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Management of thyroid disorders- An overview

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Abstract

The thyroid is one of the most important endocrine glands whose dysfunction causes a paralysis of almost all the major functions of the body. Awareness about this gland is very essential and a need to focus on its dysfunction as well its management has become the prime concern of every endocrinologist. Thyroid disorders are more common than diabetes or heart disease and almost half of these remain undiagnosed. The advent of new diagnostic techniques since last two decades had enabled precise diagnosis of both physiological and immunopathological aspects of thyroid. The modern methods of drug formulation had also helped in a great way in the direction of treating the disorders. This review attemps to focus on the various disorders of thyroid gland and ways of management of those disorders.

Keywords:

Thyroid;
hyperthyroidism;
hypothyroidism;
Graves' disease;
thyroid storm.

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1. Introduction

The thyroid gland comprises of two associated projections and is one of the biggest endocrine glands in our body. It is found in the foremost neck, beneath the Adam's apple, along the front of wind pipe. It influences the function of body's most important organs, including the heart, brain, liver, kidneys and skin. Ensuring the healthy condition of thyroid gland is vitally important to the body's overall well-being. The gland consists of colloid containing follicular cells. Thyroglobulin is found in the colloid which contains the thyroid hormones (T3 and T4) within its molecule. The formation of thyroxine requires dietary Iodine. The majority of the thyroid hormone released from thyroid gland is thyroxine and small percentage is triiodothyronine. T4 is at least 25 times more concentrated than T3 and is deionized in the extraglandular sites to T3 (about 80 percent of T3 is produced in this form). Approximately 40 percent of T4 is deionized to reverse T3 which is not biologically active [1]. To maintain normal levels of metabolic activity in the body, precisely the right amount of thyroid hormone must be secreted; to achieve this, specific feedback mechanisms operate through the hypothalamus (TRH) and anterior pituitary gland (TSH) to control the rate of thyroid secretion. A deficiency or overproduction of either T4 or T3 can affect adversely the growth and development of the child and will affect metabolic function in the adult. An overproduction of thyroid hormones can cause serious and lifethreatening complications if not discovered and

managed in time. Thyroid gland is also influenced by environmental factors because of its dependence on adequate supply of iodine and vulnerability to goiterogens. The environmental factors include temperature, high altitude and anoxia, light, nutrition, minerals, physical and emotional stress, surgery etc. The dietary goiterogens and antithyroid drugs also influence thyroid function. There are specific types of thyroid disorders which include hypothyroidism, hyperthyroidism, goiter, thyroid nodules and thyroid cancer. Problems within the thyroid gland can be due to abnormalities of its structure or its function. These problems may occur from before the time of birth or may be acquired later, at any time in life. A tendency to have any type of thyroid problem may run in families, and a risk for some types of thyroid disorder may be inherited on either side of the family or sometimes from both the parents' side. According to a survey conducted by SRL Diagnostics during the period of 2013-1015, it was reported that that about 42 million people in India suffer from thyroid disorders [2]. Despite the coverage of National iodine deficiency diseases control programme (NIDDCP) in India, iodine deficiency is still prevalent in many parts of India. Thyroid disorders are more prevalent in pregnant women, who are three times more prone to hypothyroidism than men. The higher prevalence in females may be associated with estrogen and progesterone [3]. It has been reported that hypothyroidism is more common than hyperthyroidism [4]. This review describes briefly the management of common thyroid disorders highlighting recent advances and unresolved issues. A comprehensive account of pathophysiology, clinical features, and investigations in all cases is not within the scope of this review.

2. Classification of thyroid disorders

Like other endocrine diseases, thyroid diseases are associated with either excess hormonal activity, or with symptoms due to under production of the hormone or with a swelling due to a neoplastic process or due to the pressure effects on surrounding structures. A correct etiological, anatomical and functional diagnosis of the thyroid problem is absolutely essential for the proper treatment and well being of the patient.

2.1Hypothyroidism-

Underactivity of thyroid gland is a very common problem. It may not cause any problems at an early age but left untreated, it may cause major health issues over time.

Table 1. Classification of hypothyroidism

Types	Status of hormone	Cause
Primary Hypothyroidism	Thyroid Stimulating Hormone is increased	Autoimmune Post therapeutic hypothyroidism Iodine deficiency Congenital goiter Intake of lithium, iodine containing drugs, check point inhibitors/ tyrosine kinase inhibitors for cancer
Secondary Hypothyroidism	Insufficient Thyrotropin releasing hormone/ Thyroid stimulating hormone	Pituitary or hypothalamic neoplasms Congenital hypopituitarism Pituitary necrosis (Sheehan's syndrome)

Table 2. Symptoms of hypothyroidism

Fatigue
Increased sensitivity to cold
Constipation
Dry skin, Weight gain, Puffy face
Hoarseness of voice, muscle weakness
Elevated blood cholesterol level
Muscle aches, tenderness and stiffness, pain, stiffness or swelling in joints,
Heavier than normal or irregular menstrual periods
Thinning hair
Slowed heart rate
Depression and Impaired memory

2.2 Congenital hypothyroidism

It is the condition of deficiency of thyroid hormones at birth. It may be permanent, requiring a life long treatment or temporary, restoring to euthyroid condition in the first few months or years of life. Primary CH results from dysgenesis of thyroid or impaired synthesis of thyroid hormones (dyshormonogenesis) at birth. The symptoms are mild and remain undiagnosed in many new borns because of the passage of maternal thyroid hormones across the placenta which gives a protective effect to the foetal brain [5, 6]. Thyroid dysgenesis may be due to thyroid ectopy in two third cases [7], while in the remaining one third cases athyreosis (complete absence of thyroid gland) and thyroid hypoplasia is the cause. In small number of cases, some genes like paired box gene eight (PAX8), TTF-2, NKX2.1 and NXK2.5 have found to be responsible for thyroid dysgenesis [8, 9, 10, 11]. The deficiency of thyroid hormone may be due to defects of TSH binding or signal transduction. The TSH resistance may be due to mutations in TSH receptor gene [12], a dominantly inherited mutation in long arm of chromosome 15 [13], pseudohypoparathyroidism type 1a caused by g protein mutation [14]. Thyroid dyshormonogenesis is due to defects of thyroid peroxidase activity [15] leading to total iodide organification defects (TIOD), mutations in the enzyme dual oxidase 2 (known as DUOX2 or THOX2) which is autosomal dominant lead to dyshormonogenesis from deficient hydrogen peroxide generation [16], mutations in the dual oxidase maturation factor (DUOXA2) gene also lead to deficient iodide organification [17]. Other, rare causes of dyshormonogenesis include defects in sodium/iodide transport, resulting from a mutation in the gene encoding the sodium-iodide symporter [18], and defective thyroglobulin action, resulting from a mutation in the gene encoding thyroglobulin [19]. A defect in the enzyme iodotyrosine deiodinase which aids in the peripheral conversion of T4 to T3 has been shown in hypothyroid individuals due to homozygous mutations in the genes DEHAL1 or SECISBP2 [19, 20].

Congenital secondary or central hypothyroidism results from defects of TSH production. Mutations in genes regulating pituitary gland development, like HESX1, LHX3, LHX4, PIT1 and PROP1 have been reported to be a cause of familial hypopituitarism. Besides TSH deficiency, other pituitary hormones are often deficient, including growth hormone, adrenocorticotrophic hormone and antidiuretic hormone. Peripheral CH can be due to resistance to thyroid hormone because of thyroid receptor b mutation, abnormalities of thyroid hormone transport, known as Allan-Herndon-Dudley syndrome (monocarboxylase transporter 8 [MCT8] gene mutation) [21]. Transient

congenital hypothyroidism is due to maternal intake of antithyroid drugs [22], transplacental passage of maternal TSH receptor blocking antibodies[23], maternal and neonatal iodine deficiency or excess, heterozygous mutations of THOX2 or DUOXA2[24], congenital hepatic hemangioma/hemangioendothelioma [25].

2.3 Hyperthyroidism

Hyperthyroidism (overactive thyroid) is a condition in which the thyroid gland produces too much of the hormone thyroxine. Hyperthyroidism can accelerate the body's metabolism significantly, causing sudden weight loss, a rapid or irregular heartbeat, sweating, and nervousness or irritability.

Table 3. Hyperthyroidism

Types	Cause
Autoimmune disorder Grave's disease	Autoimmune disorder Grave's disease the body makes an antibody (a protein produced by the body to protect against a virus or bacteria) called thyroid-stimulating immunoglobulin (TSI) that causes the thyroid gland to make too much thyroid hormone.
Toxic nodular or multinodular goitre	Lumps or nodules in the thyroid gland that cause the thyroid to produce excessive amounts of thyroid hormones
Thyroiditis	From a virus or a problem with the immune system may temporarily cause symptoms of hyperthyroidism.

Table 4. Symptoms of Hyperthyroidism

Sudden weight loss
Rapid heart beat
Increased apetite
Nervousness, anxiety, irritability
Tremors, sweating, changes in menstrual pattern
Increased sensitivity to heat
Changes in bowel patterns
Fatigue
Enlarged thyroid gland appearing as swelling at the base of neck
Sleep difficulty
Skin thinning, fine brittle hair

2.4 Thyroid disorders in pregnancy-

Thyroid disorders are the second most common endocrinopathies found in pregnancy [26] which remain undetected and untreated leading to fatality. Hyperthyroidism affects 1-4 in 1000 pregnancies of which Grave's Disease accounts for almost 90-95%. Hypothyroidism seems to be more common almost 0.3- 0.5% for overt hypothyroidism and 2–3% for subclinical hypothyroidism. Thyroid autoantibodies are found in 5–15% of women in the childbearing age and are a risk factor for hypothyroidism during pregnancy and post partum period. Hashimoto thyroiditis is the most common cause whereas Atrophic thyroiditis is less common. Postpartum thyroiditis (PPT) affects 1 in 20 women in the postpartum period [26]. Since hypothyroidism and hyperthyroidism are common endocrine disorders in women, the burden of undetected thyroid diseases in the antenatal mother is significant [27].

2.5 Thyroid nodules and malignancies- Thyroid nodules are small fluid filled protuberances, but they can become large in size and can be felt in front of the neck. The prevalence of these nodules in a given population depends on a number of factors like age, sex, diet, iodine deficiency, and even therapeutic and environmental radiation exposure. Prevalence increases with age, with spontaneous nodules occurring at a rate of 0 - 0.8% per year, beginning early in life and continuing till the age of 80 [28, 29]. STN can be classified into benign and malignant nodule. Generally, most (90%) thyroid nodules are benign and can be classified as adenomas, colloid nodules, cysts, infectious nodules, lymphocytic or granulomatous nodules, hyperplastic nodules, thyroiditis, and congenital abnormalities. 5-10% of all thyroid nodules coming to
medical attention are carcinomas [27] In areas of iodine sufficiency, papillary carcinomas are the predominant variety. Different studies from India show a predominance of papillary malignancy followed by follicular malignancies. The overall prognosis for thyroid carcinoma is worse in endemic goitre regions, in comparison with regions with an adequate dietary iodine intake. This may be due to the higher incidence
of un-differentiated thyroid malignancies in iodine deficiency areas [30]. Male predominance was reported in medullary thyroid carcinoma in contrast to differentiated thyroid malignancies [31]. Studies have revealed the prevalence of thyroid malignancies in children. 85% of the 122 patients had papillary carcinoma of thyroid. The disease was found to be more aggressive and widespread in younger age groups (< or =10 years), with male predominance and high mortality [32].

3. Assessment of thyroid disorders

With the advancements of the diagnostic techniques, the physical examination of the thyroid gland has lost importance although it is the least expensive method. But the clinical evaluation of thyroid starts from the beginning when a patient goes for consultation to a doctor. The hoarseness of voice gives some clue [33] as well as the common symptoms mentioned above which the patient complaints about. The examination starts around the neck region for any swelling, scars and asymmetry. Erythema overlying a tender swelling may be due to suppurative thyroiditis or infected thyroglossal cyst or brachial cleft cyst [34]. Sometimes thin patients have the gland located higher in the neck overlying the thyroid cartilage and give the appearance of enlarged thyroid, a condition known as pseudogoitre [35]. Over the past five decades, great improvements have been made in the sensitivity and specificity of thyroid test methodologies that have highly impacted the clinical strategies for detecting and treating thyroid disorders. Blood tests to measure TSH, T_4, T_3 and Free T_4 are readily available and widely used. According to American Thyroid Association the following tests are recommended

- Measuring TSH levels in the blood is one of the primary tests for thyroid function. A high TSH level indicates hypothyroidism where as a low TSH level indicates the hyperthyroid condition.
- Test to determine free T_4, called Free T_4 index (FTI) is one of the important parameters to determine thyroid functioning. Patients with high FTI indicate hyperthyroidism whereas patients with low FTI indicate hypothyroidism.
- T_3 tests are often used to diagnose hyperthyroid patients but are rarely helpful in hypothyroid patients. Patients can be severely hypothyroid with a high TSH and low FT_4 or FTI but have a normal T_3.
- Measuring levels of thyroid antibodies may help diagnose the cause of the thyroid problems. Two common antibodies that cause thyroid problems are directed against thyroid cell proteins: thyroid peroxidase and thyroglobulin. Positive anti-thyroid peroxidase and/or anti-thyroglobulin antibodies in a patient with hypothyroidism make a diagnosis of Hashimoto's thyroiditis. If the antibodies are positive in a hyperthyroid patient, the most likely diagnosis is autoimmune thyroid disease.
- The thyroid gland must pull a large amount of iodine out from the blood stream in order for the gland to make an appropriate amount of T_4. Therefore, this activity can be measured by means of applying radioactive iodine. By measuring the amount of radioactivity that is taken up by the thyroid gland (radioactive iodine uptake, RAIU), doctors may determine whether the gland is functioning normally. A very high RAIU is seen in individuals whose thyroid gland is overactive (hyperthyroidism), while a low RAIU is seen when the thyroid gland is underactive (hypothyroidism).

The evaluation of solitary thyroid nodule is done by taking a detailed medical history, general physical examination, metabolic profile (thyroid function tests), imaging and invasive procedures including FNAC. During Examination the following facts must be taken care of- whether the nodule benign or malignant; is the nodule causing pressure symptoms on the adjoining structures of the neck and whether the nodule secreting excess of thyroid hormone. Serum thyroglobulin level is not recommended in STN diagnosis as it cannot differentiate a beningn from a malignant nodule [36]. Serum calcitonin level is checked which becomes fairly high in medullary thyroid cancer and multiple endocrine neoplasia type II (MEN-II). Ultrasonographic imaging has no role in screening for thyroid nodules in asymptomatic patients [37]. Recently, DNA testing has become an effective method for the diagnosis of MEN 2a and 2b syndromes. RET proto-oncogene located in the para-centromeric region of the short arm of chromosome 10 is the site of mutation in 90% patients with familial medullary thyroid cancer (MTC) and MTC associated with MEN2a and 2b [37]. Scanning the thyroid with I 123 or Tc99mm can indicate the functional activity of a nodule and of the thyroid and correlate the location of palpable nodules with nodules seen with scanning. The major drawback of this imaging is its failure to differentiate between benign and malignant thyroid nodules with great accuracy, while other drawbacks include an inability to delineate thyroid gland as well as misinterpretation of the functional status of the thyroid nodule if normal functioning thyroid tissue overlies the cold solitary thyroid nodule, or if the thyroid gland is asymmetric [38]. FNAC is the most specific investigation to differentiate between benign and malignant nodules. Diagnosis is correct for papillary thyroid carcinoma in about 90 - 100% of FNAC specimens when correlated with the histology of the final surgical specimen. Undifferentiated

(anaplastic) carcinoma, MTC and primary thyroid lymphoma also have characteristic cytologic features which help in arriving at a correct diagnosis in about 90% of FNAC specimens [39, 40, 41]

4. Management of thyroid disorders

4.1 Hypothyroidism

Discursive treatment for thyroid disorders is beyond the scope of this review. The generalised recommended dose of medicine for hypothyroidism is levothyroxine sodium, or l-thyroxine, replacement at 0.25 milligrams every day and titrated according to the patient's response at monthly intervals. The appropriate initiating dose should be around 1.6 micrograms per kilogram. An extra dose may be required during pregnancy or when taken concurrently with intake of rifampin and some anticonvulsant medications [42]. Uncontrolled therapy should be clearly avoided and strict monitoring by the physician is recommended because of the possibility of causing iatrogenic hyperthyroidism. Both T4 and T3 can be combined when severe deficiency of both hormones is present [1]. People who have angina pectoris (symptomatic ischemic heart disease) should take l-thyroxine in the morning; at least 30 minutes or more before breakfast; and at least one hour before or after taking iron supplements, antacids or sucralfate [43]. Hormone dose is increased 0.25 mg every three weeks until a 1 mg/day dosage is reached. Thyroid function tests are performed at six weeks after treatment is initiated. Effectiveness of therapy is measured by a sensitive TSH assay, in which an elevated value indicates insufficient treatment. Hormone levels may need to be titrated in cases of immune-mediated hypothyroidism and in relation to interactions with certain medications. Followup should be done for TSH and T4 at six months interval once the euthyroid condition is achieved. In infantile or neonatal states, therapy should start as soon as possible owing to the risk of developmental delay. In cases of pituitary or hypothalamic hypothyroidism, however, corticosteroid treatment should precede thyroid hormone therapy to avoid the possibility of adrenal insufficiency [1]. For congenital hypothyroidism treatment should start as early as possible for prevention of any developmental delay. There are certain oral manifestations in hypothyroidism which include macroglossia, dysgeusia, delayed eruption, poor periodontal health and delayed wound healing [44]. When l-thyroxine is used, it increases the effects of warfarin sodium and, because of its gluconeogenic effects, the use of oral hypoglycaemic agents must be increased. Concomitant use of tricyclic antidepressants elevates l-thyroxine levels. Appropriate coagulation tests should be available when the patient is taking an oral anticoagulant and thyroid hormone replacement therapy [45].

4.2 Hyperthyroidism-

Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: RAI therapy,antithyroid drugs (ATDs), or thyroidectomy [46]. Recent studies show an increasing trend towards the use of ATDs rather RAI therapy among the physicians in USA, Latin America, Japan and Europe [47, 48]. RAI therapy is chosen in certain conditions such as failure of ATDs, patiens planning a pregnancy in more than 6 months from the treatment, previously operated necks or having any surgical risks, pulmonary hypertension or congestive heart failure. Pregnant women, indivuals failing to comply by the radiation safety regulations, mild goiter, increased surgical risk, need of rapid biochemical disease control should go for ATDs. Surgery is recommended for patients planning to conceive in less than six months provided their thyroid hormone levels are in control, thyroid malignancy is reported, large nodules greater than 4cm or non/ hypofunctioning to RAI and patients with moderate to severe Grave's orbitopathy [49]. Carbimazole, methimazole and propylthiouracil (PTU) are the tree common ATDs. In normalizing T3 and T4, both imazoles and PTU are equally effective. Safety profile of the

two drugs should be taken into consideration [50]. Various studies have shown that there are no significant differences in the minor side effects but when considering major adverse effects like hepatitis and agranulocytosis, imazoles appear to have a better safety profile [51]. The ATDs have certain advantages over RAI such as rapid correction of toxic symptoms, can be given in pregnancy and lactation, no adverse effects in presence of ophthalmology, no interference with daily activities, no permanent hypothyroidism, and out patient therapy. The surgery is a definitive treatment for hyperthyroidism with no radiation hazards. The choice of treatment procedure should be based on careful monitoring of the patient's medical history as pentioned previously.

Thyroid nodules larger than 1–1.5 cm should be evaluated before RAI therapy. If a RAI scan is performed, any nonfunctioning or hypofunctioning nodules should be considered for FNA because they may have a higher probability of being malignant [52]. If the cytopathology is suspicious or diagnostic of malignancy, surgery is advised after normalization of thyroid function with ATDs. Surgery should also be considered for indeterminate cytology. Disease-free survival at 20 years is reported to be 99% after thyroidectomy for GD in patients with small coexisting thyroid cancers [53]. Thyroid storm is the main complication of persistent hyperthyroidism. It is defined as the body's response to maintained thyrotoxicosis.

This is common in postoperative states in patients who have uncontrolled or undiagnosed hyperthyroidism.

It also can be triggered by a surgical emergency, sepsis and trauma. Some case reports describe acute renal failure, lactic acidosis and absence of fever [54]. The initiating stimulus for thyroid storm is unknown. It has been hypothesized that it is not caused by glandular hyperfunction but rather by a decrease in protein binding

capacity. Severe cardiac dysrhythmias and blockages can occur secondary to long-term exposure to thyroid hormones. The treatment strategy for thyroid storm can be broadly divided into (i) therapy directed against thyroid hormone secretion and synthesis; (ii) measures directed against the peripheral action of thyroid hormone at the tissue level; (iii) reversal of systemic decompensation; (iv) treatment of the precipitating event or intercurrent illness; and (v) definitive therapy [55]. A number of therapeutic measures are specifically intended to decrease T4-to-T3 conversion, such as the preferential use of PTU over MMI [56, 57], glucocorticoid therapy [58], and the use of b-adrenergic blocking agents such as propranolol, with selective ability to inhibit type 1 deiodinase [59]. Prevention of thyroid storm involves recognizing and actively avoiding common precipitants, educating patients about avoiding abrupt discontinuation of ATD therapy, and ensuring that patients are euthyroid prior to elective surgery, labor and delivery, or other acute stressors [49]. Both plasmapheresis/ plasma exchange and emergency surgery have been used to treat thyroid storm in patients who respond poorly to traditional therapeutic measures [60]. The oral manifestations of hyperthyroidism are salivary gland enlargement, macroglossia, glossitis, delayed dental eruption, compromised periodontal health—delayed bone resorption, dysgeusia. Oral health care professionals should recognize the signs and symptoms of a thyroid storm, as the patient could present for dental care during its

initial phase or when undiagnosed. Patients who have hyperthyroidism have increased levels of anxiety, and stress or surgery can trigger a thyrotoxic crisis. Epinephrine is contraindicated, and elective dental care should be deferred for patients who have hyperthyroidism and exhibit signs or symptoms of thyrotoxicosis.

Stress management are important for patients who have hyperthyroidism. Treatment should be discontinued if signs or symptoms of a thyrotoxic crisis develop and access to emergency medical services should be

available [1].

5. Conclusion

This review describes the adverse effects of thyroid dysfunction as and recommends treatment approaches aimed at decreasing perioperative risk. The ubiquitous effects of both thyroid hormone deficiency and thyroid hormone excess throughout multiple organ systems predispose patients with either condition to specific perioperative complications, some of which can be severe or even fatal. Thyroid disorders have different types of clinical expressions. It is therefore necessary for a medical practioner to be very vigilant on each suspected case of thyroid disease and recommend appropriate laboratory evaluation. Combination of these can lead to an appropriate treatment for thyroid disorders. Regular monitoring is also necessary to forecast prospective consequences. It is essential to preserve the link between patients, physicians and scientists to devise a judicious and comprehensive way of dealing with thyroid disorders in future.

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