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A Clinical Debate: Subclinical Hypothyroidism

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1. Introduction

Case Vignette
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Ms. N.N., a 42-year-old married woman, came to the Endocrine clinic to consult about her recent screening laboratory test results. She is an office employee and has a 7-year-old daughter. Four months ago, a serum thyrotropin (TSH) level of 6.3 mU/L (reference range: 0.4 - 5.0 mU/L) was detected in laboratory tests which had been requested because of some nonspecific complaints including fatigue, weight gain and hair loss. Her recent laboratory test results are as follows: TSH = 6.8 mU/L, free thyroxine (fT4) = 14 pmol/L (normal range, 10 - 23 pmol/L), thyroid peroxidase antibodies (TPOAb) = 40 IU/mL (< 35 IU/mL is normal).

Her past medical history is not significant. Her menstruation is normal and she has no plan for pregnancy. She takes no medications. There is no family history of thyroid disease. In clinical examination, body mass index is 27 kg/m^2 and a firm 25-g thyroid gland is palpable.

According to the history and laboratory test results, she wants to know if she should initiate thyroid hormone therapy.

Option 1: When should subclinical hypothyroidism be treated?

Option 2: When should subclinical hypothyroidism not be treated?

Herewith, comments of two thyroid experts based on the existing evidence and their own experience are reviewed.

2. Option 1: When Should Subclinical Hypothyroidism be Treated?

Sina Jasim, MD, MPH; Hossein Gharib, MD, MACP, MACE

Subclinical hypothyroidism (SCH) is a biochemical condition defined by elevated serum thyroid stimulating hormone (TSH) and normal free thyroxine (FT4) and free triiodothyronine (FT3) concentrations. The incidence of SCH varies and can range from 3% to 15% (1-3). Higher incidence can be seen in women, those with family history of thyroid disease, low iodine intake, and increasing age. The wide range reported is because of differences in age groups, gender, iodine intake, and the lack of consensus on appropriate TSH threshold for definition of this condition (1-5).

SCH is mild when serum TSH is between the upper limit of reference range and 10 mU/L, and moderate when TSH level is 10 mU/L or higher (2, 6); the majority of SCH patients have TSH levels between 5 and 10 mU/L (7).

TSH reference range is wide and can be anywhere between 0.3 to 5.0 mIU/L; however TSH values may differ according to age and higher TSH values are seen in older age groups with and without positive anti-thyroid antibodies (TPOAb) (4). However, data suggest that current reference limits of TSH may not reflect the true normal range for TSH which likely has a narrower range of 0.4 - 2.5 mIU/L (8). The National Academy of Clinical Biochemistry (NACB) has suggested that "normal" TSH range should be between 0.4 and 2.5 mIU/L (9). This notion was also supported by various studies (10, 11). Furthermore, a small decrease in FT4 can result in relatively large increase in serum TSH leading to a TSH value above the reference range. This may progress to overt hypothyroidism as the TSH continues to increase and FT4 declines below reference range; therefore, SCH can be considered a mild form of thyroid failure continuum mostly seen with autoimmune thyroid disease (2).

In around 60% of patients with mild (grade 1) form of SCH, the TSH may revert to normal range within 5 years (12, 13). However, the risk of progression of SCH to overt hy-

pothyroidism can range from 2% to 6% per year especially in those patients with positive TPOAb, in women, and in those with low-normal FT4 or higher TSH levels (3, 12, 14-16); incidence of progression is higher if TSH > 10 mIU/L (17). As SCH is frequently transient (13), it is recommended that a second high TSH level be confirmed 1-3 months after the initial evaluation. Generally, we favor treatment of SCH in the right clinical scenario and this argument is based on the discussion below:

1- Lipids and Cardiovascular Disease (CVD) in SCH: Screening for hypothyroidism is usually done when evaluating secondary causes for abnormal lipid profile especially elevated low-density lipoprotein cholesterol (LDL-C) and triglyceride levels (18). Various reports linked hyperlipidemia and early CVD to SCH, specifically, increased levels of total cholesterol (TC) and LDL-C in SCH patients compared to controls (19). Hyperlipidemia tends to be worse in patients with higher TSH concentrations or in patients with elevated LDL-C at baseline (20). A meta-analysis of observational studies has confirmed increased concentrations of serum TC, LDL-C, and triglyceride levels in patients with moderate (grade 2) SCH (21). This was recently supported by an updated meta-analysis (22).

The above changes may suggest that patients with untreated SCH may be at increased risk of adverse cardiovascular outcomes. Some studies suggest that treatment with levothyroxine (LT4) had beneficial effects on surrogate markers for cardiovascular risk including improved serum cholesterol levels (23). Another meta-analysis of 12 RCTs compared LT4 treatment versus placebo in more than 900 patients with SCH and concluded that LT4 treatment has clear benefits on TC and LDL-C, including those with mild SCH (24).

Overall, data about the risk of cardiovascular disease (CVD) in SCH are conflicting, although many studies suggest some degree of CVD risk in patients with SCH (25-27). An association of SCH with ischemic heart disease and mortality was also suggested (28, 29). However, the increased cardiovascular risk was only seen in younger individuals (30).

Studies also suggested increased 10-year mortality in men with SCH compared to euthyroid individuals (31); moreover, the increased cardiovascular risk is usually seen in individuals with TSH concentrations of 7 mIU/L or higher (6). In TSH levels between 4.5 and 10 mIU/L, deaths occurred in about 13% compared to 7% of euthyroid cardiac patients (32). The CVD risk is higher with higher TSH levels (33, 34) indicating the severity of SCH is associated with greater CVD risk. A meta-analysis of patients aged < 60 years suggested those with SCH had significantly worse parameters for left ventricular diastolic function when assessed by Doppler echocardiogram compared with age and gender matched controls with normal thyroid function (35).

Although observational studies show a significant association between SCH and cardiovascular outcomes, there is a paucity of data from randomized, controlled trials to inform the effects of LT4 treatment of SCH on these clinical outcomes (2); however, the lack of evidence does not necessarily equate to the lack of benefits.

Observational studies involving patients with SCH have shown a significantly lower risk of heart failure events (36), death from any cause (37) and events associated with ischemic heart disease (38) among patients who received LT4 than patients who did not receive LT4. A systematic review of 12 studies concluded that treatment with LT4 had beneficial effects on surrogate markers for cardiovascular risk such as lowering TC/LDL-C levels and improved cardiac function (23).

2- Symptoms in SCH: Overall, there are differences in symptomatic response to LT4 treatment that is likely due to the differences in TSH levels and the extent of symptoms at baseline as well as patient age or gender. In a randomized, controlled trial, 100 participants (mean age, 54 years) received either LT4 or placebo for SCH (mean TSH 6.6 mIU/L); some benefit of treatment with LT4 for certain symptoms especially tiredness was reported (39). In addition, some clinical trials have shown improvement in memory function after treatment with LT4 for SCH (40, 41).

3- Pregnancy and Fertility in SCH: There are large variations in the prescription of LT4 to pregnant women with SCH in the United States (42). Clinicians may offer thyroid hormones because of possible adverse outcomes of maternal SCH (43).

It is important to consider other risk factors for hypothyroidism when evaluating women with positive TPOAb and high normal TSH values such as family history, pregnancy history, and other variables that might help clinicians make the decision to treat or monitor. There is more agreement, however, on treating women with SCH undergoing artificial reproductive techniques as more evidence are available from randomized controlled trials suggesting therapy with LT4 results in improved pregnancy outcomes and lower miscarriage rates (44, 45).

Numerous observational studies and meta-analyses have demonstrated the association of SCH with adverse pregnancy and neonatal outcomes (46). Reports showing reduced pregnancy loss and preterm delivery with LT4 use are encouraging (47, 48).

The American Thyroid Association (ATA) recommends that women with SCH who are pregnant undergoing IVF be treated with LT4 to achieve a TSH concentration of 2.5 mU/L (49).

4- What Clinical Guidelines Recommend in SCH: Clinical guidelines have different recommendations for or against treating SCH reflecting the level of evidence and the large knowledge gap due to the absence of large randomized trials that include symptomatic patients with var-

ious age groups and TSH levels.

The consensus panel of the Joint Statement of the American Association of Clinical Endocrinologists (AACE), the ATA and The Endocrine Society (ES) on the management of subclinical thyroid disease (50) recommended against routine (or reflex) treatment of patients with serum TSH levels of 4.5 - 10 mU/L, with the key word here being "routine". However, it was recommended that most patients with serum TSH levels of 4.5 - 10 mU/L should be considered for treatment based on the clinical judgment of the physician with proper consideration of the patient's clinical features to make such decisions.

The combined ATA and AACE guidelines suggest universal treatment when TSH > 10 mIU/L and consideration of treatment if TSH $\leq$ 10.0 mIU/L based on individual factors such as symptoms of hypothyroidism, TPOAb positivity, and evidence of CVD as discussed earlier (51).

The European Thyroid Association (ETA) recommends to consider a trial of treatment in patients aged < 65 years with elevated TSH < 10 mU/L if symptoms of hypothyroidism are present (52).

The National Institute for health and Care Excellence (NICE) suggests considering a trial of treatment with LT4 if the TSH is 4 - 10 mIU/L in patients aged < 65 years (53).

A recent clinical practice guideline recommended against the routine treatment of SCH (54); however, this recommendation was largely based on a systematic review of 21 RCTs in 2192 participants (46% female, mean age: 50 years,) with SCH and mean TSH level of 6.7 mIU/L at baseline, comparing thyroid hormone treatment with placebo or no treatment (55) which was dominated by a large (TRUST) trial specifically addressing older people with SCH. Furthermore, this recommendation did not include women at childbearing age and at risk of unplanned pregnancy.

5- Our Decision to Treat: While benefits of LT4 are not convincing in older patients, it is likely to have favorable outcomes in younger age. For patients < 65 years and TSH level of 4.5 - 6.9 mU/L, treatment trial is optional based on individual patient factors, including the extent of TSH elevation and whether the patient has symptoms of hypothyroidism, TPOAb, goiter, persistent and progressively increasing TSH levels, plan for pregnancy, evidence of atherosclerotic or CVD, heart failure, or other associated risk factors (2, 6, 38, 51, 52).

Proper discussion of the risks and benefits of LT4 treatment will be initiated with this patient and offering a treatment trial is appropriate if she agrees to do so. Although the data about hypothyroid symptoms are not strong, it remains possible that treatment with LT4 could improve her symptoms and a 6-month trial should be appropriate if the decision to treat is based on symptoms only.

We consider LT4 therapy beneficial in this case considering her age, symptoms, progressive increase of TSH level and positive TPOAb. The possibility of pregnancy is another reason favoring treatment. The potential risk of developing hyperthyroidism due to LT4 over-treatment is avoided by careful follow-up. Of note, untreated patients also require follow-up office visits and laboratory monitoring. Since the degree of thyroid dysfunction is mild, a small dose of LT4 (50 μg) seems adequate to restore normal serum TSH levels. TSH levels should be assessed 6 weeks after initiating LT4 and at 6-week intervals after subsequent dose changes. The treatment goal is to normalize TSH level. We consider therapeutic target TSH level for this patient around 1 - 3 mIU/L, which is consistent with the ETA TSH target in the lower half of reference range (0.4 to 2.5 mIU/L) for younger patients ($\leq$ 70 years of age) (52). LT4 remains our treatment of choice (51, 52, 56). Treatment can always be discontinued in the unlikely event of side effects or if no improvement in symptoms is reported by the patient.

3. Option 2: When Should Subclinical Hypothyroidism Not be Treated?

Bernadette Biondi, MD

Persistently increased serum TSH represents the most important test for the evaluation of subclinical hypothyroidism (SCH); the sensitivity of the hypothalamic-pituitary-thyroid axis allows in fact clinicians to diagnose this condition, which is usually based more on laboratory than clinical evaluation. Serum FT4 evaluation is only slightly useful because it remains within its reference interval and decreases only when SCH progresses to overt disease (2, 5).

According to international guidelines and expert opinions, SCH is classified as: mild (or grade 1 SCH) when serum TSH is between 4.5 - 9.9 mU/L, and severe when TSH is $\geq$ 10 mU/L (grade 2 SCH) (2, 5, 51, 52, 56, 57). The majority of patients with SCH have a serum TSH $\leq$ 10 mU/L (2, 5, 6, 12, 51, 52, 56, 57).

The prevalence of SCH is about 5% - 15% in adults and increases in iodine-replete countries, women and older patients (6). Chronic autoimmune thyroiditis represents the main cause of SCH in adults and some drugs (namely lithium carbonate, iodine-containing compounds, interferon alfa, tyrosine kinase inhibitors, immune check point inhibitors for cancer immunotherapy) can induce persistent SCH, especially in patients with an underlying Hashimoto thyroiditis. Subacute thyroiditis, infiltrative disorders of the thyroid gland, partial thyroidectomy and a previous treatment of hyperthyroidism with radioiodine can also induce SCH (2, 5, 6).

This case vignette refers to a symptomatic 42-year-old married woman with a moderate TSH increase (6.3 mU/L) at the first evaluation. She refereed no family history of thyroid disease.

The first step for the correct diagnosis of SCH is to assess the persistence of this laboratory condition and the risk of potential progression to a more severe form of hypothyroidism. TSH levels can be transiently raised in subjects recovering from non-thyroidal illnesses, following the administration of some drugs interfering with the thyroid function, or in case of a transient thyroiditis (2, 5, 6). Conditions such as extreme obesity or untreated adrenal insufficiency can be associated with a mild elevation in serum TSH levels, inducing a false diagnosis of SCH (5, 6). Moreover, a laboratory pattern indistinguishable from SCH can be observed in presence of human anti-mouse antibodies in some immunoassays, which can falsely increase serum TSH levels (58). Mutations in the TSH receptor causing TSH resistance should be investigated in patients with a family history of raised serum TSH concentrations but without thyroid autoimmunity (59). Rarely, increased serum TSH levels can be due to a "macro TSH", a condition in which a complex binding of TSH to other plasma proteins, most often immunoglobulins, results in elevated plasma TSH with low biological activity and clinical euthyroidism (60).

At the subsequent assessment four months later, our patient had a serum TSH level of 6.8 mU/L; free thyroxine was in the normal reference range and thyroid peroxidase antibodies (TPOAb) were within the upper limits of the laboratory reference range. Her medical history was negative for comorbidity and medications. The thyroid gland was palpable. These data support the thesis that our patient's TSH is persistently increased and, therefore, she suffers from moderate SCH.

Our patient complained about fatigue, weight gain and hair loss which are non-specific symptoms of hypothyroidism and can be detected also in subjects with a normal thyroid function. More definite symptoms of thyroid hormone deficiency are dry skin, poor memory, slow thinking, muscle weakness, fatigue, muscle cramps, cold intolerance, puffy eyes, constipation, bradycardia and neurocognitive deficits (12). Although the onset of these clinical symptoms is more frequent in patients with overt hypothyroidism, they should be investigated in our patient, because the detection of new and more specific symptoms of hypothyroidism could further support the diagnosis of thyroid hormone deficiency (12). If other symptoms of hypothyroidism are not present, then other potential causes of her unwellness should be excluded.

Cardiovascular abnormalities (left ventricular systolic and diastolic dysfunction, impaired vascular function with increased systemic vascular resistance and altered endothelial-mediated relaxation and vascular compliance) have been reported even in patients with mild SCH (6). Severe SCH (TSH > 10 mU/L) has been associated with metabolic alterations (elevated LDL cholesterol and triglycerides levels, insulin resistance and nonalcoholic fatty liver steatohepatitis) (5, 6, 12). An assessment of the cardiovascular risks should be performed before administering LT4 treatment to patients with moderate SCH.

Treatment of SCH is recommended by international guidelines in patients with serum TSH > 10 mU/L (51, 52, 56, 57) because of the high cardiovascular mortality for heart failure and coronary disease reported in two important meta-analyses including individual participant data (IPD) from large prospective studies (33, 34). Expert opinions support replacement therapy with LT4 in patients with serum TSH of 7.0 - 9.9 mU/L (6) because of the increased risk of fatal stroke and mortality from coronary heart disease documented by IPD meta-analyses (34, 61).

Treatment of patients with a mild serum TSH increase is still debated. The ATA and the AACE recommend to proceed with replacement therapy in presence of certain individual factors and especially in the presence of symptoms suggestive of hypothyroidism, positive thyroperoxidase antibodies, evidence of atherosclerotic cardiovascular disease, heart failure, or risk factors for these diseases (51). The ETA supports treatment of mild SCH following repeated measurement of serum TSH and in presence of symptoms compatible with hypothyroidism. If a symptomatic response is not reached within 3 - 4 months after TSH normalization, treatment should be suspended (52).

I am inclined to treat this patient. However, based on the aforementioned debates, I would consider two options: (1) a wait-and-see strategy to evaluate the possibility of a TSH normalization and the potential improvement of symptoms after 2 - 3 months of lifestyle intervention; (2) the use of replacement doses of LT4 after carefully excluding transient conditions of isolated hyperthyrotropinemia or situations that can induce a false diagnosis of SCH.

I would discuss these two possible choices as well as the benefits/risks of LT4 therapy with the patient and take her preference into account.

In the first case scenario, the patient would remain untreated with the necessity of periodic follow-ups to evaluate the persistence or progression to a more severe SCH. The risk of progression is particularly high in women with high iodine intake, serum TSH > 10 mU/L and positive thyroid auto-antibodies (2, 5, 6). No treatment can lead to a potential worsening of some of the symptoms and an increased cardiovascular risk. I would also dissuade the patient from and warn her against resorting to alternative drugs to treat her persistent symptoms, as websites often suggest high doses of thyroid extracts or liothyronine as an alternative to LT4.

In the second case scenario, I would start treating the patient with low doses of LT4 to normalize her serum TSH. A potential improvement of the symptoms should be assessed after 6 months. However, I would inform the patient that her symptoms might not benefit from LT4 treatment

and advise her of the potential adverse effects of overtreatment. A large meta-analysis reported that LT4 treatment does not improve symptoms or body mass index in the vast majority of patients with mild SCH (55). However, these data were derived from available randomized controlled trails which prevalently included older patients (62), supporting the necessity of further studies to evaluate the possibility that younger patients might benefit from LT4 replacement therapy. I would periodically assess serum TSH during LT4 therapy to perform a correct replacement therapy and improve the potential increased cardiovascular risk of untreated SCH.

Footnotes

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References

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;**160**(4):526–34. doi: 10.1001/archinte.160.4.526. [PubMed: 10695693].
2. Peeters RP. Subclinical Hypothyroidism. *N Engl J Med*. 2017;**376**(26):2556–65. doi: 10.1056/NEJMcp1611144. [PubMed: 28657873].
3. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)*. 1995;**43**(1):55–68. doi: 10.1111/j.1365-2265.1995.tb01894.x. [PubMed: 7641412].
4. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. 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*. 2002;**87**(2):489–99. doi: 10.1210/jcem.87.2.8182. [PubMed: 11836274].
5. Cooper DS, Biondi B. Subclinical thyroid disease. *Lancet*. 2012;**379**(9821):1142–54. doi: 10.1016/S0140-6736(11)60276-6. [PubMed: 22273398].
6. Biondi B, Cappola AR, Cooper DS. Subclinical Hypothyroidism: A Review. *JAMA*. 2019;**322**(2):153–60. doi: 10.1001/jama.2019.9052. [PubMed: 31287527].
7. Blum MR, Bauer DC, Collet TH, Fink HA, Cappola AR, da Costa BR, et al. Subclinical thyroid dysfunction and fracture risk: a meta-analysis. *JAMA*. 2015;**313**(20):2055–65. doi: 10.1001/jama.2015.5161. [PubMed: 26010634]. [PubMed Central: PMC4729304].
8. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. *J Clin Endocrinol Metab*. 2005;**90**(9):5483–8. doi: 10.1210/jc.2005-0455. [PubMed: 16148345].
9. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid*. 2003;**13**(1):3–126. doi: 10.1089/105072503321086962. [PubMed: 12625976].
10. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. *Clin Endocrinol (Oxf)*. 2003;**58**(2):138–40. doi: 10.1046/j.1365-2265.2003.01681.x. [PubMed: 12580927].
11. Volzke H, Alte D, Kohlmann T, Ludemann J, Nauck M, John U, et al. Reference intervals of serum thyroid function tests in a previously iodine-deficient area. *Thyroid*. 2005;**15**(3):279–85. doi: 10.1089/thy.2005.15.279. [PubMed: 15785248].
12. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocr Rev*. 2008;**29**(1):76–131. doi: 10.1210/er.2006-0043. [PubMed: 17991805].
13. Meyerovitch J, Rotman-Pikielny P, Sherf M, Battat E, Levy Y, Surks MI. Serum thyrotropin measurements in the community: five-year follow-up in a large network of primary care physicians. *Arch Intern Med*. 2007;**167**(14):1533–8. doi: 10.1001/archinte.167.14.1533. [PubMed: 17646608].
14. Diez JJ, Iglesias P. 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*. 2004;**89**(10):4890–7. doi: 10.1210/jc.2003-032061. [PubMed: 15472181].
15. Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P, et al. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. *J Clin Endocrinol Metab*. 2002;**87**(7):3221–6. doi: 10.1210/jcem.87.7.8678. [PubMed: 12107228].
16. Somwaru LL, Rariy CM, Arnold AM, Cappola AR. The natural history of subclinical hypothyroidism in the elderly: the cardiovascular health study. *J Clin Endocrinol Metab*. 2012;**97**(6):1962–9. doi: 10.1210/jc.2011-3047. [PubMed: 22438233]. [PubMed Central: PMC3387427].
17. Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. *J Clin Endocrinol Metab*. 2010;**95**(3):1095–104. doi: 10.1210/jc.2009-1977. [PubMed: 20097710].
18. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz C, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *Circulation*. 2014;**129**(25_suppl_2). doi: 10.1161/01.cir.0000437738.63853.7a.
19. Caraccio N, Natali A, Sironi A, Baldi S, Frascerra S, Dardano A, et al. Muscle metabolism and exercise tolerance in subclinical hypothyroidism: a controlled trial of levothyroxine. *J Clin Endocrinol Metab*. 2005;**90**(7):4057–62. doi: 10.1210/jc.2004-2344. [PubMed: 15855263].
20. Duntas LH, Wartofsky L. Cardiovascular risk and subclinical hypothyroidism: focus on lipids and new emerging risk factors. What is the evidence? *Thyroid*. 2007;**17**(11):1075–84. doi: 10.1089/thy.2007.0116. [PubMed: 17900236].
21. Liu XL, He S, Zhang SF, Wang J, Sun XF, Gong CM, et al. Alteration of lipid profile in subclinical hypothyroidism: a meta-analysis. *Med Sci Monit*. 2014;**20**:1432–41. doi: 10.12659/MSM.891163. [PubMed: 25124461]. [PubMed Central: PMC4144946].
22. Kotwal A, Cortes T, Genere N, Hamidi O, Jasim S, Newman CB, et al. Treatment of Thyroid Dysfunction and Serum Lipids: A Systematic Review and Meta-analysis. *J Clin Endocrinol Metab*. 2020;**105**(12). doi: 10.1210/clinem/dgaa672. [PubMed: 32954428].
23. Villar HC, Saconato H, Valente O, Atallah AN. Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database Syst Rev*. 2007;(3). CD003419. doi: 10.1002/14651858.CD003419.pub2. [PubMed: 17636722]. [PubMed Central: PMC6610974].
24. Li X, Wang Y, Guan Q, Zhao J, Gao L. The lipid-lowering effect of levothyroxine in patients with subclinical hypothyroidism: A systematic review and meta-analysis of randomized controlled trials. *Clin Endocrinol (Oxf)*. 2017;**87**(1):1–9. doi: 10.1111/cen.13338. [PubMed: 28342184].
25. Biondi B, Fazio S, Palmieri EA, Carella C, Panza N, Cittadini A, et al. Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab*. 1999;**84**(6):2064–7. doi: 10.1210/jcem.84.6.5733. [PubMed: 10372711].
26. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. *Ann Intern Med*. 2002;**137**(11):904–14. doi: 10.7326/0003-4819-137-11-200212030-00011. [PubMed: 12458990].

27. Moon S, Kim MJ, Yu JM, Yoo HJ, Park YJ. Subclinical Hypothyroidism and the Risk of Cardiovascular Disease and All-Cause Mortality: A Meta-Analysis of Prospective Cohort Studies. *Thyroid*. 2018;**28**(9):1101–10. doi: 10.1089/thy.2017.0414. [PubMed: 29978767].
28. Inoue K, Ritz B, Brent GA, Ebrahimi R, Rhee CM, Leung AM. Association of Subclinical Hypothyroidism and Cardiovascular Disease With Mortality. *JAMA Netw Open*. 2020;**3**(2). e1920745. doi: 10.1001/jamanetworkopen.2019.20745. [PubMed: 32031647].
29. Rodondi N, Aujesky D, Vittinghoff E, Cornuz J, Bauer DC. Subclinical hypothyroidism and the risk of coronary heart disease: a meta-analysis. *Am J Med*. 2006;**119**(7):541–51. doi: 10.1016/j.amjmed.2005.09.028. [PubMed: 16828622].
30. Tsai TY, Tu YK, Munir KM, Lin SM, Chang RH, Kao SL, et al. Association of Hypothyroidism and Mortality in the Elderly Population: A Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab*. 2020;**105**(6). doi: 10.1210/clinem/dgz186. [PubMed: 31829418].
31. Imaizumi M, Akahoshi M, Ichimaru S, Nakashima E, Hida A, Soda M, et al. Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. *J Clin Endocrinol Metab*. 2004;**89**(7):3365–70. doi: 10.1210/jc.2003-031089. [PubMed: 15240616].
32. Iervasi G, Molinaro S, Landi P, Taddei MC, Galli E, Mariani F, et al. Association between increased mortality and mild thyroid dysfunction in cardiac patients. *Arch Intern Med*. 2007;**167**(14):1526–32. doi: 10.1001/archinte.167.14.1526. [PubMed: 17646607].
33. Gencer B, Collet TH, Virgini V, Bauer DC, Gussekloo J, Cappola AR, et al. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. *Circulation*. 2012;**126**(9):1040–9. doi: 10.1161/CIRCULATIONAHA.112.096024. [PubMed: 22821943]. [PubMed Central: PMC3884576].
34. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*. 2010;**304**(12):1365–74. doi: 10.1001/jama.2010.1361. [PubMed: 20858880]. [PubMed Central: PMC3923470].
35. Chen X, Zhang N, Cai Y, Shi J. Evaluation of left ventricular diastolic function using tissue Doppler echocardiography and conventional doppler echocardiography in patients with subclinical hypothyroidism aged <60 years: a meta-analysis. *J Cardiol*. 2013;**61**(1):8–15. doi: 10.1016/j.jjcc.2012.08.017. [PubMed: 23084577].
36. Rodondi N, Bauer DC, Cappola AR, Cornuz J, Robbins J, Fried LP, et al. Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health study. *J Am Coll Cardiol*. 2008;**52**(14):1152–9. doi: 10.1016/j.jacc.2008.07.009. [PubMed: 18804743]. [PubMed Central: PMC2874755].
37. Razvi S, Weaver JU, Vanderpump MP, Pearce SH. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. *J Clin Endocrinol Metab*. 2010;**95**(4):1734–40. doi: 10.1210/jc.2009-1749. [PubMed: 20150579].
38. Razvi S, Weaver JU, Butler TJ, Pearce SH. Levothyroxine treatment of subclinical hypothyroidism, fatal and nonfatal cardiovascular events, and mortality. *Arch Intern Med*. 2012;**172**(10):811–7. doi: 10.1001/archinternmed.2012.1159. [PubMed: 22529180].
39. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. 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*. 2007;**92**(5):1715–23. doi: 10.1210/jc.2006-1869. [PubMed: 17299073].
40. Aghili R, Khamseh ME, Malek M, Hadian A, Baradaran HR, Najafi L, et al. Changes of subtests of Wechsler Memory Scale and cognitive function in subjects with subclinical hypothyroidism following treatment with levothyroxine. *Arch Med Sci*. 2012;**8**(6):1096–101. doi: 10.5114/aoms.2012.32423. [PubMed: 23319987]. [PubMed Central: PMC3542502].
41. Correia N, Mullally S, Cooke G, Tun TK, Phelan N, Feeney J, et al. Evidence for a specific defect in hippocampal memory in overt and subclinical hypothyroidism. *J Clin Endocrinol Metab*. 2009;**94**(10):3789–97. doi: 10.1210/jc.2008-2702. [PubMed: 19584178].
42. Maraka S, Mwangi R, Yao X, Sangaralingham LR, Singh Ospina NM, O'Keeffe DT, et al. Variation in treatment practices for subclinical hypothyroidism in pregnancy: US national assessment. *J Clin Endocrinol Metab*. 2019. doi: 10.1210/jc.2019-00057. [PubMed: 31127823]. [PubMed Central: PMC6667278].
43. Maraka S, Ospina NM, O'Keeffe DT, Espinosa De Ycaza AE, Gionfriddo MR, Erwin PJ, et al. Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. *Thyroid*. 2016;**26**(4):580–90. doi: 10.1089/thy.2015.0418. [PubMed: 26837268]. [PubMed Central: PMC4827301].
44. Abdel Rahman AH, Aly Abbassy H, Abbassy AA. Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women. *Endocr Pract*. 2010;**16**(5):792–7. doi: 10.4158/EP09365.OR. [PubMed: 20350920].
45. Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD, Kang BM. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. *Fertil Steril*. 2011;**95**(5):1650–4. doi: 10.1016/j.fertnstert.2010.12.004. [PubMed: 21193190].
46. Velasco I, Taylor P. Identifying and treating subclinical thyroid dysfunction in pregnancy: emerging controversies. *Eur J Endocrinol*. 2018;**178**(1):D1–D12. doi: 10.1530/EJE-17-0598. [PubMed: 29070512].
47. Maraka S, Mwangi R, McCoy RG, Yao X, Sangaralingham LR, Singh Ospina NM, et al. Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. *BMJ*. 2017;**356**. i6865. doi: 10.1136/bmj.i6865. [PubMed: 28122781]. [PubMed Central: PMC5266622].
48. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. *Eur J Endocrinol*. 2017;**176**(2):253–65. doi: 10.1530/EJE-16-0548. [PubMed: 27879326].
49. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid*. 2017;**27**(3):315–89. doi: 10.1089/thy.2016.0457. [PubMed: 28056690].
50. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *J Clin Endocrinol Metab*. 2005;**90**(1):581–5. discussion 586-7. doi: 10.1210/jc.2004-1231. [PubMed: 15643019].
51. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid*. 2012;**22**(12):1200–35. doi: 10.1089/thy.2012.0205. [PubMed: 22954017].
52. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. *Eur Thyroid J*. 2013;**2**(4):215–28. doi: 10.1159/000356507. [PubMed: 24783053]. [PubMed Central: PMC3923601].
53. National Institute for Health Care Excellence. *Clinical Knowlegde Summaries. Subclinical hypothyroidism (non-pregnant)*. 2018.
54. Bekkering GE, Agoritsas T, Lytvyn L, Heen AF, Feller M, Moutzouri E, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. *BMJ*. 2019;**365**:l2006. doi: 10.1136/bmj.l2006. [PubMed: 31088853].
55. Feller M, Snel M, Moutzouri E, Bauer DC, de Montmollin M, Aujesky D, et al. 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*. 2018;**320**(13):1349–59. doi: 10.1001/jama.2018.13770. [PubMed: 30285179]. [PubMed Central: PMC6233842].
56. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid*. 2014;**24**(12):1670–751. doi: 10.1089/thy.2014.0028. [PubMed: 25266247]. [PubMed Central: PMC4267409].
57. Brenta G, Vaisman M, Sgarbi JA, Bergoglio LM, Andrada NC, Bravo

PP, et al. Clinical practice guidelines for the management of hypothyroidism. *Arq Bras Endocrinol Metabol*. 2013;**57**(4):265–91. doi: 10.1590/s0004-27302013000400003. [PubMed: 23828433].
58. Koulouri O, Moran C, Halsall D, Chatterjee K, Gurnell M. Pitfalls in the measurement and interpretation of thyroid function tests. *Best Pract Res Clin Endocrinol Metab*. 2013;**27**(6):745–62. doi: 10.1016/j.beem.2013.10.003. [PubMed: 24275187]. [PubMed Central: PMC3857600].
59. Tonacchera M, Di Cosmo C, De Marco G, Agretti P, Banco M, Perri A, et al. Identification of TSH receptor mutations in three families with resistance to TSH. *Clin Endocrinol (Oxf)*. 2007;**67**(5):712–8. doi: 10.1111/j.1365-2265.2007.02950.x. [PubMed: 17697008].
60. Hattori N, Ishihara T, Yamagami K, Shimatsu A. Macro TSH in patients with subclinical hypothyroidism. *Clin Endocrinol (Oxf)*. 2015;**83**(6):923–30. doi: 10.1111/cen.12643. [PubMed: 25388002].
61. Chaker L, Baumgartner C, den Elzen WP, Ikram MA, Blum MR, Collet TH, et al. Subclinical Hypothyroidism and the Risk of Stroke Events and Fatal Stroke: An Individual Participant Data Analysis. *J Clin Endocrinol Metab*. 2015;**100**(6):2181–91. doi: 10.1210/jc.2015-1438. [PubMed: 25856213]. [PubMed Central: PMC4454799].
62. Stott DJ, Rodondi N, Kearney PM, Ford I, Westendorp RGJ, Mooijaart SP, et al. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. *N Engl J Med*. 2017;**376**(26):2534–44. doi: 10.1056/NEJMoa1603825. [PubMed: 28402245].