Clinical aspects, laboratory investigation, and treatment of hyperthyroidism and hypothyroidism are reviewed in light of recent information. Special circumstances, such as hyperthyroidism during pregnancy, Graves ophthalmopathy, iodine-induced hyperthyroidism, and subclinical hypothyroidism, are also considered.

Arch Intern Med. 2000;160:1067-1071

Hyperthyroidism and hypothyroidism are common disorders, especially in women. In the 20-year follow-up of the original Whickham survey, which involved several thousand randomly selected adults 18 years or older at enrollment, 0.8 per 1000 surviving women per year developed hyperthyroidism and 3.5 per 1000 per year developed spontaneous hypothyroidism.1 In 1995, the American Thyroid Association published guidelines for the management of these disorders.2 In this article, I provide an update of their management in light of more recent information.

HYPERTHYROIDISM

Although the terms hyperthyroidism and thyrotoxicosis are frequently used interchangeably, in the strictest sense hyperthyroidism refers to hyperfunction of the thyroid gland, whereas thyrotoxicosis refers to any state characterized by thyroid hormone excess, including ingestion of excess thyroid hormone and thyroiditis. This article, therefore, will be principally concerned with the management of hyperthyroidism caused by Graves disease or associated with toxic nodular goiter.

Clinical Considerations

A diagnosis of hyperthyroidism is suggested by the presence of a constellation of symptoms and signs. In patients older than 70 years, however, the classic clinical manifestations may be lacking and goiter may be absent.3 Instead, anorexia with wasting, atrial fibrillation, or congestive heart failure may be the predominant manifestations. Furthermore, the cause of hyperthyroidism will differ between young and elderly patients. In young patients Graves disease is almost always the cause, whereas in elderly patients toxic nodular goiter is also a common cause.

Laboratory Investigation

Measurement of serum thyrotropin, using at least a second-generation assay (detection limit, approximately 0.05 mIU/L), is the most sensitive test for screening for hyperthyroidism, a normal result virtually excluding hyperthyroidism, except in the rare instance where it is due to thyrotropin hypersecretion. An undetectable value is the hallmark of hyperthyroidism, but a low or sometimes undetectable value using a second-generation assay may occur in some healthy elderly patients, in patients with nonthyroid illness, or in patients taking a glucocorticoid or dopamine hydrochloride. In these circumstances, a third-generation assay (detection limit, approximately 0.005 mIU/L) will afford the necessary distinction, because in hyperthyroidism serum thyrotropin is still undetectable, whereas in the other conditions thyrotropin is almost always detectable, albeit low.4 Confirmation is sought in measurement of serum free...
thyroxine (FT₄). Occasionally, measurement of serum free triodo-
thyronine (FT₃) will be necessary in a patient with clinical manifesta-
tions of hyperthyroidism and an undetectable serum thyrotropin and normal serum FT₄ levels, defining the entity of triiodothyro-
nine toxicity.

In a patient with overt oph-
thalmopathy, no additional testing is required, because the patient cer-
tainly has Graves disease. However, in a woman of child-bearing age, it is essential to determine whether she is pregnant, because this will clearly influence the subsequent management (vide infra). In a patient without ophthal-
mopathy, measurement of thyroid radiiodine (¹³¹I) uptake should be per-
formed to establish the cause of thyrotoxicosis, ie, whether it is due to hyperthyroidism, in which case the uptake will be high, or to some other condition where thyroid hyperfunction is lacking, such as thyroid hormone ingestion or thy-
roiditis, in which case the uptake will be low. A ¹³¹I scintiscan may be
helpful in a patient with a nodular goiter, because it will serve to
define the functional characteristics of the gland.

Treatment

Hyperthyroidism may be treated with antithyroid drugs, ¹³¹I, or subtotal thyroidec-
tomy, the type of treatment being determined by the form of hyperthyroidism, the age of the pa-
tient, the size of the goiter, and the presence of coexisting conditions.

Antithyroid Drugs. Methimazole and propylthiouracil, the 2 drugs available in the United States, are
thioamides that are concentrated in thyroid tissue and inhibit hormone biosynthesis. In the United King-
dom and Europe, carbimazole is the commonly used drug; it is virtually completely converted to methima-
zele in vivo. In large doses, propyl-
thiouracil also inhibits the periph-
eral tissue conversion of thyroxine to triiodothyronine. Methimazole is
used in preference to propylthioura-
cil, because it has a longer inhibi-
tory effect on glandular hormone synthesis and can therefore be taken
as a single daily dose, improving compliance. Moreover, in doses up to 30 mg/d, methimazole may carry a
lower risk of agranulocytosis.

Treatment is usually initiated
with 30 mg of methimazole daily or 100 mg of propylthiouracil 3 times
daily. The patient should be alerted to the major, albeit rare (<1%), ad-
dverse effects of these drugs, including agranulocytosis, liver disease,
and a lupuslike syndrome that tend to occur within the first several months of therapy. Baseline labora-
tory data should include a leuko-
cyte count and liver function tests,
and monitoring of the leukocyte count may predict agranulocytosis.
The patient should be instructed to
notify the physician immediately if symptoms suggesting one of these
adverse reactions appear. With-
drawal of the drug will result in reso-
lution of the adverse reaction, but
both antithyroid drugs are contra-
indicated thereafter, and the pa-
tient will have to be treated with ¹³¹I or surgery. With minor adverse re-
actions, such as pruritus, the patient
can be switched to the alternate
agent.

After treatment has been initi-
ated, the patient should be fol-
lowed up at approximately monthly intervals and the antithyroid drug
dose reduced to a maintenance dose
as a euthyroid state is approached.
The speed with which this is at-
tained is determined by the sever-
ity of disease, goiter size, and dose of antithyroid drug. During this in-
terim period, a β-adrenergic recep-
tor blocking agent, such as pro-
pranolol hydrochloride, may be used to
control the hyperadrenergic mani-
festations, such as tremor, anxiety,
and palpitations, if these are trouble-
some, provided the patient does not
have obstructive pulmonary dis-
ease or other contraindications to its
use. Measurement of serum FT₄ rather than thyrotropin should be
used to monitor treatment, since se-
rum thyrotropin may remain unde-
tectable for many months after a eu-
thyroid state is restored. Thereafter,
the patient should be seen every 3
months if long-term therapy is
planned.

Long-term antithyroid drug
therapy is only appropriate for
Graves hyperthyroidism, since this
disorder has the potential to enter
a spontaneous remission. It is gen-
erally considered the treatment of
choice for young patients with a
small goiter or patients with active
ophthalmopathy (vide infra). Anti-
thyroid drugs are not indicated as
long-term therapy in toxic nodular
goiter, since hyperthyroidism does
not remit. The likelihood of a long-
term remission is positively influ-
cenced by the duration of antithy-
roid drug therapy, and a duration of
1 to 2 years is recommended, with
reported remission rates ranging
from 37% to 70%. Initial work had
suggested that adding levothyrox-
mine sodium to long-term antithy-
roid drug therapy in patients with
Graves disease resulted in a greater
likelihood of remission when the an-
tithyroid drug was withdrawn. The
rationale for this approach was that
the antithyroid drugs might also ex-
ert an immunosuppressive action,
and combination therapy permitted
the use of a higher dose of anti-
thyroid drug. However, several more
recent studies have failed to con-
firm these earlier findings. There are
no absolute predictors of outcome
following withdrawal of therapy, but
certain features, such as a small goi-
ter, favor remission, whereas oth-
ers, such as persistence of undetect-
able thyrotropin or high thyrotropin
receptor antibody titer, favor re-

Following withdrawal of long-
term therapy, the patient should
continue to be seen every 3 months
for the first year, since relapse is most
likely within this period. Thereaf-
ter, the patient should be seen an-
nually, since relapse may occur in
later years. Should relapse occur, the
patient should be treated with ¹³¹I or
subtotal thyroidectomy, although
antithyroid drug therapy could be re-
stituted if the patient wishes to
avoid ablative therapy.

Radiodine. ¹³¹I is the treatment of
choice for patients with Graves hy-
perthyroidism who relapse after
long-term antithyroid drug therapy,
for patients with severe thyroc-
cardiac disease, for most patients with
toxic multinodular or uninodular
goiter, and for patients with a ma-
jor adverse reaction to antithyroid
drugs. ¹³¹I therapy is absolutely con-
toxic nodular goiter, larger doses are required to achieve a euthyroid state. Pretreatment with propylthiouracil, but perhaps not methimazole, may reduce the one-dose cure rate of $^{131}$I through a putative radioprotective effect. Accordingly, methimazole should only be used before $^{131}$I treatment in patients with severe hyperthyroidism or a very large goiter to forestall exacerbation of hyperthyroidism as a result of the transient radiation thyroiditis. In these circumstances, the antithyroid drug is given to restore euthyroidism and then stopped 3 to 5 days before the administration of $^{131}$I.

In more than 80% of patients, hyperthyroidism will be cured and the goiter will decrease with a single dose of $^{131}$I. Since it may take several months for euthyroidism to be restored, patients with severe hyperthyroidism may require treatment with an antithyroid drug or a $\beta$-adrenergic receptor blocking agent during this interim period. Women of child-bearing age should be advised to postpone conception for at least 6 months after treatment with $^{131}$I.

Permanent hypothyroidism is the major complication of $^{131}$I therapy, its prevalence at 1 year being determined by the dose given. Thereafter, the prevalence rises at a rate of 2% to 3% per year. Accordingly, the patient should be followed up at monthly intervals initially and at increasing intervals once euthyroidism is restored, with monitoring of serum FT$_4$ and thyrotropin levels. Transient hypothyroidism may occur during the first 6 months after $^{131}$I therapy. When hypothyroidism emerges or persists for more than 6 months after $^{131}$I therapy, it is likely to be permanent, and levothyroxine treatment should be instituted. Other adverse effects of therapeutic doses of $^{131}$I for hyperthyroidism are minimal. Data from the Swedish Cancer Registry suggest a slight overall increase in cancer risk but no increase in risk for leukemia or lymphoma. Accordingly, since young tissue is more sensitive to ionizing radiation, $^{131}$I therapy is generally not considered as the initial treatment for children. There is no evidence for increased rates of teratogenesis with the doses of $^{131}$I used for hyperthyroidism.

**Subtotal Thyroidectomy.** Subtotal thyroidectomy is indicated in pregnant patients and children who have a major adverse reaction to propylthiouracil or methimazole. It is also appropriate therapy for patients with large goiters that extend retrosternally and lead to compressive manifestations and for patients with thyroid carcinoma complicating a toxic goiter. The patient must be restored to a euthyroid state before surgery to forestall postoperative thyrotropic crisis. This is accomplished with propylthiouracil or methimazole as described earlier, and in the 7 to 10 days before surgery for Graves hyperthyroidism, inorganic iodide is added to further reduce thyroid vascularity. Inorganic iodide should not be given to patients with toxic nodular goiter, because it may lead to exacerbation of hyperthyroidism. If the patient is unable to take propylthiouracil or methimazole, a $\beta$-adrenergic receptor blocking agent may be given in the 7 to 10 days before surgery along with inorganic iodide. The early complications of subtotal thyroidectomy, which include hypoparathyroidism and recurrent laryngeal nerve damage, are rare, but permanent hypothyroidism will eventually occur in a significant percentage of patients. Accordingly, the patient should be followed up in 1 month and then at increasing intervals thereafter, with monitoring of serum FT$_4$ and thyrotropin.

**Special Circumstances**

**Hyperthyroidism During Pregnancy.** Hyperthyroidism that complicates pregnancy may lead to increased fetal loss and should therefore be treated with antithyroid drugs, using the smallest dose that maintains a euthyroid state. Propylthiouracil is usually given in preference to methimazole because of its reported lower transplacental passage, although recent work does not corroborate this difference. Since pregnancy attenuates the course of Graves hyperthyroidism, probably as a result of the increased immune tolerance, the antithyroid drug can often be withdrawn in the third trimester but will usually have to be reinstituted in the early postpartum period. Breastfeeding can be continued, since propylthiouracil is poorly transferred into breast milk. Although methimazole is readily transferred into breast milk, a recent study suggests that thyroid function remains normal in breast-fed infants of lactating mothers taking a maintenance dose of methimazole. If subtotal thyroidectomy is indicated, it should be undertaken in the middle of the second trimester.

**Ophthalmopathy.** Clinically overt ophthalmopathy is seen in approximately 50% of patients with Graves disease and runs a course that may be independent of the hyperthyroid component. In patients with active ophthalmopathy, $^{131}$I therapy should be postponed or avoided, especially if they are cigarette smokers, because it may lead to worsening of the eye disease. If, for other reasons, $^{131}$I is the only reasonable therapeutic option, it should be administered as a fully ablative dose and followed by a 3-month course of glucocorticoid therapy, which will forestall aggravation of the eye disease.

**Iodine-Induced Hyperthyroidism (Jod-Basedow Disease).** Excess iodine has the potential to lead to hyperthyroidism in some patients with multinodular goiter or other states of relative thyroid autonomy. The iodine excess usually results from use of a radiographic contrast agent or...
a medication such as amiodarone, which is composed by weight of 37% iodine. Amiodarone may also cause thyrotoxicosis by producing thyroiditis.) Treatment involves the use of potassium perchlorate, a drug that blocks thyroid iodide transport, and propylthiouracil or methimazole to inhibit hormone biosynthesis.

**HYPOTHYROIDISM**

Hypothyroidism refers to any state that results in a deficiency of thyroid hormone, including hypothalamic or pituitary disease and generalized tissue resistance to thyroid hormone, and disorders that affect the thyroid gland directly. Since the former 2 forms of hypothyroidism are rare (<5%), this article will address the management of primary thyroid failure.

**Clinical Considerations**

The clinical manifestations of hypothyroidism emerge insidiously, are nonspecific, and often are attributed to aging. They include a general slowing down, mental depression, modest weight gain, intolerance of cold, constipation, vague aches and pains, dryness of the skin, and brittleness of the scalp hair. As the disorder becomes more fully established, the classic features of nonpitting edema (myxedema) of the skin, periorbital edema, hoarseness, sinus bradycardia, decrease in body temperature, and delayed relaxation of the deep tendon reflexes appear. Laboratory investigation may reveal a mild anemia, increased creatine phosphokinase concentrations, and an abnormal lipid profile with increased total and low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol concentrations. In the United States, primary thyroid failure is most often caused by chronic autoimmune thyroiditis, with or without goiter, or by prior surgical or 131I ablative therapy.

**Laboratory Investigation**

The laboratory hallmark of primary hypothyroidism is an increased serum thyrotropin concentration. Measurement of serum thyrotropin is the most sensitive test for detecting early thyroid failure, since an increase will antedate a decline of serum FT4 to subnormal by many months and sometimes years (subclinical hypothyroidism). Confirmation of clinical hypothyroidism is sought in a decreased serum FT4 level. In patients with no prior history of thyroid ablative therapy, the presence in serum of thyroperoxidase antibody will confirm chronic autoimmune thyroiditis as the cause. Because of its clinical or immunologic overlap with other autoimmune diseases, such as pernicious anemia and adrenal insufficiency, the physician should be on the alert for these in a patient with chronic autoimmune thyroiditis.

**Treatment**

With the exception of certain conditions that lead to self-limited hypothyroidism, treatment of hypothyroidism will be lifelong. Levothyroxine is the drug of choice, because its conversion to L-triiodothyronine will be appropriately regulated by the tissues. The mean dose of levothyroxine sodium required to restore euthyroidism (replacement dose) in adults is approximately 1.6 µg/kg daily. Neonates and children require larger replacement doses. In patients without evidence of preexisting coronary heart disease, treatment is initiated with 50 µg/d of levothyroxine sodium and in young patients can be initiated with a full replacement dose. Serum thyrotrpin, not FT4, is used to monitor replacement. Since it takes at least 4 weeks for thyrotropin to stabilize in response to levothyroxine, dose increases should not occur more frequently. Accordingly, the patient should be followed up at 1- to 2-month intervals initially, and the dose of levothyroxine should be increased gradually until the patient is clinically euthyroid, with the serum thyrotropin level in the normal range.

In patients with preexisting angina pectoris, treatment will aggravate angina in about one fifth and result in no change or improvement in the remainder. In some patients without preexisting angina, treatment will provoke the onset of angina, and some patients with coronary heart disease will experience a myocardial infarction at some time after initiation of therapy. Accordingly, for patients with angina pectoris, treatment should be initiated with 25 µg/d or less of levothyroxine sodium and the dose gradually increased at approximately 6-week intervals. Angina should be managed in the usual manner with a β-adrenergic blocking agent, but smaller-than-usual doses will be required because of its reduced clearance in the hypothyroid state. If angina cannot be controlled despite careful dosing with levothyroxine, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting should be undertaken, since mortality and major morbidity do not appear to be greater than in persons in the euthyroid state.

Ideally, levothyroxine should be taken on awakening at least 30 minutes before eating, because some fiber or bran products may impair absorption. Moreover, if the patient is taking other medications, such as iron, antacids, sucralfate, or bile acid sequestrants, ingestion of these drugs and levothyroxine should be separated by hours. Finally, the dose of levothyroxine may have to be increased when its metabolic disposition is accelerated by pregnancy or by drugs that induce hepatic microsomal mixed function oxygenases, such as rifampin, phenytoin, or carbamazepine. Once the patient has been restored to a euthyroid state, follow-up is required only at 6- to 12-month intervals with measurement of serum thyrotropin and FT4 levels. Overtreatment must be avoided, because thyroid hormone excess may lead to a decrease in bone mineral density in postmenopausal women and to adverse cardiac consequences.

**Special Circumstances: Subclinical Hypothyroidism**

Subclinical hypothyroidism refers to the state in which an increased serum thyrotropin level is accompanied by a normal serum FT4 level in an asymptomatic patient. Progression to overt hypothyroidism is likely...
if the serum thyrotropin level exceeds 10 mIU/L or if thyroid antibodies are present in high titer. Accordingly, if either of these findings is present, a case can be made for levothyroxine replacement. Moreover, some of these patients will have an abnormal serum lipid profile that may be corrected by replacement therapy.

Accepted for publication July 12, 1999.

Reprints: Kenneth A. Woeber, MD, FRCPE, UCSF/Mount Zion, Campus Box 1640, San Francisco, CA 94143-1640.

REFERENCES

12. Tuttle RM, Patience T, Budd S. Treatment with propylthiouracil before radioactive iodine therapy is associated with a higher treatment failure rate than therapy with radioactive iodine alone in Graves' disease. Thyroid. 1995;5:243-247.