Endocrine (2019) 66:27–34
https://doi.org/10.1007/s12020-019-02039-z

REVIEW

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Thyroid hormone therapy for subclinical hypothyroidism

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Received: 12 July 2019 / Accepted: 29 July 2019

Abstract
Subclinical Hypothyroidism (SCH) is defined as a raised level of serum TSH level in the presence of normal circulating free thyroid hormones. SCH is a highly prevalent condition displaying some peculiarities, both in terms of the diagnostic and therapeutic approach, when specific population and/or concomitant diseases are taken into account. The debate upon whether LT4 therapy should be initiated or not in patients with SCH is a long lasting one and still it remains controversial. Current evidence supports the concept that the clinical consequences of SCH may be profoundly different in relation to several patient-specific characteristics. Aim of the present review is to provide updated indications for SCH treatment in specific clinical settings. These will include the management of SCH in obese and diabetic patients, in pregnant women, and in specific age groups. Treatment modalities, including LT4 doses and recommended follow-up strategy will also be discussed. In the era of "precision medicine" the decision to-treat-not-to-treat SCH should be individualized taking into account risks and beneficial outcomes of LT4 therapy. With this in mind, we reviewed the most relevant studies in the recent literature in order to provide evidence for or against LT4 replacement therapy for SCH in specific clinical settings.

Keywords Subclinical hypothyroidism · Levothyroxine · Cardiovascular system · Thyroid · Pregnancy · Selected populations

Introduction

Subclinical hypothyroidism (SCH) is a biochemical condition characterized by elevated serum thyrotropin (TSH) levels in association with free thyroxine (FT4) and free triiodothyronine (FT3) concentrations within the population reference range [1]. Because several clinical conditions could induce a transient increase in serum TSH level, the diagnosis of SCH usually needs a second measurement of TSH and FT4 after 2–3 months to confirm the diagnosis [2]. The conditions responsible for a transient increase of serum TSH level in the presence of normal free T4 concentration include: the recovery phase from nonthyroidal illness or from subacute thyroiditis, low compliance to levothyroxine treatment and drug-induced thyroid dysfunction (such as amiodarone and lithium), and macro-thyrotropin [3]. According to comprehensive epidemiological surveys performed in Europe and in the United States, the incidence of SCH ranges from 4 to 10%, the corresponding prevalence being around 5–10% [4, 5]. SCH more frequently occurs in Caucasian women and elderly people living in iodine sufficient areas [2]. In the majority of patients, SCH is a mild condition characterized by TSH serum levels lower than 10 mU/L. The prevalence of TSH concentrations higher than 10 mU/L is about 10% [6]. American and European guidelines define SCH as mild, when TSH levels are lower than or equal to 10 mUI/L [2, 7]. In mild SCH, spontaneous normalization of TSH may occur in 20–50% of cases [2]. Patients with higher serum levels of TSH, antibodies to thyroid peroxidase (AbTPO), low-normal FT4 levels, and diffuse hypoechogenicity of the thyroid on US have a 2–6% risk per year of progressing to overt hypothyroidism [8]. A prospective study investigated patients with SCH being diagnosed after repeated measurements of serum TSH and TPOAb and by thyroid US pattern. It was found that an initial serum level of TSH >8 mIU/L, the presence of thyroiditis (as assessed by positive TPOAb or US pattern) predicted the need for LT4 therapy due to a progression rate to hypothyroidism of ~4% per year [9]. In this study an initial serum TSH >8 mUI/L was the most important predictor of progression to clinical dysfunction. In areas of

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iodine sufficiency, the main cause of permanent SCH is chronic autoimmune thyroiditis (CAT), a condition characterized by infiltration of the thyroid with sensitized T lymphocytes and serologically by circulating thyroid autoantibodies. CAT is 5–10 times more common in women than in men, its prevalence increasing with age and in subjects with other autoimmune disease [6]. Other causes of SCH include previous 131-I therapy or hemithyroidectomy, and undertreatment of overt hypothyroidism or excessive dose of antithyroid drugs for hyperthyroidism. A mild serum TSH elevation is frequently observed in elderly subjects. However, there is a general consensus that this mild TSH increase represents a consequence of normal aging rather than a true thyroid dysfunction [7, 10]. Cancer therapy with tyrosine kinase inhibitors is significantly associated with thyroid dysfunction and SCH, due to direct toxicity on follicular cells, increased thyroid hormone clearance, thyroid vascular bed regression, and impaired iodide uptake [11]. Antitumor treatment with immune checkpoint inhibitors may also produce thyroid dysfunction [12].

Diagnosis

The diagnosis of SCH requires assays for serum TSH and FT4. Confirmatory thyroid function tests should be performed within 2–3 months. The finding of circulating thyroid autoantibodies (AbTPO and/or antithyroglobulin antibodies -AbTG), and/or the demonstration of an hypoechoic pattern of the gland at US supports the diagnosis of CAT [13]. The typical US pattern may be present before the appearance of circulating thyroid autoantibodies and in serum-negative CAT [14].

Rationale for thyroid hormone treatment

Thyroid hormone replacement therapy with levothyroxine (LT4) has been the "gold standard" for the treatment of overt and SCH for more than 60 years. Theoretically, using liothyronine (T3) or combined LT4/liothyronine in the treatment of hypothyroidism might offer advantages. Actually, there is no clear-cut evidence to support this therapeutic choice in the majority of hypothyroid patients. With a few differences among international guidelines, LT4 treatment for SCH is indicated, when serum TSH levels are higher than 10 mIU/L and in subjects with milder TSH elevation, who complain of hypothyroid symptoms [2, 7, 10].

Symptoms

Although many patients with SCH are asymptomatic, several nonspecific complains characterize the condition. The most frequently reported ones are fatigue, muscle weakness, depressed mood, decline in memory and cognition, cold intolerance, and (moderate) weight gain [2]. The symptoms' severity is not always strictly correlated with the degree of TSH elevation [15]. The effect of LT4 treatment on SCH-related symptoms remains controversial, limited evidence existing from RCTs. According to ETA and ATA guidelines [2, 7] a trial with LT4 replacement therapy should be considered in AbTPO-positive SCH patients younger than 65 years complaining of hypothyroid symptoms. However, a recent systematic review and meta-analysis of RCTs in nonpregnant adults with SCH found no effect of LT4 therapy on thyroid-related symptoms [16]. As pointed out by Razvi et al. [17], the results of this meta-analysis may be flawed by an overall effect size derived from the inclusion of a double-blind, randomized, and placebo-controlled study involving subjects older than 65 years with persisting SCH (TSH levels 4.60–19.99 mIU/L). Independently from serum TSH levels, no consistent beneficial effect of LT4 treatment on thyroid-related symptoms was found in this study of elderly people [18]. Similar results were reported by RTCs involving younger SCH patients, an improvement of tiredness representing the main exception [19]. A recent systematic review also indicates that thyroid hormone therapy does not produce clinically relevant benefits on quality of life or thyroid-related symptoms, including depressive symptoms and fatigue [20].

Progression to overt hypothyroidism

Although up to 46% of SCH patients having mild elevations of TSH usually normalize their thyroid tests within 2 years [21], a progression to overt hypothyroidism has been observed, with a rate of 2–6% per year. This progressive deterioration of thyroid function supports the rationale for thyroid hormone treatment, also considering the association between overt hypothyroidism and several disease risk factors.

Dyslipidemia

Thyroid hormones are involved in lipid synthesis, mobilization, and degradation. Thus, dyslipidemia commonly occurs in overt hypothyroidism and results in an increased risk for cardiovascular (CV) atherosclerotic disease [7]. Several observational studies addressed the relationship between SCH and dyslipidemia, but results were heterogeneous [22]. Early epidemiological data pointed to a positive association between raised serum TSH levels and dyslipidemia [4], but this was subsequently confirmed only in women, and particularly in the elderly ones [23]. The effect of LT4 treatment on lipid profile in SCH patients is also debated since years. Early studies on this topic, both

observational and RTCs, reported conflicting results [24]. Recently, two meta-analysis including randomized placebo-controlled trials [24, 25] analyzed the relationship between LT4 treatment and lipid profile. Pooling data from 5 to 12 pertinent papers, respectively, the two meta-analysis showed that, compared with placebo, LT4 treatment significantly improved total and LDL cholesterol serum levels in SCH patients. No significant effect on serum triglycerides and HDL cholesterol emerged. Although in the meta-analysis by Li et al. [24] the favorable effect of LT4 administration on total and LDL cholesterol faded after 6 months of treatment, it is important to emphasize that even a mild decline in total and LDL cholesterol might significantly prevent atherosclerosis, coronary artery disease, and stroke.

Cardiovascular system

Thyroid hormones have direct genomic and nongenomic effects on the heart and blood vessels. Thus, even mild alteration of thyroid status may cause CV changes, including impaired left ventricular (LV) diastolic function at rest and LV systolic dysfunction during exercise [26]. SCH was also associated with increased vascular resistance and arterial stiffness, endothelial dysfunction, and atherosclerosis [26]. Prospective and observational studies reported an association between SCH and increased risk of heart failure (HF), both in patients with [27] and without [28] previous CV diseases. These data support the concept that SCH is an independent risk factor for the onset, progression, and worsening of HF. A recent meta-analysis showed that SCH can increase the risk of all-cause mortality, cardiac death, and/or hospital admission in HF patients [29]. These findings were recently confirmed in a large prospective cohort of patients with preexisting HF. SCH (TSH ≥7 mIU/L) was associated with a greater than threefold risk of HF severity, atrial fibrillation, and composite end point of ventricular assist device placement [30]. Even in patients without a preexisting HF, those with a serum TSH ranging from 7.0 to 9.9 mIU/L and, more significantly, those with a serum TSH greater than 10 mIU/L had a higher risk for developing a low ejection fraction, compared with euthyroid subjects [31, 32].

Lipid abnormalities; vascular dysfunction; and changes in homocysteine, high-sensitive C-reactive protein, and coagulation parameters, often but not consistently observed in SCH, could increase the risk for coronary heart disease (CHD) in these patients. Indeed, endogenous SCH was reported to be associated with ischemic heart disease and related mortality [33]. A 2017 meta-analysis, which included recent studies (from 2010 onwards), found that in patients with mean age <65 years SCH are significantly associated with increased risk of CHD and cardiovascular mortality. This association was not evident in SCH patients older than 80 years [34]. Intervention studies demonstrate a normalization of several cardiac function parameters in LT4-replaced patients with SCH. Treatment with LT4 prevented the progressive LV dysfunction and improved systolic and diastolic function, systemic vascular resistance and endothelial function [26]. In a retrospective observational study, LT4 treatment reduced the risk of fatal and nonfatal CHD events in SCH patients aged 40–70 years [35].

On the other hand, a recent Danish cohort study found no association between LT4 treatment and improved risk of myocardial infarction and mortality, with the relevant exception of younger patients in whom a marginal protective effect on all-cause mortality was evident [36]. In the same study, LT4 treatment produced no benefit on established cardiovascular disease [37]. A recent double-blind, randomized, and placebo-controlled trial involving SCH patients older than 65 years also failed to show a positive effect of LT4 treatment on the occurrence of serious cardiovascular events, such as atrial fibrillation and HF [18]. It should be considered that the study was underpowered to detect a significant difference in terms of cardiovascular events between the two study groups. Taken together, these data do not provide conclusive evidence for a positive effect of LT4 treatment on long-term cardiovascular outcomes. Future large prospective multicenter studies are needed to assess the possible usefulness of thyroid hormone administration on cardiovascular disease in SCH patients and/or to identify the subgroups of patients who might benefit from replacement treatment.

Special populations

Obese people

Obesity, and morbid obesity in particular, is frequently associated with a raised serum level of TSH. Thus, early studies concluded that SCH is highly prevalent (20–25%) in obese patients. More recent studies support the concept that this raised serum TSH is rather a consequence of obesity and that, by itself, cannot be considered as diagnostic of SCH, unless a coexistent autoimmune thyroiditis can be demonstrated [38]. No study so far addressed the issue of whether this hyperthyrotropinemia of obesity might benefit of LT4 treatment. On the other hand, once a diagnosis of autoimmune SCH is supported by evidence of circulating TPOAb and/or TgAb, LT4 treatment should be considered. Usually, the replacement LT4 dose is lower in obese patients than that predicted by their body weight due to the fact lean mass, rather than fact mass, is a major predictor of thyroid hormone requirements [38].

Patients with Type 1 and Type 2 diabetes

Thyroid dysfunction is more prevalent in patients with Type 1 (T1) and Type 2 (T2) diabetes mellitus (DM). SCH is highly prevalent in T1MD patients, due to the clustering of autoimmune diseases, and its incidence increases with disease duration [39]. Patients with T2DM also carry a nearly double risk for SCH as compared with healthy controls, but the reasons for this association are not fully understood [39]. In view of the previously reported considerations, the possible role of associated obesity in patients with T2DM should be taken into account in the diagnostic workup. As recently reviewed, SCH is often associated with poor control of diabetes [36]. Both the ETA and ATA clinical guidelines recommend LT4 treatment in SCH in patients with diabetes, when TSH serum levels exceed the cut off of 10 mIU/L [2, 7]. Although prospective studies assessing the potential benefits of LT4 treatment in patients with milder TSH elevations are not available, the notion that SCH is associated with insulin resistance and dyslipidemia would support this option [39]). Prevention of overt hypothyroidism is also an issue to recommend LT4 treatment in SCH patients with DM. Progression from subclinical to overt hypothyroidism was reported to occur more frequently in patients with T2DM, and especially in affected women [40]. A further issue supporting LT4 treatment regards the risk for statin-induced myopathy, which was reported to be higher in patients with coexistent SCH and DM [41]. Having a completely normal thyroid function could provide additional therapeutic benefits through a reduction of fasting insulin and an improved insulin sensitivity [39]. When treating diabetic patients with LT4 for SCH, it is important to remember that the concomitant administration of metformin was reported to produce a TSH-lowering effect. Thus, titration of LT4 on serum TSH level alone might be misleading [42].

Pregnant women

Although, trimester-specific reference intervals for TSH would be required in order to render a diagnosis of SCH in pregnancy, this still appears to be a goal rather than a reality, although in the US most laboratories do have trimester-specific ranges. In this instance, the latest ATA guidelines recommend that the upper limit of the normal range in pregnancy should be calculated by subtracting ~0.5 mIU/L from the nonpregnant TSH reference range, thus obtaining a 4.0 mIU/L cut off for most commonly used assays [43]. Based on this new TSH threshold, the prevalence of SCH is estimated to be between 3 and 5% of pregnant women [40]. Observational studies reported that SCH would be associated with increased rates of both maternal and fetal complications [43]. However, the issue of treating SCH in pregnant women remains a controversial one, since intervention trials failed to document benefits of LT4 treatment on pregnancy outcome [44], even if some limitations of these trials were highlighted in the accompanying editorial [45]. The above considerations mainly account for the fact that a consensus on whether SCH should be treated in all pregnant women has not yet been reached. According to the most recent clinical guidelines on thyroid dysfunction in pregnancy, SCH in pregnant women should be treated in all cases when thyroid Ab are positive. Although the recommendation was based on low-quality evidence, it was advised that in the presence of negative tests for thyroid Ab, LT4 treatment should be always performed in those patients whose serum TSH is >10 mIU/L, while it could be considered for lower degrees of TSH elevation [40]. The latter recommendation was recently questioned [46] mainly based upon two arguments: (i) SCH may result from serum-negative autoimmune thyroiditis [14]; (ii) false negative tests for thyroid Ab may occur in pregnant women due to the physiological immune-suppression of pregnancy. As a final consideration, there is general consensus that once SCH is found in pregnant women a starting dose of 50 mcg/d is typically required for effective treatment of most SCH patients [40].

Children

CAT may be responsible for SCH in the pediatric age. However, in some children the etiology of SCH cannot be identified, being these children referred to as having idiopathic SCH. The prevalence of SCH in children and adolescents is estimated to be <2%, a definitely lower figure compared with other age groups [47, 48]. SCH is reported at higher prevalence in specific pediatric populations including children with Turner syndrome (TS), Down's syndrome (DS), Williams syndrome, celiac disease, cystic fibrosis, chronic renal failure, and taking antiseizure medications [49]. Apart from these conditions, the issue of congenital hypothyroidism, which is not object of the present article, should also be mentioned. The question of whether SCH in children should be treated or not is still debated [48]. A major concern regarding the decision to treat with LT4 stems from the fact that, once started, LT4 therapy is generally maintained for many years or even lifelong, which makes it relevant to assess the real need for treatment. Spontaneous reversion to euthyroidism, which mainly occurs in children with idiopathic/mild SCH, as well as the risk of progression to overt hypothyroidism are major issues in the decision to treat [50]. Biochemical and clinical aspects upon which the decision to treat should be based include baseline TSH and cause of SCH. Baseline serum TSH level is the most reliable predictor of future thyroid function in children with SCH, an higher than 10 mIU/L

level indicating a greater risk of progressing to overt hypothyroidism [49, 51]. The etiology of SCH is also important, because longitudinal studies indicated that children with idiopathic SCH display a negligible risk for progression to overt hypothyroidism. Compared with adults, a more rapid and severe deterioration of thyroid function was observed in SCH children with CAT [49, 51]. From these data stems the recommendation to treat children with SCH and a serum TSH level above 10 mIU/L, mainly when they are diagnosed with CAT [51]. The need for treating SCH children with lower degrees of TSH elevation is still debated [51]. This is because children with mild SCH, were left untreated, did not show, throughout a 2- to 5-year follow-up period, growth retardation, increase in body mass index, bone maturation defects, and cognitive dysfunction [47]. SCH children with either TS or DS deserve special consideration, because their thyroid function more frequently deteriorates [50]. Similarly, the presence of SCH in children with celiac disease would be associated with a more aggressive course of the disease [49]. Mild alterations in the lipid profile (i.e., low HDL cholesterol and high triglyceride/HDL-C ratio), possibly associated with a higher atherogenic risk, have been reported in SCH children, thus making an argument for LT4 treatment [52]. Thus, LT4 should be always initiated in SCH children with TS, DS or other associated autoimmune conditions, and when metabolic abnormalities are present [47, 49, 51, 52]. LT4 replacement would not be indicated in children with idiopathic and mild (TSH <10 mIU/L) SCH [48, 49, 51]. If a decision to only observe is taken, clinical symptoms assessment and thyroid function tests should be checked every 6 months, in order to identify those children who might benefit from treatment [47, 49, 51]. (1). After 2 years with stable thyroid function tests, less strict thyroid surveillance would be adequate [47, 51].

Elderly/frailty subjects

The number of elderly people is increasing worldwide leading to an increased prevalence of frailty, an independent geriatric syndrome [53]. Based on data from the Danish-Thyroid-Diseases registry, older people showed threefold to fourfold higher incidence rates of hypothyroidism than young adults, with SCH being the most prevalent condition [54]. The first concept to be considered in elderly patients with SCH is that, in the thyroid disease-free population, the TSH distribution curve shifts to higher levels with increasing age. This observation implies that age-specific reference ranges for TSH should be used in elderly patients [55]. Studies in the elderly failed to demonstrate a clear associations between SCH and lipid alterations and/or increased CV risk [55]. As indicated by two meta-analyses, SCH plays a dual role depending on the age at which it develops: an increased risk of adverse CV outcomes is observed in patients younger than 65 years, but not in the older ones [19, 56]. More importantly, the Leiden Study reported a prolonged life span in elderly people having a raised serum TSH level [57], even if other studies failed to clearly confirm this observation [58]. Thus, while the need for treating overt hypothyroidism in the elderly is not questioned, the potential benefits of LT4 treatment for SCH is still highly controversial. Also, preventing a long-term progression to overt hypothyroidism is not a relevant argument for treatment in elderly patients. In this regard, Gussekloo et al. found that, during a 3-year follow-up period, >50% of elderly (≥85-year-old) patients with SCH spontaneously normalized their thyroid function, while none progressed to overt disease [57]. A Japanese study in an elderly population with SCH reported similar findings, in that 50% of patients normalized their serum TSH and only 7% progressed to overt hypothyroidism over a 4.2-year observation period. Noteworthy, however, is that recovery from SCH did not occur in patients with a baseline serum TSH level >8 mIU/L [8]. SCH is also less symptomatic in elderly patients, who often complain of nonspecific symptoms unrelated to thyroid dysfunction [59]. These symptoms, according to the recent, controlled and randomized TRUST trial, do not revert with LT4 therapy [18]. In the elderly, treatment with LT4 also failed to improve cognitive function and mood, and to produce statistically significant benefits in the prevention of cardiovascular events [58]. When frail old people are considered, the guidance for prescriptions in frail adults indicate that LT4 therapy should, in almost all cases, be prescribed or maintained to cure overt hypothyroidism [60]. No definite recommendation is given regarding SCH [60]. In general, the decision to treat-or-not-to-treat elderly patients with SCH should not rely on clinical symptoms and must always consider the risk of overtreatment, due to its harmful repercussions in old, frail patients [58]. Indeed, the prevalence of LT4 overtreatment increases with age, as well as the risk of bone and CV complications, the latter being exemplified by atrial fibrillation [55, 58, 59]. As proposed by Cooper et al. [55, 58, 59]; and in line with the recent European-Thyroid-Association (ETA) guidelines [2], the decision to treat elderly patients with SCH should be individualized and based upon the degree of TSH elevation (usually a >10 mIU/L TSH is required), patient's age and life expectancy, potentially associated risk factors, and comorbid conditions [2]. In old patients with milder TSH elevation (<10 mIU/L) a wait-and-see approach with close monitoring of thyroid function is warranted [2]. Once the decision to treat has been made, lower doses of LT4 are required in elderly patients owing to the age-dependent decrease in thyroid hormone requirements and the increase in LT4 half-life [2, 58]. Both the ETA and the ATA guidelines agree with the 'start-low, go-slow'' recommendation in elderly and frail patients recommending a starting dose of 12.5–25 μg/day (ETA) [2]. LT4 should be

progressively increased by 12.5–25 µg daily every 4–8 weeks and TSH should be targeted to 4–6 mIU/L in persons older than 70–80 years [2, 10]. To make the issue even more controversial, a recent study reported that the mortality rate of old patients having a "normal TSH level (0.5 and 5.0 mIU/L)", while on LT4 for hypothyroidism was lower than that of patients with a TSH between 5.0 and 10.0 mIU/L [61].

Concluding remarks

In conclusion, the main message of the present review is that, as clearly indicated in guidelines from professional societies and expert opinions, SCH represents an heterogenous clinical condition. The different clinical settings, in which SCH may be encountered, stress the need for different diagnostic and therapeutic decisions. Indeed, the presence of SCH, as assessed by a raised serum TSH, should be regarded differently according to patient's clinical status. Concomitant diseases including obesity, diabetes, cardiovascular diseases, dyslipidemia, as well as anthropometric factors such as age or physiological condition as pregnancy, all profoundly impact the decision making process on whether treat or not to treat SCH. Furthermore, even when a decision to treat is made, the appropriate LT4 dose and follow-up strategies should be individualized. The issue is further complicated by the well established notion that the normal range for TSH is more dynamic than previously thought. As a final consideration, it should be highlighted that the debate on treating or not treating SCH is a long lasting one, and perhaps, one of the most controversial issue in endocrine clinical practice. With this in mind, the final message of the present review, is that, based on current knowledge of SCH and its potential clinical significance, the diagnostic steps, the therapeutic decision, and the modality of clinical surveillance of treated and untreated patients displaying a raised serum level of TSH should always be personalized.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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References

1. B. Biondi, A.R. Cappola, D.S. Cooper, Subclinical hypothyroidism: a review. JAMA **322**(2), 153–160 (2019)
2. S.H. Pearce, G. Brabant, L.H. Duntas, F. Monzani, R.P. Peeters, S. Razvi, J.L. Wemeau, 2013 ETA guideline: management of subclinical hypothyroidism. Eur. Thyroid J. **2**(4), 215–228 (2013)
3. N. Hattori, T. Ishihara, N. Matsuoka, T. Saito, A. Shimatsu, Anti-thyrotropin autoantibodies in patients with macro-thyrotropin and long-term changes in macro-thyrotropin and serum thyrotropin levels. Thyroid **27**(2), 138–146 (2017)
4. G.J. Canaris, N.R. Manowitz, G. Mayor, E.C. Ridgway, The Colorado thyroid disease prevalence study. Arch. Intern. Med. **160**(4), 526–534 (2000)
5. M.P. Vanderpump, W.M. Tunbridge, J.M. French, D. Appleton, D. Bates, F. Clark, J. Grimley Evans, D.M. Hasan, H. Rodgers, F. Tunbridge et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin. Endocrinol. **43**(1), 55–68 (1995)
6. J.G. Hollowell, N.W. Staehling, W.D. Flanders, W.H. Hannon, E. W. Gunter, C.A. Spencer, L.E. Braverman, 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**(2), 489–499 (2002)
7. J.R. Garber, R.H. Cobin, H. Gharib, J.V. Hennessey, I. Klein, J.I. Mechanick, R. Pessah-Pollack, P.A. Singer, K.A. Woeber, Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid **22**(12), 1200–1235 (2012)
8. M. Imaizumi, N. Sera, I. Ueki, I. Horie, T. Ando, T. Usa, S. Ichimaru, E. Nakashima, A. Hida, M. Soda, T. Tominaga, K. Ashizawa, R. Maeda, S. Nagataki, M. Akahoshi, Risk for progression to overt hypothyroidism in an elderly Japanese population with subclinical hypothyroidism. Thyroid **21**(11), 1177–1182 (2011)
9. P.W. Rosario, M. Carvalho, M.R. Calsolari, Natural history of subclinical hypothyroidism with TSH </=10 mIU/l: a prospective study. Clin. Endocrinol. **84**(6), 878–881 (2016)
10. J. Jonklaas, A.C. Bianco, A.J. Bauer, K.D. Burman, A.R. Cappola, F.S. Celi, D.S. Cooper, B.W. Kim, R.P. Peeters, M.S. Rosenthal, A.M. Sawka, Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid **24**(12), 1670–1751 (2014)
11. M.G. Lechner, C.M. Vyas, O.R. Hamnvik, E.K. Alexander, P.R. Larsen, T.K. Choueiri, T.E. Angell, Risk factors for new hypothyroidism during tyrosine kinase inhibitor therapy in advanced nonthyroidal cancer patients. Thyroid **28**(4), 437–444 (2018)
12. L.S. Chang, R. Barroso-Sousa, S.M. Tolaney, F.S. Hodi, U.B. Kaiser, L. Min, Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. Endocr. Rev. **40**(1), 17–65 (2019)
13. T. Rago, V. Cantisani, F. Ianni, L. Chiovato, R. Garberoglio, C. Durante, A. Frasoldati, S. Spiezia, R. Farina, G. Vallone, A. Pontecorvi, P. Vitti, Thyroid ultrasonography reporting: consensus of Italian Thyroid Association (AIT), Italian Society of Endocrinology (SIE), Italian Society of Ultrasonography in Medicine and Biology (SIUMB) and ultrasound chapter of Italian Society of Medical Radiology (SIRM). J. Endocrinol. Investig. **41**(12), 1435–1443 (2018)
14. M. Rotondi, F. Coperchini, F. Magri, L. Chiovato, Serum-negative autoimmune thyroiditis: what's in a name? J. Endocrinol. Investig. **37**(6), 589–591 (2014)
15. H. Zulewski, B. Müller, P. Exer, A.R. Miserez, J.J. Staub, Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. J. Clin. Endocrinol. Metab. **82**(3), 771–776 (1997)
16. M. Feller, M. Snel, E. Moutzouri, D.C. Bauer, M. de Montmollin, D. Aujesky, I. Ford, J. Gussekloo, P.M. Kearney, S. Mooijaart, T. Quinn, D. Stott, R. Westendorp, N. Rodondi, O.M. Dekkers,

Association of thyroid hormone therapy with quality of life and thyroid-related symptoms in patients with subclinical hypothyroidism: a systematic review and meta-analysis. JAMA **320**(13), 1349–1359 (2018)
17. S. Razvi, R. Peeters, S.H.S. Pearce, Thyroid hormone therapy for subclinical hypothyroidism. JAMA **321**(8), 804 (2019)
18. D.J. Stott, N. Rodondi, P.M. Kearney, I. Ford, R.G.J. Westendorp, S.P. Mooijaart, N. Sattar, C.E. Aubert, D. Aujesky, D.C. Bauer, C. Baumgartner, M.R. Blum, J.P. Browne, S. Byrne, T.H. Collet, O. M. Dekkers, W.P.J. den Elzen, R.S. Du Puy, G. Ellis, M. Feller, C. Floriani, K. Hendry, C. Hurley, J.W. Jukema, S. Kean, M. Kelly, D. Krebs, P. Langhorne, G. McCarthy, V. McCarthy, A. McConnachie, M. McDade, M. Messow, A. O'Flynn, D. O'Riordan, R.K.E. Poortvliet, T.J. Quinn, A. Russell, C. Sinnott, J.W.A. Smit, H.A. Van Dorland, K.A. Walsh, E.K. Walsh, T. Watt, R. Wilson, J. Gussekloo, Thyroid hormone therapy for older adults with subclinical hypothyroidism. N. Engl. J. Med **376**(26), 2534–2544 (2017)
19. S. Razvi, A. Shakoor, M. Vanderpump, J.U. Weaver, S.H. Pearce, The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. J. Clin. Endocrinol. Metab. **93**(8), 2998–3007 (2008)
20. G.E. Bekkering, T. Agoritsas, L. Lytvyn, A.F. Heen, M. Feller, E. Moutzouri, H. Abdulazeem, B. Aertgeerts, D. Beecher, J.P. Brito, P.D. Farhoumand, N. Singh Ospina, N. Rodondi, M. van Driel, E. Wallace, M. Snel, P.M. Okwen, R. Siemieniuk, P.O. Vandvik, T. Kuijpers, M. Vermandere, Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. Bmj **365**, l2006 (2019)
21. R.P. Peeters, Subclinical hypothyroidism. N. Engl. J. Med. **376** (26), 2556–2565 (2017)
22. L.H. Duntas, G. Brenta, The effect of thyroid disorders on lipid levels and metabolism. Med Clin. N. Am. **96**(2), 269–281 (2012)
23. S. Tognini, A. Polini, G. Pasqualetti, S. Ursino, N. Caraccio, M. Ferdeghini, F. Monzani, Age and gender substantially influence the relationship between thyroid status and the lipoprotein profile: results from a large cross-sectional study. Thyroid **22**(11), 1096–1103 (2012)
24. X. Li, Y. Wang, Q. Guan, J. Zhao, L. Gao, The lipid-lowering effect of levothyroxine in patients with subclinical hypothyroidism: a systematic review and meta-analysis of randomized controlled trials. Clin. Endocrinol. **87**(1), 1–9 (2017)
25. I.M. Abreu, E. Lau, B. de Sousa Pinto, D. Carvalho, Subclinical hypothyroidism: to treat or not to treat, that is the question! A systematic review with meta-analysis on lipid profile. Endocr. Connect. **6**(3), 188–199 (2017)
26. B. Biondi, The management of thyroid abnormalities in chronic heart failure. Heart Fail. Clin. **15**(3), 393–398 (2019)
27. D. Nanchen, J. Gussekloo, R.G. Westendorp, D.J. Stott, J.W. Jukema, S. Trompet, I. Ford, P. Welsh, N. Sattar, P.W. Macfarlane, S.P. Mooijaart, N. Rodondi, A.J. de Craen, Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. J. Clin. Endocrinol. Metab. **97**(3), 852–861 (2012)
28. N. Rodondi, D.C. Bauer, A.R. Cappola, J. Cornuz, J. Robbins, L. P. Fried, P.W. Ladenson, E. Vittinghoff, J.S. Gottdiener, A.B. Newman, Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The cardiovascular health study. J. Am. Coll. Cardiol. **52**(14), 1152–1159 (2008)
29. G. Yang, Y. Wang, A. Ma, T. Wang, Subclinical thyroid dysfunction is associated with adverse prognosis in heart failure patients with reduced ejection fraction. BMC Cardiovasc. Disord. **19**(1), 83 (2019)
30. L. Kannan, P.A. Shaw, M.P. Morley, J. Brandimarto, J.C. Fang, N.K. Sweitzer, T.P. Cappola, A.R. Cappola, Thyroid dysfunction in heart failure and cardiovascular outcomes. Circ. Heart Fail. **11** (12), e005266 (2018)
31. B. Biondi, Mechanisms in endocrinology: heart failure and thyroid dysfunction. Eur. J. Endocrinol. **167**(5), 609–618 (2012)
32. B. Gencer, T.H. Collet, V. Virgini, D.C. Bauer, J. Gussekloo, A. R. Cappola, D. Nanchen, W.P. den Elzen, P. Balmer, R.N. Luben, M. Iacoviello, V. Triggiani, J. Cornuz, A.B. Newman, K.T. Khaw, J.W. Jukema, R.G. Westendorp, E. Vittinghoff, D. Aujesky, N. Rodondi, Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation **126**(9), 1040–1049 (2012)
33. S. Razvi, J.U. Weaver, M.P. Vanderpump, S.H. Pearce, The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. J. Clin. Endocrinol. Metab. **95**(4), 1734–1740 (2010)
34. J. Sun, L. Yao, Y. Fang, R. Yang, Y. Chen, K. Yang, L. Tian, Relationship between subclinical thyroid dysfunction and the risk of cardiovascular outcomes: a systematic review and meta-analysis of prospective cohort studies. Int. J. Endocrinol. **2017**, 8130796 (2017)
35. C. Redford, B. Vaidya, Subclinical hypothyroidism: should we treat? Post Reprod. Health **23**(2), 55–62 (2017)
36. M.N. Andersen, A.M. Olsen, J.C. Madsen, J. Faber, C. Torp-Pedersen, G.H. Gislason, C. Selmer, Levothyroxine substitution in patients with subclinical hypothyroidism and the risk of myocardial infarction and mortality. PLoS ONE **10**(6), e0129793 (2015)
37. M.N. Andersen, A.S. Olsen, J.C. Madsen, S.L. Kristensen, J. Faber, C. Torp-Pedersen, G.H. Gislason, C. Selmer, Long-Term outcome in levothyroxine treated patients with subclinical hypothyroidism and concomitant heart disease. J. Clin. Endocrinol. Metab. **101**(11), 4170–4177 (2016)
38. F. Santini, P. Marzullo, M. Rotondi, G. Ceccarini, L. Pagano, S. Ippolito, L. Chiovato, B. Biondi, Mechanisms in endocrinology: the crosstalk between thyroid gland and adipose tissue: signal integration in health and disease. Eur. J. Endocrinol. **171**(4), R137–152 (2014)
39. B. Biondi, G.J. Kahaly, R.P. Robertson, Thyroid dysfunction and diabetes mellitus: two closely associated disorders. Endocr. Rev. **40**(3), 789–824 (2019)
40. R.S. Gray, D.Q. Borsey, W.J. Irvine, J. Seth, B.F. Clarke, Natural history of thyroid function in diabetics with impaired thyroid reserve: a four year controlled study. Clin. Endocrinol. **19**(4), 445–451 (1983)
41. R. Bitzur, H. Cohen, Y. Kamari, D. Harats, Intolerance to statins: mechanisms and management. Diabetes Care **36**(Suppl 2), S325–330 (2013)
42. C. Cappelli, M. Rotondi, I. Pirola, B. Agosti, A. Formenti, E. Zarra, U. Valentini, P. Leporati, L. Chiovato, M. Castellano, Thyreotropin levels in diabetic patients on metformin treatment. Eur. J. Endocrinol. **167**(2), 261–265 (2012)
43. E.K. Alexander, E.N. Pearce, G.A. Brent, R.S. Brown, H. Chen, C. Dosiou, W.A. Grobman, P. Laurberg, J.H. Lazarus, S.J. Mandel, R.P. Peeters, S. Sullivan, 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of thyroid disease during pregnancy and the postpartum. Thyroid **27** (3), 315–389 (2017)
44. J.H. Lazarus, J.P. Bestwick, S. Channon, R. Paradice, A. Maina, R. Rees, E. Chiusano, R. John, V. Guaraldo, L.M. George, M. Perona, D. Dall'Amico, A.B. Parkes, M. Joomun, N.J. Wald, Antenatal thyroid screening and childhood cognitive function. N. Engl. J. Med. **366**(6), 493–501 (2012)
45. D.S. Cooper, E.N. Pearce, Subclinical hypothyroidism and hypothyroxinemia in pregnancy—still no answers. N. Engl. J. Med. **376**(9), 876–877 (2017)

46. M. Rotondi, L. Chiovato, F. Pacini, L. Bartalena, P. Vitti, Management of subclinical hypothyroidism in pregnancy: a comment from the Italian Society of Endocrinology and the Italian Thyroid Association to the 2017 American Thyroid Association Guidelines-"The Italian Way". Thyroid **28**(5), 551–555 (2018)
47. M. Salerno, D. Capalbo, M. Cerbone, F. De Luca, Subclinical hypothyroidism in childhood - current knowledge and open issues. Nat. Rev. Endocrinol. **12**(12), 734–746 (2016)
48. A. Monzani, F. Prodam, A. Rapa, S. Moia, V. Agarla, S. Bellone, G. Bona, Endocrine disorders in childhood and adolescence. Natural history of subclinical hypothyroidism in children and adolescents and potential effects of replacement therapy: a review. Eur. J. Endocrinol. **168**(1), R1–R11 (2013)
49. G. Crisafulli, T. Aversa, G. Zirilli, G.B. Pajno, D. Corica, F. De Luca, M. Wasniewska, Subclinical hypothyroidism in children: when a replacement hormonal treatment might be advisable. Front Endocrinol. **10**, 109 (2019)
50. M. Wasniewska, T. Aversa, M. Salerno, A. Corrias, M.F. Messina, A. Mussa, D. Capalbo, F. De Luca, M. Valenzise, Five-year prospective evaluation of thyroid function in girls with subclinical mild hypothyroidism of different etiology. Eur. J. Endocrinol. **173**(6), 801–808 (2015)
51. J. Lazarus, R.S. Brown, C. Daumerie, A. Hubalewska-Dydejczyk, R. Negro, B. Vaidya, 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur. Thyroid J. **3**(2), 76–94 (2014)
52. M. Cerbone, D. Capalbo, M. Wasniewska, S. Alfano, G. Mattace Raso, U. Oliviero, A. Cittadini, F. De Luca, M. Salerno, Effects of L-thyroxine treatment on early markers of atherosclerotic disease in children with subclinical hypothyroidism. Eur. J. Endocrinol. **175**(1), 11–19 (2016)
53. A. Clegg, J. Young, S. Iliffe, M.O. Rikkert, K. Rockwood, Frailty in elderly people. Lancet **381**(9868), 752–762 (2013)
54. P. Laurberg, S. Andersen, I. Bülow Pedersen, A. Carlé, Hypothyroidism in the elderly: pathophysiology, diagnosis and treatment. Drugs Aging **22**(1), 23–38 (2005)
55. R.M. Ruggeri, F. Trimarchi, B. Biondi, Management of endocrine disease: l-Thyroxine replacement therapy in the frail elderly: a challenge in clinical practice. Eur. J. Endocrinol. **177**(4), R199–R217 (2017)
56. N. Ochs, R. Auer, D.C. Bauer, D. Nanchen, J. Gussekloo, J. Cornuz, N. Rodondi, Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann. Intern. Med. **148**(11), 832–845 (2008)
57. J. Gussekloo, E. van Exel, A.J. de Craen, A.E. Meinders, M. Frölich, R.G. Westendorp, Thyroid status, disability and cognitive function, and survival in old age. JAMA **292**(21), 2591–2599 (2004)
58. D.S. Cooper, Thyroid disease in the oldest old: the exception to the rule. JAMA **292**(21), 2651–2654 (2004)
59. B. Biondi, D.S. Cooper, The clinical significance of subclinical thyroid dysfunction. Endocr. Rev. **29**(1), 76–131 (2008)
60. V.M. Polypharmacy. *Guidance for Prescribing in Frail Adults.* (NHS Highland Polypharmacy Action Group, Scotland, 2011)
61. A. Akirov, H. Gimbel, A. Grossman, T. Shochat, I. Shimon, Elevated TSH in adults treated for hypothyroidism is associated with increased mortality. Eur. J. Endocrinol. **176**(1), 57–66 (2017)