

## BEST PRACTICE

## Subclinical hyperthyroidism: to treat or not to treat?

E H Hoogendoorn, M den Heijer, A P J van Dijk, A R Hermus

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Subclinical hyperthyroidism may be defined as the presence of free thyroxine and tri-iodothyronine levels within the reference range and a reduced serum thyroid stimulating hormone (TSH) level. In this review the prevalence of low TSH in the population and health consequences of subclinical hyperthyroidism, for example, effects on heart and bone mass, are discussed. Guidelines for treatment are given, based on expert opinion.

Subclinical hyperthyroidism may be defined as the presence of free thyroxine and tri-iodothyronine levels within the reference range and a reduced serum thyroid stimulating hormone (TSH) level. The cause is either exogenous thyroid hormone therapy or endogenous overproduction of thyroxine and/or tri-iodothyronine. Subclinical hyperthyroidism has to be differentiated from other causes of low serum TSH levels, such as non-thyroidal illness or the use of TSH suppressing medication other than thyroid hormone (for example, glucocorticoids, dopamine).<sup>1</sup> Exogenous subclinical hyperthyroidism can be due to overzealous thyroid hormone replacement therapy or intentional suppressive thyroid hormone therapy, as in patients with thyroid cancer, thyroid nodules, or goitre. In endogenous subclinical hyperthyroidism, the source of the mild excess of thyroid hormone in the circulation is the thyroid itself, as in Graves' disease, multinodular goitre, solitary functioning thyroid nodules, or thyroiditis. Iatrogenic subclinical hyperthyroidism may not be the same condition as endogenous subclinical hyperthyroidism, but there is no clear evidence supporting this statement.

With the easy availability of sensitive TSH assays in the last decades, the diagnosis subclinical hyperthyroidism is made more often.<sup>2</sup> An absence of symptoms was once part of the definition but we now understand that subtle symptoms or signs of thyrotoxicosis may be present.<sup>3</sup> There seems to be an individual set point for thyroid hormone values in each individual.<sup>4</sup> TSH outside the reference range is likely to indicate that tri-iodothyronine and thyroxine levels are not normal for that particular person. Due to the log linear negative feedback relationship between serum thyroid hormone and TSH, even a small increase in serum thyroid hormone can suppress TSH secretion. Whether there is a difference between patients with a low, but detectable TSH versus patients with a fully suppressed TSH is unclear.

## PREVALENCE OF LOW TSH IN THE POPULATION

Bagchi *et al* found serum TSH values  $<0.1$  mU/l in 2.5% of 968 United States citizens over age 55, two thirds of whom were taking thyroid hormone preparations.<sup>5</sup> In the original Framingham Heart Study cohort—2575 ambulatory persons older than 60 years—3.9% had a serum TSH  $<0.1$  mU/l, and about half of them were taking thyroid hormone. Overt hyperthyroidism was only found in 0.2%.<sup>6</sup> In a cross sectional study, conducted in 1995 in Colorado with 25 862 participants, TSH levels  $<0.3$  mU/l were found in 2.1% of people over 18 years of age, in 1.3% due to thyroid hormone use. One out of five patients treated with thyroid hormone showed suppression of TSH.<sup>7</sup> The third National Health and Nutrition Examination Survey in the United States from 1988 to 1994 found TSH levels  $<0.1$  mU/l and normal thyroxine ( $<169.9$  nmol/l) in 0.7% of people over 12 years of age.<sup>8</sup> In the subgroup of 820 persons self reporting thyroid disease or taking thyroid medications, 10.9% had subclinical hyperthyroidism. In a cross sectional survey in a previously iodine deficient area of Germany thyroid function was measured in 3941 participants without known thyroid disease between the ages of 20 and 79 years. A TSH  $<0.3$  mU/l was found in 11.3%.<sup>9</sup> Subclinical hyperthyroidism (TSH  $<0.1$  mU/l and normal serum free thyroxine and free tri-iodothyronine levels) was found in 1.8%, distributed similarly among women and men, but age dependent with higher percentages in the older decades. In conclusion, the prevalence of subclinical hyperthyroidism varies depending on the criteria used and is age dependent (table 1).

There are few data on the follow up of thyroid function in patients with suppressed TSH levels. It is important to know that not infrequently on retesting some time later, TSH levels have returned to normal. For instance, Parle *et al* followed up 66 patients with TSH results below normal found in a cohort of 1193 subjects aged over 60 years, not taking thyroid medication. Of the 50 subjects with a TSH level between 0.05 and 0.5 mU/l at initial testing, 38 (76%) returned to normal at 12 months; of those 16 with a TSH level  $<0.05$  mU/l, 14 (87.5%) remained low at 12 months. Only one subject (who had an undetectable TSH) developed overt hyperthyroidism.<sup>10</sup> Besides that seven of those with a low TSH level were using oral glucocorticoids—a known cause of suppression of TSH—it is likely that non-thyroidal illness, instead of subclinical

**Abbreviations:** BMD, bone mineral density; TSH, thyroid stimulating hormone

See end of article for authors' affiliations

Correspondence to:  
Dr E H Hoogendoorn,  
Department of  
Endocrinology, University  
Medical Center Nijmegen,  
PO Box 9101, 6500 HB  
Nijmegen,  
The Netherlands;  
e.hoogendoorn@  
endo.umcn.nl

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**Table 1** Prevalence of a suppressed serum TSH level in community based surveys. The studies by Parle *et al*<sup>10,14</sup> are based on the same cohort

Author	Year	No of subjects	Age (years)	Cut off value (mU/l)	% TSH suppressed	% Overtly hyperthyroid	% Thyroid hormone use
Bagchi <i>et al</i> <sup>6</sup>	1990	986	55–92	<0.1	2.5	?	1.7
Parle <i>et al</i> <sup>10</sup>	1991	1210	>60	<0.5	Male 5.5 ; female 6.3	?	0.0
Sawin <i>et al</i> <sup>6</sup>	1991	2575	>60	<0.1	3.9	0.2	2.0
Canaris <i>et al</i> <sup>7</sup>	2000	25862	>18	<0.3	2.2	0.1	1.3
Parle <i>et al</i> <sup>14</sup>	2001	1191	>60	<0.1	1.7	0.1	0.0
Hollowel <i>et al</i> <sup>6</sup>	2002	17353	>12	<0.1	1.2	0.5	?
Volzke <i>et al</i> <sup>6</sup>	2003	3941	20–79	<0.3	11.3	0.4	0.0
				<0.1	2.2		

hyperthyroidism, was responsible for a number of the mildly decreased TSH values in this study.

In endogenous subclinical hyperthyroidism due to multinodular goitre, there seems to be a pattern of slow progression towards overt hyperthyroidism. In a Dutch study of 90 patients with euthyroid multinodular goitre, mainly women with a mean age of 55 years, eight became hyperthyroid within seven years and all of them had autonomous function before becoming hyperthyroid.<sup>11</sup> Faber *et al* followed up 12 women with subclinical hyperthyroidism due to multinodular goitre, median age 62 years, for two years, and none of them became overtly hyperthyroid nor euthyroid during that time.<sup>12</sup>

### HEALTH CONSEQUENCES OF SUBCLINICAL HYPERTHYROIDISM

The influence of subclinical hyperthyroidism on health is not yet clear. Evidence is accumulating that it has important clinical effects.<sup>13</sup> The most prominent physical consequences seem to be adverse effects on cardiac function, most significantly a higher incidence of atrial fibrillation and a decrease in bone density (particularly of cortical bone). Furthermore, it is debated whether subclinical hyperthyroidism is associated with excess mortality. In a population based study in the United Kingdom among 1191 people older than 60 years not receiving thyroid hormone or antithyroid therapy, 1.7% had TSH concentrations less than 0.1 mU/L, and 4.3% had concentrations between 0.1 and 0.5 mU/L.<sup>14</sup> Mortality from all causes was significantly higher at years 2, 3, 4, and 5 (hazard ratios 2.1, 2.2, 1.8, and 1.8, respectively), but not at the end of the study (hazard ratio 1.2), in the subjects with suppressed TSH.<sup>14</sup> Most of the increased mortality was due to cardiovascular disease. However, these data should be viewed cautiously, because, as mentioned before, in a number of subjects low serum TSH concentrations may have been caused by non-thyroidal illness or use of TSH suppressing medication instead of subclinical hyperthyroidism.

#### Effects on the heart

Overt hyperthyroidism causes palpitations, with some degree of exercise impairment and a widened pulse pressure, resulting from both an increase in sympathetic tone and a decrease in parasympathetic tone, combined with direct effects of thyroid hormone on cardiac muscle.<sup>15</sup> It can induce significant cardiac dysfunction, for example atrial fibrillation and heart failure.<sup>16</sup> Most patients who develop heart failure during hyperthyroidism have intrinsic cardiac disease, but also thyrotoxic persons without underlying heart disease can develop so-called rate related heart failure.

Whether subclinical hyperthyroidism can also induce cardiac dysfunction is less clear. Biondi *et al* found more atrial premature beats and a 20% higher mean heart rate in

20 relatively young patients with iatrogenic subclinical hyperthyroidism, compared with controls. In addition, echocardiographic measurements showed evidence of left ventricular hypertrophy in six of 20 patients.<sup>17</sup> Reduced exercise tolerance, diastolic dysfunction, and impaired systolic function during exercise are other findings in a group of 10 subjects, all of whom had been treated with TSH suppressive doses of L-thyroxine for at least five years and all of whom complained of exertional dyspnoea.<sup>18</sup> Both myocardial hypertrophy and diastolic dysfunction improved after treatment with  $\beta$ -blocking agents.<sup>19,20</sup> Six months of individual tailoring of the TSH suppressive L-thyroxine dose aiming at a TSH of 0.1 mU/L was associated with normalisation of echocardiographic parameters and an increase in maximal workload.<sup>21</sup> In contrast to these studies, Shapiro *et al* found hardly any cardiac effects in 17 patients chronically treated with TSH-suppressive doses of L-thyroxine.<sup>22</sup> All studies mentioned above were done in patients with a TSH level <0.1 mU/L. However, it should be noted that Shapiro *et al* studied patients only minimally different from controls with respect to results of a symptom score questionnaire, while Biondi *et al* and Mercurio *et al* studied patients who had a clear increase in symptom scores.

There is little known about the effects of endogenous subclinical hyperthyroidism on the heart. Biondi *et al* demonstrated an increase of left ventricular mass, more specifically an increase of septal and posterior wall thickness, enhanced resting systolic function and significantly impaired Doppler parameters of diastolic function in relatively young patients (mean age 43 years).<sup>23</sup> Two small recent studies suggest a beneficial effect of treatment of subclinical hyperthyroidism on cardiac function. Faber *et al* treated six elderly women with subclinical hyperthyroidism due to multinodular goitre with radioiodine resulting in euthyroidism and found a significant reduction in heart rate, cardiac output and an increase in systolic vascular resistance.<sup>24</sup> Sgarbi *et al* treated 10 patients, median age 59 years, with endogenous subclinical hyperthyroidism due to a multinodular goitre (n = 5), a solitary functioning thyroid nodule (n = 2), or a diffuse goitre (n = 3) for six months with antithyroid therapy.<sup>25</sup> After reaching euthyroidism they found a significant decrease in heart rate and in the number of atrial and ventricular premature beats. Echocardiography demonstrated a reduction of the left ventricular mass index, interventricular septum thickness, and left ventricular posterior wall thickness at diastole.

A major concern is that subclinical hyperthyroidism is associated with an increased incidence of atrial fibrillation. It is well known that overt hyperthyroidism is associated with atrial fibrillation: atrial fibrillation occurs in approximately 15% of all thyrotoxic patients and hyperthyroidism accounts for 15% of all patients with newly diagnosed atrial fibrillation.<sup>26</sup> Tenerz *et al* followed up 40 patients, mainly women

with a mean age of 65 years, with subclinical thyrotoxicosis (TSH below 0.1 mU/l) mostly due to multinodular goitre for two years. They found that atrial fibrillation was present in 28% of the patients (in eight patients at the start of the study and in three more after two years) compared with 10% of the controls (four at the start and no new cases during follow up).<sup>27</sup> Researchers from the Framingham Heart Study followed 2007 subjects over 60 years of age for 10 years.<sup>28</sup> The cumulative incidence of atrial fibrillation varied with the serum TSH concentration: it was 28% in those with serum TSH values <0.1 mU/l, 16% in those with values between 0.1 and 0.4 mU/l, and 11% in those with normal TSH values. Only two of the 13 patients with suppressed TSH values who developed atrial fibrillation also developed overt hyperthyroidism during the follow up period. In a large retrospective study by Auer *et al* the relative risk of atrial fibrillation in subjects with a TSH of <0.4 mU/l and normal free thyroxine and tri-iodothyronine concentrations was 5.2 (95% confidence interval 2.1 to 8.7), compared with those with normal concentrations of serum TSH.<sup>29</sup> They also found that atrial fibrillation is as common in patients with subclinical hyperthyroidism (12.7%) as in those with overt hyperthyroidism (13.8%). Restoration of euthyroidism resulted in conversion to sinus rhythm in only 19% of patients with subclinical hyperthyroidism. There are no data available as to whether treatment of subclinical hyperthyroidism prevents the development of atrial fibrillation.

In conclusion, the majority of data suggest that thyroid hormone levels above the hypothalamic-pituitary set point have a negative effect on cardiac function and morphology. Furthermore, subclinical hyperthyroidism is associated with a significantly increased risk on atrial fibrillation.

### Effects on bone mass

Overt hyperthyroidism is associated with increased bone resorption and, to a lesser extent, increased bone formation. The changes are more prominent in cortical bone (for example, wrist and hip) than in trabecular bone (for example, lumbar spine).<sup>30</sup> Studies of the effects of exogenous subclinical hyperthyroidism on bone have provided conflicting results. Two large meta-analyses reached a similar conclusion, namely that TSH suppressive doses of L-thyroxine decrease bone mineral density (BMD) in postmenopausal but not in premenopausal women and in men.<sup>31, 32</sup> Preserved oestrogen production is considered to protect against loss of bone mass in premenopausal women with suppressed TSH.

Endogenous subclinical hyperthyroidism seems to confer the same risks as suppressive L-thyroxine doses, although considerably fewer data are available. Mudde *et al* studied 23 women (six premenopausal and 17 postmenopausal) with subclinical hyperthyroidism due to untreated multinodular goitre. They found significantly lower bone densities at the forearm in patients than in age and menopausal status matched euthyroid controls.<sup>33</sup> Treatment of subclinical hyperthyroidism has probably a beneficial effect on BMD, as demonstrated in two small studies. Mudde *et al* normalised serum TSH in eight subclinically hyperthyroid postmenopausal women by treating them with methimazole. After two years a cessation of further bone loss was demonstrated as measured over the distal forearm, compared with untreated controls.<sup>34</sup> Faber *et al* treated 16 postmenopausal women with subclinical hyperthyroidism due to multinodular goitre in a non-randomised manner with radioiodine, and found unchanged BMD at the spine and hip two years later, while in contrast in the control group (n = 12) BMD showed a decline of 2% per year.<sup>12</sup>

While overt hyperthyroidism is known to be associated with increased fracture risk, data are less clear for subclinical

hyperthyroidism.<sup>35</sup> A study on 1180 patients on thyroxine replacement therapy (90% female, 75% over 50 years of age) found no excess of fractures in patients with TSH <0.05 mU/l compared to those with normal TSH levels.<sup>36</sup> However, a large prospective study with a mean follow up of 3.7 years found that women over age 65 with a low TSH level (<0.1 mU/l) have a threefold increased risk for hip fracture and a fourfold increased risk for vertebral fracture compared with women who had normal TSH levels (0.5–5.5 mU/l).<sup>37</sup> In the group with suppressed TSH, 86% reported thyroid hormone use. Unfortunately, tri-iodothyronine and thyroxine were not measured in this study, so it is not clear how many of these women had overt compared with subclinical hyperthyroidism.

In conclusion, it seems that postmenopausal women with subclinical hyperthyroidism have a lower BMD but there is no firm evidence that there is an increased risk of fractures in this group.

### Quality of life, mood, and dementia

Biondi *et al* have reported that relatively young patients with endogenous subclinical hyperthyroidism have impaired quality of life as assessed by the Short Form 36 Health Survey.<sup>23</sup> In contrast, in a non-hospital setting, an improvement in mood has been reported by subclinically hyperthyroid workers of a chemical plant, taking part in a screening programme.<sup>38</sup> Oomen *et al* determined thyroid function in all patients admitted to three psychiatric hospitals in the Netherlands between 1987 and 1990, and detected TSH levels <0.4 mU/l in 4.1% (134/3316). They found that affective disorders (particularly depression in females and mania in males) were more prevalent in patients with a suppressed TSH level, most of whom had subclinical rather than overt hyperthyroidism.<sup>39</sup> Since the number of subclinically hyperthyroid individuals in these studies was small, it is hard to draw firm conclusions on mood, affective disorders, or quality of life.

Interestingly, in a population based prospective study among 1846 persons over 55 years of age, 61.9% females, it was found that subjects with serum TSH concentrations <0.4 mU/l at baseline had a 3.5-fold increased risk of dementia during a 2–4 year follow up period. The risk of dementia was especially increased in subjects who were positive for antithyroid peroxidase antibodies.<sup>40</sup> Further studies with a longer follow up period and a larger sample

### List of useful websites

#### Information for doctors

- [www.thyroid.org/professionals/publications/guidelines.html](http://www.thyroid.org/professionals/publications/guidelines.html)
- [www.guidelines.gov](http://www.guidelines.gov)
- [www.aace.com/clin/guidelines/hypo\\_hyper.pdf](http://www.aace.com/clin/guidelines/hypo_hyper.pdf)
- [www.thyroidmanager.org](http://www.thyroidmanager.org)

#### Information for patients

- [www.thyroid.org/patients/index.html](http://www.thyroid.org/patients/index.html)
- [www.aace.com/members/brochures.php](http://www.aace.com/members/brochures.php)
- [www.hormone.org/learn/thyroid.html](http://www.hormone.org/learn/thyroid.html)

#### Self help groups

- [www.thyroidfoundation.org](http://www.thyroidfoundation.org)
- [www.btf-thyroid.org](http://www.btf-thyroid.org)
- [www.schildklier.nl](http://www.schildklier.nl) (in Dutch)

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size are needed to confirm this finding and to investigate the mechanism behind this association.

### Guidelines for treatment

Considering the evidence that exogenous subclinical hyperthyroidism may have adverse effects on heart and bone we agree with recommendations from the American Association of Clinical Endocrinologists stating that “in patients who are receiving levothyroxine for replacement therapy, the dose should be adjusted so serum TSH values range from 0.3 to 3.0 microIU/ml. An exception is thyroid hormone replacement treatment after thyroidectomy for differentiated thyroid cancer, in which case a mildly to moderately suppressed TSH level is generally desirable”.<sup>41</sup> In the latter case we prescribe the lowest amount of thyroid hormone possible to obtain a TSH of <0.1 mU/l. In addition, some physicians treat hypofunctional thyroid nodules with levothyroxine in doses which induce suppression of the TSH level. The benefits of this therapy should be weighted against the side effects.<sup>42</sup>

In patients with a suppressed TSH level due to an endogenous cause, it should be confirmed the suppressed TSH level is persistent rather than transient. Of course, a non-thyroidal cause such as non-thyroidal illness, pregnancy, pituitary or hypothalamic insufficiency, or the use of TSH suppressing medication other than thyroid hormone has to be excluded. The American Association of Clinical Endocrinologists recommends to reassess the TSH level along with free thyroxine and tri-iodothyronine estimates after 2–4 months. We follow the same policy.

Clearly randomised clinical trials are needed to answer the question whether or not treatment of endogenous subclinical hyperthyroidism prevents cardiac problems, especially atrial fibrillation, and protects BMD. Two such trials are soon to be started, one in the Netherlands and one in the United Kingdom. Current practice is mainly based on expert opinion. Older British guidelines do not favour treatment of subclinical hyperthyroidism, stating it is debatable whether there is excess morbidity.<sup>43</sup> Clinical guidelines from the American College of Physicians state that the potential benefits of treating subclinical hyperthyroidism are theoretical.<sup>44</sup> The American Association of Clinical Endocrinologists guidelines state, “If a sustained TSH suppression (<0.1 mU/l) is established, then management should be based on an

### Self test questions (true/false; answers at end of references)

- Q1. Multinodular goitre is the most common cause of subclinical hyperthyroidism.
- Q2. Subjects with low serum TSH and normal free thyroxine and tri-iodothyronine concentrations are more likely to get atrial fibrillation, compared with those with normal concentrations of serum TSH.
- Q3. Women over age 65 years with a low TSH level (<0.1 mU/l) have a threefold increased risk for hip fracture and a fourfold increased risk for vertebral fracture compared with women who have normal TSH levels (0.5 to 5.5 mU/l).
- Q4. Exogenous subclinical hyperthyroidism should be prevented at all times.
- Q5. Subclinical hyperthyroidism is a main cause of dementia.

### Summary box

#### Serum TSH <0.1 mU/l, free thyroxine and free tri-iodothyronine within reference range:

Is the patient taking thyroid hormone therapy?

- Yes. Adjust dose so serum TSH values range from 0.3 to 3.0 mU/l unless the patient is receiving thyroid hormone treatment after thyroidectomy for differentiated thyroid cancer, in which case the lowest amount of thyroid hormone possible to obtain a TSH of <0.1 mU/l should be prescribed.
- No. Reassess TSH, free thyroxine, and free tri-iodothyronine values after 2–4 months and exclude other causes of low TSH (such as non-thyroidal illness or the use of TSH suppressing medication other than thyroid hormone (for example, glucocorticoids, dopamine). If TSH remains suppressed, consider treatment in patients with signs or symptoms of thyrotoxicosis, especially when atrial fibrillation or osteoporosis is present.

individual program. For example, patients with symptoms of hyperthyroidism, atrial fibrillation, or unexplained weight loss would be appropriate candidates for treatment. Women with osteopenia or osteoporosis should undergo assessment for treatment. In patients with multinodular goitre, treatment should be considered. The treatment options include antithyroid drugs or radioactive iodine.<sup>41</sup> We agree with these guidelines. We prefer radioiodine therapy, but another option is antithyroid drug therapy. However, after discontinuation of antithyroid drugs, endogenous subclinical hyperthyroidism nearly always returns, making life long treatment necessary. In patients who do not have symptoms or signs of excess thyroid hormone thyroid function tests should be repeated every six months, with the recognition that tri-iodothyronine concentration may become raised before thyroxine does.<sup>3</sup>

#### Authors' affiliations

E H Hoogendoorn, M den Heijer, A R Hermus, Department of Endocrinology, University Medical Center Nijmegen, Netherlands

A P J van Dijk, Department of Cardiology, University Medical Center Nijmegen, Netherlands

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## ANSWERS

1. No, thyroid hormone therapy is the most common cause but multinodular goitre is the most common cause of endogenous subclinical hyperthyroidism. 2. Yes, five times as likely, according to the study by Auer *et al.*<sup>29</sup> 3. Yes, according to the study by Bauer *et al.*<sup>37</sup> 4. No, there are conditions in which suppressive doses of thyroid hormone are thought to be advisory—for example, in patients who have been treated for differentiated thyroid carcinoma. 5. No, but an association has been found by Kalmijn *et al* between low TSH and the development of dementia.<sup>40</sup>