

Review

Hypothyroidism in adults: A review and recent advances in management

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Accepted 3 February, 2012

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone or, more rarely, from their impaired activity at tissue 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. 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. A constant reminder on progress in management of the disease is needed. Thus, the aim of this review is to bring to notice the recent advances in the diagnosis and management of hypothyroidism and to highlight the risks involved in the global movement from consuming organic animals (as the world moves towards inorganic foods, which inhibits thyroid hormones).

Key words: Hypothyroidism, thyroid gland, deficiency.

INTRODUCTION

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone or, more rarely, from their impaired activity at tissue level. 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 hypothalamus (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 (T_4) 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

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those at a particularly high long-term risk for hypothyroidism (OR = 9.7).

THYROID PHYSIOLOGY

Thyroid hormones are the only iodine-containing substances of physiologic significance in vertebrates. Thyroid cells actively extract and concentrate iodide from plasma. T_4 , a prohormone, is converted to triiodothyronine (T_3), the active form of thyroid hormone, in the peripheral tissues by 5'-deiodination. Early in the disease process, compensatory mechanisms maintain T_3 levels.

Normal thyroid produces all of the circulating T_4 and about 20% of the circulating T_3 (Surks et al., 2004). Most of the biologic activity of thyroid hormones is due to the cellular effects of T_3 , which has a greater affinity for the thyroid hormone receptor and is approximately 4 to 10 times more potent than T_4 (Surks et al., 1973; Sawin et al., 1977). 80% of serum T_3 is derived from the deiodination of T_4 in tissues such as the liver and kidney.

Once T_4 and T_3 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 T_4 and T_3 and the lowest capacity, whereas albumin has the lowest affinity and the highest capacity. Only the free (unbound) fraction of T_4 and T_3 is able to bind to specific thyroid hormone receptors in peripheral tissues and possesses biologic activity. Normally, approximately 0.03% of T_4 and 0.5% of T_3 is free (The National Academy of Clinical Biochemistry, 1996; Oppenheimer et al., 1972) (Figure 1).

Changes in the binding capacity of thyroid hormone transport proteins may significantly affect the measurement of total thyroid hormone concentration and thereby complicate the diagnosis of hypothyroidism. The accurate diagnosis of thyroid disease is more difficult in patients with multiple abnormalities in thyroid hormone-binding proteins (Robbins, 1992). Table 1 lists factors and conditions that alter thyroid hormone binding proteins and may make the diagnosis of hypothyroidism difficult.

Pathophysiology

Localized disease of the thyroid gland that results in decreased thyroid hormone production is the most common cause of hypothyroidism. Under normal circumstances, the thyroid releases 100 to 125 nmol of T_4 daily and only small amounts of T_3 . Decreased production of T_4 causes an increase in the secretion of TSH by the pituitary gland. TSH stimulates hypertrophy and hyperplasia of the thyroid gland and thyroid T_4 -5'-deiodinase activity. This in turn causes the thyroid to release more T_3 . Deficiency of the hormone has a wide range of

effects, because all metabolically active cells require thyroid hormone. 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

Thyroid hormone exerts profound effects on growth and development during the first 2 decades of life. Thyroid hormone deficiency adversely affects the development of the central nervous system (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 hypothyroxinemia 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 neurodevelopment 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 T_4 . The placenta is impermeable to TSH and permeable to TRH. Under normal circumstances, neither T_3 nor T_4 freely crosses the placenta to a large extent. However, it appears that the maternal contribution of T_4 increases in cases of congenital hypothyroidism. In a study of infants who were unable to synthesize T_4 , cord serum levels of T_4 were 35 to 70 nmol/L (Evans et al., 1999). This suggests an increased transport of T_4 from the mother to the fetus. Thus, transplacental movement of maternal T_4 may provide a partial explanation for the relatively normal clinical appearance at birth of most infants with congenital hypothyroidism.

Thyroid replacement initiated shortly after birth minimizes the risk of permanent brain damage, because two thirds of postnatal brain growth and differentiation occurs during the first 2 years of life. Thyroid hormone deficiency that develops after 3 years of age is not associated with mental impairment, but is associated with delayed somatic and linear bone growth and delayed eruption of permanent teeth. Early detection and treatment of

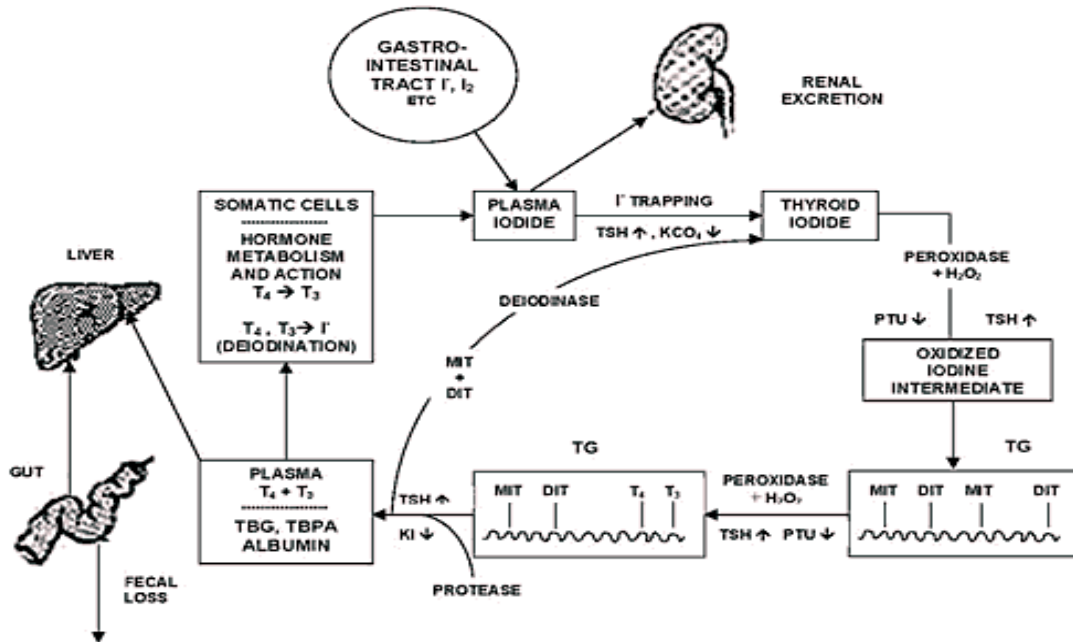


Figure 1. The iodide cycle. Ingested iodide is trapped in the thyroid, oxidized and bound to tyrosine to form iodotyrosines in thyroglobulin (TG); coupling of iodotyrosyl residues forms T₄ and T₃. Hormone secreted by the gland is transported in serum. Some T₄ is deiodinated to T₃. The hormone exerts 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.

Table 1. Conditions affecting thyroid hormone-binding proteins and their effect on the diagnosis of hypothyroidism (Langsteger et al., 1994).

Mimic	Mask
Decreased TBG concentration	Increased TBG concentration
Inherited syndromes	Inherited syndromes
Androgens, glucocorticoids	Estrogen
Nephrotic syndrome	Pregnancy
	Hepatitis, hepatoma
Competitive inhibition of T₄ binding	HIV infection
Salicylates, furosemide	
Non-thyroidal illness	Familial dysalbuminemic hyperthyroxinemia
-	Inherited syndromes
-	Pancreatic and hepatic tumors
-	Increased transthyretin binding

hypothyroidism in infants and children enables normal prepubertal and pubertal growth and achievement of maximal potential adult height (Vulsma et al., 1989).

Metabolism

One of the earliest recognized physiologic actions of thyroid hormone was its effect on the basal metabolic rate (Dickerman and De Vries, 1997). In general, thyroid

hormone deficiency results in a reduction in the metabolic rate. 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). Serum levels of total cholesterol and LDL are often increased in hypothyroid individuals (O'Brien et al., 1993; Yildirimkaya et al., 1996). The LDL particles of hypothyroid patients appear to be more susceptible to oxidation, which potentially makes them more atherogenic (Althaus et al., 1988). Thyroid hormone replacement therapy may slow the progression of coronary artery disease, because of its beneficial effects on lipids (Sundaram et al., 1997; O'Brien et al., 1994). Glucose homeostasis may be altered due to the slower rate of glucose absorption from the gastrointestinal tract. 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.

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. Hypothyroidism-associated hearing loss usually resolves with thyroid hormone replacement (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 re-establishing 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). 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 effusions, and pseudogout (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 steroidogenesis. Levels of follicle-stimulating hormone 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 (Wortzman et al., 1987). In addition, anti-thyroid peroxidase or thyroperoxidase (TPO) antibodies have been associated with a higher risk of infertility and miscarriage.

Epidemiology

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

Table 2. Factors associated with an increased risk of hypothyroidism (Wiersinga, 1995).

S/N	Factor
1	Age over 60 years
2	Female gender
3	Goiter
4	Thyroid nodular disease
5	History of hypothyroidism, hyperthyroidism, thyroiditis
6	Family history of thyroid disease
7	History of radiotherapy for head and neck cancer (external radiation and iodine 131)
8	Non-thyroid autoimmune disease
9	Drugs (lithium, amiodarone)

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). Table 2 lists some of the factors associated with an increased risk for developing hypothyroidism.

Clinical features

History

Clinical presentation may vary from mild and asymptomatic to severe and overt disease, it may depend on patient's age, gender, physical condition, and the rate at which hypothyroidism develops. 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 and menstrual disturbances.

Thus, the diagnosis of hypothyroidism is based on clinical suspicion and confirmation by laboratory testing. Subclinical

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 and nerve entrapment syndromes; blurred vision; decreased hearing; fullness in the throat, hoarseness; neck pain, sore throat, or both (Hashimoto thyroiditis); low-grade fever (Hashimoto thyroiditis).

Physical findings

Signs found in hypothyroidism are usually subtle, 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); non-pitting edema (myxedema); pitting edema of lower extremities; hyporeflexia with delayed relaxation, ataxia, or both.

Additional signs specific to different causes of hypothyroidism, such as diffuse or nodular goiter or pituitary tumor, can occur. Metabolic abnormalities associated with hypothyroidism include anemia, dilutional hyponatremia, hyperlipidemia, and reversible increase in creatinine (Nicoloff and LoPresti, 2007).

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, hypercarbia, 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 appropriate to initiate treatment (Jordan, 1995; Smallridge, 1992).

Causes

Worldwide, iodine deficiency remains the foremost cause of hypothyroidism. In the United States and other areas of adequate iodine intake, autoimmune thyroid disease is most common. 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. Pharmacologic agents such as lithium and amiodarone may also inhibit thyroid hormone synthesis (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).

Primary hypothyroidism

Autoimmune: 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., 1996) 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 ensues, 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.

In approximately 1 to 5% of patients with chronic autoimmune thyroiditis, spontaneous recovery of thyroid function takes place. Circumstances that increase the likelihood of this occurring include the presence of a goiter and thyrotropin levels higher than 10 mU/L (Comtois et al., 1995).

Subacute granulomatous thyroiditis: Inflammatory conditions or viral syndromes may be associated with transient hyperthyroidism followed by transient hypothyroidism (de Quervain or painful thyroiditis and subacute thyroiditis). These are often associated with fever, malaise, and a painful and tender gland.

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 T_4 to T_3 conversion, T_4 clearance is delayed, and T_4 may be higher than is normally observed in hypothyroidism. Many pharmacologic 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 radioactive iodine treatment for Graves' disease and sporadic

nontoxic goiter (Le Moli et al., 1999). Use of radioactive iodine for treatment of Graves' disease generally results in permanent hypothyroidism within 1 year after therapy. The frequency is much lower in patients with toxic nodular goiters and those with autonomously functioning thyroid nodules. External neck irradiation (for head and neck neoplasms, breast cancer, or Hodgkin disease) may result in hypothyroidism; patients who have received these treatments require monitoring of thyroid function.

Thyroidectomy: The vast majority of patients who undergo thyroidectomy for Graves' disease develops hypothyroidism, with the majority developing the disease during the first year after surgery.

Rare: Rare causes include 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 T_3 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 T_3 -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).

Central hypothyroidism

Central hypothyroidism (secondary or tertiary) results when the hypothalamic-pituitary axis is damaged. In contrast to primary hypothyroidism, secondary hypothyroidism is caused by pituitary gland dysfunction that results in a diminished secretion of biologically active TSH (Collu et al., 1997; Lee et al., 1995; Beck-Peccoz et al., 1985). Pituitary surgery is a prominent cause of secondary hypothyroidism. Less frequently, external radiation to the head and neck area, either for treatment of pituitary, nasopharyngeal, or laryngeal tumors, may lead to secondary hypothyroidism. Rarely, sarcoidosis (Jawadi et al., 1980) and hemochromatosis may cause it.

Autoimmune hypophysitis may occur, usually in postpartum women (Sheehan syndrome) (Lazarus, 1999). Others are pituitary adenoma, tumors impinging on the hypothalamus, and drugs (for example dopamine, lithium) (Shikha et al., 2010).

Differential diagnoses

The list of differential diagnoses for hypothyroidism is long, because the most frequent presenting symptoms are nonspecific, which is as follows: Addison disease, apnea (sleep), anovulation, autoimmune thyroid disease and iron deficiency, pregnancy, chronic fatigue syndrome, constipation, De Quervain thyroiditis, depression, eosinophilia-myalgia syndrome, erectile dysfunction, fibromyalgia, nontoxic, goiter, hypercholesterolemia, hypochondriasis, panhypopituitarism, ileus, hypothermia, menopause, myxedema coma or crisis, ovarian insufficiency, polyglandular autoimmune syndrome, sleep disorders, subacute thyroiditis, lymphomas, thyroxin-binding globulin deficiency, and euthyroid sick syndrome.

Investigations

Laboratory studies

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 T_4 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 T_4 assays are becoming popular as they measure unbound (that is, free hormone). However, free T_4 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 (T_3 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 T_3 resin uptake and total T_4 levels. No currently available kit actually measures unbound T_4 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 T_4 to T_3 occur, this maintains T_3 levels thus in early hypothyroidism, TSH levels are increased, T_4 levels are normal to low, and T_3 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 T_4 levels are decreased, and total T_3 levels are markedly decreased. This can be confused with secondary hypothyroidism. In these patients, however, the primary abnormality is the decreased peripheral production of T_3 from T_4 . They have an increased reverse T_3 , 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 T_4 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 T_4 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 studies

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-fluorodeoxyglucose 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).

Procedures (Fine-needle aspiration biopsy)

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 findings

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. In time, dense fibrosis and atrophic thyroid follicles replace the initial lymphocytic hyperplasia and vacuoles. Functional tissue destruction and infiltration may also be caused by previous administration of radioiodine, surgical fibrosis, metastasis, lymphomatous changes, sarcoidosis, tuberculosis, amyloidosis, cystinosis, thalassemia, and Riedel thyroiditis.

Treatment

Medical care

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 mIU/L) and free T_4 .

Thyroid hormone is administered to supplement or replace endogenous production. In general, hypothyroidism can be adequately treated with a constant daily dose of levothyroxine (LT_4). In majority of the patients, the optimum maintenance dose of LT_4 is approximately 1.7 mcg/kg (Nebesio et al., 2010; Hennessey et al., 1986; The Endocrine Society). Children may require higher doses of LT_4 , 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 appropriate physical examination and laboratory tests.

Patients should be monitored for symptoms and signs of overtreatment, which include tachycardia, palpitations, nervousness, tiredness, headache, increased excitability, sleeplessness, tremors, and possible angina.

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 LT_4 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. LT_4 dose should be adjusted to maintain a serum TSH less than 2.5 mIU/L. TSH and free T_4 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.

LT_4 should not be taken with prenatal vitamin preparations containing iron and calcium. After delivery, the LT_4 dose can be reduced to the pre-pregnancy level and TSH should be checked in 6 weeks.

Subclinical hypothyroidism

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 LT_4 is not given (Gyamfi et al., 2009). Oral LT_4 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 and Crapo, 1990).

New concepts on LT_4 therapy

Attention has recently focused on using the combination of $L-T_3$ and $L-T_4$ for treating hypothyroidism. This approach is based on the hypothesis that because not all tissues are equally able to convert LT_4 to LT_3 , some patients respond poorly to treatment with LT_4 alone. Bunevicius et al. (1999) recently reported that in some hypothyroid patients, the combination of LT_4 and LT_3 may result in improved mood and psychological function when compared with treatment with LT_4 alone.

However, a meta-analysis of randomized controlled trials of thyroxine-triiodothyronine combination therapy ($T_4 + T_3$) versus thyroxine monotherapy (T_4) for treatment of clinical hypothyroidism found no difference in the effectiveness of the combination versus monotherapy in bodily pain, depression, fatigue, body weight, anxiety, quality of life, total cholesterol, LDL-C, HDL-C and triglyceride levels.

Hence, T_4 monotherapy remains the treatment of choice (Hollowell et al., 2002).

Myxedema coma

An effective approach is to use intravenous LT_4 at a dose

of 4 mcg/kg of lean body weight, or approximately 200 to 250 mcg as a bolus in a single or divided dose, depending on the patient's risk of cardiac disease followed by 100 mcg 24 h later and then 50 mcg daily intravenous (IV) or orally (PO) along with stress doses of intravenous glucocorticoids. Adjustment of the dose can then be made based on clinical and laboratory results. Use of intravenous triiodothyronine is controversial and based on expert opinion. It has a higher frequency of adverse cardiac events and is generally reserved for patients who are not improving clinically on LT₄. LT₃ can be given initially as a 10 mcg IV bolus and repeated every 8 to 12 h until the patient can take maintenance oral doses of T₄. Advanced age, high dose T₄ therapy, and cardiac complications had the highest associations with mortality (Cinemre et al., 2009).

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;

- 1) 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.
- 2) Some patients with thyroiditis can develop hyperthyroidism (or symptoms consistent with hyperthyroidism) before developing hypothyroidism.
- 3) 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.
- 4) 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 ligamentous 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 brain growth 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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