

THYROID DISORDERS IN THE TROPICS

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ABSTRACT

Thyroid disorders are a major cause of noncommunicable diseases in developing nations, with the tropical regions presenting unique challenges due to diverse environmental, socio-economic, and cultural factors. lodine deficiency remains a significant public health concern, leading to conditions such as endemic goiter and cretinism. The prevalence of iodine deficiency disorders has declined due to salt iodization programs, but inconsistent implementation continues to affect many tropical areas. Autoimmune thyroid diseases, including Hashimoto's thyroiditis and Graves' disease are influenced by genetic and environmental factors in the tropics with a minor increase in prevalence following iodization. Thyroiditis, often associated with infections and inflammatory conditions prevalent in tropical regions, add to the complexity. Congenital hypothyroidism, the leading cause of preventable intellectual disability, is challenging to address due to limited newborn screening programs. A multifaceted approach is needed to address these concerns, including improving healthcare infrastructure, increasing public awareness, consistent iodine ensuring supplementation, and enhancing training for

healthcare providers. These measures can significantly improve thyroid disorder-related outcomes in tropical nations.

INTRODUCTION

Thyroid disorders are one of the leading cause of noncommunicable ailments in the developing nations (1). However, the manifestation and management of thyroid disorders is not uniform across geographic regions. Tropical climate presents a distinct milieu characterized by diverse environmental, socioeconomic, and cultural factors that alter the spectrum of thyroid diseases. A confluence of factors ranging from dietary practices to endemic diseases, imparts unique characteristics to the epidemiology, clinical presentation, and management of thyroid disorders. Iodine deficiency disorders (IDDs) remain a significant public health concern in many tropical countries, where suboptimal iodine intake precipitates a spectrum of thyroid abnormalities, including endemic goiter, hypothyroidism, and cretinism. Additionally, the occurrence of autoimmune thyroid diseases (AITDs), such as Hashimoto's thyroiditis and Graves' disease, underscores the interplay between genetic

susceptibility, environmental triggers, and immune dysregulation. This chapter highlights the altered presentation of thyroid disorders and concerns specific to the tropics.

ETIOPATHOGENESIS IN TROPICS

Thyroid disorders can be influenced by a variety of environmental factors in tropical countries. These aspects can interact with genetic predisposition and individual health behaviors to impact the functioning of the thyroid gland.

Iodine Deficiency Disorders

lodine deficiency significantly contributes to the global thyroid disease burden and leads to various metabolic and growth-related diseases (2). Though the prevalence of IDDs has decreased with iodization of salt, the condition still poses a significant health challenge in many tropical nations. In 2018 and 2019, the global age-standardized prevalence rate of iodine deficiency remained relatively stable at around 2218 and 2216 per 100,000 population, respectively. Over the period from 1990 to 2019, there was a notable decrease in this prevalence rate, with an estimated average annual percent change (EAPC) of -0.690. When examining specific countries, Somalia had the highest age-standardized prevalence rate in 2019, followed by the Democratic Republic of the Congo, Djibouti, and the Republic of the Congo. Interestingly, several countries, including the Philippines, Pakistan, and South Sudan, exhibited an increasing trend in iodine deficiency prevalence. In 2019, Central sub-Saharan Africa and South Asia reported the highest prevalence rates.(3).

Despite the environmental abundance of iodine, its low bioavailability in tropics remains a primary factor influencing the prevalence of IDD. The heavy rainfall characteristic of tropical climate accelerates rock weathering, clay formation, and soil leaching. Clayey materials and humic substances, which bind iodine strongly, act as geochemical goitrogens and significantly affect iodine bioavailability (4).

Endocrine Disrupting Chemicals

Tropical countries encounter challenges due to exposure to endocrine disrupting chemicals (EDCs), which can adversely affect thyroid function (5–7). These chemicals, found in pesticides, plastics, and industrial pollutants, stimulate or interfere with hormone signaling pathways, potentially leading to thyroid dysfunction (8). Agricultural practices, industrialization, and inadequate environmental regulations can contribute to higher EDC exposure in tropics, aggravating thyroid disorders (9).

Environmental Pollution

Household cooking with solid fuels significantly contributes to air pollution in Asian countries (10,11). Air pollution from both household and industrial sources is a major concern in the tropics (12,13). A recent study found a positive correlation between thyroid cancer incidence and air pollution, including particulate matter (r=0.23, P < 0.001) and household air pollution (r=0.52, P ≤ 0.001) (14). This suggests that air pollution may play a role in the development of thyroid cancer and calls for more research to understand the connection.

Infections

Tropical countries often face a higher burden of infectious diseases that can affect thyroid function (15). Primary infection of the thyroid is extremely uncommon. Bacteria are the typical causative organisms but fungal, parasitic, and viral infections have also been described (16). Furthermore, rare cases of mycobacterial cold abscesses have been reported, highlighting the diverse range of microorganisms that can affect the thyroid gland (17).

Nutritional Factors

The unique dietary patterns and environmental conditions in the tropics significantly influence thyroid disorders. lodine deficiency as already discussed is a prevalent problem. Additionally, diets high in goitrogens, such as cassava, millet, and certain cruciferous vegetables, can exacerbate thyroid dysfunction by interfering with iodine uptake (18). Selenium deficiency, another concern in tropical regions. further complicates thyroid hormone production (19,20). Thiocyanate overload has been documented as a goitrogen in Central Africa. When coupled with selenium deficiency, it is a risk factor for endemic myxedematous cretinism (21). Addressing these nutritional deficiencies through diet diversification and supplementation is crucial for mitigating thyroid disorders.

IODINE DEFICIENCY DISORDERS

Goiter and cretinism are two health conditions prevalent in tropical countries resulting from iodine deficiency.

Endemic Goiter

ETIOLOGY

Endemic goiter refers to a visible enlargement of the thyroid gland in regions of environmental iodine deficiency. The condition is defined by the presence of goiter in more than 5% of children aged 6–12 years. It occurs as a maladaptive response to iodine deficiency (22). The role of iodine deficiency in causation is evidenced by its correlation with low iodine levels in food and water in affected regions, reduction in goiter incidence with iodine supplementation, and expected metabolic pattern in individuals that results from iodine deficiency. Other factors such as excess thiocyanates and selenium deficiency may also play a role (2).

PATHOPHYSIOLOGY

If iodine intake is low, the thyroid undergoes significant adaptive changes to maintain adequate hormone production. These adjustments include increased iodide trapping and enhanced intrathyroidal iodine metabolism, primarily driven by elevated levels of TSH. The initial functional response to iodine deficiency involves heightened iodide uptake by the thyroid, mediated by the sodium iodide symporter (NIS), often accompanied by increased TSH levels. Usually, severe iodine deficiency is required to consistently elevate TSH levels. The thyroid's sensitivity to TSH appears to vary with iodine availability, influencing thyroglobulin secretion and iodine clearance rates. Effective adjustment to iodine deficiency can occur without goiter in certain populations, indicating varying degrees of iodine entrapment and hormone synthesis capacity (23).

THYROID HORMONE PROFILE

lodine deficiency causes thyroid gland enlargement and alters hormone production. The abnormal thyroglobulin in the thyroid releases poorly iodinated compounds such as monoiodotyrosine (MIT) and triiodothyronine (T3), and decreased levels of diiodotyrosine (DIT) and thyroxine (T4). This shift increases the MIT/DIT and T3/T4 ratios, reflecting the severity of iodine depletion. In response to iodine deficiency, the thyroid may secrete T3 and T4 in proportions found within the gland, and preferentially produce T3 or convert more T4 to T3 peripherally. The adaptation is critical as T3 is metabolically more potent and requires less iodine for synthesis, aiding in mitigating iodine deficiency effects (23).

DIAGNOSIS

In childhood, thyroid glands are often diffusely enlarged, while in adults, they tend to be nodular. Common laboratory findings include increased radioiodine uptake (RAIU) by the thyroid, normal or low T4 and free T4 (FT4), normal or elevated T3 and TSH, and reduced urinary iodine excretion. RAIU can usually be suppressed with thyroid hormone treatment. Scans with radioiodine or technetium show a mottled isotope distribution.

PREVENTION AND TREATMENT

The recommended dietary allowance (RDA) for iodine is 150 μ g per day for adults and 250 μ g per day during pregnancy. Currently, 20-40 mg of iodine per kg salt can provide the RDA.

Goiters regress in most cases when treated with iodine (24). Generally, treatment with iodine is sufficient and surgery can be avoided. However, individuals with goiters that do not regress, exhibit rebound growth after three months, or present with pressure symptoms may require surgical intervention (25).

There is a small but consistent risk of iodine supplementation causing hyperthyroidism, known as Jod-Basedow disease. Despite the risk, the benefits of iodine treatment outweigh the potential drawbacks. Individuals over the age of 50 years with latent thyroid disease, particularly those with multinodular goiters, are more likely to develop this form of thyrotoxicosis. Typically, iodine-induced thyrotoxicosis resolves naturally, sometimes within 12 months, but it can take up to 3–4 years (26).

The implementation of iodized salt programs in various countries has led to a significant reduction in the prevalence of goiter. Despite these efforts, many areas remain affected due to inconsistent iodization practices and other socio-economic factors (27–29).

Cretinism

Cretinism, a severe form of IDD, often coexists with endemic goiter in these regions. The condition leads to extreme physical and mental retardation, significantly impacting individuals' quality of life and the overall well-being of communities. Cretinism can be classified into two types: neurological and myxedematous.

NEUROLOGICAL CRETINISM

Neurological cretinism results from severe iodine deficiency during early pregnancy, causing irreversible brain damage in the fetus. Affected individuals display mental retardation, pyramidal signs in a proximal distribution, and extrapyramidal signs, along with a characteristic gait. Other common features included squint, deafness, and primitive reflexes. In iodinedeficient areas, many individuals exhibit intellectual impairments and coordination defects, with a leftward shift in the intelligence curve compared to iodinesufficient areas (23,30).

MYXEDEMATOUS CRETINISM

Myxedematous cretinism is characterized by overt hypothyroidism from early life, but less severe mental retardation than neurological cretinism. Key features include major growth retardation, immature facial features, mandibular atrophy, puffy and thickened skin, sparse hair, delayed sexual maturation, and typically absent goiter due to thyroid atrophy. Causes include thiocyanate overload from cassava consumption, selenium deficiency leading to thyroid cell destruction, and potential immunological factors. The condition was notably prevalent in Zaire and associated with severe, irreversible hypothyroidism and some neurological signs obscured by the hypothyroid state (30).

The reader is referred to the chapter lodine Deficiency Disorders in Endotext.com for a detailed review of cretinism and other IDDs (23).

Prevention and Management of Iodine Deficiency Disorders

Public health interventions to address endemic goiter and cretinism in tropical countries have included widespread salt iodization, iodine supplementation programs, and public awareness campaigns. These efforts aim to ensure consistent iodine intake across populations, particularly targeting vulnerable groups such as pregnant women and children. However, challenges remain in ensuring the reach and efficacy of these programs, especially in remote and underserved areas (31).

lodized salt is the preferred method for iodine fortification due to its widespread use across all socioeconomic groups. It is consumed consistently year-round and produced in large, centralized facilities, allowing for effective and controlled fortification. Potassium iodate, preferred for its stability in humid conditions, and potassium iodide are the two forms used. Direct iodide supplementation, iodized oils, and iodized breads are other means to prevent IDDs (23). Collaborative efforts involving governments, non-governmental organizations, and local communities are crucial for sustaining progress in preventing IDDs.

AUTOIMMUNE THYROID DISORDERS

AITDs arise from an immune system dysregulation, resulting in an immune attack on the thyroid gland. These disorders are T cell-mediated and organspecific. The prevalence of AITD is around 5%, though the occurrence of antithyroid antibodies might be even higher. AITD primarily manifests in two clinical forms: Graves' disease and Hashimoto's thyroiditis, both marked by lymphocytic infiltration of the thyroid tissue. Clinically, Graves' disease is characterized by thyrotoxicosis, while Hashimoto's thyroiditis leads to hypothyroidism. The exact mechanisms initiating the autoimmune response against the thyroid are still not clear. Epidemiological data indicate that an interaction between genetic predisposition and environmental factors is responsible for disrupting immune tolerance and triggering AITD (32). In the tropics, the prevalence, diagnosis, and management of these disorders are influenced by various regional factors.

Hashimoto's Thyroiditis

The classic example of AITD is Hashimoto's thyroiditis, also referred to as chronic lymphocytic thyroiditis. It is associated with chronic inflammation of the thyroid tissue, and causes hypothyroidism in 20-30% of cases (33).

PREVALENCE

In tropical regions, the incidence of Hashimoto's thyroiditis is increasing, which is partially attributed to enhanced iodine intake from iodization programs. While these programs have reduced goiter and cretinism, they have also been linked to an increase in AITD. A study from Sri Lanka found anti-thyroid peroxidase (TPO) antibodies in 10.3%, antithyroglobulin (Tg) antibodies in 6.4%, and subclinical hypothyroidism (SCH) int 3%. Median urinary iodine concentration was 138.5 µg/L, indicating iodine sufficiency from universal salt iodization. Despite a high anti-TPO antibody prevalence, SCH remains low. The findings suggest that early post-iodization anti-Tg antibody surge that had gone past 42%, has now settled. Goiter prevalence was 0.6%-1.93% (34).

IODINE CONSUMPTION AND THYROID AUTOIMMUNITY

Several explanations have been proposed to elucidate the link between excessive iodine consumption and thyroid autoimmunity. One hypothesis suggests that iodine may be directly toxic to thyroid tissue and stimulate immune effector cells. The role of free radical damage to thyroid tissue is widely recognized as a contributing factor in the onset or exacerbation of AITD. Experimental studies in genetically predisposed animals have shown that Tg becomes more immunogenic when exposed to excess iodine, potentially triggering autoimmune responses (35).

Previous iodine levels impact thyroid response to increased iodine intake and may be linked to the development of thyroid autoimmunity. The prevalence of thyroid antibodies, however, doesn't always predict thyroid disease. Autoimmune diseases have generally risen in recent decades, making data interpretation challenging. Long-term studies suggest that excessive iodine from uncontrolled iodine prophylaxis can lead to autoimmune thyroiditis. Careful monitoring of iodine prophylaxis is recommended to prevent both iodine deficiency and excess (36).

DIAGNOSIS AND TREATMENT

Individuals with Hashimoto's thyroiditis often present with a painless goiter, which may occur with or without overt hypothyroidism. For asymptomatic persons, it can be discovered incidentally when a goiter prompts evaluation. Others may experience typical hypothyroidism symptoms, including fatigue, weight gain, cold intolerance, constipation, depression, muscle pain, heavy menstrual bleeding, and dry skin. The diagnosis of Hashimoto's thyroiditis can be confirmed by a combination of clinical features, thyroid function test results indicating SCH or overt hypothyroidism and elevated Tg and TPO antibodies (37). Anti-TPO antibodies are found in 95% of cases with Hashimoto's thyroiditis, while anti-Tg antibodies are elevated in 60% to 80%. Treatment involves administration of levothyroxine to correct hypothyroidism (38). The challenge in many tropical regions is the limited access to these diagnostic tests, which may delay identification and treatment.

Graves' Disease

Graves' disease is the most common cause of hyperthyroidism worldwide and involves the immune system producing antibodies (thyroid-stimulating immunoglobulins) that stimulate the thyroid gland to produce excess thyroid hormones (39).

PREVALENCE

Graves' disease accounts for 70-80% of hyperthyroidism cases in iodine-sufficient regions. In contrast, in areas with iodine deficiency, Graves'

disease represents about half of all hyperthyroidism cases, with the other half occurring due to nodular thyroid disease (40,41). In Johannesburg in 1981, the incidence of Graves' disease was 5.5 per 100,000/year, significantly lower than global rates. However, over a decade, there was a 60% increase in incidence, possibly due to improved dietary iodine intake among urban migrants (42). Hospital-based studies from Ghana reveal that Graves' disease, contrary to earlier reports, now comprises 54% of all thyroid dysfunction cases, although ascertainment bias might exist. Improved iodine nutrition and better diagnosis have led to increased incidences of both Graves' disease and nodular disease post-iodization in Ghana (43). A systematic review reported higher rates in Asians, and lower incidence in African population compared to Caucasians (44).

PATHOGENESIS IN TROPICS

Genetic predisposition contributes to 79% of Graves' disease risk, primarily involving genes related to T-cell function, while environmental factors account for remaining 21%. Significant environmental factors include smoking, iodine excess, selenium and vitamin D deficiencies, and viral infections. All these factors hold relevance in the tropical context. Numerous studies have examined whether infectious agents like foamy virus, parvovirus-B19, Epstein-Barr virus (EBV), and hepatitis C virus (HCV) can trigger Graves' disease, with mixed results. EBV reactivation is linked to Graves' disease recurrence in Japanese patients but not in Caucasians. There is a well-established connection between HCV and thyroid autoimmunity, including hypothyroidism. A link between HCV-related mixed cryoglobulinemia and Graves' disease has also been demonstrated. Additionally, 2.5 to 20% of individuals with chronic HCV treated with interferonalpha develop thyroid disorders, including GD (45).

Animal experiments have studied the connection between hygiene hypothesis and Graves' disease (46). The hygiene hypothesis suggests that a lack of early childhood exposure to infectious agents, symbiotic microorganisms, and parasites can lead to a higher incidence of autoimmune diseases, such as Graves' disease. This hypothesis posits that modern sanitation practices and reduced exposure to microbes may prevent the immune system from developing appropriately, increasing susceptibility to autoimmune conditions. In the context of Graves' disease, the hygiene hypothesis implies that individuals in more sanitized environments might have a higher risk of developing the disease due to an under-stimulated immune system that becomes prone to attacking the body's own thyroid cells. The hygiene hypothesis suggests a potential protective effect on thyroid health in tropical conditions, but clinical evidence is lacking (47).

CLINICAL MANIFESTATIONS

Thyrotoxicosis is the primary presenting feature of Graves' disease, and in this region, it often manifests at a more advanced stage with various complications. Late presentation can be attributed to missed diagnoses and lack of awareness often arising from financial constraints (48). Notably, thyrotoxicosis is a significant cause of cardiac morbidity in tropical countries. In Togo, cardiac complications were reported in 46.6% of patients with thyrotoxicosis (49). Similarly, the heart failure rate was reported to be 42% in Lagos, Nigeria (50).

Ethnicity appears to influence the risk of developing disease complications. For example, Graves' ophthalmopathy is six times more common in Caucasians than in Asians (51). Additionally, the rare but serious complication of hyperthyroidism, thyrotoxic periodic paralysis, is significantly more common in Asian men (52). The genetic basis of this condition has

been extensively researched, revealing variations in certain human leukocyte antigen (HLA) haplotypes such as DRw8, A2, Bw22, Aw19, and B17 in affected Asian patients (53).

TREATMENT

Treatment options for graves' disease include antithyroid medications (e.g., methimazole or propylthiouracil), radioactive iodine therapy (RAI), and surgery. The choice of treatment depends on the severity of the disease, patient preference, and availability of medical resources. In many tropical regions, the lack of access to RAI and surgical facilities limits treatment options, making long-term medication the most feasible approach. In an online global survey conducted in 2023, RAI as the primary treatment for Graves' disease was offered by 13.1% of respondents from Africa and the Middle East and 7.5% of respondents from Latin America, but only in 5% from Asia (54). Rare cases of resistance to anti-thyroid drugs have also been described in tropical regions (55,56). A possible impairment in intrathyroidal drug accumulation could be responsible (57). Interestingly, Asians are more predisposed to insulin autoimmune syndrome after exposure to methimazole because of higher prevalence of HLA allele DRB1*04:06 (58).

SUBACUTE THYROIDITIS

The term "thyroiditis" refers to a group of inflammatory conditions affecting the thyroid gland. The causes can be diverse including autoimmunity, viral, bacterial and fungal infections, iatrogenic, trauma, radiation and idiopathic chronic sclerosing forms such as Riedel thyroiditis (Table 1) (58,59).

Table 1. Tropical Infections of the Thyroid Gland				
Type of	Etiological organism	Investigations		
presentation				
Acute	Bacterial: Streptococcus,	TFT: Normal / mild thyrotoxicosis		
pyogenic /	Staphylococcus,	USG thyroid: Hypoechoic area, abscess		
suppurative	Enterobacter	FNA followed by staining/culture can identify the		
thyroiditis	Fungal: Aspergillus,	causative organism		
	candida, histoplasma,	Thyroid scintigraphy: normal function of the		
	coccidiodes	unaffected lobe		
		HIV-AIDS to be ruled out in fungal thyroiditis		
SAT	Viral: Adenovirus,	Thyroid scintigraphy: Poor, patchy uptake. [#]		
	echovirus, Epstein Barr	TSH-receptor antibody positivity favors Graves'		
	virus, coxsackie virus,	disease (may be transiently positive in SAT)		
	H1N1 influenza,	High ESR		
	cytomegalovirus, SARS-	T3 (ng/ml): T4 (mcg/dl) ratio < 20 favors SAT		
	CoV-2, dengue.	Color Doppler shows decreased vascularity		
	Mycobacterial thyroiditis			
Thyroid nodule	Parasites:	USG for localization of lesion		
or goiter	Strongyloidiasis, Giardia,	FNA to detect causative organism		
	Entamoeba,	Eosinophilia		
	Cryptosporidium,	HIV-AIDS to be ruled out in disseminated		
	Echinococcus,	parasitic infection		
	Trypanosomes			

cut-off value for (99m)Tc-pertechnetate uptake of 1.0% - 1.55% have been proposed to differentiate SAT from Graves' disease.

TFT- thyroid function test, USG – ultrasonography, FNA – fine needle aspiration, HIV-AIDS – human immunodeficiency virus-acquired immunodeficiency syndrome, SAT – subacute thyroiditis, SARS-CoV-2 -Severe acute respiratory syndrome coronavirus 2, ESR – erythrocyte sedimentation rate.

Etiology and Pathogenesis

Subacute thyroiditis (SAT), also known as de Quervain's thyroiditis or granulomatous thyroiditis, is an inflammatory condition that often follows a viral infection (59). While the clinical presentation and course are generally consistent worldwide, there may be some differences in the pathogenesis and management in tropical countries. SAT has been linked to prior infection with adenovirus, EBV, coxsackie, mumps, measles, H1N1 influenza, dengue, St. Louis encephalitis, hepatitis A, parvovirus B19, cytomegalovirus and severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) (60–64). Cases have been reported after influenza vaccination and following interferon treatment for HCV (65,66). Non-viral infections like malaria, Q fever, and scrub typhus have also been implicated (60,67).

While some of these infections may be more prevalent in tropical regions, there is insufficient evidence to suggest a specific cause that alters the epidemiology.

Infections can induce thyroid autoimmunity by diverse mechanisms like self-antigen modification, mimicry of self-molecules, superantigen mediated polyclonal Tcell activation, immune complex formation, and induction of expression of MHC molecules on thyroid epithelium.

Certain haplotypes like HLA-B*35, HLA-B*18:01 and DRB1* confer susceptibility to SAT in different ethnicities across the world. HLA-B*35 allele has been identified in up to 70% of the cases (68,69), the alleles HLA-B*18:01 and DRB1*01 have while been identified in the remaining cases (70). In an Indian study, HLA-B*35 was reported positive in 55.56% of cases of SAT (71). Further research is needed to understand the variations in HLA haplotypes among different ethnic groups and their relationship with SAT.

Clinical Spectrum

The most common presentation of SAT is temporary thyrotoxicosis followed by transient hypothyroidism and eventual recovery. Permanent hypothyroidism can develop in a minority (72). The inflammatory process disrupts the thyroid follicles causing an enhanced release of the stored T4 and T3 leading to thyrotoxicosis. Continued damage to the follicles may lead to transient or permanent hypothyroidism. In some cases, the disease can recur (73). In a prospective study from India, the prevalence of hypothyroidism after 1 year of SAT was 19.86% (74), while a study from Saudia Arabia reported permanent hypothyroidism in 14.3% (75).

Thyrotoxic features like palpitations, tremulousness, weight loss, heat intolerance and anxiety are present but usually milder in comparison to Graves' disease (76). Inflammatory features such as neck pain, fever, malaise, fatigue, myalgia and arthralgia often dominate the clinical presentation.

Diagnosis

An upper respiratory tract infection is the usual differential diagnosis. Peripheral levels of thyroid hormones, T4 and T3, are elevated with a ratio of T4

(mcg/dl): T3 (ng/ml) > 20. This is reflective of the proportion of stored thyroid hormones within the gland, though the results may vary with the phase of the disease. Erythrocyte sedimentation rate (ESR) is almost invariably elevated, often to values above 100 mm/hr. Diagnosis is confirmed by a suppressed uptake on a 99m-technectium scintigraphy or radioiodine scan. In many tropical countries, nuclear medicine facilities are not widely available. As a result, diagnosis often relies on clinical and biochemical findings along with a non-elevated TSH-receptor antibody (TRAb). Color flow Doppler ultrasonography shows a hypoechogenic, heterogenous gland with low to normal vascularity (77).

Treatment and Prognosis

The condition is self-limiting and milder cases often require no treatment or nonsteroidal anti-inflammatory agents (NSAIDs) (76). For more severe symptoms, a course of oral prednisolone is recommended at a starting dose of 20-40 mg per day, and tapered over 4-6 weeks (78). Thyrotoxic symptoms respond to β - blockers like propranolol. The reader can refer to the chapter on subacute thyroiditis in endotext.com for a detailed review (59).

SILENT AND POSTPARTUM THYROIDITIS

Silent thyroiditis, similar to SAT, follows a typical triphasic course: initial thyrotoxicosis, followed by hypothyroidism, and finally, a return to normal thyroid function. The condition is presumed to be autoimmune in nature, as levels of anti-TPO and anti-TG antibodies are usually elevated. Histologically, it is characterized by extensive lymphocytic infiltration, sometimes with the formation of lymphoid follicles. Unlike SAT, silent thyroiditis does not present with symptoms of thyroid inflammation such as neck pain or fever. It is more prevalent in iodine-sufficient areas (79).

Postpartum thyroiditis typically occurs within six months of delivery but can rarely present up to 12 months postpartum. It shares many similarities with silent thyroiditis, including an autoimmune etiology (80). Neither silent thyroiditis nor postpartum thyroiditis exhibit any unique characteristics specific to tropical regions.

VIRAL CAUSES OF THYROIDITIS IN TROPICS

Dengue Thyroiditis

SAT can rarely develop as a manifestation of expanded dengue syndrome. This condition should be suspected in patients with dengue fever who develop painful thyroid swelling and thyrotoxic features (61,81). SAT following dengue infection is typically self-limited. In symptomatic cases, an important concern is the high risk of bleeding with the use of aspirin because of the associated thrombocytopenia. Additionally, administration of non-steroidal antiinflammatory drugs in presence of hypovolemic shock can lead to acute kidney injury. Therefore, oral prednisolone may be preferred for treatment of dengue-associated SAT.

BACTERIAL CAUSES OF THYROIDITIS

Acute Suppurative Thyroiditis

Acute suppurative thyroiditis (AST) or acute pyogenic thyroiditis is a rare but potentially life-threatening form of thyroiditis seen more commonly in tropical countries. They are mostly bacterial in origin, though rarely, fungal and parasitic infestations have also been described (82).

ETIOLOGY

The thyroid gland is generally resistant to infection due to its rich blood supply, thick fibrous capsule, and high levels of iodine and hydrogen peroxide. However, AST can occur in individuals with pre-existing thyroid disorders or in an immunocompromised state. The route of spread is typically hematogenous or lymphatic, but direct spread from the deep fascial spaces of the neck, anterior perforation of the esophagus, or infected thyroglossal cyst can rarely occur (83).

A systematic review of 200 cases of acute suppurative thyroiditis found that 94 cases were from Asia, 24 from Africa, and five from Latin America, suggesting a higher prevalence in tropical regions. Immunocompromised state and pyriform sinus fistulas were the two most common contributing factors. Other causes included disseminated infections and trauma. In 28% of cases, no apparent etiology was identified, although an undiagnosed pyriform sinus fistula remained a possibility (84). It is unclear whether poor hygiene conditions and lack of universal medical facilities in tropical regions contribute to the higher incidence of AST. Rare cases of acute emphysematous thyroiditis in immunocompromised individuals due to infection from Clostridia and Escherichia coli have been reported from tropical countries (85,86).

DIAGNOSIS AND MANAGEMENT

Individuals with AST present with high grade fever and constitutional symptoms along with severe pain and tenderness over the thyroid gland. However, thyroid function is usually normal and only a subset have thyrotoxicosis. laboratory evidence of Ultrasonography of thyroid reveals an abscess in the gland and needle aspiration may confirm the diagnosis along with identification of responsible organism. 99mtechnetium-pertechnetate scan or radioiodine uptake studies show normal function of the unaffected lobe of the thyroid gland, unlike in SAT, where thyroid activity is diffusely suppressed. In children with AST of the left lobe, a barium swallow should be ordered to rule out pyriform sinus fistula connecting the left lobe of thyroid. The left-sided predominance of pyriform sinus fistulas is thought to be due to asymmetrical development during embryogenesis (83).

Antibiotics guided by the culture and sensitivity of the offending organism should be commenced as soon as possible. Needle aspiration to drain the pus from affected lobe may be necessary. Surgical drainage may be required in lesions not responding to antibiotics. Pyriform sinus fistula is treated by endoscopic cauterization or surgical excision to prevent recurrence (87). Prognosis is favorable if managed appropriately without loss of thyroid function. For further reading please refer to the relevant chapter on endotext.com (88).

Tuberculosis

EPIDEMIOLOGY

Tuberculosis of the thyroid is an extremely rare condition, representing less than 1% of all cases of extrapulmonary tuberculosis (89). The mean age of onset is around third to fourth decade. Its incidence is higher in tropical regions where tuberculosis is endemic. Immunocompromised individuals, such as those with HIV/AIDS, are at greater risk. Thyroid tuberculosis can be secondary to miliary spread as part of disseminated tuberculosis, or can manifest as isolated lesion in the gland (90).

CLINICAL FEATURES

Thyroid tuberculosis often presents as a solitary thyroid nodule, with or without a cystic component. It may also present as a thyroid abscess with pain, fever, and other systemic features. The diagnosis can be mistaken as SAT (91). Pyrexia of unknown origin may occasionally lead to a diagnosis of thyroid tuberculosis. In rare cases, the lesion mimics thyroid malignancy, presenting with dysphagia, dysphonia, and recurrent laryngeal nerve palsy (89). A discharging sinus after thyroid surgery has been reported (92). While thyroid function is typically not impaired, extensive involvement can lead to thyrotoxicosis from follicular destruction, potentially progressing to hypothyroidism. Associated cervical lymphadenopathy and rare cases of mediastinal lymph node enlargement have also been described ((93). The pathological varieties include multiple lesions in miliary tuberculosis, goiter with areas of caseation, chronic fibrosing forms, and acute pyogenic or cold abscess (90).

DIAGNOSIS AND MANAGEMENT

Though ultrasonography and computed tomography (CT) scan might aid in localizing the lesion in the gland, the findings are nonspecific and do not help to establish the diagnosis of tuberculosis. Caseous necrosis in fine needle aspiration (FNA) cytology or biopsy implies tuberculosis. In many cases, diagnosis is only evident after surgery when the biopsy specimen reveals epithelioid granulomas and caseous necrosis (89,94). While acid-fast bacilli are diagnostic, they are not typically observed in thyroid specimens. Reverse transcription polymerase chain reaction (RT-PCR), and less commonly culture, can provide microbiologic etiology (91). An X-ray of the chest should be obtained to rule out pulmonary tuberculosis.

Therapy with anti-tuberculous drugs often lead to complete resolution of the infection. The choice of antitubercular medications and regimen differs in countries and should be guided by national guidelines. In case of a large abscess, especially with compressive features, surgical intervention may be necessary (89).

FUNGAL CAUSES OF THYROIDITIS

Fungal infections account for 15% of AST cases, with aspergillus being the most common, followed by candida. Other fungal causes include *Cryptococcus neoformans, Pseudoallescheria boydii*, and *Pneumocystis jiroveci*. Suppurative thyroiditis due to opportunistic mycoses predominantly occurs in immunocompromised individuals. Endemic mycoses like coccidioidomycosis, paracoccidioidomycosis, and histoplasmosis are usually restricted to certain geographic regions of the tropics.

Thyroid involvement is usually insidious and often accompanies a broader disseminated disease. Symptoms include pain, thyroid swelling, and fever, resembling SAT. Severe involvement can lead to dysphagia and respiratory distress due to esophageal and tracheal obstruction. The condition often starts with thyrotoxicosis and progresses to hypothyroidism, with recovery typically taking weeks to months.

The diagnosis is established by demonstration of fungi on FNA. In many cases the etiology becomes apparent on histopathological examination of a surgically removed specimen. Treatment involves antifungal medications, with or without surgery. The mortality rate for disseminated opportunistic fungal infections is high. For more detailed information, refer to the chapter on "Fungi and Endocrine Dysfunction" in endotext.com (95).

Aspergillus

Thyroid gland is involved in 7-26% of cases disseminated aspergillosis (96). In the past, this condition was typically identified postmortem in immunocompromised individuals. However. advancements in treatment for underlying conditions and improved antifungal therapies have shifted diagnoses to occur more frequently to antemortem stage (97). Thyroid involvement may be silent or can mimic subacute thyroiditis. А characteristic manifestation of aspergillosis is vascular invasion with thrombosis and infarction (98).

The presence of aspergillus hyphae in a thyroid specimen, along with areas of pus, necrotic debris, and hemorrhage, confirms the etiology. Fungal culture of the aspirate might be helpful in equivocal cases. Treatment involves antifungal therapy, sometimes combined with surgical intervention. Voriconazole is recommended as the first-line treatment for invasive aspergillosis, while liposomal amphotericin B and isavuconazole are alternative options (99). The mortality rate remains high, particularly in cases of disseminated infection.

Candida

Candida thyroiditis, is rare and typically results from secondary dissemination in immunocompromised states. Due to coexisting immunosuppression, signs of thyroid inflammation may be minimal. Unlike other fungal thyroiditis, candida infection can be associated with thyroid function abnormalities such as transient thyrotoxicosis followed by hypothyroidism (100,101). Rare cases of thyroid storm leading to heart failure necessitating treatment with plasmapheresis during the thyrotoxic phase has been reported (102).Treatment comprises systemic antifungal therapy, management of thyroid dysfunction, and potentially surgical intervention. The antifungal options include echinocandins, liposomal amphotericin B, fluconazole, and voriconazole. Resistance to azoles in Candida albicans and Candida tropicalis is an emerging threat in Asia and Latin America (103).

Histoplasma

Histoplasmosis is a fungal infection endemic in certain areas of tropics including Central and South America, Africa, and several countries of South East Asia including Malaysia, Indonesia. Thailand. Singapore, and (104). infection is India The associated with exposure to birds or poultry. The condition often presents as SAT, diffuse goiter, or a nodule accompanied by constitutional features like fatigue and weight loss. Diagnosis involves FNA cytology or biopsy to confirm the presence of Histoplasma capsulatum. In biopsy, granulomas may be seen and the fungus appears as oval 2 to 4 micrometers narrow-based budding yeast cells with Gomori methenamine silver or periodic acid. Serology, antigen testing, and molecular techniques like PCR may provide additional information (105). Treatment ranges from oral itraconazole for non-severe cases to

liposomal amphotericin B for severe cases. Posaconazole is another therapeutic option (106).

Coccidioides

Coccidioidomycosis, caused by inhaling coccidioides arthroconidia, often presents with flu-like symptoms or pneumonia, with 1-5% of cases disseminating to various organs. Risk factors for extrapulmonary disease include age, African or Filipino ancestry, pregnancy, and immunosuppression (107). The presentation of thyroid involvement can range from asymptomatic to thyroid nodules, or even features of subacute thyroiditis. Imaging studies, FNA, and serologic testing help to ascertain the diagnosis. Treatment typically includes antifungal medication, and in some cases, surgical removal of the affected thyroid tissue. Choice and duration of therapy is not well-defined but generally involves high-dose fluconazole, with itraconazole or posaconazole as alternative options (108).

PARASITIC THYROIDITIS

Parasitic infections of the thyroid gland is extremely rare and characteristically occurs in the setting of disseminated disease in an immunocompromised host. Protozoal infections are caused by Giardia lamblia, Entamoeba histolytica, and Cryptosporidium parvum, in tropical regions (109). Helminthic infections such as Strongyloides stercoralis may cause cystic lesions and resemble thyroglossal cysts (110). Trypanosoma brucei. which causes African Trypanosomiasis (sleeping sickness), has been linked to elevated TSH and low free T4 levels, mimicking primary hypothyroidism (111). Trypanosomes can be identified as spindle-shaped cells in blood or FNA fluid. Filariasis can also affect the thyroid, with microfilariae visible in FNA samples.

THYROID NEOPLASM

Global Trends

The global rise in thyroid cancer incidence has raised concerns. Analysis of data from the 2019 Global Burden of Disease study and the UN's World Population Prospects 2022, suggests that thyroid cancer incidence increased across all income groups, while mortality modestly decreased except in lowermiddle-income groups. The divergent trends in thyroid cancer incidence and mortality suggest potential overdiagnosis in higher-income countries, while highlighting the need to reduce health inequalities and improve access to diagnostic and therapeutic services in tropical lower-middle income countries (112). A study from Central and South America evaluating data between 1997 and 2008, revealed that the incidence of papillary thyroid cancer increased by 9.1-15.0% annually in females, while mortality remained stable. Trends in thyroid cancer among males during this period were stable (113).

Iodine Supplementation and Thyroid Cancer Risk

lodine supplementation has a complex relationship with thyroid cancer. lodine deficiency decreases the prevalence of follicular thyroid cancer, while populations with adequate iodine intake have higher rates of papillary thyroid cancers (114). It has been hypothesized, that iodine-induced oxidative stress may lead to genetic alterations, resulting in a higher rate of the BRAF V600E mutation over time in areas with excess iodine intake (115,116). Iodine supplementation has been associated with a decreasing trend in undifferentiated or anaplastic thyroid carcinoma (113,117).

Other Factors

Environmental radiation exposure, particularly in iodine-deficient areas, is associated with an increased risk of papillary thyroid cancer. However, specific data analyzing these factors in tropical nations are lacking (118).

Bisphenol A (BPA), a widely used organic compound in manufacturing processes in tropical countries, acts as an endocrine disruptor by binding to thyroid hormone receptors and inhibiting thyroid hormoneregulated gene expression. A study investigating the link between BPA levels, excessive iodine intake, and papillary thyroid cancer found that both urinary iodine concentration and urinary BPA concentration were higher in individuals with papillary thyroid carcinoma compared to controls. BPA and iodine may interact through shared pathways in the development of papillary thyroid carcinoma (119).

Management

Practice patterns for thyroid cancer care differ across countries due to variations in ethnic and racial populations, healthcare systems, economies, and cultures. The expertise and outcomes of thyroid surgery can vary significantly by region. While radioiodine treatment is available in many countries, its accessibility varies. Laboratory services for thyroid function monitoring are generally available, and most countries offer thyroglobulin assays. Recombinant thyrotropin is available in only a few countries, Advanced imaging technologies, such as positron emission tomography (PET), are limited to certain countries (120).

CONGENITAL HYPOTHYROIDISM

Congenital hypothyroidism (CH) is the primary cause of preventable intellectual disability. Since the 1970s, newborn screening for CH has been implemented in many parts of the world. Despite its proven benefits, universal screening for CH is yet to be adopted in many resource-limited tropical countries (121–124). Thyroid dysgenesis is identified as the most common cause of congenital CH in North America and Europe (125). Studies from Asia, however, indicate a higher prevalence of dyshormonogenesis (121,126,127). Cord blood screening with a TSH cut-off of 20 mIU/L has been employed for screening in many tropical nations due to its cost-effectiveness, immediate action, and lower recall rate (121,128). Levothyroxine at a dosage of 10-15 μ g/kg should be started immediately after diagnosis (129).

DRUG-INDUCED THYROID DYSFUNCTION

Iodine Induced Thyroid Dysfunction

A number of medications containing high amounts of iodine are still used in the tropical countries. These include the anti-arrhythmic agent amiodarone (75 mg iodine/tablet), expectorants containing iodinated glycerol (15 mg/tablet), topical antiseptics containing povidone iodine (10 mg/ml), and the anti-amoebic agent iodoquinol (134 mg/tablet). Additionally, traditional and alternative medicines are sometimes rich in iodine. Iodine inhibits T4 and T3 formation and release, predominantly by downregulation of the NIS. A healthy thyroid gland escapes the down-regulation, known as the Wolff Chaikoff effect. However, in the presence of underlying thyroid disorders like Hashimoto's thyroiditis, non-systemic illnesses like chronic kidney disease, thalassemia major, and exposure to drugs like interferons and lithium, this compensatory mechanism fails, leading to persistent Wolff Chaikoff effect and occurrence of hypothyroidism (130). The resultant increase in TSH leads to further increase in iodide entry into the gland triggering a vicious cycle and leading to hypothyroidism and goiter.

Other Agents

Rifampicin, commonly used in tropical countries for tuberculosis, leprosy, and meningococcal prophylaxis, enhances T4 metabolism, and may increase levothyroxine requirement. Hence, close thyroid function monitoring is prudent in such situations. Ethionamide, another anti-tuberculosis drug, inhibits thyroid hormone synthesis and release (131). Prolonged use of minocycline has been reported to cause blackening of the thyroid (132). Biotin, frequently used as a hair fall supplement in many tropical countries, occupy the streptavidin-binding sites in biotin-streptavidin two-site sandwich ELISA assay for TSH, leading to falsely low TSH. On the other hand, T4 is measured by competitive immunoassay and therefore, the falsely low signal due to biotin binding to streptavidin-binding sites, is interpreted as falsely elevated T4. Therefore, it is necessary to withhold biotin-containing supplements with doses of up to 10 mg once daily, for 8-h. If biotin intake is more than 10 mg per day, sampling should be delayed for a more extended period (up to 73 h) (133,134).

CHALLENGES TO MANAGEMENT IN THE TROPICS

Managing thyroid diseases in the tropics presents a unique set of challenges that encompass a range of socio-economic, healthcare infrastructure, and environmental factors. (Table 2).

Delayed Diagnosis

One of the primary challenges is the late presentation of patients, which is often due to limited access to healthcare facilities. In many tropical regions, healthcare services are scarce, particularly in rural areas, leading to delays in diagnosis and treatment. This delay can result in the progression of thyroid diseases to more severe stages, making management more complex.

Non-Availability Of Ethnicity Specific Reference Ranges For Thyroid Hormones

Inter-population differences in thyroid function are significant, as thyroid hormone reference intervals are influenced by both genetic factors, such as TSH polymorphisms, and environmental factors. Most tropical countries lack population-specific ranges and rely on Western standards. A study found that a small fraction of South Asians could have a functionally normal TSH variant due to a novel TSH β point mutation, to which some monoclonal antibodies fail to bind, resulting in falsely undetectable TSH levels and potential mistreatment as hyperthyroidism (135).

Iodine Deficiency And National Iodization Policies

Several factors, including dietary habits of consuming alternative salts, overheating during cooking, salt packaging, and economic and administrative issues, can hinder the goal of effective iodization. Studies in tropical countries found iodine deficiency in 30 out of 143 countries. Clinical observations in Uganda, Cambodia, Ethiopia, Cameroon, Mali, Burkina Faso, and India still show prevalence of large goiters causing neck compression (136).

Urinary iodine measurement is considered the standard for iodine intake assessment at the population level. The limitations of urinary iodine estimation include specimen integrity issues, sample authenticity concerns, and high pre-analytic variability. To address these limitations, alternative epidemiologic markers of iodine deficiency should be considered, such as percent of newborns with TSH values > 5 mIU/L, serum thyroglobulin measurement, thyroid volume measurement by palpation or ultrasonography. These markers may provide an alternative assessment of iodine status at the population level (137).

Screening Programs For Pregnant Women

Untreated hypothyroidism in pregnancy has short- and long-term consequences. While, universal screening for maternal hypothyroidism during pregnancy isn't generally agreed upon, testing during pregnancy can be beneficial, particularly in tropical regions where thyroid disorders might be underdiagnosed.

Neonatal Screening For Congenital Hypothyroidism

Many tropical countries lack national newborn screening programs for congenital hypothyroidism due to inadequate infrastructure for collecting, transporting, and analyzing dried blood spots, as well as challenges in follow-up care. TSH stability in these samples can be compromised by temperature and humidity, and confirmatory tests require advanced equipment and trained personnel. Increasing the use of point-of-care TSH assays and telecommunication could help overcome these obstacles and improve screening efforts.

Challenges To Diagnosis And Management Of Thyroid Cancer

In the tropics, there is inadequate access to molecular diagnostics and radioactive iodine facilities. Due to unavailability of radioiodine ablative facilities. management of differentiated thyroid cancer relies mostly on surgical management in many places. In cases of indeterminate nodules like BETHESDA 3,4 the use of molecular techniques to detect somatic mutations in 8-gene panel comprising BRAF-V600E, RET/PTC3, RET/PTC1, TERT promoter, HRAS, NRAS, KRAS, and PAX8-PPARG is recommended. However, this is not available in most tropical countries outside research settings, making decisionmaking difficult and leading to unnecessary surgeries. In cases with medullary thyroid cancers, genetic analysis of RET gene is not easily available and thus prophylactic thyroidectomy is often delayed.

Table 2. Challenges and Proposed Solutions to Management of Thyroid Disorders				
in the Tropics				
Challenges	Description	Solutions		
Delayed	Often due to limited healthcare	Improve healthcare infrastructure		
diagnosis	access, leading to advanced	and community outreach to		
	disease stages at diagnosis.	promote earlier diagnosis.		
Non-availability	Lack of local reference ranges	Develop local reference ranges		
of ethnicity-	for thyroid hormones, causing	based on regional population data.		
specific	potential misdiagnosis.			
reference				
ranges				
lodine	Inadequate iodization and	Implement more robust and		
deficiency and	challenges in maintaining iodine	monitored iodization programs to		
national	intake standards.	ensure optimum iodization avoiding		
iodization		both deficiencies and excess		
policies				
Storage and	High temperature and humidity	Levothyroxine tablets should be		
stability of	can affect the potency of thyroid	stored in a cool dry place away		
thyroid	medications, making them less	from light below 25°C. Ensure		
medications	effective	adherence to global standards of		
		packaging in tropical nations		

Infection and	Tropical infections can directly or	Focused research and increased
thyroid	indirectly affect thyroid gland	awareness to understand and
disorders		manage the complex interplay
		between infection and thyroid
		functioning
Drug	Many drugs used for treatment	Closely monitor for potential drug
interactions and	for tuberculosis and other	interactions between thyroid
thyroid	tropical disorders can potentially	medications and treatments for
disorders	affect thyroid functioning and	infectious diseases and other
	laboratory results	conditions prevalent in tropics
Endocrine	Chemicals in pesticides and	Regulatory measures, monitoring
disrupting	herbicides, industrial by-	policies, sustainable practices, and
chemicals	products, and plasticizers can	focused research can help to
	impact thyroid functioning	mitigate the effect on thyroid
		disorders
Screening	Inadequate screening for	Comprehensive screening guided
programs for	maternal hypothyroidism,	by prevalence and individual and
pregnant	impacting maternal and fetal	regional risk factors
women	health	
Neonatal	Lack of newborn screening	Universal screening with
screening for	programs for congenital	methodology guided by local
congenital	hypothyroidism due to	resources and healthcare
hypothyroidism	infrastructural limitations	infrastructure
Challenges to	Limited access to molecular	Increase access to necessary
diagnosis and	diagnostics and radioactive	diagnostic tools and technologies,
management of	iodine facilities	and develop protocols to manage
thyroid cancer		cases with limited resources
Lack of trained	Trained healthcare providers are	Leveraging telemedicine to connect
medical	often not available in remote	patients in remote areas with
professional	areas	endocrinologists and specialists.

CONCLUSION

Thyroid disorders in the tropics present unique challenges due to socio-economic, healthcare infrastructure, and environmental factors. Late diagnosis, financial constraints, and limited healthcare access exacerbate the severity of these conditions. lodine deficiency remains a significant issue, contributing to the prevalence of goiter and cretinism. Autoimmune thyroid diseases are influenced by environmental triggers and genetic susceptibility. Additionally, congenital hypothyroidism remains underdiagnosed due to inadequate newborn screening programs. Addressing these challenges requires improving healthcare infrastructure, ensuring consistent iodine supplementation, and enhancing public and professional awareness to improve the management and outcomes of thyroid disorders in tropical regions.

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