STATE-OF-THE-ART REVIEW IN ENDOCRINOLOGY

Update on subclinical thyroid dysfunction

Koshi Hashimoto

Department of Diabetes, Endocrinology, and Hematology, Dokkyo Medical University Saitama Medical Center, Saitama 343-8555, Japan

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 was 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
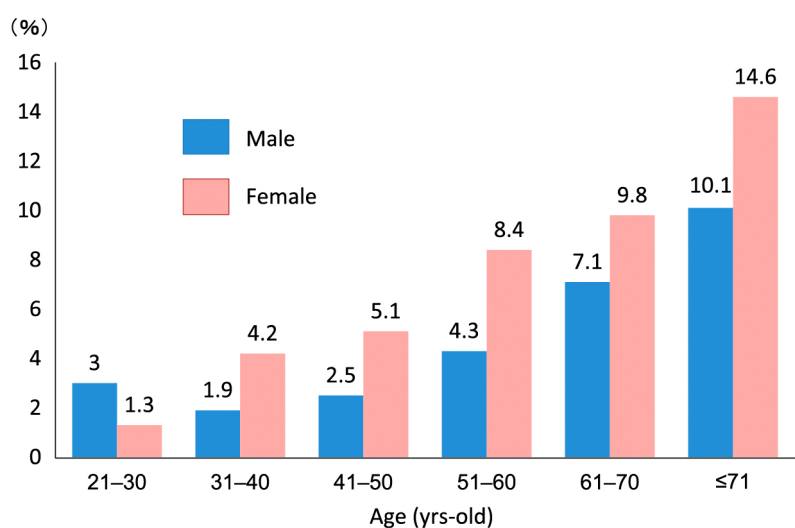
Fig. 1 Percentage of patients with SCH by age and sex
Numbers above graph bars indicate percentage (%). yrs: years.
Depicted based on Ref #9.

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, Gsα 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 contained 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 ($\beta = -0.26$, $p = 0.014$), 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
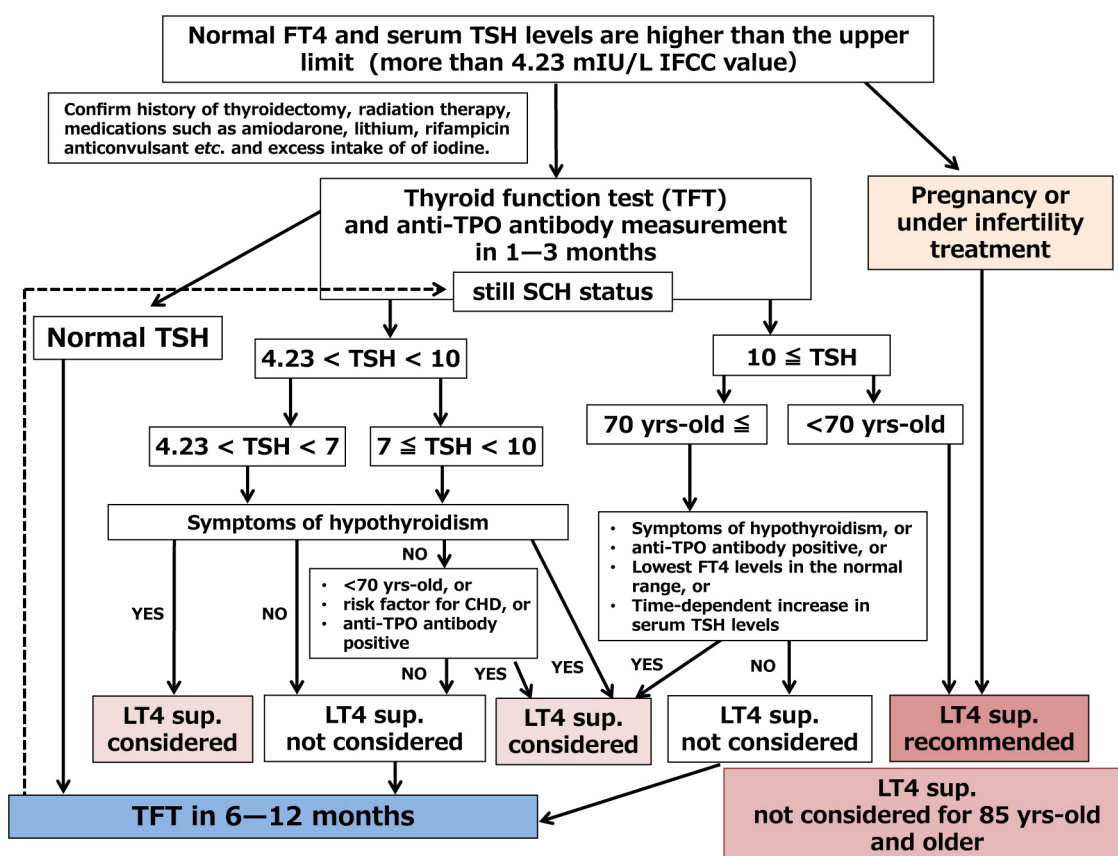
```
┌─────────────────────────────────────────────────────┐
│ Normal FT4 and serum TSH levels are higher than the  │
│     upper limit (more than 4.23 mIU/L IFCC value)    │
└─────────────────────────────────────────────────────┘
```

Confirm history of thyroidectomy, radiation therapy, medications such as amiodarone, lithium, rifampicin anticonvulsant *etc.* and excess intake of of iodine.

Thyroid function test (TFT) and anti-TPO antibody measurement in 1—3 months

still SCH status

Pregnancy or under infertility treatment

Normal TSH

4.23 < TSH < 10

10 ≦ TSH

4.23 < TSH < 7

7 ≦ TSH < 10

70 yrs-old ≦

<70 yrs-old

Symptoms of hypothyroidism

NO

- <70 yrs-old, or
- risk factor for CHD, or
- anti-TPO antibody positive

- Symptoms of hypothyroidism, or
- anti-TPO antibody positive, or
- Lowest FT4 levels in the normal range, or
- Time-dependent increase in serum TSH levels

YES   NO   NO   YES   YES   YES   NO

LT4 sup. considered

LT4 sup. not considered

LT4 sup. considered

LT4 sup. not considered

LT4 sup. recommended

TFT in 6—12 months

LT4 sup. not considered for 85 yrs-old and older

Fig. 2 An algorithm of medical management of SCH patients
CHD: coronary heart disease. sup.: supplementation.
Depicted based on Refs #4, 13 and 77.

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 the 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-

mester or higher.

2) In cases where the serum TSH levels are 10 mIU/L or higher even though anti-TPO antibody is negative.

In addition, LT4 supplementation should be considered in the following situations:

3) In cases where the anti-TPO antibody is positive and serum TSH levels are 2.5 mIU/L or higher but lower than the upper limit of each trimester.

4) In cases where the anti-TPO antibody is negative and serum TSH levels are the upper limit of each trimester or higher but lower than 10 mIU/L.

It is important to note that serum TSH levels should be lower than 2.5 mIU/L during pregnancy under LT4 supplementation. On the other hand, LT4 supplementation is not considered in cases where the anti-TPO antibody is negative and the serum TSH levels are lower than the upper limit of each trimester and within the normal range. Moreover, serum TSH levels should be lower than 2.5 mIU/L by LT4 supplementation for patients with SCH undergoing infertility treatment such as *in vitro* fertilization.

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.

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

Table 1 Origins and differential diagnosis of SCHyper

	Transient	Persistent
Endogenous	Silent thyroiditis Subacute thyroiditis Postpartum thyroiditis Gestational transient hyperthyroidism, *etc*.	Graves' disease AFTN TMNG, *etc*.
Exogenous	Drug-induced (Immune checkpoint inhibitors, *etc*.)	Excess of LT4 intake

AFTN: autosomal functional thyroid nodules
TMNG: toxic multinodular goiter

[84]. 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 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].

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 excessed 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 mU/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
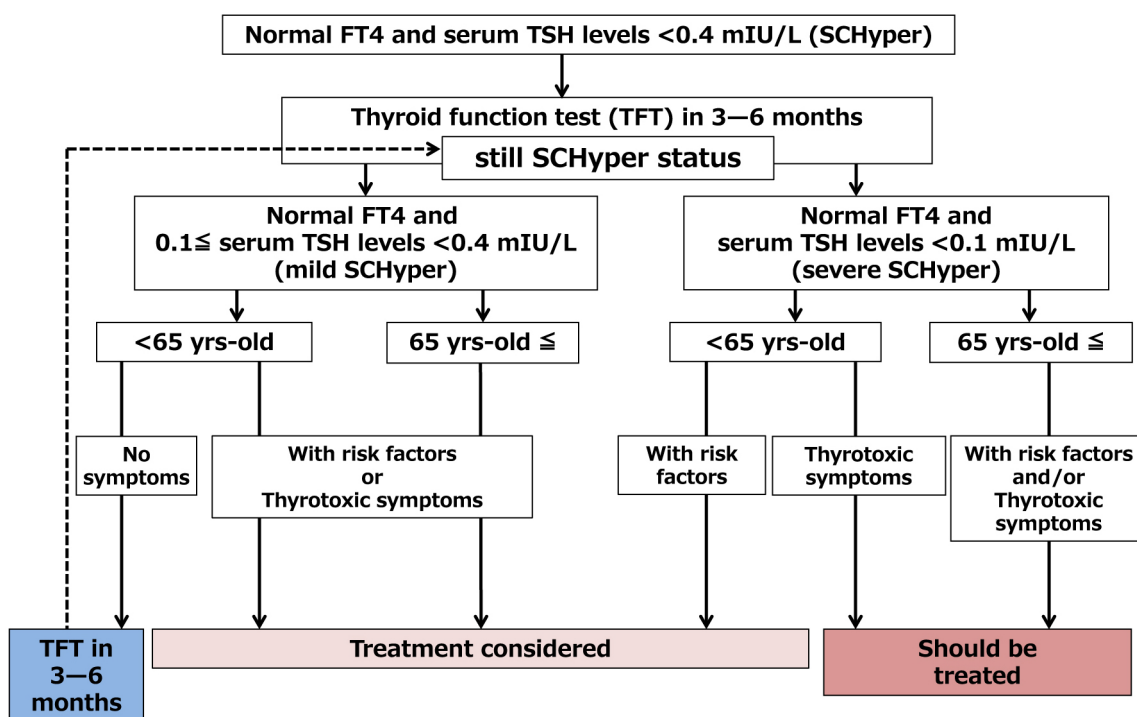
Fig. 3 An algorithm of medical management of SCHyper patients
Risk factors: cardiac disease, osteoporosis, and menopausal women not on estrogens or bisphosphonates.
Depicted based on Refs #85, 90 and 91.

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.

References

1. Peeters RP (2017) Subclinical hypothyroidism. *N Engl J Med* 376: 2556–2565.

2. Biondi B, Cappola AR, Cooper DS (2019) Subclinical hypothyroidism: a review. *JAMA* 322: 153–160.

3. Cooper DS, Biondi B (2012) Subclinical thyroid disease. *Lancet* 379: 1142–1154.

4. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, *et al.* (2013) 2013 ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J* 2: 215–228.

5. Evron JM, Papaleontiou M (2021) Decision making in subclinical thyroid disease. *Med Clin North Am* 105: 1033–1045.

6. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC (2000) The Colorado thyroid disease prevalence study. *Arch Intern Med* 160: 526–534.

7. Somwaru LL, Rariy CM, Arnold AM, Cappola AR (2012) The natural history of subclinical hypothyroidism in the elderly: the cardiovascular health study. *J Clin Endocrinol Metab* 97: 1962–1969.

8. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, *et al.* (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 291: 228–238.

9. Nakajima Y, Yamada M, Akuzawa M, Ishii S, Masamura Y, *et al.* (2013) Subclinical hypothyroidism and indices for metabolic syndrome in Japanese women: one-year follow-up study. *J Clin Endocrinol Metab* 98: 3280–3287.

10. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, *et al.* (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 87: 489–499.

11. Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, *et al.* (2002) Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. *J Clin Endocrinol Metab* 87: 3221–3226.

12. Meyerovitch J, Rotman-Pikielny P, Sherf M, Battat E, Levy Y, *et al.* (2007) Serum thyrotropin measurements in the community: five-year follow-up in a large network of primary care physicians. *Arch Intern Med* 167: 1533–1538.

13. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, *et al.* (2012) Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract* 18: 988–1028.

14. Thienpont LM, Van Uytfanghe K, De Grande LAC, Reynders D, Das B, *et al.* (2017) Harmonization of serum thyroid-stimulating hormone measurements paves the way for the adoption of a more uniform reference interval. *Clin Chem* 63: 1248–1260.

15. Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, *et al.* (2005) Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. *J Clin Endocrinol Metab* 90: 4019–4024.

16. Kinoshita S, Hayashi T, Wada K, Yamato M, Kuwahara T, *et al.* (2016) Risk factors for amiodarone-induced thyroid dysfunction in Japan. *J Arrhythm* 32: 474–480.

17. Takeuchi D, Honda K, Shinohara T, Inai K, Toyohara K, *et al.* (2015) Incidence, clinical course, and risk factors of amiodarone-induced thyroid dysfunction in Japanese adults with congenital heart disease. *Circ J* 79: 1828–1834.

18. Laurberg P, Andersen S, Carle A, Karmisholt J, Knudsen N, *et al.* (2011) The TSH upper reference limit: where are we at? *Nat Rev Endocrinol* 7: 232–239.

19. Koulouri O, Moran C, Halsall D, Chatterjee K, Gurnell M (2013) Pitfalls in the measurement and interpretation of thyroid function tests. *Best Pract Res Clin Endocrinol Metab* 27: 745–762.

20. Salerno M, Capalbo D, Cerbone M, De Luca F (2016) Subclinical hypothyroidism in childhood-current knowledge and open issues. *Nat Rev Endocrinol* 12: 734–746.

21. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, *et al.* (2018) Thyroid hormones and cardiovascular function and diseases. *J Am Coll Cardiol* 71: 1781–1796.

22. Sue LY, Leung AM (2020) Levothyroxine for the treatment of subclinical hypothyroidism and cardiovascular disease. *Front Endocrinol (Lausanne)* 11: 591588.

23. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, *et al.* (2000) Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med* 132: 270–278.

24. Lindeman RD, Romero LJ, Schade DS, Wayne S, Baumgartner RN, *et al.* (2003) Impact of subclinical hypothyroidism on serum total homocysteine concentrations, the prevalence of coronary heart disease (CHD), and CHD risk factors in the New Mexico Elder Health Survey. *Thyroid* 13: 595–600.

25. Kvetny J, Heldgaard PE, Bladbjerg EM, Gram J (2004) Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in males below 50 years. *Clin Endocrinol (Oxf)* 61: 232–238.

26. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, *et al.* (2005) Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med* 165: 2467–2472.

27. Tseng FY, Lin WY, Lin CC, Lee LT, Li TC, *et al.* (2012) Subclinical hypothyroidism is associated with increased risk for all-cause and cardiovascular mortality in adults. *J Am Coll Cardiol* 60: 730–737.

28. Razvi S, Weaver JU, Vanderpump MP, Pearce SH (2010) The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the

Whickham Survey cohort. *J Clin Endocrinol Metab* 95: 1734–1740.

29. Iervasi G, Molinaro S, Landi P, Taddei MC, Galli E, *et al.* (2007) Association between increased mortality and mild thyroid dysfunction in cardiac patients. *Arch Intern Med* 167: 1526–1532.

30. Moon S, Kong SH, Choi HS, Hwangbo Y, Lee MK, *et al.* (2018) Relation of subclinical hypothyroidism is associated with cardiovascular events and all-cause mortality in adults with high cardiovascular risk. *Am J Cardiol* 122: 571–577.

31. McQuade C, Skugor M, Brennan DM, Hoar B, Stevenson C, *et al.* (2011) Hypothyroidism and moderate subclinical hypothyroidism are associated with increased all-cause mortality independent of coronary heart disease risk factors: a PreCIS database study. *Thyroid* 21: 837–843.

32. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, *et al.* (2010) Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 304: 1365–1374.

33. Collet TH, Bauer DC, Cappola AR, Asvold BO, Weiler S, *et al.* (2014) Thyroid antibody status, subclinical hypothyroidism, and the risk of coronary heart disease: an individual participant data analysis. *J Clin Endocrinol Metab* 99: 3353–3362.

34. Inoue K, Ritz B, Brent GA, Ebrahimi R, Rhee CM, *et al.* (2020) Association of subclinical hypothyroidism and cardiovascular disease with mortality. *JAMA Netw Open* 3: e1920745.

35. Asvold BO, Bjoro T, Nilsen TI, Gunnell D, Vatten LJ (2008) Thyrotropin levels and risk of fatal coronary heart disease: the HUNT study. *Arch Intern Med* 168: 855–860.

36. Asvold BO, Bjoro T, Platou C, Vatten LJ (2012) Thyroid function and the risk of coronary heart disease: 12-year follow-up of the HUNT study in Norway. *Clin Endocrinol (Oxf)* 77: 911–917.

37. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, *et al.* (2006) Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA* 295: 1033–1041.

38. Hyland KA, Arnold AM, Lee JS, Cappola AR (2013) Persistent subclinical hypothyroidism and cardiovascular risk in the elderly: the cardiovascular health study. *J Clin Endocrinol Metab* 98: 533–540.

39. Waring AC, Harrison S, Samuels MH, Ensrud KE, LeBlanc ES, *et al.* (2012) Thyroid function and mortality in older men: a prospective study. *J Clin Endocrinol Metab* 97: 862–870.

40. LeGrys VA, Funk MJ, Lorenz CE, Giri A, Jackson RD, *et al.* (2013) Subclinical hypothyroidism and risk for incident myocardial infarction among postmenopausal women. *J Clin Endocrinol Metab* 98: 2308–2317.

41. Tohidi M, Derakhshan A, Akbarpour S, Amouzegar A, Mehran L, *et al.* (2018) Thyroid dysfunction states and incident cardiovascular events: the Tehran thyroid study. *Horm Metab Res* 50: e1.

42. Moutzouri E, Lyko C, Feller M, Blum MR, Adam L, *et al.* (2021) Subclinical thyroid function and cardiovascular events in patients with atrial fibrillation. *Eur J Endocrinol* 185: 375–385.

43. Singh S, Duggal J, Molnar J, Maldonado F, Barsano CP, *et al.* (2008) Impact of subclinical thyroid disorders on coronary heart disease, cardiovascular and all-cause mortality: a meta-analysis. *Int J Cardiol* 125: 41–48.

44. Razvi S, Shakoor A, Vanderpump M, Weaver JU, Pearce SH (2008) The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. *J Clin Endocrinol Metab* 93: 2998–3007.

45. Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, *et al.* (2008) Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Ann Intern Med* 148: 832–845.

46. Moon S, Kim MJ, Yu JM, Yoo HJ, Park YJ (2018) Subclinical hypothyroidism and the risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. *Thyroid* 28: 1101–1110.

47. Razvi S, Weaver JU, Butler TJ, Pearce SH (2012) Levothyroxine treatment of subclinical hypothyroidism, fatal and nonfatal cardiovascular events, and mortality. *Arch Intern Med* 172: 811–817.

48. Andersen MN, Olsen AM, Madsen JC, Faber J, Torp-Pedersen C, *et al.* (2015) Levothyroxine substitution in patients with subclinical hypothyroidism and the risk of myocardial infarction and mortality. *PLoS One* 10: e0129793.

49. Stott DJ, Rodondi N, Kearney PM, Ford I, Westendorp RGJ, *et al.* (2017) Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med* 376: 2534–2544.

50. Duntas LH (2002) Thyroid disease and lipids. *Thyroid* 12: 287–293.

51. Ineck BA, Ng TM (2003) Effects of subclinical hypothyroidism and its treatment on serum lipids. *Ann Pharmacother* 37: 725–730.

52. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, *et al.* (2017) Thyroid hormones and cardiovascular disease. *Nat Rev Cardiol* 14: 39–55.

53. Asvold BO, Vatten LJ, Nilsen TI, Bjoro T (2007) The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. *Eur J Endocrinol* 156: 181–186.

54. Hueston WJ, Pearson WS (2004) Subclinical hypothyroidism and the risk of hypercholesterolemia. *Ann Fam Med* 2: 351–355.

55. Duntas LH, Wartofsky L (2007) Cardiovascular risk and subclinical hypothyroidism: focus on lipids and new emerging risk factors. What is the evidence? *Thyroid* 17: 1075–1084.

56. Treister-Goltzman Y, Yarza S, Peleg R (2021) Lipid profile in mild subclinical hypothyroidism: systematic review and meta-analysis. *Minerva Endocrinol (Torino)* 46: 428–440.

57. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, *et al.* (2007) The beneficial effect of L-thyroxine on

cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. *J Clin Endocrinol Metab* 92: 1715–1723.

58. Caraccio N, Ferrannini E, Monzani F (2002) Lipoprotein profile in subclinical hypothyroidism: response to levo-thyroxine replacement, a randomized placebo-controlled study. *J Clin Endocrinol Metab* 87: 1533–1538.

59. Monzani F, Caraccio N, Kozakowa M, Dardano A, Vittone F, *et al.* (2004) Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 89: 2099–2106.

60. Jaeschke R, Guyatt G, Gerstein H, Patterson C, Molloy W, *et al.* (1996) Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? *J Gen Intern Med* 11: 744–749.

61. Kong WM, Sheikh MH, Lumb PJ, Naoumova RP, Freedman DB, *et al.* (2002) A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. *Am J Med* 112: 348–354.

62. Kotwal A, Cortes T, Genere N, Hamidi O, Jasim S, *et al.* (2020) Treatment of thyroid dysfunction and serum lipids: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 105.

63. Jasim S, Abdi H, Gharib H, Biondi B (2021) A clinical debate: subclinical hypothyroidism. *Int J Endocrinol Metab* 19: e115948.

64. Rieben C, Segna D, da Costa BR, Collet TH, Chaker L, *et al.* (2016) Subclinical thyroid dysfunction and the risk of cognitive decline: a meta-analysis of prospective cohort studies. *J Clin Endocrinol Metab* 101: 4945–4954.

65. Pasqualetti G, Pagano G, Rengo G, Ferrara N, Monzani F (2015) Subclinical hypothyroidism and cognitive impairment: systematic review and meta-analysis. *J Clin Endocrinol Metab* 100: 4240–4248.

66. van Vliet NA, van Heemst D, Almeida OP, Asvold BO, Aubert CE, *et al.* (2021) Association of thyroid dysfunction with cognitive function: an individual participant data analysis. *JAMA Intern Med* 181: 1440–1450.

67. Chaker L, Ligthart S, Korevaar TI, Hofman A, Franco OH, *et al.* (2016) Thyroid function and risk of type 2 diabetes: a population-based prospective cohort study. *BMC Med* 14: 150.

68. Biondi B, Kahaly GJ, Robertson RP (2019) Thyroid dysfunction and diabetes mellitus: two closely associated disorders. *Endocr Rev* 40: 789–824.

69. Nishi M (2018) Diabetes mellitus and thyroid diseases. *Diabetol Int* 9: 108–112.

70. Kalra S, Aggarwal S, Khandelwal D (2021) Thyroid dysfunction and dysmetabolic syndrome: the need for enhanced thyrovigilance strategies. *Int J Endocrinol* 2021: 9641846.

71. Rong F, Dai H, Wu Y, Li J, Liu G, *et al.* (2021) Association between thyroid dysfunction and type 2 diabetes: a meta-analysis of prospective observational studies. *BMC Med* 19: 257.

72. Han C, He X, Xia X, Li Y, Shi X, *et al.* (2015) Subclinical hypothyroidism and type 2 diabetes: a systematic review and meta-analysis. *PLoS One* 10: e0135233.

73. Shimizu Y, Kawashiri SY, Noguchi Y, Nakamichi S, Nagata Y, *et al.* (2022) Effect of subclinical hypothyroidism on the association between hemoglobin A1c and reduced renal function: a prospective study. *Diagnostics (Basel)* 12: 462.

74. Handisurya A, Pacini G, Tura A, Gessl A, Kautzky-Willer A (2008) Effects of T4 replacement therapy on glucose metabolism in subjects with subclinical (SH) and overt hypothyroidism (OH). *Clin Endocrinol (Oxf)* 69: 963–969.

75. Lupoli R, Di Minno A, Tortora A, Ambrosino P, Lupoli GA, *et al.* (2014) Effects of treatment with metformin on TSH levels: a meta-analysis of literature studies. *J Clin Endocrinol Metab* 99: E143–E148.

76. Cappelli C, Rotondi M, Pirola I, Agosti B, Gandossi E, *et al.* (2009) TSH-lowering effect of metformin in type 2 diabetic patients: differences between euthyroid, untreated hypothyroid, and euthyroid on L-T4 therapy patients. *Diabetes Care* 32: 1589–1590.

77. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, *et al.* (2014) Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid* 24: 1670–1751.

78. Bekkering GE, Agoritsas T, Lytvyn L, Heen AF, Feller M, *et al.* (2019) Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. *BMJ* 365: l2006.

79. Sawka AM, Cappola AR, Peeters RP, Kopp PA, Bianco AC, *et al.* (2019) Patient context and thyrotropin levels are important when considering treatment of subclinical hypothyroidism. *Thyroid* 29: 1359–1363.

80. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, *et al.* (2011) Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 21: 1081–1125.

81. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, *et al.* (2012) Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 97: 2543–2565.

82. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, *et al.* (2017) 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 27: 315–389.

83. Mitchell AL, Pearce SH (2010) How should we treat patients with low serum thyrotropin concentrations? *Clin Endocrinol (Oxf)* 72: 292–296.

84. Tsai K, Leung AM (2021) Subclinical hyperthyroidism: a review of the clinical literature. *Endocr Pract* 27: 254–260.

85. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, *et al.* (2016) 2016 American Thyroid Association guidelines for diagnosis and management of

hyperthyroidism and other causes of thyrotoxicosis. *Thyroid* 26: 1343–1421.

86. Vejbjerg P, Knudsen N, Perrild H, Laurberg P, Carle A, *et al.* (2009) Lower prevalence of mild hyperthyroidism related to a higher iodine intake in the population: prospective study of a mandatory iodization programme. *Clin Endocrinol (Oxf)* 71: 440–445.

87. Vadiveloo T, Donnan PT, Cochrane L, Leese GP (2011) The thyroid epidemiology, audit, and research study (TEARS): the natural history of endogenous subclinical hyperthyroidism. *J Clin Endocrinol Metab* 96: E1–E8.

88. Mariotti S, Barbesino G, Caturegli P, Bartalena L, Sansoni P, *et al.* (1993) Complex alteration of thyroid function in healthy centenarians. *J Clin Endocrinol Metab* 77: 1130–1134.

89. Aghini-Lombardi F, Antonangeli L, Martino E, Vitti P, Maccherini D, *et al.* (1999) The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. *J Clin Endocrinol Metab* 84: 561–566.

90. Biondi B, Bartalena L, Cooper DS, Hegedus L, Laurberg P, *et al.* (2015) The 2015 European Thyroid Association guidelines on diagnosis and treatment of endogenous subclinical hyperthyroidism. *Eur Thyroid J* 4: 149–163.

91. Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, *et al.* (2011) Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid* 21: 593–646.

92. Donangelo I, Suh SY (2017) Subclinical hyperthyroidism: when to consider treatment. *Am Fam Physician* 95: 710–716.

93. Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, *et al.* (2012) Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med* 172: 799–809.

94. Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FD, *et al.* (2007) Association between serum free thyroxine concentration and atrial fibrillation. *Arch Intern Med* 167: 928–934.

95. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, *et al.* (2012) The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ* 345: e7895.

96. Gencer B, Cappola AR, Rodondi N, Collet TH (2022) Challenges in the management of atrial fibrillation with subclinical hyperthyroidism. *Front Endocrinol (Lausanne)* 12: 795492.

97. Selmer C, Olesen JB, Hansen ML, von Kappelgaard LM, Madsen JC, *et al.* (2014) Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. *J Clin Endocrinol Metab* 99: 2372–2382.

98. Gencer B, Collet TH, Virgini V, Bauer DC, Gussekloo J, *et al.* (2012) Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. *Circulation* 126: 1040–1049.

99. Chaker L, Baumgartner C, Ikram MA, Dehghan A, Medici M, *et al.* (2014) Subclinical thyroid dysfunction and the risk of stroke: a systematic review and meta-analysis. *Eur J Epidemiol* 29: 791–800.

100. Wollenweber FA, Zietemann V, Gschwendtner A, Opherk C, Dichgans M (2013) Subclinical hyperthyroidism is a risk factor for poor functional outcome after ischemic stroke. *Stroke* 44: 1446–1448.

101. Lee SH, Jang MU, Kim Y, Park SY, Kim C, *et al.* (2019) Subclinical hyperthyroidism could predict poor outcomes in patients with acute ischemic stroke treated with reperfusion therapy. *Front Neurol* 10: 782.

102. Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, *et al.* (2020) American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis- 2020 update executive summary. *Endocr Pract* 26: 564–570.

103. Zhu H, Zhang J, Wang J, Zhao X, Gu M (2020) Association of subclinical thyroid dysfunction with bone mineral density and fracture: a meta-analysis of prospective cohort studies. *Endocrine* 67: 685–698.

104. Blum MR, Bauer DC, Collet TH, Fink HA, Cappola AR, *et al.* (2015) Subclinical thyroid dysfunction and fracture risk: a meta-analysis. *JAMA* 313: 2055–2065.

105. Siru R, Alfonso H, Chubb SAP, Golledge J, Flicker L, *et al.* (2018) Subclinical thyroid dysfunction and circulating thyroid hormones are not associated with bone turnover markers or incident hip fracture in older men. *Clin Endocrinol (Oxf)* 89: 93–99.

106. Lee K, Lim S, Park H, Woo HY, Chang Y, *et al.* (2020) Subclinical thyroid dysfunction, bone mineral density, and osteoporosis in a middle-aged Korean population. *Osteoporos Int* 31: 547–555.

107. Du Puy RS, Poortvliet RKE, Mooijaart SP, den Elzen WPJ, Jagger C, *et al.* (2021) Outcomes of thyroid dysfunction in people aged eighty years and older: an individual patient data meta-analysis of four prospective studies (towards understanding longitudinal international older people studies consortium). *Thyroid* 31: 552–562.

108. Gan EH, Pearce SH (2012) Clinical review: the thyroid in mind: cognitive function and low thyrotropin in older people. *J Clin Endocrinol Metab* 97: 3438–3449.

109. Bensenor IM, Lotufo PA, Menezes PR, Scazufca M (2010) Subclinical hyperthyroidism and dementia: the Sao Paulo Ageing & Health Study (SPAH). *BMC Public Health* 10: 298.

110. Aubert CE, Bauer DC, da Costa BR, Feller M, Rieben C, *et al.* (2017) The association between subclinical thyroid dysfunction and dementia: the health, aging and body composition (Health ABC) study. *Clin Endocrinol (Oxf)* 87: 617–626.

111. Staffurth JS, Gibberd MC, Fui SN (1977) Arterial embolism in thyrotoxicosis with atrial fibrillation. *Br Med J* 2: 688–690.

112. Tribulova N, Knezl V, Shainberg A, Seki S, Soukup T (2010) Thyroid hormones and cardiac arrhythmias. *Vascul*

Pharmacol 52: 102–112.

113. Gong IY, Atzema CL, Lega IC, Austin PC, Na Y, *et al.* (2021) Levothyroxine dose and risk of atrial fibrillation: a nested case-control study. *Am Heart J* 232: 47–56.

114. Gluvic Z, Obradovic M, Stewart AJ, Essack M, Pitt SJ, *et al.* (2021) Levothyroxine treatment and the risk of cardiac arrhythmias—focus on the patient submitted to thyroid surgery. *Front Endocrinol (Lausanne)* 12: 758043.

115. Biondi B, Cooper DS (2018) Subclinical hyperthyroidism. *N Engl J Med* 378: 2411–2419.

116. Grais IM, Sowers JR (2014) Thyroid and the heart. *Am J Med* 127: 691–698.

117. Kasagi K, Takahashi N, Inoue G, Honda T, Kawachi Y, *et al.* (2009) Thyroid function in Japanese adults as assessed by a general health checkup system in relation with thyroid-related antibodies and other clinical parameters. *Thyroid* 19: 937–944.

118. Li Y, Teng D, Shan Z, Teng X, Guan H, *et al.* (2008) Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes. *J Clin Endocrinol Metab* 93: 1751–1757.