Chapter 9
Introduction

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Thyroid hormones are unique in that they are formed from the coupling and iodination of a nonessential amino acid, tyrosine. The thyroid almost exclusively produces thyroxine (T4), a precursor of the active hormone, triiodothyronine (T3). T3 is largely derived from deiodination of T4 in peripheral tissues, a still partially understood method for regionally regulating T3 levels. The thyroid also secretes a small amount of T3, but the physiological relevance of this is unclear. Upon binding with its ubiquitous nuclear receptors, T3 facilitates or activates transcription of a great variety of genes throughout almost all organ systems [1]. It is therefore not surprising that lack of thyroid hormones affects several physiologic pathways. Since T4, (after being deiodinated in the tyrotroph to T3) is largely predominant in the regulation of TSH production at the pituitary-hypothalamic levels and since TSH is the only natural regulator of T4 production, serum TSH levels are very tightly correlated to serum T4 levels. However changes in T4 result in TSH changes on a logarithmic scale. As a consequence, when the hypothalamic-pituitary-thyroid axis feedback mechanism is preserved, thyroid function can be effectively tested through TSH measurements.

Thyroid Underactivity

Thyroid underactivity or hypothyroidism is defined as the condition deriving by insufficient thyroid hormone levels in the circulation. In primary hypothyroidism, the defect is at the thyroid gland level. In primary hypothyroidism, free T4 levels are low, while the intact pituitary responds with elevated TSH levels. Elevated TSH

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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

levels, with normal free T4 levels, define subclinical primary hypothyroidism. Patients with elevated TSH (usually >10 mIU/L) and low FT4 are said to have overt hypothyroidism. In central hypothyroidism, the defect is at the hypothalamus-pituitary level and results in low free T4 levels, with low or inappropriately normal TSH levels. In both conditions, T3 levels are often normal and are therefore of little help in the diagnosis. The symptoms of hypothyroidism vary greatly depending on the severity of the insufficiency, the rate of drop in thyroid hormones, the age of the patient and poorly understood individual factors. As mentioned before, most, if not all, organ systems are affected. Table 9.1 shows a concise list of most commonly described symptoms of hypothyroidism.

Causes of Hypothyroidism

World-wide, iodine deficiency remains the most significant cause of hypothyroidism. Thyroid autoimmune disease (Hashimoto's thyroiditis) [2] is the most common cause of spontaneous primary hypothyroidism in regions with normal or even moderately low iodine intake. The degree of hypothyroidism is most often mild (subclinical) and slowly progressive in Hashimoto's thyroiditis, but all degrees of hypothyroidism can be seen and sudden onset is sometimes seen. Many patients with Hashimoto's thyroiditis have a rubbery goiter, diffusely hypoechoic and vascular on neck ultrasound. In some cases, the thyroid becomes completely atrophic and cannot be palpated. Thyroid peroxidase antibody tests are almost universally positive in Hashimoto's thyroiditis. Almost all other forms of primary hypothyroidism are iatrogenic, caused by either thyroid surgery, or radioactive iodine treatment of hyperthyroidism. Inflammatory or toxic forms of hypothyroidism can occur as a consequence of medications (amiodarone) or viral insults (subacute thyroiditis) and may result in transient forms of primary hypothyroidism. Central hypothyroidism is vastly less common than primary and usually occurs in the setting of multiple pituitary hormone insufficiencies.

Management of Hypothyroidism

Hypothyroidism is usually diagnosed by finding of an elevated serum TSH [3]. In many laboratories, "reflex" serum T4 or freeT4 levels confirm the diagnosis. A normal TSH does not rule-out central hypothyroidism, but normal FT4 does. All patients with overt hypothyroidism and with central hypothyroidism should receive treatment with thyroid hormone. The benefit of treating asymptomatic patients with subclinical hypothyroidism remains uncertain and may be limited to patients of younger age, especially women in the childbearing age [4]. The goal of hypothyroidism treatment is restoration of normal TSH levels and resolution of symptoms. Synthetic L-thyroxine is the most appropriate treatment for most patients with hypothyroidism. Athyreotic patients will require 1.6 mcg/kg BW/day to achieve complete thyroid replacement, but patients with subclinical hypothyroidism typically need lower doses due the contribution of their residual thyroid function. T4/T3 combination therapy has been studied, based on the finding that thyroid hormone production includes a small amount of T3 and on data indicating a slightly lower FT3 in many patients treated with T4, when compared with euthyroid patients with similar TSH levels. There is also the desire to help those patients whose symptoms are not resolved when normal TSH levels are re-established with T4 alone. The available studies have not confirmed a statistically significant beneficial effect of combined therapy. However the understanding of these issues is limited and therefore we administer combination to the occasional patient on an empiric basis.

Treatment with thyroid hormone is usually very well tolerated and very efficient in restoring euthyroidism. In select cases, such as cardiac or elderly patients, replacement should be initiated with smaller doses. The fact that by measuring TSH and T4 we actually measure the medication, rather than relying on an indirect measure of its effect, allows for very precise titration and quick recognition of instances of malabsoprtion or noncompliance [5].

References

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