Hyperthyroidism: An Overview of the Disease and Current Treatment Approach

by

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at BRAC University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. I/We have acknowledged all main sources of help.

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Approval

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Ethics Statement

This project does not involve any kind of animal and human trial**.**

Abstract

Hyperthyroidism is a condition where the thyroid gland produces excessive amounts of thyroid hormone thyroxine and triiodothyronine, affecting approximately 0.2%–2.5% of the global adult population, with rates generally higher in iodine-sufficient areas and more prevalent in women. Hyperthyroidism prevalence in Bangladesh is generally lower than hypothyroidism, with studies indicating rates of approximately 0.86%-1.04% for overt hyperthyroidism and around 0.65%-1.73% for subclinical hyperthyroidism. The most common type is Graves' disease (GD), toxic multinodular goiter and toxic adenoma. Hyperthyroidism impacts many different systems of the body including the integument, musculoskeletal, immune, ophthalmic, reproductive, gastrointestinal and cardiovascular systems. Management options for hyperthyroidism include anti-thyroid medications, radioactive iodine, and surgery. Anti-thyroid medications are often used temporarily to treat thyrotoxicosis in preparation for more definitive treatment with radioactive iodine or surgery. The present review provides an overview of hyperthyroidism disease, epidemiology of the disease, causes of hyperthyroidism, highlighting the key considerations in diagnosis and current treatment of hyperthyroidism along with providing future directions for research and improved management of the disease.

Keywords: Hyperthyroidism; Thyroid hormone; Graves' disease; Subclinical hyperthyroidism; Autoimmune disease, Antithyroid drugs.

Dedication

Dedicated to my Supreme Creator, beloved parents, and my siblings who constantly support me on this journey. I also extend my sincere gratitude to a special person and to my dear friends for their constant encouragement, motivation, and support during the completion of this work.

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List of Acronyms

GD: Graves' Disease

GO: Graves' Orbitopathy

PTM: Pretibial Myxoedema

TSH: Thyroid Stimulating Hormone

TSHR: Thyroid Stimulating Hormone Receptor

T3: Triiodothyronine

T4: Thyroxine

RAI: Radioactive Iodine

Treg: Regulatory T Cells

IGF1: Insulin-like Growth Factor 1

MHC: Major Histocompatibility Complex

NSAIDs: Non-steroidal Anti-inflammatory Drugs

RCT: Randomized Controlled Trials

Chapter 1
Introduction

Chapter 1

1.1 Introduction

Hyperthyroidism is a condition of release of an excessive amount of thyroid hormone releasing from the thyroid gland. Thyrotoxicosis is a disease where the tissues are affected by too much thyroid hormone, leading to systemic symptoms (1). In the United States the prevalence of hyperthyroidism is 1.2% of which 0.5% have overt hyperthyroidism and 0.7% (2,3,4) have subclinical hyperthyroidism (1,5,6). The causes of hyperthyroidism, its clinical signs and diagnosis, and the various alternatives for treating the most prevalent forms of hyperthyroidism, including thyroid storm (TS), an uncommon but dangerous hyperthyroidism consequence. Subclinical hyperthyroidism affects approximately 0.7% to 1.4% of people worldwide, while overt cases range from 0.2% to 1.4% (7). Consider a continent for analysis of the rates as Asia, the people are mostly affected by it and mostly are women. The records said that in India (the urban cross-sectional survey) Hypothyroidism prevalence was ~10.95%, including ~8% subclinical cases; women were affected at ~15.9% vs. ~5% of men (8)**.** In another record, the Korean 2018 data said that Approximately 2.48 per 1,000 people (~0.25%) had hyperthyroidism, with greater incidence in older age groups and women (9) In Bangladesh the record is high, according to 925 participants in a community-based study conducted in Khulna area, the prevalence of thyroid disorders was 20.43% overall, divided into: Overt hyperthyroidism: 0.86% and Subclinical hyperthyroidism: 0.65% (10).

Graves' disease (GD) or von Basedow disease is a disease that is a result of an autoimmune disease and has three distinct characteristics. The initial one is an overproduction of thyroid hormones caused by an enlarged and hyperplastic thyroid (Graves hyperthyroidism). This imbalance may

lead to symptoms including the loss of weight, heart acceleration, heat intolerance, and anxiety increase (1,5). The second symptom is ocular abnormalities, also called Graves orbitopathy (GO) and is characterized by inflammation and swelling around the eyes. This usually causes the eyes to come out, the eyes to dry and develop irritation and in the worst scenario, the eye muscles will be involved leading to vision impairment (6). The third characteristic of Graves' disease is the localized alterations on the skin which is referred to as pretibial myxedema (PTM) where the skin becomes swollen, thickened and in some cases reddish brown particularly on the shins. These three symptoms are all indicative of the autoimmune nature of Graves' disease whereby the immune system of the body wrongly invades several tissues (7,8).

TSHR autoantibodies are agonists that prompt the thyroid cells to make too many thyroid hormones. It is a characteristic of the Graves' disease (GD) patients. Another type, that is worse and may be life-threatening, and is the so-called thyroid storm or faster. Some patients with Graves' hyperthyroidism have extrathyroidal complications due to the role of TSH receptor autoantibodies and TSHR-specific T cells on TSH receptors on non-thyroidal tissues, including fibroblasts and adipocytes, which constitute what is referred to as the Graves Triad which also includes Graves orbital pathology (GO) and pretibial myxoedema (PTM) (1,3,4). Even though imaging examinations indicate that GO tends to be more prevalent in a mild form among GD patients, approximately 5% of patients have clinically significant GO. This disorder is characterized by the deposition of glycosaminoglycans which result in edema and retro-orbital inflammation which involve extraocular muscles. Another complication is PTM which occurs due to the deposition of glycosaminoglycans in the dermis that leads to non-pitting edema which progresses gradually. In a few patients of GD, PTM may progress to severe deformity (5,6). The clinical presentation of

GD is diverse, which highlights the variability of the pathophysiology of the disease in a wide range of individuals (8,9, 10).

Although there has not been much of a change in GD treatment in recent years, the use of traditional remedies has advanced. Replacing partial thyroidectomy with complete thyroidectomy has prevented the upsetting incidents of recurrence after surgery, despite the fact that the majority of patients attempt to avoid surgery. Due to its intrinsic nature and the possibility of GO worsening following treatment, radioiodine therapy has also lost favor. However, the antithyroid medication methimazole (also known as carbimazole) has become increasingly popular, particularly in light of the liver toxicity concerns surrounding the antithyroid medication propylthiouracil. However, methimazole can also occasionally result in birth abnormalities and agranulocytosis. As a result, there is still room for improvement in the medical care of GD (7,8,9,10).

1.2 Causes

The most frequent causes of hyperthyroidism are the disease of Graves (GD), toxic multinodular goiters (TMNG), and toxic adenomas (TA). GD is an autoimmune disease, which is characterized by the immune system of the body attacking its own cells and subsequently losing immune tolerance and producing thyrotropin receptor antibodies (TRAb). These antibodies combine with the TSHRS on gland and produce too many thyroid hormones that are not needed in the body, and this results in hyperthyroidism (11).

The lumps or nodules in the thyroid gland initially do not create any problem or do not produce (11) too much hormone so they are called nontoxic nodular goiters, but with time they changed or developed themselves and started working without any control and produce extra hormone which cause hyperthyroidism (12). The condition occurs because of mutation of genes that helps to

stimulate the thyroid hormone and the thyroid hormone receptor, it is an auto immune (13) condition which means the immune system itself does not cause any trouble, it comes or inherits from the family or sporadic (randomly). Iodine deficiency and aging increased the risk of TAs and TMNGs (14).

Some other causes of hyperthyroidism are too much iodine intake or induce from dietary or supplements, TSH-producing pituitary tumors which is a rare brain tumor in the pituitary gland that induce thyroid hormone formation, trophoblastic and germ cell tumors, struma ovary is an uncommon condition. Here thyroid tissue grows in the ovary, thyroid cancer, silent or painless thyroidism which is happened during pregnancy or Factors that may be able to affect thyroid functions are pregnancy, some types of medications such as lithium or tyrosine kinase inhibitors, painful thyroiditis, thyroiditis, which is induced by amiodarone (a heart medication), and intake of exogenous thyroid hormone (1,14,15,16).

During pregnancy the hyperthyroidism developed is mostly overt hyperthyroidism. Most commonly it is caused by Graves' disease (GD) (14) or subacute thyroiditis in the post-partum (painful thyroiditis) period (after delivery, within one year postpartum). It is a temporary thyroid condition that can happen after having a baby. Thyrotoxicosis occurs which means the thyroid gland becomes over active and produce extra hormone, after that it becomes underactive and slower the production of hormone and goes to hypothyroidism (too much low production of hormone) and then go back to its normal state and recover the thyroid function (17). This is a self-fixed condition, so there is no need for antithyroid medicine and radioactive iodine (RAI) treatment. Those patients need to monitor after the condition and during the further pregnancy because there is a risk of it affecting them again. Painful thyroiditis, which may be brought about by an infection, is self-limiting. Beta blockers can be used to manage it to relieve thyrotoxicosis

symptoms. More serious situations can be treated with non-steroid anti-inflammatory drugs (NSAIDs) or steroids to down-regulate the inflammation and treat the pain (12, 13).

Thyroiditis is a result of amiodarone and may occur in two variants, i.e., type I and type II (14). Type I is found in patients of thyroid diseases that already have TMNG or GD. Anti-thyroid drugs and potassium perchlorate are used in the treatment of type I. Type II, however, is a destructive type of thyroiditis resulting due to amiodarone toxicity, which destroys the thyroid gland and gets released releasing the stored thyroid hormone. It is generally self-limiting and not necessarily the one requiring the discontinuation of amiodarone. Type II management can consist of steroids or even surgery in the worst-case scenario when the condition becomes refractory (14).

1.3 Clinical Symptoms

Thyroid hormones and especially T3 (triiodothyronine) possess extensive effects on different systems in the body adding to the clinical manifestations of hyperthyroidism. The effect of this results in weight loss, fatigue, and the inability to feel the heat. Skin changes are also habitual, such as, warm moist skin, loss of hair and in case of Graves' disease (GD), pretibial myxedema. Musculoskeletal manifestations could be such as weakness, augmented bone resorption, osteoporosis, and an augmented vulnerability to fracture. There are gastrointestinal problems that can be experienced, including difficulties in swallowing, frequent bowel movements and hunger (15). Hyperthyroidism is a condition that may result in cardiovascular problems, and it is imperative to identify it promptly and introduce the needed treatment (15). Hypertension (HTN) and tachycardia are two most common cardiovascular diseases in hyperthyroidism (16) T3 are important for maintaining homeostasis but under normal levels. When the amount of T3 is increased over normal levels it starts causing trouble and Thyroid hormones have a direct effect of

increasing cardiac contractility and, according to research (16, 18), they lead to dilation of arterioles subsequently lowering systemic vascular resistance and filling the arteries. The high levels of thyroid hormone also enhance the activity of the kidneys and renin is released, which triggers the angiotensin-aldosterone axis (19). Furthermore, endothelial nitric oxide synthase activity, which helps regulate blood pressure and vascular tone, is influenced by calcium/calmodulin-dependent kinase IV, one of the ion channels that thyroid hormone targets (16,20,21).

Hyperthyroidism may also be associated with various symptoms. More serious symptoms, including confusion or high metabolic rate, could turn into a thyrotoxic crisis. It is a critical condition that may be induced due to some events (22). Patients with hyperthyroidism in pregnancy need special care and careful evaluation but the proper disease management, medication like antithyroid drugs can decrease the rate of consequences and help to prevent the major complications (22).

1.4 Aim of the Review

The aim of the review is to give an overview of hyperthyroidism disease, epidemiology of the disease, causes of hyperthyroidism, highlighting the key considerations in diagnosis and current treatment of hyperthyroidism along with providing future directions for research and improving management of the disease.

Chapter 2

Methodology

Chapter 2

2.1 Methodology

This review article includes original published studies, systematic reviews, meta-analyses, and international health documentation, all contributing to an overall understanding of hyperthyroidism, prevalence of the disease, causes and current management of the disease. Standardized protocol and flexible methods have been followed to get access to relevant scholarly articles from reputable scientific databases, including PubMed, ScienceDirect, Google Scholar, MedLine, Embase, Cochrane Database and the World Health Organization (WHO) publications. The search included specific terms ("hyperthyroidism," "epidemiology of hyperthyroidism," "risk factors," "causes of hyperthyroidism," "treatment", "modalities," "management," "advanced treatment strategies of hyperthyroidism"), relying on applicable articles as well. This article includes publications from the beginning of hyperthyroidism research to the most current findings available in 2025, to provide historical depth and current relevance. Parameters for source selection criteria were based on scientific enforcement, citation frequency, relevance to the study's subtopics, and publication in peer-reviewed journals to ensure accuracy and utility. Publications that specifically deal with the classification of hypothyroidism (Example: primary hyperthyroidism, Grave's disease, overt and subclinical hyperthyroidism, secondary hyperthyroidism), signs and symptoms of the diseases, standard treatment of hyperthyroidism were prioritized. After a thorough search and analysis of relevant papers from reliable sources, relevant and updated information was gathered, and "Hyperthyroidism: An Overview of the Disease and Current Treatment Approach" was compiled and prepared. Finally, accurate citation has been used in order to give full attribution to the original author of the work and all the articles have been cited to provide additional details in the Reference list.

Chapter 3

Epidemiology and Causes of Hyperthyroidism

Chapter 3

3.1 Epidemiology

3.1.1 Grave's Hyperthyroidism

Around 2% of women and 0.2% (24,25) of males worldwide suffer from Grave's Disease (GD), a frequent condition with a female to male ratio of about 10:1 (24, 26, 27). According to epidemiological research, there are around 20–40 occurrences of GD for every 100,000 people annually. It is likely that most people with hyperthyroidism under 40 years of age have GD (28), as GD is most prevalent in adults between the ages of 20 and 50. As previously mentioned, the incidence of GD varies according to the methodologies used and the places studied. According to a Danish study, for instance, the incidence of GD as determined by cases documented using a highly sensitive diagnostic algorithm was higher than the frequency estimated at a referral center (29).

This discrepancy, which hinders studies conducted in hospitals and referral centers, is most likely due to referral bias (29). But in Denmark, individual prospective follow-up has made it possible to diagnose new instances of hyperthyroidism in detail, which has assisted in recording the true incidence of GD (30).

According to a study comparing East Jutland, Denmark, a region with low iodine intake, and Iceland, a country with abundant iodine intake, 84% of patients with newly diagnosed hyperthyroidism in Iceland had GD, while EJ only had 39% (31). However, this difference was not caused by a lower prevalence of GD. It is true that these two groups had comparable lifetime risks for GD. In Denmark, the age-standardized incidence reduced after almost 20 years of iodine supplementation but did not change with iodine intake (32). Monitoring prescriptions for

antithyroid medications, another method of gauging the prevalence of GD that ignores the rare usage of antithyroid medications in multinodular goiter, further supported this finding (33). A Chinese survey examined three groups with varying levels of iodine intake, from mild deficiency to high consumption. The survey showed that both of the entire incidence (1.2%) and occurrence (0.7%) of GD were consistent among these groups, which were also undergoing a 5-year follow-up (34,35). These findings provide credence to the idea that iodine levels alone cannot adequately explain the epidemiology of GD, in contrast to multinodular goiter. A genetic component to the autoimmune story (36) indicated by correlations (37) and other related characteristics (38), along with new findings of ethnic differences in the prevalence of GD (39,40), should be explored.

Box 1 | Risk factors for GO and PTM

Graves' hyperthyroidism may develop as a result of any of the risk factors listed below. However, it is important to consider other unique risk factors that seem to predispose people to pretibial myxoedema (PTM) and Graves' orbitopathy (GO).

High TSHR autoantibody titers

The most severe cases of Graves' orbitopathy (GO) are more complicated in patients with the highest degree of autoantibodies in the TSHR, and in some cases in patients with pretibial myxedema (PTM). This encompasses patients with ocular complications that are threatening to vision, e.g., dysthyroid optic neuropathy or corneal breakdown. The intensity of GO is often proportional to the levels of expression of these autoantibodies (41). This association is more likely in those who make their presentations with the "Graves trifecta" or thyroid, ocular and skin manifestations.

Smoking

Many research investigations indicate that smoking enhances the probability of ocular participation in Graves' disease. It is unclear if inflammation, tissue hypoxia, or stress are to blame for this (42-44).

Radioiodine

GO is made worse by radioiodine (45), which may be temporary and may be caused by the increase in autoimmunity that follows radioiodine therapy, as seen by higher levels of TSHR autoantibodies (46).

Trauma

Research has demonstrated that physical trauma to the orbit contributes to the development and worsening of PTM and GO-related retro-orbital inflammation (47,48,49). In fact, it has been demonstrated that surgical debridement of PTM worsens the illness and is an inappropriate course of treatment.

Anatomy

There is little information on the role that orbital structure has in Graves orbitopathy (GO), however, it is proposed that shorter orbits can be more susceptible to the development of restrictive eye disease (50). The degree of the proptosis may be between absent and severe, and the outcomes of orbital decompression surgery point to the fact that bone constraint is a major factor in the severity of the case.

3.1.2 Graves’ orbitopathy and pretibial myxoedema

According to the European Group on Graves' Orbitopathy (EUGOGO), the prevalence of Graves' Orbitopathy (GO) is 10 cases per 10,000 people in Europe and 16 cases per 10,000 people in Japan (51, 52). Therefore, although many people have less apparent disease, approximately 5% of GD patients exhibit unmistakable indications of GO. Additionally, GO symptoms may emerge prior to, during, or following hyperthyroidism. Furthermore, almost 50% of these patients require decompression surgery after developing severe GO with optic neuropathy, which typically

manifests as impaired vision and restricted upward gaze (53). PTM with GO is an even more uncommon GD (51) consequence, with a reported frequency of 0.15 per 10,000 people.

3.2 Risk factors

The occurrence of GD is a result of genetic and environmental interactions where genetic predisposition to the disease is enhanced by environmental triggers, including the microbiota, epigenetics, and similar. All these are aspects that trigger an immunological process which becomes a cause of the disease. Although genetic research has demonstrated that concordance is high, GD is most probable to be acquired when the accumulated influence of such genetic and environmental factors surpasses a set level.

3.2.1 Genetic susceptibility

Graves' disease has a strong genetic component in its etiology. Twin studies have established the presence of a gene susceptibility to GD in that identical twins have a higher incidence rate for the condition than non-identical twins. Family studies provide further support for this as siblings of GD patients have an increased chance of developing the disease ($\lambda s = 11.6$) (54-56).

There has been a well-established association between heightened vulnerability. For example, white people with GD have a higher frequency of the HLADR3 and DQA10501 haplotypes than their controls (57, 58). However, the HLA region only accounts for about 5% of the total genetic susceptibility to GD, by only increasing the risk by 2-4 times (59, 60). Other genetic loci also seem to be involved in the risk of GD, including some of the immune genes, such as FOXP3, PTPN22, CD25 (61), CD40 (70) and CTLA4. These genes are involved in immune regulation and T cell signaling but have a somewhat small individual impact as risk ratios are usually <2.0 (62).

Gene-environment interactions may, however, be more important (63). Notably, pronounced polymorphic variants in TG and TSHR have been linked as genes uniquely linked to GD, a thyroid-specific GD genetic susceptibility (64). TSHR expression in the thymus, the site for autoreactive T cell deletion, is also important to understand GD pathophysiology (65). In patients who are predisposed to GD, expression of TSHR in the thymus may offer important clues as to how or why immune tolerance develops, or fails to develop (66). If the immune system cannot kill TSHR specific T cells, these T cells may play a role in the development of GD.

There is a lot of speculation in the literature, but no evidence of a specific genetic risk associated with GO has been published. Instead, it suggests that some patients have increased retro-orbital inflammation due to environmental or structural variables and the strength of their immune response (66, 67) (Box 1).

3.2.2 Sex

Women are 5-10 times as likely than men to have GD. GD does not become less common after menopause, despite becoming more common after puberty. Instead of sex steroids. There has been conflicting evidence, nevertheless, linking FOXP3 (found at Xp11.23) to autoimmune thyroid disease (68,69). Although this link has not been shown, the phenomenon of improper X chromosome inactivation, that is, the silencing of one X chromosome has also been frequently mentioned in GD, highlighting the X chromosome's involvement even more (70-73).

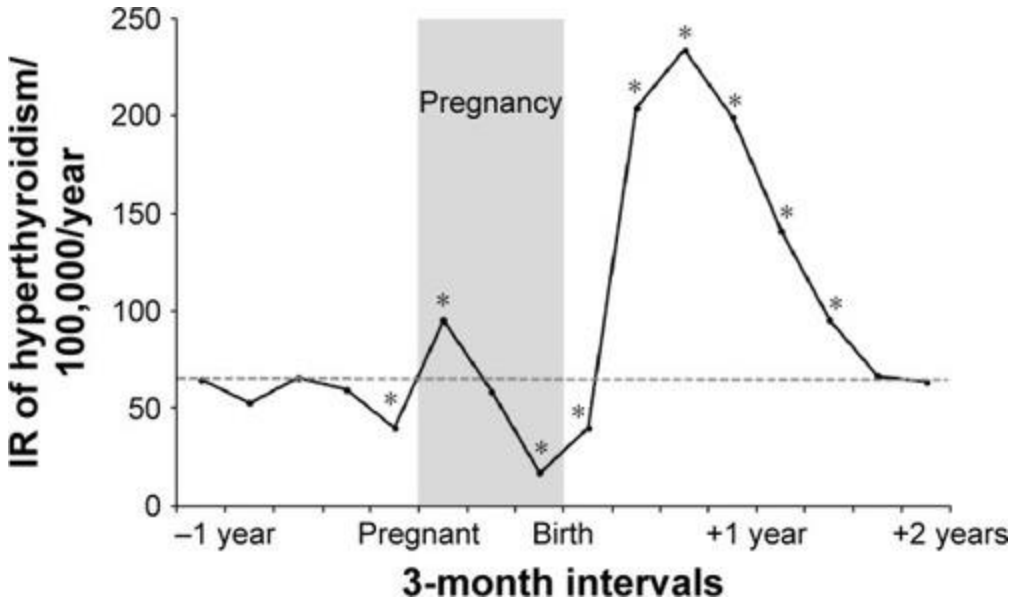

Fig. 1| The prevalence of hyperthyroidism during pregnancy is seen in Fig. 1. The prevalence of maternal hyperthyroidism at 3-month intervals during pregnancy is seen in the graph. (Adapted from DOI: 201) from REF, Oxford University Press, with permission.

3.2.3 pregnancy

The incidence of Graves' hyperthyroidism varies significantly during pregnancy, a period of significant immunological alterations (Fig. 1) (74). Graves' hyperthyroidism may worsen in the first few months of pregnancy (75) and in the year following delivery (76-79). Nonetheless, hyperthyroidism is thought to be a reproductive inhibitor (80). Only about 0.5% of pregnant women present with Graves' disease (GD), and 0.2% of patients are treated during pregnancy (81). The risk of developing GD during pregnancy is extremely low, on the order of 0.05% (82). As pregnancy progresses, GD often improves, which is due to increasing activity of regulatory T cells and strengthening of the mother's immune tolerance due to changes in T cell and B cell function

(83). However, postpartum autoimmune thyroid disease can occur as a result of one's immune system rebound after the birth of a child (84). Within 12 months after receiving a GD diagnosis, 30% of women of reproductive age in retrospective Swedish research reported having previously been pregnant (85).

3.2.4 Stress

Significant stress, such as that brought on by a divorce, death in the family, or losing one's work, has frequently been linked to a higher risk of GD (86). Through the release of corticotropin-releasing hormone, stress is known to cause an excessive amount of cortisol, which can depress the immunological response (86,87). Additionally, cortisol levels decrease in the postpartum phase (144), for instance, elevated autoantibody titers indicate an overreaction after the loss of immunological tolerance when the stress of pregnancy is alleviated by delivery (88). Increased immunological reactivity and the development or recurrence of autoimmune illness may be the outcomes of this rise.

3.2.5 Infection

Specificity crossover, sometimes referred to as similarities in arrangement, structure, or both about structure or compliance between distinct antigens, can result from molecular mimicry (89). According to one study, 4% of monoclonal antibodies produced against different viruses interacted with tissue antigens (90). It has long been believed that harmful microbes like Helicobacter pylori and Yersinia enterocolitica are suggested as a potential causal factor in the pathophysiology of GD (91). Thyroid autoantibodies are linked to viral diseases that impact the thyroid gland, including hepatitis C, congenital rubella, and subacute thyroiditis, but they are not always the first to cause GD (92). Nonetheless, one of the primary theories regarding the etiology of GD is the possible

impact of several common illnesses (such influenza and Epstein-Barr viruses) on the epigenetic features of certain susceptibility genes. Theoretically, these prevalent viral infections could alter genes linked to GD vulnerability epigenetically. Actually, utilizing pathway analysis, (93) and RNA-seq, we (R.L. and T.F.D.). discovered that thyroid tissue from GD patients had higher levels of gene expression pathways perhaps linked to viral infection as compared to normal thyroid tissue (93). To further suggest the pathogenesis of GD may involve virus-related cytokines. According to a different research, interferon-α (IFNα) boosted thyroglobulin's lysosomal breakdown, producing pathogenetic peptides that might cause thyroid autoimmunity, (94).

3.2.6 Iodine and related drugs

In persons who are genotypically predisposed, GD or its recurrence can be induced by iodine and iodine-containing substances, such as amiodarone and iodine-containing contrast agents used in CT scans (95, 96). Iodine overloading during thyroid hormone synthesis may increase TH and increase the antigenicity of thyroglobulin, one of GD autoantigens that may be a precipitating factor. Additionally, iodine can have a direct thyroid damaging effect through thyroid cell release of thyroid antigens in the immune system (97).

3.2.7 Radiation

Treatment with radioiodine caused GD in certain patients with toxic multinodular goitre. Following treatment for Graves' hyperthyroidism, radioiodine causes a sharp, temporary rise in TSHR autoantibodies (106,105). This finding may indicate that the individuals have a nodular variant of GD rather than pure multinodular goiter (46). Even five years after radioiodine therapy, studies have shown that TSHR autoantibody levels are frequently significantly greater than those following antithyroid medication or surgery (45). Further explanations for this observation include

the release of thyroid antigens such as TSHR from the thyroid injured by the radioiodine along with the sensitivity of regulatory T (Treg) cells to radiation causes decreased immune suppression. This in turn leads to enhancement of the reactivity of TSHR autoantibodies and T cells. This "flare" in autoimmunity may also be the reason why about 15% of individuals with GD receiving radioiodine develop clinical GO (symptomatic GO) or have it worsened (45).

3.2.8 Immune-modulating agents

According to reports, GD arises after immunological (or lymphocyte) reconstitution following bone marrow transplantation, anti-CD (155) monoclonal antibody treatment, or anti-retrovirus therapy), During the recovery from diseases such as lymphopenia, the immune cells in the pathogenetic state proliferate and undergo activation (99). A comprehensive meta-analysis has found that endocrine glands in general, the thyroid in particular, are highly vulnerable to the adverse effect of immune checkpoint inhibitors (100). Only a few case reports mentioned GD, and destructive thyroiditis accounted for the majority of thyroid-related side symptoms described (100).

3.2.9 Microbiota

Researchers are using next-generation sequencing methods to look into how the microbiome affects autoimmune thyroid disorders. Changes in bacterial variety and function, or dysbiosis, have been linked to autoimmune disorders such rheumatoid arthritis, multiple sclerosis, type I diabetes mellitus, and, more recently, GD (101). Patients with GD, with or without GO (102-104), have provided data on their gut flora. Gut microbiota in GO (105) has been the subject of considerable research in Europe thanks to the project has produced some good results but also bad. Studies in a mouse model of Graves' disease (GD) have found the adipocyte proliferation and macrophage

accumulation retro-orbital, which is compatible with the characteristics recorded in Graves' orbitopathy (GO). These findings indicate a complex interaction of factors in the development of GO, though more research needs to be conducted to fully understand the mechanisms involved (106, 107) which raises the possibility that thyroid function and gut microbiota are interacting (108). Further research is necessary since these observations may have treatment-related ramifications.

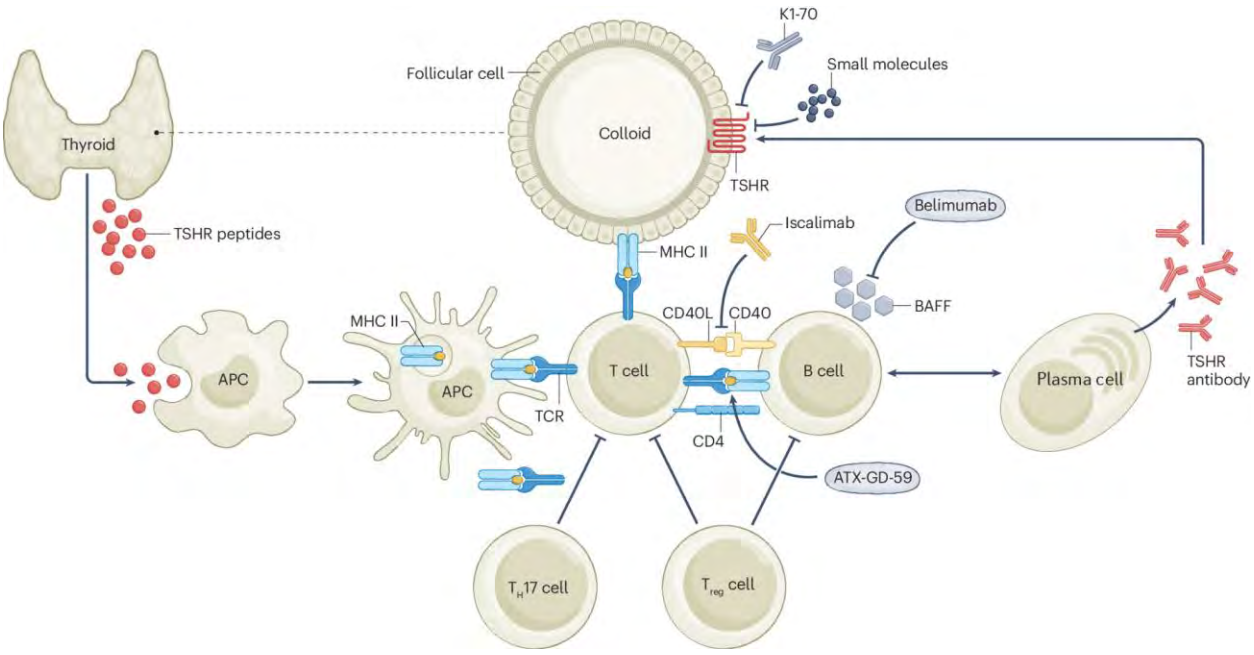

Fig. 2| The pathophysiology of Graves' disease-induced hyperthyroidism is gene expression activation of thyroid cells by autoantibodies against the TSH-R. (Adapted from DOI: 201).

Chapter 4

Diagnosis, Screening and Prevention of Hyperthyroidism

Chapter 4

4.1 Diagnosis, Screening and Prevention

The most frequent, though not exclusive, primary cause of hyperthyroidism is GD. Transient hyperthyroidism results from the self-limited release of previously held thyroid hormone in destructive thyroiditis of any etiology. Factitious hyperthyroidism, struma ovary, and amiodarone-induced hyperthyroidism are uncommon causes. As available treatments differ greatly based on the precise etiology of hyperthyroidism's inception, diagnosis of hyperthyroidism is crucial.

4.2 Clinical Presentation

Regardless of the underlying reason, hyperthyroidism can appear with a wide range of symptoms. Clinical hyperthyroidism can manifest as either Hyperthyroidism can manifest itself in an overt form with elevated levels of thyroid hormones and dozens of symptoms such as anxiety, weight loss, palpitations and insomnia. Alternatively, it can be in a moderate or subclinical form with subnormal TSH levels and normal thyroid hormone level. Cardiovascular symptoms, which in the case of elderly people may go from sinus tachycardia to atrial fibrillation, as well as heart failure, are particularly common (109). Neurogenic symptoms including anxiety and tremor are more common in younger patients (less than 50 years old); in rare instances, overt psychosis may manifest (109). The abrupt onset of symptoms in contrast to the gradual progression of toxic multinodular goiter may be a characteristic of GD. Extrathyroidal symptoms, including GO, are frequently linked to a more severe form of hyperthyroidism and a larger goiter in GD.

4.3 Diagnosis

Clinical criteria frequently allow for the rapid establishment of a trustworthy GD diagnosis. Diffuse goiters that have persisted for several months in a patient with any indication of GO

solidify the diagnosis. One can easily rule out the existence of nodules if ultrasonography is available. On a clinical basis, the diagnosis is frequently not immediately apparent, though, as in the case of patients who solely exhibit hyperthyroidism and lack any of the other distinguishing symptoms (110).

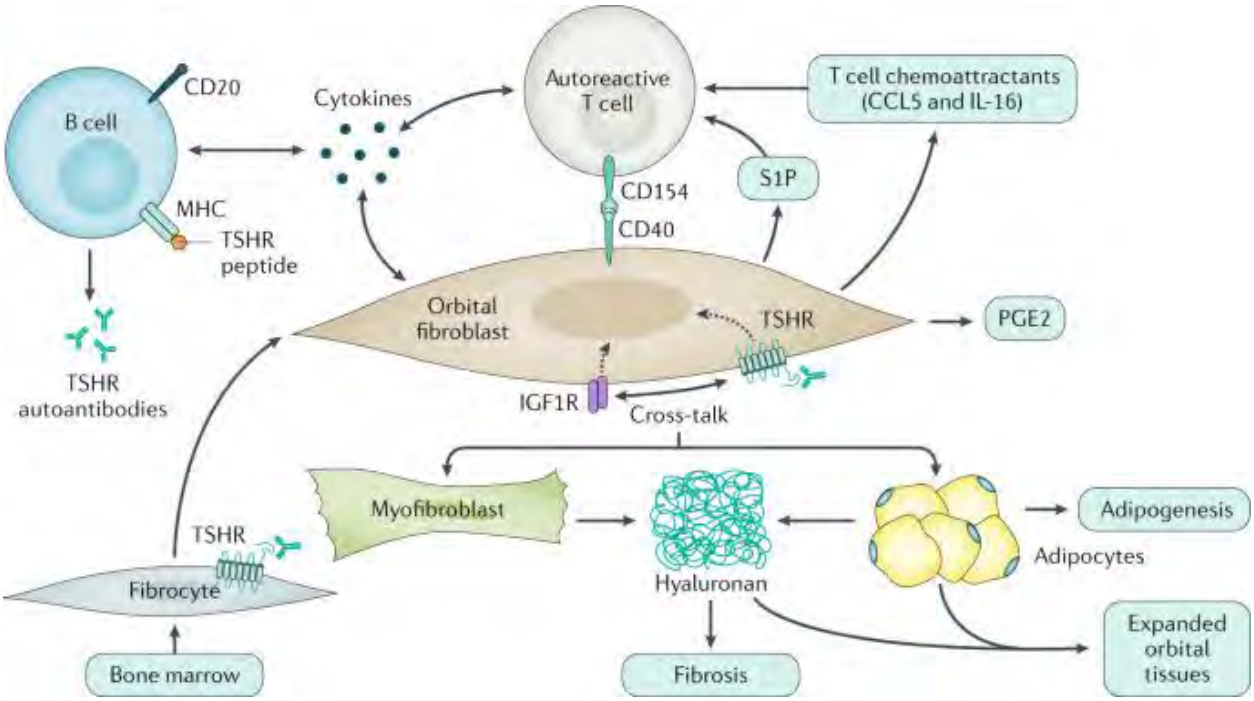

Fig. 3 | The pathophysiology of the orbitopathy in Graves' disease involves multiple cell interactions and processes. (Adapted from DOI: 201) Fibroblasts located in the orbit are able to morph into adipocytes and myofibroblast, developing tissues. They also secrete hyaluronic acid which disrupts the extraocular muscles.

Thyroid hyperactivity is often identified by the assessment of serum TSH and free thyroxine concentrations. In cases where a GD diagnosis cannot be established exclusively by clinical

criteria, the detection of TSHR autoantibodies in the bloodstream, with TSH and free thyroxine levels, facilitates the confirmation of the diagnosis (Fig. 4). Upon confirmation of a diagnosis, suitable management options.

4.3.1 TSHR autoantibody tests

A patient with hyperthyroidism exhibiting stimulating TSHR autoantibodies in serum has been conclusively confirmed as Graves' disease. Given the patient's previous diagnosis of hyperthyroidism, labor-intensive and costly bioassays utilizing TSHR-transfected cells are no longer recommended as the first-line diagnostic method of choice in the diagnosis of Graves' disease (GD). Instead, third-generation receptor bindings in the majority of clinics are now highly recommended as a first line diagnostic tool for GD (112). These assays provide for the ease of screening for TSHR autoantibodies automatically at a fraction of the cost of a thyroid scan (113). Modern tests are available that allow sensitivities and specificities of over 95% for identification of Grave's disease in people with overt hyperthyroidism (114). The efficacy of these tests in different cohorts of persons with mild (subclinical) hyperthyroidism remains little researched. Binding tests may lack efficacy compared to bioassays, which exhibit greater sensitivity when the receptor assay yields negative results in these patients. A thyroid scan and radioiodine uptake are essential for the uncommon people with negative receptor antibody testing, despite their typical diagnosis of thyroiditis.

4.3.2 Thyroid Ultrasonography

In the late 1960s, two researchers invented thyroid ultrasonography, which was first widely used to distinguish between cystic and solid nodules (115,116). The overdiagnosis of tiny thyroid tumors, which are typically clinically quiescent, is a potential disadvantage of this method (117).

However, ultrasonography has developed into a valuable and useful tool for thyroid ologists; on a patient's initial visit, the physician can quickly and affordably differentiate between toxic multinodular goiter and GD without the requirement for radiological imaging. With the exception of looking for enlarged lymph nodes in cases of thyroid cancer, CT and MRI scans are less accurate and do not provide additional information to the ultrasonographical evaluation.

4.3.3 Radioiodine uptake and thyroid scan

A thyroid scan and radioiodine uptake assessment can yield an accurate evaluation of thyroid function. Following 24 hours of oral administration of a radioactive iodine (122) tracer dose, images of the thyroid glands iodine uptake are generated. A diminished iodine absorption of less than 1% may indicate factitious thyrotoxicosis, destructive thyrotoxicosis or struma ovary. A heterogeneous pattern of iodine uptake indicates multinodular or uninodular toxic goiter, whereas a diffuse pattern confirms the diagnosis of Graves' disease. The gold standard for diagnosis was previously a radioiodine scan; however, this is no longer applicable because of its high cost, developments in TSHR binding tests, and the extensive availability of ultrasonography (118).

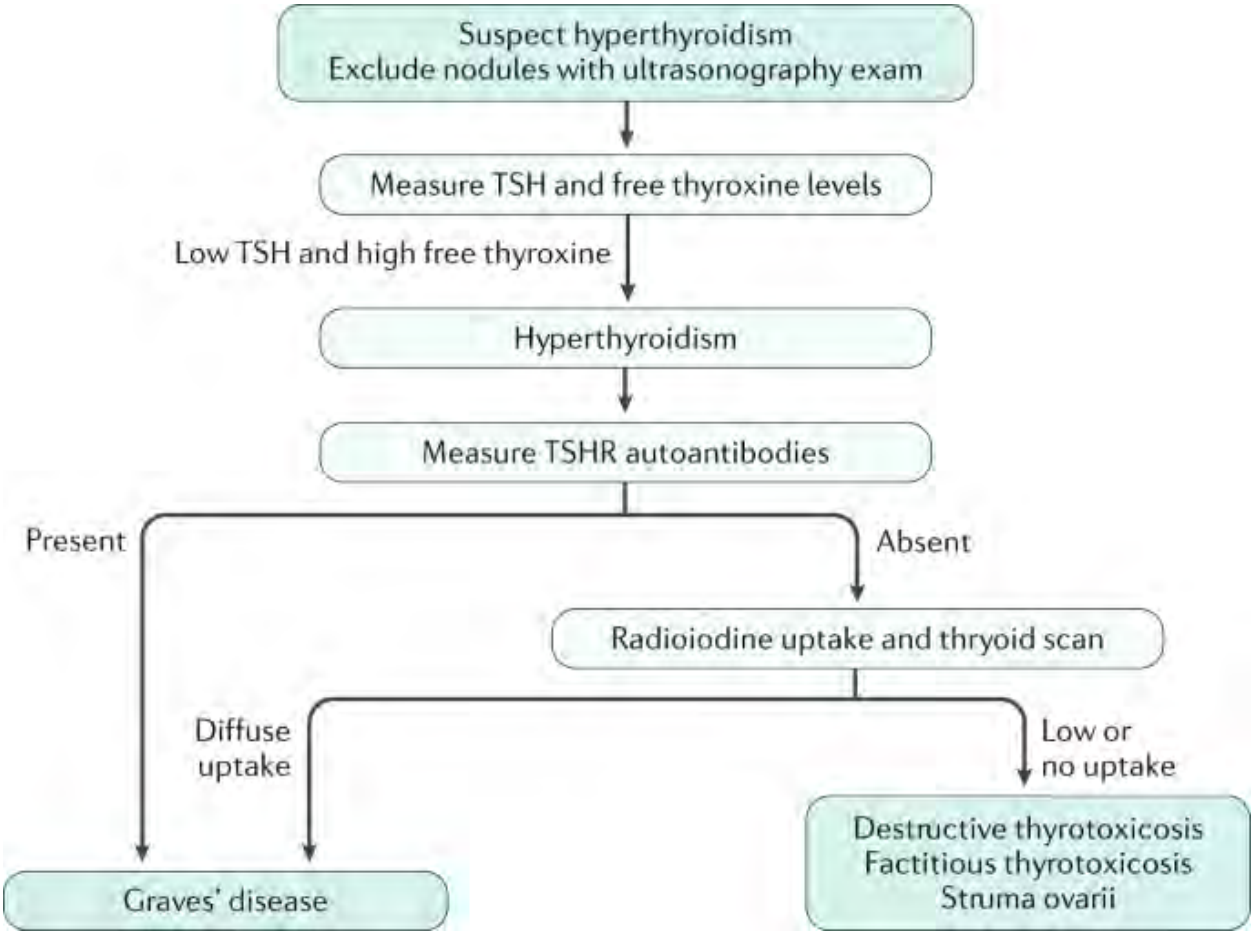

Fig. 4 | Graves' disease (GD) diagnosis. (Adapted from DOI: 201) In instances where patients present with clear clinical symptoms, including Graves' orbitopathy, doctors often advise the patient from any further diagnostic tests or assessments.

4.4 Graves' orbitopathy

Patients with Graves' disease often display irritation, tearing, inflammation, and discomfort behind the eye, along with varying degrees of orbitopathy. In extreme instances, retro-orbital inflammation and extraocular muscle edema resulting from tissue expansion and glycosaminoglycan accumulation lead to exophthalmos, or proptosis, characterized by the anterior

displacement of the eyes. The subsequent damage to the ocular muscles causes diplopia and may compromise vision. Muscle hypertrophy, resulting in pressure at the orbital apex (referred to as apical crowding), is associated with vision-threatening symptoms. Potential consequences encompass dysthyroid optic neuropathy due to apical crowding, (119) corneal ulcers resulting from lagophthalmos, and increased intraocular pressure.

Graves' orbitopathy (GO) is classified according to international criteria, which in the EU GO is defined by the EUGOGO system into three classes: mild, moderate and severe. To further classify the patients into active or inactive disease categories, these systems measure several parameters, including the patient's perception of pressure, pain associated with eyes movement, and the 5 major inflammatory signs. They also take into consideration the dynamics of the disease, such as disease progression, improvement, or stability, and proptosis, motility, and visual acuity. The ITEDS classification can give up to 20 points (120,121) to evaluate the severity of GO. Usually, the disease goes from an active stage with changing inflammation to a stabilized inactive phase, which can also be associated with considerable residual damage.

4.5 Graves’ dermopathy

Graves' disease (GD)-associated dermopathy, which is most commonly seen on the lower legs (pretibial myxedema, PTM), may also be seen on the toes, elbows and feet. In severe cases of the disease, it may involve the whole of the lower leg. The classic finding of PTM is the erythematous, non-pitting thickening of the dermis in the pretibial area, which is often delimited by a clear, palpable boundary separating the actively involved from uninvolved dermis. In mild cases, there may be a micronodular texture of the skin, resembling "orange peel." Because of its fibrous invasion, PTM can either be modest or gradually worsen and inflict noticeable damage. PTM is frequently challenging to treat even though it is not cancerous. Although poor circulation and

recurrent injury are frequently identified as contributory causes, it is unclear why PTM most frequently manifests in the lower legs.

4.6 Thyroid acropachy

A rare form of Graves' is acropachy which is observed in only a subset of patients with both Graves' ophthalmopathy and pretibial myxedema. It is characterized by fingers and toes becoming club footed and swollen. On x-ray, acropachy is diagnosed by periosteal new bone growth (123). This condition is believed to be caused by peripheral bone changes caused by the increased cardiac output that occurs with severe cases of hyperthyroidism. Due to earlier detection and treatment of grave disease the acropachy, once quite common, is now a rare incident.

4.7 Pregnancy

If TSHR autoantibody tests are negative, diagnosing GD during pregnancy might be very challenging. Inexperienced practitioners may become confused by the signs of pregnancy, such as sweating and palpitations, as well as elevated serum total thyroxine levels brought on by increased estrogen production. However, as pregnancy goes on, the condition typically becomes inactive due to increasing immunological tolerance, and therapy is rarely necessary. High levels of stimulating TSHR autoantibodies are seen in women with chronic illness, which is helpful in making a diagnosis.

Since the early 2000s, there has been continuous discussion over the necessity of screening all pregnant women for thyroid disorders. The debate on universal screening, in this case, screening all pregnant women, has almost entirely ignored the negative consequences of overt thyroid disease during the gestational period. The WHO issued standards for evaluating new screening methods in 1968(124). The most crucial factors to consider when assessing overt hyperthyroidism

screening during pregnancy are whether the condition has a negative impact on the mother or fetus, whether a low-cost screening test and approved treatments are widely accessible, and whether treating overt hyperthyroidism is economical. Overt hyperthyroidism during pregnancy has a prevalence of 0.64%, or more than one in every 200 pregnant women, according to a recent meta-analysis (125). Serum TSH values are being used in many countries to screen pregnant women for thyroid dysfunction, and we still advise that all pregnant women undergo thyroid illness screening.

Chapter 5
Treatment of Hyperthyroidism

Chapter 5

5.1 Management

The main aim of treating Graves' disease is to regulate hyperthyroidism through normalizing of the thyroid hormones. The choice of treatment also depends on the presence or absence of goiter and/or Graves' ophthalmopathy (GO). The American Thyroid Association (112) and the European Thyroid Association (126) have guidelines, which include therapies that attempt to relieve the symptoms and offer a potential "cure" for Graves' disease (GD).

5.2 Antithyroid drugs

A class of antithyroid medications known as thioamides prevents the production of thyroid hormone (127). Thioamides can lower thyroid hormone levels and promote remission in GD both immediately and over time. While the carbimazole is such a halogenated compound (carboethoxy derivative of methimazole), and while methimazole and propylthiouracil in weapons in the United States, are the most available thioamides. Methimazole also has a longer duration of action (9 hours vs. 1-2 hours for propylthiouracil) and lower incidence of adverse effects, methimazole (also known as carbimazole) is the medication of choice for the majority of people. However, because methimazole has more teratogenic effects during the first trimester of pregnancy, propylthiouracil is recommended (128). A rash, which is typically temporary and sensitive to diphenhydramine, is the most frequent side effect of thioamides (129). Additionally, patients with an absolute neutrophil count of less than 1,000 cells/μl or elevated liver transaminases (>5-fold the upper limit of normal) should not take any thioamide due to the risk of hepatotoxicity (129-131), pancreatitis, and bone marrow toxicity (granulocytopenia) (128,132,133). Because hyperthyroidism itself can result in abnormalities, a review of these tests is necessary prior to starting these medications.

Patients on antithyroid medications should also be told to call their doctor if they have a fever or pharyngitis. A longer treatment course has been linked to a higher remission rate (>1 year without active disease), and treatment is typically advised for at least 12 months (134,135). Persistently low TSH levels and persistently high TSHR autoantibody levels are indicators of poor responsiveness during treatment (134,135). Each patient experiences high TSHR autoantibodies for a different amount of time. Even if more than a year is the recommended duration of treatment, consistently elevated TSHR autoantibody levels beyond this time are the best indicator of a low.

These autoantibodies wax and wane over time and can be challenging to treat therapeutically. A "block and replace" strategy, which gives both an antithyroid medication and levothyroxine (used to treat the caused hypothyroidism) simultaneously, may occasionally be beneficial in these patients. GD is less frequent in children than in adults, and methimazole (136) is the most effective treatment for GD in children. After puberty, a more effective treatment may be offered if the illness continues.

5.3 Radioiodine

In many countries, radioiodine is also often considered to be the therapy of choice especially in patients with small goiters (<50 g), in patients who are difficult to control with thioamides or when thioamides are contraindicated. If the symptoms of hyperthyroidism are mild and there has been no history of heart issues, then treatment after diagnosis can start immediately, and thioamide pretreatment is not required. To avoid radiation-induced thyroiditis, which may cause further elevation of thyroid hormone levels, it is suggested that many patients be brought to a euthyroid state (normal thyroid hormone levels) before undergoing radioiodine therapy.

When administered orally, radioactive sodium iodide (Na) (136) quickly accumulates in the thyroid gland. Ablation of the thyroid gland results in a reduction of thyroid hormone levels occurring between 6 to 18 weeks following substantial tissue damage (137). Thyroid hormone replacement therapy is started after hypothyroidism has reached. Less than 15% of patients need more than one round of radioiodine to ablate their thyroid gland when treated adequately with potentially ablative doses (138). Due to its intrinsic potential to exacerbate GO, radioiodine is not advised for patients with GO or during pregnancy or lactation. Since smokers are more likely than non-smokers to develop GO, radioiodine treatment is likewise discouraged for them. Although some research has shown that individuals receiving radioiodine had a higher long-term risk of cancer, this risk is minimal or nonexistent at the levels used in GD (139,140).

5.4 Surgery

For patients with large goiters (>80 g) and patients with moderate to severe Grave's ophthalmopathy (GO), thyroidectomy (either partial or total) is the definitive treatment of choice. This treatment was the first treatment of Graves' disease (GD) worldwide. Surgery is also considered in those patients in whom thioamides are not appropriate, women planning to bear within six months, those with confirmed or suspicious thyroid cancer, those having large (more than 4 cm) thyroid nodules, and in the rare cases when associated hyperparathyroidism is present (141). However, thyroidectomy is usually not performed in the third trimester because of the risk of premature delivery (142) and in the first trimester because of the teratogenic activity and the risk of increased fetal death following anesthesia.

In order to prevent surgical problems, a high-volume thyroid surgeon is typically recommended (143-145). Perhaps as a result of the disorder's high vascularity or inflammatory characteristics, Thyroid surgeries for Graves' disease may be especially associated with hypocalcemia.

To attain a euthyroid state and heart rate regulation, patients should ideally receive preoperative treatment with thioamides and β-blockers (see below). Patients who have a high risk of parathyroid injury are given vitamin D and calcium prior to surgery in order to prevent postoperative hypocalcemia (146). In exceptional circumstances, the patient may require a regimen of β-blockers, potassium iodide, glucocorticoids, and potentially cholestyramine during the immediate preoperative phase (seven days prior to surgery) to reduce thyroid hormone levels when attaining a euthyroid state before surgery is unfeasible due to an urgent necessity for thyroidectomy or when thioamides are contraindicated (130-133). Following a thyroidectomy, the patient receives thyroid hormone replacement therapy to treat their hypothyroid condition. Serum TSH levels are checked every four to six weeks to modify the dosage.

5.5 β-blockers

When other treatments are unable to reduce thyroid hormone levels, β-blockade can give individuals with moderate to severe hyperthyroidism immediate relief. The two most widely used selective β1 receptor blockers at the moment are atenolol and metoprolol (extended release). Since propranolol has been shown to slow down the rate at which thyroxine (T4) is deiodinated to tri-iodothyronine (T3) (steps involved in thyroid hormone production), it is frequently the β-blocker of choice in cases of severe hyperthyroidism that need hospitalization (147). It is possible to discontinue using β-blockers if symptoms go away and thyroid hormone levels significantly drop.

5.6 Graves' orbitopathy

To treat Graves' orbitopathy (GO), ophthalmologists and thyroid experts work together closely (148). Treatment is stage-dependent and takes into account the dynamics, duration, and risk factors for the advancement of the disease (149). Rehabilitative surgery is only done when functional and

cosmetic effects are stable throughout the passive period; anti-inflammatory medication is advised during the active, progressive stages of illness. Customized to the patient's requirements, squint (150), lid surgery (151), and rehabilitative orbital surgery (152), are carried out one step at a time and rely on the expertise of the local specialists. However, because existing medicines do not completely alleviate GI symptoms, many patients experience a decline in their quality of life.

5.7 First-line therapies

For treatment to be successful, a euthyroid condition is required, and radioiodine therapy should be avoided in cases of active progressive GO (153). Due to smoking's detrimental consequences on disease progression and treatment, all patients should be actively encouraged to give it up (154). Patients with mild GO may benefit from a "wait and watch" approach. Because of its anti-inflammatory properties, selenium administration can be advised to stop further deterioration (155). Patients may be eligible for intravenous glucocorticoid treatment based on the course of their illness (persistent redness and tears). Oral steroids are an alternative, although their effects take longer to manifest and can occasionally have severe side effects (156).

For patients with active moderate to severe Graves' Ophthalmopathy (GO) (156-158), several RCTs demonstrated that intravenous glucocorticoids are the initial treatment of choice.

Within weeks of only one week of the treatment, the effects of injectable glucocorticoids are visible (159). A meta-analysis showed that patients treated with intravenous glucocorticoids achieved a 1.14mm reduction in proptosis and a 33% reduction in diplopia (double vision) from right factorial randomized clinical trials (RCTs). Non-randomized trials showed a reduction of 1.58 mm in proptosis and 25% in diplopia (85). The procedure should be reevaluated completely, in terms of the activity and severity of the disease, after six weeks. If the patient's condition deteriorates six

weeks after glucocorticoid therapy given intravenously, for example, he or she is less likely to benefit from continuing therapy. At this stage treatment should be supplemented with or changed to second-line medications as only one-third of nonresponsive patients improve by continuing the same medication (161). Emergency orbital decompression should be done in patients with severe GO, especially if they present optic disc edema, severe inflammation or substantial functional loss (152,162). Given the side effects of glucocorticoids are dose-dependent (157, 163), cumulative doses greater than 8 g should be avoided if liver damage is to be avoided.

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High dosages of glucocorticoids are not indicated in patients with recent viral hepatitis, severe hepatic impairment, serious cardiac problems, uncontrolled high blood pressure, and mental health problems. As an alternative, oral corticosteroids may be used which may have more frequent and

severe side effects and the outcome of treatment could be longer to be seen as compared to intravenous glucocorticoids.

Localized therapy is also helpful and appropriate for any stage affected by the disease. Prisms (such as Fresnel prisms or prism glasses) or occlusion, typically of the non-young eye, can assist in the correction of diplopia in the main gaze position, apart from occasions when the prevailing eye is more restricted. Botulinum toxin injection could be used in orbital muscles or fibrosed and retracted upper eyelid muscles, causing paresis and thus reducing muscle range of motion. For dry-eye symptoms that are due to low tear production, tear replacement solutions, ointments, and local anti-inflammatory therapy are essential especially for the management of lid retraction and elevation deficits.

5.8 Second-line therapies

Patients with GO now have additional alternatives for second-line treatment thanks to RCTs. For instance, in patients with moderate to severe active Graves' ophthalmopathy (GO), the monoclonal antibody teprotumumab against the IGF1R has been demonstrated to have significant improvements. It resulted in a decrease in proptosis of -2.82 mm compared to -0.54 mm with placebo, one class reduction in diplopia in 68% of patients in comparison to 29% with placebo, and a decrease in disease activity scores below 2 in 59% of patients compared to 21% with placebo (164). Teprotumumab is a recently created drug, and its long-term effects are still unknown. Similarly, although cyclosporine was unsuccessful when compared to steroids, mycophenolate mofetil, a commonly available medication, was more beneficial when given in combination with intravenous glucocorticoids (71%) than when given alone (53%), according to RCTs (165, 166). Analogously, azathioprine outperformed radiation or oral steroids alone when used in conjunction with them (167). In addition, when administered in the early stages of the disease, rituximab, a

humanized monoclonal antibody that depletes B cells, was 100% more effective than intravenous glucocorticoids; the effectiveness rate of the former was 69%. Additionally, it raised PTM (168); however, it was ineffective if administered more than a year after the start date (169). Similarly, intravenous glucocorticoids were less efficacious than Tocilizumab is a humanized recombinant IL-6R monoclonal antibody which is promising in the treatment of Graves ophthalmopathy. Proptosis reduced by >= 2 mm in 33.3% of rituximab treated patients as opposed to 6.35% in the intravenous glucocorticoid group (170).

Orbital irradiation might be considered in cases of limited motility, in which it may reduce the impact of fibroblast activation and release of proinflammatory cytokines increased from activated lymphocytes (171,172). Radiation therapy may also strengthen the effects of oral/intravenous glucocorticoids (173,174). For instance, the combination therapy had no impact on the anti-inflammatory effect (65% versus 64%) but markedly improved motility and decreased proptosis (62% against 45% in intravenous glucocorticoids alone) (22). Conversely, oval irradiation is uncommon, necessitates a licensed radiotherapist, and has been linked to uncommon retinopathy. The price of these treatments is something that should be discussed with payers and insurance providers.

5.9 Treatment for Graves' dermopathy

PTM treatment is still challenging and inadequate. The most popular method is still injecting corticosteroids directly into the lesions or applying potent corticosteroid creams like mometasone or fluocinolone under plastic wrapping (175). These individuals typically have extremely high TSHR autoantibody levels, which may significantly drop but seldom go away following a thyroidectomy. Nevertheless, a clinical reaction to this decrease in autoantibody levels is

uncommon. Although the outcomes are mixed, studies involving patients receiving A discernible improvement have been observed with systemic steroids, rituximab, mycophenolate mofetil, and other immunosuppressive drugs.

5.10 Management of GD/Hyperthyroidism during pregnancy

One of the difficult clinical problems endocrinologists' faces is managing GD during pregnancy. The mother's health, the effects of hyperthyroidism on the developing baby, the thioamides' possible adverse reactions, the danger of overtreating to cause prenatal hypothyroidism, the development of the unborn thyroid beginning at the conclusion of the first trimester, and the thyroid of the child at birth condition at birth are all factors that must be taken into account at the same time.

5.10.1 Preconception

Preconception is the greatest time to start providing the best treatment possible for a pregnant lady with GD. According to 2017 American Thyroid Association Guidelines for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum (176), thyroid function tests should indicate euthyroid status for at least two tests performed 1 month apart before a woman becomes pregnant without changing the treatment regimen. Therefore, it is advisable to advise women to delay getting pregnant until they are in a euthyroid condition. The lowest dose required to reach a euthyroid state should be administered to women receiving thioamide treatment. Similarly, before attempting to conceive, women receiving thyroidectomy should make sure they are in a stable euthyroid condition while taking levothyroxine. In order to allow the body to eliminate radioiodine and to give levothyroxine enough time to attain a euthyroid state, women receiving radioiodine ablation should refrain from getting pregnant for at least six months

following therapy. It is usually avoided prior to conception because the developing baby may be more susceptible to prenatal or neonatal thyrotoxicosis (177). Lastly, there is an 84% risk of GD recurrence in the postpartum period for females who are in remission after successful therapy with antithyroid medications without being pregnant, compared to a 56% relapse incidence for ladies who are in remission yet don't become pregnant again (178).

5.10.2. Pregnancy

Treatment for mild hyperthyroidism is typically not necessary in the early stages of pregnancy. Thioamides are still the preferred treatment for pregnant patients with mild to severe GD. Pregnancy is obviously not a good time to use radioiodine, and surgery is usually only advised in the second trimester if there is a significant reaction or resistance to thioamides. Maternal thyroid function testing has established the objective of thioamide therapy, which has changed over time. A large prospective observational trial found that untreated subclinical hyperthyroidism during pregnancy, which is when the TSH level is low (<2 μU/ml) and the free thyroxine level is normal, doesn't hurt the mother or the baby (179). Furthermore, it has been demonstrated that over-treatment with thioamides might cause fetal hypothyroidism and/or goiter (180). Therefore, achieving a normal amount of maternal free thyroxine at or just over the top limit of normal (181) is now the aim of treatment. A normal TSH level should not be the goal of therapy since doing so could affect the fetus.

Chapter 6
Conclusion and Future Directions

Chapter 6

Conclusion and Future Direction

Hyperthyroidism is a condition where the thyroid gland produces and secretes inappropriately high amounts of thyroid hormone which can lead to thyrotoxicosis. There are many different causes of hyperthyroidism, and the most common causes include Graves' disease (GD), toxic multinodular goiter and toxic adenoma. The diagnosis can be made based on clinical findings and confirmed with biochemical tests and imaging techniques including ultrasound and radioactive iodine uptake scans. This condition impacts many different systems of the body including the integument, musculoskeletal, immune, ophthalmic, reproductive, gastrointestinal and cardiovascular systems. To summarize, hyperthyroidism is a complex pathology with many etiologies and therefore multiple diagnostic modalities can be utilized to choose the best treatment according to patient need. The treatment choice is preference-sensitive and should involve a shared decision-making process between the patient and the healthcare practitioner. Although GD patients have not seen significant changes in treatment in many years, significant developments are imminent. Clinical trials are already underway for a number of novel treatments that should not have the same problems as the existing methods. In the latter regard, a phase I trial (141,182) is evaluating human anti-TSHR mAb (K1-70) in patients with GD and Graves' Ophthalmopathy (GO). The possibility of non-traditional signaling associated with this antibody that is unrelated to TSH activity is a significant worry. TSHR-selective small-molecule antagonists have also been described in investigations, albeit they still need a lot of work to be done (183,184). In patients with untreated GD, a small, controlled trial showed that a combination of distinct TSHR peptides (185) that can produce Treg cells and inhibit the immunological response to TSHR produced a short-term response (186). Additionally, the FDA in the USA has recently approved teprotumumab. Two

TNF blockers, adalimumab (187) and etanercept (188); small uncontrolled trials of patients with GO utilizing these medications did not consistently show any effect. However, two RCTs (n >300) have shown that mycophenolate mofetil had positive benefits. These studies also have a reassuring safety profile and a very favorable risk to benefit ratio (189,190,191). In an open-label research, tocilizumab produced remarkable outcomes on extra-ocular motility, disease activity, and disease severity in patients with steroid-resistant disease (192). Nevertheless, a later RCT cast doubt on these results' reproducibility (193). Different TSHR autoantibody levels, shorter orbitopathy durations, and Two RCTs that looked at rituximab produced diverse results, which might have been because the patients were different ages (169,170). Even while lower doses can help avoid these problems (194), the substantial number of drug-related adverse effects (such ocular edema and visual neuropathy) may make it hard to utilize rituximab. Calimab, an antibody that targets CD (195), which is expressed on the surface of thyroid cells and orbital cells (196,197), had a response rate of around 50% in persons with untreated Graves' hyperthyroidism (198) and is now receiving further investigation. So, identifying and creating novel, stronger, and more selective small molecules (199,200), biologics, and receptor peptides (186) that target the TSHR may help lessen the harmful effects of TSHR autoantibodies. To better comprehend their biological activity and come up with new treatments, it is important to know how TSHR autoantibodies are made and how the immune system responds to the TSHR antigen.

In conclusion, hyperthyroidism is a complicated condition with several possible causes that may be detected using different diagnostic tools. utilized to ascertain the best line of action. As part of preference-sensitive treatment of choice, the therapist and the patient should work together to create decisions. Patient education is crucial to ensure that everyone is aware of their alternatives and may select the course of action that best satisfies their needs. Numerous studies have recorded

successful interventions for hyperthyroidism. Patients and doctors should still be hopeful about the possible advantages of the existing treatment modalities, even though future research may fill up some of the gaps in long-term results.

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