A postmenopausal woman with subclinical hyperthyroidism

ALBERT HSIEH MB BS, BSc(Med), MMed(Clin Epi)
ELIZABETH L. CHUA MB BS, PhD, FRACP

Untreated subclinical hyperthyroidism may lead to significant cardiovascular and musculoskeletal complications. Investigations such as thyroid scintigraphy and thyroid antibody status will help define the underlying aetiology so treatment can be targeted.

Case scenario

Thyra is a postmenopausal woman aged 70 years. During her annual check up with her GP, her thyroid function test (TFT) showed a low but detectable thyroid-stimulating hormone (TSH) level of 0.32 mIU/L (reference range: 0.5–4.5 mIU/L) and free thyroxine level (free T4) of 13 pmol/L (reference range: 10–20 pmol/L). As she was clinically euthyroid, her GP monitored her TFT for 12 months. In January 2011, Thyra's TSH level reduced to 0.06 mIU/L so she was referred to an endocrine outpatient clinic.

When Thyra was reviewed at the endocrine outpatient clinic in April 2011, she was clinically euthyroid, her body mass index was 22.3 kg/m2, her pulse rate was 76 beats per minute and she was normotensive. On thyroid examination, she had a multinodular goitre with no retrosternal extension and Pemberton's sign was negative. There were no signs of ophthalmopathy. Her TSH level was undetectable (<0.04 mIU/L), but she had a normal free T4 level of 16 pmol/L and a normal free triiodothyronine (free T3) level of 5.8 pmol/L (reference range: 3.5–6.0 pmol/L).

What is subclinical hyperthyroidism?

Suppressed TSH levels with normal free T_4 and free T_3 levels occur in approximately 1% of the general population (National Health and Nutrition Examination Survey 0.7%,[2] Busselton study 1.7%[3]). As TFT results can fluctuate over time, it is recommended to repeat these tests after three to six months. When TSH levels are persistently low and free T_4 and free T_3 levels are normal, a diagnosis of subclinical hyperthyroidism is made.[1]

Case continued

Over the ensuing months, Thyra noticed episodes of palpitations particularly when she was at rest but denied any symptoms of heat intolerance, weight change or appetite change. She could consciously feel the goitre when she was swallowing or moving her neck, but denied dysphagia or airway symptoms. TFTs in June 2011 showed an undetectable TSH level of less than 0.04 mIU/L, midnormal free T_4 level of 15 pmol/L and mildly elevated free T_3 level of 6.2 pmol/L.

A thyroid nuclear scintigraphy scan showed three hot nodules (see Figure 1), which corresponded to the three nodules seen on an ultrasound examination. Uptake of radiotracer throughout the rest of the gland was partially suppressed, findings consistent with

© SCIENCE PHOTO LIBRARY/JOHN BAVOSI

Key points

- **Subclinical hyperthyroidism is defined as persistently suppressed thyroid-stimulating hormone levels with normal free thyroxine and free triiodothyronine levels.**
- **The most common cause of subclinical hyperthyroidism in people over 65 years of age is toxic multinodular goitre.**
- **Subclinical hyperthyroidism can lead to cardiovascular, musculoskeletal and neurological complications.**
- **All individuals over 65 years of age with subclinical hyperthyroidism should be considered for treatment.**

ENDOCRINOLOGY TODAY 2013; 2(4): 32-35

Dr Hsieh is an Endocrinology Fellow at the Department of Endocrinology, Royal Prince Alfred Hospital, Sydney; and a PhD Scholar at Sydney Medical School, The University of Sydney.
Dr Chua is Director of the Endocrinology and Metabolism Centre, Royal Prince Alfred Hospital, Sydney; and Clinical Senior Lecturer at Sydney Medical School, The University of Sydney, Sydney, NSW.

autonomously functioning nodules in a multinodular goitre. As a part of screening for complications, bone mineral densitometry was carried out even though Thyra had no history of fracture, exogenous corticosteroid use or early menopause. Her lumbar spine T-score was -2.7, consistent with a diagnosis of osteoporosis (see Figure 2).

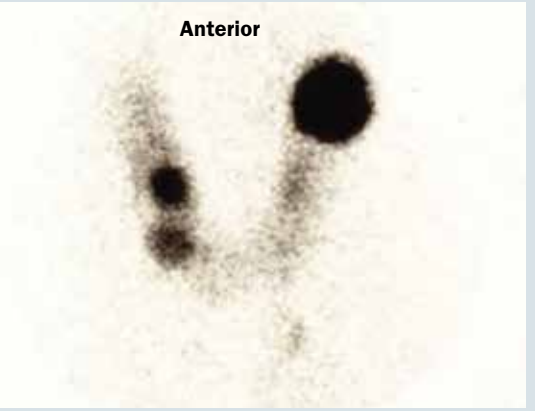

Figure 1. Thyroid nuclear scintigraphy scan showing three hot nodules

2011

Scan site	Region	BMD	Young adult T-score SD	Classification
Anteroposterior spine	L2-L4	0.881 g/cm²	-2.7	Osteoporosis
Left femur	Total	0.778 g/cm²	-1.9	Osteopenia

2013

Scan site	Region	BMD	Young adult T-score SD	Classification	Change (%)
Anteroposterior spine	L2-L4	0.907 g/cm²	-2.4	Osteopenia	3.0
Left femur	Total	0.854 g/cm²	-1.2	Osteopenia	9.8

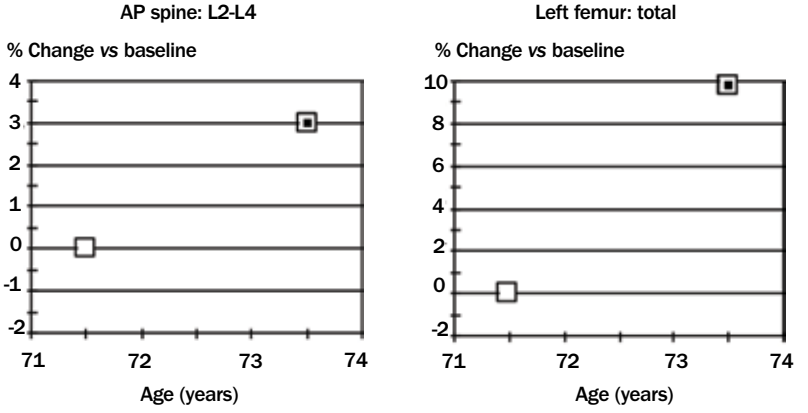

Figure 2. Bone mineral density (BMD) scan results in 2011 (before radioactive iodine therapy) and in 2013 (after treatment).

What investigations would help define the nature of the thyroid problem?

The most common cause of subclinical hyperthyroidism in people over 65 years of age is toxic multinodular goitre (common causes and differential diagnoses of subclinical hyperthyroidism are listed in the boxes on page 34). Thyroid nuclear scintigraphy will demonstrate focal areas of increased uptake with suppression of the surrounding thyroidal tissue. In patients with a single toxic adenoma, there will be focal uptake in the nodule with partial or complete suppression of the rest of the gland depending on the degree of hyperthyroidism.

TSH receptor antibodies for Graves' disease will be negative in patients with toxic multinodular goitre or a single toxic adenoma. Antibodies to thyroid peroxidase and thyroglobulin will be negative unless there is coexisting autoimmune thyroiditis (Hashimoto's disease), which is also common in patients over 65 years of age.

What are the risks of persistent subclinical hyperthyroidism?

Overt hyperthyroidism is well recognised to be associated with systemic morbidity. However, persistent subclinical hyperthyroidism can also have deleterious effects on cardiovascular, musculoskeletal and neurological systems (see the box on page 34).

It is reported that there is a 2.8-fold risk of atrial fibrillation in people over 60 years of age with low TSH levels (less than 0.10 mIU/L).[4,5] Some uncontrolled studies have shown improvement in haemodynamic parameters with restoration of normal TFT results.[6,7]

Mildly suppressed TSH levels have been associated with increased fracture rates in postmenopausal women with persistent subclinical hyperthyroidism.[8] This is likely to be secondary to increased bone turnover[9] and loss of protective effect from oestrogen. When subclinical hyperthyroidism is treated, there is evidence of improvement in bone mineral density.[10,11]

In addition to the systemic adverse effects, the rate of progression to overt hyperthyroidism is 0.5 to 1% per year.[12,13] On serial TFTs, TSH becomes more suppressed, followed by mild elevation of free T_3 (T_3 toxicosis). Over time, free T_4 also becomes elevated.

Causes of subclinical hyperthyroidism

- Toxic multinodular goitre
- Solitary toxic adenoma
- Graves' disease

Differential diagnosis of subclinical hyperthyroidism

- Central hypothyroidism
- Sick euthyroid syndrome
- Corticosteroid therapy

Potential morbidities of subclinical hyperthyroidism

- Atrial fibrillation
- Reduced bone mineral density, osteoporosis, increased fracture risk
- Reduced muscle mass and muscle strength
- Altered cognitive function in individuals with cognitive impairment
- Progression to overt hyperthyroidism

Mortality data in subclinical hyperthyroidism are varied. Some studies suggest that all-cause mortality risk progressively increases with age;[13-15] however, two longitudinal studies and a meta-analysis reported no increase in overall mortality.[3,5,16]

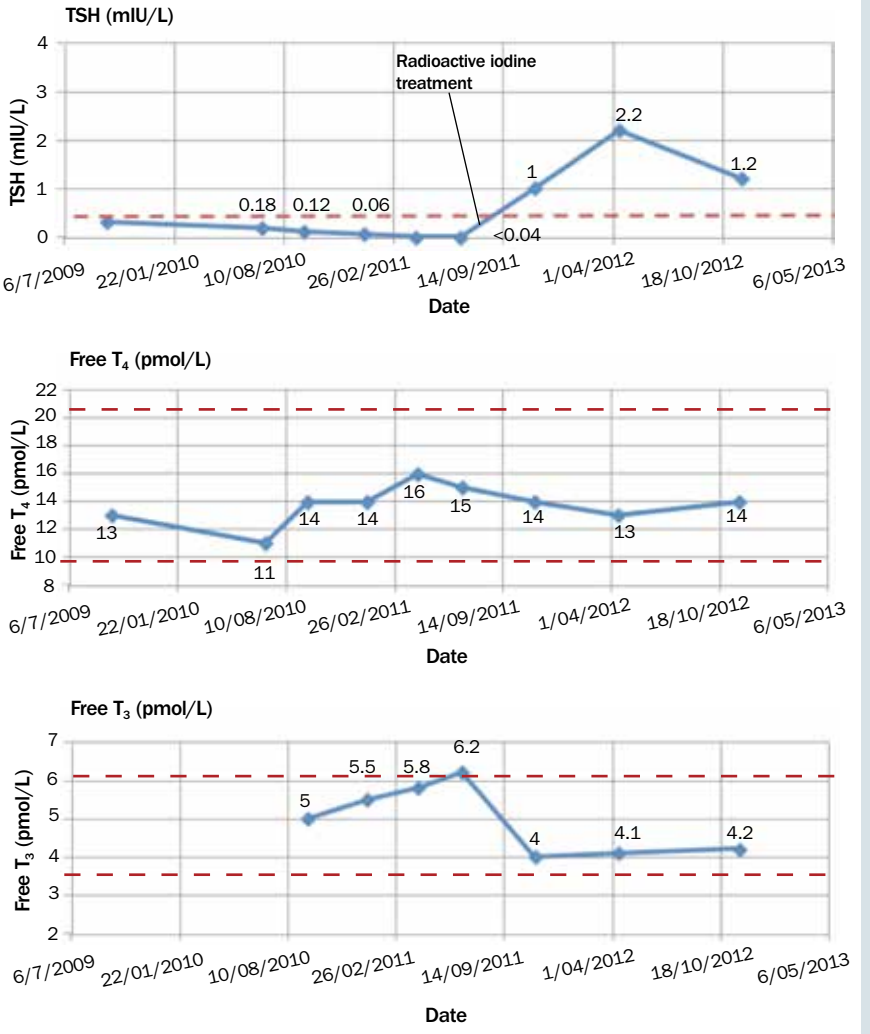

Figure 3. Progressive thyroid function test results from 2009 to 2013.

Case concluded

Thyra elected to have radioactive iodine (RAI) therapy and was given 15 mCi (555 MBq) of I-131. Progressive TFTs showed normalisation of thyroid function and there was also significant improvement in bone mineral density (see Figures 2 and 3).

When is treatment indicated?

According to the American Thyroid Association (ATA) guidelines, when the TSH level is persistently less than 0.1 mIU/L in individuals 65 years of age or over, treatment should be strongly considered.[1] Although there have been no controlled interventional studies on outcome, the benefits of treatment based on published studies were considered as sufficient evidence to recommend this approach.

Although there are insufficient data to recommend general treatment for individuals less than 65 years of age, those with risk factors should be treated. Patients with risk factors are: postmenopausal women who are not taking oestrogens or bisphosphonates; people with cardiac risk factors, heart disease or osteoporosis; and individuals with hyperthyroid symptoms.

When the TSH level is over 0.1 mIU/L but persistently below the lower limit of normal, the ATA guidelines recommend considering treatment for people over 65 years and individuals less than 65 years with comorbidities (see Table).[1]

What are the treatment options?

Treatment should be planned to target the underlying aetiology. RAI is an appropriate treatment option for older patients with toxic multinodular goitre. If the patient's free T_4 and free T_3 levels are within the normal range or mildly elevated, use of antithyroid medications is not necessary because the risk of thyroid storm from RAI treatment is very low. Patients with both hot and cold nodules on thyroid scintigraphy are not ideal candidates for RAI therapy. Surgery would be the preferred option if the patient experiences compressive symptoms or dysphagia, or there are nodules suspicious for malignancy. Low-dose antithyroid drugs (e.g. carbimazole)

would be a suitable treatment alternative for patients who are either poor surgical candidates or prefer conservative management, but medication is likely to be needed lifelong.

As RAI is preferentially absorbed in hyperfunctioning nodules, most patients remain euthyroid after treatment. In an individual who has a toxic multinodular goitre or adenoma without any comorbidities or hyperthyroid complications, the ideal time for RAI therapy is when the thyroid scintigraphy shows suppression of uptake of the surrounding tissue. This results in less accumulation of RAI in normal thyroid tissue and minimises the risk of hypothyroidism post-RAI. All patients should be followed up six to eight weeks after RAI treatment. TSH may remain suppressed with low T_4 and T_3 levels as it takes time for the paranodular tissue to recover its function. Depending on the result, subsequent TFTs can be checked two to three monthly. Thereafter, patients who are euthyroid post-RAI should have annual TFT monitoring.

If subclinical hyperthyroidism is secondary to Graves' disease, antithyroid medications are regarded as the first-line therapy for the first episode. These usually induce remission without the risk of hypothyroidism post-RAI or surgery.[17]

When to refer to a specialist?

If subclinical hyperthyroidism is documented and there are significant cardiovascular and/or musculoskeletal comorbidities, or if thyrotoxic symptoms are present, it is best to refer the patient to an endocrinologist or physician experienced in thyroid care. Serial TFTs, thyroid nuclear scintigraphy and ultrasound examination for nodular goitres, and testing for TSH receptor antibodies and antithyroid antibodies, if clinically indicated, will be appropriate investigations to start with.

If an individual is clinically thyrotoxic, appropriate beta blockers can be initiated to control the symptoms. Antithyroid medication should only be commenced after thyroid scintigraphy (if indicated) has been carried out and only to individuals who have high free T_4 and free T_3 levels.

Table. When to treat subclinical hyperthyroidism[1]

TSH (mIU/L)	Age (years)	Symptoms/ comorbidities/ menopausal	Treatment
<0.1	≥65	Yes	Yes
<0.1	≥65	No	Yes
<0.1	<65	Yes	Yes
<0.1	<65	No	Consider treating
0.1–0.5 (or lower level of normal reference range)	≥65	Yes	Consider treating
0.1–0.5 (or lower level of normal reference range)	≥65	No	Consider treating
0.1–0.5 (or lower level of normal reference range)	<65	Yes	Consider treating
0.1–0.5 (or lower level of normal reference range)	<65	No	No

Adapted from 2011 American Thyroid Association and American Association of Clinical Endocrinologists guidelines.[1]

Summary

Subclinical hyperthyroidism should be considered on the same continuum as overt hyperthyroidism. Although the early clinical manifestations may be subtle, untreated subclinical hyperthyroidism may lead to significant cardiovascular and musculoskeletal complications. Investigations such as thyroid scintigraphy and thyroid antibody testing will help define the underlying aetiology. Treatment should be individualised based on the patient's age, TSH level and clinical manifestations. ET

References

1. Bahn Chair RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 2011; 21: 593-646.
2. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002; 87: 489-499.
3. Walsh JP, Bremner AP, Bulsara MK, et al. Subclinical thyroid dysfunction and blood pressure: a community-based study. Clin Endocrinol (Oxf) 2006; 65: 486-491.
4. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994; 331: 1249-1252.
5. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA 2006; 295: 1033-1041.
6. Sgarbi JA, Villaca FG, Gardeline B, Villar HE, Romaldini JH. The effects of early antithyroid therapy for endogenous subclinical hyperthyroidism in clinical and heart abnormalities. J Clin Endocrinol Metab 2003; 88: 1672-1677.
7. Faber J, Wiinberg N, Schifter S, Mehlsen J. Haemodynamic changes following treatment of subclinical and overt hyperthyroidism. Eur J Endocrinol 2001; 145: 391-396.
8. Bauer DC, Ettinger B, Nevitt MC, Stone KL; Study of Osteoporotic Fractures Research Group. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. Ann Intern Med 2001; 134: 561-568.
9. Tauchmanovà L, Nuzzo V, Del Puente A, et al. Reduced bone mass detected by bone quantitative ultrasonometry and DEXA in pre- and postmenopausal women with endogenous subclinical hyperthyroidism. Maturitas 2004; 48: 299-306.
10. Faber J, Jensen IW, Petersen L, et al. Normalization of serum thyrotrophin by means of radioiodine treatment in subclinical hyperthyroidism: effect on bone loss in postmenopausal women. Clin Endocrinol (Oxf) 1998; 48: 285-290.
11. Mudde AH, Houben AJ, Nieuwenhuijzen Kruseman AC. Bone metabolism during anti-thyroid drug treatment of endogenous subclinical hyperthyroidism. Clin Endocrinol (Oxf) 1994; 41: 421-424.
12. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med 1991; 151: 165-168.
13. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet 2001; 358: 861-865.
14. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. JAMA 2004; 292: 2591-2599.
15. 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.
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. Cooper DS. Antithyroid drugs. N Engl J Med 2005; 352: 905-917.

COMPETING INTERESTS: None.