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# CLINICAL PERSPECTIVE

# Subclinical Hypothyroidism Is Mild Thyroid Failure and Should be Treated

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Subclinical hypothyroidism is defined as an elevated serum TSH level associated with normal total or free $T_4$ and $T_3$ values. The overall prevalence has been reported to range from 4–10% in large general population screening surveys (1–5) and from 7–26% in studies of the elderly (1–3, 6–11). Because of the frequency with which this condition is encountered, important questions have been raised regarding its clinical relevance and appropriate management. One of the myths that surrounds subclinical hypothyroidism is that the laboratory profile of an elevated serum TSH and normal free thyroid hormone levels really represents "compensated hypothyroidism." The reasoning behind this idea is that, since the circulating levels of thyroid hormones are within the normal range with only the serum TSH being elevated, the affected subject is really euthyroid because the increased TSH is stimulating and driving the thyroid gland to produce normal thyroid hormone levels. Certainly, elevated serum TSH levels do stimulate even a diseased thyroid gland to produce and release more thyroid hormone. However, as long as the serum TSH level remains elevated, the thyroid hormone levels are not truly normal for that individual. The clearance kinetics of thyroid hormones and TSH from the circulation actually make such a conclusion inescapable. Because the half-life of $T_4$ is 7 d and that of $T_3$ is 1 d, the serum TSH, which has a half-life of less than 1 h, would certainly be expected to return to normal if thyroid hormone levels were, indeed, normal for that individual. An elevated TSH in an individual patient, thus, means that the circulating thyroid hormone concentrations are insufficient, with a few rare exceptions (TSH-secreting tumors, thyroid hormone resistance syndromes). We, indeed, believe that subclinical hypothyroidism represents mild thyroid failure and is a clinically important disorder that has adverse clinical consequences and that should be treated in most, if not all, cases. We will support this position by reviewing the reported objective data regarding its natural history, its clinical manifestations, and the benefits of treatment.

## *Natural history*

Mild thyroid failure represents an early stage of thyroid disease that will commonly progress to overt hypothyroidism. Progression has, in fact, been reported to occur in approximately 3–18% of affected patients per year (10–17). One study evaluated the natural history of mild thyroid failure in 154 female patients over a 10-yr period; 57% of patients continued to have mild thyroid failure, 34% of patients progressed to overt hypothyroidism, and 9% of patients reverted to a normal TSH level. How many of the 9% had a transient form of thyroiditis such as silent, subacute, or postpartum thyroiditis is unclear (17). The strongest predictors of progression are the presence of antithyroid antibodies, serum TSH values greater than 20 $\mu$U/ml, a history of radioiodine ablation for Graves' disease, a history of external radiation therapy for nonthyroid malignancies, and chronic lithium treatment (10–16).

## *Clinical manifestations*

*Symptoms.* Mild thyroid failure is often asymptomatic; however, nearly 30% of patients with this condition may have symptoms that are suggestive of thyroid hormone deficiency (2, 18). The Colorado Thyroid Disease Prevalence Study (2) measured serum TSH levels and conducted symptom surveys in over 25,000 state residents. Elevated serum TSH values were found in 9.5% of all subjects and in 8.9% of those who were not already on thyroid hormone therapy (Fig. 1); 75% of these individuals had serum TSH levels in the 5–10 $\mu$U/ml range. In response to a validated survey regarding symptoms of thyroid hormone deficiency, the 2,336 subjects who were identified as having mild thyroid failure significantly more often reported having dry skin (28%; $P < 0.001$), poor memory (24%; $P < 0.001$), slow thinking (22%; $P < 0.001$), muscle weakness (22%; $P < 0.001$), fatigue (18%; $P < 0.01$), muscle cramps (17%; $P < 0.001$), cold intolerance (15%; $P < 0.001$), puffy eyes (12%; $P < 0.05$), constipation (8%; $P < 0.05$), and hoarseness (7%; $P < 0.05$) than did euthyroid subjects. It is important to note that, whereas euthyroid subjects experienced a mean of 12.1% of all listed symptoms, overtly hypothyroid subjects had 16.6% of these symptoms ($P < 0.05$ *vs.* euthyroid group), and subjects with mild thyroid failure reported an intermediate 13.7% of the symptoms ($P < 0.05$ *vs.* euthyroid group) (Fig. 2). This suggests a "dosage effect" between levels of thyroid hormones and symptoms. Consistent with these findings, a Swiss study involving 332 women with hypothyroidism reported that 24% of the 93

Abbreviations: ATA, American Thyroid Association; PCP, primary care provider; RCT, randomized controlled trial.

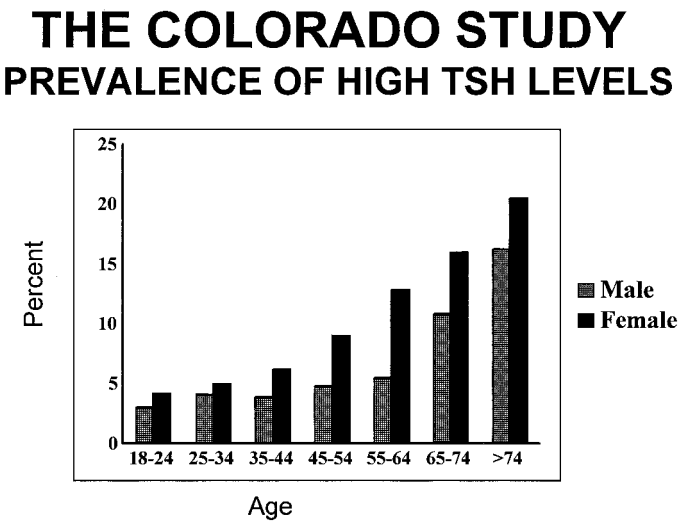


FIG. 1. The Colorado Thyroid Disease Prevalence Study (2). Shown are the age- and gender-specific prevalences of high serum TSH levels found during the screening of 25,862 Colorado state residents in 1995.

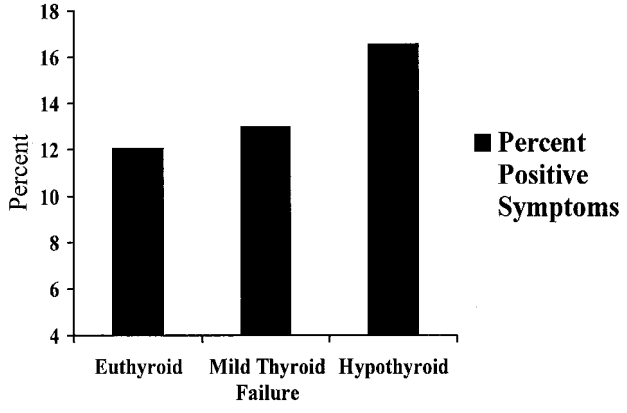


FIG. 2. The Colorado Thyroid Disease Prevalence Study (2). Participants were given a validated survey containing questions regarding symptoms of thyroid hormone deficiency. Of all the symptoms listed, euthyroid subjects (n = 22,842) reported having 12.1%, mild thyroid failure patients (n = 2,336) had 13.7%, and overtly hypothyroid patients (114) had 16.6%. Compared with the euthyroid subjects, total symptoms reported were significantly higher for both the mild thyroid failure patients ($P < 0.05$) and those with overt hypothyroidism ($P < 0.05$).

subjects with mild thyroid failure exhibited typical symptoms of hypothyroidism (18). These studies also emphasize the difficulty in making the diagnosis of primary hypothyroidism using clinical symptoms alone; euthyroid subjects and patients with mild or overt hypothyroidism all had similar constellations of symptoms. Despite statistical significance in large groups, it can be difficult in an individual patient to distinguish a euthyroid subject from one with either mild or overt thyroid disease.

*Neurobehavioral abnormalities and neuromuscular function.* Other cross-sectional studies have demonstrated evidence of specific neurobehavioral and neuromuscular dysfunction in mild thyroid failure patients (19–31). Depression (19–23), memory loss (2, 19, 24), cognitive impairment (25) and a variety of neuromuscular complaints (26, 27) have all been reported to occur more frequently in patients with this condition. Objective peripheral nerve dysfunction, manifested by decreased conduction amplitude in peripheral nerves (28), and an abnormal stapedial reflex (29) have been demonstrated in these patients. Skeletal muscle abnormalities, including elevated serum creatine phosphokinase levels (30), increased circulating lactate levels during exercise (26), and repetitive discharges on surface electromyography (27), have also been reported. Finally, there is intriguing evidence that mild thyroid failure in pregnant women may result in reduced intellectual development of their euthyroid offspring (31).

*Cardiac-pulmonary function.* Myocardial function has been reported in multiple studies to be subtly impaired in patients with mild thyroid failure (32–41). Identified functional abnormalities include impaired myocardial contractility (32–40) and diastolic dysfunction (39–41), at rest (32, 34, 37, 39–41) or with exercise (35–39). Myocardial texture has also been shown to be abnormal by videodensitometric analysis (40). In one comprehensive study of exercise capacity (38), patients with mild thyroid failure were shown to have significant impairment of exercise-related stroke volume, cardiac index, and maximal aortic flow velocity. Pulmonary testing in these same patients revealed decreased vital capacity, reduced anaerobic thresholds, and decreased oxygen uptake at the anaerobic threshold (38). These data clearly demonstrate that cardiovascular function in mild thyroid failure is slightly impaired and not identical to that in the euthyroid state. The important question is whether these differences result in clinically significant impairment of performance in affected patients.

*Cardiovascular risk factor.* Mild thyroid failure has been extensively evaluated as a cardiovascular risk factor. The condition has been shown to be associated with increased serum levels of total cholesterol (Fig. 3) and low-density lipoprotein (LDL) cholesterol in most but not all studies (2, 38, 42, 43) and with reduced high-density lipoprotein cholesterol in some studies (38). Some reports have suggested that even high normal serum TSH values may adversely affect serum lipid

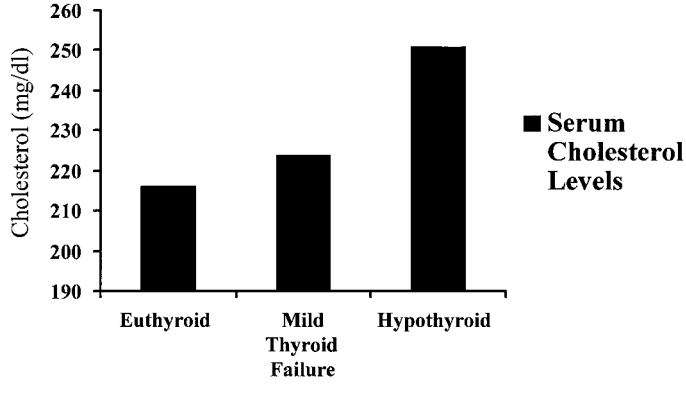


FIG. 3. The Colorado Thyroid Disease Prevalence Study (2). Shown are the mean serum total cholesterol levels in the 22,842 euthyroid subjects (216 mg/dl), the 2,336 mild thyroid failure subjects (224 mg/dl), and the 114 subjects with overt hypothyroidism (251 mg/dl); both thyroid disease groups had statistically higher total cholesterol levels and LDL cholesterol levels (data not shown) than did the euthyroid controls ($P < 0.001$).

and lipoprotein levels (44–46). It has been estimated that an increase in the serum TSH level of 1 μU/ml is associated with a rise in the serum total cholesterol concentration of 0.09 mmol/liter (3.5 mg/dl) in women and 0.16 mmol/liter (6.2 mg/dl) in men (45). The relationship between TSH and LDL cholesterol seems to be most significant in individuals who have underlying insulin resistance (46). One recent study reported that patients with mild thyroid failure, and even subjects with high normal serum TSH values, have evidence of endothelial dysfunction, manifested by impaired flow-mediated, endothelial-dependent vasodilatation (47). An association between mild thyroid failure and peripheral vascular disease was suggested by an older case-control study involving elderly women (48). A 20-yr follow-up study of the original Whickham Survey found no association between initial hypothyroidism, raised serum TSH levels, or antithyroid antibodies and the development of coronary artery disease (49). In contrast, a more recent report from the Rotterdam Study (9) concluded that patients with mild thyroid failure have a significantly increased prevalence of aortic atherosclerosis and myocardial infarctions. After adjustment for multiple known coronary artery disease risk factors, the authors found mild thyroid failure to be an independent and equivalently important risk factor for myocardial infarctions (Fig. 4).

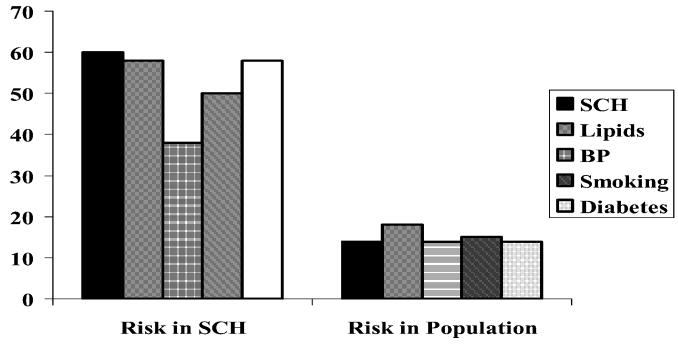


FIG. 4. The Rotterdam Study (9). Analysis of the relationship between subclinical hypothyroidism (SCH) and myocardial infarctions in this study revealed an attributable risk of 60% (SCH contributed to 60% of the myocardial infarctions in the 124 women who had SCH) and a population attributable risk of 14% (SCH was involved in 14% of all myocardial infarctions in the entire group of 1149 women). These risks were similar to those associated with the major recognized cardiovascular risk factors—hypercholesterolemia, hypertension (BP), smoking, and diabetes mellitus.

*Benefits of treatment*

Having defined the scope, natural history, clinical features, and potential morbidity of mild thyroid failure, one must next ask whether treatment of the condition has demonstrable benefits. A number of studies have addressed this issue.

*Symptoms.* There have been three randomized controlled trials (RCT) examining the effects of L-thyroxine treatment on general symptoms in subjects with mild thyroid failure (Table 1). Two of these RCTs (33, 34) reported that mild thyroid failure subjects who were treated with L-thyroxine had significantly greater improvement in general hypothyroid symptom scores than did subjects who were treated with placebo (Fig. 5). A third RCT (50) showed no symptomatic treatment benefit; in this study, however, the mean serum TSH level on L-thyroxine treatment was 4.6 μU/ml, which was at the high end of the normal range. One uncontrolled study also reported a reduction of general somatic complaints after L-thyroxine treatment was instituted (19).

*Neurobehavioral abnormalities and neuromuscular function.* Memory has been shown to improve significantly in one RCT (50) and in two uncontrolled studies in which mild thyroid

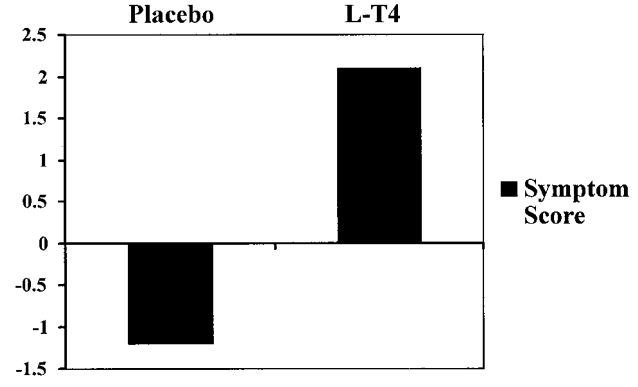


FIG. 5. A RCT of L-thyroxine (L-T4) therapy in subjects with mild thyroid failure (33). Subjects (n = 33) were randomly assigned to received L-thyroxine therapy or placebo for a period of 1 yr. L-thyroxine-treated subjects had a significant improvement in their mean symptom score compared with the placebo-treated group ($P < 0.05$).

**TABLE 1.** Randomized controlled trials investigating the effects of L-thyroxine treatment on general symptoms in patients with mild thyroid failure

| Author (Ref.) | *n* | Design | TSH (uU/ml) | | Results |
|---|---|---|---|---|---|
| | | | Pre-L-thyroxine | On L-thyroxine | |
| Cooper (33) | 33 | Randomized, double-blind, placebo-controlled (1 yr) | 10.8 | 2.6 | Symptom score improvement in L-thyroxine group ($P < 0.05$) |
| Nystrom (34) | 17 | Randomized, double-blind, placebo-controlled cross-over (6 months) | 7.7 | 1.9 | Symptom score improvement in L-thyroxine group ($P < 0.01$) |
| Jaeschke (50) | 32 | Randomized, double-blind, placebo-controlled (11 months) | 12.3 | 4.6 | Symptom score not improved in L-thyroxine group ($P$ = ns); memory improved ($P < 0.01$) |

ns, Not statistically significant.

failure patients were given L-thyroxine therapy (19, 24). Other reported benefits from uncontrolled interventional studies include reduction in neuromuscular complaints (19, 27) and normalization of initially abnormal electromyograms (27).

*Cardiac-pulmonary function.* Studies that have examined the effects of L-thyroxine treatment on cardiac function, including one RCT (40), have reported modest but relatively consistent beneficial results (Table 2). Observed responses to treatment have included enhanced cardiac contractility (32–41), improvement of diastolic function (40, 41), and normalization of videodensitometric myocardial texture (40). Increases in pulmonary vital capacity, the anaerobic threshold and oxygen uptake at the anaerobic threshold have also been demonstrated (38).

*Cardiovascular risk factor.* The reported lipid and lipoprotein responses to treatment of mild thyroid failure with thyroid hormone have been somewhat inconsistent (38). A retrospective evaluation suggested that thyroid hormone replacement had very little lipid-lowering effect in patients whose initial TSH values were less than 10 $\mu$U/ml (51). However, two quantitative literature reviews (42, 43) of the prospective studies examining this issue have concluded that L-thyroxine treatment of patients with mild thyroid failure lowers serum total cholesterol by approximately 0.2–0.4 mmol/liter (7.9–15.8 mg/dl) and LDL cholesterol by about 0.26 mmol/liter (10 mg/dl). The observed cholesterol reductions were greater in patients with inadequately treated overt hypothyroidism (0.44 mmol/liter; 17.4 mg/dl) than in those with untreated spontaneous mild thyroid failure (0.14 mmol/liter; 5.5 mg/dl) and were also greater in patients with higher initial cholesterol levels (43). There have been no reported beneficial effects on high-density lipoprotein cholesterol or triglycerides (42, 43). One intriguing, but uncontrolled, retrospective analysis (52) showed progression of coronary atherosclerosis in subjects on L-thyroxine therapy with elevated serum TSH levels compared with those with normal TSH levels ($P < 0.02$).

*Treatment goals.* Firm data-based guidelines for treatment goals have not yet been established. The distribution of serum TSH values in the normal population is skewed, with the majority of individuals having TSH values at the lower end of the normal range (53). Recent studies have reported that "high normal" TSH values may be associated with modest increases in serum cholesterol levels (44–46) and that serum cholesterol levels improve when TSH values are reduced from the high end to the low end of the normal range with L-thyroxine supplementation (44). Furthermore, individuals with high normal serum TSH levels may have endothelial dysfunction (47). Thus, although not based on prospective outcomes data, these findings would suggest to us that the optimal goal TSH range for L-thyroxine-treated patients is 0.5–2.0 $\mu$U/ml.

*Cost-effectiveness and consensus opinion.* Additional support for a decision to treat comes from a recent analysis, which concluded that screening for and treating mild thyroid failure in all adults greater than 35 yr old is as cost-effective as many other screening procedures used in the United States today (54). Finally, we have recently conducted a survey seeking opinions from both primary care providers (PCPs) and members of the American Thyroid Association (ATA) regarding the management of hypothyroidism (55). When presented the case of a 26-yr-old woman with minimally symptomatic mild thyroid failure, the majority of respondents (70% of PCPs and 65% of ATA members) indicated that they would treat the patient if antithyroid antibodies were negative, whereas 95% of ATA members recommended treatment if antibodies were positive. Responses were similar when the case was a 71-yr-old woman with minimally symptomatic mild thyroid failure; the majority (64% of PCPs and 61% of ATA members) chose to treat if antithyroid antibodies were negative, and 92% of ATA members recommended treatment if antibodies were positive.

### *Summary*

We believe that mild thyroid failure is a common disorder that frequently progresses to overt hypothyroidism. The condition may clearly be associated with somatic symptoms, depression, memory and cognitive impairment, subtle neuromuscular abnormalities, subtle systolic and diastolic cardiac dysfunction, raised serum levels of total and LDL cholesterol, and an increased risk for the development of atherosclerosis. There is documented evidence that many, if not most, of these adverse effects are improved or corrected

**TABLE 2.** Studies that have investigated the effects of L-thyroxine on cardiac function in patients with mild thyroid failure

| Author (Ref.) | *n* | TSH (uU/ml) | | Untreated | | L-thyroxine Therapy | | Methods[a] |
|---|---|---|---|---|---|---|---|---|
| | | Pre-L-thyroxine | On L-thyroxine | Rest | Exercise | Rest | Exercise | |
| Ridgway (32) | 20 | 28 | 1.9 | ↓ MC | | ↑ MC | | 1 |
| Cooper (33) | 33 | 10.8 | 2.6 | Normal | | ↑ MC[b] | | 1 |
| Nystrom (34) | 17 | 7.7 | 1.9 | ↓ MC | | ↑ MC | | 1 |
| Bell (35) | 18 | 17.9 | 3.2 | Normal | ↓ MC | | ↑ MC | 2 |
| Forfar (36) | 10 | 18.2 | 3.5 | Normal | ↓ MC | | ↑ MC | 2 |
| Foldes (37) | 17 | 10.3 | | ↓ MC | ↓ MC | ↑ MC | | 1,2 |
| Kahaly (38) | 20 | 11.2 | | Normal | ↓ MC | | ↑ MC | 1,3 |
| Arem (39) | 8 | 14.8 | 3.0 | ↓ DF | ↓ MC | | ↑ MC | 1,3 |
| Monzani (40) | 20 | 5.4 | 1.2 | ↓ MC, DF | | ↑ MC, DF | | 1,3,4 |
| Biondi (41) | 10 | 8.6 | 1.7 | ↓ DF | | ↑ MC, DF | | 3 |

MC, Myocardial contractility; DF, diastolic function.
[a] 1, Systolic time intervals; 2, ventriculography; 3, Doppler echocardiography; 4, videodensitometry.
[b] In 5 subjects with initially impaired MC.

when L-thyroxine replacement is instituted. Furthermore, treatment of mild thyroid failure has been reported to be cost-effective. Early treatment may even be justified in asymptomatic individuals to prevent the symptoms of more severe thyroid hormone deficiency that eventually develop as the thyroid gland progressively fails; this is particularly true of antithyroid antibody-positive patients, who have the highest risk of disease progression. For these reasons, we recommend L-thyroxine treatment for the majority of patients with mild thyroid failure, particularly those who have symptoms, other cardiovascular risk factors, goiters, or positive antithyroid antibodies, and in those who are pregnant. However, despite these positive indications that treatment with thyroid hormone carries a benefit, there are many unanswered questions. There are few prospective, randomized placebo-controlled studies that have been performed, a shame when compared with other common disorders such as hypercholesterolemia and osteoporosis. The potential consequences of untreated mild thyroid failure on atherosclerosis in adults and on intellectual potential in infants born to mothers with mild thyroid failure begs for definitive answers about the therapeutic benefits of thyroid hormone replacement. It is no longer scientifically or morally justifiable to argue whether mild thyroid failure is "something" or "nothing." What is clearly needed now are clean, randomized, prospective, and adequately powered trials to provide unequivocal answers to the lingering but critical questions regarding the effects of mild thyroid failure and its treatment on important end points such as intellectual function, ischemic heart disease, and quality of life.

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