ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 9, Issue, 3(I), pp. 25288-25299, March, 2018

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Review Article

SCENARIO OF HYPOTHYROIDISM AND ITS RECENT ADVANCES IN THE DIAGNOSIS AND MANAGEMENT – A REVIEW

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DOI: http://dx.doi.org/10.24327/ijrsr.2018.0903.1832

ARTICLE INFO

Article History:

Received 15th December, 2017
Received in revised form 25th January, 2018
Accepted 23rd February, 2018
Published online 28th March, 2018

Key Words:

Thyroid gland, Hypothyroidism, Body Systems, Management, Diagnosis

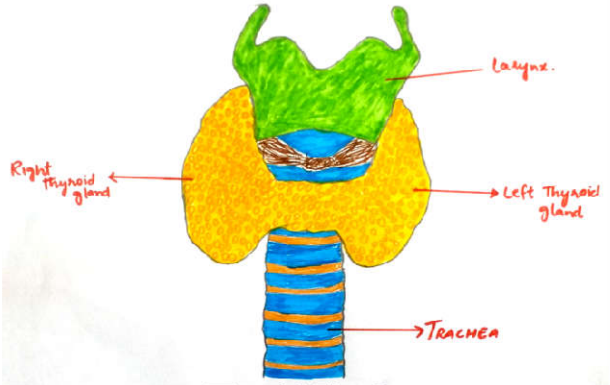
ABSTRACT

Thyroid hormones are secreted by thyroid gland located in front of neck below the Adam`s apple to control body metabolism rate, so that any alteration in their action will affect the system of many organs. Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone or, more rarely, from their impaired activity at body level. In its clinically overt form, hypothyroidism is a relatively common condition, with an approximate prevalence of 2% in adult women and 0.2% in adult men. Deficiency of the hormone has a wide range of effects, because all metabolically active cells require thyroid hormone for their normal function. The clinical features of hypothyroidism are dependent on the patient's age, the presence of other disease, and the rate at which hypothyroidism develops. Early detection and proper management is very important. Under treatment leads to disease progression with gradual worsening of symptoms and further metabolic derangements. Fortunately, in most patients older than 3 years, the signs and symptoms of hypothyroidism are reversed with thyroid hormone treatment. With increased rate of thyroid abnormalities in current scenario there is need of more advancement in diagnostic technology and there should be proper management and awareness camps in Hospitals and in general public via Running the public awareness programmes on electronic media (Radio, TV, etc) and news papers. Thus, the aim of this review paper is to bring to notice the recent advances in the diagnosis and management of hypothyroidism and to highlight the risks involved in the disease, therefore this review will give in detail a clear picture of the hypothyroidism.

INTRODUCTION

Thyroid gland is a vital link in the endocrine system. It is a butterfly-shaped organ that sits at the front of neck below the Adam`s apple. It produces two related hormones, thyroxin (T4) & triiodothyroxine (T3). These hormones play a critical role in cell differentiation during development & help to maintain thermogenic & metabolic homeostasis. Disorders of thyroid gland result primarily from autoimmune processes that either stimulate the over production of thyroid hormone or cause glandular destruction and underproduction of thyroid hormones (hypothyroidism). Hypothyroidism is defined as a deficiency of thyroid activity and is a common endocrine disorder resulting from deficiency of thyroid hormone or, more rarely, from their impaired activity at tissue level (Majid S., *et al*).

Hypothyroidism is a condition characterized by abnormally low thyroid hormone production.



Thyroid Gland

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There are many disorders that result in hypothyroidism. These disorders may directly or indirectly involve the thyroid gland. Because thyroid hormone affects growth, development, and many cellular processes, inadequate thyroid hormone has widespread consequences for the body.

Subclinical hypothyroidism is much more common and less easily recognized, because of the variety of symptoms. The following are symptoms of hypothyroidism: fatigue, loss of energy, lethargy; weight gain; decreased appetite; cold intolerance; dry skin; hair loss; sleepiness; muscle pain, joint pain, weakness in the extremities; depression; emotional lability, mental impairment; forgetfulness, impaired memory, inability to concentrate; constipation; menstrual disturbances, impaired fertility; decreased perspiration; paresthesia (abnormal sensation such as tingling, pricking, numbness or burning of a persons skin with no apparent physical cause) and nerve entrapment syndromes; blurred vision; decreased hearing; fullness in the throat, hoarseness(voice involuntarily sounds breathy, raspy, or is softer in volume); neck pain, sore throat, or both (Hashimoto thyroiditis); low-grade fever (Hashimoto thyroiditis) (James., *et al* 2015, Melissa Gillett 2004)

Significant controversy persists regarding the treatment of patients with mild hypothyroidism. Some have argued that treatment of these patients improves symptoms, prevents progression to overt hypothyroidism, and may have cardioprotective benefits. Reviews by an independent expert panel (Negro *et al*., 2006) found inconclusive evidence to recommend aggressive treatment of patients with TSH levels of 4.5 to 10 mIU/L. However, the Endocrine Society recommends thyroxine replacement in pregnant women with subclinical hypothyroidism (US Preventive Services Task Force, 2004).

Treatment of subclinical hypothyroidism has been shown to reduce total cholesterol, non-high density lipoprotein (HDL) cholesterol, and apolipoprotein B (Ito *et al*., 2007) and to decrease arterial stiffness and systolic blood pressure (Peleg *et al*., 2008). In patients with concomitant subclinical hypothyroidism and iron deficiency anemia, iron supplementation may be ineffective if LT4 is not given (Gyamfi *et al*., 2009). Oral LT4 should be administered on an empty stomach. A serum TSH value in the low-normal range is probably the best indicator of appropriate thyroid hormone replacement therapy (Helfand., *et al* 1990).

Thyroid Physiology

In vertebrates Thyroid hormones are the only iodine-containing substances of physiologic significance. Thyroid cells actively extract & concentrate iodide from plasma. T4, a proharmone, is converted to triiodo-thyronine (T3), the active form of thyroid hormone, in the peripheral tissues by 5'-deiodination. Early in the disease process, compensatory mechanisms maintain T3 levels.

Normal thyroid produces all of the circulating T4 and about 20% of the circulating T3 (Surks *et al*., 2004). Most of the biologic activity of thyroid hormones is due to the cellular effects of T3, which has a greater affinity for the thyroid hormone receptor and is approximately 4 to 10 times more potent than T4 (Surks *et al*., 1973; Sawin *et al*., 1977). 80% of serum T3 is derived from the deiodination of T4 in tissues such as the liver and kidney.

Once T4 and T3 are released into the circulation, they are bound by thyroxine-binding globulin (TBG), transthyretin (thyroxine-binding prealbumin), and albumin. Thyroxine-binding globulin has the highest affinity for T4 and T3 and the lowest capacity, whereas albumin has the lowest affinity and the highest capacity. Only the free (unbound) fraction of T4 and T3 is able to bind to specific thyroid hormone receptors in peripheral tissues and possess biologic activity. Normally, approximately 0.03% of T4 and 0.5% of T3 is free (The National Academy of Clinical Biochemistry, 1996; Oppenheimer *et al*., 1972) (Figure 1).

Complications arise in the diagnosis of hypothyroidism when changes occur in the binding capacity of thyroid hormone transport proteins which significantly affect the measurement of total thyroid hormone concentration. The patients having multiple abnormalities in thyroid hormone-binding proteins show more difficulty in accurate diagnosis of thyroid disease.

Pathophysiology

Localized disease of the thyroid gland that results in decreased thyroid hormone production is the most common cause of hypothyroidism. Under normal conditions, the thyroid releases 100 to 125 nmol of T4 daily and only small amounts of T3. Decreased production of T4 causes an increase in the secretion of TSH by the pituitary gland. TSH stimulates hypertrophy and hyperplasia of the thyroid gland and thyroid T4-5'- deiodinase activity. This in turn causes the thyroid to release more T3. All metabolically active cells need thyroid harmone so its deficiency creates a wide range of effects in our body systems. Systemic effects are due to either derangements in metabolic processes or direct effects by myxedematous infiltration (that is, accumulation of glucosaminoglycans in the tissues).

Subsequently, the effects of thyroid hormone deficiency on growth and development, on intermediary metabolism, on central nervous system development and function, and on cardiovascular, skeletal, gastrointestinal, and reproductive system activity have been characterized. They are briefly summarized subsequently.

Growth and development

During the first 2 decades of life thyroid hormone exerts profound effects on growth and development. There is adverse affect to the development of the central nervous system when there is deficiency of Thyroid hormone. (Langsteger *et al*., 1994; Rodriguez-Pena, 1999; Bernal and Nunez, 1995), auditory system (Dussault and Ruel, 1987), and skeletal system (Sohmer and Freeman, 1996). Hypothyroidism also delays dental development and eruption (Williams *et al*., 1998).

The combination of maternal and fetal hypo-thyroxinemia produced by iodine deficiency is associated with irreversible fetal central nervous system damage (Pirinen, 1995). Preliminary evidence suggests that low maternal free thyroxine concentration may impair neuro development in the healthy fetus (Fisher, 1997). A recent study indicates that maternal hypothyroxinemia produces alterations in the activity of neurotransmitter metabolic enzymes that have putative neurotropic functions in brain development (James *et al*., 1999).

Although, the function of the fetal hypothalamic-pituitary axis develops autonomously of the mother, it is dependent on maternal supply of iodine derived mostly from placental deiodination of T4. The placenta is impermeable to TSH and permeable to TRH. Under normal circumstances, neither T3 nor T4 freely crosses the placenta to a large extent. However, it appears that the maternal contribution of T4 increases in cases of congenital hypothyroidism. In a study of infants who were unable to synthesize T4, cord serum levels of T4 were 35 to 70 nmol/L (Evans *et al*., 1999). This suggests an increased transport of T4 from the mother to the fetus. Thus, transplacental movement of maternal T4 may provide a partial explanation for the relatively normal clinical appearance at birth of most infants with congenital hypothyroidism.

The risk of permanent brain damage can be minimized by initiating thyroid replacement shortly after birth, as two-thirds of postnatal brain growth & differentiation occurs during the first 2 years of life. Deficiency of thyroid hormone that developes after 3years of age is associated with delayed linear & somatic bone growth & delayed eruption of permanent teeth but not associated with mental impairment. Early detection and treatment of hypothyroidism in infants & children enables normal prepubertal & pubertal growth & achievement of maximal potential adult height (vulsma-*et al* 1989).

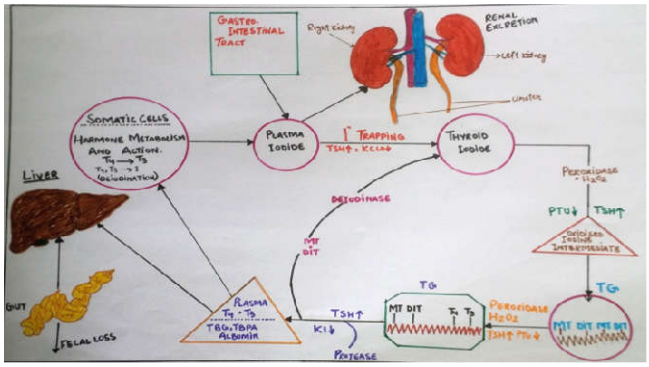

Figure 1 The iodide cycle

Ingested iodide is trapped in the thyroid, oxidized and bound to tyrosine to form iodotyrosines in thyroglobulin (TG); coupling of iodotyrosyl residues forms T4 and T3. Hormone secreted by the gland is transported in serum. Some T4 is deiodinated to T3. The hormone exerts its metabolic effect on the cell and is ultimately deiodinated; the iodide is reused or excreted in the kidney. A second cycle goes on inside the thyroid gland, with deiodination of iodotyrosines generating iodide, some of which is reused without leaving the thyroid.

Metabolism

One of the earliest recognized physiologic actions of thyroid hormone was its effect on the basal metabolic rate (Dickerman and De Vries, 1997). Generally reduction in the usual metabolic rate is the cause of deficiency of thyroid harmone. This is manifested as the intolerance to cold temperatures experienced by many hypothyroid patients. Thyroid hormone is also an important modulator of intermediary metabolism. Hypothyroidism is associated with an increase in serum concentrations of intermediate-density lipoprotein and low-density lipoprotein (LDL) cholesterol due to a change in metabolic clearance. Hyperlipidemia may contribute to the higher risk for developing coronary artery disease associated with hypothyroidism (Freake and Oppenheimer, 1995). Total cholesterol & LDL serum levels are often increased in hypothyroid individuals (O'Brien *et al*., 1993; Yildirimkaya *et al*., 1996). The LDL particles of hypothyroid patients are potentially more atherogenic, because of their increased susceptibility to oxidation (Althaus *et al*., 1988). Coronary artery disease progression can be decreased by Thyroid hormone replacement therapy due to its beneficial effects on lipids (Sundaram *et al*., 1997; O'Brien *et al*., 1994). Decreased rate of glucose absorption from the gastrointestinal tract alteres the glucose homeostasis. Insulin secretion in response to a glucose load varies in hypothyroid individuals, but there is evidence of insulin resistance and reduced glucose utilization (Fowler *et al*., 1996; Pedersen *et al*., 1988). Hypothyroid patients generally exhibit a decreased appetite. Contrary to popular belief, obesity is not a feature of hypothyroidism. Although, some patients experience weight gain, the amount is modest and mostly attributed to fluid accumulation.

Impact of hypothyroidism on body systems: Thyroid gland produces hormones that regulate the body's energy use, along with many other important functions. Hypothyroidism condition occurs in the body when the thyroid gland is hypoactive due to which the thyroid hormone production drops & the body's processes slow down and change. The symptoms might be mild to severe depending on how the thyroid hormone production drops. The thyroid is a perfect example of all these complex interactions and connections so that hypothyroidism can affect many different systems in your body.

Nervous system

The generalized neurologic manifestations of hypothyroidism include headache, vertigo or tinnitus, relaxation of deep tendon reflexes, psychiatric disorders, cognitive deficits, and visual disturbances. Sensory disorders such as numbness, tingling, and paraesthesias are frequently reported. Thyroid hormone replacement ordinarily resolves hypothyroidism-associated hearing loss (Ober, 1985). It has been recommended that thyroid function be evaluated in hypothyroid patients, especially if they are elderly, prior to initiating any form of treatment, because these patients often manifest symptoms of depression (Anand *et al*., 1989). If symptoms of affective disorders are related to hypothyroidism, they may improve or resolve on reestablishing euthyroidism.

Cardiovascular system

The cardiovascular effects of hypothyroidism are extensive and produce symptoms consistent with heart failure (Manciet *et al*., 1995). The myxedematous changes in the heart result in decreased contractility, pulse rate and stroke volume are diminished, and cardiac output is often decreased to half the normal value (Polikar *et al*., 1993). Pericardial effusion is evident (Wieshammer *et al*., 1988). By narrowing arteries this condition can also raise Blood pressure. Thyroid hormone replacement therapy reverses most of these pathologic changes (Kabadi and Kumar, 1990; Moruzzi *et al*., 1996), but must be cautious in the elderly to avoid precipitating or exacerbating angina pectoris, acute myocardial infarction, ventricular arrhythmias, and congestive heart failure (Bernstein *et al*., 1995).

Musculoskeletal system

One of the most obvious manifestations of hypothyroidism is the delayed relaxation of deep tendon reflexes (Aronow, 1995). Hypothyroid patients may also exhibit arthralgias-(joint pain), joint effusions, and pseudogout-(a type of arthritis that cause spontaneous, painful swelling in the joints) (Westphal, 1997). There is some evidence of reduced bone turnover (McLean and Podell, 1995). In children, hypothyroidism is associated with delayed linear bone growth and skeletal maturation (Sohmer and Freeman, 1996).

Gastrointestinal (GI) system

In the GI tract, achlorhydria and decreased intestinal transit with gastric stasis can occur (Allain and McGregor, 1993). Achlorhydria caused by atrophic body gastritis has been associated with thyroiditis (Kahraman *et al*., 1997). Parietal cell antibodies have been found in patients with Hashimoto's thyroiditis (Centanni *et al*., 1999) and pernicious anemia is thought to occur more often in patients with autoimmune thyroid disease (Kogawa, 1975).

Reproductive system

The effects of hypothyroidism on fertility are mediated by a disruption of gonadotropin secretion and steroidgenesis. Levels of follicle-stimulating hormone(FSH) and leuteinizing hormone (LH) may be increased, normal, or decreased, and the preovulatory LH surge may be absent (Ottesen *et al*., 1995). In females, hypothyroidism is associated with menstrual irregularities, anovulation, and infertility (Stradtman, 1993). In males, hypothyroidism is associated with abnormalities of gonadal function (Joshi *et al*., 1993). Hypothyroidism is a rare cause of delayed puberty (Wortsman *et al*., 1987). In addition, antithyroid peroxidase or thyroperoxidase (TPO) antibodies have been associated with a higher risk of infertility and miscarriage.

Respiratory system

Respiratory system like other body systems and organs is affected by hypothyroidism. The spectrum of diseases involvement can range from mild dyspnoea (shortness of breath) to more severe and life threatening respiratory failure (Mcquade., *et al* 2011). Hypothyroidism exerts different effects on the respiratory system. One of the major effects of hypothyroidism is its influence on the central ventilatory control. Hypoxic ventilatory drive is significantly depressed in both untreated myxoedema and during brief periods of thyroid hormone insufficiency. This depression is particularly striking in myxoedema. Hypoxic ventilatory drive increases dramatically with hormone replacement therapy (Datta., *et al* 2004). Hypothyroidism may lead to the development of myopathy, and has been evaluated particularly for the inspiratory and expiratory muscles. Inspiratory and expiratory muscle strength is linearly related to the degree of hypothyroidism and suppletion restores respiratory muscle function.

Signs and symptoms

Clinical presentation may vary from mild and asymptomatic to severe and overt disease, it may depend on patient's age, gender, physical condition, the rate at which hypothyroidism develops and may affect adults differently than children. The disease commonly manifests as a slowing in physical and mental activity. In most spontaneous cases, a decrease in thyroid function occurs gradually, with subclinical hypothyroidism progressing over time to overt hypothyroidism. It may be associated with either a decrease or an increase (goiter) in thyroid size. Some patients will present with obvious symptoms of hypothyroidism and minimal changes in thyroid hormone levels, whereas others will have subtle symptoms despite markedly abnormal thyroid function.

Classic signs and symptoms, such as cold intolerance, puffiness, decreased sweating, and coarse skin, previously reported in 90 to 97% of patients, may actually occur in only 50 to 64% of younger patients. Many common symptoms are nonspecific. Individuals can also present with obstructive sleep apnea (secondary to macroglossia) or carpal tunnel syndrome. Females can present with galactorrhea (spontaneous flow of milk from the breast, unassociated with childbirth or nursing) and menstrual disturbances. Thus, the diagnosis of hypothyroidism is based on clinical Signs found suspicion and a careful physical examination is required for their detection. Most of the signs are nonspecific and can be overlooked if the disease is mild or if the patient has coexisting conditions that have similar symptoms. This is especially true in elderly patients.

Clinicians should consider a diagnosis of hypothyroidism when the following signs are present

hypothermia; weight gain; slowed speech and movements; dry skin; jaundice; pallor; coarse, brittle, straw like hair; loss of scalp hair, axillary hair, pubic hair, or a combination; dull facial expression; coarse facial features; periorbital puffiness; macroglossia; goiter; hoarseness; decreased systolic blood pressure and increased diastolic blood pressure; bradycardia; pericardial effusion; abdominal distension, ascites (uncommon); nonpitting edema (myxedema); pitting edema of lower extremities; hyporeflexia with delayed relaxation, ataxia, or both.

Causes of hypothyroidism

Iodine deficiency remains the foremost cause of hypothyroidism worldwide. Autoimmune thyroid disease is mostly common in the United States and other areas of adequate iodine intake. The prevalence of antibodies is higher in women, and increases with age. Hypothyroidism may be caused by dysfunction of the thyroid gland (primary), pituitary (secondary), or hypothalamus (tertiary). In more than 95% of patients, hypothyroidism is caused by primary dysfunction of the thyroid gland. Primary hypothyroidism is caused by a decreased production of thyroid hormones by the thyroid gland. It is a relatively common disease in both iodine-deficient and iodine-sufficient populations. The most common cause is destruction of the thyroid gland by autoimmune disease or by ablative therapies (iodine 131 therapy or external radiation to the head and neck). Hypothyroidism may also be caused by factors that negatively affect the synthesis of thyroid hormones, such as iodine deficiency or excess, and inherited defects in thyroid hormone biosynthesis. Thyroid hormone synthesis can be inhibited by pharmacologic agents such as lithium and amiodarone (Gittoes and Franklyn, 1995; Jordan, 1995; Smallridge, 1992). Much rarer causes are hemochromatosis (Shirota *et al*., 1992) sarcoidosis (Bell, 1991), and amyloidosis

(Rich, 1995). Rarely, hypothyroidism is caused by mutations of thyroid hormone receptors, which produces a syndrome characterized by a variable resistance to the actions of thyroid hormone (Chatterjee,1997;jansson *et al*.,1983).

The most frequent cause of acquired hypothyroidism is chronic autoimmune thyroiditis (Hashimoto thyroiditis). Hashimoto's thyroiditis is an autoimmune disorder associated with specific T and B cell abnormalities (Kasagi *et al*., l996) that result in the presence of microsomal thyroid peroxidase or thyroglobulin antibodies (Hayashi *et al*., 1985). The body recognizes the thyroid antigens as foreign, and a chronic immune reaction gets generated, resulting in polyclonal lymphocytic infiltration (Eskes *et al*., 2010), of the gland and progressive destruction of functional thyroid tissue. Up to 95% of the affected individuals have circulating antibodies to thyroid tissue. Antimicrosomal or antithyroid peroxidase (anti-TPO) antibodies are found more commonly than antithyroglobulin antibodies (95 versus 60%). These antibodies may not be present early in the disease process and usually disappear over time (Hayashi *et al*., 1985). The incidence is approximately 0.3 to 5 cases per 1000 individuals per year, and it occurs 15 to 20 times more frequently in women than in men. There is evidence that the incidence is increasing. The Hashimoto goiter has a firm consistency which may regress with time (Hayashi *et al*., 1985).

Silent or painless thyroiditis and postpartum thyroiditis are variant forms of chronic autoimmune thyroiditis that are usually self limiting (Woeber, 1991; Kung *et al*., 1992). High titers of anti-TPO antibodies during pregnancy have been reported to be 97% sensitive and 91% specific for postpartum autoimmune thyroid disease. The frequency of postpartum thyroiditis may be as high as 25% in women with type 1 diabetes mellitus.

Inborn errors of thyroid hormone synthesis

Thyroid hormone resistance syndrome:- These are rare disorders that can be classified as 2 entities: generalized resistance to thyroid hormone and central resistance to thyroid hormone (Refetoff *et al*., 1993, 1972). Patients with generalized resistance exhibit a reduced peripheral sensitivity to thyroid hormone. It is a familial condition caused by mutations of the T3 receptor, which results in a lower affinity for thyroid hormone. Usually, this is a single base mutation, although the patients initially studied by Refetoff *et al*. (1967, 1972) had a larger deletion in the T3-receptor beta gene. In both disorders, mutations to the thyroid hormone receptor are localized to the hormone-binding domain. Iodine deficiency or excess: Excess iodine, as in radiocontrast dyes, amiodarone, health tonics, and seaweed, inhibits iodide organification and thyroid hormone synthesis. Most healthy individuals have a physiologic escape from this effect; however, those with abnormal thyroid glands e.g. patients with autoimmune thyroiditis, surgically treated Graves hyperthyroidism (subtotal thyroidectomy) and prior radioiodine therapy may not (Kreisman and Hennessey, 1999).

Recent advancement in Laboratory diagnosis of hypothyroidism

Over the past five decades, improvements in the sensitivity and specificity of thyroid test methodologies have dramatically impacted the clinical strategies for detecting and treating thyroid disorders. In the 1950s, only one thyroid test was available- an indirect estimate of the serum total (free + protein-bound) thyroxine (TT4) concentration, using the protein bound iodine (PBI) technique. Since 1970, technological advances in radioimmunoassay (RIA) and immunometric assay (IMA) methodologies have progressively improved the specificity and sensitivity of the methods. The present scenario currently, thyroid testing is performed on serum specimens using either manual or automated methods employing specific antibodies. Methodology is still evolving as performance standards are established by the professional organizations and new technology and instruments are developed by manufacturers. A multitude of tests are currently available for testing thyroid function:

- Serum-based methods are available for measuring both total (TT4 and TT3) and free (FT4 and FT3) thyroid hormone concentrations.
- In addition, measurements can be made of the thyroid hormone binding proteins, Thyroxine Binding globulin (TBG), Transthyretin (TTR)/Prealbumin (TBPA) and Albumin, as well as for the pituitary thyroid stimulator, thyrotropin (thyroid stimulating hormone, TSH) and the thyroid hormone precursor protein, Thyroglobulin (Tg).
- The recognition of autoimmunity as the leading cause of thyroid dysfunction, has led to the development and incorporation of tests to determine thyroid autoantibodies – thyroid peroxidise antibodies (TPOAb), thyroglobulin antibodies (TgAb), and TSH receptor antibodies (TRAb).

Biochemical Investigations

Third-generation TSH assays are readily available and are generally the most sensitive screening tool for primary hypothyroidism. The generally accepted reference range for normal serum TSH is 0.40 to 4.2 mIU/L and rises with advancing age (Shikha *et al*., 2010). TSH levels peak in the evening and are lowest in the afternoon, with marked variations due to physiologic conditions such as illness, psychiatric disorders, and low energy intake (Surks *et al*., 2004).

If TSH levels are above the reference range, the next step would be to measure total T4 with a measure of binding proteins. Thyroxine is highly protein bound (99.97%) (Surks *et al*., 2004). The levels of these binding proteins can vary by hormonal status, inheritance, and in various disease states. Hence, free T4 assays are becoming popular as they measure unbound (that is, free hormone). However, free T4 assays can be unreliable in the setting of severe illness. Free thyroid hormone levels can be estimated by calculating the percentage of available thyroid hormone-binding sites (T3 resin uptake) or by measuring the concentration of TBG. A free thyroxine index (FTI) serves as a surrogate of the free hormone level. The FTI is the product of the T3 resin uptake and total T4 levels. No currently available kit actually measures unbound T4 directly.

Patients with primary hypothyroidism have elevated TSH levels and decreased free hormone levels. Patients with elevated TSH levels but normal free hormone levels or estimates are considered to have mild or subclinical hypothyroidism. Primary hypothyroidism is virtually the only

disease that is characterized by sustained, rising TSH levels. As the TSH level increases early in the disease, an increased conversion of T4 to T3 occur, this maintains T3 levels thus in early hypothyroidism, TSH levels are increased, T4 levels are normal to low, and T3 levels are normal (Shikha *et al*., 2010).

Evaluation of the presence of thyroid autoantibodies (antimicrosomal or anti-TPO antibodies) and antithyroglobulin (anti-Tg) may be helpful in determining the etiology of hypothyroidism or in predicting future hypothyroidism. In patients with non-thyroid disease who are severely ill, TSH secretion is normal or decreased, total T4 levels are decreased, and total T3 levels are markedly decreased. This can be confused with secondary hypothyroidism. In these patients, however, the primary abnormality is the decreased peripheral production of T3 from T4. They have an increased reverse T3, which can be measured. Other abnormalities seen in patients who are critically ill include decreased TBG levels and abnormalities in the hypothalamic-pituitary axis. During recovery, some patients have transient elevations in serum TSH concentrations (up to 20 mIU/L). Hence, thyroid function should not be evaluated in a critically ill person unless thyroid dysfunction is strongly suspected, and, if so, screening with TSH alone is insufficient (Shikha *et al*., 2010).

In patients with hypothalamic or pituitary dysfunction, TSH levels do not increase in appropriate relation to the low free T4 levels. The absolute levels may be in the normal or even slightly elevated range, but inappropriately low for the severity of the hypothyroid state (Shikha *et al*., 2010). Hence, when secondary or tertiary hypothyroidism is suspected, a serum TSH measurement alone is inadequate; a free T4 should be measured.

Secondary hypothyroidism resulting from mutations of the TRH receptor is characterized by low levels of TSH and thyroid hormones (Collu *et al*., 1997). These patients exhibit no response to exogenous TSH. The TRH stimulation test is rarely needed currently, because of improved TSH assays.

Imaging Investigations

Ultrasonographic scanning of the neck and thyroid can be used to detect nodules and infiltrative disease. It has little use in hypothyroidism per se unless a secondary anatomic lesion in the gland is of clinical concern. Hashimoto thyroiditis is usually associated with a heterogeneous ultrasonographic image. It can be rarely associated with lymphoma of the thyroid. Serial images with fine-needle aspiration of suspicious nodules may be useful (Surks *et al*., 2004). For radioactive iodine uptake (RAIU) and thyroid scanning, patients with Hashimoto thyroiditis may have relatively high early uptake (after 4 h), but do not have the usual doubling of uptake at 24 h consistent with an organification defect.

Patients undergoing whole-body F18-fluorodeoxy-glucose positron emission tomography (FDG-PET) for non-thyroid disease often show significant thyroid uptake as an incidental finding ((Liu, 2009). In general, diffuse uptake by the thyroid on fluorodeoxyglucose positron emission tomography (FDG-PET) is considered a benign finding and is typical of thyroiditis and/or hypothyroidism.

Ultrasonography may have prognostic value in sub-clinical hypothyroidism. In an Italian study, progression to overt hypothyroidism occurred more often in patients whose ultrasonographic thyroid scan showed diffuse hypoechogenicity (an indication of chronic thyroiditis) (Yamada and Mori, 2008).

Fine-needle aspiration biopsy Investigations

Thyroid nodules are often found incidentally during physical examination, chest radiograph, computed tomography (CT) scan, or magnetic resonance imaging (MRI). Thyroid nodules can be found in patients who are hypothyroid, euthyroid, or hyperthyroid. Fine-needle aspiration (FNA) biopsy is the procedure of choice to evaluate suspicious nodules.

About 5 to 6% of solitary nodules are malignant. Suspicious nodules are those that are larger than 1 cm in diameter or those with suspicious features found on a sonogram (e.g., irregular margins, intranodular vascular spots, micro calcifications). Risk factors for thyroid nodules include age greater than 60 years, history of head or neck irradiation, or family history of thyroid cancer.

Histologic Investigations

Autoimmune thyroiditis causes a decrease in intra thyroidal iodine stores, an increased iodine turnover, and defective organification. Chronic inflammation of the gland causes progressive destruction of the functional tissue with widespread infiltration by lymphocytes and plasma cells with epithelial cell abnormalities. Timely, initial lymphocytic hyperplasia & vacuoles are replaced by dense fibrosis and atrophic thyroid follicles. Previous administration of radioiodine, surgical fibrosis, metastasis, lymphomatous changes, sarcoidosis, tuberculosis, amyloidosis, cystinosis, thalassemia, and Riedel thyroiditis may also cause functional tissue destruction & infiltration.

Treatment

The treatment goals for hypothyroidism are the reversal of clinical progression and the corrections of metabolic derangements as evidenced by normal blood levels of TSH (0.4 to 4.0 mU/L) and free T4. Thyroid hormone is administered to supplement or replace endogenous production. In general, hypothyroidism can be adequately treated with a constant daily dose of levothyroxine (LT4). In majority of the patients, the optimum maintenance dose of LT4 is appro-ximately 1.7 mcg/kg (Nebesio *et al*., 2010; Hennessey *et al*., 1986; The Endocrine Society). Children may require higher doses of LT4, whereas the elderly may require less. Thyroid hormone replacement should be started cautiously, as it is believed that in some patients an abrupt increase in levels of thyroid hormone may increase myocardial oxygen demand and result in cardiac injury (Bernstein *et al*., 1995).

Clinical benefits begin in 3 to 5 days and level off after 4 to 6 weeks. Follow-up thyroid hormone tests should be conducted 4 to 6 weeks after starting treatment. Once the patient is maintained on a dose, thyroid function should be assessed every 6 to 12 months by an appro-priate physical examination and laboratory tests. Patients should be monitored for symptoms and signs of over treatment, which include tachycardia, palpitations, nervousness, tiredness, headache, increased excitability, sleeplessness, tremors, and possible angina.

***Drugs**:* Medications such as amiodarone, interferon alpha, thalidomide, lithium, and stavudine have also been associated with primary hypothyroidism. Most patients with amiodarone-induced hypothyroidism have an elevated TSH. If amiodarone inhibits T4 to T3 conversion, T4 clearance is delayed, and T4 may be higher than is normally observed in hypothyroidism. Many pharma-cologic agents can interfere with thyroid physiology, the biochemical assessment of thyroid function (Singh and Hershman, 1999). The magnitude and clinical importance of these effects are likely to vary among patients.

Iatrogenic: A leading cause of hypothyroidism is radio-active iodine treatment for Graves' disease and sporadic Myxedema coma.

Myxedema coma refers to the rare, severe form of hypothyroidism, a life-threatening condition that results in an altered mental status, hypothermia, bradycardia, hyper-carbia, and hyponatremia. Cardiomegaly, pericardial effusion, cardiogenic shock, and ascites may be present, and it commonly occurs in individuals with undiagnosed or untreated hypothyroidism who is subjected to an external stress, such as low temperature, infection, or medical intervention (e.g., surgery or hypnotic drugs). However, because this is a life-threatening condition that requires immediate intervention, there may not be time to wait for results of thyroid function tests. In the proper clinical setting, especially if the patient exhibits changes in mental capacity or is comatose has hypothermia, or has cardiac involvement such as pericardial effusion, it is ap-propriate to initiate treatment (Jordan, 1995; Smallridge, 1992).

In pregnancy

The management of hypothyroidism during pregnancy is complex, as the requirement for exogenous thyroid hormone typically increases by more than 50% during gestation (Mandel *et al*., 1990). Most of this increased requirement occurs during the first and second trimesters. Inadequate thyroid hormone replacement during pregnancy increases the risk of giving birth to a low-weight or stillborn infant. The maternal complications of hypothyroidism include miscarriage, preterm delivery, hypertension, and postpartum hemorrhage.

Studies have suggested that patients with hypothyroidism should augment the LT4 dose by 30% at the confirmation of pregnancy, followed by adjustments according to TSH levels. For previously diagnosed women, serum TSH should be measured every 3 to 4 weeks during the first half of pregnancy and every 6 weeks thereafter. LT4 dose should be adjusted to maintain a serum TSH less than 2.5 mIU/L. TSH and free T4 levels should be measured every 3 to 4 weeks after every dosage adjustment (Grozinsky-Glasberg *et al*., 2006).

Autoimmune thyroid disease without overt hypothyroidism has been associated with a higher miscarriage rate. Negro *et al*. (2006) showed that euthyroid Caucasian women with positive anti-TPO antibodies treated with levothyroxine during the first trimester had lower miscarriage rates when compared with those who were not treated. They also had lower incidence of premature delivery, comparable to women without thyroid antibodies. LT4 should not be taken with prenatal vitamin preparations containing iron and calcium. After delivery, the LT4 dose can be reduced to the pre-pregnancy level and TSH should be checked in 6 weeks.

Epidemiology and prevalence

In its clinically overt form, hypothyroidism is a relatively common condition, with an approximate prevalence of 2% in adult women and 0.2% in adult men increasing to 15% by age 75 years (Bates, 1993; Tunbridge *et al*.,, 1977). Hypothyroidism is most prevalent in elderly populations, with 2 to 20% of older age groups having some form of hypothyroidism. Older adults, particularly those over 60 years of age, have a higher incidence of subclinical disease when compared with younger adults with prevalence of ≈6% in older women and 2% in older men (Tunbridge *et al*., 1977). The Framingham study found hypothyroidism (TSH >10 mIU/L) in 5.9% of women and 2.4% of men older than 60 years (Wiersinga, 1995).

The occurrence varies with genetics with a high prevalence in Caucasians, and the disease is more common in populations with a high iodine intake. The prevalence of PPTD in iodine-sufficient areas is 5 to 10% (Sawin *et al*., 1985). In the National Health and Nutrition Examination Survey (NHANES 1999 to 2002), the odds of having hypothyroidism were 5 times greater in persons age 80 and older than in individuals of age 12 to 49 (Aoki *et al*., 2007). Hypothyroidism is more common in women with small body size at birth and low body mass index during childhood (Kajantie *et al*., 2006).

Prevalence is 1.9% in women, and it increases with age. It may be a primary process in which the thyroid gland produces insufficient amounts of thyroid hormone (e.g. autoimmune thyroiditis, previous radio-iodine or surgical treatment of hyperthyroidism), but can also be secondary, that is, lack of thyroid hormone secretion due to inadequate secretion of either thyrotropin (that is, thyroid-stimulating hormone [TSH]) from the pituitary gland or thyrotropin releasing hormone (TRH) from the hypo-thalamus (secondary or tertiary hypothyroidism). The patient's presentation may vary from asymptomatic to, rarely, coma with multisystem organ failure (myxedema coma). The most common cause in the United States is autoimmune thyroid disease (Hashimoto thyroiditis). It may begin in utero or later in life. Hypothyroidism is characterized by a generalized reduction in metabolic function that most often manifests as a slowing of physical and mental activity. Subclinical hypothyroidism, referred to as mild hypothyroidism, is defined as normal serum free thyroxine (T4) levels with slightly high serum TSH concentration. The clinical features of hypothyroidism are dependent on the patient's age, the presence of other disease, and the rate at which hypothyroidism develops.

Recently, in a 12-year longitudinal study, Stuckey *et al*. (2010) reported the long-term risk of hypothyroidism in women who previously had postpartum thyroid dysfunction (PPTD). The study involved 409 women, 71 of whom had previously been diagnosed with PPTD. At 12-year follow-up, 27 women in the PPTD group and 14 women in the non-PPTD group (38 and 4%, respectively) were found to have hypothyroidism. The authors concluded that within the PPTD group, women who had been diagnosed with postpartum hypothyroidism were among those at a particularly high long-term risk for hypothyroidism.

Management:-The below information is very important regarding the management of hypothyroidism

Surgical care

Surgery is indicated for large goiters that compromise tracheoesophageal function; surgery is rarely needed in patients with hypothyroidism.

Consultations: Endocrinologist most be consulted in;

Patients with a nodular thyroid, suspicious thyroid nodules, or compressive symptoms such as dysphagia, pregnant women, patients with underlying cardiac disorders or other endocrine disorders, persons younger than 18 years, and those unresponsive to treatment.

1. Some patients with thyroiditis can develop hyperthyroidism (or symptoms consistent with hyper-thyroidism) before developing hypothyroidism.
2. Suspected myxedema coma is a medical emergency with a high risk of mortality that requires initiation of parenteral (intravenous) LT4 and glucocorticoids prior to laboratory confirmation.
3. Rarely, an increase in size of a goiter in a patient with autoimmune thyroid disease could be a lymphoma.

Precautions

1. Patients who have hypothyroidism have generalized hypotonia and may be at risk for ligamental injury, particularly from excessive force across joints. Thus, patients should exercise caution with certain activities, such as contact sports or heavy physical labor.
2. Patients may have difficulty maintaining concentration in low-stimulus activities and may have slowed reaction times, so they should use caution if an activity has a risk of injury (e.g., operating presses or heavy equipment, driving).
3. Patients with severe hypothyroidism, myxedema, require aggressive management in an inpatient setting.
4. Over replacement with LT4 may precipitate tachyarrhythmias or, rarely, thyroid storm, which may require hospitalization. Risk is higher with T3.
5. Patients who require long-term continuous tube feeding require IV LT4 replacement, as the absorption of oral agents is impaired by contents of tube feeds.

Prevention

1. No universal screening recommendations exist for thyroid disease for adults. All neonates mandated to be screened at birth.
2. The American Thyroid Association recommends screening at age 35 years and every 5 years thereafter, with closer attention to patients who are at high risk (e.g., pregnant women, women >60 years, patients with type 1 diabetes or other autoimmune disease, patients with history of neck irradiation) (American Association of Clinical Endocrinologists, 2002).
3. The American College of Physicians recommends screening all women older than 50 years who have one or more clinical features of disease (Wartofsky, 2006).
4. The American Association of Clinical Endocrinologists recommends TSH measurements of all women of child-bearing age before pregnancy or during the first trimester (American College of Physicians, 1998).
5. The World Health Organization recommends a daily dietary iodine intake of 150 mcg for adults, 200 mcg for pregnant and lactating women, and 50 to 120 mcg for children (Shikha *et al*., 2010).

Side effects:-Thyroid hormone replacement can precipitate adrenal crises in patients with untreated adrenal insufficiency. If suspected, the presence of adrenal insufficiency should be confirmed or ruled out and should be treated prior to treatment of hypothyroidism. Aggressive replacement of thyroid hormone may compromise cardiac function in patients with existing cardiac disease. In these patients, administer smaller initial doses of LT4 with small incremental increases.

Subclinical hyperthyroidism, which can result from treatment with L-thyroxine, is more common, but its relationship to osteoporosis and fracture is unclear. Nonetheless, patients at risk for osteoporosis (e.g., women who are estrogen deficient) and individuals receiving a long-term suppressive of LT4 (e.g., patients with differentiated thyroid cancer) should be closely monitored. Note that patients with thyroid cancer are usually on a higher dose of LT4. Desired TSH depends on the staging of their thyroid cancer. In patients with stage IV thyroid cancer, it is desirable to keep their TSH below 0.1 mIU/L (Helfand and Redfern, 1998). Advise patients that vision may temporarily worsen when starting hormone therapy. Rarely, pseudotumor cerebri occurs.

Patients with depression may develop mania, and psychosis may be exacerbated in patients with severe psychological illness. Untreated hypothyroidism in infants can cause irreversible mental retardation, because most of brain growth & development occurs in the first 2 years of life. Older infants are spared nervous system damage, but continue to have slowed physical and linear bone growth. They also have delayed dental development.

Prognosis:- Under-treatment leads to disease progression with gradual worsening of symptoms and further metabolic derangements. Fortunately, in most patients older than 3 years, the signs and symptoms of hypothyroidism are reversed with thyroid hormone treatment. With treatment, circulating lipid levels should improve to a mild degree. This may result in a decrease of coronary artery disease (CAD).

Patient education:- The clinician should clearly discuss the life-long nature of hypothyroidism, the need for life-long therapy, the proper way to take medicine, and the minimum need for annual TSH testing.

CONCLUSION AND FUTURE PROSPECTS

Clinician must be able to identify those patients who are most at risk for developing hypothyroidism and recognize the subtle clinical signs and symptoms of the disease, because majority of the effects of hypothyroidism can be prevented or reversed by thyroid hormone replacement. It is important to consider that there may be a wide variation in the clinical presentation.

Routine screening programs identify hypothyroid neonates, so that treatment can be started shortly after birth. Hypothyroidism should be suspected when there is evidence of underlying thyroid, pituitary, or hypothalamic disease or when the patient has been previously exposed to any treatment that may disrupt the function of the hypothalamic-pituitary-thyroid axis.

Laboratory assessment of thyroid function is the optimal approach to confirm the diagnosis. However, thyroid function tests may not accurately reflect thyroid status in individuals with non-thyroidal illness, conditions that affect thyroid binding to plasma proteins, and thyroid hormone resistance. Consequently, the clinician must integrate clinical observations with laboratory data to properly diagnose and manage the hypothyroid patient. The goals of thyroid hormone replacement are to relieve symptoms and to provide sufficient thyroid hormone to decrease raised serum TSH levels to the reference range. Many decades of experience show the efficacy of treating hypothyroidism with LT4 alone (Clyde *et al*., 2003).

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How to cite this article:

Saleema Jabeen *et al*.2018, Scenario of Hypothyroidism And Its Recent Advances In The Diagnosis And Management – A Review. *Int J Recent Sci Res.* 9(3), pp. 25288-25299. DOI: http://dx.doi.org/10.24327/ijrsr.2018.0903.1832

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