Subclinical Hyperthyroidism

10

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Abstract

Because of screening tests with sensitive TSH assays, subclinical hyperthyroidism is being recognized more commonly. Subclinical hyperthyroidism is defined as undectectable thyrotrophin (TSH) concentration in patients with normal levels of T4 and T3. Subtle symptoms and signs of thyrotoxicosis may be present.

It be classified as endogenous in patients with thyroid hormone production associated with nodular thyroid disease or underlying Graves' disease; and as exogenous in those with undectectable serum thyrotropin concentrations as a result of treatment with levothyroxine. Subclinical hyperthyroidism is often found in older subjects with autonomous function of a multinodular goiter or nodule.

Osteoporosis and atrial fibrillation are complications of subclinical hyperthyroidism that may be an indication for treatment. Studies suggest a possible increase in all-cause mortality in patients with subclinical hyperthyroidism with an increase beyond the age of 60, especially in aging men.

In many patients with endogeneous subclinical hyperthyroidism who do not have nodular thyroid disease or complications of excess thyroid hormone, treatment is unnecessary, but thyroid-function tests should be performed every 6 months. In older patients with atrial fibrillation or osteoporosis that could have been caused or exacerbated by the mild excess of thyroid hormone, ablative therapy with ^{131}I is the best initial option.

In patients with exogeneous subclinical hyperthyroidism, the dose of levothyroxine should be reduced, excluding those with prior thyroid cancer in whom thyrotropin suppression may be required. The dose of levothyroxine used for treating hypothyroidism may be reduced if the patient develops new atrial fibrillation, angina, cardiac failure or accelerated bone loss.

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S.K. Imam, S.I. Ahmad (eds.), *Thyroid Disorders: Basic Science and Clinical Practice*,
DOI 10.1007/978-3-319-25871-3_10

Introduction

The accessibility of sensitive tests for thyroid-stimulating hormone (TSH) has resulted in the diagnosis of patients who have low serum TSH concentrations (<0.5 mU/L) with normal serum free thyroxine (T4) and triiodothyronine (T3) levels; a range of biochemical findings which are described as subclinical hyperthyroidism.

Subclinical hyperthyroidism is biochemically diagnosed by a low serum thyroid-stimulating hormone levels (TSH) but normal serum free thyroxine (T4) and triiodothyronine (T3) values. Patients with subclinical hyperthyroidism frequently have few or no symptoms of hyperthyroidism

Subclinical hyperthyroidism is biochemically described as low or undetectable serum thyroid-stimulating hormone (TSH), with normal free thyroxine (T4) and total or free triiodothyronine (T3) concentrations [1]. Presently used techniques can detect TSH as low as 0.01–0.02 mIU per L. Subclinical hyperthyroidism can be divided into two types; low but detectable TSH levels (0.1–0.4 mIU per L), and suppressed TSH levels (less than 0.1 mIU per L) [1]. It can occur due to increased endogenous secretion of thyroid hormone, prescription of thyroid hormone for treatment of thyroid carcinomas, or inadvertent excessive thyroid hormone administration. Progression to obvious hyperthyroidism is higher in persons who have suppressed thyroid-stimulating hormone concentration as opposed to those who have low but detectable levels. Subclinical hyperthyroidism is linked with an increased risk of atrial fibrillation in older patients, and with decreased bone mineral density in postmenopausal females.

Subclinical hyperthyroidism is linked with an increased risk of atrial fibrillation and, mainly in postmenopausal women, reduced bone mineral density

Although there is convincing proof that treatment of suppressed TSH is cost-effective, especially in elderly patients, the significance of judicious detection and treatment of low but measurable TSH levels is contentious.

The most frequent causes of subclinical hyperthyroidism are therapy with exogenous thyroxine and autonomously functioning thyroid adenomas and multinodular goiters

Causes

Subclinical hyperthyroidism may be due to endogenous excess production of thyroid hormone; or it may be exogenous as a result of deliberate administration of thyroid hormone to suppress thyroid cancer, or inadvertent excessive hormone administration in patients with hypothyroidism. Frequent causes of endogenous subclinical hyperthyroidism are Graves disease, hyper functioning thyroid adenoma, and toxic multinodular goiter. Temporary TSH suppression may occur during subacute, painless, or postpartum thyroiditis. The correlation between population iodine intake and the prevalence of autonomous thyroid dysfunction is inversely related with a higher occurrence with iodine-deficiency [2].

The differential diagnoses of subclinical hyperthyroidism are the same as that of frank hyperthyroidism and, like hyperthyroidism, subclinical hyperthyroidism can be persistent or transitory.

Exogenous Subclinical Hyperthyroidism

In the United States as many as 10 million people, and possibly 200 million persons globally, are prescribed thyroid hormone. Most of them are at risk of subclinical hyperthyroidism, either deliberate or inadvertent. Patients who are taking thyroxine (T4), about 25 % have low serum thyroid-stimulating hormone (TSH) concentration and in one study, 5.8 % had TSH under 0.1 mU/L [3–5].

Several of these patients have hypothyroidism, and subclinical hyperthyroidism in them is not the target of thyroid hormone replacement. However, subclinical hyperthyroidism is the aim of thyroxine administration in patients with thyroid cancer and in some patients with thyroid nodules, multinodular or diffuse goiters, or a history of head and neck irradiation. In these patients, the advantages of TSH suppression offset the risks of subclinical hyperthyroidism.

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Endogenous Subclinical Hyperthyroidism

Independently thyroid hormone producing adenomas and multinodular goiters are the most frequent causes of endogenous or internal subclinical hyperthyroidism. In persons over 55 years old, subclinical hyperthyroidism due to multinodular goiters was diagnosed in 57 % of patients, while due to Graves' disease in 6 % only [6]. One study showed that, 22 % of patients with multinodular goiter had subclinical hyperthyroidism, and 28 % had autonomous hyperfunctioning area(s) on imaging of the thyroid gland [7].

Thyroiditis can also cause subclinical hyperthyroidism, and has been shown to occur in 63 % of euthyroid cases with Graves' ophthalmopathy and 4 % of Graves' patients in remission [8–10]. It may also be seen in patients with early Graves' disease before the commencement of frank hyperthyroidism. Moreover, pregnant females, mostly in the first trimester and those with hyperemesis gravidarum or trophoblastic disease, with high serum chorionic gonadotropin concentrations, may be diagnosed to have subclinical hyperthyroidism.

Epidemiology and Natural History

Numerous large studies have looked into the prevalence of subclinical hyperthyroidism [11–17]. The data from these studies, mainly in persons over the age of 55–60 years, is presented as follows:

The reported occurrence of subclinical hyperthyroidism varies among different studies because of the variability in defining the TSH level for subclinical hyperthyroidism, age of the patient population studied, and administration of thyroid hormone. The occurrence of subclinical hyperthyroidism in the population varies from 0.7 to 12.4 %. In the U.S, the National Health and Nutrition Examination Survey (NHANES III), which did not include individuals with known thyroid disease, 0.7 % of 16,533 persons were reported to have subclinical hyperthyroidism (TSH <0.1 mU/L) [18]. Subclinical hyperthyroidism is more widespread in areas with mild to moderate iodine scarcity.

However the prevalence of subclinical hyperthyroidism has been shown to be as high as 15 % in patients older than 70 years in iodine-lacking areas [19]. It is most frequent in individuals on thyroid hormone treatment, where the prevalence may be as high as 20 % [3, 4]. Moreover, subclinical thyroid dysfunction is more frequent in females, smokers, and older persons [18, 20].

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Mostly subclinical hyperthyroidism will not progress to frank hyperthyroidism. The associations and the risk factors that seem to influence the natural course include the level of TSH inhibition and the primary cause. One prospective study evaluated 102 females more than 60 years old with subclinical hyperthyroidism with TSH concentrations between 0.1 and 0.4 mIU/L [21]. Amongst these women, 2.9 % developed overt hyperthyroidism; in 3.9 % TSH levels reduced to less than 0.1 mIU/L, with normal T3 and T4 values; in 23.5 % the TSH normalized; and in 69.5 % TSH levels remained within 0.1–0.4 mIU/L over an average follow-up of 41

months. This is equivalent to a 1 % development to obvious hyperthyroidism per year. The only reliable association of progression was a preliminary TSH value of less than 0.2 mIU/L. Females more than 65 years with subclinical hyperthyroidism and TSH concentrations less than 0.1 mIU/L had a 27 % chance of developing obvious hyperthyroidism over the next 2 years [22], showing that the chances of progression are higher in patients with TSH levels less than 0.1 mIU/L.

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A retrospective investigation of the natural course of subclinical hyperthyroidism showed that the history of disease is more unpredictable in patients with Graves disease than in toxic multinodular goiter [23]. In Graves disease, patients can go into remission, progress, or may not change in up to a 3 years of follow-up, while the majority of patients with multinodular goiter were seen to have steady thyroid function during the same period of follow-up. Multinodular goiter is more frequent in iodine-depleted areas, and administration of iodine including iodine-containing medications, such as amiodarone can precipitate subclinical hyperthyroidism [24].

When investigated prospectively, 40–60 % of subjects with subclinical hyperthyroidism have normal results [12, 13]. This is most liable to arise in persons with only slightly below normal serum TSH results (e.g., between 0.1 and 0.5 mU/L) when initially investigated. In a study of a primary care system that included 422,242 subjects without known thyroid dysfunction, 52 % who had a serum TSH level <0.35 mU/L at baseline had a normal TSH afterward without any treatment [25].

There are inconsistent data regarding the incidence of progression from subclinical to frank hyperthyroidism [11, 14, 21, 22, 26, 27]. Progression to frank hyperthyroidism appears to be associated with the level of subclinical hyperthyroidism and the underlying diagnosis.

In a community based report from Scotland, 2024 persons with at least two subnormal (<0.4 mU/L) TSH levels examined 4 months apart with normal free or total thyroxine (T4) and total triiodothyronine (T3) [27]. During the initial year of the study, the overall development from subclinical to overt hyperthyroidism was 6.1 %. In subjects with steady state subclinical hyperthyroidism who did not progress in the subsequent year, further progression rates at 2, 5, and 7 years were 0.6, 0.7, and 0.5 %, respectively. It was noted that the number of patients who progressed to clear hyperthyroidism was small, progression was around twice as common in patients with serum TSH <0.1 mU/L as compared to TSH between 0.1 and 0.4 mU/L.

In a study from New Zealand of 96 patients with endogenous subclinical thyrotoxicosis (TSH <0.25 mU/L), development of hyperthyroidism occurred in 8 % at 1 year, and amplified to 26 % at 5 years. At 5 years, overt hyperthyroidism in subclinical hyperthyroidism due to Graves' disease, nodular goiter, and autonomous nodules was seen in 9, 21, and 61 % of patients respectively [27].

In a study from Brazil of 48 women <65 years who had twice confirmed TSH ≤0.1 mU/L, 20 % with nodular disease and 40 % with Graves' disease progressed to overt hyperthyroidism over a 2-year period [22]. In another study of females ≥60 years with minimal thyrotoxicosis (TSH 0.1–0.4 mU/L), progression to overt hyperthyroidism was infrequent (approximately 1 % per year) [21].

A UK based study showed that, 20.3 % of patients with subclinical hyperthyroidism with TSH <0.1 mU/L developed overt hyperthyroidism over an average of 32 months, as compared to 6.8 % with TSH 0.1–0.39 mU/L [28].

In >60 years old in Framingham study with a TSH <0.1 mU/L, only 4.3 % of patients progressed to overt hyperthyroidism after a follow up of 4 years [11].

Clinical Findings

The major target tissues negatively affected by subclinical hyperthyroidism, are bones and the cardiovascular system although abnormalities in other systems are effected too (see Table 10.1).

Cardiovascular Mortality Risk

Cardiovascular abnormalities of subclinical hyperthyroidism include an increased heart rate, risk of atrial arrhythmias, bigger left ventricular mass, and reduced variability in heart rate [29, 30]. Decreased heart rate variability was prominent in patients with subclinical and overt hyperthyroidism as compared with control subjects, which may indicate an increased risk of later cardiac events [30]. In a retrospective analysis of adults more than 65 years old, the frequency of atrial fibrillation in persons with subclinical hyperthyroidism whose TSH concentration was less than 0.4 mIU/L was 12.7 %, as compared to 2.3 % in those with normal TSH. The age adjusted risk of atrial fibrillation is 2.8 in patients with subclinical hyperthyroidism compared with normal controls [31]. Likewise, two large cohorts of subjects 60–65 years of age found that subclinical hyperthyroidism is linked with an increased relative risk of developing atrial fibrillation over the course of 10 years [20, 32].

Subclinical hyperthyroidism is linked with cardiovascular and all-cause mortality, even though the data are inconsistent. A prospective systematic review of cohort studies evaluating coronary heart disease and mortality in subclinical hyperthyroidism (TSH levels less than 0.3–0.5 mIU per L) found a modest trivial increase in risk [33]. Nonetheless, a meta-analysis concerning different studies reported that subclinical hyperthyroidism is associated with a 41 % increased risk of all-cause mortality compared with normal control patients, and that this risk increases with advancing age [34]. Two population based cohort studies from Germany and Brazil had incompatible results regarding the relationship between low TSH levels and mortality [35, 36]. In an 8.5-year follow-up study from Germany, adjusted all-cause mortality was not adversely effected in middle-aged subjects with TSH levels less than 0.25 mIU/L [35]. On the contrary, in Brazilian patients about 60 years of age who had TSH levels less than 0.45 mIU/L had a significant 20.3 % enhanced all-cause mortality in 7.5 years, but not elevated cardiovascular ailment [36].

Two studies looked into the cardiovascular effects of treatment of low TSH with methimazole [37] or radioactive iodine [38]. The first study showed that methimazole treatment in patients with suppressed TSH levels considerably decreased heart rate, atrial and ventricular premature beats, and left ventricular wall thickness 6 months after normalization of TSH levels, reaching same proportions to that of the normal control group [37]. Similarly in another report, treatment with radioactive iodine in persons with

Table 10.1 Clinical manifestations of subclinical hyperthyroidism

Heart disease
Increased heart rate and incidence of premature atrial beats
Increased cardiac contractility
Increased left ventricular mass and septal and posterior wall thickness
Increased atrial fibrillation
Bone disease
Decreased bone density, particularly in postmenopausal women
Elevated biochemical markers of increased bone resorption
Increased urinary pyridinoline and deoxypyridinoline excretion
Increased urinary hydroxyproline excretion
Other
Disturbed sleep
Mood disorders
Laboratory abnormalities
Increased serum concentration of sex hormone-binding globulin
Increased serum concentrations of hepatic enzymes and creatine kinase
Decrease in serum total and LDL-cholesterol concentrations

subclinical hyperthyroidism (TSH levels less than 0.1 mIU/L) due to multinodular goiter caused an 11 % decrease in heart rate, 19 % drop in cardiac output, and a simultaneous 30 % raised systemic vascular resistance after a mean follow-up period of 224 days after TSH normalization; though, in this study a euthyroid control group was missing [38].

Atrial Fibrillation

The collective incidence of atrial fibrillation in persons with subclinical hyperthyroidism is reported by the findings of a prospective cohort study of around 2000 subjects older than 60 years (without atrial fibrillation) followed for 10 years [17]. For patients with TSH values <0.1 mU/L, 0.1–0.4 mU/L, or within the normal range, the overall incidence of atrial fibrillation was 28, 16, and 11 %, respectively [17].

In biochemically euthyroid persons, TSH and free T4 concentrations may also be linked with atrial fibrillation risk. In a population-based study of 1426 subjects, euthyroid individuals with a TSH in the lowest levels had a higher risk of atrial fibrillation than those in the upper quartile [39]. Comparable findings were seen in another population-based study of 5519 euthyroid (normal serum TSH and free T4) elderly subjects [40]. Higher serum free T4 concentrations (but within the normal limits) were independently linked with atrial fibrillation [40].

Coronary Heart Disease, Heart Failure, and Other Cardiac Factors

In a meta-analysis consisting of 22,437 participants, 718 with endogenous subclinical hyperthyroidism, the risk of coronary heart disease was elevated in patients with endogenous subclinical hyperthyroidism (HR 1.21, 95 % CI 0.99–1.46). Similar findings were noted in a study from Scotland [41]. Endogenous subclinical hyperthyroidism was linked with an increased risk of non-fatal cardiovascular disease (HR 1.39, 95 % CI 1.22–1.58) [41].

Subclinical hyperthyroidism is also associated with an increased risk of heart failure [42–44]. In a group of males and females aged 70–82 years with a history of cardiovascular disorder (5316 participants, 71 with subclinical hyperthyroidism, five on thyroxine replacement), the risk of heart failure over 3.2 years of follow-up was more as compared with euthyroid subjects (HR 2.93, 95 % CI 1.37–6.24), and in another combined analysis of individual data from six prospective cohort studies (25,390 participants, 648 with subclinical hyperthyroidism), patients with TSH levels <0.10 mU/L had a higher risk of heart failure than euthyroid controls (16 events in 154 participants [10.4 %] versus 1762 events in 22,674 [7.8 %], HR 1.94, 95 % CI 1.01–3.72). The risk remained (HR 1.8, 95 % CI 1.04–3.13) even when those using thyroid hormone were excluded from the analysis.

Subclinical hyperthyroidism has numerous other effects on cardiac function, same but of lower severity and lower frequency than frank hyperthyroidism. These include sinus tachycardia, atrial premature beats, increased left ventricular hypertrophy, increased cardiac contractility, abnormal endothelial function, reduced exercise capacity, reduced heart rate variability, and an increase in markers of coagulopathy [45–50]. The incidence of cardiovascular findings is inconsistent, possibly due to the level of TSH suppression, the underlying disorder, and individual sensitivity to thyroid hormone excess.

The level of TSH inhibition that indicates poor cardiovascular effects is indefinite. Nevertheless, in a small study of exogenous subclinical hyperthyroidism, cardiovascular findings that were abnormal at high doses of thyroxine became normal when the dose was lowered so that the measured TSH was around 0.1 mU/L [51].

Cardiovascular Mortality

Subclinical hyperthyroidism has been associated with many cardiovascular risk factors, it is indefinite whether there is an increased mortality. In five population-based studies meta-analysis investigating the relationship between subclinical

hyperthyroidism (TSH less than 0.3–0.5 mU/L) and cardiovascular and all-cause mortality, the risk for all-cause and cardiovascular mortality was not significant (relative risks [RRs] 1.12, 95 % CI 0.89–1.42 and 1.19, 95 % CI 0.81–1.76, respectively) [33]. However, another meta-analysis showed a considerably increased risk of all-cause mortality (HR 1.41, 95 % CI 1.12–1.79) [34]. Increased mortality after finding of subclinical hyperthyroidism depended upon age, with an increase beyond the age of 60 years. However, in a subsequent population-based study, subclinical hyperthyroidism was associated with reduced survival only in individuals < age 65 years [52].

The meta-analyses included both exogenous and endogenous subclinical hyperthyroidism patients. Serum triiodothyronine (T3) levels are more in persons with endogenous than exogenous subclinical hyperthyroidism, and this may give a higher mortality risk [45]. In the meta-analysis of 10 prospective cohort studies (52,674 participants, 2188 with endogenous subclinical hyperthyroidism) studying only patients with endogenous subclinical hyperthyroidism, there was an elevated risk of both all cause (HR 1.24, 95 % CI 1.06–1.46) and cardiovascular (HR 1.29, 95 % CI 1.02–1.62) mortality in patients with endogenous subclinical hyperthyroidism [53]. The risk of cardiovascular mortality was more for TSH levels <0.1 mU/L as compared to concentrations between 0.1 and 0.44 mU/L (HRs 1.84 versus 1.24).

In a study investigating patients with exogenous subclinical hyperthyroidism only, there was a higher risk of cardiovascular or all-cause mortality only in patients with totally suppressed TSH levels [54]. In this evaluation of 17,684 persons (mean age 61.6 years) on T4 replacement treatment, TSH levels were fully suppressed (<0.03 mU/L) or low (0.04–0.4 mU/L) in 6 and 21 % of subjects, respectively. In comparison to patients with normal TSH, patients with suppressed TSH levels (<0.03 mU/L) had raised cardiovascular morbidity and mortality (adjusted HR 1.37, 95 % CI 1.17–1.60), while those who had serum TSH concentration between 0.04 and 0.4 mU/L had a lesser increase in risk that was insignificant (adjusted HR 1.10 [95 % CI 0.99–1.23]). In general, the increased risk of mortality from subclinical hyperthyroidism appears to be little but rises with the extent of TSH suppression.

Bone and Mineral Metabolism

Subclinical hyperthyroidism may decrease bone mineral density (BMD), predominantly in cortical bones, though the effect is possibly influenced by the period of the disease, other associated risk factors for loss of bone, and the level of TSH inhibition. Loss of bone density with hyperthyroidism is a consequence of increased bone turnover due to imbalance between bone resorption and formation, resulting in decrease in BMD and increased bone turnover markers [55]. Though frank hyperthyroidism is linked with increased risk of fractures, the data is inconsistent for subclinical hyperthyroidism.

The effect of subclinical hyperthyroidism on BMD is significant in postmenopausal women. In a cross-sectional analysis of females with endogenous subclinical hyperthyroidism (TSH levels of 0.01–0.1 mIU/L), postmenopausal women had considerably lower BMD at the level of the femur and lumbar regions, while premenopausal women had only a modestly lower BMD in the femur area compared with corresponding euthyroid control patients [56]. A 12 studies meta-analysis also found a relationship between markedly decreased BMD in postmenopausal women, but not in premenopausal females or males [57].

There is proof that subnormal TSH results in increased bone turnover markers, particularly in postmenopausal women with exogenous subclinical hyperthyroidism. There is an inadequate data on bone turnover marker in endogenous subclinical hyperthyroidism; nonetheless the findings are similar. The data supports bone improvement from treating postmenopausal females with subclinical hyperthyroidism. In one study, postmenopausal women with subclinical hyperthyroidism (TSH levels less than 0.2 mIU/ L) due to multinodular goiter who were treated or not treated with radioactive iodine ablation, and followed up for 2 years [58]. Patients receiving

radioactive iodine treatment had normal TSH levels and had no significant change in lumbar and hip BMD, while the untreated patients with low TSH levels had persistent loss of bone mass of approximately 1–2 % per year. One more study noted a prominent increase in BMD in patients with overt or subclinical hyperthyroidism (2.8 and 1.5 %, respectively) after 6 months of euthyroid status [59].

Dementia Cognitive Function

The relationship between low TSH concentration and dementia is contentious. Though data are inconsistent, subclinical hyperthyroidism may also be associated with an increased possibility of dementia [41, 60–62].

The prospective population-based Rotterdam study analyzed a random sample of 1846 patients more than 55 years old, and noted that TSH concentrations less than 0.4 mIU/L were associated with a 3.5-fold elevated risk of dementia and Alzheimer disease in a 2–4-year follow-up [63]. This association was significantly stronger for patients with both low TSH levels and positive antithyroid peroxidase antibodies, raising the likelihood of an autoimmune mechanism. Though another study among the same population did not confirm the relationship between incident dementia or Alzheimer disease and TSH levels in a follow-up of 5-year [63]. Another population-based study from Italy discovered that persons older than 65 years with TSH below 0.46 mIU/L had poorer Mini-Mental State Examination results compared with euthyroid age-matched control patients (22.61 ± 6.88 versus 24.72 ± 4.52, respectively ($P < .03$)) [62]. Moreover in multivariate regression analysis, same patients had a more than twofold increased probability of cognitive impairment compared with age-matched control patients [62]. Further studies are required to elucidate whether there is a causal link between subclinical hyperthyroidism and cognitive deterioration, or whether the relationship between low TSH and dementia is due to a higher occurrence of nonthyroidal illness in older adults.

In a prospective cohort study of 1864 subjects (mean age of 71 years and TSH of 0.1–10 mU/L), followed for an average of 12.7 years, only females whose TSH levels was in the lowest range had a 2.39 elevated risk of developing Alzheimer disease compared with the higher levels [61].

Similar data were noted in a population-based study of 1171 participants in whom subclinical hyperthyroidism (TSH <0.46 mU/L) was linked with cognitive dysfunction (HR 2.26, 95 % CI 1.32–3.91) [62].

In a community-based analysis from Scotland (n = 2004), continuous endogenous subclinical hyperthyroidism (TSH <0.4 mU/L) was associated with an increased risk of dementia (adjusted HR 1.79, 95 % CI 1.28–2.51) [45].

In another prospective population based study from Korea, 54 out of 313 patients who showed deterioration in cognitive function had lower TSH levels within the normal reference range compared with subjects whose cognitive function remained stable or got better [64].

While in contradiction, cross-sectional analysis of primary care patients in England [65], thyroid cancer subjects from Korea [66], and females taking T4-suppressive therapy in the United States [67] failed to show an association of subclinical hyperthyroidism with cognitive function.

Quality of Life

Persons with subclinical hyperthyroidism may have increased feeling of adrenergic over activity, especially those younger than 50 years. Quality of life and over activity of excess thyroid hormone were analyzed in 23 patients about 43 years old, who had TSH levels less than 0.3 mIU/L [29]. Compared with euthroid age and sex-matched control patients, those with low TSH had a higher frequency of nervousness, tremor, heat intolerance, palpitations, and sweating, and lower functional health and well-being. However, other studies did not find a relationship between TSH concentrations and health-related quality of life scores in subjects who had been treated for

hyperthyroidism [68], or in a population-based study of females that included participants with subclinical hyperthyroidism [69].

In patients with exogenous subclinical hyperthyroidism, sleep disturbances and reduced functional capacity have been reported with or without considerable effect on temperament or psychological well being [65, 67, 70–72]. In a study, hypothyroid subjects at random assigned to the standard dose of T4 versus higher dose T4, the physical aspect and general health scale were worse in the subclinical hyperthyroid group [72]. While, psychological health, temperament, and physical learning were better.

In another 6-months randomized study of T4 escalated to establish continuation of TSH suppression versus normalization of TSH in 24 patients with a history of thyroid carcinoma, there were no important changes in any quality of life components in either group [71].

In another open study in which subjects were given a thyroxine dose that was 50 mcg higher or less than the normal dose, subjects on the higher dose had improved "well-being" using a visual analog scale compared with baseline [73].

In patients with endogenous subclinical hyperthyroidism, scores for both the physical and psychological health apparently are lower than in euthyroid control patients [32]. The low performance was due to clinical symptoms related to thyroid hormone excess.

Thus, quality of life may be effected in some patients with subclinical hyperthyroidism, mainly those with endogenous subclinical hyperthyroidism [45]. The inconsistency in results is possibly related to differences in duration of subclinical hyperthyroidism, degree of TSH suppression, and patient populations.

Evaluation

Patients with subclinical hyperthyroidism should be asked about symptoms of hyperthyroidism (eg, tremor, palpitations, heat intolerance), also a past history of thyroid disease, exposure to iodine-containing radiographic contrast material or iodine containing herbal products, and therapy that may suppress thyroid-stimulating hormone (thyroxine, high-dose glucocorticoids). Women of childbearing age should be inquired about the possibility of pregnancy. Moreover, all patients should be assessed for the presence of thyroid gland enlargement and nodularity.

Diagnosis

The negative feedback association between serum thyroxine and triiodothyronine and thyroid-stimulating hormone levels is directly proportional. Thus, even small elevation in serum T4 and T3 concentrations (whether caused by exogenous or endogenous thyroid hormone excess) suppresses TSH secretion [73]. There is a general consensus that measurement of serum TSH is the most sensitive indicator of thyroid hormone activity without pituitary or hypothalamic disease. Mostly the initial screening test for thyroid disease is the serum TSH.

If the serum TSH concentration is subnormal (<0.5 mU/L in many laboratories), the TSH evaluation should be repeated along with a serum free T4 and T3 to confirm the diagnosis of subclinical hyperthyroidism. The diagnosis of subclinical hyperthyroidism depends upon the combination of a low serum TSH level and normal serum free T4 and T3 level. It may be symptomatic or asymptomatic for hyperthyroidism. Because the serum TSH concentration can be temporarily reduced, a serum TSH level, together with a free T4 and T3, should be reassessed after 1–3 months to verify the diagnosis.

Subclinical hyperthyroidism should be differentiated from other diagnoses of low TSH concentrations that are not associated with relative thyroid over activity, for example, central hypothyroidism; some patients with central hypothyroidism have low serum TSH and normal (but usually low or low-normal) free T4 and T3 concentrations; nonthyroidal illness, euthyroid patients with nonthyroidal illness, especially those receiving high-dose glucocorticoids or dopamine, may have low serum TSH and low-normal free T4 and T3 concentrations; recovery from hyperthyroidism. Serum TSH concentrations may remain low for up to several

months after normalization of serum T4 and T3 concentrations in patients treated for hyperthyroidism or recovering from hyperthyroidism caused by thyroiditis and psychiatric conditions, especially emotional disorders. T4 and T3 levels are generally lower in patients with these disorders, while patients with subclinical hyperthyroidism may have T4 and T3 concentrations in the mid to high normal reference range.

When the diagnosis of subclinical hyperthyroidism is doubtful, assessment of 24-h thyroid radioactive iodine uptake and scan may be supportive. A high or relatively high 24-h uptake, relative to the low serum TSH levels or a focal area of increased radionuclide uptake would support the diagnosis of subclinical hyperthyroidism.

In patients not taking T4 who have persistent subnormal TSH values and in whom treatment is considered, a radioactive iodine uptake and scan is obtained to help establish the etiology of subclinical hyperthyroidism (Table 10.2). Women of childbearing age should have a negative pregnancy test before having radioactive iodine scanning.

If the scan shows one or more focal areas of increased uptake, this could explain for the low serum TSH. If there are focal areas of increased uptake, a thyroid ultrasound would then be useful in determining the presence of distinct nodules. In patients with low or no uptake on radioiodine scan, the cause may be thyroiditis or recent iodine exposure.

In postmenopausal women or other patients at risk for osteoporosis, a bone densitometry study may be useful in making a decision to treat subclinical hyperthyroidism or observe.

Table 10.2 Causes of subclinical hyperthyroidism

Hyperthyroidism with a normal or high radioiodine uptake
Autonomous thyroid tissue (uptake may be low if recent iodine load led to iodine-induced hyperthyroidism)
Toxic adenoma
Toxic multinodular goiter
Autoimmune thyroid disease
Graves' disease
Hashitoxicosis
Human chorionic gonadotropin-mediated hyperthyroidism
Hyperemesis gravidarum
Trophoblastic disease
TSH-mediated hyperthyroidism
TSH-producing pituitary adenoma
Non-neoplastic TSH-mediated hyperthyroidism
Hyperthyroidism with a near absent radioiodine uptake
Exogenous thyroid hormone intake
Excessive replacement therapy
Intentional suppressive therapy
Factitious hyperthyroidism
Amiodarone (also may cause iodine-induced hyperthyroidism)
Thyroiditis
Subacute granulomatous (de Quervain's) thyroiditis
Painless thyroiditis (silent thyroiditis, lymphocytic thyroiditis)
Postpartum thyroiditis
Palpation thyroiditis
Radiation thyroiditis
Ectopic hyperthyroidism
Struma ovarii
Metastatic follicular thyroid cancer

Pregnancy

The diagnosis of real subclinical or frank hyperthyroidism during pregnancy may be complicated because of the changes in thyroid function that happen during normal pregnancy. Transient subclinical hyperthyroidism in the first trimester is considered a normal physiologic finding. True subclinical hyperthyroidism may occur, but it is not classically associated with negative outcomes during pregnancy [74] and does not necessitate therapy. Moreover, in pregnant women with clear hyperthyroidism, the aim of treatment is to maintain serum free T4 concentrations in the high-normal range and serum TSH concentrations in the low-normal or suppressed range (i.e. to maintain constant but minimal mild hyperthyroidism).

Screening Guidelines

There is no agreement concerning screening for subclinical hyperthyroidism in the general population. Criterion for approving a screening test

should be that diagnosis and treatment of a condition in asymptomatic subjects would result in significant improvement in health outcomes compared with people who are not screened. The U.S. Preventive Services Task Force determined in 2004 that there is enough evidence that suppressed TSH concentration is a risk factor for future development of atrial fibrillation, but there is no data showing whether any therapy would prevent this complication [75]. Likewise, a group comprising of members of the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society published the conclusions of their consensus with a proposal against population-based screening for thyroid disease [1]. Nonetheless, it is also stressed that recommendations derived from evidence-based medicine are population-based, and that doctors should use their best clinical judgment in the situation of screening the individual patients.

Management

Patients on T4 for the Treatment of Hypothyroidism

Low bone density and atrial fibrillation can both result in considerable morbidity in older patients and, therefore, subclinical hyperthyroidism should be avoided. Patients receiving thyroid replacement therapy who have thyroid-stimulating hormone (TSH) concentrations below normal should have their dose titrated to keep up a normal serum TSH level (approximately 0.5–5.0 mU/L).

> Patients receiving thyroid replacement treatment for hypothyroidism and who have TSH values below normal should have their dose titrated to maintain a normal serum TSH level(approximately 0.5–5.0 mU/L)

Patients on Suppressive Levothyroxine Therapy

Subclinical hyperthyroidism is inevitable when thyroid hormone is given to suppress TSH release in an effort to prevent or reduce goiter size or prevent relapse of thyroid cancer, since it is the aim of therapy. Nevertheless, the undesirable effects of suppressive treatment can be avoided by treatment with the lowest possible dose of thyroxine (T4) required to meet the desired goal [51, 76].

In patients with thyroid cancer, subclinical hyperthyroidism is the goal of thyroid hormone therapy, the benefits of TSH suppression outweigh the risks of subclinical hyperthyroidism.

However postmenopausal patients given suppressive doses of thyroxine should be given calcium and vitamin D supplementation, and consideration should be given to starting antiresorptive treatment to prevent bone loss.

> For patients with thyroid malignancy and in some patients with benign nodular thyroid goiter, subclinical hyperthyroidism is the aim of thyroid hormone treatment. In these patients, the benefits of TSH inhibition are thought to outweigh the risks of subclinical hyperthyroidism

Endogenous Subclinical Hyperthyroidism

There is little data to direct clinical decisions concerning the therapy of patients with endogenous subclinical hyperthyroidism. In some patients the results are normal on rechecking weeks or months later, so that treatment should not be instituted unless constantly low TSH results are confirmed [12, 14].

Latent benefits of intervention include enhancement in certain cardiovascular parameters and in bone mineral density. There is no data on long-term benefits of correcting subclinical hyperthyroidism, mainly studies with clinically important results, such as cardiovascular disease and fracture. For Instance, in a prospective but uncontrolled study of subjects with subclinical

hyperthyroidism, antithyroid drugs lowered heart rate, atrial and ventricular premature beats, left ventricular mass, inter ventricular septal thickness, and left ventricular posterior wall thickness [37]. Similar benefits in hemodynamic measurements were observed in another study with radioiodine treatment [38].

Similarly in two other non-randomized trials, postmenopausal subjects with nodular goiter and subclinical hyperthyroidism given antithyroid drugs or radioiodine for 2 years had higher bone density than matched patients who were not treated [58, 77].

Thus, in certain persons with subclinical hyperthyroidism, normalization of TSH results in improvement in surrogate outcomes. Long-term clinical studies are needed to verify if correcting subclinical hyperthyroidism improves cardiovascular or skeletal outcomes. Due to deficiency of data to guide patients with endogenous subclinical hyperthyroidism for therapy, it is suggested to decide to treat on the bases of clinical risk for complications of subclinical hyperthyroidism and the degree of TSH suppression.

Patients at High Risk for Complications

In persons at increased risk for cardiac or skeletal complications (e.g., old patients >65 years of age, persons at risk factors for cardiac arrhythmias, and postmenopausal females with or at risk for osteoporosis), the following approach is suggested:

- If the TSH level is <0.1 mU/L, treat the primary cause of subclinical hyperthyroidism.
- If the TSH is 0.1–0.5 mU/L, treat if there is associated cardiovascular problem or low bone density.

Also consider treatment if a thyroid radionuclide scan shows one or more focal areas of high uptake. Subclinical hyperthyroidism due to autonomous nodule(s) is more likely to advance to frank hyperthyroidism than subclinical hyperthyroidism due to Graves' disease. Only observation is advised if the bone density is normal and the radionuclide thyroid scan fails to show a focal area of increased uptake. Observation may also be considered if a patient is on a beta-adrenergic blocker for another reason. In observed patients, check TSH, free T4, and triiodothyronine (T3) every 6 months.

> In persons with endogenous subclinical hyperthyroidism at high risk for cardiac or skeletal complications (i.e., older adults) and who have a TSH levels less than 0.1 mU/L, treatment of the underlying cause of subclinical hyperthyroidism is recommended. For comparable patients who have TSH concentrations between 0.1 and 0.5 mU/L, treatment is recommended if the bone density is low and/or if the thyroid radionuclide scan shows one or more focal areas of high uptake. If bone density is normal and the thyroid scan fails to show a focal area of increased uptake, patients are typically observed. In these patients, TSH, free T4, and T3 is measured every 6 months

Patients at Low Risk for Complications

In persons at low risk for complications of hyperthyroidism (young subjects, premenopausal patients), following approach is advised:

- If the serum TSH concentration is <0.1 mU/L, treat the main cause of subclinical hyperthyroidism if the patient is symptomatic of hyperthyroidism and/or if a radionuclide thyroid scan discovers one or more focal areas of high uptake.
- If the TSH is between 0.1 and 0.5 mU/L, observation alone is appropriate and TSH, free T4, and T3 should be measured every 6 months.

Above guidelines are in agreement with those of a clinical panel (comprised of representatives

from The Endocrine Society, the American Thyroid Association [ATA], and the American Association of Clinical Endocrinologists [AACE]) [1].

For patients with endogenous subclinical hyperthyroidism at low risk for cardiac or skeletal complications (young individuals, premenopausal women) and TSH values less than 0.1 mU/L, treatment is advised if the radionuclide scan shows one or more focal areas of high uptake. For low risk patients who have a TSH value between 0.1 and 0.5 mU/L, only observation is advised. TSH, free T4, and T3 is measured every 6 months

Treatment Options

Therapy options for patients with subclinical hyperthyroidism are similar to those for frank hyperthyroidism and depend upon the basic etiology. Beta-blockers are useful for symptomatic control of adrenergic hyperactivity (eg, palpitations, tremor).

In persons with Graves' disease or nodular thyroid disease with autonomy, treatment options include thionamides, radioiodine, or surgery.

In patients with low or no uptake on thyroid radioiodine scan, the etiology of subclinical hyperthyroidism may be thyroiditis or exogenous thyroid hormone intake (Table 10.2). Majority of patients with thyroiditis need no treatment since thyroid dysfunction is infrequently severe and is temporary. Nevertheless, thyroid functions should be repeated, at the outset every 4–8 weeks, until normalized. Symptomatic patients may benefit from beta-blockade.

The treatment options for patients with subclinical hyperthyroidism are similar as those for frank hyperthyroidism and depend upon the basic etiology

Summary and Recommendations

- Subclinical hyperthyroidism is biochemically diagnosed by a low serum thyroid-stimulating hormone levels (TSH) but normal serum free thyroxine (T4) and triiodothyronine (T3) values. Patients with subclinical hyperthyroidism frequently have few or no symptoms of hyperthyroidism.
- The most frequent causes of subclinical hyperthyroidism are therapy with exogenous thyroxine and autonomously functioning thyroid adenomas and multinodular goiters.
- Subclinical hyperthyroidism is linked with an increased risk of atrial fibrillation and, mainly in postmenopausal women, reduced bone mineral density.
- Patients receiving thyroid replacement treatment for hypothyroidism and who have TSH values below normal should have their dose titrated to maintain a normal serum TSH level (approximately 0.5–5.0 mU/L).
- For patients with thyroid malignancy and in some patients with benign nodular thyroid goiter, subclinical hyperthyroidism is the aim of thyroid hormone treatment. In these patients, the benefits of TSH inhibition are thought to outweigh the risks of subclinical hyperthyroidism.
- In persons with endogenous subclinical hyperthyroidism at high risk for cardiac or skeletal complications (ie, older adults) and who have a TSH levels less than 0.1 mU/L, treatment of the underlying cause of subclinical hyperthyroidism is recommended.
- For comparable patients who have TSH concentrations between 0.1 and 0.5 mU/L, treatment is recommended if the bone density is low and/or if the thyroid radionuclide scan shows one or more focal areas of high uptake. If bone density is normal and the thyroid scan fails to show a focal area of increased

uptake, patients are typically observed. In these patients, TSH, free T4, and T3 are measured every 6 months.

- For patients with endogenous subclinical hyperthyroidism at low risk for cardiac or skeletal complications (young individuals, premenopausal women) and TSH values less than 0.1 mU/L, treatment is advised if the radionuclide scan shows one or more focal areas of high uptake. For low risk patients who have a TSH value between 0.1 and 0.5 mU/L, only observation is advised. TSH, free T4, and T3 are measured every 6 months.
- The treatment options for patients with subclinical hyperthyroidism are similar as those for frank hyperthyroidism and depend upon the basic etiology.

Conclusion

Subclinical hyperthyroidism is defined by low or undetectable serum thyroid-stimulating hormone levels, with normal free thyroxine and total or free triiodothyronine levels. It can be caused by increased endogenous production of thyroid hormone, administration of thyroid hormone for treatment of malignant thyroid disease, or unintentional excessive thyroid hormone therapy. The rate of development of overt hyperthyroidism is elevated in subjects who have suppressed thyroid-stimulating hormone levels compared with those who have low but detectable levels. Subclinical hyperthyroidism is linked with higher risk of atrial fibrillation in older adults, and with reduced bone mineral density in postmenopausal females. Possible relationships between subclinical hyperthyroidism and quality of life factors, cognition, and increased mortality rates are controversial. Prospective randomized controlled trials are required to address the results of early treatment on potential morbidities to help determine whether screening should be advocated in the asymptomatic general population.

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