MANAGEMENT OF ENDOCRINE DISEASE

Subclinical thyrotoxicosis: prevalence, causes and choice of therapy

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Abstract

Subclinical thyrotoxicosis is a condition affecting up to 10% of the population in some studies. We have reviewed literature and identified studies describing prevalences, causes and outcomes of this condition. Treatment should be considered in all subjects if this biochemical abnormality is persistent, especially in case of symptoms of thyrotoxicosis or in the presence of any complication. In particular, treatment should be offered in those subclinically thyrotoxic patients with a sustained serum TSH below 0.1 IU/L. However it is important to recognise that there are no large controlled intervention studies in the field and thus there is no high quality evidence to guide treatment recommendations. In particular, there is no evidence for therapy and there is weak evidence of harm from thyrotoxicosis if serum TSH is in the 0.1–0.4 IU/L range. In this review, we describe the different causes of subclinical thyrotoxicosis, and how treatment should be tailored to the specific cause. We advocate radioactive iodine treatment to be the first-line treatment in majority of patients suffering from subclinical thyrotoxicosis due to multinodular toxic goitre and solitary toxic adenoma, but we do generally not recommend it as the first-line treatment in patients suffering from subclinical Graves' hyperthyroidism. Such patients may benefit mostly from antithyroid drug therapy. Subclinical thyrotoxicosis in early pregnancy should in general be observed, not treated. Moreover, we advocate a general restriction of therapy in cases where no specific cause for the presumed thyroid hyperactivity has been proven.

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Invited Authors' profiles

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Allan Carlé, MD, PhD, is a senior researcher, Aalborg University Hospital, Aalborg, Denmark. His research has focused on nosological classification of various subtypes of hypothyroidism. He has explored the field of hypo- and hyper-thyroidism with special focus on the occurrence in the population, biochemical findings at diagnosis, the symptom presentation across gender and age, the magnitude of avoiding referral bias in population-based studies, and he has studied several risk factors for both hyper- and hypo-thyroidism. The research frame has been DanThyr (The Danish Investigation on Iodine Intake and Thyroid Diseases).

Allan Carlé

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Introduction

Thyrotoxicosis is a common disease worldwide and may be caused by inappropriately high thyroid hormone secretion (hyperthyroidism), passive release of thyroid hormone from a damaged thyroid or from extra-thyroidal sources of excess thyroid hormone. In hyperthyroid patients, the inappropriate thyroid hyperactivity can be treated with antithyroid drugs, radioactive iodine, or surgery and optimal therapy depending on the cause and severity of the disorder. In some thyrotoxic conditions, there is a probability of disease remission with restoration of normal thyroid function. In such patients, irreversible thyroid ablation using radioactive iodine is only rarely indicated. On the other hand, some subtypes of hyperthyroidism would generally not spontaneously remit, and radioiodine therapy would often be the first choice. Current consensus guidelines from the American Thyroid Association (1) provide treatment recommendations based on the degree of TSH suppression and patients' age. This review aims to provide detailed information regarding the causes and long-term consequences of subclinical thyrotoxicosis, and to discuss the risks and benefits associated with treatment of this common condition.

In subclinical thyrotoxicosis, the serum concentrations of thyroid hormones, total T4/free T4 and total T3/free T3, are within the laboratory reference range, but TSH is abnormally low, and patients may have only few or no clinical signs of thyrotoxicosis. It is beyond the scope of the present review to enter into a detailed discussion of the various assays used to diagnose subclinical thyrotoxicosis, but extensive reviews are available elsewhere (2, 3). In this review, we advocate that radioactive iodine treatment may be the treatment of choice for many patients diagnosed with subclinical hyperthyroidism, at least in countries with current or recent low iodine intake, where many elderly people suffer from the consequences of previous iodine deficiency. On the other hand, patients suffering from Graves' disease with only subclinical hyperthyroidism may often enter remission during a course of antithyroid drug therapy.

Subclinical thyrotoxicosis and its nosological types

Since early 1970s, the entity of subclinical hypothyroidism with isolated elevated serum TSH concentration was defined (4), and in the mid-1980s new TSH assays with a sensitivity of 0.1 U/L (5) made it possible to identify subnormal serum TSH concentrations. Thus, a new group

of patients was identified with a low serum TSH but with T4 and T3 within the laboratory reference ranges. The new term 'subclinical' thyrotoxicosis is rather misleading as the diagnosis is based solely on biochemical testing and not on the presence or absence of any symptom (5). In the ATA/AACE thyrotoxicosis treatment guidelines by Bahn *et al.* (6) and the recent European Guidelines by Biondi *et al.* (7) it is proposed that clinical outcomes may depend on the degree of TSH suppression, and the physician should distinguish between patients with TSH lower than 0.1 U/L and those with only mildly suppressed TSH between 0.1 and the lower assay reference limit.

However, only a proportion of the thyrotoxic patients fulfilling the above criteria suffer from endogenous subclinical hyperthyroidism, and other causes should be ruled out such as exogenous thyroid hormone use, the consumption of other TSH-suppressing drugs (e.g. dopamine or glucocorticoids), non-thyroidal illness (low T3 syndrome), low serum TSH during first trimester of pregnancy, pituitary and hypothalamic insufficiency, or falsely undetectable TSH caused by assay problem (8). The TSH reference range broadens with age and there is mounting evidence for increased upper limits (9) as well as decreased lower limits (10, 11). As a general rule, therapy should only be given when the cause for mild hyperthyroidism has been revealed. To focus more on the disorder than on the biochemistry, it has been suggested to abandon the term 'subclinical' (12).

Depending on the study population, subclinical thyrotoxicosis may be very common. Most studies reported a low TSH to be present in approximately 1–5% of the investigated people (Table 1, (13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44)). Some of these studies documented normal serum T4 concentrations; others did only measure serum TSH. Some of the studies provided prevalences on subclinical thyrotoxicosis in terms of different serum TSH cut-off values (13, 14, 16, 20, 32, 36, 43, 45) and showed that most cases of subclinical thyrotoxicosis presented with serum TSH above 0.1 U/L. Thus, up to eight-fold lower prevalence of subclinical thyrotoxicosis was found if the serum TSH cut-off was changed from the lower laboratory reference value of 0.3–0.4 U/L and down to 0.1 U/L. The prevalence is as may be anticipated, fundamentally dependent on the TSH threshold chosen. Another limitation is that the methods used and the cohorts investigated in the studies listed in Table 1 are heterogeneous.

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Table 1 Prevalence of suppressed serum TSH concentrations in various populations in order of frequency.

First author	Year	Country	Prevalence of low serum TSH (%)	Serum TSH lower cut-off (U/L)
Völzke (13)*/**	2003	Germany	11.3	0.3
Sawin (14)*/**	1994	US	10.2	0.4
Muller (15)	1997	South Africa	9.4	0.4
Parle (16)*/**	2001	UK	7.6	0.5
Seck (17)	1997	Germany	6.6	0.3
Aghini-Lombardi (18)*	1999	Italy	6.4	0.4
Sgarbi (19)*	2010	Brazil + Japan	6.2	0.45
Parle (20)**	1991	UK	5.9	0.5
Knudsen (21)*	2000	Denmark	4.9	0.4
Manciet (22)**	1995	France	4.2	0.4
Eggertsen (23)*	1988	Sweden	3.5	0.2
Gussekloo (24)	2004	Netherlands	3.4	0.3
Sowers (25)	2003	US	3.2	0.5
Delitala (26)*	2014	Italy	2.8	0.4
Teng (27)	2011	China	2.7	0.3
Bagchi (28)	1990	US	2.5	0.1
Gamage (29)*	2007	UK	2.4	0.4
Wilson (30)*	2006	UK	2.4	0.4
Völzke (13)*/**	2003	Germany	2.2	0.1
Sawin (31)*	1991	UK	2.1	0.3
Bjorndal (32)*/**	2008	Norway	2.1	0.5
Knudsen (33)*	1999	Denmark	2.0	0.15
Boekholdt (34)	2010	UK	1.9	0.4
Manciet (22)**	1995	France	1.9	0.2
Sundbeck (35)*	1991	Sweden	1.9	0.2
Hollowell (36)*/**	2002	US	1.8	0.4
Selmer (37)*	2012	DK	1.8	0.2
Parle (16)*/**	2001	UK	1.7	0.1
Cappola (38)*	2006	US	1.6	0.44
Brochmann (39)	1988	Norway	1.5	0.1
Parle (20)**	1991	UK	1.4	0.05
Sawin (14)*/**	1994	UK	1.3	0.1
Nanchen (40)	2012	Netherlands + Scotland + Ireland	1.3	0.45
Meyerovitch (41)*	2007	Israel	1.2	0.35
Canaris (42)*	2000	US	1.0	0.3
Bjoro (43)*/**	2000	Norway	0.6	0.2
Konno (44)*	1993	Japan	0.6	0.15
Bjorndal (32)*/**	2008	Norway	0.44	0.2
Hollowell (36)*/**	2002	US	0.4	0.1
Bjoro (43)*/**	2000	Norway	0.34	0.05
Bjorndal (32)*/**	2008	Norway	0.24	0.05

*Studies that provided prevalence data or from which we calculated the prevalence of low serum TSH among subjects with no thyroid disease. **Some studies gave several prevalences of low TSH according to different serum TSH cut-off levels (13, 14, 16, 20, 32, 36, 43).

A comprehensive list of possible causes of endogenous subclinical thyrotoxicosis was published by Cooper and Biondi (46). In different populations, the relative distribution of the various nosological types of thyrotoxicosis may differ substantially in both overt and subclinical thyrotoxicosis. Most studies on the prevalence of thyrotoxicosis did not take into account that the disease entity is comprised by several different subtypes. Similarly, most incidence rates have only focused on a few entities within the thyrotoxic spectrum. Thus, knowledge of the distribution of various subtypes of thyrotoxicosis mostly relies on studies of overt thyrotoxicosis. Graves' disease

and toxic nodular disease are by far the most common causes (47), and the balance between these two entities is largely dependent on the iodine intake of the population (48, 49). Implementation of iodine fortification also has large impact on the occurrence of thyrotoxicosis (50, 51).

Graves' disease is the dominating cause of overt thyrotoxicosis in iodine-replete countries such as Iceland (52), whereas toxic multinodular goitre may be as common as Graves' disease in countries with mild-to-moderate iodine deficiency (47). The thyroid autonomy developing after a long period of low iodine intake may not disappear after an increase in iodine intake

('iodine memory' (48)) and toxic multinodular goitre may also be common among elderly people living in areas with iodine intake that is currently sufficient, but was previously deficient. Also, people who emigrated from areas with low iodine intake to areas with sufficient iodine intake may have high prevalence of thyroid autonomy. Because overt hyperthyroidism caused by nodular autonomy may develop gradually over years, whereas Graves' hyperthyroidism based on current knowledge tend to develop more rapidly, nodular autonomy is rather common in subclinical thyrotoxicosis.

Two Danish studies (21, 52) combined with data from a study recently published (53) depict the causal importance of iodine intake on the occurrence of subclinical thyrotoxicosis (Fig. 1, (21, 52, 53)). While subclinical thyrotoxicosis was rare in iodine-excess Iceland subjects aged approximately 70 years, 2–4% of the elderly population residing in moderate-to-mild iodine-deficient Danish areas had a serum TSH <0.1 U/L. Furthermore, 8–10% of the Danish women and 4–6% of the men had a

serum TSH <0.4 U/L. Results are corroborated by a recent Dutch study (54) on serum TSH and fT4 in laboratory databases. In the historically iodine-deficient parts of the Netherlands, a negative correlation between age and serum TSH was observed, presumably because the thyroid gland of many older people harboured autonomously functioning nodules.

The overall risk for being diagnosed with a certain subtype of thyrotoxicosis depends on a number of factors such as gender (21, 28, 33, 36, 43), age (18, 21, 26, 33, 42, 43), ethnicity (25, 28, 36) and smoking (55, 56). A few studies have classified subclinical thyrotoxicosis according to the cause of disease (32, 44, 57, 58). According to those studies, Graves' disease was the cause of subclinical thyrotoxicosis in 15% of patients in iodine-sufficient but previously iodine-deficient Norway. In iodine-abundant Japan (44) approximately 64% of all subclinically thyrotoxic cases could be attributed to Graves' disease.

Within the spectrum of subclinical thyrotoxicosis, complete suppression of serum TSH is associated with higher risks of suffering from Graves' disease compared to the other subtypes of thyrotoxicosis. This was shown by Bjorndal *et al.* (32), who found that Graves' disease was the cause in 40% of severely subclinically thyrotoxic patients (serum TSH <0.05 U/L) but it was the cause for only 15% of those with mild subclinical thyrotoxicosis (serum TSH between 0.05 and 0.49 U/L). Rosario (57) also found that Graves' disease was a rather uncommon cause (7% compared to 93% due to nodular autonomy) among those with a serum TSH between 0.1 and 0.4 U/L.

Consequences of 'wait and see'

The clinical significance of subclinical thyrotoxicosis has been extensively reviewed by Biondi *et al.* (7). Sustained subclinical thyrotoxicosis is associated with a broad spectrum of physiological changes, of which some are at least partly reversible. However, one must remember that many patients with isolated low serum TSH may have their thyroid function normalised without treatment and that therapy should never be based on single biochemical testing of thyroid function. Rosario *et al.* (57) reported that 13% of subjects having subclinical thyrotoxicosis by a single thyroid function testing had experienced spontaneous normalisation of thyroid function tests within 3 months, and within a 12-month period serum TSH normalised spontaneously in 38 out of 50 patients in a study by Parle *et al.* (20).

On the other hand, subclinical thyrotoxicosis may progress to overt thyrotoxicosis. The rate of progression

Figure 1

The prevalence of low serum TSH (<0.1 U/L on the left; <0.4 U/L on the right) in Danish and Icelandic population-based studies performed in areas with different iodine intake levels: Iceland (high iodine intake, age 66–70 years, $n=100$ (52)); Copenhagen, Denmark (mild iodine deficiency, 60–75 years, $n=937$ (21, 53)); Aalborg, Denmark (moderate iodine deficiency, 60–75 years, $n=935$ (21, 53)); Randers, Denmark (moderate iodine deficiency, 68-year-old citizens, $n=423$ (52)). In all populations, subjects previously diagnosed with biochemical thyroid disease were excluded.

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Table 2 Annual progression rates from biochemical subclinical to overt thyrotoxicosis in order of frequency.

First author	Year	Country	Annual rate of progression* from subclinical to overt thyrotoxicosis (%)
Stott (59)	1991	Scotland	41.0
Rosario (57)	2010	Brazil	11.6
Diez (60)	2009	Spain	9.7
Schouten (61)	2011	New Zealand	8.0
Das (64)	2012	UK	4.4
Muller (15)	1997	South Africa	4.0
Tenerz (62)	1990	Sweden	3.3
Gussekloo (24)	2004	Netherlands	2.0
Parle (20)	1991	UK	1.5
Parle (16)	2001	UK	1.4
Sawin (31)	1991	UK	1.0
Vadiveloo (63)	2011	Scotland	0.3

*To allow for direct comparison, we calculated the yearly progression rate from study data.

varies widely between studies (Table 2, (15, 16, 20, 24, 31, 57, 59, 60, 61, 62, 63, 64)), and depends on a number of factors such as initial serum TSH (57, 60, 64), presence of symptoms (60), the cause of endogenous hyperthyroidism (61), and probably frequency of testing as shown for subclinical hypothyroidism by Karmisholt *et al.* (65). Overall, approximately 1–5% may progress to overt thyrotoxicosis annually, and this rate is somewhat higher in nodular toxic disease than in subclinical Graves' hyperthyroidism (61).

Even if stable, subclinical thyrotoxicosis may lead to various complications such as sinus tachycardia (66) and atrial fibrillation (14, 29, 37, 38, 62, 67, 68, 69), as well as a variety of other long-term cardiac effects, including heart failure (68, 70). Sawin *et al.* (14) reported the 10-year cumulative incidence for developing atrial fibrillation to be 28% if serum TSH was <0.1 U/L compared with 11% among those with normal serum TSH. In a five-study meta-analysis performed by Collet *et al.* (68), the hazard ratio for atrial fibrillation was 1.68 (1.16–2.43). In the study by Selmer *et al.* (37), the risk for developing atrial fibrillation increased with decreasing serum TSH levels. Moreover, studies have shown coagulation (71, 72), high plasma fibrinogen levels (73), carotid artery plaques formation and higher prevalence of stroke (73, 74) among patients with subclinical thyrotoxicosis. Additionally, patients with cardiac disease have higher mortality in the presence of subclinical thyrotoxicosis, at least in regions with multinodular toxic goitre as the prominent cause for thyrotoxicosis (75). Finally, Selmer *et al.* (76) showed that the increased mortality in subclinical thyrotoxicosis was mainly caused by heart failure.

Another concern is osteopenia and osteoporosis that may emerge if the 'wait and see' strategy is selected. Lower densitometric values have been reported in postmenopausal women (77, 78) but neither in premenopausal women (77, 79) nor in men (80) with subclinical thyrotoxicosis. In the study of Tauchmanova *et al.* (81) the detrimental bone effects of subclinical thyrotoxicosis was more prominent in post- vs premenopausal women. Recently, some studies have examined the bone effect of endogenous subclinical thyrotoxicosis excluding cases with endogenous overt thyrotoxicosis and those with thyrotoxicosis due to L-T4 overtreatment of thyroid failure. In the study of Garin *et al.* (82), no association was found with BMD or hip fracture. Lee *et al.* (83) studied 3567 community-dwelling adults and found no association between serum TSH and fractures in women, but did report a five times higher risk for hip fractures in men with endogenous subclinical thyrotoxicosis. In the study of Leader *et al.* (84), an association was found between hip fractures and low serum TSH within the reference range, but only in women. Despite studying relatively high numbers of subjects ($n=14\,325$), findings were only borderline statistically significant ($P=0.029$) after adjustment for co-morbidity and other confounders. In 2014, a meta-analysis by Wirth *et al.* (85) reported a 2.2 higher risk for hip fractures and a 1.4 higher risk for non-vertebral fractures in subclinical thyrotoxicosis. In 2015, a meta-analysis comprising more than 70 000 participants revealed a 3.57 (1.88–6.78) higher risk for spine fractures among subjects with serum TSH lower than 0.10 U/L (86). Sensitivity analyses of the latter study showed a 1.79 (1.04–3.09) higher risk for spine fractures in endogenous thyrotoxicosis.

Several studies have investigated the effects of subclinical thyrotoxicosis on mortality, and only meta-analyses will be mentioned here. In 2007, Völzke *et al.* (87) found no increase in mortality in their meta-analysis comprising 5744 subjects from three studies. One year later, Hantjaens *et al.* reported a 41% higher mortality in subclinical thyrotoxicosis in a meta-analysis comprising seven studies (88). In 2010, Sgarbi *et al.* (19) reported on a three times higher all-cause and cardiac mortality among 1100 Japanese-Brazilian subjects with subclinical thyrotoxicosis. A few years later, Collet *et al.* (89) performed the largest meta-analysis to date based on ten studies comprising 52 674 patients, and calculated a 24% higher all-cause mortality in subclinical thyrotoxicosis irrespective of gender and ethnic origin. In that study, the coronary heart disease mortality was 29% higher with the highest relative risk in subjects aged below 50 years (89).

It is beyond the scope of the present review to also contemplate on the association between subclinical hyperthyroidism and depression, dementia and physical performance.

In conclusion, evidence for treating subclinical thyrotoxicosis arises from epidemiological studies of community-dwelling individuals who had a single estimation of thyroid function and not from those with persistent endogenous subclinical hyperthyroidism referred to endocrinologists. Nonetheless, current guidelines for treatment (1) are based on the associations between mild hyperthyroidism and deleterious consequences for the cardiovascular system, the skeleton, mood and cognition as well as increased mortality. Importantly, the evidence for recommending treatment is not based on large high-quality randomised controlled intervention trails and further studies are required.

Individual therapy based on the cause of subclinical thyrotoxicosis

The possible regimes for treating subclinical thyrotoxicosis consist of antithyroid medication, radioactive iodine and thyroid surgery. The choice of treatment in the individual patient depends on a number of factors of which the specific subtype of subclinical thyrotoxicosis and the patient's preference are the most important. In general, surgical therapy is only considered in specific situations such as a solitary hot nodule, suspicion of a malignant nodule, compressive symptoms from a goitre, failure of radioiodine treatment or intolerance to antithyroid drugs (90). Before considering any treatment, the physician must ensure that the patient has sustained biochemical subclinical thyrotoxicosis by a confirmatory thyroid function testing performed several months later. Moreover, it is mandatory to diagnose the cause of the disease. Patients having suppressed TSH in early pregnancy should not be treated for thyrotoxicosis. Due to low thyroidal iodine uptake, radioactive iodine treatment has no role in treatment of patients with excess iodine intake. Neither antithyroid medicine nor radioiodine should be used in patients suffering from one of the various forms of thyroiditis as they may cause disruption of the thyroid tissue integrity. As the inflammation causing the damaged thyroid tissue is a temporal phenomenon in nearly all cases, no specific treatment is required.

Patients with subclinical hyperthyroidism caused by Graves' disease would most often have mild autoimmune abnormalities that may even enter remission

spontaneously during the beta-blocker therapy (91), or enter lasting remission if given antithyroid drug therapy (92). TSH-receptor antibodies (TRAbs) are detectable in most patients with Graves' hyperthyroidism, but subsets of those with very mild disease are TRAb negative (93). A thyroid gland with a diffuse thyroidal Tc-scintigraphy uptake despite suppressed serum TSH would most often be diagnostic for Graves' disease in a hyperthyroid patient. Some other but rare causes are hCG producing molar, choriocarcinoma or germinoma (94), and genomic TSH receptor mutation. We only advocate radioactive iodine in patients with subclinical Graves' hyperthyroidism in specific situations such as intolerance to antithyroid drug therapy or symptoms from a large goitre.

The use of radioiodine treatment in benign thyroid disease has been extensively debated in a review by Bonnema and Hegedüs (95). In patients with very large goitres extending into the intrathoracic compartment, a hyperthyroid state may well be treated with radioactive

Table 3 Causes of subclinical thyrotoxicosis (our preferred treatment is provided in italics). This table only includes biochemical subclinical thyrotoxicosis having the causes listed above, and not biochemical aberrations caused by other diseases and drugs as discussed elsewhere.

Autonomous thyroid hormone secretion
Multinodular autonomous goitre (<i>radioactive iodine</i>)
Solitary hyperfunctioning adenoma (<i>radioactive iodine</i>)
Genomic constitutive activating TSH-receptor mutation (<i>surgery</i>) (101)
Excessive TSH-receptor stimulation
Graves' disease (<i>antithyroid medication</i>)
Gestational transient thyrotoxicosis (<i>wait and see</i>)
hCG-producing molar or choriocarcinoma (<i>surgery</i>)
Familial gestational thyrotoxicosis (<i>antithyroid medication</i>) (102)
TSH-producing pituitary adenoma (<i>surgery</i>)
Follicle destruction with thyroid hormone release (<i>all wait and see</i>)
Subacute granulomatous 'de Quervains' thyroiditis
Painless (silent) thyroiditis
Acute suppurative thyroiditis
Manipulation thyroiditis
Iatrogenic thyroiditis due to immunotherapy or other drugs
Extrathyroidal sources of thyroid hormone
Iatrogenic overreplacement with thyroid hormone (<i>adjust L-T4 doses</i>)
Self-administered thyroid medication (<i>stop treatment</i>)
Food and supplements with thyroid hormone (<i>stop intake</i>)
Functional thyroid cancer metastases (<i>radioactive iodine</i>)
TSH suppressive therapy with steroids or dopamine (<i>none</i>)
Struma ovarii (<i>surgery</i>)
Other
TSH assay artefact (<i>none</i>)
Old age

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Table 4 Advantages of various therapy regimes in subclinical hyperthyroidism.

(a) Radioactive iodine (RI) therapy in nodular hyperthyroidism
- Low risk of permanent hypothyroidism following RI treatment (10–20% compared to 80–100% in Graves' hyperthyroidism)
- Decrease in thyroid volume of around 50%
- Often requires only single administration
(b) Antithyroid drug therapy in Graves' disease
- Low dose of drug associated with less side effects
- High likelihood of remission of autoimmune abnormality
- Good probability of returning to 'life without medication'

iodine despite the risk of inducing hypothyroidism (96). The thyroid size may decrease with 30–60% (96, 97, 98, 99, 100). Furthermore, any compressive effect of the goitre affecting the inspiratory phase of the respiration may benefit from radioactive iodine treatment (96). Table 3 ((101, 102)) shows the main causes for subclinical thyrotoxicosis and how we propose to address them. The central indication for the use of radioactive iodine therapy in subclinical hyperthyroidism is disease caused by a solitary or by multiple autonomously functioning thyroid nodules (Table 4). These two entities are very common causes of both overt and subclinical hyperthyroidism in countries with current (47) or previously low iodine intake (103). If radioactive iodine is given to patients without pretreatment with antithyroid drugs, the preferential uptake of ¹³¹I in the hyperactive nodules may to some degree spare the surrounding normal thyroid tissue, and patients may become euthyroid with no need to take medication. This was shown by Faber *et al.* (104), who reported that 16 women with nodular goitre and subclinical thyrotoxicosis who underwent radioactive iodine treatment became euthyroid within 2 years compared to no normalisation in any of the 12 patients who were not treated. Moreover, the beneficial effects of such therapy were demonstrated; 2 years following the study start those in the treated and now biochemically euthyroid group had higher spine and hip BMD compared to non-treated subjects who were still subclinically hyperthyroid. The positive effects on serum TSH and BMD were similar in the study of Rosario *et al.* (105), who included both patients with subclinical hyperthyroidism due to uninodularity and multinodularity and found that 83% had normalisation of thyroid function within a year after radioiodine treatment. Effects of treatment in patients diagnosed with multinodular goitre and subclinical hyperthyroidism have been shown including partial normalisation of heart rate (106), cardiac output (106) and systemic vascular resistance (106).

Side effects of subclinical hyperthyroidism therapy

A few potential side effects of radioactive iodine treatment should be mentioned. The risk of iatrogenic hypothyroidism following radioiodine therapy is higher in Graves' hyperthyroidism compared to treatment of subclinical hyperthyroidism caused by thyroid autonomy.

No data are available on the risk for development of hypothyroidism after radioiodine therapy of subclinical thyrotoxicosis caused by autonomy. However, the risk for iatrogenic thyroid failure following radioiodine therapy in overt thyrotoxicosis caused by autonomy is approximately 5% after 1 year (107, 108, 99, 109), 15% after 5 years (109), and more than 60% after 20 years (107, 108) depending on the doses administered. The highest risk has been observed in patients whose serum TSH due to antithyroid pretreatment was no more suppressed (110).

Approximately 5% of patients treated for autonomous hyperthyroidism may develop thyroid hormone receptor antibodies (TRAb) in the months and the first year after the treatment (111). In addition, Graves' patients may experience enhancement of serum TRAb levels and worsening of eye symptoms. In the weeks following radioactive iodine treatment, the thyroid tissue may become inflamed, and thyroid volume expansion of approximately 10% and transient overt thyrotoxicosis may emerge.

Several long-term follow-up studies have indicated increased mortality (112, 113, 114, 115, 116) in overtly thyrotoxic patients who have previously undergone radioactive iodine treatment, but no study has evaluated survival in patients with subclinical thyrotoxicosis after such therapy. The current ATA/ACEE guidelines on hyperthyroidism include a table on estimated risk of incidence of cancer mortality after radioiodine therapy (117). The hypothetical lifetime risk of cancer after 15 mC (555 MBq) ¹³¹I is 9.9% in a 1-year old,

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4% in a 5-year old, 0.8% in a 20-year old and 0.46% in a 60-year old, all on top of a background risk of 25%. Thus, radioiodine therapy should preferably be used in older patients.

The adverse effects to antithyroid medication of subclinical hyperthyroidism are those also observed during therapy of overt hyperthyroidism (118). Approximately 5% of patients may experience minor (119), mostly cutaneous adverse effects to the drugs, and very few will have severe adverse effects. Most adverse effects to antithyroid drugs seem to be dose-dependent (118), and the low doses of methimazole (approximately 5 mg per day) used to treat subclinical hyperthyroidism caused by Graves' disease are unlikely to have many side effects. No study gives exact information on the frequency of side effects when low-dose antithyroid drugs are used to treat subclinical hyperthyroidism. In large studies, the risk of agranulocytosis from methimazole use (all doses) was approximately 0.1–0.3% (120, 121, 122) and liver failure was less common (122). Such side effects mostly develop during the initial months of the therapy (120, 121, 122).

A special situation is the therapy of subclinical hyperthyroidism in women who may become pregnant, and women who are pregnant. Antithyroid drugs may be teratogenic with the highest risk (birth defects in 1/30 exposed to methimazole (123, 124), 1/40 exposed to propylthiouracil (124, 125)) in weeks six to ten of pregnancy (126). Thus, women who are treated with antithyroid drugs for subclinical hyperthyroidism and who may potentially become pregnant should be instructed to test for pregnancy very early (the first week of a missing or unusually weak menstruation), to stop the medication if the test is positive, and to immediately contact the physician responsible for the therapy to plan further management (127). Women whose biochemical test results indicate subclinical hyperthyroidism in the first trimester of pregnancy should not be treated with antithyroid drugs, but the condition should be observed with thyroid testing every 1–3 weeks taking into account the early pregnancy variation in results of thyroid function tests (128). In a large study performed in the US, subclinical hyperthyroidism in early pregnancy was not associated with any pregnancy complication (129).

If surgery is performed in a patient with subclinical hyperthyroidism, the post-surgery complications are those also experienced following thyroid surgery for overt thyrotoxicosis (130).

Conclusion

Subclinical thyrotoxicosis is a condition affecting up to 10% of the population depending on the TSH cut-off value for defining the condition and the iodine intake of the population. Many cases of subclinical hyperthyroidism would have been prevented by sufficient iodine intake. Treatment should be considered in all subjects with symptoms of thyrotoxicosis or other complications to the abnormalities, and especially in those with a sustained serum TSH below 0.1 U/L. Treatment should be tailored to the specific cause of subclinical thyrotoxicosis. We advocate radioactive iodine treatment to be first-line consideration in subclinical thyrotoxicosis due to nodular autonomy (multinodular toxic goitre and solitary adenoma). On the other hand, we do recommend antithyroid drugs as the first-line treatment in the group of patients suffering from subclinical hyperthyroidism caused by Graves' disease. Special precautions are necessary when using antithyroid drug therapy for subclinical hyperthyroidism in women who may in the future become pregnant, or who are already pregnant.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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