Suppressive therapy with levothyroxine for solitary thyroid nodules: a double-blind controlled clinical study and cumulative meta-analyses

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Authors' objectives
To assess the effect of suppressive doses of levothyroxine (T4) on the volume of benign solitary thyroid nodules (STN) and bone mineral density (BMD).

Searching
The authors searched the MEDLINE electronic database (January 1985 to December 1997). No further search details are reported.

Study selection
Study designs of evaluations included in the review
Prospective controlled clinical trials with a sufficient dose of T4 for TSH suppression. Additional study inclusion criteria were:

1. A minimum study period of 6 months.
2. STN volume monitored by ultrasonography.

Specific interventions included in the review
Levothyroxine (T4) varying in dose from 1.7 to 3 micrograms/kg per day for the intervention groups and placebo for the control groups.

Participants included in the review
Patients undergoing treatment for solitary thyroid nodules. Participants in the intervention group were: 18 males, 224 females, with a mean age of 42.5 years. Participants in the control group were: 13 males, 158 females, with a mean age of 42.7 years.

Outcomes assessed in the review
The capacity of T4 suppressive therapy to decrease a STN volume to less than 50% of its baseline value.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

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

Data extraction
The authors have not reported who, or how many of the reviewers, performed the data extraction. Data were extracted for the categories of study identification and year of reporting, the number of patients. This data were presented in two figures which also displayed the individual risk differences and 95% confidence intervals in a graphical format.

Methods of synthesis
How were the studies combined?
A cumulative meta-analysis for risk difference was performed using the Der Simonian and Laird method.
How were differences between studies investigated?
A Q-test was used to examine heterogeneity.

Results of the review
Seven RCTs were included in the review with 242 participants in the intervention group and 171 participants in the control group.

The proportion of patients with nodule volume decrease more than 50% after 1 year was higher in the T4 groups (mean 26.5%; range 14.3 to 39.1%) than in placebo or no-treatment groups (mean: 12.3%; range: 0 to 20%) in six of the seven trials, but reached statistical significance was achieved in only 2 of the trials. When all seven trials were included in the cumulative meta-analysis the observed risk difference was 16.7%, (95% CI: 5.8, 27.6%).

The data do not suggest any significant decrease in BMD after 1 year of treatment with suppressive doses of T4.

Authors’ conclusions
T4 treatment is associated with decreased nodule volume in 17% of patients and may inhibit growth in another 10%.

CRD commentary
The authors have clearly stated their research question and their inclusion and exclusion criteria. The literature search is limited to MEDLINE and may, therefore, have missed studies published outside the USA. The authors do not report whether there were any language restrictions or whether they sought unpublished data.

The data extraction is reported narratively in the text (one table reports only the results of one trial conducted by the authors) and the statistical analysis was appropriate. The quality of the included studies was not assessed, and the authors provide no information about how the articles were selected for inclusion or how many reviewers were involved in the data extraction. The authors did test for homogeneity.

The limitations of this review mean that the results should be viewed with some caution.

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

Research: The authors state that future studies are needed to identify properly those nodules that are more prone to volume reduction after suppressive treatment and that a 1-year trial of suppressive doses of T4 for pre-menopausal women and men without cardiovascular contra-indications could be offered.

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