Chapter 2
Classification of Thyroid Diseases

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2.1 Introduction

Alterations of the circulating thyroid hormones levels, namely hypothyroidism and hyperthyroidism, are common conditions with potentially devastating health consequences that affect all populations worldwide [1]. Thyroid dysfunction is common, readily identifiable, and easily treatable. Nonetheless, if undiagnosed or untreated, it can have profound adverse effects. Despite an increase in thyroid disease awareness and the availability of sensitive laboratory assays for the measurement of thyroid hormones, cases of extreme thyroid dysfunction occasionally still occur. Hypothyroidism and hyperthyroidism commonly arise from pathological processes within the thyroid gland (primary thyroid disease), although in rare cases, they can arise from disorders of the hypothalamus or pituitary (central hypothyroidism) or from peripheral causes, such as struma ovarii, or functional thyroid cancer metastases. Iodine nutrition is a key determinant of thyroid disease risk; however, other factors, such as aging, smoking status, genetic susceptibility, ethnicity, endocrine disruptors, and the advent of novel therapeutics, including immune checkpoint inhibitors, also influence thyroid disease epidemiology [1]. Nodular thyroid disorders are prevalent in areas where iodine deficiency is common, while autoimmune thyroid (AIT) disorders, including Hashimoto thyroiditis and Graves' disease, occur more frequently in iodine-replete populations. Indeed, a number of other risk factors, including genetic and ethnic susceptibility, sex, smoking status, alcohol consumption, presence of other autoimmune conditions, syndromic conditions and exposure to therapeutic drugs, also influence thyroid disease epidemiology. In this general epidemiological setting, the incidence of thyroid cancer worldwide has

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increased significantly over the past three decades, due mostly to an increase in papillary thyroid cancer cases. Although most of these cancers are small and localized, population-based studies have documented a significant increase in thyroid cancers of all sizes and stages, in addition to incidence-based mortality for papillary thyroid cancer. Increasing incidence of thyroid cancer seems to be due in large part to increasing surveillance and overdiagnosis, but researchers agree that there is also a true increase in new cases of thyroid cancer [2]. The detection of thyroid dysfunction has been driven over the past two decades by the progressive lowering of treatment thresholds, together with increased thyroid function testing with sensitive assays, determining a higher prevalence of borderline or mild cases. The complex inverse association between the pituitary-derived TSH and T4 and T3 indicates TSH as the most sensitive marker of thyroid status. Accordingly, *overt hypothyroidism* is defined as TSH concentrations above the reference range and free T4 levels below the reference range, while *subclinical hypothyroidism* is defined as TSH levels above the reference range when levels of free T4 are within the population reference range (Table 2.1). Likewise, the reverse hormone pattern is applied in the definition of *overt* (low TSH and high free T4) and *subclinical hyperthyroidism* (low TSH and normal free T4) (Table 2.1). In the present chapter, the main clinical thyroid disorders will be presented focusing on epidemiological and clinical features (Table 2.1).

2.2 Hypothyroidism

Hypothyroidism is common throughout the world. Iodine deficiency and autoimmune disease (known as Hashimoto thyroiditis) are the prevalent causes of primary hypothyroidism [3]. In iodine-sufficient countries, the prevalence of hypothyroidism ranges from 1% to 2% [4, 5], rising to 7% in individuals aged more than 85 years [6]. Hypothyroidism is approximately ten times more prevalent in women than men. The prevalence of overt hypothyroidism in the general population ranges from between 0.2% and 5.3% in Europe [7, 8] and 0.3% and 3.7% in the USA [9].

2.2.1 Autoimmune Thyroiditis

Hashimoto thyroiditis is the most frequent autoimmune thyroid (AIT) disorders. It causes a chronic inflammation of the thyroid tissue, and hypothyroidism occurs in about 20–30% of patients [10]. AIT incidence is about 0.3–1.5/1000 subjects/year, with a major frequency in women than in men (from 4 to 10 times). Hashimoto thyroiditis is considered to depend on a combination of genetic susceptibility and environmental risk factors, which determines the breakdown of immunological tolerance, with a resulting autoimmune attack to the thyroid itself. Lymphocytic infiltration, especially of T cells, and follicular destruction are the histological AIT hallmark, which can induce progressive thyroid atrophy and fibrosis.

Table 2.1 Classification of thyroid diseases and associated thyroid hormone alterations

	Hypothyroidism	Euthyroidism	Hyperthyroidism
Hormonal patterns			
TSH	↑		↓
FT4	N/↓		N/↑
FT3	N/↓		N/↑
Frequency (overt disease)	0.2–5.3%		0.1–1.3%
Etiology			
Congenital			
Thyroid dysgenesis	+	+	
Thyroid dyshormonogenesis	+		
Acquired			
Autoimmunity			
Hashimoto thyroiditis	+	+	+
Postpartum thyroiditis	+		+
Graves' disease			+
Iodine status			
Severe iodine deficiency	+		
Mild to severe iodine excess	+		
Infections			
Viral	+		+
Postpartum (De Quervain syndrome)			
Bacterial	+	+	+
Thyrocytes proliferation			
Uninodular goiter		+	+
Multinodular goiter		+	+
Malignant neoplasia			
Papillary		+	
Follicular		+	+
Medullary		+	
Anaplastic		+	
Iatrogenic			
Radioiodine	+		
Surgery	+		
Drugs[a]	+		+
Secondary (central)			
Hypothalamic failure/dysfunction	+		
Pituitary macroadenoma and/or apoplexia	+		
Resistance to TSH or TRH	+		
Drug-induced[b]	+		
Inappropriate TSH secretion[c]			+
Extra-thyroidal			
Consumptive hypothyroidism[d]	+		

(continued)

Table 2.1 (continued)

	Hypothyroidism	Euthyroidism	Hyperthyroidism
Tissue-specific due to genetic mutations[e]	+		
Excess intake of thyroid hormone			+
Ectopic thyroid hormone secretion[f]			+

TSH thyroid stimulating hormone, *FT4* free tiroxine, *FT3* free triiodiotirosine, *N* within normal range, *TRH* thyrotropin releasing hormone

[a]Amiodarone, lithium, monoclonal antibodies, sodium valproate (anti-epileptic), tyrosine kinase inhibitors and immune checkpoint inhibitors

[b]Dopamine, somatostatins

[c]TSH secreting pituitary adenoma or pituitary resistance to thyroid hormone

[d]It is a paraneoplastic syndrome, resulting from the aberrant uncontrolled expression of the type 3 deiodinase (D3) that can induce a severe form of hypothyroidism by inactivating T4 and T3 in defined tumor tissue

[e]*THRα, THRβ, MCT8/SLC16A2*

[f]Struma ovarii and functional thyroid cancer metastases

It is worth noting that there is an association between AIT disorders and other organ specific/systemic autoimmune disorders. It is not unusual to find patients with more than one immune-mediated endocrine disorder. As a result, polyglandular autoimmune syndromes (PAS), characterized by the failure of different endocrine glands, occur. Most of these patients showed Addison's disease, hypogonadism, Graves' disease, AIT, vitiligo, alopecia, pernicious anemia, and type 1 diabetes mellitus. In most cases (48%), the first manifestation of PAS was the type 1 diabetes–AIT disorders association [11].

Moreover, AIT is associated with papillary thyroid cancer and thyroid autoimmunity, and high TSH levels are considered independent risk factors for thyroid cancer [12]. Ten to 30% of patients with papillary thyroid cancer and AIT disorders show an aggressive form of the disease [13].

2.2.2 Subclinical Hypothyroidism

Subclinical hypothyroidism exists when serum thyroid hormone levels are within the reference range, but serum TSH levels are elevated outside the reference range. In iodine-sufficient populations, subclinical hypothyroidism affects up to 10% of the population, being highly prevalent among women and elderly individuals [14]. However, it should be considered that (1) subclinical hypothyroidism frequently reverts to euthyroidism, and (2) TSH levels rise as people without thyroid disease age, making it likely that the prevalence of subclinical hypothyroidism has been overestimated. Subclinical hypothyroidism may be categorized as grade 1, when TSH levels are between the upper limit of the reference range and 9.9 mU/L, and as grade 2, when serum TSH levels are 10 mU/L or higher. Approximately 90% of patients with subclinical hypothyroidism have serum TSH levels lower than

10 mU/L. Autoimmune thyroiditis is the most common cause of mildly elevated serum TSH levels. Indeed, older individuals with mildly elevated serum TSH in the absence of thyroid disease are not at risk of increased morbidity and mortality. A number of clinical conditions unrelated to primary thyroid diseases, able to induce increase in TSH levels, should be considered; they include external radiotherapy to the neck, drugs (such as lithium), laboratory anomalies (heterophilic antibodies in the serum), untreated adrenal insufficiency, mutations in the TSH receptor gene, obesity, critical illness, circulating macroTSH (similar to macroprolactin, in which TSH is complexed to antithyrotropic IgG to form a high molecular weight complex with low biological activity) and thyroid lobectomy for benign or malignant thyroid nodules. In the last setting, permanent hypothyroidism, typically subclinical, can occur in up to 60% of patients after thyroid lobectomy and more than 1 year after surgery. In 60% of patients with grade 1 subclinical hypothyroidism, TSH declines to the normal range over 5 years [15, 16]. The annual rate of progression to overt disease is about 2–4% in such patients, depending on anti-thyroperoxidase (TPO) antibody status [16–19]. Grade 2 subclinical hypothyroidism is associated with increased rates of progression to overt hypothyroidism, especially in women and in patients with positive anti-TPO antibodies. Grade 1 subclinical hypothyroidism is rarely associated with hypothyroid and neuropsychiatric symptoms or alterations in mood or cognition. Cardiovascular abnormalities (left ventricular systolic and diastolic dysfunction and impaired vascular relaxation) have been described in patients with grade 1 and grade 2 subclinical hypothyroidism. Hypothyroidism is one of the most frequent secondary causes of dyslipidemia (elevated low-density lipoprotein [LDL] cholesterol and triglyceride levels), and screening for hypothyroidism is recommended for individuals with hypercholesterolemia. Metabolic alterations can develop in grade 2 subclinical hypothyroidism, mainly in patients with insulin resistance. A meta-analysis performed by the Thyroid Studies Collaboration, a consortium of cohort studies with data from more than 75,000 participants, showed that TSH levels of 10 mU/L or higher were associated with increased risk of heart failure, coronary heart disease events, and mortality from coronary heart disease compared with normal TSH values [20]. In addition, TSH values of 7.0–9.9 mU/L were associated with increased risk of fatal stroke and mortality from coronary heart disease. Association of subclinical hypothyroidism with dementia, kidney function decline, bone mineral density, and fracture risk has been investigated, though conclusive results is lacking [14].

2.2.3 Iodine-Induced Hypothyroidism

Iodine-induced hypothyroidism is attributed to a failure of thyroid adaptive mechanisms to an acute iodide load, known as the Wolff–Chaikoff effect. Common sources of excess iodine include supplementation, diet, iodinated contrast agents, and medication. Further details have been provided in Chap. 1.

2.2.4 Drug-Induced Hypothyroidism

Several drugs can cause hypothyroidism. Here the drugs that are most frequently associated with hypothyroidism are briefly presented [1]:

1. *Lithium* therapy causes overt hypothyroidism in 5–15% of patients treated; the use of lithium increased the risk of hypothyroidism by more than twofold.
2. *Amiodarone*-induced hypothyroidism may be more common than amiodarone-induced thyrotoxicosis in iodine-sufficient areas, with amiodarone-induced hypothyroidism occurring in 6.9–22.0% of patients in iodine-sufficient areas and amiodarone-induced thyrotoxicosis occurring in between 2.0% and 12.1% of patients.
3. *Immune checkpoint inhibitors*, used both as single agents or in combination, have emerged as key treatments in managing advanced cancers, making the disease chronic. Immune checkpoint inhibitors are antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA4), such as ipilimumab; programmed cell death protein 1 (PD1), such as nivolumab and pembrolizumab; and anti-PD1 ligand molecules (PDL1 and PDL2), such as atezolizumab and durvalumab. These agents have been approved for a variety of cancers, including melanoma, non-small-cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, and head and neck cancers. Immune checkpoint inhibitors reactivate the immune system against cancer cells but can also induce autoimmune adverse effects that particularly affect the hypothalamic–pituitary–thyroid axis. Patients taking immune checkpoint inhibitors can develop primary or secondary hypothyroidism and primary hyperthyroidism. Secondary hypothyroidism is more common in patients treated with anti-CTLA4 antibodies, whereas primary hypothyroidism is observed more frequently in patients taking anti-PD1 and anti-PDL1 monoclonal antibodies. Hypothyroidism has been reported to occur in 1.5–6.8% of patients on ipilimumab, 9.0–10.8% of patients on nivolumab, and 5.5–9.6% of patients on durvalumab. In combination therapy with nivolumab and ipilimumab, hypothyroidism occurs even more frequently in 4–27% of cases.
4. *Alemtuzumab*, a novel treatment for multiple sclerosis, has also been associated with a high prevalence of hypothyroidism.
5. *Tyrosine kinase inhibitors* can result in an increased risk of hypothyroidism with 27% of treated patients requiring levothyroxine replacement during their treatment.

2.2.5 Congenital Hypothyroidism

Primary congenital hypothyroidism (CH) is the most common preventable cause of mental retardation and is associated with 12-fold increased risk of multiple neonatal malformations that may cause additional disease complications [21–23]. A tendency toward an increased CH detection has been described in several

socio-economically advanced countries, and it has been related to improved outcome of CH more frequently allowing transmission of heritable defects, endocrine disrupting chemicals, and the lower threshold of neonatal TSH screening [22–24]. With the introduction of the neonatal screening of congenital hypothyroidism, the incidence is 1:1500–1:2000. CH occurs due to defective thyroid gland development or hormone biosynthetic function and is traditionally sub-classified as thyroid dysgenesis or dyshormonogenesis [25, 26]. Thyroid dysgenesis refers to a spectrum of aberrant thyroid gland development, most commonly involving thyroid ectopy, an abnormally situated and mostly small thyroid gland. Complete absence of the thyroid gland (athyreosis) occurs in 20–30% of cases with thyroid dysgenesis, while a small minority exhibit a normally located though hypoplastic thyroid gland. Dyshormonogenesis refers to failure of thyroid hormone production by a normally located, sometimes enlarged goitrous thyroid gland in which the molecular pathway for thyroid hormone biosynthesis is disrupted. Thyroid dysgenesis is generally considered to be a sporadic disease for which the underlying etiology is usually not clear. Genetic causes involve genes mediating thyroid differentiation, migration, and growth. However, in less than 5% of cases with thyroid dysgenesis, a loss-of-function mutation in a known thyroid dysgenesis-associated gene can be detected, namely *TSHR* (TSH receptor), *NKX2.1/TTF1*, *PAX8*, *FOXE1/TTF2*, *GLIS3*. Additional genes associated with thyroid dysgenesis include *NKX2.5*, *JAG1*, *CDCA8*, and *NTN1*/Netrin 1. Recent evidence suggests the existence of hypomorphic alleles of these candidate genes, whose combination can explain a significant portion of congenital hypothyroid cases [25]. The oligogenic involvement should be considered as a solid hypothesis for the genetic etiology of congenital hypothyroidism: variants with a modest functional impairment can produce a negligible effect on thyroid function when expressed alone, but the sum of minor alleles, even acting at different levels (thyroid morphogenesis or hormonogenesis), can justify the birth of a child with congenital hypothyroidism in families with a history of minor thyroid defects or without any previously recognized thyroid disease [25]. In contrast, the majority of individuals with dyshormonogenesis harbor mutations in genes encoding known components of the thyroid hormone biosynthesis machinery, including *TG* (thyroglobulin), *TPO* (thyroperoxidase), *SLC26A4* (pendrin), *SLC5A5* (sodium/iodide symporter), *DUOX2* (dual oxidase 2), *DUOXA2* (dual oxidase maturation factor 2), *IYD* (iodotyrosine deiodinase).

2.2.6 Central Hypothyroidism

Central hypothyroidism is characterized by a defect in thyroid hormone secretion, resulting from the insufficient stimulation of a healthy thyroid gland by TSH. It can be a consequence of an anatomic or a functional disorder of the pituitary gland and/or the hypothalamus [27]. Central hypothyroidism can be congenital, caused by genetic defects, or acquired, resulting from lesions such as tumors, traumas, or cerebrovascular accidents that affect the hypothalamic–pituitary axis. Central

hypothyroidism may present as an isolated defect of pituitary function, while in most patients it occurs in combination with other pituitary hormone deficiencies. The global prevalence of central hypothyroidism ranges from 1 in 20,000 to 1 in 80,000 individuals in the general population, representing a rare cause of hypothyroidism (1 out of 1000 patients with hypothyroidism). Central hypothyroidism affects patients of all ages and both sexes equally. Defects in TSH secretion can be quantitative (due to reduced TSH reserve), qualitative (sustained by reduced bioactivity of the released TSH molecules), or both. In the congenital forms of central hypothyroidism the defect is usually quantitative. By contrast, the defect is frequently both quantitative and qualitative in acquired central hypothyroidism. The secretion of bioinactive TSH can occur following hypothalamic–pituitary tumors or injuries sustained during a breech delivery, external radiation for head tumors and Sheehan syndrome. The clinical features of central hypothyroidism depend on the etiology, the severity of the hypothalamic–pituitary impairment, the extent and severity of associated hormone deficiencies, and the age of the patient at the time of disease onset. Congenital central hypothyroidism is clinically more severe than the acquired forms. The symptoms and signs of central hypothyroidism, which include fatigue, depression, cold intolerance, hoarseness, dry skin, constipation, bradycardia, and hyporeflexia, are usually the same but milder than those of primary hypothyroidism, and goiter is seldom present. In the presence of combined pituitary deficiencies, other endocrine manifestations, for example, growth failure, delayed puberty, adrenal insufficiency and diabetes insipidus, lead the patients to seek medical attention before their hypothyroidism manifests. Patients with congenital central hypothyroidism present with various syndromic and complex clinical features depending on the genes involved.

2.3 Hyperthyroidism

The prevalence of overt hyperthyroidism ranges from 0.2% to 1.3% in iodine-sufficient parts of the world [1]. Graves' disease is the most common cause of hyperthyroidism in iodine-replete populations. Other common causes include toxic multinodular goiter and autonomously functioning thyroid adenoma [28]. Less common causes of hyperthyroidism are thyroiditis, pituitary TSH secreting adenoma, and drug-induced hyperthyroidism. In iodine-sufficient countries, Graves' disease accounts for 70–80% of patients with hyperthyroidism, whereas in areas with iodine deficiency, Graves' disease constitutes about 50% of all cases of hyperthyroidism, with the other half attributable to nodular thyroid disease [29].

The clinical phenotype in hyperthyroidism also shows geographical variation. Moreover, compared with patients with nodular disease, patients with Graves' disease are younger, have higher thyroid hormone levels, and are more likely to present with overt hyperthyroidism than subclinical hyperthyroidism. Cardiovascular complications resulting from hyperthyroidism seem to be more prevalent in areas where toxic multinodular goiters are common, in part because patients with nodular

disease are typically older. Ethnicity does seem to influence the risk of developing certain disease complications. For example, Graves' ophthalmopathy is six times more common in white populations than in Asian populations. Furthermore, the rare but serious complication of hyperthyroidism, thyrotoxic periodic paralysis, is markedly more common in Asian men [1, 30].

2.3.1 Graves' Disease

Graves' disease is a systemic autoimmune disorder caused by thyroid stimulating autoantibodies directed against the TSH receptor on thyroid follicular cells that results in follicular cell hypertrophy, thyroid enlargement, increased synthesis of thyroid hormone, and hyperthyroidism. Ophthalmopathy and pretibial myxedema can also occur. Graves' ophthalmopathy occurs in 20–30% of patients, while pretibial myxedema is rarely observed. Graves' disease affects approximately 0.5% of the population and is the most common cause of hyperthyroidism, accounting for 50–80% of all cases [29]. Graves' disease predominantly affects women with a female to male ratio of 8:1, typically in their third to fifth decade of life. The clinical phenotype of Graves' disease, at least in Western countries, is becoming milder, presumably due to earlier diagnosis and treatment.

2.3.2 Toxic Nodular Disease

Toxic nodular goiter is the most frequent cause of thyrotoxicosis in elderly individuals, especially those in iodine-deficient areas. Solitary toxic nodules are more common in women than in men, with a likely male:female ratio of 1:5 [31]. In areas where low iodine intake is prevalent, the incidence of toxic multinodular goiter is significantly higher in areas with low iodine intake (18.0 cases/100,000/year) compared with high-iodine-intake areas (1.5 cases/100,000/year) [32]. The incidence of solitary toxic nodules is similarly higher in low-iodine-intake areas than in high-intake areas.

2.3.3 Thyroiditis

Thyroiditis is characterized by a self-limiting course of thyrotoxicosis, followed by hypothyroidism and then return to normal thyroid function. The condition is slightly more common in females than males (female:male ratio of 1.5:1), and permanent hypothyroidism occurs in 10–20% of cases overall [3]. Acute painful thyroiditis often presents following a respiratory tract infection, while painless thyroiditis can occur postpartum in up to 9% of otherwise healthy women [33].

2.3.4 Drug-Induced Hyperthyroidism

The iodine-rich compound amiodarone is widely prescribed as an anti-arrhythmic agent. Amiodarone-induced thyrotoxicosis is more common in iodine-deficient areas and appears to be more common in men with a male:female ratio of up to 3:1. Other drugs that cause thyrotoxicosis include interferon (IFN)-α, lithium, tyrosine kinase inhibitors, highly active antiretroviral therapies, immune checkpoint inhibitors, and the humanized monoclonal antibodies used in the treatment of multiple sclerosis, alemtuzumab. Although these drugs can cause transient thyrotoxicosis through destructive thyroiditis, immune-modifying agents such as IFN-α, highly active antiretroviral therapies, and alemtuzumab can also induce Graves' disease through less well-defined immune reactivation mechanisms [34].

2.3.5 Iodine-Induced Hyperthyroidism

Iodine-induced hyperthyroidism, which is also known as the Jod–Basedow phenomenon, is more common in older persons with longstanding nodular goiter and in regions of chronic iodine deficiency where the populace is undergoing iodine supplementation [35]. Iodization programs temporarily increase the risk of iodine-induced hyperthyroidism; elderly individuals who might have coexisting cardiac disease and also those with limited access to health care are principally at risk [35]. Radiographic contrast agents can also cause iodine-induced hyperthyroidism. Individuals with preexisting multinodular goiter or those from iodine-deficient areas are at greatest risk of iodine-induced hyperthyroidism following the administration of a radiographic contrast agent [36].

2.3.6 Subclinical Hyperthyroidism

The prevalence of subclinical mild hyperthyroidism has been estimated ranging from 1% to 5% [37]. Data from the NHANES III study suggest a bimodal peak at age 20–39 years and at >80 years of age [38]. The NHANES III study also showed that women were more likely to have subclinical hyperthyroidism. The greatest risk factor for subclinical hyperthyroidism, aside from levothyroxine use, is iodine deficiency. The prevalence of subclinical hyperthyroidism increases from around 3% in iodine-sufficient areas to 6–10% in iodine-deficient areas, largely owing to toxic nodular goiters. Data on the risk of progression from subclinical to overt hyperthyroidism are limited. In a Scottish database including more than 2000 cases of subclinical hyperthyroidism, the most untreated patients did not progress to overt hyperthyroidism, and one-third of patients returned to normal thyroid status 7 years after initial diagnosis [39]. Other studies showed that patients with more severe grades of subclinical hyperthyroidism progressed more frequently to overt disease.

2.4 Thyroid Nodular Diseases

Thyroid nodules are defined as discrete lesions within the thyroid gland, distinct from surrounding thyroid parenchyma [40]. Thyroid nodules are common, being detected in up to 65% of the general population. Approximately 90% of thyroid nodules are benign and 95% are asymptomatic, remain so during follow-up, and can be safely managed with a surveillance program. The main goal of initial and long-term follow-up is identification of the small subgroup of nodules that harbor a clinically significant cancer (≈10%), cause compressive symptoms (≈5%), or progress to functional disease (≈5%) [41].

There is considerable heterogeneity between thyrocytes in the same follicle in terms of iodine retention, hormone synthesis, and mitotic response to proliferative stimuli [42]. These physiological variations cause differences in the hyperplastic nodules originating from these cells. TSH is the main mitotic factor. Elevation of serum TSH levels causes significant increases in thyroid volume, and even minimal elevations over an adequate amount of time are sufficient for goiter formation. Iodine deficiency is the leading cause of increases in TSH levels. Thus, the incidence of nodules is high in regions with endemic goiter due to iodine deficiency. Selenium deficiency also causes goiter and nodular goiter. Some chemicals (e.g., nitrate and perchlorate) can cause goiter by affecting iodine uptake or hormone synthesis. There is an increased incidence of thyroid nodules despite the use of iodine prophylaxis in many countries [43]. Other factors involved in the development of thyroid nodules include radiation, environment (nitrates, benzene, formaldehyde, pesticides, bisphenol A, polychlorinated biphenyl, polyhalogenated aromatic hydrocarbons, and polybrominated diphenyl ether), gene mutations (*RAS*, *PAX8/PPARγ*, *RET/PTC*, *BRAF*), metabolic syndrome, insulin resistance, and obesity [44].

One of the leading causes of nodule detection is the increased use and sensitivity of radiological imaging. Ultrasound can currently detect nodules as small as 1–2 mm, causing the incidence of nodules to increase to 60,000–70,000/100,000 adults in a population. This number was below 10,000 when palpation and scintigraphy were the only methods used for nodule evaluation. However, many studies have found that the incidence of nodular goiter is increased even when this factor is eliminated. The cancer rate of nodular goiter is around 5%. The rate does not differ between single nodules and multinodular goiter [1].

Risk factors for malignancy include childhood irradiation (mainly head and neck and whole body radiation), exposure to ionizing radiation from fallout in childhood or adolescence, family history of thyroid cancer or hereditary syndromes that include thyroid cancer [multiple endocrine neoplasia syndrome type 2 (MEN2A and 2B), family with ≥3 affected relatives, or genetic syndromes such as Cowden disease, familial adenomatous polyposis, Carney complex], rapid nodule growth, or hoarseness [41]. Family history plays a significant role in the development of thyroid cancer, and having first-degree relatives with not only medullary, but also papillary thyroid cancer strongly predicts the risk of developing the malignant thyroid disease. In contrast, benign thyroid disorders in family history do not lead to the development of thyroid cancer [45].

Thyroid cancer is the fifth most common cancer in women in the USA. The incidence continues to rise worldwide. Differentiated thyroid cancer is the most frequent subtype of thyroid cancer [46, 47]. Although over 90% are small, nonpalpable, benign lesions that will never become clinically significant tumors, some patients have nonpalpable or palpable lesions that are malignant. Identification of malignant thyroid nodules is important, especially those that will cause morbidity if not diagnosed early. Thyroid cancers are distinct in follicular-derived thyroid cancers and neuroendocrine C-cell-derived thyroid cancers. The follicular-derived cancers include differentiated and anaplastic thyroid cancers. From a genetic point of view, most thyroid cancers harbor mutations along the mitogen-activated protein kinase (MAPK) cellular signaling pathway [46].

2.4.1 Follicular-Derived Thyroid Cancers

2.4.1.1 Differentiated Thyroid Cancers

Differentiated thyroid cancer is the most common thyroid cancer, accounting for more than 95% of cases, and originates from thyroid follicular epithelial cells [48]. This category includes papillary thyroid cancer, follicular thyroid cancer, and Hurthle cell thyroid cancer. Poorly differentiated thyroid cancer is a more aggressive follicular-derived thyroid cancer than differentiated thyroid cancer. Papillary thyroid cancer is the most common subtype and carries the best overall prognosis. Metastases most commonly involve cervical lymph nodes and, less commonly, the lungs. Follicular thyroid cancer, Hurthle cell thyroid cancer, and poorly differentiated thyroid cancers are high-risk cancers that have a tendency to metastasize hematogenously to distant sites, in particular, to lung and bones.

2.4.1.2 Anaplastic Thyroid Cancers

Anaplastic thyroid cancer is a rare form of thyroid cancer (<1%) [48] that usually presents as a rapidly growing neck mass. Patients often develop hoarseness, dysphagia, and dyspnea. The most common site of distant metastatic disease is the lung, followed by bones and brain. Anaplastic thyroid cancer often arises from and can coexist with differentiated thyroid cancer, but can also occur de novo.

2.4.2 Neuroendocrine C-Cell-Derived Thyroid Cancer

2.4.2.1 Medullary Thyroid Cancers

Medullary thyroid cancer accounts for 1–2% of all thyroid cancers and originates in the parafollicular neuroendocrine cells of the thyroid [48]. It most commonly presents as a solitary thyroid nodule in patients in the fourth to sixth decade of life. A

quarter of medullary thyroid cancer cases occur in patients with the inherited type 2A multiple endocrine neoplasia syndrome (MEN2A;OMIM#171400), type 2B multiple endocrine neoplasia syndrome (MEN2B;OMIM#162300), and familial medullary thyroid cancer (MTC;OMIM#155240).

References

1. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, Okosieme OE. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol. 2018;14:301–16. https://doi.org/10.1038/nrendo.2018.18.
2. Seib CD, Sosa JA. Evolving understanding of the epidemiology of thyroid cancer. Endocrinol Metab Clin N Am. 2019;48:23–35. https://doi.org/10.1016/j.ecl.2018.10.002.
3. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017;390:1550–62. https://doi.org/10.1016/S0140-6736(17)30703-1.
4. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull. 2011;99:39–51. https://doi.org/10.1093/bmb/ldr030.
5. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf). 1991;34:77–83. https://doi.org/10.1111/j.1365-2265.1991.tb01739.x.
6. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. JAMA. 2004;292:2591–9. https://doi.org/10.1001/jama.292.21.2591.
7. Asvold BO, Vatten LJ, Bjoro T. Changes in the prevalence of hypothyroidism: the HUNT study in Norway. Eur J Endocrinol. 2013;169:613–20. https://doi.org/10.1530/EJE-13-0459.
8. McGrogan A, Seaman HE, Wright JW, de Vries CS. The incidence of autoimmune thyroid disease: a systematic review of the literature. Clin Endocrinol. 2008;69:687–96. https://doi.org/10.1111/j.1365-2265.2008.03338.x.
9. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526–34. https://doi.org/10.1001/archinte.160.4.526.
10. Ragusa F, Fallahi P, Elia G, Gonnella D, Paparo SR, Giusti C, et al. Hashimotos' thyroiditis: epidemiology, pathogenesis, clinic and therapy. Best Pract Res Clin Endocrinol Metab. 2019;33:101367. https://doi.org/10.1016/j.beem.2019.101367.
11. Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. J Clin Endocrinol Metab. 2003;88:2983–92. https://doi.org/10.1210/jc.2002-021845.
12. Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. Autoimmun Rev. 2015;14:174–80. https://doi.org/10.1016/j.autrev.2014.10.016.
13. Moon S, Chung HS, Yu JM, Yoo HJ, Park JH, Kim DS, Park YJ. Associations between Hashimoto thyroiditis and clinical outcomes of papillary thyroid cancer: a meta-analysis of observational studies. Endocrinol Metab (Seoul). 2018;33:473–84. https://doi.org/10.3803/EnM.2018.33.4.473.
14. Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: a review. JAMA. 2019;322:153–60. https://doi.org/10.1001/jama.2019.9052.
15. Meyerovitch J, Rotman-Pikielny P, Sherf M, Battat E, Levy Y, Surks MI. Serum thyrotropin measurements in the community. Arch Intern Med. 2007;167:1533–8. https://doi.org/10.1001/archinte.167.14.1533.
16. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008;29:76–131. https://doi.org/10.1210/er.2006-0043.
17. Díez JJ, Iglesias P. Spontaneous subclinical hypothyroidism in patients older than 55 years. J Clin Endocrinol Metab. 2004;89:4890–7. https://doi.org/10.1210/jc.2003-032061.

18. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community. Clin Endocrinol. 1995;43:55–68. https://doi.org/10.1111/j.1365-2265.1995.tb01894.x.
19. Díez JJ, Iglesias P, Burman KD. Spontaneous normalization of thyrotropin concentrations in patients with subclinical hypothyroidism. J Clin Endocrinol Metab. 2005;90:4124–7. https://doi.org/10.1210/jc.2005-0375.
20. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al., Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA. 2010;304:1365–74. https://doi.org/10.1001/jama.2010.1361.
21. Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, et al. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab. 2014;99:363–84. https://doi.org/10.1210/jc.2013-1891.
22. Corbetta C, Weber G, Cortinovis F, Calebiro D, Passoni A, Vigone MC, et al. A 7-year experience with low blood TSH cutoff levels for neonatal screening reveals an unsuspected frequency of congenital hypothyroidism (CH). Clin Endocrinol. 2009;71:739–45. https://doi.org/10.1111/j.1365-2265.2009.03568.x.
23. Olivieri A, Corbetta C, Weber G, Vigone MC, Fazzini C, Medda E, Italian Study Group for Congenital Hypothyroidism. Congenital hypothyroidism due to defects of thyroid development and mild increase of TSH at screening: data from the Italian National Registry of infants with congenital hypothyroidism. J Clin Endocrinol Metab. 2013;98:1403–8. https://doi.org/10.1210/jc.2012-3273.
24. Rapaport R. Congenital hypothyroidism: an evolving common clinical conundrum. J Clin Endocrinol Metab. 2010;95:4223–5. https://doi.org/10.1210/jc.2010-1711.
25. Persani L, Rurale G, de Filippis T, Galazzi E, Muzza M, Fugazzola L. Genetics and management of congenital hypothyroidism. Best Pract Res Clin Endocrinol Metab. 2018;32:387–96. https://doi.org/10.1016/j.beem.2018.05.002.
26. Peters C, van Trotsenburg ASP, Schoenmakers N. Diagnosis of endocrine disease: congenital hypothyroidism: update and perspectives. Eur J Endocrinol. 2018;179:R297–317. https://doi.org/10.1530/EJE-18-0383.
27. Beck-Peccoz P, Rodari G, Giavoli C, Lania A. Central hypothyroidism - a neglected thyroid disorder. Nat Rev Endocrinol. 2017;13:588–98. https://doi.org/10.1038/nrendo.2017.47.
28. Bobanga ID, McHenry CR. Treatment of patients with Graves' disease and the appropriate extent of thyroidectomy. Best Pract Res Clin Endocrinol Metab. 2019;33:101319. https://doi.org/10.1016/j.beem.2019.101319.
29. Brent GA. Clinical practice. Graves' disease. N Engl J Med. 2008;358:2594–605. https://doi.org/10.1056/NEJMcp0801880.
30. Tellez M, Cooper J, Edmonds C. Graves' ophthalmopathy in relation to cigarette smoking and ethnic origin. Clin Endocrinol. 1992;36:291–4. https://doi.org/10.1111/j.1365-2265.1992.tb01445.x.
31. Vitti P, Rago T, Tonacchera M, Pinchera A. Toxic multinodular goiter in the elderly. J Endocrinol Investig. 2002;25:16–8.
32. Laurberg P, Pedersen KM, Vestergaard H, Sigurdsson G. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area versus high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. J Intern Med. 1991;229:415–20. https://doi.org/10.1111/j.1365-2796.1991.tb00368.x.
33. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27:315–89. https://doi.org/10.1089/thy.2016.0457.
34. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a

systematic review and meta-analysis. JAMA Oncol. 2018;4:173–82. https://doi.org/10.1001/jamaoncol.2017.3064.
35. Stanbury JB, Ermans AE, Bourdoux P, Todd C, Oken E, Tonglet R, et al. Iodine-induced hyperthyroidism: occurrence and epidemiology. Thyroid. 1998;8:83–100. https://doi.org/10.1089/thy.1998.8.83.
36. Roti E, Uberti ED. Iodine excess and hyperthyroidism. Thyroid. 2001;11:493–500. https://doi.org/10.1089/105072501300176453.
37. Carle A, Andersen SL, Boelaert K, Laurberg P. Management of endocrine disease: subclinical thyrotoxicosis: prevalence, causes and choice of therapy. Eur J Endocrinol. 2017;176:R325–37. https://doi.org/10.1530/EJE-16-0276.
38. Hollowell JG, Staehiling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87:489–99. https://doi.org/10.1210/jcem.87.2.8182.
39. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The Thyroid Epidemiology, Audit, and Research Study (TEARS): the natural history of endogenous subclinical hyperthyroidism. J Clin Endocrinol Metab. 2011;96:E1–8. https://doi.org/10.1210/jc.2010-0854.
40. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26:1–133.
41. Durante C, Grani G, Lamartina L, Filetti S, Mandel SJ, Cooper DS. The diagnosis and management of thyroid nodules: a review. JAMA. 2018;319:914–24. https://doi.org/10.1001/jama.2018.0898.
42. Studer H, Peter HJ, Gerber H. Natural heterogeneity of thyroid cells: the basis for under standing thyroid function and nodular goiter growth. Endocr Rev. 1989;10:125–35. https://doi.org/10.1210/edrv-10-2-125.
43. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol. 2013;2013:965212. https://doi.org/10.1155/2013/965212.
44. Yildirim Simsir I, Cetinkalp S, Kabalak T. Review of factors contributing to nodular goitre and thyroid carcinoma. Med Princ Pract. 2020;29:1–5. https://doi.org/10.1159/000503575.
45. Kust D, Staničić J, Mateša N. Bethesda thyroid categories and family history of thyroid disease. Clin Endocrinol. 2018;88:468–72. https://doi.org/10.1111/cen.13538.
46. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet. 2016;388:2783–95. https://doi.org/10.1016/S0140-6736(16)30172-6.
47. La Vecchia C, Negri E. Thyroid cancer: the thyroid cancer epidemic - overdiagnosis or a real increase? Nat Rev Endocrinol. 2017;13:318–9. https://doi.org/10.1038/nrendo.2017.53.
48. Howlader N, Noone AM, Krapcho M. SEER cancer statistics review, 1975–2013. Bethesda: National Cancer Institute; 2016. http://seer.cancer.gov/csr/1975_2013. Accessed 12 May 2016.