Assessing the effects of thyroid suppression on benign solitary thyroid nodules: a model for using quantitative research synthesis


Authors' objectives
To evaluate and develop standards of care for levothyroxine (L-T4) suppression therapy in patients with benign solitary thyroid nodules.

Searching
A search of MEDLINE, and a manual search of the literature, were performed from 1950 to 1998 using the MeSH 'levothyroxine' and 'thyroid nodule'. English and non-English language articles were reviewed.

Study selection
Study designs of evaluations included in the review
All study designs were eligible for inclusion in the review. Case reports, open-label cohort studies (controlled and uncontrolled), randomised controlled trials (RCTs) and non-RCTs were included.

Specific interventions included in the review
Thyroid hormone therapy: thyroid USP, thyroid preparation (thyranon), L-T4, triiodothyronine (T3), liothyronine (L-T3)). Control groups received placebo, no treatment or another thyroid hormone treatment or dose. Suppression dose was defined as more than 110 microg/day L-T4 (or equivalent).

Participants included in the review
People with benign solitary thyroid nodules detected by palpation or ultrasound.

Outcomes assessed in the review
Reduction or increase in nodule size (clinically-significant reduction was 50% or more).

How were decisions on the relevance of primary studies made?
Each study was independently reviewed by two authors.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Each study was independently reviewed by two authors. Methodology and results of each study were summarised into tables. Data were extracted in the following categories: study details, study design, number of patients, treatment, duration, assessment technique, size of baseline nodule, change in nodule size, and reviewers' comments.

Evidence of effect (reduction in nodule size) for each study was assessed using a 4-point likert scale with the descriptors 'uninterpretable', 'unlikely', 'questionable' and 'likely'. Any discrepancies between reviewers in interpretation of retrieved data or likert scores were resolved by consensus, and the conclusions were confirmed by the remaining authors.

Methods of synthesis
How were the studies combined?
A narrative synthesis of all the studies was performed. A meta-analysis was then conducted of studies which met the following criteria: inclusion of a control group (no treatment or placebo); randomisation; thyroid suppression with L-
T4 to subnormal thyroid-stimulating hormone level; use of ultrasound to assess changes in nodule size; assessment of clinically-significant reduction (at least 50%) in nodule size. Five studies were included in the meta-analysis. Pooled relative risks (RRs) were calculated using the Mantel-Haenszel fixed-effect method and the DerSimonian and Laird random-effects method.

How were differences between studies investigated?
In the meta-analysis, a Breslow-Day test of homogeneity was used to assess heterogeneity. In the narrative synthesis, differences between studies were discussed.

Results of the review
Thirty (n=1,924) published reports were included, of which five were included in the meta-analysis.

Narrative synthesis (all 30 studies): interpretation of the results was hampered by the use of different thyroid hormone preparations, different doses and study durations, and the use of an imprecise method for estimating nodule size in some studies. Twenty of the 30 studies reported a partial to complete reduction of the nodule in at least 25% of the patients receiving thyroid hormone. All but one of these studies used thyroid hormone doses above those for usual replacement therapy (L-T4 equivalent doses of greater than 110 microg/day) in some or all patients. Nine of the 30 studies described a clinically-significant (at least 50%) reduction of nodule size in more than 25% of thyroid hormone-treated patients. The review’s authors stated that 12 studies showed a likely therapeutic benefit, 11 studies indicated a questionable benefit, 5 showed an unlikely benefit and 2 were uninterpretable due to poor design and/or insufficient information. Studies were discussed.

Meta-analysis (5 RCTs): L-T4 suppression therapy was associated with a 2.11 (random-effects; 95% confidence interval, CI: 0.90, 4.94, p=0.086) to 2.49 (fixed-effect; 95% CI: 1.41, 4.40, p=0.008) times greater probability of achieving at least a 50% reduction in nodule size, although effect sizes were heterogeneous (p=0.001). Once the study with the greatest likelihood of therapeutic benefit was removed, the remaining 4 studies were homogeneous (p=0.22) and the probability of achieving at least a 50% reduction in nodule size remained significant (p<0.05) with the fixed-effect model (RR 1.86, 95% CI: 1.01, 3.41).

Fixed-effect RR was also calculated by pooling the above 5 studies with another 5 which did not meet all the meta-analysis criteria (4 of the 5 additional studies were non-randomised). Pooled RRs were 1.92 (95% CI: 1.11, 3.32, p=0.019) and 2.24 (95% CI: 1.52, 3.29, p=0.001) for the random-effects and fixed-effect methods, respectively. Heterogeneity was noted (p=0.03). Reanalysis, after removing the study with the greatest likelihood of therapeutic benefit, revealed homogeneity (p=0.16) and a fixed-effect RR of 1.93 (95% CI: 1.30, 2.88, p=0.001) for achieving at least a 50% reduction in nodule size.

Authors’ conclusions
Systematic review of the available information with a modified, largely quantitative method of research synthesis disclosed that an initial trial of thyroid hormone suppression therapy leads to a clinically-significant (at least 50%) reduction of nodule size, or arrest of nodule growth in a subset of patients with benign solitary thyroid nodules. In fact, in addition to objective improvements due to decreasing nodule size, L-T4 suppression therapy may benefit patients by reducing perinodular thyroid volume. Consequently, both pressure symptoms and cosmetic complaints may improve.

CRD commentary
The authors of this review took an unusually broad approach to systematic review. In addition to the literature review and meta-analysis reported in this abstract, they also conducted a survey of opinions on appropriateness of L-T4 suppression, which was sent to endocrinology practitioners, and carried out a retrospective study of patients at a large clinical centre. These last two analyses are not reported here as they are additional to the systematic review. The methods used in this systematic review were poorly described, with much necessary information only included in the results section. In the systematic review, study inclusion criteria are broad in terms of study design, and validity is not assessed. The classification of studies used in the review is confusing. In the narrative synthesis, study design is not taken into account, which limits the usefulness of the reported results. The meta-analysis, which pooled five studies,
does seem appropriate as all pooled studies were RCTs and perhaps more confidence can be placed in these results. The assessment of causality seems to take into account the results of the survey of opinions and the retrospective study, neither of which are as strong in terms of level of evidence as the systematic review. The assessment of causality is, therefore, also of limited use as it dilutes the strong evidence in the systematic review with weaker forms of evidence. The literature search for the systematic review may have been inadequate as it seems that only MEDLINE was searched. Details of review methodology are given. The authors’ conclusions do, however, follow from the results of the meta-analysis.

**Implications of the review for practice and research**

**Practice:** The authors state that the therapeutic benefit of L-T4 suppression therapy on benign solitary thyroid nodules is limited to a subset of patients. There is no consensus on markers to predict response.

**Research:** The authors state that additional studies are warranted for the assessment of risks versus benefits of supraphysiological doses of L-T4, and to determine the optimal level of thyroid suppression, the dose needed to achieve this magnitude of reduction, the optimal length of the initial trial, and the conditions for the continuation of L-T4 thyroid suppression therapy, as well as for the identification of markers for patients most likely to respond to this therapy.

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