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(REVIEW ARTICLE)

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Ablation vs antithyroid drugs vs thyroidectomy in Graves' disease: A literature review

Vania Helsa Ardhani [1] and Hermawan Susanto [2,*]

[1] *Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[2] *Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia*.

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Abstract

Backgrounds: Graves' disease (GD) is the most common cause of hyperthyroidism, characterized by autoimmune stimulation of the thyroid gland. Long-term treatment options include antithyroid drugs (ATDs), radioactive iodine (RAI), and thyroidectomy, but there is no universal agreement on which treatment approach is best. Each modality has different benefits and limitations, making comparative evaluation is important to help guide individual treatment decisions.

Methods: This literature review summarizes evidence from clinical trials, meta-analyses, and observational studies evaluating the efficacy, recurrence rates, safety profiles, and long-term outcomes of antithyroid drugs (ATD), RAI, and thyroidectomy in the management of Graves disease. Databases such PubMed, SpringerLink, ScienceDirect, and references inside the extracted studies were used.

Results: ATDs remain the preferred first-line therapy in many regions due to their non-invasive approach and potential for remission, although 30–70% of patients relapse after discontinuation. Long-term low-dose therapy can reduce recurrence but requires monitoring for hepatotoxicity. RAI demonstrates high cure rates (>90%) and is cost-effective, but frequently results in permanent hypothyroidism and may worsen orbitopathy. Thyroidectomy provides the most definitive treatment, with a relapse rate about zero and rapid achievement of euthyroidism, although it carries risks such as recurrent laryngeal nerve injury and hypoparathyroidism. Comparative studies consistently show superior remission with surgery, followed by RAI, while ATDs have the highest recurrence.

Conclusions: Each treatment modality for GD offers distinct advantages and disadvantages. Thyroidectomy provides the most reliable cure, RAI offers effective and economical definitive therapy, and ATDs remain valuable first-line options. Optimal treatment selection should be individualized based on patient preference, comorbidities, and desired long-term outcomes.

Keywords: Graves' Disease; Hyperthyroidism; Antithyroid Drugs; Radioactive Iodine Therapy; Thyroidectomy

1 Introduction

Hyperthyroidism is a syndrome due to an inappropriately high synthesis and secretion of thyroid hormone (TH), resulting in high concentration of T3 and T4 in the blood [1, 2]. The most common causes are Graves disease (GD), toxic multinodular goiter, toxic adenoma and various forms of thyroiditis [2], but prevalence of GD is relatively high compared to other causes, which is around 60%-80% of all hyperthyroidism cases [3]. These findings may be affected by regional factors, especially iodine intake.

* Corresponding author: Hermawan Susanto

Graves disease (GD) is an organ-specific autoimmune disorder of the thyroid [4]. The main manifestation is the Merseburger triad that consists of thyrotoxicosis, diffuse goiter, and ophthalmopathy (orbitopathy) [3]. For the past 70 years, the therapeutic options available have remained unchanged [5]. The classical modalities for GD treatment consists of anti-thyroid drugs, surgery, and Radioactive Iodine (RAI) treatment, with each of the treatments having either limited efficacy or significant drawbacks [3, 5]. Such relapse may occur after stopping antithyroid drugs and the lack of functional thyroid tissue after treatment with radioiodine or surgery results in hypothyroidism, leading to a lifelong use of levothyroxine [5].

The fact that this disease is part of the autoimmune disease, GD is a relapse and remission disease. Relapsing cases are common which can lead to prolonged time of treatment and remission time cannot be determined [3]. Unfortunately, significant patient satisfaction with outcome and quality of life remains a concern [5]. Besides, there is still no consensus on how to choose the best treatment for these patients [6]. For these reasons, comparing the treatment is very important to see which treatment is suitable for each patient in this case.

2 Material and Methods

A search for this literature review was completed in Pubmed, ScienceDirect, and SpringerLink. Key recommendations were then extracted from the selected studies and organized into thematic categories. It extracted evidence from clinical trials, meta-analyses, and observational studies evaluating the efficacy, relapse rates, safety profiles, and long-term outcomes of ATDs, RAI, and thyroidectomy in the management of Grave Disease. Some studies are also taken from the references of the extracted studies.

3 Review Content

3.1 Grave's Disease

3.1.1 Pathophysiology

Graves' disease is associated with an abnormal number of autoreactive B cells that produce antibodies which bind to thyroid-stimulating hormone receptors (TSHR), overstimulating the thyroid and causing uncontrolled secretion of excessive thyroid hormone [5, 7]. TSHR autoantibodies (TRAbs) became the major disease-causing agents of GD. There are three categories of TRAbs, TSHR-stimulating (agonist) antibodies (TSAb), TSHR-blocking (antagonist) antibodies (TBAb), and neutral antibodies [7]. However, TSAbs are typically the most prevalent in a GD patient because TSAb-TSHR bond mimics the activity of TSH-TSHR bond, which induces thyroid growth and secretion of thyroid hormones (T4 and T3) [7], [8].

Grave disease (GD) clinically presents with endocrine ophthalmopathy (bulging eyes, known as proptosis), thyroid enlargement (goiter), hyperthyroidism-related symptoms, such as palpitations, tachycardia, weight loss even with normal eating habits, heat intolerance, tremor and fatigue [8, 9]. Endocrine ophthalmopathy is caused by additional antibodies in the eye muscles and surrounding connective tissue causing exophthalmos with protruding eyeballs [10]. Ophthalmopathy is highly presented in GD patients, about 30–50%, and the characteristic signs are proptosis (exophthalmos), tearing, and periorbital edema [8].

3.1.2 Epidemiology and Etiology

Population differences in iodine nutrition have a major role in the global prevalence of thyroid disease and autoimmune thyroid disorders, including Grave disease, occur more frequently in iodine-sufficient populations or areas with adequate iodine intake [11]. However, GD is thought to be influenced by a multitude of other risks, such as genetic (susceptibility), other autoimmune predispositions, the effect of environmental or endogenous factors, and sex (hormones) [5, 11]. The risk of GD is 3% for women and 0.5% for men, between 30 and 50 years of age [10]. Higher risk of women may be because of endocrinological changes during their lifetime, such as puberty and menopause, also additional transition during pregnancy with or without breastfeeding, which can influence their susceptibility to autoimmunity [12].

3.2 Treatment

3.2.1 Overview

The main treatments for GD are antithyroid drugs (ATDs), radioactive iodine (RAI) therapy or ablation, and in some cases, surgery (thyroidectomy) [7]. In United States (US), RAI is the most preferred therapy, while in Europe, Latin

America, and Asia, ATD is more of an option for the physician to avoid ablation and help some patients achieve long-term remission [11, 13]. The clinical shortcoming of ATD is the high possibility of relapse when therapy is discontinued. For this reason, in some cases, RAI or thyroid surgery is often recommended. However the convenience of ATD treatment cannot be denied and the fact that this will not permanently compromise the thyroid has made Long-term low-dose ATD treatment a rational choice [13].

3.2.2 Treatment Options

Anti-thyroid Drugs (ATDs)

ATDs, which are Methimazole (MMI) and Propylthiouracil (PTU), considered as the first-line treatment worldwide [3, 14]. MMI became the ATD of choice or first line of treatment due to the lower risk of hepatotoxicity compared to PTU. In country where methimazole is unavailable, carbimazole (CBZ) may be a choice because it acts as a prodrug that is quickly metabolized into MMI, with 10 mg of CBZ providing an effect comparable to about 6 mg of MMI [15].

Methimazole works by inhibiting thyroid peroxidase, thereby disrupting the iodination of tyrosine residues on thyroglobulin. This inhibition prevents the formation of thyroid hormones, ultimately reducing the synthesis of thyroxine (T4) and triiodothyronine (T3). Severe adverse reactions associated with MMI may include agranulocytosis, liver toxicity, and teratogenic effects. In any case side effects may arise, treatment consists of discontinuing the drug [16]. Because of its teratogenic potential, MMI should be avoided during early pregnancy, making PTU the preferred option for women in their first trimester [16]. PTU is frequently used as a second treatment option after MMI due to higher risk of hepatotoxicity, as well as in patients with a contraindication to MMI. Propylthiouracil acts by inhibiting thyroid peroxidase, thereby blocking the oxidation of iodine and its attachment to tyrosine residues, which prevents the formation of monoiodotyrosine and diiodotyrosine. PTU has not been found to be teratogenic and has an additional benefit of inhibiting peripheral conversion of T4 to the more potent T3, which makes PTU beneficial in acute treatment of thyroid storm [16, 17]. Liver injury is one of the most concerning adverse reactions associated with Propylthiouracil. It most commonly appears within the first six months of therapy, though it may develop at any time. The condition may improve with drug withdrawal, but some cases may require additional immunosuppressive management [16].

Both MMI and PTU administration routes are by oral. The use of ATD as primary therapy should be given for at least 12-18 months (standard course) and will be stopped as the concentrations TSH and TRAb reach normal value [3]. In cases where relapse happens with standard course treatment, long-term ATD treatment may be necessary. A study from Azizi, F. and Malboosbaf, R. [13] showed that long-term ATD treatment (≥24 months) showed a high remission rate and decreased relapse [14, 18] with low rates of complications, especially in adults. Despite all the advantages, ATDs have a high risk of recurrence. About 30%–70% of patients relapse into hyperthyroidism after discontinuation [5].

Radioactive Iodine Therapy (RAI) Followed by Levothyroxine

RAI is considered as a first-line definitive treatment unless ATDs are likely to achieve remission [19]. RAI may be an alternative for patients with risks of anti-thyroid drugs side effects and patients with comorbidities [3, 7]. The 2019 National Institute for Health and Care Excellence (NICE) guidelines also recommends radioiodine as the first line treatment for Graves Disease in the UK because of its superior cost-effectiveness and efficacy of radioiodine compared to ATDs [20]. In Australia, it is generally used as therapy for relapsed or persistent disease [21].

Radioiodine ablation with an iodine-131 (^{131}I) dose of 150 to 200 mcCi/g [17] works by inducing thyroid tissue necrosis and functional ablation following its uptake into the thyroid gland [19]. On average, it takes about 6 to 18 weeks before an euthyroid or hypothyroid state is achieved following radioactive iodine-131 treatment. Most patients achieve remission with a single dose. Those who require a second dose (around 15–25% of patients) are more likely to have higher TSH receptor antibody titres at diagnosis [21]. Due to hypothyroid state from this treatment, the patients have to consume a lifelong hormone replacement therapy, such as levothyroxine (LT4) [7, 18]. Additionally, RAI may worsen orbitopathy and involve exposure to radioactive material, making it unsuitable for young children, pregnant women, or individuals planning pregnancy [20].

Thyroidectomy (Total or Subtotal)

Subtotal and total thyroidectomy are the main types of surgery in hyperthyroidism cases [3]. Thyroidectomy has known to be as effective as ATDs and RAI in normalizing serum thyroid hormone levels within 6 weeks of therapy [22]. Thyroidectomy is indicated in patients with large goiters, those experiencing airway compression or dysphagia, and individuals with moderate to severe ophthalmopathy, as radioiodine may exacerbate ocular symptoms. It is also recommended for pregnant or breastfeeding women, for cases of persistent hyperthyroidism despite prior

radioablation or antithyroid drug therapy, and for patients who have thyroid nodules with suspicious or abnormal cytology on fine-needle aspiration (FNA) [23]. It can be an effective option in severe or persistent cases, but also requires skilled and high-volume surgeons [14]. Similar to RAI, it leads to hypothyroidism, so the post surgery patients required a lifelong hormone replacement therapy [7]. Additionally, it also carries the potential complications of recurrent laryngeal nerve injury [20].

3.3 Efficacy of Treatments: ATDs vs RAI vs Thyroidectomy

ATDs provide the possibility of achieving remission without requiring lifelong thyroid hormone replacement and may be the safest option because it's not an invasive procedure, but only around 45% of patients maintain remission in the long term. In contrast, definitive treatments (ablative with radioactive iodine and thyroidectomy) offer higher remission rates and eliminate the poor adherence of ATDs [20].

Radioiodine therapy remains highly effective, with cure rates exceeding 90%, and it can lower both overall and cardiovascular mortality when hypothyroidism is corrected promptly [24]. From a practical standpoint, radioiodine also offers the convenience of being administered in a single outpatient session and avoids the risks and resource demands associated with surgery.

A meta-analysis study from Zheng, X. et al [25], shows that hyperthyroid cure rates were higher for patients who underwent thyroidectomy than to those patients who received ATD treatment. In addition for Zheng, X. et al [25] s study, studies from Mu, L., et al [26] and Liu, Z.W. et al [27] state that total thyroidectomy is more effective than subtotal thyroidectomy at preventing recurrent hyperthyroidism in Graves disease. A previous meta-analysis of eight studies involving 1402 individuals with hyperthyroidism reported that thyroidectomy resulted in the lowest relapse rate (10%), compared with 15% for radioactive iodine therapy (RAI) and 52% for antithyroid drugs (ATD). Another meta-analysis similarly demonstrated that total thyroidectomy achieved a complete cure rate of 100% in treated patients [17]. However, both ablative with radioactive iodine and thyroidectomy approaches result in the need for permanent levothyroxine supplementation.

Another study, Veríssimo, D. et al [28], shows among 245 patients with Graves disease, antithyroid drugs were administered across 250 treatment cycles, yielding a cumulative remission rate of 41.7%. Relapses occurred predominantly within the early years: 50.9% within the first year, 76.3% within three years, and 98.3% by nine years. Treatment durations of 12–24 months were associated with improved remission outcomes and reduced relapse compared with longer courses. Radioiodine therapy (I-131) or RAI, used in 103 cycles, achieved an 82.5% remission rate with a relapse rate of 7.1%. Meanwhile, all 29 cases treated with thyroidectomy achieved complete remission without any recurrence, also confers the lowest mortality among definitive therapies and does not provoke Graves orbitopathy, unlike RAI which is associated primarily with de novo or worsening orbitopathy [29]. This phenomenon may be attributed to the sharp rise in TSH receptor antibody levels that occurs within the first six months following radioiodine therapy [30].

Another comparison, between RAI and thyroidectomy in a study from Davis, J. R., et al [31] with samples consisting of 121 patients receiving RAI and 96 patients who underwent thyroidectomy, showed that both treatment groups achieved an euthyroid state (71% vs 65%, $p = 0.39$). However, thyroidectomy patients reached euthyroid state faster (3 months) than patients who received RAI (9 months), $p < 0.001$ [18, 32].

Thyroidectomy offers the benefit of providing rapid and definitive management of Graves disease while avoiding the long-term risks associated with antithyroid drugs (ATDs) or radioiodine therapy (RAI). Nonetheless, it remains the least favored treatment option for hyperthyroidism. This preference is influenced by concerns over possible postoperative complications, including injury to the recurrent laryngeal nerve, hypoparathyroidism, permanent hypothyroidism, and visible neck scarring [29].

Based on a cost-utility analysis on the lifetime cost-effectiveness therapies for Graves disease in England and Australia, showed that radioiodine was the least expensive therapy than antithyroid drugs or surgery, but ATD is likely to be a cost-effective alternative, unlike the thyroidectomy [31].

4 Conclusion

Overall, thyroidectomy delivers the most definitive treatment with the lowest likelihood of recurrence, whereas RAI achieves fast remission and may be the least expensive therapy, but typically results in permanent hypothyroidism and may worsen orbitopathy. Antithyroid drugs remain the preferred initial therapy because they avoid surgery, though

they require close follow-up due to the risk of relapse and potential medication-related adverse effects. Ultimately, optimal treatment selection should be individualized based on patient preference and the desired long-term outcomes.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest.

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