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Review Article

Toxic Diffuse Goiter: A Review

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ABSTRACT

Graves' disease (GD) is an autoimmune condition defined by the presence of TSH receptor autoantibodies. It is the leading cause of hyperthyroidism worldwide. Though GD can occur at any age, it is more common in adults aged 20 to 50. Women are more likely to get GD. GD is predominantly a thyroid disease, but it also affects the heart, liver, muscle, eyes, and skin. Symptoms and indications are caused by hyperthyroidism or an underlying autoimmune condition. The most common symptoms include weight loss, weariness, heat sensitivity, tremor, and palpitations. Diffuse goiter occurs in the majority of younger people with thyrotoxicosis, but it is less common in elderly patients. Graves' ophthalmopathy and pretibial myxedema are extrathyroidal symptoms of GD caused by TSHR autoantibodies binding to TSHR found on fibroblasts, adipocytes, and T cells in extrathyroidal tissue. Antithyroid medications, radioiodine, and surgery are all options for treating GD.

INTRODUCTION

Graves' Disease (GD) is the leading cause of hyperthyroidism globally [1, 2]. It was first described by the German physician Carl Adolf von Basdow. It is an autoimmune condition defined by the presence of TSH receptor autoantibodies [3]. These autoantibodies trigger TSH receptors on thyroid cells, causing hypertrophy and hyperplasia, which result in thyroid gland enlargement. TSHR autoantibodies also lead to enhanced thyroid hormone production and release. GD is predominantly a thyroid disease, but it also affects the heart, liver, muscle, eyes, and skin. Graves' ophthalmopathy and pretibial myxedema are extrathyroidal symptoms of GD caused by TSHR autoantibodies binding to TSHR found on fibroblasts, adipocytes, and T cells in extrathyroidal tissue.

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EPIDEMIOLOGY: Graves' Disease accounts for 70-80% of hyperthyroidism cases in iodine-sufficient populations, but only 50% in iodine-deficient portions of the world [4, 5].

The annual incidence of GD is 20-50 per 100,000 population, and the lifetime risk of getting GD is 3% for women and 0.5% for males [6, 7]. Though GD can occur at any age, it is most common in adults aged 20 to 50 [8]. Caucasians have a higher incidence of GD than Asians, whereas black Africans have the lowest incidence [9, 10].

RISK FACTORS:

GENETIC FACTORS:

The genetic component is regarded as a significant risk factor for the development of GD. Twin studies suggest that the concordance rate of GD in monozygotic twins is between 0.29 and 0.36, and in dizygotic twins between 0.00 and 0.04 [11]. The GD tendency appears to be polygenic [12]. Recently, bioinformatics and next-generation sequencing (NGS)-based pan genomic investigations have discovered numerous predisposing genes linked to autoimmune disease, autoimmune thyroid disease, and Graves' disease [13]. Several genes contribute to the development of GD, including cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), TSH-R.

SEX:

Females are more likely to develop GD, which is typically associated with estrogen receptor ESR2 polymorphisms. The association between illness fluctuation and fluctuations in estrogen levels observed throughout pregnancy, the menstrual cycle, and menopause clarifies its function in disease pathogenesis [15].

ENVIRONMENTAL FACTORS:

Smoking harms the immune system and thyroid gland health. Current smoking doubles the chance of Graves' hyperthyroidism and triples the risk of developing Graves' ophthalmopathy (GO); however, the effect is dose dependent and more pronounced in women [16, 17, 18]. In contrast, four substantial studies demonstrate that smoking reduces the likelihood of hypothyroidism and autoimmune thyroid disorders (AITD) via lowering anti-TPO antibodies [19,20,21,22]. Three major studies have indicated that smoking reduces serum TSH levels while slightly increasing blood levels of FT3 and FT4, with the impact being dose dependent [18, 19, 20].

Pesticides and halogenated organochlorides have thyroid-disrupting characteristics and can change thyroid function by binding to thyroid hormone transport proteins [23].

STRESS:

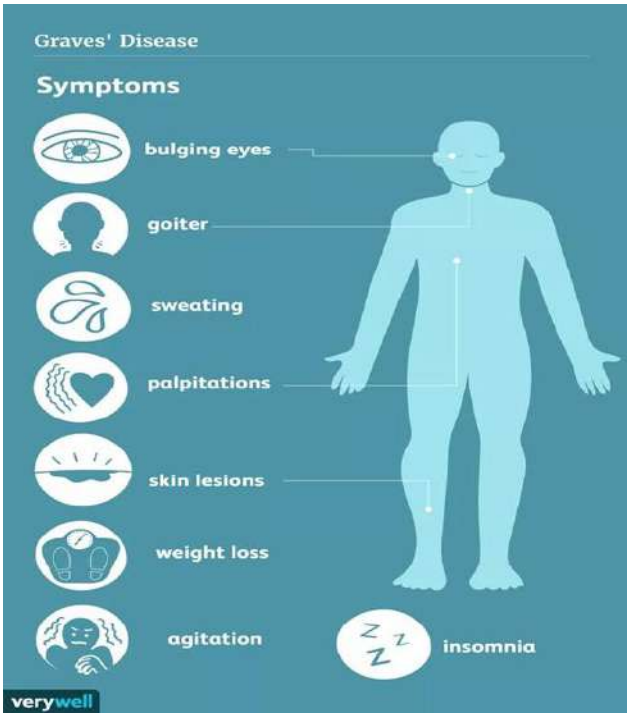
The link between stressful life events and the start of GD first recognized in 1825. Major stress has a favorable association with an elevated risk of GD. Stress, by regulating the cortisol pathway, can also affect the course of many other autoimmune illnesses [24].

PREGNANCY:

Pregnancy is associated with significant changes in thyroid structure and function. GD hyperthyroidism is more prevalent during early pregnancy and after childbirth. As pregnancy progresses, GD tends to improve, which could be related to increased maternal immunological tolerance or altered B and T cell activities [25]. Decreased immunological tolerance after delivery may lead to an increase in autoimmune thyroid disorders in the postpartum period.

VIRUSES: Many viruses impact the thyroid gland, and some of them are related with the existence of thyroid autoantibodies, such as congenital rubella, hepatitis C virus, and subacute thyroiditis. However, these do not appear to be related with the development or progression of GD [26]. However, the potential impact of common infections (such as Epstein-Barr virus and influenza virus) on the epigenetic features of a range of susceptibility genes is still a prominent theory for the etiology of GD.

CLINICAL FEATURES: Clinical signs of Graves' Disease are related to the age of initiation, severity, and duration of hyperthyroidism. Symptoms and indicators (Table 1) are the outcome of hyperthyroidism or an underlying autoimmune. Weight loss, weariness, heat intolerance, tremor, and palpitations are the most prevalent symptoms, affecting more than half of patients. Elderly people are more likely to appear with weight loss, decreased appetite, and heart symptoms. More than 10% of the elderly have atrial fibrillation, whereas it is unusual in younger patients. Goiter occurs in the majority of younger people with thyrotoxicosis, but it is less common in elderly patients. Goiter is most usually seen as diffuse thyroid enlargement, but nodular goiter can occasionally occur, particularly in persons living in iodine-deficient areas.



(Table 1) Major symptoms and physical sign of GD

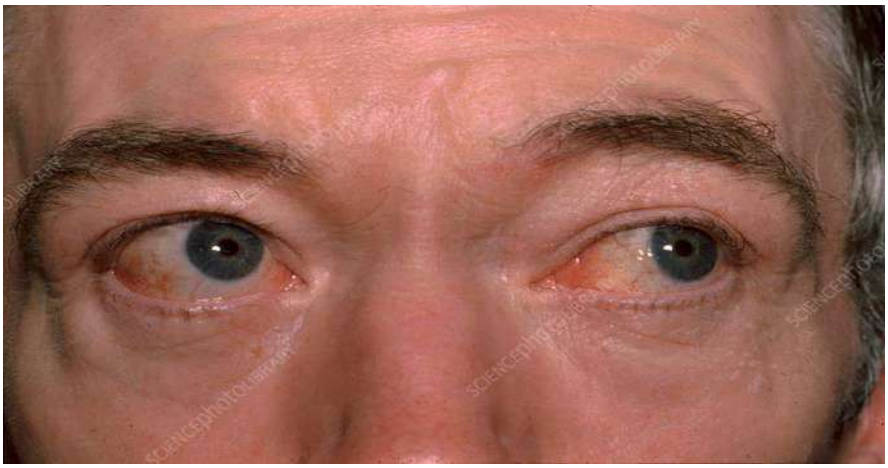


Figure 1

GRAVES ORBITOPATHY: In GD, the degree of orbital involvement varies as a result of thyroid autoimmunity, which occurs along with thyroid involvement. It frequently causes tears, congestion, redness, and irritation in the eyes.

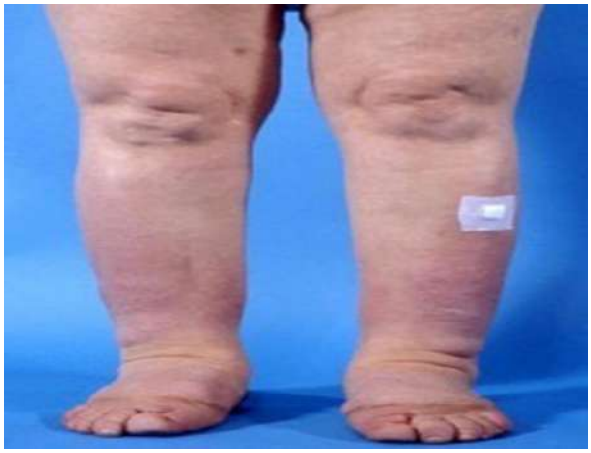


Figure 2

GRAVES DERMOPATHY: Graves' dermopathy occurs in 1-4% of all cases of GD. It is most commonly observed in the pretibial region, but it can also be found on the elbow, feet, toes, and in sites of trauma.

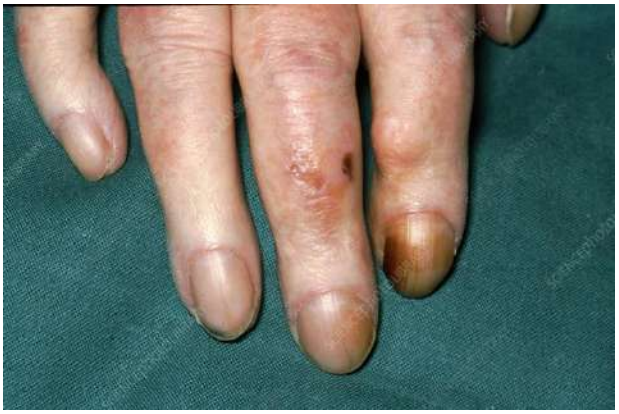


Figure 3

THYROID ACROPACHY: Acropachy is an extremely rare extrathyroidal symptom of GD. (Fig 3) Acropachy is defined as skin tightness, digital clubbing, small-joint pain, and soft tissue edema that progresses over months or years, resulting in gradual finger curvature and expansion [27].

DIAGNOSIS:

GRAVES HYPERTHYROIDISM: GD is diagnosed based on clinical thyrotoxicosis symptoms and biochemical abnormalities. If orbitopathy is present, the diagnosis of GD is certain; however, in the absence of orbitopathy, serum TSH Receptor Antibody (TRAb) and imaging may be necessary for the diagnosis.

THYROID HORMONE: Serum TSH measurement is the most sensitive and specific blood test used to diagnose suspected thyrotoxicosis. When serum TSH, free T4, and total T3 levels are measured at the beginning of the examination, diagnostic accuracy increases.

TSH RECEPTOR ANTIBODIES(TRAB): A hyperthyroid patient with a diffuse goiter and a recent history of orbitopathy is likely to have GD, therefore no further testing is required; however, a hyperthyroid patient with a diffuse goiter and no definitive orbitopathy may benefit from TRAb assessment to differentiate GD from alternative etiologies.

RADIOIODINE UPTAKE AND THYROID SCAN: RAIU calculates the percentage of injected RAI that is concentrated in thyroid tissue after a set time, typically 24 hours. Technetium uptake measurements use pertechnetate, which is trapped by the thyroid but not organized.

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