Clinical Evidence Concise

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Hyperthyroidism

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This clinical content conforms to AAFP criteria for evidence-based continuing medical CME Quiz on page 939.

What are the effects of drug treatments for primary hyperthyroidism? **LIKELY TO BE BENEFICIAL**

**Antithyroid Drugs (Carbimazole, Propyl-thiouracil, and Thiamazole)**

We found no randomized controlled trials (RCTs) comparing antithyroid drug treatments for primary hyperthyroidism, although there is consensus that treatment is beneficial. We found no RCTs comparing antithyroid drugs (carbimazole, propylthiouracil, or thiamazole) with each other. One systematic review found that fewer persons relapsed with 18 months of higher dose treatment than with six months; however, it found no significant difference for more than 18 months compared with 12 to 18 months of lower-dose treatment. One systematic review found that a similar number of persons relapsed to hyperthyroidism with antithyroid drugs alone (titration) and drugs plus thyroxine (block replace). One RCT found a similar proportion of persons who relapsed and who became euthyroid between high- and low-dose thiamazole. However, it found that adverse effects were lower with titration regimens. There have been concerns about bone marrow suppression, neutropenia, and agranulocytosis with antithyroid drugs. The doses of antithyroid treatments are generally used in practice.
Radioactive Iodine (in Persons Without Ophthalmopathy; May Increase Ophthal with Graves' Disease)

We found no RCTs comparing radioiodine with placebo in persons with hyperthyroidism. There is consensus that treatment is beneficial. Cohort studies found that radioiodine therapy for hyperthyroidism is associated with increased incidence of thyroid and extrathyroid cancers but not overall incidence of cancer. RCTs found that radioiodine treatment for hyperthyroidism may worsen ophthalmopathy in persons with Graves' disease compared with other treatment options. (Based on consensus because RCTs would be considered unethical.)

UNLIKELY TO BE BENEFICIAL

Adding Thyroxine to Antithyroid Drugs (Carbimazole, Propylthiouracil, and Thiamazole)

One systematic review found that a similar number of persons relapsed to hyperthyroidism with antithyroid drugs plus thyroxine (block replace) and antithyroid drugs alone. However, it found that adverse effects were higher with block replace regimens. Another systematic review found no significant difference in relapse between thyroxine and no treatment after antithyroid treatment.

What are the effects of surgical treatments for primary hyperthyroidism?

LIKELY TO BE BENEFICIAL

Thyroidectomy

We found no RCTs comparing surgery with placebo in persons with hyperthyroidism, and consensus that treatment is beneficial. One systematic review and subsequent RCT found that total thyroidectomy decreased hyperthyroidism and increased euthyroidism and hypothyroidism compared with subtotal thyroidectomy. However, another subsequent RCT found no significant difference among bilateral subtotal, unilateral total, and contralateral subtotal, and total thyroidectomy in Graves' ophthalmopathy. The systematic review and RCTs did not find sufficient evidence that adverse effects were worse with total or subtotal thyroidectomy. (Based on consensus that RCTs would be considered unethical.)

What are the effects of treatments for subclinical hyperthyroidism?

LIKELY TO BE BENEFICIAL

Any Antithyroid Treatment

One controlled clinical trial found that thyroid-stimulating hormone (TSH; also known as thyrotropin) was lower and bone mineral density was higher in women given radioiodine compared with no treatment in women with no compression symptoms from a nodular goiter.

DEFINITION

Hyperthyroidism is characterized by high levels of serum thyroxine (T4), high triiodothyronine (T3), or both, and low levels of T3. Subclinical hyperthyroidism is characterized by decreased levels of TSH (less than 0.1 mIU per L) but with levels of T4 and T (total T4: 5 to 11 mcg per dL [64 to 142 nmol per L]; total T3: 65.19 to 162.97 ng per dL [1.0 to 2.5 nmol per L], depending on assay type). The terms hyperthyroidism and thyrotoxicosis are used synonymously; however, they refer to slightly different conditions. Hyperthyroidism refers to overactivity of the thyroid gland leading to excessive production of thyroid hormones. Thyrotoxicosis refers to the clinical effects of unbound thyroid hormones, whether or not the thyroid gland is the primary source.

Secondary hyperthyroidism owing to pituitary adenomas, thyroiditis, iodine-induced treatment of children and pregnant or lactating women are not covered in this review. Hyperthyroidism can be caused by Graves' disease (diffusely enlarged thyroid gland on palpation, ophthalmopathy, and dermopathy), toxic multinodular goiter (thyrotoxicosis; uptake with multinodular goiter on palpation), or toxic adenoma (benign hyperthyroidism, usually due to an autonomous function of a thyroid adenoma)....

neoplasm presenting as a solitary thyroid nodule). We have not included treatment of Graves' ophthalmopathy in this review, although we do report on worsening of Grave radioiodine. We also have not included euthyroid sick syndrome (a condition for example, pneumonia, acute myocardial infarction, cancer, and depression; levels of TSH and T₃).

**Diagnosis**
The diagnosis of hyperthyroidism is established by a raised serum total or free T₃ level, and high radioiodine uptake in the thyroid gland with features of thyrotoxicosis. The usual symptoms are irritability, heat intolerance and excessive sweating, palpitations, weight loss with increased appetite, increased bowel frequency, and oligomenorrhea. Persons often have tachycardia, fine tremors, warm and moist skin, muscle weakness, and eyelid retraction or lag.

**Incidence and Prevalence**
Hyperthyroidism is more common in women than in men. One study (2,779 persons in the United Kingdom; median age 58 years; 20 years' follow-up) found an incidence of clinical hyperthyroidism of 0.8 per 1,000 women a year (95% confidence interval [CI], 0.5 to 1.4 per 1,000 women). This study reported that the incidence was negligible in men.

In areas with low iodine intake, the incidence of hyperthyroidism is higher than intake because suboptimal iodine intake induces nodular goiter, and by the time the autonomic, hyperthyroidism develops. In Denmark, with moderate iodine intake, the incidence of hyperthyroidism (defined as low levels of TSH) is 9.7 percent in Iceland with high iodine intake. The prevalence in the Danish study was 38.7 and two per 100,000 men a year.

**Etiology**
Smoking is a risk factor, with an increased risk of Graves' disease (odds ratio 3.5) and toxic nodular goiter (OR = 1.7; 95% CI, 1.1 to 2.5). In areas with high iodine intake, the major cause is Graves' disease, whereas nodular goiter is the major cause in areas with low intake because of a lack of iodine. A correlation between diabetes mellitus and thyroid dysfunction has been described. In a Scottish population with diabetes, the overall prevalence of thyroid disease was 13 percent; the prevalence was highest in women with type 1 diabetes (31 percent). As a result of screening, new thyroid disease was diagnosed in 7 percent of persons with diabetes (hyperthyroidism in 1 percent).

**Prognosis**
Clinical hyperthyroidism can be complicated by severe cardiovascular or neuropsychiatric illness requiring hospital admission or urgent treatment.

**MORtality**
One population-based 10-year cohort study of 1,191 persons at least 60 years mortality among persons who had a low initial TSH level. The excess in mortality was attributable to cardiovascular diseases. However, the persons in this study who had a low TSH level had a higher prevalence of other illnesses, and adjustment was done only for age and sex. We found another population-based study evaluating 3,888 persons with hyperthyroidism who were treated and stabilized, but an increased risk of dysrhythmias was found in persons treated for hyperthyroidism compared with the standard population (standardized incidence ratio = 2.71; 95% CI, 1.63 to 4.24).
ATRIAL FIBRILLATION IN PERSONS WITH OVERT HYPERTHYROIDISM

We found one cohort study evaluating the incidence of atrial fibrillation in persons with low serum TSH concentrations (0.1 mIU per L or less). It found that low TSH concentrations were associated with an increased risk of atrial fibrillation (diagnosed by electrocardiography) at 10 years (61 persons with low TSH and 1,576 persons with normal TSH; incidence of atrial fibrillation 28 per 1,000 person-years with low TSH values versus 11 per 1,000 person-years with normal TSH values; relative risk [as calculated by Clinical Evidence to 4.20]).

A population-based study including 40,628 persons diagnosed with hyperthyroidism in Denmark from 1977 to 1999 found that 8.3 percent were diagnosed with atrial fibrillation within 30 days from the date of diagnosis of hyperthyroidism.

QUALITY OF LIFE

The quality of life of persons with thyroid problems can be reduced in many ways if left untreated, and this can continue in the long term. In a long-term follow-up (179 persons, treated for 14 to 21 years before investigation), persons with Graves' disease had diminished vital and mental quality aspects even after years of treatment compared with a large Swedish reference population.

FRACTURE RATE AND BONE MINERAL DENSITY

Hip and spine bone mineral density levels can decrease if hyperthyroidism is untreated, and bone mineral density can increase to normal levels when treated. The risk of fracture is higher in persons with hyperthyroidism. Progression from subclinical to overt hyperthyroidism occurs in persons with nodular goiter but not in persons found by screening without other signs of disease.

A meta-analysis (search date 1996), based on data from screening studies, year 1.5 percent of women and 1.0 percent of men who had a low TSH level and normal free T4 or T3 levels developed an elevated free T4 or T3 level. Ophthalmopathy is a complication of hyperthyroidism. Treatment can be problematic and usually involves topical or external radiation of the eye muscles.

THYROID VOLUME AND THE NODULARITY OF THE GLAND INFLUENCE THE CURE RATE OF HYPERTHYROIDISM

In a controlled study of 124 persons with newly diagnosed hyperthyroidism, remission rates were calculated after treatment with a combined antithyroid drug plus T4 for about two years. Persons with Graves' disease who did not have a goiter or had a small goiter had a significantly higher remission rate compared with persons with Graves' disease who had a medium- or large-size multinodular goiter. Most persons with multinodular goiter had a relapse within the first year after stopping medication.

Author disclosure: Nothing to disclose.

EDITOR'S NOTE In the United States, carbimazole is not available, thiamazole is called methimazole, and thyrotropin is only available in the injectable form.

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REFERENCES


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