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The case for more aggressive screening and treatment of mild thyroid failure

ABSTRACT

“Subclinical” (mild) thyroid failure is not benign: it tends to progress to overt thyroid failure and it has adverse clinical effects. We believe it should be screened for more aggressively in the general population, and treated with levothyroxine.

KEY POINTS

In nearly half of patients, mild thyroid failure progresses to overt hypothyroidism within 5 to 7 years; the risk of progression is especially high in elderly women and in patients with antithyroid antibodies.

Evidence is accumulating that levothyroxine therapy alleviates symptoms and prevents coronary artery disease when started early in mild thyroid failure.

Guidelines from the American Thyroid Association recommend measuring serum thyroid-stimulating hormone levels as part of routine health examinations in adults, but those from the American College of Physicians do not.

WHAT DO YOU DO if a patient has a mildly elevated thyroid-stimulating hormone (TSH) level but normal levels of thyroid hormones and no obvious signs or symptoms of hypothyroidism?

Although many physicians would do nothing, we hope to change their minds. In this article we argue that this condition, variously called subclinical hypothyroidism or mild thyroid failure, is not benign and should be treated.

THE EARLY STAGE OF THYROID FAILURE

Like many disorders, hypothyroidism may become manifest earlier or later in its course. In the earliest and mildest form of hypothyroidism, the TSH level is slightly elevated, while the serum levels of total thyroxine (T_4), free T_4 , total triiodothyronine (T_3), and free T_3 are normal (or more accurately, within their laboratory reference ranges)—albeit probably lower than when the patients were truly euthyroid (FIGURE 1).

The normal range for TSH is approximately 0.3 to 4.0 $\mu\text{IU/mL}$, depending on the laboratory. In the early stages of thyroid failure, if the thyroid gland has any remaining reserve, mild elevations in TSH (between 4 and 10 $\mu\text{IU/mL}$) can stimulate it enough to maintain relatively normal serum T_4 and T_3 levels.¹⁻⁷

HYPOTHYROIDISM IS COMMON

Hypothyroidism is common. Various surveys⁸⁻¹⁴ found the prevalence to be from as low as 1% to as high as 14%, depending on the TSH level used as the criterion and the population studied. The prevalence was higher in:

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Screen for thyroid function during pregnancy

- Whites than in blacks
 - Women than in men
 - Older people than in younger people.
- Other risk factors for hypothyroidism include:
- High iodine intake (urinary iodide > 1 mg/G creatinine)^{8,9}
 - Antithyroid antibodies (either antithyroperoxidase or antithyroglobulin)
 - Family history of thyroid disease
 - Hypercholesterolemia
 - Diabetes
 - Pregnancy or postpartum status.

Mild thyroid failure (defined as TSH > 4.5 μ U/mL with normal T₄ levels) accounted for 38% of cases of thyroid failure in a study by Flatau et al.¹³ The overall prevalence of hypothyroidism was 14% in this population (1,110 men and women ages 65 to 92).

Pregnant women at special risk

Pregnancy often brings an increased demand for thyroid hormone, and if the thyroid gland is already mildly compromised it may not be able to meet that demand.

Glinoyer et al¹⁵ reported that the risk of progression from normal to frankly elevated TSH levels during pregnancy approached 50%

in women with positive antithyroid antibody titers.

The detection and treatment of mild thyroid failure during pregnancy is beneficial not only to the health of the mother, but also to the subsequent neurophysiologic development of the offspring.^{16–19} Experts around the world now recommend thyroid function screening during pregnancy.^{20–22}

After delivery, hypothyroidism may be a prominent presentation of postpartum thyroiditis, and although usually transient, it may last for months. It is best managed by temporary levothyroxine therapy.

Diabetes is associated with autoimmune thyroid disease, and postpartum thyroid dysfunction occurs in 25% of pregnant diabetic women.²³

■ CAUSES OF MILD THYROID FAILURE

As in overt primary hypothyroidism or myxedema, the most common cause of mild thyroid failure is chronic autoimmune (Hashimoto) thyroiditis.²⁴

Other causes include conditions and treatments that affect thyroid hormone production, such as thyroid ablation with radioactive iodine, antithyroid drugs, external beam radiation, partial thyroidectomy, and drugs such as lithium.

Amiodarone, antitussives, radiographic contrast agents, and health supplements such as kelp tablets are rich in iodine and may cause mild hypothyroidism, particularly in patients with underlying thyroid disease.¹

■ THE ARGUMENT FOR TREATING MILD THYROID FAILURE

We base our argument for treating mild thyroid failure on three lines of evidence:

- Without treatment, mild thyroid failure tends to progress to overt thyroid failure
- Thyroid replacement therapy may ameliorate symptoms that had not previously been attributed to hypothyroidism
- Thyroid replacement therapy may reduce the cardiovascular risks of ongoing atherogenesis.



Mild thyroid failure tends to progress to overt hypothyroidism

Follow-up studies indicate that, without treatment, mild thyroid failure progresses to overt hypothyroidism within 5 to 7 years in approximately half of cases.^{11,25,26}

The highest rate of progression is in women older than 65 years with TSH values greater than 10 μ IU/mL and with detectable serum antithyroid antibodies.¹¹

We generally attribute the increased prevalence of thyroid failure with age to Hashimoto disease, in which cytotoxic antibodies destroy thyroid follicular cells over time, causing a progressive decline in thyroid function. A study of outpatients²⁵ reported that 80% of geriatric patients with an antimicrosomal antibody titer greater than 1:1,600 and a TSH level greater than 4 μ IU/mL developed frank hypothyroidism in 4 years.

Elevations in TSH may be transient, however. In a study in children and adolescents, autoimmune thyroiditis evolved to frank hypothyroidism in only 1 of 18 patients during a mean follow-up of 5.8 years.²⁷ One explanation for transient mild to moderate hypothyroidism could be TSH receptor-blocking antibodies.^{28–30}

Moreover, some experts postulate that insults to the thyroid gland such as partial thyroidectomy or neck radiation can lead to “euthyroidism with reset thyrostat,”³¹ in which TSH levels are elevated but T₄ and T₃ levels are normal. In this view, the condition is permanent and does not necessarily progress to frank thyroid failure. We believe that this is a matter of semantics and that such patients simply have mild thyroid failure.

Thyroid replacement may ameliorate symptoms

Part of the reason physicians have been reluctant to treat mild thyroid failure is the belief that patients do not have any symptoms. But although the symptoms may be so mild as to be overlooked, some presenting complaint must have prompted the physician to order thyroid function tests in the first place.

Furthermore, Cooper et al³² found that nearly half of patients with mild thyroid failure improved with levothyroxine therapy but not with placebo. However, a retrospective

study at a primary care geriatric clinic³³ showed no association between TSH levels and hypothyroid symptoms.

Peripheral nerve dysfunction. Misiunas et al³⁴ reported significant peripheral nerve dysfunction (manifested as shortening of motor and sensory amplitudes) in patients with TSH levels over 20 μ IU/mL. On the other hand, Ozata et al,³⁵ in a study of patients with a mean TSH level of 18.05 μ IU/mL, found that neither peripheral nerve conduction velocity nor brain auditory evoked potentials were affected.

Memory. A study in 37 middle-aged or older patients with elevated serum TSH levels³⁶ found statistically significant improvement in composite psychometric memory scores with levothyroxine therapy.

Monzani et al³⁷ administered two neurobehavioral tests, the Crown and Crisp Experiential Index (CCEI) and the Wechsler Memory Scale (WMS), to 50 control subjects and 14 patients with subclinical hypothyroidism before and after levothyroxine therapy (0.1–0.15 mg/day). At baseline, the patients with subclinical hypothyroidism showed significant memory impairment on the WMS; the CCEI showed significant impairment in total score, which specifically included anxiety, depression, somatic complaints, and hysteria. The WMS and CCEI scores were both significantly improved by levothyroxine treatment.

Baldini et al³⁸ compared the effects of levothyroxine therapy in patients with either mild thyroid failure or euthyroid goiter and found that, although psychometric tests showed no differences in affective function, patients with mild thyroid failure had a significant decrement in memory skills, which improved with levothyroxine therapy.

Fatigue, muscle dysfunction. Beyer et al³⁹ studied 10 patients with overt hypothyroidism and 13 patients with mild thyroid failure and noted a positive correlation between levels of the muscle enzyme creatine phosphokinase and TSH, even in patients with mild thyroid failure.

Monzani et al⁴⁰ measured lactate and pyruvate levels at rest and during exercise in 12 patients with mild thyroid failure and in 10 normal, matched controls. With exercise, blood lactate levels rose significantly higher in

Most patients with elevated TSH but normal T₄ develop overt hypothyroidism

the patients with mild thyroid failure, and the increment was related to the duration of thyroid failure rather than the degree of TSH elevation. The authors concluded that mild thyroid failure was associated with impaired energy metabolism that could account for fatigue with exercise and early muscle dysfunction.

In more recent studies, muscle fatigue, weakness, paresthesias, and muscle cramps improved with levothyroxine therapy.⁴¹

Depression. The evidence supporting a link between mild thyroid failure and depression (similar to the risk in frank hypothyroidism⁴²) includes a report⁴³ of a series of depressed patients, 10% of whom met the criteria for mild thyroid failure.

Haggerty et al⁴⁴ reported a 56% lifetime frequency of depression in patients with mild thyroid failure vs 20% in euthyroid patients.

Bipolar disorder. Haggerty et al⁴⁵ observed that patients with bipolar manic-depressive disorder have a higher prevalence of autoimmune thyroid disease (positive antithyroid antibodies), and that the depression may respond to levothyroxine therapy.

High intraocular pressure. An unexpected observation, by Centanni et al,⁴⁶ was that patients with mild thyroid failure had substantially higher intraocular pressures than controls, but that the pressures returned to normal in nearly all patients after only 2 months of levothyroxine therapy.

Therapy may reduce cardiovascular risk

Lipids. In profound hypothyroidism, elevations in LDL cholesterol are associated with an increased risk for atherosclerotic coronary artery disease.

The data are far from definitive about the impact of mild thyroid failure on lipids, however. Several studies^{32,47–52} showed little if any elevation in total cholesterol, LDL, or lipoprotein A levels in people with mild thyroid failure, or no changes in these levels after levothyroxine therapy.

On the other hand, the bulk of the data seem to indicate the opposite.^{14,53–65} An extensive meta-analysis⁶² concluded that levothyroxine therapy for mild thyroid failure could reduce total cholesterol levels by a mean of 15 mg/dL. Another meta-analysis,⁶⁴ covering 247 patients in 13 studies, concluded that

thyroxine therapy was associated with a reduction in mean total cholesterol and LDL levels. The greatest benefit was in patients with the greatest degree of pre-therapy hyperlipidemia.

Larger, well-controlled, prospective studies may be required to better delineate the lipid abnormalities in mild thyroid failure and their response to therapy.

Coronary artery disease was associated with mild thyroid failure in some^{66,67} but not all studies.⁶⁸

The Whickham study⁵¹ showed no association between mild thyroid failure and coronary artery disease, but mild thyroid failure was linked to electrocardiographic abnormalities.

Perk and O'Neill⁶⁹ performed serial coronary angiography to study the association between levothyroxine dose (based on TSH levels) and coronary artery disease progression. They found that 5 of 7 patients receiving adequate levothyroxine doses showed no progression of coronary plaque, whereas all 6 patients taking inadequate doses of levothyroxine (0.1 mg or less) showed progression over 8 to 24 months.

Hak et al⁷⁰ examined 1,149 elderly women and found that 10.8% met their criteria for mild thyroid failure (a normal free T₄ level and TSH > 4.0 μIU/mL). The patients with mild thyroid failure had a greater incidence of aortic atherosclerosis (odds ratio 1.7) and myocardial infarction (odds ratio 2.3). A positive antibody titer increased the odds ratio for aortic atherosclerosis to 1.9 and for myocardial infarction to 3.1.

Heart function. Profound hypothyroidism can cause significant left ventricular (LV) dysfunction,⁷¹ diastolic hypertension, increased systolic time intervals, pericardial effusion, and bradycardia.

However, the effects of mild thyroid failure are less evident. Early efforts to study its impact on myocardial contractility have concentrated on measuring systolic time intervals and LV ejection fraction.^{32,50,72,73}

The systolic time interval is the interval between electromechanical systole and the ejection period, as measured by Doppler carotid ultrasonography and electrocardiography. Although this measurement is not as sensitive as radionuclide ventriculography, multiple studies have used it to estimate LV function.

In one study, muscle fatigue, weakness, and cramps improved with levothyroxine treatment



An increased systolic time interval has been reported in about 50% of patients with mild thyroid failure,⁷¹ and significant reductions of the interval were observed after levothyroxine therapy.⁷²

Although a subsequent study failed to show any changes in the mean systolic time interval, significant improvement was noticed in a subgroup of treated patients with the highest TSH values.³²

Studies that used LV ejection fraction as an estimate of LV function suggest that some patients with mild thyroid failure have impaired myocardial contractility. One study reported a suboptimal increase in LV ejection fraction during exercise,⁷³ while another observed a decrease in LV ejection fraction at rest.⁷⁴

A more recent study using Doppler echocardiography⁷⁵ reported a beneficial effect of levothyroxine therapy on LV diastolic dysfunction in mild thyroid failure.

■ POPULATION SCREENING

The American Thyroid Association⁷⁶ recommends that serum TSH levels be measured as part of routine health examinations in adults (especially women) every 5 years starting at age 35. This recommendation is based on a cost-utility analysis⁷⁷ that found screening for mild thyroid dysfunction to be as cost-effective as screening for breast cancer or hypertension.

On the other hand, the American College of Physicians⁷⁸ does not recommend general population screening for mild thyroid failure, contending that it is not cost-effective and that the potential benefits of early detection and treatment might be outweighed by the associated costs of therapy, follow-up testing, and the theoretical risks of mislabeling such patients.

Given the known associations and risk factors for thyroid failure and the greater prevalence with age, screening for mild thyroid failure should be most beneficial and cost-effective in specific groups:

- The elderly (especially those with functional physical or cognitive impairment)
- Women (especially if pregnant, postpartum, or postmenopausal)

- Patients with a family history or personal past medical history of thyroid disorders or treatment
- Patients with diabetes mellitus, cardiovascular dysfunction, hypercholesterolemia, or other endocrinopathy
- Patients with signs of underlying mild thyroid failure such as unexplained bradycardia, depression, or sleep apnea.

■ DIAGNOSING MILD THYROID FAILURE

The serum TSH level is the cornerstone of the diagnosis of mild thyroid failure and should be measured in all patients at risk.

The free T₄ level should be measured next to confirm hypothyroidism. Secondary (pituitary or hypothalamic) hypothyroidism should be strongly suspected with the finding of a low free T₄ level and a TSH level in the low-normal or normal range.

Antithyroid antibody titers confirm autoimmune thyroid disease and predict progression to frank hypothyroidism, especially in the elderly.

Rule out false and transient TSH elevations

Causes of **transient TSH elevation** must be ruled out before committing a patient to a lifetime of levothyroxine therapy. Hospitalized patients often have slightly elevated TSH levels,⁷⁹ and transient elevations occur during the recovery phase of subacute thyroiditis or during the evolution of other illnesses. Critically ill patients who have euthyroid sick syndrome in the recovery phase may have TSH values from 5 to 20 μ IU/mL.⁸⁰

False TSH elevations. Heterophilic antibodies may interfere with the TSH assay, resulting in false elevations.⁸¹ Antiemetics and antipsychotics may also elevate TSH by interfering with the dopaminergic (TSH-inhibitory) pathway. Antiretroviral therapies such as protease inhibitors and nucleoside analogue reverse transcriptase inhibitors may cause significant false elevations in 8% to 12% of patients.

Other causes of TSH elevation. Patients with primary adrenal insufficiency or TSH-producing adenomas may give an erroneous impression of thyroid failure because of associated high TSH levels.^{82–84}

Measure serum TSH in all patients at risk

TREATMENT RECOMMENDATIONS

The risk-benefit ratio of therapy in mild thyroid failure is difficult to establish, because no placebo-controlled longitudinal interventional trials have shown therapy to have unequivocally demonstrable effects on specific metabolic markers of thyroid state and positive overall benefit by outcomes analysis. Conceivably, the metabolic abnormalities in mild thyroid failure are either too mild or too transient to significantly affect such variables as free water excretion, creatine kinase levels, and metabolic rate.³²


In the absence of this information, what do we recommend?

First, we focus on identifying any previous insult to the thyroid, such as radioactive iodine, antithyroid drugs, or surgical intervention. Drugs such as iodine and lithium have a greater likelihood of inducing hypothyroidism in patients with a marginally compensated gland. Because antithyroid antibodies predict progression to overt hypothyroidism, an antibody titer may be helpful. We recommend a trial of levothyroxine therapy in antibody-positive patients. A negative antibody titer should not exclude consideration for therapy, however, especially if the patient has signs and

symptoms suggesting thyroid failure, and particularly since a small fraction of patients with Hashimoto disease are seronegative.⁸⁵

The goal of therapy is to maintain TSH levels within the normal biological range (generally between 0.5 and 1.5 $\mu\text{IU/mL}$, as opposed to the laboratory reference range, which is typically 0.3 to 5.0 $\mu\text{IU/mL}$). This can be achieved using the dose of 1.6 to 1.7 $\mu\text{g/kg}$ of ideal body weight.⁸⁶

In elderly patients and patients with coronary artery disease, an initial low dose (eg, 25 $\mu\text{g/day}$) should be used. The dose can be cautiously titrated upward, as patient age and underlying cardiovascular status permit, until the goal of optimal replacement is achieved. In general, we start with an initial daily dose of 25 to 50 μg and increase by 25 to 50 μg at 4-to-6-week intervals until the TSH level is normalized, or down to the range of 0.5 to 1.5 $\mu\text{IU/mL}$.

Cautions. Special caution should be exercised in patients with ischemic heart disease and mild hypothyroidism. In these cases, a more conservative approach to starting therapy is indicated to prevent dysrhythmias, worsening angina, or even precipitation of myocardial infarction. 

REFERENCES

1. Ayala AR, Wartofsky L. Minimally symptomatic (subclinical) hypothyroidism. *Endocrinologist* 1997; 7:44–50.
2. Elte JW, Mudde AH, Nieuwenhuijzen Kruseman AC. Subclinical thyroid disease. *Postgrad Med J* 1996; 72:141–146.
3. Surks MI, Ocampo E. Subclinical thyroid disease. *Am J Med* 1996; 100:217–223.
4. Wiersinga WM. Subclinical hypothyroidism and hyperthyroidism. I. Prevalence and clinical relevance. *Neth J Med* 1995; 46:197–204.
5. Woeber KA. Subclinical thyroid dysfunction. *Arch Intern Med* 1997; 157:1065–1068.
6. Wallace K, Hofmann MT. Thyroid dysfunction: how to manage overt and subclinical disease in older patients. *Geriatrics* 1998; 53:32–41.
7. Samuels MH. Subclinical thyroid disease in the elderly. *Thyroid* 1998; 8:803–813.
8. Hollowell JG, Stachling NW, Hannon WH, et al. Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from National Health and Nutrition examination surveys I and III (1971–1974 and 1988–1994). *J Clin Endocrinol Metab* 1998; 83:3401–3408.
9. Konno N, Makita H, Yuri K, Iizuka N, Kawasaki K. Association between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan. *J Clin Endocrinol Metab* 1994; 78:393–397.
10. Brown CA, Hennessey JV. Clinical significance of mildly elevated thyrotropin levels with normal thyroxine levels. *South Med J* 1989; 82:681–685.
11. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Wickham survey. *Clin Endocrinol* 1995; 43:55–68.
12. Helfand M, Crapo LM. Screening for thyroid disease. *Ann Intern Med* 1990; 112:840–849.
13. Flatau E, Trougouboff P, Kaufman N, et al. Prevalence of hypothyroidism and diabetes mellitus in elderly kibbutz members. *Eur J Epidemiol* 2000; 16:43–46.
14. Canaris GJ, Manowitz NR, Mayor GM, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000; 160:526–534.
15. Glinoe D, Riahi M, Grun JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune disorders. *J Clin Endocrinol Metab* 1994; 79:197–204.
16. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999; 341:549–555.
17. Pop V, Kuipens JL, van Baar AL, et al. Low normal maternal free T4 concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol (Oxf)* 1999; 50:149–55.
18. Glinoe D. The systematic screening and management of hypothyroidism and hyperthyroidism during pregnancy. *Trends Endocrinol Metab* 1998; 10:403–411.
19. Glinoe D, Delange F. The potential repercussions of maternal, fetal, and neonatal hypothyroxinemia on the progeny. *Thyroid* 2000; 10:871–887.
20. Fukushi M, Honma K, Fujita K. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child [Letter]. *N Engl J Med* 1999; 341:2016.



21. **Morreale de Escobar G, Obregon MJ, Escobar del Rey F.** Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia? *J Clin Endocrinol Metab* 2000; 85:3975–3987.
22. **Endocrine Society.** August 18, 1999. Pregnant women should be tested for thyroid disorders to prevent mental deficiencies in unborn children. <http://www.endo-society.org/publications/pressReleases/archives/1999/hypothyroid.cfm>. Accessed 1/7/02.
23. **Alvarez-Marfany M, Roman SH, Drexler AJ, et al.** Long-term prospective study of postpartum thyroid dysfunction in women with insulin dependent diabetes mellitus. *J Clin Endocrinol Metab* 1994; 79:10–16.
24. **Tunbridge WM, Brewis M, French JM, et al.** Natural history of autoimmune thyroiditis. *BMJ* 1981; 282:258–262.
25. **Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS.** Thyroid failure in the elderly: microsomal antibodies as discriminant for therapy. *JAMA* 1987; 258:209–213.
26. **Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC.** Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol* 1991; 34:77–83.
27. **Moore D.** Natural course of “subclinical” hypothyroidism on childhood and adolescence. *Arch Pediatr Adolesc Med* 1996; 150:293–297.
28. **Okamura K, Sato K, Yoshinara M, et al.** Recovery of the thyroid function in patients with atrophic hypothyroidism and blocking type TSH binding inhibitor immunoglobulin. *Acta Endocrinol* 1990; 122:107–114.
29. **Takasu N, Yamada T, Takasu M, et al.** Disappearance of thyrotropin-blocking antibodies and spontaneous recovery from hypothyroidism in autoimmune thyroiditis. *N Engl J Med* 1992; 326:513–518.
30. **Kamijo K, Saito T, Sato M, et al.** Transient subclinical hypothyroidism in early pregnancy. *Endocrinol Jpn* 1990; 37:397–403.
31. **Kabadi UM.** Subclinical hypothyroidism: natural course of the syndrome during a prolonged follow-up study. *Arch Intern Med* 1993; 153:957–961.
32. **Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway EC.** L-Thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. *Ann Intern Med* 1984; 101:18–24.
33. **Bemben DA, Hamm RM, Morgan L, et al.** Thyroid disease in the elderly. Part 2. Predictability of subclinical hypothyroidism. *J Fam Pract* 1994; 38:583–588.
34. **Misiunas A, Niepomniszcze H, Ravera B, Faraj G, Faure E.** Peripheral neuropathy in subclinical hypothyroidism. *Thyroid* 1995; 5:283–286.
35. **Ozata M, Ozkardes A, Coraki A, Gundogan M.** Subclinical hypothyroidism does not lead to alterations either in peripheral nerves or brainstem auditory evoked potentials. *Thyroid* 1996; 5:201–205.
36. **Jaeschke R, Guyatt G, Gerstein H, et al.** Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? *J Gen Intern Med* 1996; 11:744–749.
37. **Monzani F, Del Guerra P, Caraccio N, et al.** Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment. *Clin Invest* 1993; 71:367–371.
38. **Baldini IM, Vita A, Mauri MC, et al.** Psychopathological and cognitive features in subclinical hypothyroidism. *Prog Neuropsychopharmacol Biol Psychiatry* 1997; 925–935.
39. **Beyer IW, Karmali R, Demeester-Mirkine N, Cogan E, Fuss MJ.** Serum creatine kinase levels in overt and subclinical hypothyroidism. *Thyroid* 1998; 8:1029–1031.
40. **Monzani F, Caraccio N, Siciliano G, et al.** Clinical and biochemical features of muscle dysfunction in subclinical hypothyroidism. *J Clin Endocrinol Metab* 1997; 82:3315–3318.
41. **Monzani F, Caraccio N, Del Guerra P, et al.** Neuromuscular symptoms and dysfunction in subclinical hypothyroid patients: beneficial effect of L-T₄ therapy. *Clin Endocrinol* 1999; 51:237–242.
42. **Haggerty JJ Jr, Prange AJ Jr.** Borderline hypothyroidism and depression. *Annu Rev Med* 1995; 46:37–46.
43. **Joffe RT, Levitt AJ.** Major depression and subclinical (grade II) hypothyroidism. *Psychoneuroendocrinology* 1992; 17:215–221.
44. **Haggerty JJ Jr, Stern RA, Mason GA, Beckwith J, Morey CE, Prange AJ Jr.** Subclinical hypothyroidism: a modifiable risk factor for depression? *Am J Psychiatry* 1993; 150:508–510.
45. **Haggerty JJ Jr, Garbutt JC, Evans DL, et al.** Subclinical hypothyroidism: a review of neuropsychiatric aspects. *Int J Psychiatr Med* 1990; 20:193–208.
46. **Centanni M, Cesareo R, Verillo O, et al.** Reversible increase of intraocular pressure in subclinical hypothyroid patients. *Eur J Endocrinol* 1997; 136:595–598.
47. **Althaus BU, Staub JJ, Ryff-de-Leche A, Oberhansli A, Stahelin HB.** LDL/HDL changes in subclinical hypothyroidism: possible risk factors for coronary heart disease. *Clin Endocrinol* 1988; 28:157–163.
48. **Tzotzas T, Krassas GE, Konstantinidis T, Bougoulia M.** Changes in lipoprotein(a) in overt and subclinical hypothyroidism before and after treatment. *Thyroid* 2000; 10:803–808.
49. **Vierhapper H, Nardi A, Gresser P, Raber W, Gessl A.** Low-density lipoprotein cholesterol in subclinical hypothyroidism. *Thyroid* 2000; 10:981–984.
50. **Nystrom E, Caidahl K, Fager G, et al.** A double-blind crossover 12 month study of L-thyroxine treatment of women with “subclinical” hypothyroidism. *Clin Endocrinol* 1988; 29:63–76.
51. **Tunbridge WMG, Evered DC, Hall R, et al.** Lipid profiles and cardiovascular disease in the Whickham area with particular reference to thyroid failure. *Clin Endocrinol* 1977; 7:495–508.
52. **Arem R, Escalante DA, Arem N, et al.** Effect of L-Thyroxine therapy on lipoprotein fractions in overt and subclinical hypothyroidism, with special reference to lipoprotein(a). *Metabolism* 1995; 44:1559–1563.
53. **Caron PH, Calazel C, Parra HJ, Hoff M, Louvet JP.** Decreased HDL cholesterol in subclinical hypothyroidism: the effect of L-thyroxine therapy. *Clin Endocrinol* 1990; 33:519–523.
54. **Arem R, Patsch W.** Lipoprotein and apolipoprotein levels in subclinical hypothyroidism. *Arch Intern Med* 1990; 150:2097–2100.
55. **Engler H, Riezen WF.** Effect of thyroid function on concentrations of lipoprotein(a). *Clin Chem* 1993; 39:2466–2469.
56. **Kung AWC, Pang RWC, Janus ED.** Elevated serum lipoprotein(a) in subclinical hypothyroidism. *Clin Endocrinol (Oxf)* 1995; 43:445–459.
57. **Yildirimkaya M, Ozata M, Yilmaz K, et al.** Lipoprotein(a) concentration in subclinical hypothyroidism before, and after L-T₄ therapy. *Endocrinol J* 1996; 43:731–736.
58. **Tsimihodimos V, Bairaktari E, Tzallas C, et al.** The incidence of thyroid function abnormalities in patients attending an outpatient lipid clinic. *Thyroid* 1999; 9:365–368.
59. **Staub J-J, Althaus BU, Engler H, et al.** Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. *Am J Med* 1992; 92:631–642.
60. **Bogner U, Arntz H-R, Peters H, Schleusener H.** Subclinical hypothyroidism and hyperlipoproteinaemia: indiscriminate L-thyroxine treatment not justified. *Acta Endocrinologica* 1993; 128:202–206.
61. **Lerch M, Meier C, Staub JJ.** Is there a need for treatment in subclinical hypo- and hyperthyroidism? *Ther Umsch* 1999; 56:369–373.
62. **Tanis BC, Westendorp GJ, Smelt AHM.** Effect of thyroid substitution on hypercholesterolemia in patients with subclinical hypothyroidism: a reanalysis of intervention studies. *Clin Endocrinol (Oxf)* 1996; 44:643–649.
63. **Michalopoulou G, Alevizaki M, Piperigos G, et al.** High serum cholesterol levels in persons with “high-normal” TSH levels: should one extend the definition of subclinical hypothyroidism? *Eur J Endocrinol* 1998; 138:141–145.
64. **Danese MD, Ladenson PW, Meinert CL, Powe NR.** Effect of thyroxine therapy on serum lipoproteins in patients with MTF: a quantitative review of the literature. *J Clin Endocrinol Metab* 2000; 85:2993–3001.
65. **Kahaly GJ.** Cardiovascular and atherogenic aspects of subclinical hypothyroidism. *Thyroid* 2000; 10:665–679.
66. **Dean JW, Fowler PB.** Exaggerated responsiveness to TRH: a risk factor in women with coronary artery disease. *BMJ* 1985; 290:1555–1561.
67. **Tieche M, Lupi GA, Gutzwiller F, Grob PJ, Studer H, Burgi H.** Borderline low thyroid function and thyroid autoimmunity. Risk factors for coronary heart disease? *Br Heart J* 1981; 46:202–206.



68. **Heinonen OP, Gordin A, Aho K, Punsar S, Pyorala K, Puro K.** Symptomless autoimmune thyroiditis in coronary heart disease. *Lancet* 1972; 1:785-786.
69. **Perk M, O'Neill BJ.** The effect of thyroid hormone therapy on angiographic coronary artery disease progression. *Can J Cardiol* 1997; 13:273-276.
70. **Hak AE, Pols HAP, Visser TJ, Drexhage HA, Hofman A, Witteman JCM.** Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam study. *Ann Intern Med* 2000; 132:270-278.
71. **Ridgway EC, Cooper DS, Daniels GH, Francis GS, Maloof F.** Cardiac function in mild and severe primary hypothyroidism. *Life Sci* 1982; 30:651-659.
72. **Ridgway EC, Cooper DS, Walker H, Rodbard D, Maloof F.** Peripheral responses to thyroid hormone before and after L-thyroxine therapy in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab* 1981; 53:1238-1242.
73. **Forfar JC, Wathen CG, Todd WT, et al.** Left ventricular performance in subclinical hypothyroidism. *QJM* 1985; 57:857-865.
74. **Foldes J, Istvanfy M, Halmagyi M, et al.** Hypothyroidism and the heart: examination of left ventricular function in subclinical hypothyroidism. *Acta Medica Hungarica* 1983; 44:337-347.
75. **Biondi B, Fazio S, Palmieri EA, et al.** Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab* 1999; 84:2064-2067.
76. **Ladenson PW, Singer PA, Ain KB, et al.** American Thyroid Association guidelines for detection of thyroid dysfunction. *Arch Intern Med* 2000; 160:1573-1575.
77. **Danese M, Powe N, Sawin C, Ladenson P.** Screening for MTF at periodic health examination. A decision and cost-effectiveness analysis. *JAMA* 1996; 276:285-291.
78. **Helfand M, Redfern C.** Clinical guideline, Part 1. Screening for thyroid disease. *Ann Intern Med* 1998; 129:1141-1143.
79. **Spencer C, Eigen A, Shen D, Duda M, et al.** Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. *Clin Chem* 1987; 33:1391-1396.
80. **Wartofsky L, Burman KD.** Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome." *Endocr Rev* 1982; 3:164-217.
81. **Hamburger JI.** Factitious elevations of thyrotropin in euthyroid patients. *N Engl J Med* 1985; 313:267-268.
82. **Takamatsu J, Nishikawa M, Horimoto M, Oshawa N.** Familial unresponsiveness to thyrotropin by autosomal recessive inheritance. *J Clin Endocrinol Metab* 1993; 77:1569-1573.
83. **Topliss DJ, White EL, Stockigt JR.** Significance of thyrotropin excess in untreated primary adrenal insufficiency. *J Endocrinol Metab* 1980; 50:52-56.
84. **Smith S.** Commonly asked questions about thyroid function. *Mayo Clin Proc* 1995; 70:573-577.
85. **Baker JR Jr, Saunders NA, Tseng Y-C, et al.** Seronegative Hashimoto thyroiditis with thyroid autoantibody production localized to the thyroid. *Ann Intern Med* 1988; 108:26-30.
86. **Hennessey JV, Evaul JE, Tseng Y-CL, et al.** L-thyroxine dosage: a reevaluation of therapy with contemporary preparations. *Ann Intern Med* 1986; 105:11-15.

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