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## Diagnosis and Management of Graves' Disease

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# Diagnosis and Management of Graves' Disease

## INTRODUCTION

Hyperthyroidism and thyrotoxicosis are common endocrine disorders caused by several distinct pathologic conditions of the thyroid gland or by overt or covert ingestion of thyroid hormone. The term *thyrotoxicosis* generally describes the clinical syndrome that results from elevated levels of thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) in the circulation, which may or may not originate from the thyroid gland. *Hyperthyroidism* refers to a state of increased production and release of thyroid hormone from the thyroid gland, which may not necessarily lead to thyrotoxicosis. The most common cause of hyperthyroidism, responsible for almost two thirds of cases, is Graves' disease, an autoimmune process of the thyroid gland that also exhibits extra-thyroidal manifestations.

Most of the symptoms and signs of thyrotoxicosis are independent of the underlying cause, but in many cases certain clinical features will point to the etiology. These include, most importantly, the size and shape of the thyroid gland and the presence of extra-thyroidal features of Graves' disease. Confirming the diagnosis biochemically is rarely difficult, and determining the underlying etiology is straightforward in most cases. The treatment of thyrotoxicosis is most commonly directed toward destruction of the thyroid gland. Consequently, most patients require lifelong replacement of thyroid hormone, and all patients require lifelong monitoring of thyroid function.

## PATHOPHYSIOLOGY

Graves' disease is an autoimmune disease of the thyroid gland and certain extra-thyroidal tissues, most notably the eyes and skin.<sup>1</sup> The hyperthyroidism manifested by these patients is caused by the production of autoantibodies against the thyroid-stimulating hormone (TSH) receptor, which mimic many of the effects of TSH on thyroid cells, thereby stimulating autonomous production of  $T_4$  and  $T_3$ . The alteration of immune function that leads to the production of these antibodies is complex, involving the interaction of B cells and T cells in the production of antibodies against several autoantigens in addition to the TSH receptor (**Figure 1**). TSH receptor

antibodies (TSHRAb) are detectable in the serum of almost all patients with Graves' disease and may be used clinically in making the diagnosis. Lymphocytic infiltrates commonly are seen in the thyroid gland of patients with Graves' disease. A considerable overlap in histologic appearance exists between Graves' disease and Hashimoto's disease, with only the presence of hypertrophic follicles differentiating the former from the latter. It is not surprising, then, that approximately 30% to 50% of patients with Graves' disease undergo spontaneous remission or develop hypothyroidism in the long term.<sup>1</sup> This may result from autoimmune destruction of the gland or from the production of TSH receptor–blocking antibodies, which also may be seen in Hashimoto's disease or autoimmune atrophic hypothyroidism.

The presence of lymphocytic infiltrates in the extraocular muscles of patients with Graves' ophthalmopathy (although not in the subcutaneous tissues of patients with dermatopathy) is evidence of the systemic nature of the autoimmune process. It is unclear what links these apparently distinct manifestations of the disease, although the search for common antigens continues. An association also exists between Graves' disease and other organ-specific autoimmune syndromes, including pernicious anemia, diabetes mellitus, vitiligo, Addison's disease, and myasthenia gravis. These associations support the hypothesis that autoimmunity is the result of a subtle but generalized immune system abnormality.

## CLINICAL MANIFESTATIONS

### SIGNS AND SYMPTOMS OF THYROTOXICOSIS

The signs and symptoms of thyrotoxicosis are listed in **Table 1**.

### EXTRATHYROIDAL MANIFESTATIONS

In addition to thyrotoxicosis, Graves' disease often is associated with extrathyroidal manifestations (ophthalmopathy, dermatopathy, acropachy) that are distinct components of a multiorgan autoimmune process. Although seen most commonly in association with thyrotoxicosis, these manifestations can occur independently, and their time course in relationship to the