

Review: Available evidence does not support a benefit for thyroid hormone replacement in adults with subclinical hypothyroidism

Villar HC, Saconato H, Valente O, Atallah AN. **Thyroid hormone replacement for subclinical hypothyroidism.** *Cochrane Database Syst Rev.* 2007;(3):CD003419.

Clinical impact ratings: GIM/FP/GP ★★★★★☆ Endocrinology ★★★★★☆☆

QUESTION

In adults with subclinical hypothyroidism, what is the effect of thyroid hormone replacement on cardiovascular mortality and morbidity, symptoms, and quality of life?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, CINAHL, and LILACS to May 2006; Cochrane Library (2006, Issue 1); Current Controlled Trials; references of relevant studies and systematic reviews; experts; and pharmaceutical companies.

Study selection and assessment: Randomized controlled trials (RCTs) that compared thyroid hormone replacement therapy (triiodothyronine [T₃], thyroxine [T₄], or both) with placebo or no treatment in adult outpatients with subclinical hypothyroidism and no severe illness. Treatment was given for ≥ 1 month with ≥ 3 months of follow-up. Subclinical hypothyroidism was defined as a thyroid-stimulating hormone (TSH) level greater than the upper limit of the test reference value. 12 RCTs (*n* = 485, > 75% women) met the selection criteria; all com-

pared levothyroxine replacement (LT₄) with placebo (11 RCTs) or no treatment (1 RCT). Daily LT₄ doses varied from 65 µg (4 trials) to 150 µg (1 trial), and study duration was 6 to 14 months. All trials were of moderate or good quality (Jadad scale ≥ 3).

Outcomes: Cardiovascular mortality or morbidity, hypothyroidism signs and symptoms, and health-related quality of life. Secondary outcomes included all-cause mortality and adverse effects.

MAIN RESULTS

No trials reported on mortality (cardiovascular or all-cause) or cardiovascular morbidity, and groups did not differ in any trial for hypothyroid signs and symptoms (7 trials,

Table), quality of life (2 trials), or adverse effects (4 trials). In 1 trial (*n* = 66), thyroid hormone replacement improved cognitive function (weighted mean difference 2.4, 95% CI 0.3 to 4.5, *P* = 0.03).

CONCLUSION

In adults with subclinical hypothyroidism, evidence does not support a benefit for thyroid hormone replacement therapy.

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Thyroid hormone replacement vs placebo or no treatment in adults with subclinical hypothyroidism*

Outcomes	Number of trials (n)	Standardized mean difference (95% CI)
Symptom score improvement	4 (155)	-0.30 (-0.62 to 0.02)†
Change in symptom score	3 (164)	-0.24 (-0.54 to 0.07)†

*Abbreviations defined in Glossary. Data were pooled using a fixed-effects model.

†Favors thyroid hormone replacement but is not statistically significant.

COMMENTARY

Data on the prevalence, diagnosis, and management of subclinical thyroid disease (hyperthyroidism and hypothyroidism), a common laboratory diagnosis whose management remains controversial, has increased over the past decade. Subclinical hypothyroidism is particularly common, affecting 4% of the U.S. population, with much higher frequency in the elderly. A recent expert panel did not favor treatment of subclinical hypothyroidism (1), whereas another group of experts suggested early treatment (2).

The usual parameters studied in subclinical hypothyroidism include symptoms and quality of life, lipid profile, and cardiovascular morbidity and mortality. Those concerned with treatment also raise the issue of cost and potential side effects of long-term T₄ therapy. Villar and colleagues reviewed the recent literature and found that T₄ replacement therapy for subclinical hypothyroidism did not improve quality of life, although it did improve some lipid parameters and left ventricular function. No trials reported on survival or cardiovascular morbidity.

What should clinicians do? I think it is premature to conclude that all patients with subclinical hypothyroidism should not be treated with thyroid replacement therapy. It is important to remember that "lack of definitive evidence for a benefit does not equate to evidence for lack of benefit" (2). Mild hypothyroidism, usually defined by serum TSH levels of 5 to 10 mIU/L, is expected to have milder side effects, and demonstration of beneficial treatment effects would accordingly require large patient groups and longer treatment periods. Therefore, I do not

believe the available evidence is sufficient to prove or disprove that treatment is beneficial.

Controversy around the management of subclinical hypothyroidism will continue until prospective, long-term randomized studies evaluate the efficacy of treatment for clinically important events. In the meantime, I favor treating most patients with mild TSH elevation (5 to 10 mIU/L) for 4 reasons: 1) some studies do report improvements in some outcomes (e.g., cognition, lipids, measures of heart function); 2) the risks related to thyroid replacement therapy are low; 3) the cost of thyroid replacement therapy is low; and 4) it will prevent the development of symptoms of clinical hypothyroidism, which occurs in 5% of patients per year. Physicians taking care of these patients need the flexibility to exercise their best clinical judgment in each case.

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