Chapter 9
Introduction

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The thyroid hormones are unique among the hormones in that their structure contains a micronutrient in short supply, iodine. The dependence on iodine, a scarce element in many regions of the world, exposes the thyroid gland to dietary iodine deficiency. In addition, the synthesis of thyroid hormone requires a number of complex enzymatic processes, including the concentration of iodine in the follicular cell; the organification of iodine into the side chain of tyrosine; the coupling of tyrosines to form T4; the incorporation of T4 in the primary structure of a large storage protein, thyroglobulin; and the secretion of stored thyroid hormone. This array of unique proteins such as thyroglobulin and thyroid peroxidase, and the TSH receptor, makes the thyroid particular susceptible to faulty immune tolerance, so that the thyroid is the most common target of organ-specific autoimmunity. As a consequence thyroid underactivity, or hypothyroidism, is one of the most common endocrine dysfunctions encountered in clinical practice. In addition, these complex processes expose the thyroid gland to surprisingly rare congenital defects affecting T4 production.

Causes of Thyroid Underactivity

In the past, severe iodine deficiency has represented a major cause of hypothyroidism worldwide, especially in the pediatric age. Nowadays severe iodine deficiency has become rare [1]. In moderately iodine-deficient regions, hypothyroidism is now more common than in iodine-sufficient regions. In both moderately

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iodine-deficient and iodine-sufficient regions, spontaneous hypothyroidism is almost always caused by thyroid autoimmunity, in the form of chronic lymphocytic, or Hashimoto's, thyroiditis (HT). In HT, autoimmune T and B cell lymphocytes reactive to thyroid antigens invade the gland and progressively exhaust it. This results in variable and variably progressive compromise of the gland's ability to synthesize thyroid hormone [2]. Iatrogenic thyroid underactivity is the second most common cause, resulting from total or partial thyroidectomy or from radioactive iodine treatment for a number of conditions, such as toxic multinodular goiter or Graves' disease. Interesting, but very rare cause of hypothyroidism includes inherited errors in the biosynthesis of thyroid hormone. Congenital hypothyroidism is mostly due to developmental or metabolic errors. Rarely, hypothyroidism may result from pituitary dysfunction, leading to insufficient TSH production.

Diagnosis

The diagnosis of hypothyroidism is based on the measurement of serum TSH. Since any minimal change in thyroid hormone results in logarithmic changes in TSH, and since there are no other significant physiologic determinants of the TSH level, a TSH measurement is considered the most sensitive test for hypothyroidism. A normal TSH level rules out hypothyroidism, with the rare exception of central hypothyroidism, in which the TSH may be normal or low. Central hypothyroidism is diagnosed by the finding of low thyroxine in a subject with low or normal TSH. The actual thyroid hormone level may be useful in assessing the severity of hypothyroidism. In subclinical hypothyroidism, the TSH is midly elevated, but thyroid hormones are in the normal range, while overt hypothyroidism is defined by abnormally low thyroid hormones. This distinction is somewhat artificial, as there is clearly a continuum of thyroid dysfunction, but it has been adopted in many published studies.

Clinical Manifestations

Symptoms of hypothyroidism depend on the severity of the dysfunction, but there is also individual variation in the response. Patients with subclinical hypothyroidism are typically asymptomatic, but several studies show a number of subtle cardiovascular, metabolic, and neurologic adverse changes, mostly in subjects younger than 65 and in those with TSH >10 mcIU/mL [3]. Whether subclinical hypothyroidism has significant untoward effects in the elderly remains unclear. With overt hypothyroidism more prominent symptoms are often observed, affecting virtually all organ systems (Table 9.1).

Table 9.1 A concise list of symptoms of hypothyroidism

Organ system	Manifestations
Cardiovascular	Bradycardia, heart failure, pericardial effusion
CNS	Depression, fatigue, cognitive dysfunction, myxedema coma
Hematopoietic	Macrocytic anemia, target cells
Metabolic	Hyperlipidemia, weight gain
Musculoskeletal	Arthralgias, myositis
Gastrointestinal	Constipation
Renal	Hyponatremia
Reproductive	Polymenorrhea, galactorrhea, erectile dysfunction, infertility
Skin and appendages	Alopecia, coarse hair, dry and discolored skin, myxedema

Treatment of Hypothyroidism

In the absence of symptoms, treatment of subclinical hypothyroidism is recommended only in the younger group of patients after confirmation of the diagnosis with a repeat test a few weeks after the first [3]. There is general agreement that overt hypothyroidism should always be treated [4]. While T3 is the only active thyroid hormone in all target tissues, the hormonal defect in hypothyroidism is lack of T4 production from the thyroid gland. Effective treatment is therefore achieved with the oral administration of T4 (levothyroxine), to be later deiodinated to T3 in peripheral tissues. This is indeed the most effective form of hormone replacement in medicine. Owing to its long half-life, levothyroxine achieves stable T4 levels and restores euthyroidism. Restoration of euthyroidism is verified by the achievement of normal serum TSH levels. There are remaining areas of uncertainty. In spite of biochemical euthyroidism, many patients continue to experience non-specific symptoms such as fatigue, weight gain, and subjective cognitive abnormalities. Thyroid hormone replacement with a mixture of T4 and T3 has been tried and generally proven ineffective in this regard, so that the practice is typically not recommended in most cases [5]. The bioavailability of oral levothyroxine is imperfect at best and a relatively common cause of inconsistent euthyroidism during treatment. Interaction with other drugs in the gastrointestinal tract is the most common cause [6]. Novel soft gel and liquid preparations of levothyroxine have recently been developed, but their role remains to be defined by well-designed studies [7].

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