Thyroid hormone therapy for obesity and nonthyroidal illnesses: a systematic review
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CRD summary
This review found insufficient data on the effectiveness or otherwise of thyroid hormone therapy for treatment of euthyroid adults who were obese or had non-thyroidal illnesses. The review was generally well-conducted and authors' cautious conclusions reflect the limitations of the evidence presented.

Authors' objectives
To evaluate the effectiveness and safety of thyroid hormone therapy in euthyroid patients who are obese and undergoing caloric deprivation and in euthyroid patients with acute or chronic non-thyroidal illnesses.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to December 2008 for relevant published articles. Previous publications, reviews and chapters were also searched.

Study selection
Randomised controlled trials (RCTs) or prospective observational studies that reported morbidity or mortality data for comparisons of thyroid hormone therapy were eligible for inclusion. Studies used either triiodothyronine (T3) or thyroxine (T4). Therapy needed to be administered for at least 24 hours and compared to placebo in euthyroid adults who were either obese and undergoing caloric deprivation (<1,000kcal per day) or diagnosed with acute or chronic non-thyroidal illnesses.

Studies were excluded for use of before-and during-treatment study designs or if they were of adults who received thyroid hormone therapy perioperatively for less than 24 hours. Also excluded were studies of patients with primary diagnoses of infertility, premenstrual syndrome, psychiatric disorders, hyperlipidaemia, chronic urticaria and angioedema, supraventricular tachycardia, bronchial asthma, hypertension or Raynaud's phenomenon.

Most studies assessed T3 in obese adults (as defined by study authors; further details were reported in the review). Other participants included those diagnosed with acute renal failure, burns, congestive heart failure or patients in intensive care units or who received coronary artery bypass grafts, which were mainly treated by T4. Patient age varied from 17 to 69 years. Studies included male and female participants. The synthetic thyroid hormones T3 and T4 were used at a range of doses in the included trials. For all included patients, serum thyroid stimulating hormone (TSH) and TSH response after T3 or T4 administration were evaluated.

Additional outcomes measured in obese patients were total weight loss, urinary 3-methylhistidine excretion, nitrogen balance, resting metabolic rate, and pulse rate arrival time. For patients with non-thyroidal illnesses, outcomes assessed were heart rate, cardiac output, systemic vascular resistance, morbidity and mortality.

Three reviewers reviewed studies for inclusion. Any disagreements were resolved by discussion.

Assessment of study quality
The reviewers assessed methodological quality using items that concerned study design, conduct and analysis as derived from the Agency for Healthcare Research and Quality. Items included: use of a concurrent control; representativeness of the target population; randomisation; blinding; and loss to follow-up (<20%). The overall quality of a study was based on the sum of the scores from the three different components. An overall quality score of 6 to 8 points indicated a good-quality study.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Three reviewers used standardised forms to extract data separately for the effects of T₃ and T₄ therapy (according to different doses and durations). For most outcomes, the ratio of the mean and its 95% confidence intervals (CIs) was calculated; for nitrogen balance, differences in means were used. Evidence of no clinical effect was defined as CIs between 0.9 and 1.1 (for nitrogen balance ±1g per day).

Methods of synthesis
The authors stated that pooling of data was considered inappropriate due to substantial clinical heterogeneity of the included studies. A vote-counting method was used and the results were presented in tables and graphs that accompanied the text.

Results of the review
Twenty-one studies (n=491) were included in the review including 13 RCTs. The effects of thyroid hormone therapy were evaluated in 14 studies of obese patients and seven studies of patients with non-thyroidal illnesses. Sample sizes in the included studies ranged from eight to 80 patients. T₃ therapy was evaluated in 14 studies of obese patients and one study of patients with burns. Of the six studies that evaluated T₄ therapy, five evaluated the effects in patients with non-thyroidal illnesses and one study evaluated T₂ therapy in obese patients. The methodological quality of one study was rated as excellent, 10 studies were rated as good quality and the remaining studies were rated as being of poor quality.

Obese patients (six RCTs, eight observational studies): During calorific deprivation, there were statistically significant decreases observed in basal serum TSH levels in (four of nine studies, dose of T₃ 25 to 28μg/70kg per day given for seven to 21 days) and serum T₄ levels (nine studies, dose as above). Consistent effects of T₃ and T₄ therapy on weight loss, leucine and ketone metabolism, oxygen consumption and cardiac outcomes were not established.

Patients with non-thyroidal illnesses (seven RCTs): Significant reductions were observed in two trials with a T₃ dose of 125μg/70kg per day (given for seven and 12 days) in serum basal TSH levels and serum free T₄ levels. There were no significant differences observed for heart rate, cardiac output and systemic vascular resistance. Mortality was assessed in four studies and in one study was significantly increased 3.3-fold with T₄ administered at 300μg/70kg per day for two days in patients with acute renal failure. Effects in cardiac, critically ill and burns patients were not established.

Authors' conclusions
Available data were inconclusive on the effectiveness of thyroid hormone therapy for treatment of adults who were obese or had non-thyroidal illnesses. There was some evidence that thyroid hormone therapy can result in subclinical hypothyroidism.

CRD commentary
The review addressed a clear question. Criteria for the inclusion of studies were stipulated. Unpublished studies were not eligible for inclusion, which meant that there was a risk of publication bias. The risk of language bias was unclear as the authors did not state whether any language restrictions were imposed. Steps to minimise reviewer error and bias were taken for some parts of the review process, but were not reported for assessment of methodological quality. The authors’ decision not to pool results appeared justified given the clinical heterogeneity of patients, doses of thyroid hormone therapy and follow-up, and heterogeneity in study designs. Data may have been summarised according to study design, as results of uncontrolled studies are subject to substantial biases. There was wide variation in study quality, which suffered from a number of methodological limitations that may have adversely affected the reliability of the results. The authors’ conclusions were based on the evidence presented and they correctly acknowledged limitations of the results given the small sizes of the studies in which comparisons were made. This was a generally well-conducted review and the authors’ cautious conclusions adequately reflect the limitations of the evidence.

Implications of the review for practice and research
Practice: The authors stated that thyroid hormone therapy should be discouraged in euthyroid patients given the insufficient data available to assess the effects of this therapy and the possibility of detrimental effects resulting from induced subclinical hypothyroidism.

Research: The authors stated that future large multicentre randomised placebo-controlled trials were necessary to prove any beneficial or detrimental effects of thyroid hormone therapy for induced fat loss in obese patients and reduced
relevant morbidity and mortality endpoints in euthyroid patients with non-thyroidal illnesses.

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