Pharmacotherapy for thyroid nodules: a systematic review and meta-analysis

Richter B, Neises G, Clar C

Authors' objectives
To determine the effect of thyrotropin (thyroid-stimulating hormone, TSH) in the suppression of thyroid hormone in patients with thyroid nodule growth.

Searching
The Cochrane Controlled Trial Register in the Cochrane Library (Issue 4, 2001) and MEDLINE (1966 to 10, 2001) were searched; the search terms were provided. In addition, the authors checked the reference lists of eligible studies and reviewed editorials, narrative reviews and book chapters for other eligible trials.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that assessed thyroid hormone versus placebo or no therapy for a duration of at least 3 months were eligible for inclusion. In the included studies, the dose of triiodothyronine was 75 microg daily and the doses of levothyroxine (L-T4) ranged from 1.94 to 3 microg/kg daily. Five of the included studies were placebo controlled, whilst the remaining four had a 'no treatment' control group. Studies of percutaneous ethanol injections for the treatment of cystic thyroid nodules, or tetracycline for sclerosis of thyroid cysts, were excluded, as were studies of the effect of TSH suppression therapy on the recurrence of thyroid nodules after surgery or irradiation.

Participants included in the review
Participants with a diagnosis of benign thyroid nodule, established by cytologic examination of a fine-needle aspirate, were eligible for inclusion. Most of the studies examined women aged from 36 to 48 years.

Outcomes assessed in the review
Studies that reported nodule size, thyroid cancer incidence and mortality, or TSH and thyroxine (T4) serum levels as the primary outcome, and adverse effects, participant compliance, health-related quality of life, cost or socioecomic effects as a secondary outcome measure, were eligible for inclusion.

All of the studies included in the review reported a measure of nodule volume or nodule size. Most of the studies also evaluated T4 and TSH serum levels.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed each identified study to determine eligibility for inclusion, and resolved any disagreements by discussion.

Assessment of study quality
The validity of the primary studies was assessed according to the method of randomisation, allocation concealment, whether the studies were blinded, description of withdrawals and drop-outs, and intention-to-treat analysis. Two reviewers independently evaluated the methodological quality of each study. The authors did not state how any disagreements were resolved.

Data extraction
Two reviewers independently extracted data about the study population, intervention and outcomes using a standard data extraction form. The relative risk (RR) for each outcome measure reported was calculated.
Methods of synthesis
How were the studies combined?
The studies were pooled using both random-effects (DerSimonian and Laird) and fixed-effect (Mantel-Haenszel) models.

How were differences between studies investigated?
Differences between the studies was assessed using the z score and the chi-squared test for heterogeneity. Statistical significance was set at a level of P less than 0.10. A sensitivity analysis was conducted; this took into account whether the study used placebo or no treatment as the therapeutic intervention in the control group.

Results of the review
Nine RCTs (total n=596; 301 intervention participants, 175 placebo control participants and 120 ‘no treatment’ control participants) were included.

Nodule volume.
L-T4 treatment resulted in a mean change in nodule volume of 0.2 mL (range: -1.4 to 1.3). In the control group nodules changed in volume by 0 mL (range: -2 to 0.8).

Nodule size.
L-T4 treatment resulted in a mean change in maximal module diameter of 0.5 cm (range: -1.7 to 0.1). In the control group, the maximal module diameter changed by 0.4 cm (range: -1.8 to 0.1).

Hormone levels.
T4 and TSH levels changed significantly in almost all of the studies after TSH suppression therapy: the mean changes in T4 and TSH levels were 46.1 nmol/L, (range: 25.7 to 64.6) and 1.1 mU/L (range: -2 to 0.79), respectively. Hormone levels did not change significantly in the control group: the mean changes in T4 and TSH levels were 1.9 nmol/L (range: -7.7 to 2) and 0 mU/L (range: -0.4 to 0.15), respectively.

Changes in nodule size.
Thirty-nine of the 180 patients in the L-T4 group and 18 of the 178 patients in the control group showed a reduction in nodule volume that was greater than or equal to 50%. The random-effects model gave a pooled RR of 1.83 (95% confidence interval, CI: 0.90, 3.73), while the fixed-effect model gave an RR of 2.1 (95% CI: 1.27, 3.57). There was no significant heterogeneity between the studies. The pooled estimate was also robust to the choice of placebo or no treatment for the control group (pooled non significant RR 1.93, 95% CI: 0.67, 5.48), regardless of the choice of meta-analysis model.

In the 6 studies that reported the proportion of patients that experienced nodule growth, 59 of the 237 patients who received thyroid hormone and 89 of the 234 patients in the control group exhibited nodule growth. Pooling using the random-effects model gave a pooled RR of 0.66 (95% CI: 0.51, 0.86) indicating that L-T4 significantly inhibited nodule growth. However, the chi-squared statistic indicated significant heterogeneity between the studies.

Adverse effects of TSH suppression therapy.
One of the 9 studies reported a significant weight reduction of 1.6 kg following L-T4 therapy, compared with an increase of 0.2 kg after placebo therapy. Another study reported a high incidence of tachycardia (16%) after treatment with L-T4.

Authors’ conclusions
TSH suppression therapy inhibits solitary thyroid nodule growth and reduces nodule size. However, uncertainty about
the impact of the therapy on outcomes that are important to patients leaves considerable doubts about the use of T4 suppression therapy.

CRD commentary
The review question was well defined in terms of the study design, interventions, participants and outcomes. A number of sources were searched for relevant studies, and efforts were made to minimise publication bias. However, the authors did not state whether any language restrictions were applied. The methods used to select the studies for inclusion in the review, extract the data, and assess the quality of the studies were adequate. Efforts were made to reduce both bias and errors in the review process. The data were combined appropriately in meta-analyses, and differences between the studies were adequately explored. Overall, the authors' conclusions are consistent with the evidence reviewed, and appear to be robust.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that larger and longer high-quality studies assessing the effects of TSH suppression therapy on patient-orientated outcomes, such as thyroid cancer incidence, quality of life and long-term adverse events, are needed.

Bibliographic details

PubMedID
12227128

Indexing Status
Subject indexing assigned by NLM

MeSH
Humans; Randomized Controlled Trials as Topic; Thyroid Nodule /drug therapy; Thyroxine /therapeutic use; Triiodothyronine /therapeutic use

AccessionNumber
12002002094

Date bibliographic record published
31/05/2005

Date abstract record published
31/05/2005

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.