HYPERTHYROIDISM: RELEVANT INVESTIGATIONS AND GUIDELINES FOR MANAGEMENT

ABSTRACT
Hyperthyroidism is a common endocrine disorder and has significant morbidity attached. Graves’ disease is the commonest cause of hyperthyroidism with female preponderance and it is important to differentiate it from subacute thyroiditis, as the former requires definitive therapy and latter is self-limiting. There are two basic investigations – biochemical confirmation of hyperthyroidism with T3, T4 & TSH and a thyroid scan. There are three treatment options – anti-thyroid medications, radioablation and surgery. Each of these modalities has its own merits and demerits. Successful treatment of hyperthyroidism is rewarding both to the treating physician and the patient.

INTRODUCTION
Thyrotoxicosis and hyperthyroidism in general practice are used interchangeably. Thyrotoxicosis is manifestation of thyroid hormone excess without distinguishing the source whereas hyperthyroidism should be used when there is sustained overproduction of hormone from the thyroid gland. The most common cause of thyrotoxicosis is Graves’ disease.

DIAGNOSIS
Clinical diagnosis of hyperthyroidism is quite simple and straightforward. It has to be suspected whenever a patient presents with unexplained weight loss, palpitations, heat intolerance, excessive diaphoresis, increased stool frequency, tremulousness and a swelling in the neck. Examination of the patient might give additional information like the nature of goitre and eye signs. A soft, diffuse goitre with symptoms over months favors Graves’ disease whereas a firm goitre with symptoms spanning weeks might point towards subacute thyroiditis. Clinical examination also picks up solitary nodule and toxic multinodular goitre. Eye involvement is more commonly seen in Graves’ disease.

Initial evaluation begins with estimation of T3, T4 and TSH. Biochemically toxicosis is confirmed by an elevated T3 and T4 with a suppressed TSH. Confirmation of the etiology is aided by performing a radioactive iodine uptake (RAIU) scan (Fig 1). RAIU scan is performed using 123I (upto 300 μCi) and uptake assessed at 6 and 24 hours. The normal values for the 24-hour radioiodine uptake range between 5% and 25%, and the average 6-hour uptake reference range is between 5% and 15%.

TREATMENT
Once a diagnosis of thyrotoxicosis is made the patient should be treated except in cases of thyroiditis. In this condition as there is destruction of the thyroid tissue and release of preformed hormones is occurring without increased new hormone formation, anti-thyroid drugs are of no value. There are various modalities available in managing a case of thyrotoxicosis (Fig 2). Ever since the introduction of anti-thyroid drugs, till date these have been the first line treatment options. Other modalities include radioiodine ablation and surgery.

Medical Management
This line of management has been used in two scenarios. First, as the initial line of treatment in Graves’ disease. Secondly, in preoperative preparation in ATN or toxic MNG.

Various options are available

ANTITHYROID DRUGS
Antithyroid drugs have been in use for treatment of hyperthyroidism for more than five decades now and they remain the cornerstone. Once a decision is taken to start ATD few questions need to be answered. Which drug to use? How long to treat? What are the chances of remission? Which regimen to use?

Mechanism of action.
These drugs are thionamides and have multiple actions. They actively concentrate in the thyroid follicles and inhibit thyroid hormone synthesis by interfering with thyroid peroxidase–mediated iodination of tyrosine residues in thyroglobulin. In addition PTU can block conversion of T4 to T3 in thyroid and peripheral tissues. ATD may also have clinically important immunosuppressive effects - serum concentrations of antithyrotropin-receptor antibodies decrease with time, induce apoptosis of intrathyroidal lymphocytes, increased number of circulating suppressor T cells
and a decreased number of helper T cells natural killer cells and activated intrathyroidal T cells.

Which drug to use?

Currently there are three drugs which are available – carbimazole, methimazole and propylthiouracil (PTU). In normalizing T3 and T4, both imazoles and PTU are equally effective. The other issue in initiating therapy is the safety profile of the two drugs. Various studies have shown that there are no significant differences in the minor side effects but when considering major adverse effects like hepatitis and agranulocytosis, imazoles appear to have a better safety profile.9 Next issue is regarding the compliance of the patient. Initially imazoles and PTU are given in multiple doses but once T3 & T4 normalize imazoles can be given in single dose while PTU needs to be continued in thrice daily dosage. Once daily dosage with imazoles have been shown to have better compliance. Finally, patients on ATD are known not to enter remission or relapse. These patients will require radio iodine treatment. PTU and not imazoles are shown to have radioresistant effects and the dose of radiiodine in patients who were treated with PTU require the dose of radiiodine to be increased by 25% to overcome this resistance.10 Considering the above issues it would be advisable to start the therapy with imazoles. Table 1 compares the two group of drugs.

How long to treat?

In treating patients with Graves’ disease one has to consider the natural course of the disease. About 20 percent of patients with mild hyperthyroidism who are treated with beta-adrenergic antagonists for one year will become clinically and biochemically euthyroid, but the frequency of permanent euthyroidism is unknown. Thirty to 40 percent of patients who are treated with an antithyroid drug remain euthyroid for prolonged periods after the drug is discontinued. Randomized studies found no differences between 12 vs. 24 months, 6 vs. 12 months, and 18 vs. 42 months. Therefore, treating for longer than 12–18 months is not likely to yield a higher remission rate compared with longer treatment periods.
Hyperthyroidism due to Graves’ disease

- Severe biochemical hyperthyroidism (e.g., markedly elevated serum T4 & T3), very large goitre (>4 times) or serum T3:T4 ratio > 20
  - Definitive therapy with radioiodine preferred in adults
- Mild or moderate hyperthyroidism, small or moderately enlarged thyroid; children or pregnant or lactating women; patients with severe eye disease
  - Primary antithyroid drug therapy should be considered
  - Normalization of thyroid function with antithyroid drugs before therapy in elderly patients and those with heart disease
    - Start Carbimazole, 30-40 mg per day, after discussing side effects and obtaining CBC and differential count; propylthiouracil preferred in pregnant women
    - Monitor thyroid function every 4-6 weeks until euthyroid.
    - Discontinue drug therapy after 12-18 months
    - Monitor thyroid function every 2 months for 6 months and then less frequently
      - Relapse
      - Define radioiodine therapy in adults
      - Second course of antithyroid drugs in children and adolescents
      - Monitor thyroid function annually indefinitely

Fig. 2: Algorithm for the Use of Antithyroid Drugs among Patients with Graves’ Disease. Adapted from: Cooper DS. N Engl J Med 2005;352:905-917

Table 1: Comparison between imazoles and propylthiouracil

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Imazoles</th>
<th>Propylthiouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half life</td>
<td>About 4 – 6 hours</td>
<td>45 minutes</td>
</tr>
<tr>
<td>Effect on 5’ iodinase</td>
<td>No effect</td>
<td>Blocks</td>
</tr>
<tr>
<td>Effectiveness (at equivalent doses)</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Time to achieve euthyroid</td>
<td>Weeks</td>
<td>Months</td>
</tr>
<tr>
<td>Dosing schedule</td>
<td>Once daily</td>
<td>Twice to thrice daily</td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>Dose dependant</td>
<td>Idiosyncratic</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Extremely rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Extremely rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Resistance to radioablation</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

What are the chances of remission?

Studies have shown that ATD facilitate induction of remission and as said above about 30-40% of patients who have received ATD maintain remission.1 Are there any predictors for remission? Though there are no sure predictors for remission, following set of patients have a better chance:

1. Female sex  
2. Age (> 40 yr)  
3. High TPO antibody positivity  
4. Small goitre  
5. Mild hyperthyroidism
6. TSH receptor antibody-negative

Which regimen to use?

The most common used regimen is the titration regimen where the ATD are started with higher dose and the titrated downwards when T3 & T4 have normalized. Of late few centres across the world have been practicing what has been termed block and replace regimen. The logic behind prescribing a full dose of a thionamide drug and adding T3 supplements to prevent the patient from becoming hypothyroid is twofold. First, a few patients are difficult to keep euthyroid with thionamide therapy alone, and a block-and-replace regimen can be helpful and requires fewer office visits. Second, the immunosuppressive action of the thionamides may be helpful in attenuating the natural history of the autoimmune thyroid diseases directly. Although some investigators found the relapse rate after the block-and-replace approach to be much reduced, others have found no difference.\(^{13}\)

Beta adrenergic drugs.

Drugs that block the response to catecholamines at the receptor site (e.g., propranolol) ameliorate some of the manifestations of thyrotoxicosis and are often used as adjuncts in management.\(^{14}\) Tremulousness, palpitations, excessive sweating, eyelid retraction, and heart rate decrease; effects are rapidly manifested and appear to be mediated largely through modulating the increased sensitivity to the sympathetic nervous system induced by excess thyroid hormone mentioned earlier. Propranolol (but not other β-adrenergic agents) may also weakly block the conversion of T4 to T3 via a mechanism independent of its effect on catecholamine signaling. Propranolol is the most widely used agent because it is relatively free from adverse effects and has a short half-life, allowing for easy control. It can be given orally in a dose of 20 to 60 mg every 6 or 8 hours.

Inorganic iodide.

Iodine may be administered directly or may be contained in contrast media used therapeutically. However, iodine is now rarely used as a sole therapy. The mechanism of action of iodine in relieving thyrotoxicosis differs from that of the thionamides. Although quantities of iodine in excess of several milligrams can acutely inhibit organic binding (acute Wolff-Chaikoff effect), this transient phenomenon probably does not contribute to the therapeutic effect. Instead, the major action of iodine is to inhibit hormone release. Administration of iodine increases glandular stores of organic iodine, but the beneficial effect of iodine is evident more quickly than the effects of even large doses of agents that inhibit hormone synthesis. In patients with Graves’ disease, iodine acutely retards the rate of secretion of T3, an effect that is rapidly lost when iodine is withdrawn. These features of iodine action provide both disadvantages and advantages. The enrichment of glandular organic iodine stores that occurs when this agent is given alone may retard the clinical response to subsequently administered thionamide, and the decrease in RAIU produced by iodine prevents the use of radiiodine as treatment for several weeks. Furthermore, if iodine is withdrawn, resumption of accelerated release of hormone from an enriched glandular hormone pool may exacerbate the disorder. Iodine still has a place in management of thyroid storm.

Potassium perchlorate.

Potassium perchlorate is a competitive inhibitor of iodide transport. Because of adverse effects, it rarely is used, except in iodine-induced—specifically amiodarone-induced—thyrotoxicosis. In that situation it has proven effective when combined with an ATD.

Lithium carbonate.

Lithium carbonate also inhibits thyroid hormone secretion, but, unlike iodine, it does not interfere with the accumulation of radioiodine. Lithium, 300 to 450 mg every 8 hours, is employed only to provide temporary control of thyrotoxicosis in patients who are allergic to both thionamide and iodide. It can also be used with patients who have had hepatitis on ATD as it doesn’t have any metabolism in liver. This is because the blocking effect is often lost with time. The goal is to maintain a serum lithium concentration of 1 mEq/L. Another short-term use for lithium has been as an adjunct to radiiodine therapy in that the drug slows the release of iodine from the thyroid.

Rituximab.

RTX is a monoclonal chimeric human/mouse antibody directed against the surface molecule CD20, which is expressed by pre-B cells but lost upon differentiation into plasma cells. The drug rapidly causes B-cell depletion in the circulation as well as in the target organs of autoimmune diseases, such as the thyroid. The mechanisms of action are thought to comprise (1) decrease of autoantibody production caused by depletion of B lymphocytes, thereby preventing the development of new autoantibody-producing plasma cells, (2) abrogation of B lymphocyte-mediated antigen presentation to T-helper cells, and (3) abrogation of cytokine production from B lymphocytes.

In a recent study it was shown that rituximab was able to maintain remission for more than a year.\(^{15}\) It is given as intravenous infusions in a dose of 375 mg/m² body surface area on day 1, 8, 15 and 22.

RADIOABLASTION

Introduced in the mid-1940s, \(^{131}\)I has become the most widely used therapy for hyperthyroidism, although international questionnaire studies show that geographic differences do exist. RAI is considered effective, safe, and relatively inexpensive. The isotope of choice is \(^{131}\)I. It is given orally (in a capsule or in water) and is absorbed rapidly and completely, after which it is concentrated, oxidized, and organified by follicular thyroid cells. The ionizing effect of β particles, with a path length of 1 to 2 mm, destroys the thyroid cells by an early inflammatory response, necrosis of follicular cells, and vascular occlusion. Subsequently chronic inflammation and fibrosis result in a decrease in thyroid size and an impaired ability to secrete thyroid hormone. Ultimately, almost all patients develop hypothyroidism following \(^{131}\)I.
Table 2: Advantages and disadvantages of different modalities of treatment for Graves’ disease

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Antithyroid drugs</td>
<td>Rapid correction of toxic symptoms</td>
<td>High recurrence rate</td>
</tr>
<tr>
<td></td>
<td>Can be given in pregnancy and lactation</td>
<td>Frequent monitoring required</td>
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<tr>
<td></td>
<td>No adverse effects in presence of ophthalmology</td>
<td>Common mild side effects</td>
</tr>
<tr>
<td></td>
<td>No interference with daily activities</td>
<td>Rare but potentially lethal side effects</td>
</tr>
<tr>
<td></td>
<td>No permanent hypothyroidism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Out patient therapy</td>
<td></td>
</tr>
<tr>
<td>Radioablation</td>
<td>Definitive treatment of hyperthyroidism</td>
<td>Potential radiation hazards</td>
</tr>
<tr>
<td></td>
<td>Outpatient therapy, rapidly performed</td>
<td>Worsening of thyroid eye disease</td>
</tr>
<tr>
<td></td>
<td>Rapid control of hyperthyroidism</td>
<td>Adherence with radiation regulations</td>
</tr>
<tr>
<td></td>
<td>in most</td>
<td>Decreasing efficacy with increasing goiter size</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td>May need to be repeated</td>
</tr>
<tr>
<td></td>
<td>Side effects mild, rare, and transient</td>
<td>Hypothyroidism eventually develops in most cases</td>
</tr>
<tr>
<td></td>
<td>Normalizes thyroid size within 1 year</td>
<td>Close contact with children and pregnant lady should be avoided</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraindicated in pregnancy and lactation</td>
</tr>
<tr>
<td>Surgery</td>
<td>Definitive treatment of hyperthyroidism</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>No radiation hazard</td>
<td>Inpatient therapy</td>
</tr>
<tr>
<td></td>
<td>Rapid normalization of thyroid dysfunction</td>
<td>Anesthesiologic risk</td>
</tr>
<tr>
<td></td>
<td>Definitive histology</td>
<td>Hypoparathyroidism (1%–2%)</td>
</tr>
<tr>
<td></td>
<td>Most effective in cases with pressure symptoms</td>
<td>Damage to the recurrent laryngeal nerve (1%–2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of bleeding, infection, unsatisfactory scarring</td>
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</table>

**Dose Calculation:** Ideally, the smallest possible $^{131}I$ dose that rapidly renders the patient euthyroid and does not lead to hypothyroidism should be administered. The dose of $^{131}I$ is determined most often according to the following algorithm:

$$\text{Dose (mCi)} = \frac{80 - 200 \text{ microCi} \times \text{g thyroid}}{24 \text{ hour radioiodine uptake}} \times \text{estimated thyroid gland weight (g)}$$

Using dose-calculation algorithms, typical activities are in the range of 5 to 15 mCi $^{131}I$, yielding an absorbed radiation dose of 50 to 100 Gy.

Because most patients become euthyroid and eventually develop hypothyroidism, and because determining an individualized dose is costly and time consuming, fixed activities of $^{131}I$ are widely used in many health care environments. The fact that a fixed dose simplifies and reduces cost of $^{131}I$ therapy and the lack of a significant difference in outcome between patients randomized to fixed and calculated $^{131}I$ doses favor the use of fixed doses. Typically a patient with Graves’ disease requires 5 – 15 mCi, 10 – 29 mCi in patients with toxic nodule and toxic MNG.

Not all patients respond to $^{131}I$ and these patients may require multiple doses at 6 – 12 monthly intervals. Patients who can be predicted to have poor response are 14:

1. Age (> 40 yr)
2. Female sex
3. Severe hyperthyroidism
4. Medium or large goiters (> 40 g, visible)
5. ATD pretreatment (especially with propylthiouracil)

**Surgery**

Although the oldest and most definitive treatment for Graves’ disease is surgery but it is now the least preferred treatment. The procedure of choice is near total thyroidectomy or more recently total thyroidectomy. There are few indications for surgery in Graves’ disease:

1. Patient preference.
2. Large goiters which are causing compressive symptoms or cosmetic reasons.
3. Graves’ disease super imposed on endemic goitre with multiple cold nodules.
4. Suspicion of malignancy.
5. Associated with ophthalmopathy.

**Pre operative preparation**

No date for surgery should be set until a normal metabolic state has been restored as thyroid storm might be precipitated in hyperthyroid status. This is achieved with ATD. Beta blockers are also added. Once eumetabolism is achieved SSki is added, 2 – 3 drops twice daily, for 7 – 10 days.

Table 2 compares the three modalities of treatment options available.

**Treatment of subacute thyroiditis**

Treatment is usually supportive and symptomatic.17 Pain is relieved with NSAIId. If pain persists despite maximal NSAID’s, prednisolone in a dose of 40 mg per day for 7 – 10 days followed...
by tapering over 1 – 2 weeks. In painless variant, symptoms are controlled with beta blockers.

REFERENCES