Medical Management of Hyperthyroidism

a report by
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Hyperthyroidism mainly affects the female population, occurring in around 2% of women and 0.2% of men.[1] The majority of patients with hyperthyroidism have Graves' disease (GD) and, less often, solitary toxic nodule or toxic multinodular goiter. Other causes of hyperthyroidism are relatively rare and are summarized in *Table 1*. Establishing the accurate cause of hyperthyroidism is important as this influences treatment strategy and is usually achieved by a combination of clinical assessment, thyroid function tests—including thyroid autoimmune screening—and radionuclide scans with ^{123}I, ^{131}I, or ^{99m}Tc for difficult cases. This review will focus on the medical management of hyperthyroidism with special emphasis on GD.

Medical Management of Hyperthyroidism

Antithyroid drugs and radioactive iodine (RAI) remain the mainstay of medical treatment for patients with GD or toxic nodular goiter, although surgery still has a place in some cases. Patients with severe symptoms may require additional symptomatic treatment.

Graves' Disease

Antithyroid Drugs

Known as thionamides, this group of drugs includes propylthiouracil, carbimazole, and its active metabolite methimazole. These agents interfere with the action of thyroid peroxidase, thereby inhibiting thyroid hormone production. In addition, they have an immunosuppressive action, which helps in inducing disease remission, although the basis of this effect remains in debate.[2] Propylthiouracil is the only antithyroid agent that inhibits peripheral deiodination, thereby blocking the conversion of thyroxine to the active hormone tri-iodothyronine, although this effect does not seem to be clinically important.[3] Antithyroid drugs are given in two different ways: either as titration or as block and replace regime. In titration therapy, treatment is usually continued for 18–24 months, whereas most use the block and replace regimen for six months, as longer treatment is not associated with higher remission rate.[4] Using either program, however, the remission rate is disappointingly low, as half to two-thirds of patients relapse. Recurrence usually occurs within the first 6–12 months after stopping treatment but may occur years later.[5] Other regimens using low-dose antithyroid drugs in combination with thyroxine or antithyroid drugs alone for 12–18 months, followed by thyroxine treatment, have not shown any difference in relapse rate and therefore these regimes cannot be advocated.[4]

Side effects of antithyroid drugs (summarized in *Table 2*) are marginally higher with the block and replace compared with the titration regime, but advantages of the former are quicker control and less fluctuation of thyroid function, fewer hospital visits, and shorter period of treatment. The most serious complication is agranulocytosis and all patients are advised to report immediately to their physician if they develop a temperature, sore throat, or mouth ulcers while on treatment. Switching from one antithyroid agent to another is possible in cases of mild side effects, but agranulocytosis with any of the antithyroid drugs represents a contraindication to the further use of these agents.

Unfortunately, there is no reliable clinical marker that can predict relapse,[6] but patients with severe thyrotoxicosis, a large goiter, or extrathyroidal complications are less likely to enter remission.[3] Individuals with high thyroid-stimulating hormone (TSH) receptor antibodies post-treatment are more likely to relapse, but the converse is not true, and therefore antibody measurement has a limited role in planning treatment strategy.[7] Patients who relapse after antithyroid treatment are usually offered RAI treatment or surgery. A minority opt for long-term antithyroid drug therapy, which can effectively control thyroid function with no long-term side effects.[8]

Radioactive Iodine

Although this treatment is safe and effective, it is not yet routinely used as first-line therapy for GD in Europe. A significant number of patients are reluctant to undergo this treatment due to unfounded fear of radiation. Some patients are also concerned about permanent hypothyroidism post-RAI necessitating thyroid hormone replacement for life. RAI treatment carries a small risk of aggravating thyroid eye disease, particularly in smokers.[9] This risk of cancer after RAI has been addressed in a number of studies. A comprehensive study by Franklyn and colleagues showed no increase in general cancer rates post-RAI, but a small increase in thyroid and bowel cancer was documented.[10] More recent work in Finland failed to show an

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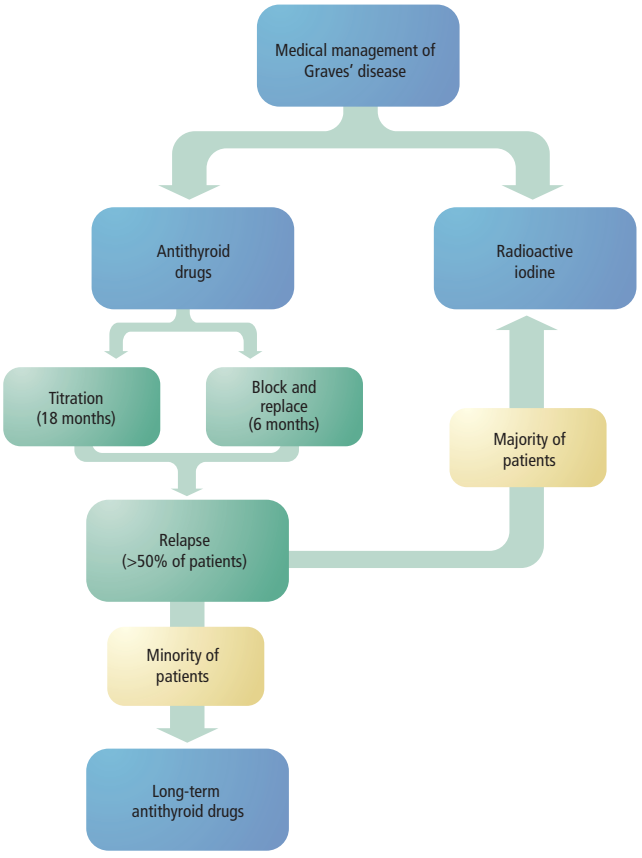
Figure 1: Medical Management of Graves' Disease



First-line treatment for Graves' disease in Europe is antithyroid drugs, although radioactive iodine can be considered initially after discussion with the patient. Antithyroid drugs are given for 6–18 months either as block and replace or titration regime. More than 50% of patients relapse after antithyroid drug treatment and most are subsequently treated with radioactive iodine.

increase in thyroid cancer after RAI but found a significant increase in stomach, kidney, and breast cancers.[11] However, the absolute risk was quite small and mainly found in older patients with nodular disease; therefore, the increased cancer incidence in this study could not be conclusively attributed to RAI treatment. An increase in cardiovascular risk after RAI treatment has also been suggested.[12–14] However, Metso and colleagues found that hypothyroidism post-RAI offered protection from cardiovascular disease, suggesting that hyperthyroidism *per se* rather than RAI treatment is responsible for the increased cardiovascular events in these patients.

Complex calculations to administer 'the optimal dose' of RAI are unnecessary and a fixed-dose approach is preferred as it simplifies treatment and has a similar success rate with no increase in side effects.[15] The failure rate of RAI treatment is less than 20%; therefore, this form of therapy should be considered initially and discussed with GD patients. Antithyroid drugs should not be given immediately before or after RAI as this may increase treatment failure rate.[16] Furthermore, the use of carbimazole or methimazole prior to RAI is preferred over the use of propylthiouracil, which is associated with higher RAI treatment failure, although this effect is perhaps smaller than previously thought.[16] Immediate side effects of RAI are rare and include transient nausea and pain over the thyroid gland 1–3 days after administration.[17] Thyroid storm may occur rarely after RAI, particularly in those with large goiters and severe hyperthyroidism.[18] *Figure 1* summarizes the medical management of GD.

Symptomatic Treatment

In a minority of patients with severe symptoms, non-selective β-adrenergic blocking agents can be used, which provide partial relief from symptoms such as palpitations, tremors, and anxiety without affecting thyroid hormone levels.[19] These agents can also be used by individuals intolerant to antithyroid drugs, while considering other forms of therapy including RAI or surgery.

Other Agents

Individuals who develop serious side effects secondary to antithyroid drugs

Table 1: Causes, Etiology, and Diagnosis of Hyperthyroidism

Cause of Hyperthyroidism	Frequency and Etiology	Diagnosis
Graves' disease	80%, thyroid-stimulating antibodies	Clinical examination (especially for ophthalmopathy) Thyroid autoantibodies Thyroid uptake scan in difficult cases
Toxic nodule or toxic multinodular goiter	15%, activating mutations in TSH receptor and Gsα protein	Clinical examination Thyroid uptake scan
Thyroiditis	2–4%, autoimmune-, viral-, or drug-related (amiodarone)	Clinical examination Thyroid uptake scan Erythrocyte sedimentation rate (ESR)
TSH-secreting tumor	<1%	Raised TSH and thyroid hormones Pituitary imaging α subunit assay
Exogenous thyroid hormone administration	Variable, excess ingestion of thyroid hormones	Clinical assessment
Hyperemesis, gravidarum, and choriocarcinoma	Rare, raised human chorionic gonadotropin (hCG)	Clinical assessment Absence of thyroid autoimmunity Known pregnancy Imaging of the pelvis
Struma ovarii	Rare, ectopic ovarian thyroid tissue	Clinical assessment Thyroid/pelvic uptake scan Imaging of the pelvis
Thyroid-hormone resistance	Rare, pituitary resistance to thyroid hormones	Clinical assessment Family history Must be differentiated from TSH-secreting pituitary adenoma

should be considered for RAI or surgery. In patients with severe hyperthyroidism who require medical treatment prior to RAI or surgery, lithium can be used, which may suppress thyroid hormone production,[20] whereas sodium perchlorate is usually reserved for life-threatening cases or severe amiodarone-induced thyrotoxicosis.[21–23] Lugol's iodine, or other forms of stable iodine, suppress thyroid hormone production temporarily and can be used prior to surgery with the added advantage of reducing the vascularity of the gland, making the operating procedure less hazardous.[24]

Toxic Nodule and Toxic Multinodular Goiter

Antithyroid drugs can be used to induce euthyroidism, but, unlike GD, these agents do not induce remission from the disease. Therefore, the best treatment strategy for these patients is RAI administration.[19] Surgery is reserved for subjects with large goiters causing compressive symptoms or to those with suspicious nodules.

Management of Special Cases

Hyperthyroidism in Pregnancy

Around one in 1,000 pregnancies is complicated by hyperthyroidism and the majority of cases are due to GD,[25–27] which should be differentiated from the gestational thyrotoxicosis seen in hyperemesis gravidarum, secondary to high human chorionic gonadotrophin levels. Patients who are diagnosed with GD during pregnancy, or those who have the disease and become pregnant, can be safely treated with antithyroid drugs, whereas RAI is clearly contraindicated. Both types of antithyroid drugs can be used, but propylthiouracil is preferred as there is a possible risk of congenital malformations with carbimazole, including aplasia cutis and choanal/esophageal atresia, although conclusive evidence for a causal relationship is still lacking.[28] The lowest dose of antithyroid drug should be used, keeping thyroid hormones in the upper normal range, or marginally above the normal range, and thyroid-stimulating hormones (TSH) in the lower normal range or mildly suppressed. The block and replace regime is contraindicated as it predisposes the fetus to hypothyroidism (thyroxine does not cross the placenta). As pregnancy progresses, GD frequently undergoes remission, necessitating a reduction in the dose of antithyroid drugs and even discontinuation of therapy altogether. The reason for this is related to the general immunosuppressive effect of pregnancy or a change in the ratio of TSH receptors stimulating and blocking antibodies. Therefore, regular monitoring of thyroid function during pregnancy is mandatory as frequent adjustments in the dose of antithyroid drugs are often required.

Although the risk of fetal and neonatal hyperthyroidism secondary to the transfer of thyroid-stimulating antibodies is generally small, maternal TSH receptor antibody status can provide helpful predictive information;[25,29] high levels of TSH receptor antibodies in the last trimester should alert the physician to the possibility of neonatal hyperthyroidism. TSH receptor antibody status should also be checked in euthyroid or hypothyroid GD patients previously treated with thyroidectomy or RAI, but not in those who are in remission after antithyroid drug treatment.

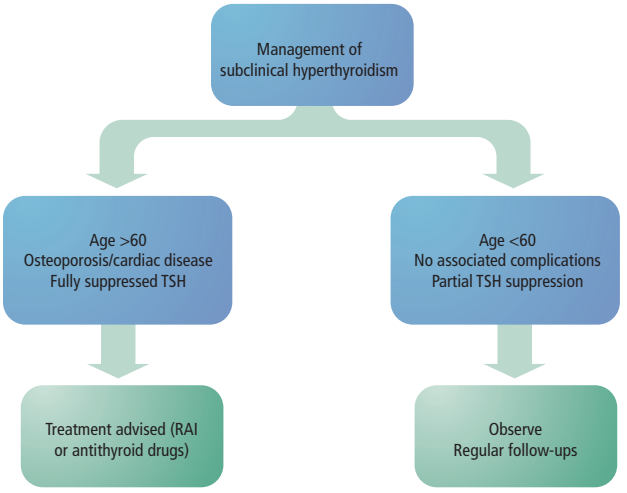
Hyperthyroidism in Children and Adolescents

The vast majority of children with hyperthyroidism will have GD with a strong female predominance. Similarly to the adult population, they can be treated with antithyroid drugs, but the remission rate is only 15–30%, being particularly low in pre-pubertal children.[30,31]

Table 2: Side Effects of Antithyroid Drugs

Common	Rare
Skin reactions	Agranulocytosis
Gastrointestinal symptoms	Hepatotoxicity
Arthralgia	Vasculitis
Dysguesia	Insulin autoimmune syndrome causing hypoglycemia

Figure 2: Management of Subclinical Hyperthyroidism



Older individuals with associated risk factors should be considered for treatment, particularly those with a fully suppressed thyroid-stimulating hormone (TSH).

The side effects of antithyroid drugs are generally increased in children,[32] and up to 0.5% develop serious complications. Although RAI has been successfully used in the pediatric population,[33] many endocrinologists avoid this form of treatment in the pre-pubertal period, as long-term safety data in this age group are limited. Therefore, one option in children with GD is antithyroid drug therapy initially with RAI in the post-pubertal period in those who relapse. Thyroidectomy should be considered in children who develop side effects following antithyroid drug treatment.

Amiodarone-induced Thyrotoxicosis

A full review of this topic can be found elsewhere[23] and only a brief discussion is provided here. Individuals with type 1 amiodarone-induced thyrotoxicosis (AIT) can be treated with high-dose antithyroid drugs (carbimazole 40–80mg daily); amiodarone withdrawal has no short-term effect and indeed may not be feasible. In difficult cases, sodium perchlorate (200mg qds) can be used and patients should be carefully monitored for the possible development of aplastic anemia. RAI is usually ineffective due to the low thyroid iodine uptake secondary to amiodarone therapy, but may be considered as a prophylactic treatment after stopping amiodarone in case re-introduction of this drug is essential.[34] Subjects with type 2 AIT should be treated with high-dose steroids, which can be tapered off during a period of 6–12 weeks.[23] In mixed type 1 and type 2 AIT, antithyroid drugs and carbimazole should be used in combination. Alternative treatments include lithium,[35] plasmapheresis,[36] and thyroidectomy in difficult cases.[37]

Subclinical Hyperthyroidism

A low serum TSH with normal thyroid hormone levels is termed subclinical

hyperthyroidism. The prevalence of this condition varies according to the cut-off of TSH used as well as to the iodine intake of the population studied and ranges from 0.6 to 16%.[38–40] The underlying etiology is the same as for patients with full-blown hyperthyroidism and therefore the majority will have GD or toxic goiter, the latter being particularly common in the elderly and in iodine-deficient areas.[40]

Untreated subclinical hyperthyroidism predisposes to osteoporosis and is also associated with cardiovascular complications, including atrial fibrillation and left ventricular hypertrophy.[40,41] Although the term subclinical hyperthyroidism suggests asymptomatic disease, individuals with this condition may experience thyrotoxic symptoms, which can affect their quality of life.[42,43] Only a limited number of studies have investigated the effects of treating this condition on the prevention of osteoporosis and cardiovascular complications, and therefore conclusive evidence for a beneficial effect of treatment is still lacking.

Guidelines drawn up by an expert panel recommend treatment for older individuals and those with risk factors acknowledging that treatment in these individuals is based on 'fair evidence' only.[44] Also, the decision to treat may be influenced by the degree of TSH suppression,[41] as the risk of complications in subjects with no history of heart disease or osteoporosis and partial TSH suppression (TSH >0.1) is probably small (see *Figure 2*).

RAI is frequently the first-line therapy for these patients, particularly as toxic goiter is a common underlying etiology, but antithyroid drugs can also be used. Future studies are needed to clarify the role of treating subclinical hyperthyroidism on prevention of osteoporosis and cardiovascular complications, particularly in younger patients and in those with marginal TSH suppression.

Conclusion

The mainstay of medical treatment for GD remains antithyroid drugs and RAI. The former is used as first-line therapy in Europe and results in disease remission in around 40% of patients. RAI is used in most GD patients who relapse after antithyroid drugs, but can also be considered as initial treatment, particularly in patients who find the high relapse rate after antithyroid drug treatment unacceptable. RAI should be considered as first-line treatment in subjects with a toxic nodule or toxic multinodular goiter, as antithyroid drug treatment does not induce remission in these cases. Although RAI has been used in children with no apparent long-term side effects, this form of treatment is best avoided in pre-pubertal children until more evidence of long-term safety becomes available. Treatment of individuals with subclinical hyperthyroidism should be considered in the older age group and in those at high risk of osteoporosis or cardiac disease. ■

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