Clinical perspective of hypothyroidism

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ABSTRACT

Thyroid dysfunction, mostly hypothyroidism is a frequent disorder in the general population, especially among women. Hypothyroidism is defined as a deficiency of thyroid activity. Hypothyroidism is a clinical syndrome that results from insufficient production or action of thyroid hormones, leading to a total decrease of metabolic processes. It results from reduced secretion of both thyroxine (T4) and triiodothyronine (T3). The disorder slows the metabolism, with classic symptoms of slowness of movement, tiredness, low energy, change in appearance and voice, weight gain, cold intolerance, poor libido and constipation. Furthermore, abnormalities of lipid metabolism, hyperhomocysteinemia, and arterial hypertension occur with increased frequency in hypothyroidism and are associated with an increased risk of premature atherosclerotic vascular disease. Treatment with thyroid hormones results in an increase in basal energy expenditure, which affects the synthesis, mobilization and degradation of lipids.

Key words: Thyroid hormones, Hypothyroidism, thyroxine, dyslipidemia.

INTRODUCTION

Hypothyroidism is a clinical syndrome that results from insufficient production or action of thyroid hormones, leading to a total decrease of metabolic processes (Braverman and Utiger, 1984). Thyroid hormone biosynthesis depends on the normal functioning of a series of proteins and enzymes such as thyroglobulin and thyroperoxidase, which is necessary for the uptake of iodine into thyrocytes (Francis-Lang et al., 1992; Civitareale et al., 1994).

Nuclear thyroid hormone receptors are intimately associated with chromatin and bind thyroid hormone with high affinity and specificity. It then binds to thyroid hormone receptors, which may already be prebound to thyroid response elements located in promoter regions of target genes. The formation of ligand-bound thyroid hormone receptor complexes that are also bound to thyroid response elements is the critical first step in the positive or negative regulation of target genes and the subsequent regulation of protein synthesis (Oppenheimer et al., 1987; Samuels et al., 1988).

PREVALENCE

The prevalence of hypothyroidism is three times higher among women than men. The prevalence in an unselected community population of young, middle aged and elderly individuals is about 1.4 percent and the estimated annual incidence rate is one to two per 1,000 women. Hypothyroidism is one of the most common endocrine disorders, occurring in up to 5% of the population of the United States and the United Kingdom (Vanderpump et al., 1995; Hollowell et al., 2002). Surveys of geriatric populations have yielded estimated prevalence rates for hypothyroidism of 0.2 percent to 3 percent (Canadian Task Force on the Periodic Health Examination, 2003).
ETIOLOGY

A number of conditions can lead to hypothyroidism (Table 1) (Hueston, 1997).

Table 1: Various causes of primary and secondary hypothyroidism

<table>
<thead>
<tr>
<th>Primary hypothyroidism (95% of cases)</th>
<th>Secondary hypothyroidism (5% of cases)</th>
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<tbody>
<tr>
<td>Idiopathic hypothyroidism</td>
<td>Pituitary or hypothalamic neoplasms</td>
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<tr>
<td>Hashimoto’s thyroiditis</td>
<td>Congenital hypopituitarism</td>
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<td>Irradiation of the thyroid subsequent</td>
<td>Proritary necrosis (Shehan’s syndrome)</td>
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<td>to Graves’ disease</td>
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<td>Surgical removal of the thyroid</td>
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<td>Late-stage invasive fibrous thyroiditis</td>
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<td>Iodine deficiency</td>
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<td>Drug therapy (e.g., lithium, interferon)</td>
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<tr>
<td>Infiltrative diseases (e.g., sarcoidosis, amyloidosis, scieroderma, hemochromatosis)</td>
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SIGNS AND SYMPTOMS

Primary hypothyroidism have classical symptoms of fatigue, weight gain, cold intolerance, and constipation. Fatigue, one of the major complaints, together with depression (Esposito et al., 1997), neuromuscular signs and symptoms (Duyff et al., 2000), and diastolic dysfunction (Tielens et al., 2000) can all lead to an impaired quality of life in patients with hypothyroidism. Patients with hypothyroidism generally present with signs and symptoms that may include lethargy, weight gain, hair loss, dry skin, forgetfulness, constipation and depression. Not all of these signs and symptoms occur in every patient, and many may be blunted in patients with mild hypothyroidism. Furthermore, abnormalities of lipid metabolism, hyperhomocysteinemia, and arterial hypertension occur with increased frequency in hypothyroidism (Diekman et al., 1998; Fommei and Iervasi, 2002) and are associated with an increased risk of premature atherosclerotic vascular disease (Cappola and Ladenson, 2003).

CLASSIFICATION

I) Primary Hypothyroidism

Primary hypothyroidism is defined as the deficiency of thyroid activity. It results from reduced secretion of both T4 and T3 (Seely and Williams, 2001). Biochemically decrease in T4 and T3 concentrations lead to hypersecretion of pituitary TSH and an amplified increase in serum TSH levels. This is a key laboratory finding, particularly in the early detection of thyroid failure. Hypercholesterolemia is favored due to the hormone deficit and to the decreased activity of the lipoprotein lipase (Galesanu et al., 2004). The pituitary hormone thyrotropin (thyroid-stimulating hormone) is responsible for maintaining normal thyroid morphology and for providing the primary stimulus for synthesis and secretion of the thyroid hormones thyroxine (T4) and triiodothyronine (T3) (Spencer, 1986). Primary hypothyroidism is a graded disorder, with a wide spectrum of severity between mild and overt disease (Meier et al., 2003).

II) Subclinical Hypothyroidism

Sub clinical hypothyroidism is defined by the presence of elevated TSH levels but normal T4 levels, and is reasonably common. Its prevalence in the general population is 1–10% but approaches about 15% in women who are over 60 yr of age (Canaris et al., 2000). Clinical manifestations of subclinical hypothyroidism include abnormal lipid metabolism (Pucci et al., 2000), cardiac dysfunction (Kahaly, 2000) and neurological and mental dysfunction (Mozzani et al., 1993). Several cross-sectional studies have suggested that it confers an elevated risk of atherosclerosis and coronary heart disease (Hak et al., 2000).

III) Central Hypothyroidism

Central hypothyroidism arises from an inadequate stimulation by TSH of an otherwise normal thyroid gland (Martino et al., 1996). In most cases, central hypothyroidism is acquired by patients with pituitary and/or hypothalamic diseases and may result from one or more of the following mechanisms:

1) A reduced mass of functioning thyrotroths,
2) Defects in thyrotropin releasing hormone (TRH) stimulation of TSH secretion,
3) A reduced bioactivity of circulating TSH (Martino et al., 1996).

Restoration and maintenance of euthyroidism represent the therapeutic goals in central hypothyroidism. Specific therapies, such as oral TRH administration have been abandoned because of their cost and their restricted applicability to few patients with hypothyroidism (Beck-Peccoz et al., 1985; Beck-Peccoz and Medri, 1988). Thus, patients with central hypothyroidism are treated with levothyroxine, but serum TSH levels cannot be used in either the diagnosis or the monitoring of levothyroxine therapy as in case of primary hypothyroidism (Toft, 1994; Lazarus, 1996).

IV) Congenital Hypothyroidism

Congenital hypothyroidism is detected at a rate of 1 in 3000 to 4000 live births, making it the most common congenital endocrine disorder (Toub lanc, 1992). On a worldwide basis, hypothyroidism, including congenital forms, results most commonly from iodine deficiency. Otherwise congenital thyroid gland insufficiency results from developmental abnormalities at any level of the hypothalamic-pituitary-thyroid axis. Congenital hypothyroidism is most commonly caused by defects in thyroid development leading to thyroid dysgenesis (85%) (Grant et al., 1992). The remaining cases are associated with either a goitre or a normal thyroid gland (Medeiros-Neto and Stanbury, 1994).

V) Drug-Induced Hypothyroidism

Many medications can alter thyroid function, including amiodarone and lithium, two commonly prescribed medications. Amiodarone can induce both hypothyroidism and hyperthyroidism (Surks and Sievert, 1995; Harjai and Licata, 1997). Hypothyroidism can occur at any time during the course of therapy regardless of the cumulative dose, and occurs in 6 percent to 10 percent of long-term users (Harjai and Licata, 1997). Lithium may cause hypothyroidism by inhibiting the release of T4 and T3 from the thyroid gland.

Radioactive iodine is indicated for thyroid ablation therapy in patients with hyperthyroidism. The radioisotope $^{131}$I is a
emitter that is absorbed into the thyroid gland. After a few weeks, the thyroid gland tissue is destroyed. Administration of \(^{131}I\) can result in iatrogenic hypothyroidism.

**Diagnosis**

In hypothyroidism, serum T4 levels are frequently within the normal range, and their concentrations are influenced by binding proteins. Moreover, T4 levels vary in a given individual from day to day (Kuusi et al., 1988). In contrast, TSH is not protein bound and varies little from day to day. Thus, TSH provides a sensitive and reliable index of the severity of primary hypothyroidism and has become accepted as the most reliable thyroid analyte (Browning et al., 1986).

The diagnosis of hypothyroidism is made by clinical findings and laboratory data such as serum thyroxine (T4), triiodothyronine (T3), and thyrotropin (TSH) levels (Yamada et al., 1982; Yamada et al., 1984). An elevated TSH concentration and a low T4 indicate primary hypothyroidism.

**COMPLICATIONS**

Possible complications associated with primary hypothyroidism are:

1. Primary hypothyroidism, defined as low thyroid hormone levels accompanied by elevated TSH levels is associated with cardiovascular disease, presumably because of hypercholesterolemia and hypertension (Vanhaelst et al., 1967; Steinberg, 1968). Hypothyroidism is associated with cardiovascular dysfunction: decreased cardiac contractility, cardiac output, heart rate, and left ventricular compliance as well as increased total peripheral vascular resistance (Klein and Ojamaa, 2000). The presence of hypertension (Streeten et al., 1988) and hypercholesterolemia (O’Brien et al., 1993) also contributes to an increased risk of atherogenesis in this condition.

2. During pregnancy, there is an increased risk of developing some pregnancy complications. For example: pre-eclampsia, anaemia, premature labour, low birth weight, stillbirth, and serious bleeding after the birth.

3. Hypothyroid coma (myxoedema coma) is a very rare complication.

However, with treatment, the outlook is excellent. With treatment, symptoms usually go, and the individual is unlikely to develop any complications.

**TREATMENT**

T4 replacement for hypothyroidism usually achieves complete restoration of euthyroidism. Replacement thyroxine is the cornerstone of therapy for hypothyroidism. A dose of 1.6 µg per kg body weight daily is the average required in adults. The principal determinant of dose is lean body mass, so patients in old age may need as little as 50 µg/day. In patients with ischaemic heart disease, a low initial thyroxine dose is recommended (12.5–50 µg/day) to avoid exacerabating angina, but in some patients thyroxine replacement is impossible until coronary artery bypass surgery has been performed, with extreme attention to drug and fluid therapy. As thyroxine has a half-life of 1 week, once-daily administration is fully adequate to maintain stable levels. It should be taken on an empty stomach, separately from other drugs (Chopra and Baber, 2003). Dose should not be adjusted until after a minimum of three to five half-lives to allow a steady state to be attained. In primary hypothyroidism, normalization of serum TSH level is the best biochemical marker of adequate therapy. Occasionally, symptoms of hypothyroidism appear to persist when TSH level is at the upper end of the reference range. In pregnancy, the dose may need to be increased. Maintaining a normal TSH level is important for fetal development (Haddow et al., 1999).

Treatment goals for patients with hypothyroidism are to

1. Restore normal thyroid hormone concentrations in the tissue
2. Provide symptomatic relief
3. Prevent neurologic deficits in newborns and children
4. Reverse the biochemical abnormalities of hypothyroidism.

Product types available for thyroid replacement therapy include synthetic and natural combinations of T3 (liothyronine) and T4 (levothyroxine), and desiccated natural thyroid, with levothyroxine alone considered the drug of choice for thyroid replacement therapy.

**INITIATION OF REPLACEMENT THERAPY:**

Physicians must tailor treatment and management of hypothyroidism to individual patients. Individualized doses are important because even small changes in the administered dose of levothyroxine can shift a patient from a euthyroid to a hyperthyroid or hypothyroid state. A small study comparing fixed-dose to individually titrated levothyroxine in hypothyroid patients showed that fixed-dose levothyroxine therapy can cause hyperthyroid symptoms, modifications in myocardial structure, and altered cardiopulmonary function, primarily during physical activity (Mercuro et al., 2000). After a patient’s TSH level has normalized, the maintenance dosage should be continued with an annual or semiannual TSH test or when the patient demonstrates a change in symptoms. Requirements may change with patient age, severe illness, and pregnancy.

If a patient shows no appreciable benefit after 3 months, the need for treatment should be reassessed and referral to an endocrinologist considered.

**THYROID OVERREPLACEMENT:**

Some evidence indicates that up to 20% of patients receiving levothyroxine are overtreated (Gharib et al., 2005). This may result in overt or subclinical hyperthyroidism, which may cause cardiac hypertrophy, atrial fibrillation, and accelerated bone turnover (Vestergaard and Mosekilde, 2003; Burman, 1995). One meta-analysis demonstrated a clear relationship between hyperthyroidism and decreased bone mineral density, with normalization of bone mineral density upon normalization of the thyroid state (Vestergaard and Mosekilde, 2003). However, timely identification and correction can prevent the cardiac and bone problems of thyroid overreplacement.
INTERACTING CONDITIONS AND DRUGS

Dosing requirements may be affected by malabsorptive states or drug interactions. Many medications are known to cause drug induced hypothyroidism or hyperthyroidism. Other medications may alter thyroid function tests without inducing thyroid dysfunction; for example, estrogen, even at low doses, increases serum levels of thyroxine binding globulin.

Therefore, euthyroid patients receiving any form of estrogen generally show elevated total T3 and T4 values, while serum TSH, free T3, and free T4 levels remain unchanged.

EFFECTS OF CONCOMITANT MEDICATIONS

Concomitant medications can influence the absorption and clearance of levothyroxine. Ferrous sulfate, cholestyramine, dietary fiber supplements, calcium carbonate, sucralfate and aluminum hydroxide have been shown to reduce levothyroxine’s intestinal absorption (Liel et al., 1996; Singh et al., 2000). Enzyme inducers such as rifampin, carbamazepine and possibly phenytoin augment T4 clearance (Mandel et al., 1993). A high TSH measurement may indicate increased levothyroxine requirements.

ADVERSE EFFECTS

Adverse effects and intolerance to thyroid hormone therapy are rare when therapy is properly dosed and monitored, but include allergic reactions, decreased bone mineral density and cardiovascular disease. Overreplacement of thyroid hormone can cause iatrogenic hyperthyroidism. Allergic reactions to thyroid hormones are infrequent, occurring most often with the animal-derived thyroid hormones and least with the synthetic products. For hypersensitive patients, the agent containing the least number of excipients and no dye is Synthroid® (levothyroxine sodium, USP) in 50 mcg tablets.

If iatrogenic hyperthyroidism is suspected, measure the TSH concentration. If hyperthyroidism is confirmed, discontinue the levothyroxine dose for one week and restart at a lower dose (Singer et al., 1995).

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