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REVIEW ARTICLE

Subclinical hypothyroidism: new trials, old caveats

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Abstract
The indications for levothyroxine replacement therapy for subclinical hypothyroidism (SH) remain a subject of debate, especially when prescribed for older adults. The results of the recent TRUST trial indicate that levothyroxine does not improve clinical symptom scores among elderly patients with SH. While there is much concern regarding the dilemma of introducing or withholding levothyroxine, less attention may be paid to the differential diagnosis of an elevated TSH level, which is the prerequisite for diagnosing SH. Herein, we review these issues facing endocrinologists and internists/generalists either in practice or in training. When a patient presents abnormal thyroid test results compatible with SH, a series of issues need to be addressed before the implementation of replacement therapy is considered: first, an isolated TSH elevation not linked to a primary thyroid pathology should be excluded; second, the persistent nature of the patient's TSH elevation and SH profile should be verified; third, SH symptoms and potential complications relevant for the specific patient should be documented; fourth, expectations from levothyroxine substitution therapy for SH in the specific patient should be clarified. Only then can the decision be made whether levothyroxine substitution should be introduced or not.

Keywords Subclinical hypothyroidism · TRUST · Guidelines · Personalized medicine

Introduction

In contrast to overt hypothyroidism (prevalence of ~0.3%), whose management is well established, the indications for levothyroxine replacement therapy for subclinical hypothyroidism (SH), which represents the most common form of primary hypothyroidism (prevalence of ~4–10%), remain a subject of debate, especially with regard to older adults and pregnant women [1, 2]. The results of the recent randomized clinical trial TRUST (Thyroid Hormone Replacement for Untreated older adults with Subclinical Hypothyroidism: a randomized placebo-controlled trial) indicate that levothyroxine treatment does not improve clinical symptom scores among elderly patients with SH [3]. Thus, there is apprehension as to whether or not to introduce levothyroxine, with clinicians of different specialties being impacted by this discussion, including, inter alia, endocrinologists, internists and general medicine specialists, cardiologists, psychiatrists, and geriatricians. However, there is the risk that proportionally less attention is paid to the differential diagnosis of an elevated TSH level, which is the necessary prerequisite for diagnosing SH. The aim of this article is to provide clinicians in practice or in training with a brief practical outline of the differential diagnosis of SH, including general conditions not linked to thyroid disease, drug interferences, and analytical pitfalls. We also discuss the issue of replacement therapy in patients with SH, including the elderly, in view of the TRUST trial results. Published studies were identified from the PubMed database and by hand-searching published reviews.

Subclinical hypothyroidism is defined as a level of serum TSH above the upper limit of the reference range with a level of serum free T4 within the reference range. The reference range for serum TSH in the general adult population (excluding pregnant women) is roughly 0.4–4.0 mIU/l [4]. In the NHANES III reference population (no self-reported thyroid disease, negative antithyroid antibodies, not pregnant, not on thyroid medications, estrogens, androgens, or lithium), the

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upper normal value of TSH was 4.12 mIU/l. [5] Accordingly, the Hanford Thyroid Disease Study identified a TSH upper reference value of 4.10 mIU/l in a population with no clinical, serologic, or ultrasonographic evidence of thyroid disease [6].

When a patient presents abnormal thyroid test results compatible with SH, a series of issues need to be addressed *before* the implementation of replacement therapy is considered (Table 1).

Exclude an isolated elevation of TSH not linked to a primary thyroid disorder

Recovery from non-thyroidal illness

TSH levels can transiently increase during the phase of recovery from "euthyroid sick syndrome," also known as "non-thyroidal illness syndrome," which is a common condition in hospitalized patients. This entity likely corresponds to an adaptive response of the organism aiming to limit energy expenditure in the context of acute generalized disease of moderate or high severity; it is characterized by a first phase of reduced activity of the hypothalamic-pituitary-thyroid (HPT) axis (as well as of the other axes, except for the hypothalamic-pituitary-adrenal axis). This is followed by a second phase of spontaneous recovery with a transient increase of TSH levels, generally not exceeding 20–25 mIU/l. For instance, when thyroid hormones were measured during recovery from severe systemic illness in 31 patients, TSH increased at a time when T3 was rising but was still below normal (mean TSH ± SEM, 6.5 ± 0.8 mIU/l) [7]. In such settings, no substitution therapy is warranted. Serum TSH concentrations can also be transiently elevated during the acute phase of non-thyroidal illness, as occurs during elective abdominal surgery [8]. In patients admitted to an intensive care unit, TSH concentrations are most often in the normal range [9].

Table 1 Causes of elevated TSH unrelated to chronic SH in subjects not treated with levothyroxine

Transiently elevated TSH with normal free T4
Recovery from non-thyroidal illness
Recovery phase of thyroiditis
Drug interference (amiodarone, lithium, metoclopramide, amphetamine, ritonavir, St. John's Wort)
Persistently elevated TSH with normal free T4
Obesity
Advanced chronic kidney disease
Adrenal insufficiency
TSH resistance (partial)
Assay interference

Drug interference

An acute and transient elevation of TSH levels can be observed on initiation of antiarrhythmic treatment with amiodarone which functions via a double mechanism: amiodarone not only inhibits the deiodination of T4 into T3 [10] but also antagonizes the T3 receptor at the level of thyrotrope cells, thus disrupting the negative feedback of T3 on TSH [11]. In the absence of any underlying thyroid disease, thyroid function tests become normal within 2–3 months. As a reminder, for patients receiving amiodarone, periodic monitoring of thyroid function at least every 3–4 months is recommended [12]. Other possible drug interferences also exist, for example, dopamine receptor antagonists such as metoclopramide can induce a "functional" TSH increase without thyroid disease. Amphetamine, ritonavir, and St. John's Wort may also increase TSH serum levels, although the underlying mechanisms are unclear [13].

General medical conditions

Inaugural adrenal insufficiency may be associated with a moderate elevation of TSH levels due to a reduction in the cortisol-mediated negative feedback on pituitary thyrotrope cells [14]. In such a case, the differential diagnosis should include an autoimmune polyglandular syndrome combining Addison's disease and Hashimoto's hypothyroidism (also known as Schmidt syndrome). TSH levels normalize a few days after the introduction of hydrocortisone replacement therapy. Moreover, it is crucial to remember that even in cases of concomitant overt hypothyroidism, levothyroxine replacement must not be started until the patient has received coverage with hydrocortisone.

Obesity is associated with alterations in thyroid function without overt thyroid disease. TSH serum levels correlate positively with BMI in adults as well as in children, while SH is more frequent in obese subjects compared to non-obese subjects [15, 16]. In obese subjects, TSH values consistent with mild SH may revert to normal after weight loss [17, 18]. For example, in subjects maintaining 10% weight reduction, TSH serum levels decreased by 18% (from 5.0 to 4.1 mIU/l) [19]. In obesity, activation of the HPT axis by leptin is likely the cause of the observed increase in serum TSH levels, which is associated with normal or slightly increased serum free T4 levels [20].

Overt hypothyroidism and SH are the most commonly observed alterations in the setting of advanced chronic kidney disease (CKD) and dialysis. In a large patient population with moderate-to-severe CKD, a reduction of estimated GFR by 10 ml/min increased the risk of hypothyroidism by 18% and was associated with an increase of TSH levels by 0.11 mIU/l. [21] However, TSH alterations may also be observed in the

absence of thyroid disease in end-stage renal disease patients. These may include elevated basal TSH values, blunted TSH response to TRH, diminished or absent TSH diurnal rhythm, altered TSH glycosylation, and impaired TSH and TRH clearance [22].

Assay interference

Rarely, an isolated elevation of TSH that is discordant with the clinical presentation (e.g., in an asymptomatic patient) may be due to analytical artifacts in the measurement method. This includes the presence of heterophilic antibodies (human anti-mouse antibodies, HAMA), anti-TSH antibodies (macro-TSH), or rheumatoid factor, which can all interfere especially with immunometric methods of the "sandwich" type. To validate the presence of analytical interference and to elucidate its source, close collaboration with a specialized laboratory is necessary [23].

Central hypothyroidism

On rare occasions, central hypothyroidism in the context of a pituitary pathology (e.g., adenoma, craniopharyngioma) can manifest with a moderate increase in TSH (in general < 6–7 mIU/l) associated with a reduced bioactivity of the TSH molecule due to abnormal glycosylation. The serum free T4 level is usually low or low-normal in these cases [24].

TSH-secreting pituitary adenoma vs. TSH resistance

If free T4 levels are in the upper part of the reference range or frankly elevated in conjunction with an (inappropriately) elevated TSH level, this constellation should raise suspicion of central hyperthyroidism due to a TSH-secreting adenoma (TSH-oma) [25]. Obviously, no levothyroxine substitution should be introduced in such a case. Moreover, the differential diagnosis of this biological profile includes the rare syndrome of resistance to thyroid hormones, for which genetic testing is currently available [26].

Unexplained elevation of serum TSH levels with normal free T4 levels in infants, children, or young adults in the absence of goiter and in the setting of a similar pattern in other family members should arouse the suspicion of partial resistance to TSH, which is inherited in an either autosomal recessive or autosomal dominant manner [27]. Identification of mutations in the TSH receptor gene confirms the diagnosis. The defect may be fully compensated by hypersecretion of TSH, which overcomes the resistance and allows for maintenance of normal serum free T4 levels. In this case, levothyroxine treatment is not indicated.

Confirm the persistent nature of the patient's TSH elevation and SH

Among subjects who present a slightly elevated TSH (< 7 mIU/l) on a single occasion, the TSH level normalizes spontaneously in 35% of cases within 2 years [28]. Moreover, in healthy subjects, TSH levels vary over the course of a day by up to 50% on average, with a zenith at night and a nadir at the end of the afternoon [29].

Based on the above observations, in the case of a biochemical constellation compatible with SH, thyroid function tests should be repeated 2–3 months later (one of the two tests should also assess the presence of thyroid autoantibodies) before considering levothyroxine treatment [4]. Pregnancy constitutes an exception to this rule, where the tests should be repeated within a few days in order not to risk compromising the neurocognitive development of the fetus in the event of non-substituted maternal hypothyroidism [30]. The diagnosis and management of SH in pregnant women, a topic of active research and debate, is beyond the scope of this paper; the relevant guidelines have recently been updated [31].

SH may be observed in the context of thyroiditis [subacute, silent, post-partum, drug-induced] in the 3–12 months that follow the initial phase of thyrotoxicosis. In the majority of cases, SH in this context is transient. On the other hand, radioactive iodine (RAI) treatment leads to permanent overt hypothyroidism in 55 and 80% of patients with toxic nodular goiter and Graves' disease, respectively [32]. Persistent hypothyroidism secondary to external beam radiotherapy (EBRT) of the neck occurs in 20–30% of cases, with a peak incidence after 2–3 years [33]; the risk of post-EBRT hypothyroidism increases with increasing radiation dose [34].

After diagnostic or therapeutic lobectomy for a thyroid nodule, the overall risk for hypothyroidism is 22% according to a meta-analysis of 32 studies, with SH being the most prevalent. However, data on thyroid function recovery in this setting are scarce. Hypothyroidism after lobectomy can be transient in some patients [35]. Therefore, it seems prudent to refrain from rushing to introduce levothyroxine treatment for a mild case of subclinical hypothyroidism in the post-operative setting, since the rise in TSH is a physiological stimulus necessary in order for the remaining lobe to compensate. A 6-month watch-and-wait period is reasonable in this context.

For levothyroxine-treated patients with permanent primary hypothyroidism, an isolated increase in TSH may be observed if a 6–8-week period is not respected after a change in the levothyroxine dose. Other causes include poor compliance and malabsorption, the latter usually associated with concomitant medications, such as proton pump inhibitors, iron, calcium, cholestyramine, colestipol, and phosphate chelators. Other medications can increase TSH levels (e.g., recombinant TSH, Thyrogen®) or increase the need for levothyroxine, e.g.,

lithium; inducers of cytochrome p450 (CYP3A4) like rifampicin, phenytoin, phenobarbital, and carbamazepine; additionally, tyrosine kinase inhibitors (some of which are in fact employed in the treatment of radioactive iodine-refractory progressive thyroid carcinomas), the latter through reduction of thyroid vascularity and induction of type 3 deiodinase activity [13]. It is important to be aware that patients receiving levothyroxine substitution may also present fluctuations in TSH levels as part of the non-thyroidal illness syndrome, including a transient increase of TSH levels in the recovery phase [36].

Document SH symptoms and potential complications relevant to the specific patient

Patients with SH are either asymptomatic or have non-specific symptoms like fatigue, muscle weakness, cold intolerance, constipation, depressive symptoms, decline in cognitive and memory functions, and moderate weight gain (+ 0.5 kg per 1 mIU/l of TSH above the upper limit of the reference range) [37]. In general, the higher the TSH, the higher the number and the intensity of such symptoms.

SH can progress to overt hypothyroidism, especially in the context of autoimmune (Hashimoto's) thyroiditis, which is characterized by the presence of antithyroperoxidase (ATPO) and/or antithyroglobulin (ATG) antibodies and is the most common form of endogenous SH. ATPO positivity doubles the risk of progression of SH to overt hypothyroidism, with an annual incidence of 4% in women [38]. A higher TSH level (> 12–15 mIU/l) also increases this risk [38]. Thus, levothyroxine substitution for SH could result in the avoidance of possible future overt hypothyroidism with more severe symptoms.

At the cardiovascular level, SH, principally with a TSH > 10 mIU/l, is associated with an increase in cardiovascular morbidity and mortality (coronary insufficiency, heart failure, stroke). SH is also associated with surrogates of cardiovascular disease such as increased total and LDL cholesterol levels, intima-media carotid artery thickness, endothelial dysfunction, and other indices of metabolic disease (e.g., BMI, waist perimeter, non-alcoholic fatty liver disease) [39–41].

Clarify one's expectations from levothyroxine replacement therapy for SH in the specific patient

According to the recent large randomized placebo-controlled trial TRUST in older adults (> 65 years) with mild/moderate SH (mean TSH of 6.4 mIU/l) treated for up to 18 months, levothyroxine replacement therapy does not seem to ameliorate symptoms compatible with hypothyroidism [3]. However, participants with TSH levels > 10 mIU/l accounted for only 5% of the study population; thus, the results of the TRUST trial may not be generalizable to this subgroup of more severe SH. This is an important limitation given that previous studies have suggested that levothyroxine substitution might improve symptoms in cases of more pronounced SH (TSH > 10–12 mIU/l) [42]. Regarding weight, substitution does not seem to help with weight loss in this context [43].

Systematic reviews have pointed to an amelioration of surrogate markers of cardiovascular risk (decreased carotid intima-media thickness, decreased serum cholesterol levels, improved cardiac function) from levothyroxine replacement therapy for SH [43]. Treating SH was shown to reduce systolic and diastolic blood pressure, although the latter effect was only observed in the subgroup with a baseline TSH level > 7 mIU/l [44]. Observational studies involving SH patients have shown correlations with significant reduction of ischemic heart disease events [39], heart failure events [41], and death from any cause [40] among patients treated with levothyroxine compared to untreated patients. However, a reduction in cardiovascular hard endpoints has not been validated in randomized controlled trials to date. No difference was found in the TRUST trial, but this trial was admittedly too underpowered to detect any effect of levothyroxine on the incidence of cardiovascular events or mortality. Moreover, since few participants had a baseline TSH level > 10 mIU/l, the TRUST investigators acknowledged that they could not conclude whether there are benefits from treatment in this subgroup [3].

Decide whether levothyroxine substitution should be introduced or not

In the context of SH, the parameters to consider in order to determine whether there are indications for levothyroxine substitution are the following:

- The degree of TSH elevation. Two scenarios are envisaged: mild/moderate SH with TSH < 10 mIU/l (75 to 90% of cases) and SH with TSH > 10 mIU/l.
- The patient's age: After the age of 40, there is a physiological potentially adaptive increase of TSH levels; thus, the 97.5th percentile of the TSH range increases by ~ 0.3 mIU/l per decade [45]. As a consequence, a TSH level between 5 and 7 mIU/l in advanced age (> 80 years) should not necessarily be considered an indication for levothyroxine substitution. In fact, moderate SH is associated with increased longevity and decreased cardiovascular complications in subjects > 70–85 years old [46].
- The presence of symptoms compatible with hypothyroidism, keeping however in mind their non-specific nature.

- ATPO positivity. In ATPO-negative patients, ATG positivity and an ultrasonographic appearance of the thyroid parenchyma compatible with autoimmunity could arguably also be considered, if this information is available [47, 48].
- The presence of goiter.
- Cardiovascular comorbidities.
- Concurrent administration of other medications.
- The patient's desire, after proper education on the matter.

The clinical practice guidelines of the European Thyroid Association (published in 2013) and of the American Thyroid Association (published in 2012) [4, 13] stipulate how the aforementioned elements should be integrated into the decision to treat or not. It is important to note that the recommendations summarized below do not concern pregnant women, for whom a separate set of guidelines has recently been updated [31]. They have also not taken into account the results of the recent clinical trial TRUST, although, due to the various limitations mentioned above, little impact is expected from this trial on recommendations for clinical management, as discussed below. According to the guidelines:

In the case of SH with a TSH level > 10 mIU/l, levothyroxine substitution is indicated for subjects < 65–70 years old; it may also be considered for subjects > 70 years old in the presence of symptoms, goiter, ATPO, cardiovascular comorbidities, or a free T4 level at the low end of the reference range. In future updates of the guidelines, the results of the TRUST trial might be taken into consideration to invalidate symptoms and potentially cardiovascular comorbidities as indications for considering levothyroxine substitution in older subjects, but they are not expected to affect the rest of these recommendations.

In the case of SH with a TSH level < 10 mIU/l, thyroid function tests should be repeated every 3 months without levothyroxine substitution in older subjects; for subjects < 70 years old, a trial of levothyroxine substitution may be considered if one or more of the aforementioned factors are present. The results of the TRUST trial are consistent with these guidelines, and thus no impact is expected on these recommendations.

When substitution is introduced, it entails prescription of oral levothyroxine. T3 substitution is not routinely recommended, although its use for selected patients remains an area of debate and investigation [49, 50]. In the setting of overt hypothyroidism, young and middle-aged patients without cardiovascular disease may be started on the full levothyroxine replacement dose of 1.6 μg/kg/day, whereas elderly patients or those with cardiovascular disease should be started on a lower dosage (12.5–25 μg/day), with gradual increments if needed. In SH, a lower starting dose of levothyroxine is recommended compared to overt hypothyroidism, normally not exceeding 25–50 μg/day. TSH should be checked 6–8 weeks after a change in the dosing regimen; this waiting period reflects the long half-life of levothyroxine (7 days) and the progressive stabilization of TSH. The target TSH could be between 0.5–2.5 mIU/l for younger subjects and between 1 and 5 mIU/l for patients > 70 years old; however, other experts prefer to use the general reference range as the target in all patients [50].

An endocrinologist's opinion should be solicited in cases of uncertainty about the etiology of the apparent hypothyroidism, also in cases of goiter, of personal history of thyroid disease (e.g., hyperthyroidism or thyroiditis), or of cervical EBRT as well as for women who are pregnant or desire pregnancy.

In conclusion, more and better designed randomized clinical trials are needed on the subject of SH, with sufficient statistical power and a meaningful length of follow-up to fully elucidate (or refute) the potential benefits of levothyroxine replacement therapy. Ideally, such trials should specifically target patients with higher TSH levels (e.g., > 10 mIU/l), both younger and older individuals. At the same time, even in apparently simple cases, a methodological step-wide process of differential diagnosis and decision-making needs to be undertaken *before* the introduction of levothyroxine replacement therapy for individual patients with elevated TSH.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical standards This work complies with all ethical and legal regulations in Switzerland and does not contain any study with human or animal subjects performed by the authors.

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References

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC (2000) The Colorado thyroid disease prevalence study. Arch Intern Med 160: 526–534
2. Rugge JB, Bougatsos C, Chou R (2015) Screening and treatment of thyroid dysfunction: an evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 162:35–45
3. Stott DJ, Rodondi N, Kearney PM et al (2017) Thyroid hormone therapy for older hormone therapy for older adults with subclinical hypothyroidism. N Engl J Med 376:2534–2544
4. Pearce SH, Brabant G, Duntas LH et al (2013) 2013 ETA Guideline: management of subclinical hypothyroidism. Eur Thyroid J 2:215–228
5. Hollowell JG, Staehling NW, Flanders WD et al (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Survey (NHANES III). J Clin Endocrinol Metab 87:489–499
6. Hamilton TE, Davis S, Onstad L, Kopecky KJ (2008) Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism. J Clin Endocrinol Metab 93:1224–1230
7. Bacci V, Schussler GC, Kaplan TB (1982) The relationship between serum triiodothyronine and thyrotropin during systematic illness. J Clin Endocrinol Metab 54:1229–1235

8. Michalaki M, Vagenakis AG, Makri M, Kalfarentzos F, Kyriazopoulou V (2001) Dissociation of the early decline in serum T(3) concentration and serum IL-6 rise and TNFα in nonthyroidal illness syndrome induced by abdominal surgery. J Clin Endocrinol Metab 86:4198–4205
9. Van den Berghe G (2014) Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid 24:1456–1465
10. Rao RH, McCready VR, Spathis GS (1986) Iodine kinetic studies during amiodarone treatment. J Clin Endocrinol Metab 62:563–569
11. Franklyn JA, Davis JR, Gammage MD, Littler WA, Ramsden DB, Sheppard MC (1985) Amiodarone and thyroid action. Clin Endocrinol 22:257–264
12. Ross DS, Burch HB, Cooper DS (2016) 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 26:1343–1421
13. Garber JR, Cobin RH, Gharib H 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. Topliss DJ, White EL, Stockigt JR (1980) Significance of thyrotropin excess in untreated primary adrenal insufficiency. J Clin Endocrinol Metab 50:52–56
15. Kitahara CM, Platz EA, Ladenson PW (2012) Body fatness and markers of thyroid function among U.S. men and women. PLoS One 7:e34979
16. Ghergherehchi R, Hazhir N (2015) Thyroid hormonal status among children with obesity. Ther Adv Endocrinol Metab 6:51–55
17. Pacifico L, Anania C, Ferraro F, Andreoli GM, Chiesa C (2012) Thyroid function in childhood obesity and metabolic comorbidity. Clin Chim Acta 413:396–405
18. Chikunguwo S, Brethauer S, Nirujogi V et al (2007) Influence of obesity and surgical weight loss on thyroid hormone levels. Surg Obes Relat Dis 3:631–635
19. Rosenbaum M, Leibel RL (2010) Adaptive thermogenesis in humans. Int J Obes 34(Suppl 1):S47–S55
20. Witte T, Völzke H, Lerch MM (2017) Association between serum thyroid-stimulating hormone levels and visceral adipose tissue: a population-based study in Northeast Germany. Eur Thyroid J 6:12–19
21. Rhee CM, Kalantar-Zadeh K, Streja E (2015) The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease. Nephrol Dial Transplant 30: 282–287
22. Kaptein EM (1996) Thyroid hormone metabolism and thyroid diseases in chronic renal failure. Endocr Rev 17:45–63
23. Gurnell M, Halsall DJ, Chatterjee VK (2011) What should be done when thyroid function tests do not make sense? Clin Endocrinol 74: 673–678
24. Beck-Peccoz P, Amr S, Menezes-Ferreira MM, Faglia G, Weintraub BD (1985) Decreased receptor binding of biologically inactive thyrotropin in central hypothyroidism. Effect of treatment with thyrotropin-releasing hormone. N Engl J Med 312:1085–1090
25. Beck-Peccoz P, Lania A, Beckers A, Chatterjee K, Wemeau JL (2013) 2013 European thyroid association guidelines for the diagnosis and treatment of thyrotropin-secreting pituitary tumors. Eur Thyroid J 2:76–82
26. Moran C, Chatterjee K (2016) Resistance to thyroid hormone α-emerging definition of a disorder of thyroid hormone action. J Clin Endocrinol Metab 101:2636–2639
27. Refetoff S (1994) Resistance to thyroid hormone. Curr Ther Endocrinol Metab 5:117–119
28. Somwaru LL, Rariy CM, Arnold AM, Cappola AR (1994) The natural history of subclinical hypothyroidism in the elderly: the cardiovascular health study. J Clin Endocrinol Metab 97:1962–1969
29. Caron PJ, Nieman LK, Rose SR, Nisula BC (1986) Deficient nocturnal surge of thyrotropin in central hypothyroidism. J Clin Endocrinol Metab 62:960–964
30. Surks MI, Ortiz E, Daniels GH (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 291:228–238
31. Alexander EK, Pearce EN, Brent G 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
32. Chaker L, Bianco AC, Jonklaas J, Peeters RP (2017) Hypothyroidism. Lancet 390:1550–1562
33. Jereczek-Fossa BA, Alterio D, Jassem J, Gibelli B, Tradati N, Orecchia R (2004) Radiotherapy-induced thyroid disorders. Cancer Treat Rev 30:369–384
34. Vogelius IR, Bentzen SM, Maraldo MV, Petersen PM, Specht L (2011) Risk factors for radiation-induced hypothyroidism: a literature-based meta-analysis. Cancer 117:5250–5260
35. Verloop H, Louwerens M, Schoones JW, Kievit J, Smit JW, Dekkers OM (2012) Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. J Clin Endocrinol Metab 97:2243–2255
36. Wadwekar D, Kabadi UM (2004) Thyroid hormone indices during illness in six hypothyroid subjects rendered euthyroid with levothyroxine therapy. Exp Clin Endocrinol Diabetes 112:373–377
37. Garin MC, Arnold AM, Lee JS, Tracy RP, Cappola AR (2014) Subclinical hypothyroidism, weight change, and body composition in the elderly: the Cardiovascular Health Study. J Clin Endocrinol Metab 99:1220–1226
38. Díez JJ, Iglesias P (2004) Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. J Clin Endocrinol Metab 89:4890–4897
39. 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
40. 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
41. Rodondi N, Bauer DC, Cappola AR (2008) Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health study. J Am Coll Cardiol 52:1152–1159
42. Peeters RP (2017) Subclinical hypothyroidism. N Engl J Med 376: 2556–2565
43. Villar HC, Saconato H, Valente O, Atallah AN (2007) Thyroid hormone replacement for subclinical hypothyroidism. Cochrane Database Syst Rev 3:CD003419
44. Anagnostis P, Efstathiadou ZA, Slavakis A (2014) The effect of L-thyroxine substitution on lipid profile, glucose homeostasis, inflammation and coagulation in patients with subclinical hypothyroidism. Int J Clin Pract 68:857–863
45. Boucai L, Hollowell JG, Surks MI (2011) An approach for development of age-, gender-, and ethnicity-specific thyrotropin reference limits. Thyroid 21:5–11
46. Cappola AR, Arnold AM, Wulczyn K, Carlson M, Robbins J, Psaty BM (2015) Thyroid function in the euthyroid range and adverse outcomes in older adults. J Clin Endocrinol Metab 100:1088–1096
47. Rosario PW (2017) Subclinical hypothyroidism. N Engl J Med 377:1404
48. Rosário PW, Bessa B, Valadão MM, Purisch S (2009) Natural history of mild subclinical hypothyroidism: prognostic value of ultrasound. Thyroid 19:9–12
49. Perros P (2012) European thyroid association guidelines on L-t4 + L-t3 combination for hypothyroidism: a weary step in the right direction. Eur Thyroid J 1:51–54
50. Jonklaas J, Bianco AC, Bauer AJ 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