showed an increased risk of AF in people with subclinical hyperthyroidism, with the highest risk in those with a TSH level below 0.1 mIU/L.[11] In a meta-analysis of five cohort studies, subclinical hyperthyroidism was associated with a greater risk of AF; again the risk was highest for patients with a TSH level below 0.1 mIU/L.[12] A large population-based cohort study showed a progressive increase in the risk of AF as serum TSH level decreased from within the normal range to undetectable.[13] In this study, subclinical hyperthyroidism was associated with a crude incidence of AF of 12.5 events per 1000 person years.[13]

Heart failure

In a meta-analysis of six cohort studies, subclinical hyperthyroidism was associated with a near doubled risk of heart failure when TSH level was below 0.1 mIU/L (hazard ratio, 1.94; 95% confidence interval [CI], 1.01–3.72). For a TSH level of 0.1 to 0.44 mIU/L the effect was nonsignificant (hazard ratio, 1.31; 95% CI, 0.88–1.95).[14]

Cardiovascular and all-cause mortality

Several meta-analyses have shown an increase in cardiovascular and all-cause mortality in patients with subclinical hyperthyroidism.[12,15-17] The largest of these included data from 10 cohort studies (52,674 participants) and, after adjustment for age and sex, found that subclinical hyperthyroidism was associated with increased total mortality, increased mortality from coronary heart disease and increased coronary heart disease events.[12] In the Cardiovascular Health Study, lower serum TSH concentrations and higher free T4 levels were associated with increased mortality in older patients (over 65 years).[18]

Overt hypothyroidism

Overt hypothyroidism has cardiovascular effects that are, in many ways, opposite to those seen in thyrotoxicosis. Sinus bradycardia is the most common rhythm abnormality, although more sinister arrhythmias including QT interval prolongation leading to torsade de pointes have been reported.[2] Ventricular contractility is reduced, largely due to reduced expression of the myocyte sarcoplasmic reticulum calcium pump and increased expression of its inhibitor phospholamban.[2] These negative chronotropic and inotropic effects of hypothyroidism lead to a reduced cardiac output.

Overt hypothyroidism is associated with an increased risk of atherosclerosis, largely due to hypertension and dyslipidaemia. Blood pressure (mostly diastolic) is increased due to an increase in systemic vascular resistance.[1] Overt hypothyroidism has been consistently shown to cause elevations in total cholesterol and low-density lipoprotein (LDL) levels. Both synthesis and degradation of LDL-cholesterol are decreased in hypothyroidism but the latter predominates owing to reduced expression of LDL-cholesterol receptors and therefore clearance of LDL-cholesterol from the serum.[19]

Subclinical hypothyroidism

As with subclinical hyperthyroidism, diagnosis of subclinical hypothyroidism requires demonstration of persistently elevated TSH levels (with normal circulating levels of T4 and T3) on repeat testing at least two

to three months apart.[20] Causes of a transient elevation in TSH level include thyroiditis, nonthyroidal illness and use of drugs such as lithium. Mild elevations in TSH level (up to 7.5 mIU/L in people aged over 80 years) can occur with normal ageing.[21] However, for younger patients and those with greater elevation of TSH level, subclinical hypothyroidism may lead to an increased risk of dyslipidaemia, coronary artery disease and heart failure.

Dyslipidaemia

Several studies have suggested minor increases in serum lipid levels, particularly LDL-cholesterol, in patients with subclinical hypothyroidism.[22,23] In patients with dyslipidaemia, a meta-analysis suggests a small but measurable decrease in total and LDL-cholesterol levels with thyroxine treatment. Larger reductions occurred in patients with higher serum cholesterol levels.[24]

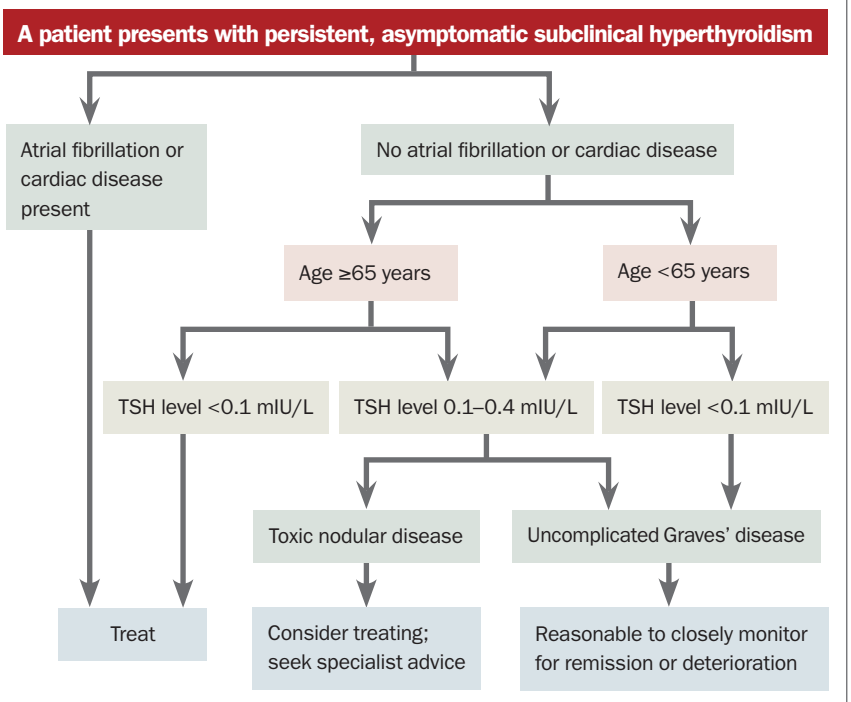
Coronary artery disease

Three meta-analyses have shown an association between subclinical hypothyroidism and coronary artery disease.[16,25,26] One of these studies analysed 55,287 patients from 11 cohort studies finding that subclinical hypothyroidism was associated with a higher risk of coronary artery disease events and coronary artery disease mortality, particularly with serum TSH levels of 10 mIU/L or greater.[25]

Some observational studies have suggested that the risk of coronary artery disease in subclinical hypothyroidism mainly applies to younger patients. In a meta-analysis, both occurrence of ischaemic heart disease and cardiovascular mortality were increased only in patients aged under 65 years.[26] In a population-based longitudinal study of patients aged over 65 years, subclinical hypothyroidism was not associated with an increased risk of coronary heart disease or cardiovascular death.[27]

There are no randomised controlled studies evaluating the effect of thyroxine replacement on coronary artery disease events. However, an observational analysis found fewer events for younger patients (under 70 years of age) treated with thyroxine, but this was not evident in older people (over 70 years of age).[28]

Suggested approach for the management of subclinical hyperthyroidism



Underlying atrial fibrillation (AF) or cardiac disease is an indication for treatment irrespective of age or degree of subclinical hyperthyroidism. For patients with TSH levels of 0.1 to 0.4 mIU/L and without underlying AF or cardiac disease, the cause of the subclinical hyperthyroidism influences the treatment decision. For example, it is possible for people with Graves' disease to spontaneously remit; thus in these patients careful observation is a reasonable approach. It is also not unreasonable to observe a patient with toxic nodular disease and a TSH level of 0.1 to 0.4 mIU/L; however, in this group, spontaneous remission usually does not occur. Furthermore, subclinical hyperthyroidism due to toxic nodular disease can be treated effectively with radioiodine or hemithyroidectomy without rendering the patient hypothyroid; specialist advice should be sought. Although this algorithm focuses on cardiovascular outcomes, treatment of subclinical hyperthyroidism should also be considered in patients with osteoporosis or who are postmenopausal where subclinical hyperthyroidism may increase bone resorption and fracture risk.

Heart failure

Several prospective studies have suggested an association between subclinical hypothyroidism and onset or progression of heart failure. A meta-analysis of six large prospective studies found a significantly higher rate of heart failure events when TSH levels exceeded 10 mIU/L, which was independent of increasing age.[14]

Should we treat thyroid disease to improve cardiac status?

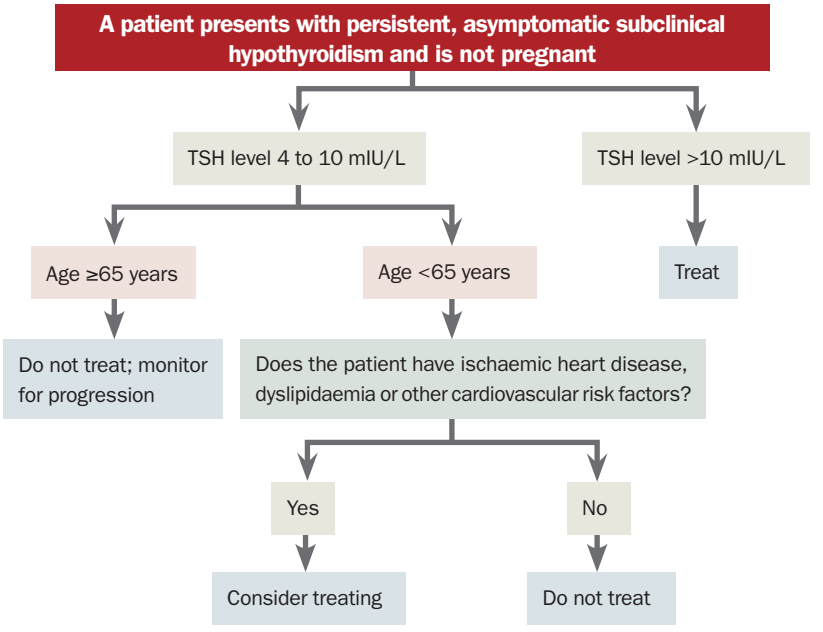
Overt thyrotoxicosis and hypothyroidism

Overt thyrotoxicosis and hypothyroidism are generally symptomatic, and treatment of persistent disease should occur irrespective of cardiac status. As noted above, cardiac effects of thyroid disease are more pronounced in this setting; therefore, it would be expected that the greatest absolute benefits for cardiac function and outcome would occur in patients with overt thyroid disease.

Subclinical hyperthyroidism

The decision of whether or not to treat a patient with persistent subclinical hyperthyroidism is not always straightforward. Depending on the cause, treatment may include antithyroid medication (carbimazole first-line outside of early pregnancy), radioiodine or thyroid surgery. In patients with underlying heart disease,

Suggested approach for the management of subclinical hypothyroidism



This flowchart does not apply to patients who are pregnant or planning to conceive, in which case the serum TSH level must be kept below 2.5 mIU/L. Patients with strongly positive antithyroid antibody titres are more likely to progress to overt hypothyroidism, and it may be reasonable to initiate treatment at an earlier stage.

When to consider referral of a patient with subclinical thyroid disease

Subclinical hyperthyroidism

- Diagnostic uncertainty
- Newly diagnosed Graves' disease
- Graves' disease with complications (e.g. thyroid eye disease)
- Multinodular goitre with suspicious nodule(s)
- Patients who would like to pursue thyroid surgery or radioiodine treatment, including those with toxic nodular disease
- Patients who are pregnant or planning to conceive

Subclinical hypothyroidism

- Diagnostic uncertainty (e.g. discordant thyroid function tests)
- Patients who are pregnant or planning to conceive
- Patients whose thyroid function tests have not normalised despite an adequate thyroxine dose
- Patients who are taking novel cancer therapies such as immune checkpoint inhibitors

most guidelines recommend treatment of subclinical hyperthyroidism with the evidence being strongest for those older than 65 years and/or a TSH level below 0.1 mIU/L. The flowchart on page 29 is a suggested outline for the management of persistent, asymptomatic subclinical hyperthyroidism.

Subclinical hypothyroidism

As with subclinical hyperthyroidism, treatment decisions for a patient with subclinical hypothyroidism need to be individualised. Thyroxine treatment is generally recommended if the TSH level exceeds 10 mIU/L. If the serum TSH level is elevated but below 10 mIU/L, the decision of whether or not to treat must incorporate patient factors, including age and whether or not there is underlying heart failure, atherosclerotic cardiovascular disease or other cardiac risk factors. The flowchart on this page is a suggested outline for the management of persistent, asymptomatic subclinical hypothyroidism in patients who are not pregnant or planning to conceive (in these cases the TSH level must be kept below 2.5 mIU/L). If thyroxine treatment is commenced, care must be taken to avoid over-treatment (i.e. TSH suppression), which may result in a deleterious risk–benefit profile for the patient.

Role of the GP in decision-making for subclinical thyroid disease

GPs play a central role in the diagnosis and management of patients with subclinical thyroid disease. Treatment decisions should be guided by evidence for the risks and benefits of therapy, local access to treatments (e.g. radioiodine and surgery) and patient preference. Situations in which a referral to an endocrinologist (or other specialist with thyroid expertise) should be considered are outlined in the Box. Irrespective of the initial approach taken, ongoing monitoring in the general practice setting is important to assess adequacy of treatment or to detect progression of disease in those patients who have not been treated.

Summary

Thyroid hormone has a number of important effects on the heart. Correspondingly, thyroid dysfunction can lead to various cardiovascular manifestations. Overt thyroid disease has the most pronounced cardiac effects and treatment is essential to prevent adverse cardiac outcomes. Subclinical thyroid disease, and the decision of whether or not to treat it for cardiovascular benefit, poses the greater clinical challenge. Subclinical hyperthyroidism is associated with adverse cardiac effects, particularly for older patients and those with a more suppressed TSH level. Subclinical hypothyroidism perhaps poses a greater cardiac risk to younger patients with underlying coronary heart disease or other cardiovascular risk factors. In all cases of subclinical thyroid disease, treatment decisions need to be individualised. The GP plays a central role in diagnosing and managing subclinical thyroid disease including identifying those patients that require a specialist review. **ET**

References

A list of references is included in the website version of this article (www.endocrinologytoday.com.au).

COMPETING INTERESTS: None.

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References

1. Klein I, Danzi S. Thyroid disease and the heart. Circulation 2007; 116: 1725-1735.
2. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001; 344: 501-509.
3. Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. Arch Intern Med 2004; 164: 1675-1678.
4. Nakazawa H, Lythall DA, Noh J, et al. Is there a place for the late cardioversion of atrial fibrillation? A long-term follow-up study of patients with post-thyrotoxic atrial fibrillation. Eur Heart J 2000; 21: 327-333.
5. Woeber KA. Thyrotoxicosis and the heart. N Engl J Med 1992; 327: 94-98.
6. Howard-Thompson A, Luckey A, George C, Choby BA, Self TH. Graves' disease and treatment effects on warfarin anticoagulation. Case Rep Med 2014; 2014: 292468.
7. Siu CW, Yeung CY, Lau CP, Kung AW, Tse HF. Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. Heart 2007; 93: 483-487.
8. Marvisi M, Zambrelli P, Brianti M, Civardi G, Lampugnani R, Delsignore R. Pulmonary hypertension is frequent in hyperthyroidism and normalizes after therapy. Eur J Intern Med 2006; 17: 267-271.
9. Scicchitano P, Dentamaro I, Tunzi F, et al. Pulmonary hypertension in thyroid diseases. Endocrine 2016; 54:578-587.
10. Biondi B, Bartalena L, Cooper DS, Hegedus L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism. Eur Thyroid J 2015; 4: 149-163.
11. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The Thyroid Epidemiology, Audit, and Research Study (TEARS): morbidity in patients with endogenous subclinical hyperthyroidism. J Clin Endocrinol Metab 2011; 96: 1344-1351.
12. 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.
13. Selmer C, Olesen JB, Hansen ML, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ 2012; 345: e7895.
14. Gencer B, Collet TH, Virgini V, et al. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation 2012; 126: 1040-1049.
15. Yang LB, Jiang DQ, Qi WB, et al. Subclinical hyperthyroidism and the risk of cardiovascular events and all-cause mortality: an updated meta-analysis of cohort studies. Eur J Endocrinol 2012; 167: 75-84.
16. Ochs N, Auer R, Bauer DC, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med 2008; 148: 832-845.
17. Haentjens P, Van Meerhaeghe A, Poppe K, Velkeniers B. Subclinical thyroid dysfunction and mortality: an estimate of relative and absolute excess all-cause mortality based on time-to-event data from cohort studies. Eur J Endocrinol 2008; 159: 329-341.
18. Cappola AR, Arnold AM, Wulczyn K, Carlson M, Robbins J, Psaty BM. Thyroid function in the euthyroid range and adverse outcomes in older adults. J Clin Endocrinol Metab 2015; 100: 1088-1096.
19. Pearce EN. Update in lipid alterations in subclinical hypothyroidism. J Clin Endocrinol Metab 2012; 97: 326-333.
20. Pearce SH, Brabant G, Duntas LH, et al. 2013 ETA Guideline: management of subclinical hypothyroidism. Eur Thyroid J 2013; 2: 215-228.
21. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab 2007; 92: 4575-4582.
22. Tognini S, Polini A, Pasqualetti G, et al. Age and gender substantially influence the relationship between thyroid status and the lipoprotein profile: results from a large cross-sectional study. Thyroid 2012; 22: 1096-1103.
23. Boekholdt SM, Titan SM, Wiersinga WM, et al. Initial thyroid status and cardiovascular risk factors: the EPIC-Norfolk prospective population study. Clin Endocrinol (Oxf) 2010; 72: 404-410.
24. Danese MD, Ladenson PW, Meinert CL, Powe NR. Clinical review 115: effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J Clin Endocrinol Metab 2000; 85: 2993-3001.
25. Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010; 304: 1365-1374.
26. Razvi S, Shakoor A, Vanderpump M, Weaver JU, Pearce SH. The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. J Clin Endocrinol Metab 2008; 93: 2998-3007.
27. Hyland KA, Arnold AM, Lee JS, Cappola AR. Persistent subclinical hypothyroidism and cardiovascular risk in the elderly: the cardiovascular health study. J Clin Endocrinol Metab 2013; 98: 533-540.
28. Razvi S, Weaver JU, Butler TJ, Pearce SH. Levothyroxine treatment of subclinical hypothyroidism, fatal and nonfatal cardiovascular events, and mortality. Arch Intern Med 2012; 172: 811-817.