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HYPERTHYROIDISM CAUSES, PATHOPHYSIOLOGY, AND MANAGEMENT

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Abstract:

Introduction: *Hyperthyroidism is a hyper metabolic state due to excessive amounts of thyroid hormone in the circulation. There are several causes and its worst presentation could be a thyroid storm, which is an endocrinal emergency and requires immediate management. Clinically, hyperthyroidism can present vaguely leading to wrong diagnosis and mismanagement.*

Methodology: *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1987, through March 2017. The following search terms were used: hyperthyroidism, thyrotoxicosis, diagnosis of hyperthyroidism, thyroid storm, management of thyroid storm, anti-thyroid drugs*

Aim: *Our aim in this study is to understand the pathophysiology of hyperthyroidism, study its diagnosis, and understand ways of management.*

Conclusion: *Due to its vague presentation, hyperthyroidism can be misdiagnosed and managed incorrectly, leading to life threatening condition known as thyroid storm. Health care physicians must keep a high degree of suspicion in order to provide immediate therapeutic measures to avoid complications as well as death of patient.*

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

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INTRODUCTION:

Using iodide (which comes from the diet of from intrinsic metabolic interactions like degradation of thyroid hormones) T4 and T3 are produced in the thyroid gland. Every day, the body uses about 100 µg of iodide to produce the daily requirements of T3 and T4. Generally, people in the United States consume about 200 to 500 µg of iodide per day. This range is mainly affected by areas, and people who reside in eastern states consume less amounts of iodide than people who reside in western states **[1]**. In the thyroid gland, epithelial cells have Na/I channels that help entering iodide to establish a concentration thirty or forty times higher than its level in plasma, therefore ensuring its presence sufficiently for hormones production. Normally, about 100 µg and 30 µg of T3 and T4 respectively, are produced every day in a normal thyroid gland. Of the T3 produced, about 80% are a result of metabolic interactions of T4 that include 5′-monodeiodination, with only 20% with de-novo synthesis. T3 is considered to be about 5 times higher activity than T4 **[2]**.

When T3 and T4 are produced in higher amounts, a hypermetabolic state (called hyperthyroidism) occurs. Anxiety, rapid pulse, nervousness, fatigability, heart palpitations, muscle weakness, tremors, heat intolerance, increased appetite, increased perspiration, weight loss, and usually goiter (thyroid enlargement) are all considered important clinical manifestations of hyperthyroidism. Most hyperthyroid patients are female, and Graves' disease, which is an autoimmune disease, is considered to be the most common cause of this state. Graves' disease results from antibodies that stimulate the receptors of TSH causing increased production of T3 and T4, with subsequent elevation of their levels, and enlarged thyroid gland. Other than Graves' disease, hyperthyroidism can result from several causes including solitary thyroid adenoma, iodide-induced hyperthyroidism, multinodular goiter, thyroiditis, drug-induced hyperthyroidism, and a TSH secreting tumor (which is very rare) **[3]**.

METHODOLOGY:

- Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1987, through March 2017. The following search terms were used: hyperthyroidism, thyrotoxicosis, diagnosis of thyrotoxicosis, thyroid storm, management of thyroid storm, anti-thyroid drugs

- Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was done after approval of ethical board of King Abdulaziz University.

PATHOPHYSIOLOGY

Most present theories support the presence of immune system defects in patients with Graves' disease. When serum samples are obtained from patients with grave's disease, high levels of immunoglobulins (IgGs) were found. These immunoglobulins were found to stimulate humans and animals thyroid glands, in both in-vivo and in-vitro experiments, therefore they were called thyroid-stimulating antibodies (TSAb) or thyroid-stimulating IgG (TSI). Other types of IgG immunoglobulins were found to inhibit TSH binding to the thyroid tissues, and were called thyrotropin binding inhibitory immunoglobulin (TBII). Antithyroglobulin and/or antimicrosomal antibodies were also detected in patients. Other features of the disease include splenomegaly, lymphadenopathy, thymic hyperplasia, thyroid deposition and infiltration with lymphocytes and immunoglobulins, retro-orbital tissues deposition and infiltration with lymphocytes and immunoglobulins **[4]**. Other autoimmune disorders may sometimes coexist with grave's disease like pernicious anemia, systemic lupus erythematosus (SLE), Hashimoto thyroiditis, myasthenia gravis, and/or idiopathic adrenal insufficiency **[5]**.

Pathogenicity of grave's disease is also affected by genetic predisposition, which is supported by solid evidence. Hashimoto thyroiditis is also suggested to be affected by genes. The simultaneous presence of Hashimoto thyroiditis and Graves' disease has been observed in identical twins. Monozygotic twins and dizygotic twins have been found to have a 50% and 9% concordance of Grave's disease, respectively. Euthyroid twins of patients with thyrotoxicosis were also found to have thyroid-stimulating immunoglobulins in their serum. These genetic mechanisms in both Hashimoto and grave's disease are suggested to be polygenic **[6]**.

In some cases, either Hashimoto disease or Grave's disease can occur simultaneously with other endocrinal deficiencies in the pancreas, parathyroids, adrenals, and/or gonads, as a part of a syndrome. Cutaneous lesions, gastric lesions, or mucocutaneous candidiasis can also occur with these endocrinal syndromes. In all these cases, the etiology appears to be autoimmune **[7]**.

THYROID STORM

The clinical presentation of thyroid storm is considered to be an extreme emergency. Diagnosis is based on thorough history along with proper physical examination and laboratory investigations. A thyroid storm can in fact affect every single organ in the body, making the clinical presentation somehow challenging to be diagnosed. On the other hand, any delay in diagnosis will lead to delay in proper management, resulting in serious and possibly fatal complications like atrial fibrillation, osteoporosis, delirium, anorexia, congestive heart failure, muscle weakness, thromboembolism, or altered mental status. All these complications can potentially lead to death if not treated properly. Pregnant women, children, and old people are at higher risk of devolving these complications. Therefore, a high clinical suspicion is essential in the emergency department in patients who present with multiple system involvement, to provide proper care and avoid failure and, possibly, death **[8]**.

DIAGNOSIS

The over-production of T3 and T4 is the cause of hyper metabolism that results in hyperthyroidism. The main signs and symptoms in this case will include tachycardia, anxiety, restlessness, nervousness, palpitations, tremors, increased appetite, muscle weakness, fatigability, high perspiration, heat intolerance, weight loss, frequent bowel movements, and goiter. Patients are more usually females. Common causes of hyperthyroidism include Graves' disease, multinodular goiter, thyroiditis, drug-induced hyperthyroidism, iodide-induced hyperthyroidism, solitary thyroid adenoma, and tumors **[9]**. To diagnose hyperthyroidism, TSH, free T3 and free T4 serum levels are measured. Typically, patients have elevated free T4 levels with low TSH levels. Sometimes, patients can have high T3 serum levels with normal T4 concentrations, which is called T3-hyperthyroidism. When serum thyroid hormone binding protein increase, this will subsequently cause a raise in total T4 serum levels. However, free T4 and TSH serum levels will not change and will stay normal. The definition of subclinical hyperthyroidism is made when patients are found to have decreased TSH levels, along with normal free T3 and free T4 levels **[10]**.

Effect of Medications on Thyroid Test Results

Sometimes, results can be affected by concomitant medications that impact thyroid functions leading to false-positive testing. Examples of this phenomena include estrogen that causes elevation in thyroid binding globulins levels, leading to higher total T4. However, free T4 serum levels stay the same along with TSH levels. Solutions that are used in coronary angiography and other imaging procedures contain iodide and can sometimes result in hypothyroidism or hyperthyroidism. Amiodarone, an anti-arrhythmic drug that contains iodide, can sometimes cause hyperthyroidism or hypothyroidism in some patients. Glucocorticoids can also decrease T3 serum levels - when administrated in high concentrations. This occurs by the inhibition of T4 conversion into T3. They can also inhibit the secretion of TSH leading to decline of both T3 and T4 levels. Heparin -an anticoagulant- can also directly affect thyroid tests by increasing the release of fatty acid in serum leading to elevated free T4 serum levels **[11]**.

Thyroid Function Testing and Non-thyroidal Illness

Another case of false-positive laboratory results is serious illness. Patients who are critically ill may sometimes have elevated thyroid hormones levels with the absence of clinical manifestations. This phenomena can occur in either acute or chronic patients and is found to relate with the severity of the disease. Therefore, laboratory results of sick difficult can be difficult to be right interpreted. This phenomenon is thought to occur due to the decreased conversion of T4 into T3, the decline in TBGs serum levels, and decreased secretion of TSH. All these laboratory changes have been found to be benign, do not cause symptomatic manifestations, and resolve spontaneously. Small changes in laboratory findings in healthy individuals should prompt further investigations, but are usually due to non-thyroidal disease **[12]**.

MANAGEMENT

Anti-thyroid Drugs

Thionamides are considered the most used anti-thyroid drugs. These include methimazole (MMI), and propylthiouracil (PTU). These drugs act by inhibiting organification of tyrosine resulting in decreased T4 synthesis. PTU also inhibits the conversion of T4 to T3 in the peripheral tissues. Therefore, thionamides control clinical hyperthyroidism after few weeks of administration in most patients. In Graves' disease patients, thionamides can also reduce levels of TSI, therefore can be used to induce a remission. In cases of toxic nodular goiter, thionamides can also be administrated for the short term treatment until definitive treatment is done. However, these drugs cannot be used in cases of thyroiditis, as this case does not involve the over production of T3 or T4 **[13]**.

On the other hand, thionamides can be associated with some minor side effects liked arthralgia, rash, fever, and urticarial. These can occur in up to 5% of

patients who take the drug. More serious side effects can occur but are, however, rare. As few as 0.5% of patients who receive thionamides can develop agranulocytosis. About 30% of patients who take PTU are noted to develop increased liver enzymes, but this is still benign, and hepatotoxicity rarely occurs. Methimazole and carbimazole can sometimes cause mild cholestasis that resolves spontaneously. Acute hepatitis can develop in very rare cases. Vasculitis has also been reported, though extremely rare, after the use of PTU **[14].**

Other drugs

Severe cases of hyperthyroidism or thyroiditis cannot be managed and treated with thionamides. In these cases, other medications can be used to achieve euthyroidism or resolve clinical symptoms. However, the underlying cause of thyrotoxicosis is not treated. Examples of these approaches include the use of beta blockers in thyroiditis causing thyrotoxicosis. Glucocorticosteroids can also be administrated in high concentrations in cases of thyroid storm, and lead to decreased conversion of T4 into T3 in the peripheral tissues **[15]**. Cases of painful subacute thyroiditis can also benefit from glucocorticoids that can decrease the pain and achieve euthyroidism. Iodide can also be used to inhibit the synthesis and release of T3 and T4, and is mainly used to treat patients who present with thyroid storm. It can also be used prior to thyroidectomy as it leads to decreased vascularity. Iopanoic acid is an oral agent that contains high concentrations if iodine, and is used to decrease the production of T3 and T4, inhibit their secretion, and inhibit T4 conversion into T3. It can be effectively used to manage thyroid storm. However, it is not effective for long-term management of hyperthyroidism **[16]**.

Radioactive iodine

Patients with toxic nodular goiter or Grave's disease can also benefit from treatment with radioactive iodine (131I). In fact, the size of goiter in toxic multi-nodular goiter patients can be reduced by up to 40% with the use of 131I. At the end, almost all patients who undergo treatment with 131I will develop irreversible hypothyroidism. Other possible adverse events of treatment with radioactive iodine include neck pain (that is usually mild), and worsening initial thyrotoxicosis (due to the leakage of T3 and T4 from the damaged gland). To prevent this from occurring, patients are pretreated with thinamides before undergoing 131I treatment to decrease the risk of developing thyrotoxicosis. On the other hand, when Graves' disease patients who have ophthalmopathy may deteriorate following treatment with 131I, with increased risk among smokers and patients with severe hyperthyroidism. Young patients and children are contraindicated to receive 131I treatment as their long-term effects in response to radiation are not well documented. Another absolute contraindication of 131I is pregnancy and lactation **[17; 18]**.

Thyroidectomy

In up to 90% of hyperthyroidism cases, thyroidectomy can cause complete resolution. It also relives symptoms related to compression from large goiters. Moreover, thyroidectomy is not associated with worsening symptoms of ophthalmopathy in Grave's disease patients. It is also accepted in pregnancy (superficially in the second trimester). Thyroidectomy carries zero risk of mortality especially when done by experts. However, complications of thyroidectomy include injury of the recurrent laryngeal nerve, and irreversible hypothyroidism, which can occur in up to 2% of patients. other potential complications include bleeding, infection, and hypocalcemia **[19]**.

Thionamides can be used before performing thyroidectomy to prevent the development of thyrotoxicosis that occurs due to secretion of T3 and T4 during the surgery. It was also found to decrease the risk of developing both operative and post-operative complications of both the surgery itself and the anesthesia **[19]**.

Treatment of Thyroid Storm

The early diagnosis and proper management of thyroid storm are essential for better outcomes. Pharmacological management mainly aims at the inhibition of T3 and T4 effects on the peripheral tissues and the regulation of the thyroid gland. Patients with thyroid storms are seriously ill, and must initially have large intravenous access placed. They also be put on strict monitoring of their cardiac activity and receive supplemental oxygen. As soon as congestive heart failure is excluded, aggressive volume resuscitation should be initiated. One of the most common causes of death in these patients is cardiovascular collapse, therefore B-Blockers must be administrated, as they decrease the severity of symptoms and inhibit sympathetic activity. Propranolol is the B-blocker of choice in these cases **[8]**. Another option is esmolol infusion. Steroids must also be given in high concentrations to maintain and improve vascular tone. In addition, steroids and B-blockers can lead to inhibition of T4 conversion into T3 in the peripheral tissues. PTU is also used and it will cause subsequent decrease in the conversion of T4 into T3. It also causes reduced synthesis of thyroid hormones. MMI and PTU are usually given orally, or per rectum, according to the clinical case.

The initial dose of PTU is 600-1000 mg, and then will be reduced to about 250 mg given every four hours **[20]**.

When thyroid storm is associated with hyperthermia, acetaminophen along with cooling devices can be used. Aspirin should not be used as it can potentially increase the levels of free T3 and T4 by decreasing TBG levels in the serum. If an infection is suspected, empiric treatment with broad-spectrum antibiotics should be initiated immediately. Hemodialysis is the last resort and is administrated to patients who deteriorate and fail to response to medical management **[8]**.

HYPERTHYROIDISM IN PREGNANCY

Mild or even moderate hyperthyroidism is generally asymptomatic in pregnancy, and patients usually tolerate the disease. When the physician is not sure of the diagnosis, it is better to repeat thyroid testing after a month before deciding the best management. Early pregnancy may cause exacerbation of Graves' disease. However, clinical picture usually improves spontaneously as pregnancy progresses. The effects of increase thyroid hormones levels on the pregnant women and the fetus vary from asymptomatic to extremely severe. If untreated, it can cause congestive heart failure, hypertension, thyroid storm that happens with labor, abortion, premature labor, stillbirth, or neonatal death. Fetal abnormalities and low birth weight can also occur following untreated hyperthyroidism in pregnancy. Therefore, hyperthyroid state must be treated properly in pregnant patients **[21]**. Several situations necessitate the measurement of antibodies in pregnant women. These include: a previous history of Grave's disease with development of fetal or neonatal hyperthyroidism in a prior malignancy, a previous history of Grave's disease requiring pharmacological treatment, the presence of intrauterine growth restriction in a euthyroid pregnant woman, the detection of fetal tachycardia in a euthyroid pregnant woman, or the presence of fetal goiter that is detected by ultrasound **[22]**.

Radioiodine treatment is absolutely contraindicated in pregnancy, and surgery carries several risks. Therefore, pharmacological therapy is the preferred approach in pregnant women. The drugs of choice in pregnancy are thioamides including propylthiouracil, methimazole, and carbimazole. These are administrated for moderate and severe hyperthyroid pregnant patients. PTU is the best choice and is usually administrated until the patient achieves a euthyroid state, and has normal thyroid testing. Then the dose should be reduced to maintain this state. Although no solid evidence is present to support this, methimazole has sometimes been linked with the development of fetal abnormalities; more specifically, aplasia cutis, and choanal or esophageal atresia. The use of beta blockers is not allowed in pregnancy, but this is a relative contraindication, and propranolol can be used in severe cases to normalize T4 levels **[23]**.

CONCLUSION:

Significant morbidity and mortality can happen as a result of hyperthyroidism and thyrotoxicosis. Establishing a diagnosis can sometimes be difficult and required high clinical suspicion, but is also essential and crucial to manage properly. The most serious form of thyrotoxicosis is thyroid storm which causes severe neurological alterations, and has high rates of mortality. Thyroid storm should always be considered in patients presenting with altered mental status.

REFERENCES:

1. **Ahad F, Ganie SA (2010):** Iodine, Iodine metabolism and Iodine deficiency disorders revisited. Indian J Endocrinol Metab, 14: 13-17.
2. **Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP (2012):** 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. Eur Thyroid J, 1: 55-71.
3. **Ginsberg J (2003):** Diagnosis and management of Graves' disease. CMAJ, 168: 575-585.
4. **Frohlich E, Wahl R (2017):** Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases. Front Immunol, 8: 521.
5. **Szyper-Kravitz M, Marai I, Shoenfeld Y (2005):** Coexistence of thyroid autoimmunity with other autoimmune diseases: friend or foe? Additional aspects on the mosaic of autoimmunity. Autoimmunity, 38: 247-255.
6. **Morshed SA, Davies TF (2015):** Graves' Disease Mechanisms: The Role of Stimulating, Blocking, and Cleavage Region TSH Receptor Antibodies. Horm Metab Res, 47: 727-734.
7. **Lesiak A, Erkiert-Polguj A, Dziankowska-Bartkowiak B, Sysa-Jedrzejowska A, Narbutt J (2010):** Chronic mucocutaneous candidiasis with endocrinopathy - case report. Arch Med Sci, 6: 464-467.
8. **Carroll R, Matfin G (2010):** Endocrine and metabolic emergencies: thyroid storm. Ther Adv Endocrinol Metab, 1: 139-145.
9. **Gurgul E, Sowinski J (2011):** Primary hyperthyroidism--diagnosis and treatment. Indications and contraindications for radioiodine

therapy. Nucl Med Rev Cent East Eur, 14: 29-32.

10. **Kravets I (2016):** Hyperthyroidism: Diagnosis and Treatment. Am Fam Physician, 93: 363-370.
11. **Dong BJ (2000):** How medications affect thyroid function. West J Med, 172: 102-106.
12. **Tibaldi JM, Surks MI (1985):** Effects of nonthyroidal illness on thyroid function. Med Clin North Am, 69: 899-911.
13. **Okosieme OE, Lazarus JH (2016):** Current trends in antithyroid drug treatment of Graves' disease. Expert Opin Pharmacother, 17: 2005-2017.
14. **Taylor PN, Vaidya B (2012):** Side effects of anti-thyroid drugs and their impact on the choice of treatment for thyrotoxicosis in pregnancy. Eur Thyroid J, 1: 176-185.
15. **Nicoloff JT, Fisher DA, Appleman MD, Jr. (1970):** The role of glucocorticoids in the regulation of thyroid function in man. J Clin Invest, 49: 1922-1929.
16. **Gallagher AE, Panciera DL (2011):** Efficacy of iopanoic acid for treatment of spontaneous hyperthyroidism in cats. J Feline Med Surg, 13: 441-447.
17. **Mumtaz M, Lin LS, Hui KC, Mohd Khir AS (2009):** Radioiodine I-131 for the therapy of graves' disease. Malays J Med Sci, 16: 25-33.
18. **Lee SL (2010):** Complications of radioactive iodine treatment of thyroid carcinoma. J Natl Compr Canc Netw, 8: 1277-1286; quiz 1287.
19. **Clark OH (1982):** Total thyroidectomy: the treatment of choice for patients with differentiated thyroid cancer. Ann Surg, 196: 361-370.
20. **Idrose AM (2015):** Acute and emergency care for thyrotoxicosis and thyroid storm. Acute Med Surg, 2: 147-157.
21. **Cooper DS, Laurberg P (2013):** Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol, 1: 238-249.
22. **Soldin OP (2006):** Thyroid function testing in pregnancy and thyroid disease: trimester-specific reference intervals. Ther Drug Monit, 28: 8-11.
23. **Grigoriu C *et al.* (2008):** Management of hyperthyroidism in pregnancy. J Med Life, 1: 390-396.