Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: XYZ

OVERVIEW OF HYPERTHYROIDISM DIAGNOSIS AND MANAGEMENT

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Abstract:

Background: Hyperthyroidism is characterized by increased metabolism resulting from an overabundance of thyroid hormone in the bloodstream. Numerous factors can contribute to its onset, with the most severe manifestation being a thyroid storm—an urgent endocrine emergency necessitating prompt intervention. Clinically, hyperthyroidism may manifest ambiguously, leading to erroneous diagnoses and improper treatment.

Aim: the aim is to comprehend the underlying mechanisms of hyperthyroidism, analyze its method of diagnosis, and acquire knowledge regarding various strategies for its management.

Methods: We conducted this review using a comprehensive search of PubMed and Google Scholar from 1997 through March 2023.

Conclusion: The text discusses the significance of thyroid hormone (TH) in regulating various physiological processes and its role in metabolism, growth, development, and nervous system function. It emphasizes the environmental factors affecting TH production and the necessity for precise regulation for proper thyroid gland development. The impact of external factors like stress and diet on thyroid hormone production is highlighted, with stress potentially contributing to thyroid dysregulation and thyroid cancer development. Hyperthyroidism can present with a wide range of symptoms and signs, affecting both the psychological and physiological aspects of an individual's health.

Keywords: hyperthyroidism, thyrotoxicosis, diagnosis of hyperthyroidism, thyroid storm, management of thyroid storm, anti-thyroid drugs, thyroidectomy.

Introduction:

Thyroid hormone (TH) is a crucial regulator of various physiological processes, including metabolism, growth, development, and nervous system function. It modulates oxygen consumption, basal metabolic rate, and the metabolism of lipids, carbohydrates, and proteins [1]. TH binds to nuclear receptors, leading to changes in the transcription of TH-responsive genes. It is essential for avian development, growth, and reproductive regulation. Environmental factors and contaminants influence TH production, metabolism, and action. Precise regulation of TH secretion is required for proper thyroid gland development and hormone production. TH plays a crucial role in developing the brain, cardiovascular system, skeletal muscle, reproductive systems, and other organs and tissues. Alterations in TH levels can lead to numerous manifestations and effects on the body system.

External factors such as stress and diet play a significant role in regulating thyroid hormone production. Stress can disrupt the hypothalamic-pituitary-thyroid (HPT) axis and lead to thyroid dysregulation, potentially contributing to the development of thyroid cancer [2]. Prolonged glucocorticoid secretion due to stress can interfere with immune system response and induce chronic inflammation, which is a risk factor for thyroid cancer. Diet also affects thyroid function, as a high-calorie diet can lead to metabolic syndrome and altered thyroid hormone levels [3]. Environmental factors such as iodine deficiency or excess, exposure to thyroid disruptors, and nutrition deficiencies can impact thyroid homeostasis.

Thyroid hormone production involves several steps. First, iodine is transported into the thyroid gland and oxidized, followed by iodination of tyrosyl residues on thyroglobulin (Tg) to produce monoidotyrosine (MIT) and diiodothyrosine (DIT). MIT and DIT then undergo a coupling reaction to form thyroxine (T4) and triiodothyronine (T3). T4 and T3 are subsequently synthesized on Tg and released into circulation through Tg pinocytosis. The production of T4 and T3 is regulated by a negative feedback mechanism involving serum T4, T3, and thyroid-stimulating hormone (TSH). TSH consists of two subunits, α and β, which combine to form bioactive TSH, produced by the anterior pituitary gland, and binds to specific cell-surface receptors on the thyroid gland, stimulating the production of T4 and T3 [4].

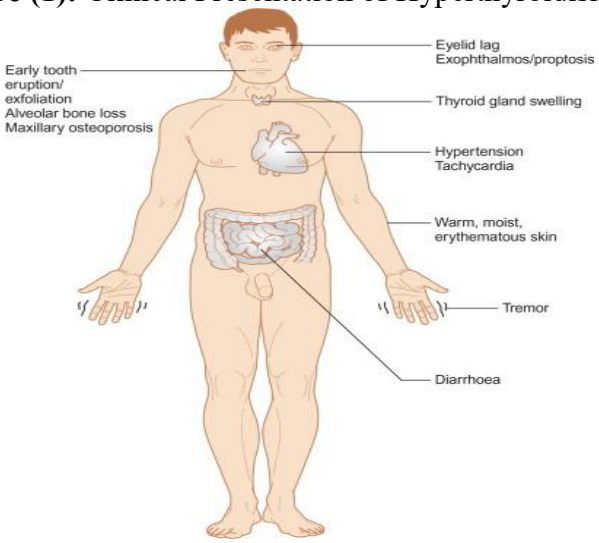
When T3 and T4 are generated in higher quantities, a condition known as hyperthyroidism is characterized by a hypermetabolic state. Clinical manifestations that are considered significant in hyperthyroidism encompass anxiety, rapid pulse, nervousness, fatigability, palpitations of the heart, muscle weakness, tremors, intolerance to heat, heightened appetite, increased perspiration, weight loss, and the presence of goiter (thyroid enlargement). The majority of individuals affected by hyperthyroidism are female, and the prevailing cause of this condition is attributed to Graves' disease, an autoimmune ailment. Graves' disease is the outcome of antibodies that stimulate the receptors of TSH, leading to an escalation in the production of T3 and T4, ultimately resulting in the enlargement of the thyroid gland. Apart from Graves' disease, hyperthyroidism may arise from various causes, including solitary thyroid adenoma, iodide-induced hyperthyroidism, multinodular goiter, thyroiditis, drug-induced hyperthyroidism, and a rare occurrence of a TSH-secreting tumor [5].

Hyperthyroidism:

Hyperthyroidism is a clinical condition characterized by the thyroid gland's excessive synthesis and secretion of thyroid hormones. There are three main types of hyperthyroidism: Graves' disease (GD), toxic multinodular goiter (TMNG), and solitary toxic adenoma. Graves' disease (also known as type I hyperthyroidism) is the leading cause of hyperthyroidism and is the most common type in the population [6]. The various clinical presentations of hyperthyroidism encompass a range of distressing symptoms that affect both the psychological and physiological well-being of individuals.

Among these manifestations, one frequently observes indications of psychic anxiety, a state characterized by excessive worry and unease. Additionally, individuals with hyperthyroidism may experience dysphoria, a general sense of dissatisfaction or unease with life, as well as irritability, which often manifests as a heightened sensitivity to external stimuli and a propensity for overreacting to even minor stressors. Emotional lability, another common symptom, refers to rapid and unpredictable shifts in mood, whereby individuals may experience intense emotions that fluctuate rapidly and unpredictably. Sleep disturbances, such as insomnia or disrupted sleep patterns, are also frequently seen in individuals with hyperthyroidism, which further exacerbate their overall well-being. Moreover, cognitive impairments, including intellectual dysfunction, are observed in some individuals, leading to difficulties with attention, concentration, and memory. The psychological impact of hyperthyroidism is not limited to the symptoms mentioned earlier, as individuals may also experience manic or depressive episodes. Mania, characterized by elevated mood, increased energy levels, and impulsive behavior, can sometimes occur. In contrast, others may experience depressive symptoms, such as persistent sadness, loss of interest or pleasure in activities, and feelings of worthlessness or guilt. Psychomotor agitation, a symptom characterized by restlessness and an increased need for physical movement, is another indicator of the psychological distress associated with hyperthyroidism. Furthermore, psychic anxiety, a form of anxiety that is not necessarily related to any specific external threat, can be present in individuals with hyperthyroidism, adding to their overall psychological burden. The physiological manifestations of hyperthyroidism are equally significant and often impact the cardiovascular system. Individuals with hyperthyroidism may experience palpitations, a sensation of rapid or irregular heartbeats, as well as exercise intolerance, which refers to the inability to engage in physical activity without experiencing excessive fatigue. Dyspnea, characterized by shortness of breath, may also occur due to the increased metabolic demands on the respiratory system. Angina, a condition characterized by chest pain or discomfort, and edema, the accumulation of fluid in the tissues, are additional cardiovascular symptoms that individuals with hyperthyroidism may experience. In severe cases, congestive heart failure, a condition in which the heart is unable to pump blood efficiently, can also occur. Electrocardiogram abnormalities are commonly observed in individuals with hyperthyroidism. Sinus tachycardia, an abnormally fast heart rate, is frequently found on electrocardiograms in these individuals. Atrial fibrillation, a condition characterized by irregular and rapid heartbeats originating in the atria, is also commonly encountered. These electrocardiogram abnormalities reflect the cardiac manifestations of hyperthyroidism and further contribute to the burden placed on the cardiovascular system. For instance, goiter, an enlargement of the thyroid gland, is often observed in individuals with hyperthyroidism. Thyroid bruit, an abnormal sound heard over the thyroid gland, can also be present. Eye signs, such as exophthalmos, protrusion of the eyeballs, or increased prominence of the eyes, are another common feature of hyperthyroidism. Skin and muscle abnormalities can also occur, including skin thinning, hair loss, and muscle weakness. Lastly, weight loss, often a prominent symptom of hyperthyroidism and frequent bowel movements, can be attributed to the increased metabolic rate and associated changes in appetite and food metabolism. (Figure 1).

Figure (1): Clinical Presentation of Hyperthyroidism [7].



Graves' disease (GD):

GD is an autoimmune disorder characterized by the production of autoantibodies against the thyrotropin receptor (TRAbs), leading to hyperthyroidism and the development of goiter. The pathophysiology of Graves' disease involves a combination of genetic and environmental factors. Multiple genes, including HLA, PTPN22, TSHR, thyroglobulin gene, FCRL3, SCGB3A2, and CTLA4, have been associated with the risk of developing Graves' disease. Also, the induction of antigen-processing and -presenting genes, potentially mediated by the type I interferon (IFN) or IFN-γ signaling pathway involved. The exact mechanisms underlying the development of Graves' disease are not fully understood. Still, it is believed that lymphocyte depletion and reconstitution caused by treatments like alemtuzumab can lead to the over-repopulation of naïve B-cells and T-lymphocyte modulation, resulting in autoimmunity. Additionally, infectious agents such as Helicobacter pylori and hepatitis C virus have been implicated in triggering the autoimmune inflammation associated with Graves' disease [8,9]. Further research is needed to fully understand the pathophysiology of Graves' disease and identify new risk factors. Additionally, Graves' disease can manifest with systemic involvement, such as hepatic involvement leading to liver function derangement [10]. In rare cases, Graves' disease can also cause increased intracranial pressure, resulting in symptoms such as headache, vomiting, visual changes, and tinnitus [11].

Toxic Multinodular Goiter:

TMNG arises due to the excessive proliferation of thyroid epithelial cells, culminating in the emergence of novel follicles. This condition is characterized by numerous independent nodules within the thyroid gland, which can secrete thyroid hormones in a manner that is not reliant on thyroid-stimulating hormone (TSH). While insufficient intake of iodine represents the most significant causative factor for TMNG, it is important to acknowledge that additional environmental, hormonal, and genetic elements also contribute to its pathogenesis. As the disease progresses, nodular autonomy typically advances gradually, initially manifesting as subclinical hyperthyroidism and eventually culminating in overt hyperthyroidism [12].

Solitary Toxic Adenoma:

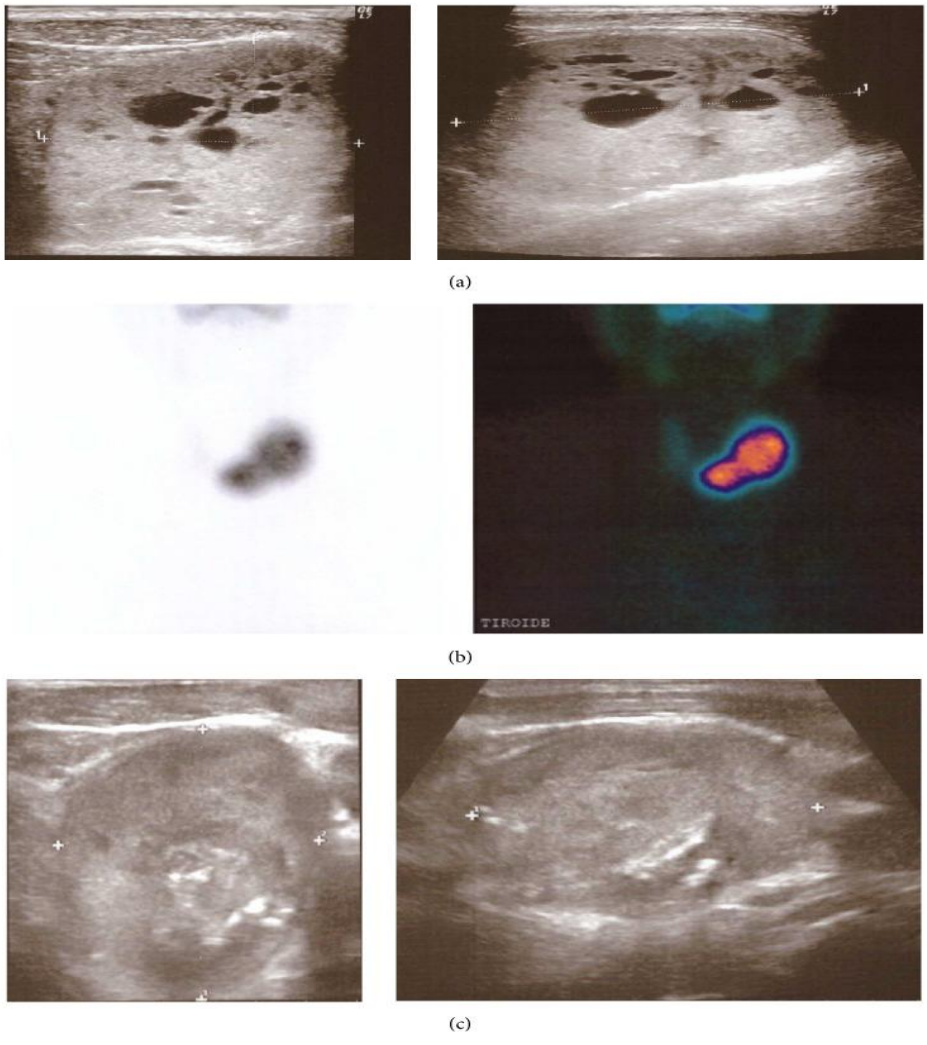
Solitary toxic adenoma refers to a condition where a single autonomous nodule in the thyroid gland becomes hyperactive and produces excessive amounts of thyroid hormones, leading to thyrotoxicosis [12,13]. This condition can be detected through ultrasound and color flow Doppler evaluation, which show a solitary nodule with blood flow within the rim and intra-parenchymally. Solitary toxic adenoma can be symptomatic, causing hyperthyroidism, and may present with signs such as asymmetric nodular goiter. The causes of solitary toxic adenoma are diverse, and while some cases

may be caused by somatic DNA point mutations, not all cases exhibit these mutations. Activating mutations in the thyrotropin receptor have been found in the TSH-binding domain, leading to increased basal cAMP levels and affinity for TSH.

How To Diagnose and Differentiate Type of Hyperthyroidism:

Hyperthyroidism can be identified and confirmed through a comprehensive clinical evaluation followed by serum thyroid functional tests [14]. The evaluation process typically commences by assessing the levels of thyrotropin (TSH), a hormone secreted by the pituitary gland that plays a crucial role in regulating thyroid function. Subsequently, in specific scenarios, the measurement of free T4 and free T3 may be conducted. To ensure an accurate diagnosis and effective management of Graves' disease, the most prevalent form of hyperthyroidism, the recent guidelines recommend the assessment of thyrotropin receptor autoantibodies[15]. By employing this diagnostic tool, healthcare professionals can ascertain the presence or absence of these autoantibodies, aiding in the identification of Graves' disease. However, in cases where the autoantibody test yields a negative result, further investigations may be required, such as a radioiodine uptake and thyroid scan. These additional tests are particularly useful in ruling out other causes of hyperthyroidism and confirming the presence of Graves' disease. Furthermore, the utilization of ultrasonography and radionuclide imaging techniques, employing substances like [^{99m}Tc] Pertechnetate or radioactive iodine isotopes, has proven to be indispensable in diagnosing hyperthyroidism, regardless of whether structural alterations in the thyroid gland are present or not.

Figure (2): (a) Ultrasound of left lobe nodule at baseline; (b) thyroid scan (^{99m}Tc-pertechnetate); and (c) ultrasound of left lobe nodule after LAT + 131I therapy [16].



Additionally, advancements in technology have given rise to the emergence of hybrid imaging methods, such as single-photon emission computed tomography (SPECT)/-(CT) or positron emission tomography (PET)-based techniques, which are now being utilized to localize ectopic thyroid tissue or in multinodular goiter cases. In situations where the measurement of thyrotropin receptor antibodies is not readily available, thyroid uptake scans and ultrasonography become particularly valuable tools to aid in the diagnosis of hyperthyroidism. Thus, by employing a combination of clinical evaluation, serum thyroid functional tests, autoantibody measurements, radioiodine uptake and thyroid scans, ultrasonography, and radionuclide imaging, healthcare professionals are equipped with an extensive toolkit to accurately diagnose and manage hyperthyroidism, ensuring optimal patient outcomes.

Figure (3): Thyroid nodule diameters measured by US [17].

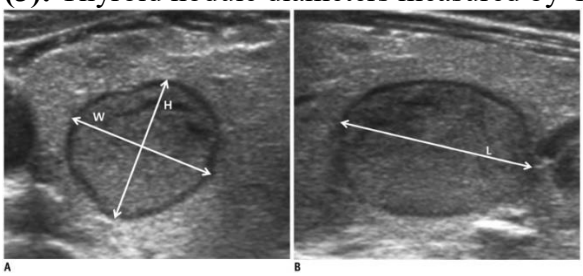
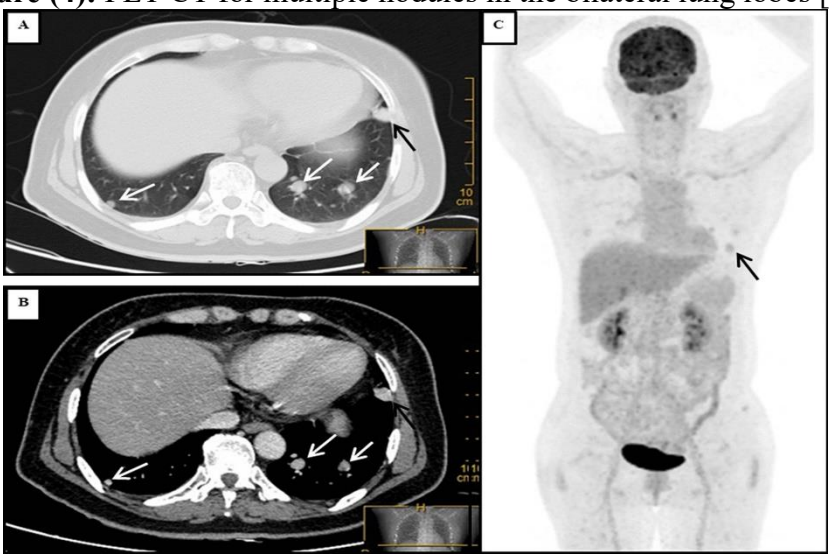


Figure (4): PET-CT for multiple nodules in the bilateral lung lobes [18].



Treatment for Hyperthyroidism:

The treatment options for hyperthyroidism include drugs, nuclear medicine, and surgery [15]. The choice of treatment depends on factors such as comorbidities, urgency of the situation, familial context, and patient's wishes. Surgery is often the preferred option for hyperthyroidism caused by various factors, such as Graves' disease, toxic multinodular goiter, and solitary toxic adenomas. Antithyroid drugs and radioactive iodine therapy are also commonly used treatments for hyperthyroidism.

Thionamides are widely acknowledged as the most frequently used anti-thyroid medications [19]. Notable examples of these drugs include methimazole (MMI) and propylthiouracil (PTU). The mechanism of action of these medications involves the inhibition of tyrosine organification, resulting in a reduction in the synthesis of T4. PTU additionally inhibits the conversion of T4 to T3 in peripheral tissues. Consequently, thionamides effectively manage clinical hyperthyroidism in the majority of patients after a few weeks of administration. In patients with Graves' disease, thionamides also demonstrate the ability to decrease levels of thyroid-stimulating immunoglobulins (TSI), making them a suitable option for inducing remission. In cases of toxic nodular goiter, thionamides can be administered temporarily until definitive treatment is undertaken. However, it is important to note that

thionamides are not suitable for use in cases of thyroiditis, as this condition does not involve excessive production of T3 or T4. Conversely, thionamides may be associated with certain minor side effects, such as arthralgia, rash, fever, and urticaria. These adverse reactions can occur in up to 5% of patients who receive this medication. Although more serious side effects can occur, they are rare occurrences. Agranulocytosis, for example, develops in as few as 0.5% of patients who are administered thionamides. Approximately 30% of patients who take PTU may experience elevated liver enzyme levels, but this is typically a benign condition, and hepatotoxicity rarely manifests. Methimazole and carbimazole can occasionally induce mild cholestasis that spontaneously resolves. Acute hepatitis is an extremely rare manifestation of thionamide usage. Vasculitis has also been reported, albeit very rarely, following the use of PTU [20].

Thionamides are not effective in the management and treatment of severe cases of hyperthyroidism or thyroiditis [21]. In such instances, alternative medications can be employed to achieve euthyroidism or resolve clinical symptoms, but the underlying cause of thyrotoxicosis remains untreated. One strategy involves the use of beta blockers in cases of thyroiditis-induced thyrotoxicosis. Glucocorticosteroids can also be administered in high concentrations during thyroid storm, resulting in reduced conversion of T4 to T3 in peripheral tissues. For cases of painful subacute thyroiditis, glucocorticoids can alleviate pain and achieve euthyroidism. Additionally, iodide can be utilized to inhibit the synthesis and release of T3 and T4, primarily in the treatment of patients presenting with thyroid storm. It can also be used pre-thyroidectomy to reduce vascularity. Iopanoic acid, an oral agent containing high concentrations of iodine, can effectively decrease the production and secretion of T3 and T4, as well as inhibit T4 conversion to T3, making it useful in managing thyroid storm. However, it is not suitable for long-term hyperthyroidism management.

Patients diagnosed with toxic nodular goiter or Grave's disease may also find therapeutic benefits from the administration of radioactive iodine (131I) [21,22]. Remarkably, the utilization of 131I has the potential to reduce the size of goiter in toxic multi-nodular goiter patients by as much as 40%. However, it is important to note that nearly all patients who undergo treatment with 131I will develop irreversible hypothyroidism. Additionally, there are other potential adverse effects associated with radioactive iodine treatment, such as mild neck pain and exacerbated initial thyrotoxicosis resulting from the leakage of T3 and T4 from the damaged gland. To mitigate this, patients are administered with thinamides prior to 131I treatment in order to reduce the risk of developing thyrotoxicosis. Conversely, it should be noted that Graves' disease patients with ophthalmopathy may experience deterioration following 131I treatment, particularly among smokers and those with severe hyperthyroidism. It is crucial to highlight that young patients and children are not recommended to receive 131I treatment due to the limited documentation regarding the long-term effects of radiation exposure on this population. Lastly, it is imperative to emphasize that pregnancy and lactation are absolute contraindications for 131I treatment.

Surgical Treatment:

In a majority of instances of hyperthyroidism, thyroidectomy has the potential to result in complete resolution, accounting for up to 90% of cases [23]. Additionally, this surgical intervention alleviates symptoms associated with the compression induced by large goiters. Furthermore, it is worth noting that thyroidectomy does not exacerbate symptoms of ophthalmopathy in individuals with Grave's disease. It is even considered a viable option during pregnancy, particularly in the second trimester. It is crucial to emphasize that thyroidectomy, when executed by skilled professionals, carries no mortality risk. Nevertheless, it is imperative to acknowledge that complications may arise, such as injury to the recurrent laryngeal nerve and the development of irreversible hypothyroidism, which may manifest in approximately 2% of patients. Other potential complications encompass bleeding, infection, and hypocalcemia.

Thyroid Storm:

Thyroid storm represents a critical manifestation of thyrotoxicosis and an urgent endocrinological situation. It is characterized by an intense state of thyrotoxicosis and the failure of multiple organs.

The Burch-Wartofsky Point Scale (Figure 5) a widely accepted diagnostic tool for thyroid storm, whereby a score of 45 signifies the presence of this condition [24,25]. Thyroid storm can be triggered by the absence of treatment or the interruption of treatment for Graves' disease, as well as other ailments such as subacute thyroiditis, whether painful or painless. The clinical presentation of thyroid storm displays a diverse range of symptoms, including fever, rapid heart rate, indications of heart failure, vomiting or diarrhea, impaired liver function, and disruptions in the central nervous system. Timely diagnosis and management play a crucial role in improving the prognosis and clinical outcomes of patients experiencing thyroid storm. Treatment involves addressing the underlying trigger, providing resuscitation, administering medications such as steroids, thionamides, iodine, and cholestyramine, as well as managing hyperthermia and restlessness.

Conclusion:

The text discusses the significance of thyroid hormone (TH) in regulating various physiological processes and its role in metabolism, growth, development, and nervous system function. It emphasizes the environmental factors affecting TH production and the necessity for precise regulation for proper thyroid gland development. The impact of external factors like stress and diet on thyroid hormone production is highlighted, with stress potentially contributing to thyroid dysregulation and thyroid cancer development. Hyperthyroidism can present with a wide range of symptoms and signs, affecting both the psychological and physiological aspects of an individual's health.

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