Hypothyroidism is one of the most common disorders encountered in an endocrine office practice. Hypothyroidism results from reduced thyroid hormone actions at the peripheral tissues. This reduction in thyroid hormone action is, in the vast majority of cases, secondary to reduced thyroid hormone synthesis and secretion by the thyroid gland. Occasionally, peripheral resistance to thyroid hormone is the culprit. The availability of sensitive biochemical tests and effective therapies has simplified the diagnosis and management of this endocrine condition. This article reviews the epidemiology, etiology, clinical presentation, diagnosis, and treatment of hypothyroidism. We emphasize some of the more recent issues, such as combination thyroid hormone therapy, management of hypothyroidism during pregnancy, and the management of subclinical hypothyroidism.

Epidemiology

Hypothyroidism is a relatively common disorder. The prevalence of hypothyroidism increases with age, and the disorder is nearly 10 times more common in females than in males. Hypothyroidism is particularly common in areas of iodine deficiency. Individuals who have thyroid peroxidase antibodies and those who have thyroid-stimulating hormone (TSH) values that are in the upper normal range are at increased risk for developing hypothyroidism.

The prevalence of overt hypothyroidism varies according to different surveys between 0.1 and 2% [1]. Subclinical hypothyroidism is more prevalent and can be seen in as many as 15% of older women. In the United States National Health and Nutrition Examination Survey (NHANES III), the...
prevalence of overt hypothyroidism was found to be 0.3%; prevalence of subclinical hypothyroidism was found to be 4.3% [2].

**Etiology**

A summary of the most common causes of hypothyroidism is given in Box 1.

**Resistance to thyroid hormones**

Hypothyroidism may be transient or permanent, central, or primary. Central hypothyroidism can accompany disorders of the hypothalamic-pituitary axis, leading to reduced TSH secretion or reduced biological activity of TSH. As a result, there is reduction in thyroid stimulation by the TSH and, secondarily, reduced thyroid hormone synthesis and secretion.

Primary hypothyroidism refers to a defect in the thyroid gland resulting in reduced synthesis and secretion of thyroid hormones.

**Central hypothyroidism**

Central hypothyroidism is classically divided into secondary hypothyroidism, where the defect is in the pituitary gland, and tertiary hypothyroidism, where the defect is in the hypothalamus. From a practical point of view,

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**Box 1. Causes of hypothyroidism**

*Central hypothyroidism*
- Pituitary tumors, metastasis, hemorrhage, necrosis, aneurysms
- Surgery, trauma
- Infiltrative disorders
- Infectious diseases
- Chronic lymphocytic hypophysitis
- Other brain tumors
- Congenital abnormalities, defects in thyrotropin releasing hormone, TSH, or both

*Primary hypothyroidism*
- Chronic autoimmune thyroiditis
- Subacute, silent, postpartum thyroiditis
- Iodine deficiency, iodine excess
- Thyroid surgery, I-131 treatment, external irradiation
- Infiltrative disorders
- Drugs
- Agenesis and dysgenesis of the thyroid
the end result is the same: a reduction in the release of biologically active TSH. A variety of disorders can cause central hypothyroidism. In clinical practice, pituitary adenomas are the most common. Less prevalent conditions include pituitary apoplexy and infiltrative disorders of the hypothalamus-pituitary axis, such as sarcoidosis, tuberculosis, and other granulomatous diseases. Depending on the extent of the damage incurred by the hypothalamus-pituitary axis, central hypothyroidism may be reversible or permanent. Although isolated deficiency of thyrotropin releasing hormone (TRH) or TSH is possible [3–5], more often the patient who has central hypothyroidism presents with deficiency of other pituitary hormones, and central hypothyroidism is only part of the larger clinical picture of hypopituitarism.

Primary hypothyroidism

Primary hypothyroidism is responsible for the majority of hypothyroid cases. The following discussion reviews the most common entities that result in primary hypothyroidism.

Chronic autoimmune (Hashimoto’s) thyroiditis is the leading cause of primary hypothyroidism in iodine-sufficient areas. Clinically, patients who have Hashimoto’s thyroiditis may present with or without goiter. Pathophysiologically, there is cell-mediated and antibody-mediated destruction of the thyroid gland [6]. Most patients have measurable autoantibodies against different components of the thyroid gland (thyroid peroxidase, thyroglobulin, TSH receptor, TSH blocking antibodies) [7–9]. Occasionally, a patient may present with thyrotoxicosis due to the presence of thyroid-stimulating autoantibodies (Hashitoxicosis) [10].

The prevalence is several times higher in women than in men. The prevalence of overt hypothyroidism varies from less than 1% to 2% of the population. Up to 15% of elderly women have thyroid autoantibodies [11]. Euthyroid individuals, who have detectable thyroid autoantibodies, are at increased risk for developing overt hypothyroidism.

Hypothyroidism due to autoimmune thyroiditis may be part of a polyglandular failure syndrome that may include autoimmune adrenal insufficiency, type 1 diabetes mellitus, hypogonadism, pernicious anemia, and vitiligo.

Iodine

Iodine deficiency is the most common cause of hypothyroidism [12]. Patients often have large goiters. Transient hypothyroidism may also result from iodine excess. This is referred to as the Wolff-Chaikoff effect. Most patients eventually escape this effect. Large amounts of iodine are found in radiographic contrast agents and in the drug amiodarone.

Thyroidectomy and radioactive iodine therapy of patients who have Graves disease, toxic thyroid nodules, or toxic multinodular goiters are common causes of hypothyroidism [13,14].
Postablative hypothyroidism develops several weeks after radioactive iodine therapy. Partial thyroidectomy may leave sufficient thyroid tissue behind to prevent the patient from taking thyroid hormone replacement [15]. Periodic monitoring of thyroid function tests is important after thyroidectomy and radioactive iodine therapy for early detection and treatment of hypothyroidism.

Hypothyroidism can occur after external radiation of the head and neck and after whole-body radiation. It usually takes several years for hypothyroidism to develop in these circumstances [16–18]. Given the relatively high incidence of hypothyroidism after head and neck irradiation, recipients of such therapy need periodic clinical and biochemical assessment of their thyroid function.

In addition to an increased risk of papillary thyroid cancer, children living in areas of radioactive fallout from the Chernobyl nuclear accident have a higher prevalence of thyroid autoantibodies [19] and may be at increased risk of developing hypothyroidism.

Amiodarone and lithium are among a number of drugs that can cause hypothyroidism. Both drugs are widely used in clinical practice. Thyroid function tests should be obtained before initiating therapy with these agents and periodically thereafter. Other incriminated drugs include perchlorate (rarely used clinically), ethionamide, interferon alfa, and interleukin-2. Thyroid function usually normalizes after discontinuation if these drugs.

Cases of primary hypothyroidism have occasionally been reported in patients who have infiltrative and infectious diseases such as fibrous thyroiditis of Riedel, sarcoidosis (which can also cause central hypothyroidism), hemochromatosis, leukemia, lymphoma, cystinosis, amyloid, scleroderma, and Mycobacterium tuberculosis and Pneumocystis carinii infection [20].

The antithyroid drugs propylthiouracil and methimazole are used to treat patients who have thyrotoxicosis. Overdosage can result in hypothyroidism.

Children and infants can present with hypothyroidism due to thyroid gland agenesis and dysgenesis and defects in thyroid hormone biosynthesis [21]. Treatment of thyrotoxic women during pregnancy with antithyroid drugs can result in hypothyroidism in the neonate.

Generalized resistance to thyroid hormone is a rare, autosomal recessive disorder caused by mutations in the tri-iodothyronine (T3) receptor gene [22]. The TSH level is usually normal. Thyroxine (T4) and T3 levels are elevated. Patients who have this disorder are usually euthyroid and do not require thyroid hormone replacement.

Transient hypothyroidism usually occurs in the setting of thyroiditis [23,24]. Common forms of thyroiditis include subacute thyroiditis, silent thyroiditis and postpartum thyroiditis, and consumptive hypothyroidism.

Subacute thyroiditis is usually preceded by a viral syndrome occurring a few weeks earlier. Patients typically present with tenderness in the anterior neck. An initial phase of hyperthyroidism is typical. This is followed by
a hypothyroid phase that may last a few weeks to several months. There is return to a euthyroid state, but permanent hypothyroidism may develop [25].

Silent thyroiditis and postpartum thyroiditis have a similar clinical course to subacute thyroiditis except for the absence of the prodromic syndrome. Postpartum thyroiditis is seen in 3% to 16% of postpartum women [26]. The disorder is more common in women who have type 1 diabetes and in those who have thyroid autoantibodies [26,27].

Consumptive hypothyroidism is a rare situation where hypothyroidism is the result of certain vascular and fibrotic tumors. A type 3 deiodinase present in these tumors metabolizes T4 and T3 into the inactive reverse T3 and T2, respectively [28].

**Subclinical hypothyroidism**

Subclinical hypothyroidism is the term used to define a state in which serum T4 and T3 levels are within normal limits, but there is underlying mild thyroid failure, as evidenced by a mild increase in serum TSH. The condition is sometimes designated as compensated, early, latent, mild, minimally symptomatic, and preclinical hypothyroidism [29,30].

The etiology of subclinical hypothyroidism is similar to that of overt hypothyroidism. Chronic autoimmune thyroiditis is the leading cause. In one study, chronic autoimmune thyroiditis was found in approximately 55% of patients who had mild thyroid failure [31]. Other common causes of subclinical hypothyroidism include thyroid ablation with radioactive iodine; partial thyroidectomy antithyroid drugs; external beam radiation; drugs such as amiodarone, lithium, or radiographic contrast agents; and inadequate T4 therapy for overt hypothyroidism (intentionally or due to poor patient compliance) [32].

**Natural history**

Mild thyroid failure represents an early stage of thyroid disease, and it has been shown that there is progression to overt hypothyroidism in approximately 4% to 18% of patients who have subclinical hypothyroidism every year [33,34]. The likelihood of progression to overt hypothyroidism increases in the presence of antithyroid antibodies, serum TSH values greater than 20 μU/mL, positive history of radiiodine ablation therapy, history of external radiation therapy for nonthyroid malignancies, and chronic lithium treatment. One study found that a significant number of patients who had subclinical hypothyroidism recovered normal thyroid function, suggesting a transient form of thyroiditis as the probable etiology.

**Symptoms**

Patients who have subclinical hypothyroidism may be asymptomatic or may present with vague, nonspecific symptoms like fatigue; generalized
weakness; depression; and memory, cognitive, and sleep disturbances. As in other thyroid disorders, there is a female preponderance. Women who have subclinical hypothyroidism may present with menstrual irregularities such as menorrhagia or fertility problems. Underlying maternal mild thyroid failure during pregnancy is an independent risk factor for adverse development in the offspring.

**Cardiovascular system**

Several epidemiologic studies have implicated subclinical hypothyroidism as a cardiovascular risk factor. The Rotterdam study [35] revealed an increased incidence of aortic atherosclerosis (odds ratio, 1.7) and myocardial infarction (odds ratio, 2.3) in women who had subclinical hypothyroidism [36]. Some studies have shown positive correlation between subclinical hypothyroidism and increased serum levels of total cholesterol and low-density-lipoprotein (LDL) cholesterol along with decreased high-density-lipoprotein cholesterol [37,38].

**Subclinical hypothyroidism in the elderly population**

A recent cross-sectional survey identified an independent association between the prevalence of subclinical thyroid dysfunction and deprivation that cannot be explained solely by the greater burden of chronic disease or consequent drug therapies in the elderly population [39]. One of the major difficulties in interpreting the results of these studies is related to the fact that thyroid function tests are not measured periodically. The TSH is sometimes obtained only at baseline with no further follow-up and therefore dose not take into accounts the possibility that a significant percentage of the study population might have progressed over time into overt hypothyroidism. Another important aspect is the fact that some studies included patients with varying degrees of TSH elevations.

**Clinical presentation**

The scope of thyroid hormone deficiency encompasses the different body systems and organs. The clinical presentation of a patient who has hypothyroidism depends on the severity of the condition. This depends on the degree of biochemical hypothyroidism. There is significant individual variation. Some patients present with mild symptoms in spite of having low levels of circulating thyroid hormones. Others who have less pronounced biochemical hypothyroidism may be more symptomatic. This is also true for patients who have thyrotoxicosis.

Many of the symptoms of hypothyroidism have poor sensitivity, and it is common for the physician to have patients referred for “thyroid dysfunction or thyroid imbalance” because of symptoms of fatigue, low energy, tiredness, weight gain, or memory changes. The increasing availability to the
consumer of medical information, sometimes with excellent scientific value and sometimes with a commercial end in mind, leads some individuals to press the physician on the thyroid issue in spite of the fact that they have normal thyroid function.

In hypothyroidism, there is accumulation of matrix glycosaminoglycans in the interstitial fluids [40]. This is due to increased synthesis of hyaluronic acid. This and the metabolic change typical of the hypothyroid state explain many of the clinical symptoms and signs reported by individuals who have hypothyroidism.

Nutrition and metabolism

In hypothyroidism, there is slowing down of the body’s metabolism. Basal metabolic rate and oxygen consumption are reduced. Reduced thermogenesis results in cold intolerance. Food intake and appetite are reduced, but body weight may increase due to water and salt retention and accumulation of fat. There is slowing down of the turnover of protein, biosynthesis of fatty acids, and lipolysis. Total and LDL cholesterol concentrations are increased due to reduced clearance of LDL cholesterol [41]. Serum triglycerides are normal or increased. A slight increase in HDL2 concentration may be seen. Plasma homocysteine level is increased [42]. The changes in lipid metabolism confer an atherogenic profile to the hypothyroid patient. Thyroid function screening should be performed in all patients who have hypercholesterolemia.

Hyponatremia is seen in patients who have profound hypothyroidism and is due to reduced renal free water excretion [43,44]. Serum creatinine is increased in many patients who have hypothyroidism [45].

Cardiovascular system

Reduction in myocardial contractility and heart rate results in reduced cardiac output and reduced exercise tolerance [46]. Systemic vascular resistance is increased, as is the diastolic blood pressure.

Hypothyroid patients can present with pericardial and pleural effusions. This accounts in part for the low voltage seen on the electrocardiographic tracings of these individuals.

Skin and appendages

Typical findings in hypothyroidism include dry, pale, sometimes yellow skin. Nonpitting edema is caused by the accumulation of glycosaminoglycans [47]. Hair is coarse and fragile. Nails are brittle. The presence of pretibial edema may be a clue to making the diagnosis of hypothyroidism. Sweating is reduced.


**Nervous system**

Sleepiness, slowing of thought processes, and memory changes are common features of hypothyroidism [48]. Functional imaging studies have shown reductions in cerebral blood flow and glucose metabolism that may account for the observed clinical changes.

A delay in the relaxation phase of deep tendon reflexes is an important bedside test when evaluating a patient suspected of having hypothyroidism. Hypothyroidism should be in the differential diagnosis of carpal tunnel syndrome.

**Respiratory system**

Hypoventilation and hypercapnia are serious complications of profound hypothyroidism. These changes are due to respiratory muscle weakness and inappropriate respiratory response to hypoxemia and hypercapnia [49,50]. Hypothyroidism may cause or worsen sleep apnea.

**Gastrointestinal system**

Constipation results from reduced intestinal motility and is a common symptom in patients who have hypothyroidism [51]. As with other autoimmune conditions, there is an increased risk of pernicious anemia and gastric atrophy in hypothyroidism.

**Reproductive system**

Oligo-amenorrhea or hypermenorrhea-menorrhagia can be present [52]. Patients who have primary hypothyroidism may have mild to moderate serum prolactin elevation due to increased prolactin secretion under the stimulatory effect of TRH. Hyperprolactinemia can result in hypogonadotropic hypogonadism. There is reduced fertility and increased risk of miscarriage.

Levels of total testosterone in men may be reduced in hypothyroidism due to a reduction in the level of sex hormone-binding globulin. In these patients, the measurement of free or bioavailable testosterone is a better indicator of their gonadal status.

**Hypothyroidism and pregnancy**

Overt hypothyroidism is seen in about 1% to 2% of pregnant women [53]. Subclinical hypothyroidism is seen in another 2.5% [54]. Most cases of hypothyroidism during pregnancy have the same etiology as in hypothyroidism in general. In pregnancy, there is increased requirement of thyroid hormone [55] because of the increased rate of metabolism of thyroid hormones in the mother’s body and transplacental transport of thyroid hormone, which is essential for the development and maturation of the different organs of the fetus [56,57]. As a result, women who have underlying thyroid disorders are more susceptible to becoming hypothyroid during pregnancy.
Some investigators recommend an automatic increase in thyroid hormone replacement dose early during pregnancy in women who have hypothyroidism. This issue is discussed later in this article.

Maternal hypothyroidism, overt and subclinical, during pregnancy is associated with a number of complications including, spontaneous abortion, pre-eclampsia, miscarriage, still birth, preterm delivery, and postpartum hemorrhage.

Negro and colleagues [58] demonstrated beneficial effects of levothyroxine treatment even in euthyroid pregnant women who had autoimmune thyroid disease. This study revealed that euthyroid women who have TPO antibodies may develop impaired thyroid function during pregnancy, and this is associated with an increased risk of miscarriage and premature deliveries. Therefore, in these women, treatment with thyroid hormone lowers the chances of miscarriage and premature delivery.

Normal thyroid function in the mother is critical for normal fetal brain development and for normal fetal neuropsychointellectual function. The fetal thyroid function begins at about 10 to 12 weeks of gestation, and the concentrations of free T4 and TSH reach mean adult values at about 36 weeks of gestation [59]. During the first and second trimester of pregnancy, when most of the development and maturation of the central nervous system occurs in the fetus, the thyroid hormone is solely derived from the mother [60]. Therefore, overt hypothyroidism in the mother during the early stages of pregnancy can lead to severe and permanent damage in the neuropsychointellectual function of the fetus, whereas hypothyroidism in the latter stages of pregnancy may lead to a less significant and partially reversible neurocognitive impairment [61].

Haddow and colleagues [62] showed that the IQ scores of offspring of women who had mildly elevated TSH during pregnancy were 4 points lower than those of offspring of matched, euthyroid women, indicating that mild thyroid failure during pregnancy may adversely affect the neurocognitive development of the fetus.

**Diagnosis**

The diagnosis of hypothyroidism is based on the combination of clinical context and laboratory tests. Imaging of the brain and pituitary gland is required for patients in whom central hypothyroidism is suspected.

In the majority of patients, making the diagnosis of hypothyroidism should not be complicated. A number of factors can affect the levels of TSH, total T4, and total T3; in particular, several medical conditions can increase or decrease the concentration of total T4 and total T3 through their effect on serum levels of thyroxine-binding globulin and albumin. Examples include estrogens, nephrotic syndrome, and other states of hypoproteinemia. The serum levels of free T4 remain normal in these circumstances and provide a better assessment of thyroid function.
We measure TSH, freeT4 (FT4), and total T3 (TT3) in patients who are suspected of having thyroid dysfunction. Some laboratories offer a thyroid panel that includes TSH, T3 resin uptake, and TT4. A free T4 “index” is calculated and offered as a substitute for a free T4. In addition, we may order thyroid peroxidase (TPO) and thyroglobulin antibodies in a subset of patients. Dynamic testing with TRH is seldom needed. Contrary to the situation in hyperthyroidism, radionuclide studies of the thyroid have much less of a role in hypothyroidism. In addition to its role in evaluating goiters and thyroid nodules, thyroid sonography can disclose the typical heterogeneous parenchymal echogenicity that characterizes Hashimoto’s thyroiditis.

Patients who have primary hypothyroidism have elevated TSH and low FT4 and TT3. TPO antibodies are detectable in many patients who have Hashimoto’s thyroiditis.

A repeatedly elevated TSH, between 4 and 15 mIU/mL, with normal FT4 and TT3 is suggestive of subclinical hypothyroidism. This is a good indication for obtaining TPO antibodies.

Routine measurement of thyroid function tests in hospitalized patients is not recommended due to the effect of nonthyroidal illness on thyroid function tests.

Patients who have central hypothyroidism have low FT4 and TT3. The TSH can be low, normal, or mildly elevated. If central hypothyroidism is suspected, the entire function of the hypothalamic-pituitary axis should be evaluated with the appropriate tests. If a diagnosis of central hypothyroidism is made, imaging of the brain and pituitary gland should be obtained (we prefer MRI as the initial study).

Several laboratory scenarios are worth mentioning here. Patients who are recovering from acute, nonthyroidal illness typically have a rebound in TSH level. T4 and T3 are usually normal in these patients. These patients should not be treated with thyroid hormone replacement, and their thyroid function should be re-evaluated after 2 to 3 weeks. Normalization of their thyroid function is the general rule.

Poor compliance with pharmacologic therapy can be encountered in patients who are taking thyroid hormone replacement. Some patients may not take their thyroid replacement pills for days and take several pills the day of their doctor’s visit. An elevated TSH with high-normal or elevated FT4 is typical. No change in the levothyroxine dose is needed in this situation; rather, emphasis should be placed on compliance with therapy and repeat thyroid function in 3 to 4 weeks.

**Treatment of hypothyroidism**

Hypothyroidism can cause considerable morbidity. The treatment of hypothyroidism is, in principle, simple. Synthetic thyroxine is the preferred form of thyroid hormone replacement therapy. Hypothyroidism in the majority of patients is permanent and should be treated lifelong. The main
exceptions are patients who have transient hypothyroidism due to subacute thyroiditis and patients who have drug-induced hypothyroidism. These patients should be treated during their hypothyroid phase.

The main goal of treatment is to restore the euthyroid state determined by measuring the serum thyrotropin levels, which should be maintained within the acceptable range. The other goals of therapy are to improve hypothyroid symptoms in these patients (although this could be highly individualized) and to decrease goiter size in patients who have goitrous autoimmune thyroiditis.

The choice of the starting dose of synthetic thyroxine should take into consideration factors such as age, presence of coronary artery disease and cardiac arrhythmias. Treatment can be started with a full replacement dose of 1.6 $\mu$g/kg/d in young and healthy adult patients who have no significant comorbidities [63], but in elderly patients or those who have significant underlying coronary artery disease, it is prudent to start thyroxine at a dose of 25 $\mu$g to 50 $\mu$g once daily. Because the plasma half-life of synthetic thyroxine is about 7 days, once-daily dosing results in a steady state being reached in about 6 weeks, with fairly stable serum T3 and T4 concentrations [63]. The dose of LT4 can then be increased by increments of 12.5 or 25 $\mu$g every 1 to 2 weeks until a normal TSH is achieved.

LT4 is a prohormone with little intrinsic activity. LT4 is converted by the peripheral tissues in the body to the active form T3, through which most of the actions of thyroid hormone are exerted. About 80% of T3 is obtained from the peripheral conversion of T4; the remaining 20% is obtained from direct thyroid secretion [64]. This is favorable in two ways: the patient’s body controls the conversion of T4 to T3 and, there is a steady and adequate supply of T3 to the body.

**T4 formulations**

Several generic and branded formulations of LT4 are available, ranging from 25 $\mu$g to 300 $\mu$g in about 12 different strengths. There has been controversy regarding the bioavailability of these formulations. The US Food and Drug Administration in 2004 rejected a petition regarding the bioequivalence of levothyroxine sodium products and approved first-time generic levothyroxine sodium for the treatment of hypothyroidism. Nevertheless, current recommendations of the American Thyroid Association, The Endocrine Society, and American Association of Clinical Endocrinologists are to encourage patients to remain on the same levothyroxine formulation [65]. When patients must switch brands or use a generic, serum TSH should be checked 2 to 4 weeks later, and the dose should be modified accordingly.

**Factors affecting T4 absorption**

T4 is primarily absorbed in the jejunum, and about 70% of the dose administered is absorbed on an empty stomach [66]. Ideally, thyroxine should be taken on an empty stomach about 30 minutes before breakfast.
In one study evaluating the effect of food on the bioavailability of thyroxine, a breakfast containing bacon, eggs, toast, hash brown potatoes, and milk reduced thyroxine absorption by about 40% [67]. Calcium, iron in supplements, antacids, proton pump inhibitors, anticonvulsants, and food products increase the requirement of thyroxine by different mechanisms.

**Monitoring of treatment**

Adequacy of treatment is monitored by measurement of serum TSH levels. Serum TSH levels must be measured 4 to 6 weeks after commencing treatment and every 4 to 6 weeks thereafter until a normal TSH is reached. Although normal serum TSH levels range from 0.4 to 4 mU/L, many physicians prefer a target range of 0.5 to 3.0 mIU/L or 0.4 to 2.0 mIU/L, particularly in young and otherwise healthy patients. This is based on data from the NHANES III survey. Once target levels of serum TSH are reached, it is prudent to measure serum TSH and Free T4 levels once a year provided no other medications that may change the requirement of synthetic thyroxine are added. In addition, the patients may report amelioration of hypothyroid symptoms, which reflects adequacy of treatment, although this may be subjective and individualized.

If the patient has to be started on medications that are known to affect the absorption or metabolism of T4, serum TSH levels should be checked 4 to 6 weeks after the initiation of these medications to make sure that the dose of synthetic thyroxine is adequate. If necessary, the dose can be adjusted until the serum TSH levels are within the normal range.

**Adverse effects of T4**

An important adverse effect of treatment with synthetic thyroxine is hyperthyroidism due to over-replacement. It is estimated that more than one fifth of patients on treatment are clinically or subclinically thyrotoxic [68]. These patients have a suppressed (below 0.1) or low (between 0.1 and 0.4 mIU/L) TSH depending on the degree of over-replacement. In women over 65 years of age, a low serum TSH level is associated with a significantly increased risk of hip and vertebral fractures [69]. In the Framingham study, a TSH below 0.1 is associated with a threefold increased risk of atrial fibrillation in patients over the age of 60 years [70]. Rare adverse effects include allergy to the dye in the tablets.

**Combination therapy with T3 and T4**

Some patients who have hypothyroidism remain symptomatic in spite of replacement and normal serum TSH concentrations. For example, in a questionnaire-based study of patients who were taking thyroxin replacement, a significant percentage of patients reported an attenuated sense of psychosomatic well-being [71]. T4 normalizes FT4 and TSH levels in about 4 to 6
weeks, during which time symptoms may persist, whereas the onset of action of T3 is faster. Therefore, it was hypothesized that a combination of T3 and T4 may prove superior to treatment with T4 alone. Several controlled clinical trials compared treatment with T4 alone and combination treatment of T4 and T3. In only one study was there a significant improvement in mood, cognitive symptoms, and quality of life in favor of the T4 and T3 combination [72]. Other randomized controlled trials have failed to show similar findings [73–75]. In these studies, there was no improvement in psychologic or psychometric performance by objective tests, although in some of these studies, patients preferred a T3 plus T4 combination therapy for reasons unexplained objectively. A recent meta-analysis evaluated the results from 11 randomized control trials that included 1216 patients. The conclusion was that T4 and T3 combination was not superior to thyroxine monotherapy with respect to bodily pain, depression, anxiety, fatigue, quality of life, body weight, total serum cholesterol, triglyceride levels, low-density lipoprotein, and high-density lipoprotein [76]. Saravanan and colleagues [77] have shown that psychologic well-being correlates with free thyroxine but not free 3,5,3’-T3 levels in patients on thyroid hormone replacement. In addition to not improving general well being in patients who have hypothyroidism, T3 preparations result in wide-ranging fluctuations in serum T3 levels due to rapid gastrointestinal absorption and rapid onset of action. This can lead to arrhythmias, especially in elderly patients and in those who have underlying cardiac disease. Recent advances have shown that a slow-release preparation of T3 combined with T4 in the treatment of hypothyroidism avoids peaks in and fluctuating levels of serum T3, although larger-scale trials are warranted in this regard. Based on the current available literature, we do not recommend the use of T4 and T3 in combination to treat patients who have hypothyroidism.

**Treatment of patients who have secondary or central hypothyroidism**

In central hypothyroidism, TSH cannot be used as marker of adequate replacement therapy; instead, one should rely on the FT4 and sometimes Free T3 (FT3) concentrations. Typically, T4 and T3 levels are obtained before the daily dose of T4 is taken. We target FT4 and FT3 levels in the mid- to upper normal range.

**Treatment of poorly compliant patients**

The half life of thyroxine is 7 days. It can be given once weekly, which is beneficial in poorly compliant patients. A crossover trial of 12 patients showed that a single weekly dose achieved fairly good therapeutic results. Weekly dosing is contraindicated in patients who have coronary artery disease [78].
Management of hypothyroidism in pregnancy

Given the importance of maternal euthyroidism for normal neurocognitive development in the fetus, it is recommended that serial monitoring of serum TSH serum concentrations be performed in hypothyroid pregnant women and pregnant women susceptible to thyroid disease.

Based on the results of a study by Alexander and colleagues [53], it was recommended that for women who are being treated for hypothyroidism, the dose of levothyroxine be increased approximately by 30% as soon as the pregnancy is confirmed. Thereafter, serum thyrotropin levels should be monitored, and the levothyroxine dose should be adjusted accordingly. We recommend monitoring of thyroid function as soon as a pregnancy is confirmed and every 2 to 3 weeks thereafter with adjustment of thyroxine dose based on the results of thyroid function tests.

The target range of TSH during pregnancy is an area of controversy. Some clinicians recommend 0.4 to 4 mIU/L, whereas other clinicians recommend 0.4 to 2 mIU/L.

In recent articles, some investigators raised the question of the utility of administering thyroxine to pregnant women who have elevated levels of TPO antibodies but who otherwise have normal thyroid function tests. Such treatment is given to reduce the risk of miscarriage and premature deliveries that seems to be increased in these women. Further studies are needed in this regard [58,79].

Universal screening of pregnant women for subclinical hypothyroidism and hypothyroxinemia is not recommended because there is no evidence to justify the efficacy of screening and treatment and there have been no interventional studies to prove that this improves outcome [80–83]. Thyroid screening is recommended for high-risk pregnant women, such as those who have a personal history of thyroid or other autoimmune disorders or those who have a family history of thyroid disorders.

Treatment of subclinical hypothyroidism

There is debate on whether to treat subclinical hypothyroidism [84]. The question is whether subclinical hypothyroidism is associated with significant clinical impairment in affected patients, and if so, whether treatment with levothyroxine leads to better outcomes. There are conflicting data and controversial reports in this respect.

There is debate on what should be a “normal” reference range for TSH. The National Academy of Clinical Biochemistry guidelines state that “greater than 95% of healthy, euthyroid subjects have a serum TSH concentration between 0.4 and 2.5 mIU/L” [85]. The latest thyroid disease guidelines of the American Association of Clinical Endocrinologists recommend a reference TSH range of 0.3 to 3.0 mIU/L [86]. Recently, an expert panel met at a joint convention organized by the Endocrine Society, American Thyroid Association, and American Association of Clinical
Endocrinologists. The consensus was that there was good evidence that treatment of patients who have TSH levels above 4.5 mU/L prevents progression to overt hypothyroidism but that there was little convincing evidence that early treatment was beneficial [87]. Another school of thought upholds that there are enough data to support thyroid replacement in individuals who have subclinical hypothyroidism [88–91]. The strongest data in favor of treatment with thyroxine seem to be related to improvement in surrogate markers of cardiovascular disease, such as lipids, vascular resistance, and cardiovascular hemodynamics. Future studies should shed more light on this subject. Studies with hard end points, such as total mortality, cardiovascular mortality, and morbidity, will determine if thyroxine replacement should become the standard care for patients who have subclinical hypothyroidism. In general, treatment is strongly recommended in the following patients who have subclinical hypothyroidism: patients who have TSH levels higher than 10 mIU/L on repeated measurements, patients who have symptoms or signs (eg, goiter) associated with thyroid failure, patients who have convincing family history of thyroid disease, pregnant patients, patients who have a strong habit of tobacco use, or patients who have severe hyperlipidemia.

Myxedema coma

Myxedema coma is a term used to describe severe manifestations of hypothyroidism. It was first reported by Ord [92] in 1879 in London. It is a medical emergency. In the past, the overall mortality rate for myxedema coma was 60% to 70%. Early diagnosis and advances in intensive care and management have reduced the mortality to 20% to 25% [93].

Most patients who have myxedema coma are elderly women who have long-standing or uncontrolled hypothyroidism. Myxedema coma usually occurs during the winter months, suggesting that the low temperatures associated with winter may be a contributing factor for the clinical deterioration of underlying hypothyroidism. Myxedema coma can be precipitated by factors such as hypothermia, acute cardiovascular events such as myocardial infarction and stroke, infection, drugs that can compromise the central nervous system, trauma, and gastrointestinal bleeding.

Clinical features

The diagnosis of myxedema coma is mainly clinical. The presence of marked stupor, confusion, or coma and hypothermia in a patient with findings of hypothyroidism is strongly suggestive of myxedema coma. Treatment should not be delayed until the results of thyroid function tests are available. Physical examination is demonstrative of hypothyroidism: dry, coarse, scaly skin; sparse or coarse hair; nonpitting edema of the skin and soft tissues; macroglossia; hoarse voice; and delayed deep tendon reflexes. Other important clinical features of myxedema coma include hypoventilation, bradycardia,
decreased cardiac contractility, decreased intestinal motility, paralytic ileus, and megacolon [94]. There is a high incidence of pericardial effusion that may contribute to the decreased cardiac contractility. Early detection of infections that may be the precipitating events for myxedema coma may be difficult because bradycardia and hypothermia are likely to mask the fever and tachycardia of infections.

Laboratory findings in myxedema coma

Elevated TSH, very low serum total T4, FT4, and TT3 concentrations confirm the diagnosis of myxedema coma. The TSH level in myxedema coma may underestimate the degree of biochemical hypothyroidism because many of these patients may have a nonthyroidal illness in addition to severe hypothyroidism, and this can lower the TSH. Other laboratory findings include anemia, hyponatremia, hypercholesterolemia, high serum lactate dehydrogenase, and creatine phosphokinase concentrations. Arterial blood gas may reveal hypoxemia, hypercapnia, and acidosis.

Management of myxedema coma

The patient who has myxedema coma should be managed in an intensive care setting under continuous monitoring. Special attention should be given to ventilatory support in these patients, and mechanical ventilation should be given as required. Hypothermia and hypotension should be corrected. Metabolic disturbances such as hyponatremia, hypoglycemia, and hypercalcemia, which can aggravate the altered mental status, should be corrected. A thorough search for all the precipitating factors for myxedema coma should be done. Cultures should be drawn, and chest radiographs should be taken to rule out infections. If present, they should be treated aggressively with adequate antibiotic therapy.

Glucocorticoid therapy

All patients in myxedema coma should be given stress-dose steroids for the first 24 to 48 hours because supplementation of thyroid hormones leads to increased metabolism and thereby increases the requirement of cortisol.

Thyroid hormone therapy

T4 alone or in combination with T3 is given. An intravenous route should initially be used. Switching to the oral route is possible when the patient’s condition has improved.

The advantages of T4 are a smooth, slow, and steady onset of action. Disadvantages include the need for extrathyroidal conversion of T4 to T3, which may be reduced in patients who have serious illnesses. The onset of action of T4 is slower.

The advantages of T3 therapy include more rapid onset of action and no need for extrathyroidal conversion. T3 crosses the blood–brain barrier more
readily than does T4 in baboons [95]. Disadvantages of T3 include rapid action and highly fluctuating serum levels, which may not be desirable in patients who have underlying coronary atherosclerosis.

A commonly used dosing regimen for T4 includes administration of an initial high dose of T4, between 300 to 600 μg. This is followed by maintenance doses of 50 to 100 μg daily [96]. T3 can be administered at a dose of 10 to 20 μg intravenously every 4 hours on the first day followed by gradual tapering over the next 2 days, after which oral administration of T3 or T4 is usually possible.

In a study of eight patients who had myxedema coma, age, the presence of cardiac comorbidities, and a high dose of thyroxine were found to be associated with worse outcome [97]. The small number of the study patients is a limiting factor. The study authors recommended avoiding large dose of thyroxine in the treatment of myxedema in elderly patients.

We usually administer intravenous thyroxine alone at an initial dose of 200 to 400 μg for 2 days followed by a physiologic dose thereafter. We always administer intravenous corticosteroids, in the form of hydrocortisone, 100 mg every 8 hours for the first 24 hours. The first dose of hydrocortisone should be given before thyroxine is administered. Any precipitating factor, such as infection or cardiovascular event, should be addressed and treated appropriately.

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