Update on subclinical thyroid dysfunction

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Abstract. Subclinical thyroid dysfunction is defined by serum thyroid-stimulating hormone (TSH) levels either greater or less than the reference range with normal thyroxine (T4) concentrations, and consists of subclinical hypothyroidism (SCH) and subclinical hyperthyroidism (SCHyper). For the proper diagnosis of SCH, it is most important to be able to correctly evaluate the serum TSH levels, which have numerous unique characteristics. We also need to be versed in TSH harmonization, which was recently launched world-wide. In this review, we will attempt to determine the best clinical approaches to the treatment of subclinical thyroid dysfunction based on recent guidelines published from several countries and novel findings of several recent large-scale clinical studies.

Key words: Subclinical hypothyroidism (SCH), Subclinical hyperthyroidism (SCHyper), TSH harmonization

Introduction

Along with the progress in laboratory medicine, thyroid function tests (TFTs) have become part of the routine clinical work. As a result, physicians may often encounter subtle abnormalities in TFTs for serum thyroid-stimulating hormone (TSH) levels. Overt thyroid dysfunction is defined by thyroid hormone levels (thyroxine [T4] and triiodothyronine [T3]) that are greater or less than the reference range, in addition to abnormal serum TSH levels. In these cases, the diagnosis of either overt hypothyroidism or overt hyperthyroidism is easily made and the treatments for them are also well-established. A significantly more common finding, however, is serum TSH levels outside of the reference range, despite normal thyroid hormone levels. This is referred to as subclinical thyroid dysfunction, and includes subclinical hypothyroidism (SCH) and subclinical hyperthyroidism (SCHyper). Despite several guidelines published for these diseases, there are still controversies regarding their clinical significance and appropriate management.

Subclinical Hypothyroidism (SCH)

Epidemiology and characteristics of SCH

SCH is defined as a disease that, despite normal serum free T4 (FT4) levels, has serum TSH levels that are higher than the reference range [1] thus it is a biochemically-defined disease. It is categorized into two groups based on serum TSH levels: mild (Grade 1) and severe (Grade 2) [1-4]. Serum TSH levels in the mild (Grade 1) type are higher than the upper limit (4.5 mIU/L in most cases) and below 10 mIU/L, whereas those in the severe (Grade 2) type are higher than 10 mIU/L [5]. Approximately 75% of all SCH patients belong to the mild (Grade 1) type [6, 7]. SCH is found in 4–10% of the general population and is as high as 7–26% of the elder population [8]. According to the Colorado study of approximately 26,000 subjects in the US, the prevalence of SCH was 9.5% in the general population and increased to 21% and 16% in females and male subjects, respectively, who were 74 years old or older [1, 6].

In Japan, a Clinical Guidelines Committee of the Japan Thyroid Association reported that SCH is found in 3.3–10.2% of the general population [9]. A study of approximately 10,000 subjects who underwent general checkup in Japan reported that SCH was found in 6.3% and 3.4% of female and male subjects, respectively, and that the prevalence of SCH increased with age in both female and male subjects (Fig. 1) [9]. However, these findings depend mainly on the nature of the serum TSH levels, which physiologically increase with age, thereby
influencing the therapeutic strategy against SCH, especially in elderly patients who are 70 years old or older, as stated later in this review.

Sixty to eighty percent of the SCH patients are found in patients with Hashimoto’s thyroiditis and those who have thyroid autoantibodies such as anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) antibodies positive [3, 6, 7, 10]. Spontaneous remission and persistent unchanged status of SCH are frequently found in mild-type SCH patients whose serum TSH levels are below 10 mIU/L [7]. Especially in SCH patients whose serum TSH levels are below 7 mIU/L, who are anti-TPO antibody negative, and whose thyroid ultrasonic findings are normal, their serum TSH levels can be restored to normal within 2 years thereafter [7, 11, 12]. On the other hand, female patients with severe type SCH, whose serum TSH levels are above 10 mIU/L, and who are anti-TPO antibody positive are likely to progress to overt hypothyroidism [1].

**Diagnosis of SCH and TSH harmonization**

SCH is diagnosed when serum FT4 levels are normal, whereas serum TSH levels are above reference range. Previously, most guidelines recommended employing the upper limit of serum TSH levels in each facility for diagnosis of SCH. Since the upper limits of serum TSH levels were generally 4.0–5.0 mIU/L in most facilities, the guidelines from the Endocrine Society, the American Thyroid Association (ATA), and the American Association of Clinical Endocrinologists (AACE) defined the upper limit of serum TSH levels as 4.5 mIU/L for the clinical practice of SCH diagnosis [10, 13]. Thus, the marker of 4.5 mIU/L has also been employed in Japan as the upper limit of serum TSH levels for diagnosis of SCH. This situation arises since there are no reference materials for the measurement of serum TSH levels. This is compounded by the fact that the measurement range is variable among measurement kits, which has been a serious problem when it came to interpreting serum TSH levels in different guidelines and meta-analyses. In 2017, to unify the reference ranges in different measurement kits of serum TSH levels, the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) Committee for Standardization of Thyroid Function Tests (C-STFT) launched the standardization of serum TSH levels of different measurement kits using conversion factors, which was referred to as “TSH harmonization and FT4 standardization”. Upon TSH harmonization, the reference range of serum TSH levels has been defined as 0.61–4.23 mIU/L in Japanese adults (20–60 years old), which is equivalent to the reference range in US adults of 0.56–4.27 mIU/L [14]. Thus, in Japan, 4.23 mIU/L should be used as the upper limit of serum TSH levels for diagnosis of SCH. However, the new reference range does not cover elderly people who are 60 years old and older, and attention needs to be paid to the diagnosis of SCH in elderly patients.

**Pitfalls when evaluating serum TSH levels**

Prior to confirming a diagnosis of SCH, serum FT4 and TSH levels should be reassessed 1–3 months later in order to rule out a transient increase of serum TSH levels due to excess intake of iodine, etc. Moreover, some factors and pathological conditions, as shown below, may
affect serum TSH levels and should be carefully reviewed:

1. **Obesity:** Leptin secretion is increased in adipose tissue from obese patients, thereby promoting TRH (thyrotropin-releasing hormone) secretion from the hypothalamus, which may result in increased serum TSH levels [15].

2. **Drugs:** Anti-thyroid agents, rifampicin, and amiodarone may increase serum TSH levels. Amiodarone is especially known to increase serum TSH levels as high as or higher than 10 mIU/L, therefore, the upper limit of serum TSH levels in such patients may be as high as 20 mIU/L [16-18].

3. **Adrenal insufficiency:** In cases of primary adrenal insufficiency and isolated ACTH deficiency, mild increase of serum TSH levels may be observed, which can be a pitfall in the diagnosis of SCH. In these cases, hydrocortisone should be supplemented prior to levothyroxine (LT4) administration [2, 3].

4. **Hypothalamic hypothyroidism:** In hypothalamic hypothyroidism, mild increase and decrease in serum TSH and FT4 levels, respectively, may often be observed, while the serum FT4 levels are sometimes normal, which is similar to SCH [2, 3].

5. **Therapeutic process of overt hypothyroidism:** At an early stage of overt hypothyroidism or due to poor compliance to LT4 administration for it, serum TSH levels may be mildly increased despite normal FT4 levels [2, 3].

6. **Non-thyroidal illness (NTI):** In the case of debilitating diseases such as cancer cachexia due to malignancy, it is possible to obtain results in thyroid function tests that are similar to SCH [2, 3].

7. **Heterophilic antibodies:** Heterophilic antibody against TSH may lead to false high levels of serum TSH, depending on the type of measurement kit. T4 autoantibody may also yield false high levels of serum FT4 even in overt hypothyroidism, which is a similar thyroid hormone status as SCH [19].

8. **Genetic disorders:** Heterogenous genetic mutations of TSH receptor gene (inactive form) are found in 11.4–29.0% of children with SCH. Mild increase in serum TSH levels can be found in patients with genetic disorders of dual oxidase 2 (DUOX2), which is important for the organification of iodine in the thyroid gland. SCH can be found in 25.3–60.0% of patients with Down’s syndrome. Moreover, mild increase in serum TSH levels can be found in patients with pseudohypoparathyroidism type 1a, a genetic disorder of the GTP-coupled protein, Gsa gene, in which the intracellular signaling pathway via cAMP is impaired, thereby yielding TSH resistance [20].

**Clinical Significance of SCH**

**Cardiovascular disease**

It has been reported that SCH is associated with various risk factors for cardiovascular disease (CVD), such as hypertension and dyslipidemia [21, 22]. A population-based cross-sectional study in Rotterdam, The Netherlands (1,149 women (mean age ± SD, 69.0 ± 7.5 years) reported that SCH was associated with the prevalence of aortic atherosclerosis (odds ratio (OR): 1.7, 95% confidence interval (CI): 1.1–2.6) and myocardial infarction (OR: 2.3, CI: 1.3–4.0) when age adjusted, in elderly women [23]. A cross-sectional study (New Mexico Elder Health Survey) of a randomly selected sample of elderly Medicare recipients (age ≥65 years) described that only those participants with the highest TSH levels (>10 mIU/L) had a significantly higher prevalence of coronary heart disease (CHD) when compared to the participants with normal serum TSH levels (≤4.6 mIU/L, p = 0.007) [24]. Another cross-sectional study of a general population demonstrated that SCH in males below 50 years was associated with CVD compared to euthyroid males (OR: 3.4, CI: 1.6–6.8) [25].

Other cross-sectional and longitudinal studies reported that SCH may be an independent risk factor for CHD and may increase the risk of cardiovascular outcomes [26-34]. Moreover, the HUNT study, a Norwegian population-based cohort study concluded that even though serum TSH levels are within normal range, they are positively and linearly associated with CHD mortality in women but not in men, indicating that normal but relatively high serum TSH levels may increase the risk of fatal CHD [35]. However, serum TSH levels were not associated with the risk of being hospitalized with myocardial infarction [36].

On the other hand, there are numerous studies, which indicate insufficient association between SCH and CVD [37-42]. Nonetheless, several meta-analyses [43-45], including the most recent analysis [46], indicate that SCH is associated with an increased CVD risk and all-cause mortality, particularly in participants younger than 65 years with high CVD risk.

There are several pro [28, 47] and con [48, 49] studies regarding the use of LT4 for improving CVD outcomes in individuals with SCH. Even though no large-scale, randomized, placebo-controlled trial to support evidence for the benefit of LT4 administration to SCH on CVD risk has been performed to date, taken together, these studies suggest that LT4 administration may not improve CVD outcomes in SCH, especially in elderly patients. Moreover, a double-blind, randomized clinical trial conducted in 6 hospitals in the United Kingdom concluded that, in patients with SCH and acute myocardial
infarction (AMI), treatment with LT4 ($n = 46$), compared with placebo ($n = 49$), did not significantly improve left ventricular ejection fraction after 52 weeks, which did not support LT4 treatment of SCH in patients with AMI [48]. However, these were the results of a small-scale study that need to be replicated in a larger-scale one.

**Dyslipidemia**

It is well-known that overt hypothyroidism is associated with hyperlipidemia [50]. Dyslipidemia is also developed in some patients with SCH [51, 52]. However, there are pro [53] and con [54] population-based studies regarding the association between SCH and hyperlipidemia. To date, severe SCH with serum TSH levels above 10 mIU/L (Grade 2) is associated with hyperlipidemia [55]. For mild SCH patients with serum TSH levels below 10 mIU/L (Grade 1), a systematic review of the studies and a meta-analysis for 35 case control and cohort studies was recently performed and reported that total cholesterol, low density lipoprotein, and triglycerides were significantly higher and that high-density lipoprotein was significantly lower in Grade 1 SCH patients compared to euthyroid individuals [56]. Randomized, placebo-controlled trials designed to assess whether LT4 supplementation for patients with SCH is beneficial against dyslipidemia also had pro [57-59] and con [60, 61] results. A recently updated meta-analysis revealed that LT4 supplementation in SCH leads to improvement in lipid profile, but with a smaller degree of improvement than in overt hypothyroidism [62, 63].

**Cognitive decline and dementia**

Some meta-analyses have been conducted regarding the association of SCH with cognitive impairment, but no association was found in elderly patients who were older than 65 or 75 years [64, 65]. A recently updated meta-analysis of 21 cohorts comprising 74,565 total participants revealed that neither SCH nor SCHyper are associated with cognitive function, cognitive decline, or incident dementia, which recommends against the practice of screening for subclinical thyroid dysfunction in the context of cognitive decline in older adults [66].

**Type 2 diabetes mellitus (T2DM) and renal function**

Evidence has accumulated which suggests an association between SCH and T2DM [67-70]. Meta-analysis of 12 prospective studies revealed that those patients with high serum TSH levels (above 2.21 mIU/L) had a 17% higher risk of T2DM (relative risk (RR): 1.17, CI: 1.01–1.36) compared to those with normal serum TSH levels [71]. Meta-analysis of 36 articles, which included a total of 61 studies, revealed that SCH might increase diabetic complications such as nephropathy (OR: 1.74, CI: 1.34–2.28), retinopathy (OR: 1.42, CI: 1.21–1.67), and neuropathy (OR: 1.87, CI: 1.06–3.28) [72].

SCH is also reported to be associated with lowering glomerular filtration rate (GFR) through accelerating endothelial dysfunction. A recent prospective study of 1,580 Japanese participants in an annual health check-up demonstrated that hemoglobin A1c (HbA1c) levels were significantly and inversely associated with annual change in estimated GFR among participants with SCH ($β = −0.26, p = 0.014$), suggesting that SCH could affect the association between HbA1c and renal function [73].

It is well-known that LT4 supplementation may significantly improve insulin sensitivity in patients with overt hypothyroidism and T2DM, by normalizing fasting hyperinsulinemia. Thus, LT4 supplementation may be beneficial to improve the insulin resistance and dyslipidemia that is associated with SCH [74]. However, prospective studies are warranted to address whether individual LT4 supplementation for SCH patients with T2DM may reduce or delay diabetic complications [68]. It is also of interest that metformin, which is popular for the first-choice oral hypoglycemic agent against T2DM, may ameliorate SCH in T2DM patients by reducing serum TSH levels without altering thyroid hormone levels [72, 75, 76].

**Therapeutic Strategy against SCH**

An algorithm of medical management of SCH patients is shown in Fig. 2 based on the guidelines published by the ATA [77] and AACE in 2012 [13] and the guidelines published by the European Thyroid Association (ETA) [4]. In the medical treatment for SCH, i.e., LT4 supplementation, there is a risk of cardiovascular events in the case of overdosage. In cases where serum TSH levels are lower than 10 mIU/L, unless the symptoms of hypothyroidism such as general fatigue, constipation, dry skin, edema, weight gain, and hoarseness are demonstrated, generally speaking, LT4 supplementation is not recommended. However, when the serum TSH levels are 7 or higher and lower than 10 mIU/L in a patient who is younger than 70 years old, LT4 supplementation ought to be taken into consideration depending on the status of the individual patient, that is, depending on the presence of risk factors for cardiovascular events, such as hypercholesterolemia, atherosclerosis, angina, and a medical history of ischemic heart disease, or anti-TPO antibody positive. On the other hand, for patients with SCH who are younger than 70 years old and whose serum TSH levels are 10 mIU/L or higher, LT4 supplementation is recommended. Generally speaking, LT4 supplementation is recommended against for patients who are 70 years old or older. However, in cases that develop symptoms of...
hypothyroidism, that are anti-TPO antibody positive, or whose serum FT4 levels are at the lowest in the normal range or whose serum TSH levels have increased in a time-dependent manner, LT4 supplementation ought to be considered depending on the status of the individual patient. Notably, to date, there is no evidence that long-term LT4 supplementation against SCH can ameliorate the symptoms of hypothyroidism, such as general fatigue and depression, thereby improving the patient’s quality of life, lowering their body mass index, or contributing to the reduction of cardiovascular events.

Recently, and controversially, the British clinical practice guidelines published in 2019 [78] recommended against LT4 supplementation for almost all patients with SCH except women who are pregnant or trying to conceive or those with serum TSH levels greater than 20 mIU/L and those with severe symptoms or those younger than 30 years old. The guideline is controversial since sufficient evidence has not been gathered to support the recommendation against LT4 supplementation for patients with SCH. Up to now, starting LT4 supplementation was decided individually based on serum TSH levels, symptoms of hypothyroidism, patient preference, and risk factors for CHD [22, 79]. Further large-scale prospective clinical trials to determine the effects of long-term LT4 supplementation against SCH are thus warranted.

**SCH in Pregnancy**

When patients with SCH become pregnant, serum TSH levels and anti-TPO antibody should be evaluated. Previously, ATA and Endocrine Society launched recommendations for a TSH upper reference limit of 2.5 mU/L in the first trimester and 3.0 mU/L in the second and third trimesters [80, 81]. However, recently significant geographic and ethnic diversity in TSH concentrations during pregnancy have been found. Thus, the latest guidelines from the ATA stated that population-based trimester-specific reference ranges for serum TSH should be defined through assessment of local population data representative of a health care provider’s practice [82].

According to the ATA guidelines, LT4 should be administered in the situations as listed below [82]:

1) In cases where the anti-TPO antibody is positive and serum TSH levels are the upper limit of each tri-
Subclinical Hyperthyroidism (SCHyper)

Definition and diagnosis

Subclinical hyperthyroidism (SCHyper) is defined as a disease where serum TSH levels are lower than reference range, despite normal serum FT4 levels [83], thus, it is also a biochemically-defined disease like SCH. SCHyper is categorized into two groups based on serum TSH levels: mild and severe. Serum TSH levels in mild type are from 0.1–0.4 mIU/L, whereas those in severe type are lower than 0.1 mIU/L. Since the mild type can be resolved, it is recommended to repeat measurements of serum TSH and FT4 levels in 3 to 6 months before confirming a diagnosis of SCHyper. On the other hand, the severe type is likely to progress to overt hyperthyroidism [84, 85].

Epidemiology

SCHyper is frequently found in the general population, but its prevalence depends on age, gender, ethnicity, genetic predisposition, and iodine status [86]. In the United States, the prevalence of SCHyper is 0.7% of the general population [10]. In the TEARS study, the prevalence was 0.63% with an incidence rate of 29 per 100,000 individuals in the general population in Scotland [87]. The same study also reported that only 0.5–0.7% of the general population developed overt hyperthyroidism over 7 years. Moreover, the majority remained as SCHyper (63%), while 36% spontaneously returned to normal serum thyroid function, especially those with serum TSH levels between 0.1 and 0.4 mIU/L, during the 7-year follow-up period [87]. In general, SCHyper occurs with higher prevalence among women, older individuals, and those living in iodine-deficient regions [10, 84, 86-88]. In fact, the frequency of SCHyper is higher in older people and can be as high as 15.4% in patients who are 75 years or older [89].

Etiology and Differential Diagnosis of SCHyper

SCHyper is derived from endogenous and exogenous origins and is also categorized into transient and persistent types (Table 1). As instances of exogenous origins, there is the case where T4 is excessively supplemented to suppress serum TSH levels to control thyroid malignancy, and the case where LT4 is inappropriately administered for weight reduction. When LT4 is excessively supplemented for hypothyroidism, SCHyper can occur. Graves’ disease is the most common condition among those of endogenous origins, which is generally found in the younger population. In addition, autosomal functional thyroid nodules (AFTN) and toxic multinodular goiter (TMNG) can be cases of SCHyper of endogenous origins which are generally found in the elder population.

LT4 Supplementation

LT4 supplementation usually starts with 25 μg/day. It is important to take it with water on an empty stomach. It should not be taken with other liquids such as coffee, green tea, or milk, which may interfere with LT4 absorption. Prior to LT4 supplementation, adrenal insufficiency should be ruled out, otherwise adrenal crisis may develop upon supplementation. For patients who have suffered from SCH for more than 6 months, have a history of ischemic heart disease, or are suspected with heart failure, LT4 supplementation should start with a low dose (12.5–25 μg/day) with gradual increases based on symptoms and serum TSH levels [77]. On the other hand, for the patients with SCH who are pregnant, higher doses of LT4 should be supplemented depending on the trimester.

In SCH, target serum TSH levels are generally 0.61–4.23 mIU/L, the reference range in Japan upon TSH harmonization [14]. However, based on the current evidence it is reasonable to raise the target serum TSH levels to 4–6 mIU/L in patients greater than age 70–80 years [5, 77]. Moreover, it is of note that serum TSH levels <0.1 mIU/L, suggesting excess levels of LT4 supplementation, may be associated with adverse outcomes, such as cardiovascular diseases and osteoporosis in older persons or postmenopausal women [77]. In the near future, a target TSH in the age-specific reference range should be determined by randomized controlled trials of LT4 supplementation in patients with SCH.
Transient SCHyper may prolong for 3 to 6 months, depending on its origin. For example, transient SCHyper may occur after radioiodine therapy or therapy for Graves’ disease. Subacute, silent, and postpartum thyroiditis may also develop into transient SCHyper. Moreover, transient SCHyper may be observed under the administration of medications such as lithium, immune checkpoint inhibitors, amiodarone, interferon, tyrosine kinase inhibitors, dopamine, somatostatin analogs, and glucocorticoids [84]. Thus, SCHyper does not necessarily warrant treatment. Human chorionic gonadotropin (hCG) is similar to TSH in structure and stimulates TSH receptors, thereby increasing production and secretion of thyroid hormones. It is a cause of gestational transient hyperthyroidism (GTH), which is one of the differential diagnoses of SCHyper. However, GTH generally resolves spontaneously as pregnancy develops and does not warrant treatment. NTI, which is called low T3 syndrome, may be observed in the terminal stages of certain malignancies and in severely-debilitating diseases. NTI is also one of the differential diagnoses of SCHyper, but generally no treatment is needed. Recently, it has been reported that coronavirus disease-2019 (COVID-19) may develop into SCHyper, which is diagnosed as destructive thyroiditis [84].

**Diagnosis**

When SCHyper is indicated by TFT, it is important to repeat that TFT in 3 to 6 months [84, 90]. Upon confirmation of SCHyper, anti-TSH receptor antibody (TRAb) or anti-TSH stimulating antibody (TSAb) is the next subject to be measured. When TRAb is determined to be positive, it is likely to be diagnosed as Graves’ disease. In cases that have a family history of autoimmune thyroid diseases, anti-Tg and anti-TPO antibodies should also be measured. Increased serum Tg levels are highly indicative of destructive thyroiditis [91]. Other laboratory test results such as erythrocyte sedimentation rate, CRP, and complete blood count may complement the diagnosis of SCHyper [84], since hemoglobin levels are often decreased in SCHyper. In addition, spot urine iodine levels are useful for a differential diagnosis of SCHyper. Evaluation of blood flow by thyroid ultrasound is helpful to diagnose Graves’ disease. $^{123}$I and $^{99m}$Tc scintigraphy are another powerful tool to determine autosomal thyroid hormone secretion. When the uptake of radioisotopes is almost absent, destructive thyroiditis is indicated, whereas a local increase of uptake indicates toxic nodules. Moreover, a diffuse increase of uptake is essential to the final diagnosis of Graves’ disease. As mentioned earlier, SCHyper may result in spontaneous remission. Therefore, the final diagnosis of SCHyper should not be made by a single TFT and it is essential to repeat the test in 3 to 6 months. However, if a patient demonstrates symptoms related to hyperthyroidism such as atrial fibrillation (Af), the TFT should be repeated in 2 to 6 weeks [85, 92].

### Clinical Significance of SCHyper

**Cardiovascular disease**

It has been revealed that SCHyper is associated with Af by both population-based studies and a meta-analysis [5, 37, 87, 93-95]. A large-scale population-based cohort study of 586,460 general practice patients (mean (SD) age 50.2 (16.9) years, 39% men) was performed in Copenhagen [95]. Compared with euthyroid individuals (562,461 (96.0%)), the incidence rates of Af increased in SCHyper (6,276 (1.0%)) with decreasing serum TSH levels [95, 96]. A meta-analysis to assess the risks of total and CHD mortality, CHD events, and Af in SCHyper employing 10 large prospective cohorts was performed and revealed that SCHyper was associated with increased total mortality (hazard ratio [HR]: 1.24, CI: 1.06–1.46), CHD mortality (HR: 1.29, CI: 1.02–1.62), CHD events (HR: 1.21, CI: 0.99–1.46), and Af (HR: 1.68, CI: 1.16–2.43) after adjusting for age and sex. It also revealed that risks for CHD mortality and Af were higher for serum TSH levels lower than 0.10 mIU/L compared with those between 0.10 and 0.44 mIU/L [93]. Thus, despite still conflicting results from several reports [37, 97], it seems apparent that SCHyper is associated with increased risks of CHD mortality and Af when serum TSH levels are lower than 0.10 mIU/L [42, 98].

| Origins and differential diagnosis of SCHyper | Transient | Persistent |
|---------------------------------------------|----------|-----------|
| Endogenous Silent thyroiditis | Graves’ disease |
| Subacute thyroiditis | AFTN |
| Postpartum thyroiditis | TMNG, etc. |
| Gestational transient hyperthyroidism, etc. | Excess of LT4 intake |
| Exogenous Drug-induced (Immune checkpoint inhibitors, etc.) | |

AFTN: autosomal functional thyroid nodules
TMNG: toxic multinodular goiter

Subclinical thyroid dysfunction

Table 1 Origins and differential diagnosis of SCHyper
At the same time the association between SCHyper and stroke remains inconclusive and needs to be further evaluated by large-scale prospective studies [84, 97, 99-101].

**Osteoporosis and fractures**

Thyroid hormone affects bone metabolism. Thyrotoxicosis induces osteoclastic activity, thereby resulting in net bone loss. Even though it is well known that overt hyperthyroidism leads to secondary osteoporosis, which increases the risk of fractures [102], the association between SCHyper and bone metabolism remains unclear. In a recent meta-analysis of 17 prospective cohort studies with a total of 313,557 individuals, SCHyper was found to be associated with an increased risk of any fracture (RR: 1.17, CI: 1.08–1.26), hip fracture (RR: 1.27, CI: 1.09–1.48), spine fracture (RR: 1.97, CI: 1.31–2.97), and non-spine fracture (RR: 1.19, CI: 1.04–1.37). Moreover, SCHyper was associated with lower distal forearm bone mineral density (BMD) in women, and ultradistal forearm BMD in both men and women [103]. Similarly, another meta-analysis found that SCHyper was associated with an increased risk of hip and any fracture defined as any non-vertebral or vertebral fracture, particularly in patients whose serum TSH levels were less than 0.10 mIU/L and those with endogenous sources of SCHyper, such as Graves’ disease and AFTN [104]. By contrast, in one large prospective cohort study with 3,338 men aged 70–89 years, of these men, 86 of them had SCHyper which was not associated with incident hip fracture [105]. Another large cohort study from Korea with 25,510 individuals (15,761 women with mean age of 45 years, 9,749 men with mean age of 48 years) found that SCHyper was not associated with BMD in the lumbar spine, femur-neck, and proximal femur sites [106].

**Dementia and cognitive dysfunction**

The findings on the association between SCHyper and dementia and cognitive dysfunction are inconsistent [84]. In an individual participant data analysis of more than 74,000 adults, both SCH and SCHyper were not associated with incident dementia or cognitive dysfunction [66]. In another individual participant data meta-analysis on source data from community-dwelling participants aged 80 years and older from The Netherlands, New Zealand, United Kingdom, and Japan, cognitive function was evaluated by Mini-Mental State Examination (MMSE). Of the total 2,116 participants at baseline (mean age 87 years, range 80–109 years), 60 (2.8%) participants who were SCHyper had similar MMSE scores compared with 1,811 (85.6%) euthyroid participants [107]. On the other hand, there are some studies which suggest associations between SCHyper and cognitive decline, dementia, and Alzheimer’s disease in men [108, 109]. Patients with SCHyper, whose serum TSH levels were less than 0.10 mIU/L, had a higher risk of developing cognitive dysfunction and dementia than those whose serum TSH levels were 0.10 mIU/L or higher [110].

**SCHyper induced by excess LT4 supplementation and its clinical outcome**

Some patients, who underwent thyroid surgery for thyroid cancer followed by TSH suppression therapy with LT4 supplementation, demonstrate SCHyper. Moreover, SCHyper may occur in the cases, to which LT4 inadequately and excessively administered for weight reduction. Sinus tachycardia and atrial flutter are also commonly associated with LT4-induced SCHyper and Af is the most common cardiac complication with significant mortality and morbidity resulting from embolic events [111-114].

**Treatment of SCHyper**

An algorithm of medical management for SCHyper patients is shown in Fig. 3. According to guidelines from the ATA and AACE, patients with SCHyper should be treated when serum TSH levels are lower than 0.1 mIU/L in those aged 65 years or older with cardiac risk factors, heart disease, or osteoporosis; postmenopausal women without estrogen or bisphosphonate administration; and in those who develop hyperthyroid symptoms [85, 91]. Treatment should also be initiated in SCHyper patients aged younger than 65 years, with thyrotoxic symptoms, whose serum TSH levels remain persistently lower than 0.1 mIU/L [91]. ETA guidelines published in 2015 [90] recommend that severe SCHyper patients aged 65 years or older and those aged younger than 65 years old with symptoms of thyrotoxicosis, whose serum TSH levels are lower than 0.1 mIU/L should be treated. The guidelines also recommend that treatment should be considered for severe SCHyper patients aged younger than 65 years old with pre-existing CVDs or other risk factors and mild SCHyper patients with symptoms of thyrotoxicosis or risk factors for CVDs whose serum TSH levels are 0.1 or higher and lower than 0.4 mIU/L (Fig. 3) [90]. These recommendations state that treatment is not warranted in asymptomatic patients aged younger than 65 years old who can be monitored with several rounds of thyroid function tests, because the risk of transition into overt hyperthyroidism is low and spontaneous remission of the SCHyper can be expected. The early treatment of SCHyper is recommended for appropriate patients to avoid the progression to overt hyperthyroidism, increased total and cardiovascular mortality, and risks of
Af and fracture [85, 89, 115, 116]. The treatment strategies for SCHyper are the same as those for overt hyperthyroidism and include thionamides (i.e., methimazole or propylthiouracil), inorganic iodines, $^{131}$I-radioisotope therapy, and thyroid surgery. It is important to inform patients about the potential benefits and also the areas in which the supporting evidence is unclear when considering the treatment of SCHyper [84].

**Conclusions**

In recent years, sufficient evidence has accumulated to demonstrate the clinical significance of subclinical thyroid dysfunction and an appropriate strategy for its treatment has almost been established by some updated guidelines. However, we still need to have large-scale randomized clinical studies to support the evidence and guidelines. For this purpose, under TSH harmonization, age-specific reference range of serum TSH levels should be determined especially for elderly patients aged 65 and over. Nonetheless, physicians should keep in mind that deep understanding and correct interpretation of the TFT results, in addition to a profound insight into the patients, are essential for the proper diagnosis and treatment of SCH or SCHyper.

**Limitations**

Due to the lack of authorized guidelines for subclinical thyroid dysfunction in Japan, in this review, I followed the guidelines published by ATA, AACE Endocrine Society and ETA, accordingly. However, there are some discrepancies between the actual circumstances in Japan and the guidelines cited in this review. For example, it has been reported that the prevalence of anti-Tg antibody is higher than that of anti-TPO antibody in 1818 Japanese who undertook a general health checkup [117]. Moreover, the prevalence of anti-Tg antibody is higher than that of anti-TPO antibody in the patients with subclinical hypothyroidism in Japan, an iodine-sufficient country [117]. It has also been reported that constant high iodine intake increases the prevalence of positive anti-Tg antibody and is a risk factor developing hypothyroidism [118]. Thus, guidelines for subclinical thyroid dysfunction in specific countries and areas should be expected in the near future.

**Disclosure**

The author declares no conflict of interests.
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