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Review article

Endocrinologic management of hyperthyroidism and the impact on thyroid eye disease

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ABSTRACT

Thyroid eye disease (TED) is a complex inflammatory disease with a poorly understood etiopathogenesis. It is often, but not always, associated with Graves' disease and the endocrinologic manifestations of hyperthyroidism. Controversy exists regarding optimal treatment of hyperthyroidism especially with regard to the progression of orbitopathy. We review the literature examining the effectiveness of antithyroid drugs, radioactive iodine, and thyroidectomy for long-term endocrinologic management, and their effect on the progression of TED. In formulating an individualized treatment plan, considerations include rates of recurrent hyperthyroidism, treatment-associated complications, and effect on TED progression.

1. Introduction

Thyroid eye disease (TED) is an autoimmune condition with a reported incidence of 16/100,000 women and 2.9/100,000 men, and calculated prevalence of 0.25%. In a study of incident cases, nearly all were associated with Graves' disease (GD) compared with a small fraction of patients with Hashimoto's thyroiditis (3.3%). Endocrine manifestations were heterogeneous, the majority of patients being hyperthyroid (90%) compared with euthyroid (5.8%), and hypothyroid (0.8%).[1] In the cohort of hyperthyroid patients, 20.3% of patients were diagnosed with thyroid dysfunction at the time of TED diagnosis, 22.2% developed TED within 6 months of hyperthyroidism, and 18.5% developed hyperthyroidism 6 months following TED diagnosis. Thus, in the majority of patients there is a short latency period between systemic and orbital disease diagnosis.[1]

Major risk factors for the development of TED in patients with GD include female sex and smoking. Women have a 2.5-fold relative risk of developing TED compared with men, which is consistent with the female predominance in most autoimmune disorders.[2] The prevalence of smoking among TED patients is greater than those with GD and other thyroid diseases.[3] Smokers have an 8-fold relative risk of developing TED compared with nonsmokers.[2] Active cigarette smokers have an increased incidence of symptomatic TED, proptosis, and diplopia compared with patients who have never smoked. Former smokers experience the same risk as those patients who never smoked, highlighting the importance of smoking cessation in the management of TED patients.[4] Smoking has also been associated with increased severity of TED, although it is unclear if this risk is dependent on the number of cigarettes consumed.[3–5] Smoking appears to confer an increased risk of TED progression in patients undergoing radioactive iodine (RAI), and reduces the effectiveness of steroid prophylaxis in these patients.[6] In a recent study, active smokers underwent an increased rate of strabismus surgery compared with past smokers.[7] Other associations including ethnicity and TED development are less clear. Although a British study suggested that European patients with GD are more likely to develop TED than Asian patients, a subsequent study demonstrated comparable incidence rates in patients of Malay, Chinese, and Indian ethnicity with those of European patients.[8,9]

The close association between GD and onset of TED suggests a common or overlapping pathogenesis. However, the relationship between thyroid gland dysfunction and progression of TED is not entirely understood. The thyroid stimulating hormone receptor (TSHR) is a known autoantigen present on thyroid follicular cells, adipocytes, and lymphocytes. Levels of TSHR antibodies (TSHR ab) have been found to correlate to both TED severity and activity.[10] Circulating bone marrow derived stem cells called fibrocytes infiltrate the orbital and thyroid tissues and express TSHR and are increased in abundance in TED patients compared with healthy

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controls, suggesting that TSHR may also play a role in TED pathogenesis.[11]

The effect of thyroid treatment on the pathogenesis of TED is complex. Studies suggest that increased T3 levels are associated with a higher probability of developing or worsening of pre-existing TED, but these results have been inconsistent.[12–14] Others have shown that regardless of treatment modality, the development of hypothyroidism and increased TSH is associated with the onset or progression of TED.[13] Consequently, the overarching goal of thyroid treatment in TED patients is to achieve a euthyroid state, as patients who are dysthyroid are more likely to have severe TED.[15] However, the ideal modality of hyperthyroid treatment that safely achieves a euthyroid state with minimal to no progression of TED is not well established. Most commonly used treatment modalities include antithyroid drugs (ATDs), RAI, and surgical thyroidectomy. Herein, we review the available data regarding the effects these treatment modalities have on the development and progression of TED.

2. Medical therapy

The mainstay of medical therapy in the management of hyperthyroid GD patients with TED is ATDs. The majority of ATDs belong to the thionamide class and include propylthiouracil, methimazole, and carbimazole. The latter is only available in Europe and Asia, whereas the former two are generally used in the USA. Each function to reduce the production of thyroid hormone by inhibiting the coupling of iodothyronines.[16] ATDs may be used for short-term management in anticipation of RAI or surgical thyroidectomy, or for long-term thyroid suppression. There are two major strategies when using ATDs, the block–replace regimen and the titration regimen. In the former strategy, thyroid hormone production is functionally "blocked" by taking a high dose of the ATD which will completely suppress hormone production (dose will vary based on the ATD used), and then "replaced" by levothyroxine at a dose that results in a euthyroid state. This compares to the later strategy, titration, where the dose of the ATD is lowered to the minimum dose required to maintain a euthyroid state. A recent Cochrane review of ATD regimens concluded that the titration regimen has fewer adverse effects and is equally effective to the block–replace regimen for the management of hyperthyroidism; however none of the 26 studies commented on the progression of TED.[17]

In the early 1990s, medical therapy utilizing ATDs were prescribed as first-line therapy by the majority of physicians in Europe and Japan, and by approximately 30% of American Thyroid Association members.[18] Preferred practice methods shifted as the numbers of ATD prescriptions in the USA increased from 1991 to 2008, indicating a trend towards medical treatment of hyperthyroidism.[19] Common side effects that may occur with ATD use include rash, fever, urticaria, and arthralgia in up to 5% of patients.[16] Rare but major side effects of their use exist and may include agranulocytosis, hepatotoxicity, aplastic anemia, and vasculitis. Patients must be counseled regarding the signs and symptoms of these potentially severe side effects, because in many cases onset may be abrupt.

3. Radioactive iodine

RAI therapy utilizes the radioactive isotope ^{131}I to inhibit thyroid hormone production and causes progressive destruction of thyroid follicular cells.[16] It may be used as a first-line treatment for hyperthyroidism or in cases of recalcitrant hyperthyroidism following ATD treatment. Owing to the ability of the radioactive isotope to cross the placental barrier and its excretion in breast milk, pregnancy and breastfeeding are contraindications to RAI therapy.[20] Reduction of hyperthyroidism may take several months, requiring some patients to remain on ATD treatment following RAI until euthyroidism is reached. In some cases of persistent hyperthyroidism, a second treatment of RAI may be required.

RAI was the first-line therapy for GD in the USA in the early 1990s, and is now the preferred modality of treatment of uncomplicated GD for 45% of practitioners.[18,21] It is effective in treating hyperthyroidism and inducing hypothyroidism, with a reported relapse rate of approximately 21–28%.[22] Relapse rates as high as 48% have, however, been reported, and large goiter size is a risk factor for recurrent hyperthyroidism.[23] RAI is also able to effectively normalize thyroid size in nearly all treated patients.[24] However, RAI treatment is associated with an initial increase in TSHR ab levels, and by the end of a 5-year randomized study, patients treated with RAI had significantly higher TSHR ab levels at all stages after treatment.[12,25] Following RAI, patients should be closely monitored for hypothyroidism and adequately replaced with levothyroxine if present, as persistent hypothyroidism following RAI has been shown to worsen TED, as discussed below.

4. Thyroidectomy

Surgical thyroidectomy involves total or subtotal removal of the thyroid gland. It provides a rapid and effective method of treating hyperthyroidism in GD. Thyroidectomy is the preferred method of thyroid ablation in Europe and Asia, whereas RAI is preferred in the USA.[26] The rate of recurrent hyperthyroidism after subtotal thyroidectomy has been reported to be as high as 9%, which is significantly higher than after total thyroidectomy.[26,27] Potential complications of thyroidectomy include recurrent laryngeal nerve paralysis and hypoparathyroidism, which may be temporary or permanent. In a systematic review of both randomized and non-randomized studies, a higher rate of both temporary and permanent hypoparathyroidism was observed with total thyroidectomy than with subtotal thyroidectomy, but there was no difference in permanent recurrent laryngeal nerve palsy.[28]

5. Endocrine management and TED

A survey of members of The Endocrine Society, The American Thyroid Society, and The American Association of Clinical Endocrinologists conducted in 2011 revealed that ATDs were the slightly preferred modality for management in uncomplicated GD (53.9% of responders, with RAI being preferred by 45% of practitioners, and thyroidectomy preferred by 0.7%).[22] For patients with TED, however, ATDs were preferred by 62.9% of practitioners, thyroidectomy by 18.5%, RAI with steroids by 16.9%, and RAI without steroids by 1.9%.[22] This change in preferred practice pattern reflects the underlying concern of GD treatment on the onset or progression of TED.

It is generally accepted that medical therapy for Graves' hyperthyroidism is not associated with progression of orbitopathy.[29] Use of ATDs causes a more rapid reduction in TSHR ab levels than surgery or RAI, with up to 90% of patients achieving undetectable levels of TSHR ab by 3 years after treatment.[25] Because TSHR ab levels have been shown to correlate with disease severity, there is a theoretical benefit to a more expedient decrease in circulating TSHR ab levels.[12] There does not appear to be a dose-dependent effect, as a study comparing two different doses of methimazole did not demonstrate a difference in the proportion of patients whose orbitopathy improved or worsened during treatment.[30]

Several studies have compared the effect of RAI on TED to that of ATDs. In one randomized trial comparing methimazole to RAI with 4 years of follow-up, 39% of patients treated with RAI experienced worsening of new onset TED, compared with 21% of methimazole-treated patients.[31] In a subanalysis, however, RAI treatment was