Treatment options of subclinical hyperthyroidism and cardiovascular risk

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Key words: Subclinical hyperthyroidism, cardiovascular risk, thyroid surgery, Radioactive iodine treatment

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Abstract

Subclinical hyperthyroidism (SCH) is common and is characterized by laboratory findings of a persistently low TSH level and normal FT4 and FT3 values. The interpretation of studies on the clinical significance of SCH have been complicated by the fact that the degree and etiology of SCH varies, but research has suggested that it is associated with osteoporosis, weight changes, adverse cardiovascular effects including an increased risk of atrial fibrillation, and an increased all-cause mortality rate. We discuss SCH and review the literature on its suspected cardiovascular effects, which are more likely to be seen in the elderly and in patients with more significant degrees of TSH suppression. We then discuss SCH treatment options in detail and suggest an algorithm for the management of SCH that takes into consideration the TSH level and the presence of clinical risk factors.

1. Definition

Subclinical hyperthyroidism (SCH) is a common disease defined exclusively by biological criteria without consideration of the presence or absence of clinical signs and symptoms of hyperthyroidism. It is defined by a persistently low serum TSH (<0.4 mU/l) associated with FT4 and FT3 values within laboratory reference ranges (1). Depending on its biological severity, SCH can be divided into two categories: grade 1 SCH, in which the TSH level is only mildly suppressed (typically between 0.1 and 0.39 mU/L), and grade 2 SCH, in which the TSH is low or undetectable (typically <0.1 mU/L) (2). The prevalence of SCH varies from...
1 to 11%, depending on age, sex, iodine intake and the lower cut-off used to define the normal TSH range. An absolute definition of SCH is difficult because it seems that each individual has his or her own normal range that is much narrower than the accepted reference range for the general population (4). Because of the absence of significant symptomatology, most patients with SCH are detected during routine thyroid screening. The main causes of persistent endogenous SCH are the presence of autonomous thyroid tissue (toxic adenoma [TA], toxic multinodular goiter [TNG]) and subclinical Graves’ disease (GD). The relative prevalence of thyroid autonomy and Graves’ disease depends on iodine intake, with thyroid autonomy being by far the predominant cause in areas with mild or moderate iodine deficiency (5-8).

In the absence of major intervention trials, most of the reported effects of SCH are derived from observational studies that must be interpreted with caution given the etiological heterogeneity of SCH; population heterogeneity in terms of age, sex and severity of SCH; the fact that the diagnosis is often based on a single TSH assay; and variability in SCH duration, which is often unknown. This heterogeneity can probably explain the conflicting results across different studies. The main suspected clinical effects of SCH are changes in bone metabolism, mineral density, body weight and heart disease, including atrial fibrillation (1).

2. Thyroid hormone effects on the heart

T4 is secreted by the thyroid gland and converted in the periphery to the biologically active hormone T3. The cellular actions of thyroid hormones are mediated by their binding to nuclear receptors, which act as transcription factors that modulate gene expression. Thyroid hormone receptor affinity is approximately ten-fold higher for T3 than for T4. Thyroid hormones’ actions on the heart are exerted via genomic and non-genomic pathways. The main physiological cardiovascular effects of thyroid hormone excess have already been extensively described and include increased resting heart rate, cardiac contractility and decreased relaxation time. The incompletely understood interactions between T3 and the adrenergic nervous system also contribute to the chronotropic effect of thyroid hormones. The effect of thyroid hormone excess manifests as tachycardia and an increased risk of atrial fibrillation (AF) (9).
2.1 Cardiovascular consequences of SCH

2.1.1 Functional and structural alterations

The effects of thyroid hormones and hyperthyroidism on the myocardium and heart rhythm have been well documented (9). Even in the presence of euthyroidism, a correlation is observed between serum T3 levels and certain parameters such as left ventricular size and heart rate (10). Compared with euthyroid controls, patients with SCH have a higher mean 24-hour heart rate and increased frequency of premature atrial and ventricular beats (11-14). Some studies have also reported changes in echocardiographic parameters such as increased left ventricular mass, relaxation disorders and diastolic dysfunction (12,13). However, two prospective studies performed in elderly subjects did not find an association between SCH and increased ventricular mass (15,16). In contrast, multiple studies have demonstrated a link between subclinical hyperthyroidism and the risk of heart failure, particularly among the elderly and subjects with grade 2 SCH (17,18).

2.1.2 Atrial fibrillation

The first observation of an association between AF and SCH was in 1994. Sawin et al. reported a two- to three-fold increased risk of AF in elderly subjects from the Framingham cohort during a 10-year follow-up period (19). In a large, retrospective cross-sectional study of 23,638 subjects, including 613 with SCH and 725 with clinical hyperthyroidism, it was shown that the risk of AF was significantly increased in subjects with SCH compared with euthyroid controls (relative risk, 5.2). The relative risk of AF was not different from that observed in subjects with clinical hyperthyroidism (20). These results were subsequently confirmed in prospective studies (21), which showed that the higher risk of AF depends on the degree of TSH suppression (22).

A relationship between thyroid function and AF exists even for euthyroid patients. This was observed in the Rotterdam Study, which found multivariate hazard ratios for AF of 1.94 between the lowest and highest quartiles for TSH and 1.62 between the highest and lowest quartiles for FT4 (23). In 2015, after more subjects were included in the Rotterdam Study and a longer follow-up period was used, the same group reported a stronger association for FT4 than TSH and a higher hazard ratio for people <65 years of age (24). Other studies have also suggested that FT4 may be a stronger predictor of AF than TSH (25). A recent systematic
review that included 30,085 participants from 11 cohorts confirmed that in euthyroid patients, FT4 levels are associated with an increased risk of AF, whereas TSH values are not. Given that TSH is a more sensitive indicator of thyroid function than FT4, this observation remains largely unexplained (26).

2.1.3 Cardiovascular mortality and total mortality

Although an association between SCH and increased cardiovascular and all-cause mortality has been reported in some prospective studies (27-29), no significant association has been found in other studies (21). However, a meta-analysis based on 5 prospective cohort studies did show an increased risk of cardiovascular events, cardiovascular mortality and total mortality (with a hazard ratio of 1.2 for all-cause mortality) among subjects with SCH, with a greater risk when TSH is <0.1 mU/L (30).

2.1.4 Impact of treatment of SCH on cardiovascular parameters

Most of the data regarding the impact of SCH treatment on cardiac parameters has been obtained from observational studies and, in the absence of large interventional trials, there is little evidence of benefit from treatment beyond normalization of thyroid function. Interventional studies of limited sample sizes (31–36) examined the changes in several cardiac and hemodynamic parameters before and after restoration of euthyroidism by radioactive iodine treatment (RAI) (32-34) or antithyroid drugs (ATDs) (31,35,36). Three of the studies included control arms of age- and sex-matched euthyroid patients (31,35,36), but only one was randomized, allocating patients to either treatment or simple follow-up (open-labelled) (31). These studies reported reduction of heart rate (8,12), decreased rates of atrial and ventricular premature beats (31,36), decreased atrial conduction time (35), decreased ventricular mass (34,36) and improved exercise capacity (9) after euthyroid restoration. Similarly, a more recent, small prospective study by Mark et al. that compared cardiac MRI in SCH patients before and after RAI (the second MRI was performed 3–4 months after TSH normalization) and included a euthyroid control group reported improvements in certain cardiac parameters, including significant decreases in heart rate (-8 beats per minute, p = 0.034), left ventricular mass (-2.7 g/m², p = 0.001) and cardiac index (-0.24 L/ min /m², p = 0.017) (37). Despite significant methodological shortcomings in the studies, these data suggest reversibility of the cardiac effects of SCH with treatment and point to a causal relationship between SCH and adverse cardiac changes. There is, however, no data in the
literature on the effect of treatment on the risks of atrial fibrillation, cardiovascular events and mortality.

2.2 The decision to treat

In the absence of evidence for or against the treatment of SCH, the decision to treat a patient with SCH relies on the extent of TSH suppression, patient age and comorbidities, and the risk of clinical thyrotoxicosis developing (38,39). The annual rate of progression of SCH to clinical hyperthyroidism differs greatly among studies and ranges from 0.3 to 41% (3,40,41). Few large prospective studies have been performed, and the great variability in the results is explained by the different methodologies used and populations studied. The more recent studies have shown that an average of 1 to 5% of patients with SCH progress to clinical hyperthyroidism annually. The rate of progression depends on the underlying pathology and the TSH level at diagnosis. The rate of progression is higher among patients with autonomous nodules, either isolated or within a multinodular goiter, than in those with Graves' disease. In the presence of Graves' disease, the progression to clinical hyperthyroidism is rare but can be relatively rapid. Spontaneous remission may be observed. Regardless of the underlying pathology, the rate of progression to clinical hyperthyroidism also depends on the TSH level at diagnosis; the risk of progression to clinical hyperthyroidism is lower in patients with grade 1 SCH (3).

Evidence is currently insufficient to support the treatment of younger patients with grade 1 SCH and no cardiovascular disease. Conversely, treatment of SCH is recommended in all patients with a history of cardiovascular disease or tachyarrhythmias and grade 2 SCH, and in patients over 65 years of age with grade 2 SCH, even in the absence of cardiac disease. Treatment should also be considered in older patients with grade 1 SCH and in younger patients with symptoms of thyroid hormone excess (38,39).

2.2.1 Choice of therapy

The three major therapeutic options—ATD, RAI and surgery—should be used according to the same criteria used for clinical hyperthyroidism (Table 1).
The therapeutic strategy primarily depends on the underlying cause of SCH (Figure 1). When SCH is due to mild Graves’ disease, ATDs can be considered for first-line treatment, especially in young patients, because there is a high likelihood of disease remission in this context. Methimazole is generally the preferred ATD due to a lower rate of adverse effects compared with propylthiouracil. Low doses of methimazole, titrated to achieve TSH normalization, is favored. The only patients for whom RAI therapy should be considered first line are fragile patients with high risks of relapse in whom hyperthyroidism recurrence may exacerbate cardiovascular disease. Hypothyroidism is an inevitable consequence of $^{131}$I therapy in the majority of patients with Graves’ disease, even with low doses, with an incidence rate of 5–50% within the first year, followed by a yearly rate of 3–5% (42,43). In the case of disease recurrence or persistence after a 12- to 18-month course of methimazole, or when ATDs are not tolerated, a more definitive therapy such as RAI therapy or surgery can be considered. Surgery is preferred in the presence of severe Graves’ orbitopathy and in the case of female patients who desire pregnancy within the subsequent 6 months. The recommended surgical procedure in this clinical setting is total or near-total thyroidectomy due to the frequent recurrences of hyperthyroidism observed following less extensive surgery (38,39).

When SCH is caused by a toxic multinodular goiter (TNG) or a toxic adenoma, thyroid dysfunction is typically persistent. Thus, if treatment is needed, RAI therapy or surgery can be considered at diagnosis. $^{131}$I treatment is usually considered a first-line treatment for SCH due to benign autonomous nodules and TNG (38,39). $^{131}$I is safe, noninvasive, readily available and cost-effective compared with surgery, because it can be administered on an outpatient basis. Therefore, it is preferable in a large proportion of patients. $^{131}$I uptake via the sodium/iodine symporter (NIS) in the thyroid cell basal membrane preferentially occurs in autonomous areas and nodules within a TNG. Thus, destruction of these autonomous areas leads progressively to the restoration of normal thyroid function. The $^{131}$I activity needed for treatment is generally 150–200 µCi (5.55–7.4 MBq)/g of thyroid tissue. One common formula used to calculate the appropriate dose is (150-200µCi/gr thyroid x estimated thyroid gland weight)/24-hour uptake (expressed as a decimal). Thus, dosing is adjusted according to the thyroid size to compensate for the relatively high radio-resistance of large glands.

Restoration of euthyroidism in patients with TNG can be achieved within 3–9 months in 75–95% of cases treated by RAI. An average reduction in the goiter volume of 40% 1 year after
treatment has been reported, and volume reduction may reach 50–60% after 3–5 years, with considerable individual variation (42). Adverse effects of $^{131}\text{I}$ include transient hyperthyroidism in the early post–treatment period, generally without clinical impact, with a transient thyroid volume increase of 12–25% almost exclusively in a subgroup of patients with large goiters, and the de novo development of anti-TSH receptor antibodies in 1–5% of patients. However, the main adverse effect of $^{131}\text{I}$ therapy is the development of hypothyroidism, which occurs in 22–58% of cases 5–8 years after therapy in patients with TNG. One of the most common problems seen in the treatment of patients with autonomous TNG is low (frequently <30% at 24 hours) and heterogeneous radioiodine uptake (RAIU). This can compromise treatment efficacy or necessitate very high activities of $^{131}\text{I}$ be used to achieve therapeutic effects. As TSH is known to increase iodine transport from the plasma into the thyroid cell, recombinant human TSH (rhTSH) has recently been used in clinical trials to optimize RAI treatment of TNG. rhTSH induces significant changes in the regional distribution of radioiodine in nodular goiters and stimulates radioiodine uptake in relatively “cold” areas more than in relatively “hot” areas, as depicted on scintigraphy, resulting in a more homogenous radioiodine distribution. Thyroid stimulation by rhTSH (with a dose range of 0.1–0.9 mg administered 24–72 hours before $^{131}\text{I}$) can result in an approximately two- to four-fold increase in the 24-hour RAIU and a 35–56% greater goiter volume reduction, but also results in a significant increase in permanent hypothyroidism (52% 5 years after rhTSH-stimulated $^{131}\text{I}$ treatment compared with 16% after $^{131}\text{I}$ alone) (44,48). Following the same rationale, a recent randomized study showed that a 6-week treatment of methimazole 30 mg/day prior to $^{131}\text{I}$ therapy induced a two-fold average increase in the 24-hour RAIU and a significant reduction in the $^{131}\text{I}$ activity needed to cure subclinical hyperthyroidism in patients with TNG, without compromising therapeutic efficacy. As observed after rhTSH stimulation, methimazole treatment also reactivated previously “resting” tissues surrounding hyperfunctioning areas (Figure 2). The consequence of the homogenization of radioiodine uptake is that perinodular thyroid tissue is irradiated as well as hyperfunctioning nodules, explaining the greater frequency of hypothyroidism and goiter volume reduction compared with the administration of $^{131}\text{I}$ alone. A 30% incidence of hypothyroidism was found after 12 months in patients pretreated with methimazole compared with 0% in the group without pretreatment, suggesting that it may be possible to further lower the administered $^{131}\text{I}$ therapeutic activity for those patients (49).
Surgery is preferred in patients with voluminous goiters causing compressive symptoms or goiters containing nodules suspicious for malignancy. Lobectomy is an adequate treatment for solitary toxic adenomas (50,51); whereas, for bilateral multinodular goiters, total thyroidectomy has replaced subtotal thyroidectomy as the procedure of choice because the latter is associated with a high goiter recurrence rate (52,53). In experienced hands, total thyroidectomy is a safe procedure and eliminates the risk of potential reoperations, which carry a higher risk of permanent complications (53,54). Besides its possible use to increase RAIU, methimazole may still have a place in the treatment of SCH due to thyroid autonomy, albeit in limited cases, in the following situations: 1) as a lifelong treatment at the lowest efficient dose in elderly nursing home patients with urinary incontinence or the inability to comply with radioprotection measures, 2) as a pretreatment before RAI therapy or surgery in particularly fragile patients with cardiac disease, 3) as a temporary treatment for patients at risk of acute exacerbation due to iodine overload (55-57).

Conclusion

Subclinical hyperthyroidism is a common clinical entity defined as a serum TSH below the normal reference range associated with normal T4 and T3 levels. Whether or not subclinical hyperthyroidism should be treated remains a matter of debate. Cross-sectional studies and longitudinal population-based studies demonstrate an association between subclinical hyperthyroidism and the risk of atrial fibrillation, osteoporosis, and cardiovascular and all-cause mortality. However, there are no randomized clinical trials addressing whether long-term health outcomes are improved by the treatment of subclinical hyperthyroidism. Therefore, in the absence of evidence for or against treatment of subclinical hyperthyroidism, it seems appropriate to follow algorithms that take into account the level of TSH and the presence of risks factors (age >65 years, osteoporosis, postmenopausal status and the presence of cardiac disease). The therapeutic strategy primarily depends on the underlying cause of SCH.

References


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**Figure Legends**

Figure 1: Proposed algorithm for the management of SCH

Figure 2: Typical findings on Tc-pertechnetate thyroid scintigraphy before (left) and after (right) 42 days of methimazole (MTZ) treatment
Table 1. Advantages and disadvantages of various therapeutic options in patients with SCH

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indication</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td><strong>ATD</strong></td>
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<tr>
<td>Graves’ disease</td>
<td>Best option</td>
<td>Possible permanent remission</td>
<td>Side effects (rare with low doses)</td>
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<td></td>
<td></td>
<td>May avoid permanent hypothyroidism</td>
<td>Risk of recurrence</td>
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<td></td>
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<td></td>
<td>Need for monitoring blood tests</td>
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<tr>
<td>TNG and TA</td>
<td>No indication for long-term therapy except in very rare cases; May be used as pretreatment before surgery or RAI</td>
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<td><strong>RAI</strong></td>
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<td>Graves’ disease</td>
<td>May be considered when ATDs are not tolerated, in the case of recurrence or in fragile patients with high risks of recurrence</td>
<td>Permanent resolution of hyperthyroidism</td>
<td>Hypothyroidism (nearly 100%)</td>
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<td>Development or worsening of Graves’ orbitopathy</td>
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<td>Possible concerns of the patient about the effect of radiation</td>
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<tr>
<td>TNG and TA</td>
<td>Best option</td>
<td>Permanent resolution of hyperthyroidism</td>
<td>Possible concerns of the patient about the effect of radiation</td>
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<td></td>
<td></td>
<td>Relatively low risk of hypothyroidism</td>
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<td>Decrease in thyroid volume</td>
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<td><strong>Surgery</strong></td>
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<tr>
<td>Graves’ disease</td>
<td>Indicated only when ATDs are not tolerated and RAI is contraindicated</td>
<td>Rapid resolution of hyperthyroidism</td>
<td>Hypothyroidism</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Risks for iatrogenic hypoparathyroidism and recurrent laryngeal nerve damage</td>
</tr>
<tr>
<td>TNG and TA</td>
<td>Should be considered in the case of a suspicious nodule or in the case of a compressive syndrome</td>
<td>Rapid resolution of hyperthyroidism</td>
<td>Hypothyroidism</td>
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<tr>
<td></td>
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<td></td>
<td>Risks for iatrogenic hypoparathyroidism and recurrent laryngeal nerve damage</td>
</tr>
</tbody>
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Figure 1

Determine the etiology of SCH
(Try thyroid scan and/or US, TSHR-Ab)

Diagnosis of GD
Diagnosis of TNG or TA

SCH Grade 1
SCH Grade 2
SCH Grade 1
SCH Grade 2

Young asymptomatic patients: consider observation because of high spontaneous remission rate

Patients who are older than 65, are postmenopausal or who have heart disease: consider treatment by low dose ATD or RAI therapy

Young patients: consider observation if asymptomatic; consider low dose ATD if symptomatic

Patients who are older than 65, are postmenopausal or who have heart disease: treat with low dose ATD or RAI therapy

Young asymptomatic patients: consider observation

Symptomatic patients or patients who are older than 65, are postmenopausal or who have heart disease: consider RAI therapy

Young asymptomatic patients: consider observation or RAI therapy

Symptomatic patients or patients who are older than 65, are postmenopausal or who have heart disease: RAI therapy