Chapter

Association of Micronutrients and Prevalence of Antibodies in Hyperthyroidism

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Abstract

Thyroid hormones play a pivotal role in the overall physiological and developmental function of the human body. Alterations in thyroid hormones drastically affect regular metabolic processes as well as physical well-being. Thyroid alterations directly influence the functioning of all major body systems including cardiovascular, neurological, gastrointestinal, etc. The thyroid hormonal imbalance is primarily classified into two major conditions: hyperthyroidism and hypothyroidism. The present chapter details the pathology of thyroid imbalance in the context of human reproductive health, autoimmunity, and micronutrient imbalance. Some novel micronutrient associations independent of iodine deficiencies are discussed. Additionally, the early predictive capability of the anti-TPO antibody as well as other autoimmune correlations are discussed. Given its role in reproductive health, the associations of various sex hormones with thyroid function were also explored.

Keywords: hyperthyroidism, micronutrients, graves' disease, iodine, hormones, antibodies

1. Introduction

Thyroid disorders are the most common type of endocrine dysfunction worldwide, with an estimated prevalence of 5–6% in the US population. Thyroid disorders can be highly differentiated from other endocrine diseases in terms of diagnosis, accessibility of treatment methods, etc. [1]. Early diagnosis and treatment of thyroid diseases remain a cornerstone of management. It's well known that thyroid hormones play crucial roles in regulating various metabolic processes. Thyroid hormone synthesis is a sensitive and feedback loop-dependent system controlled by the hypothalamus-pituitary-thyroid (HPT) axis. The regular functioning of the thyroid gland is a delicate balance among the hypothalamus, pituitary gland, and the thyroid gland [2]. The feedback loop slows down the production of thyrotropin-releasing hormone (TRH) in the hypothalamus which in turn slows

down the production of thyroid-stimulating hormone and down-regulates thyroid hormone when excess is synthesized [3], the reverse happens when the thyroid hormones are low. Any biochemical alterations in this feedback loop results in under-function or over-function of the thyroid gland resulting in catastrophic health consequences [4, 5]. Thyroid disease results from a broad spectrum of pathologies including autoimmune disorders, infectious diseases, organ damage, pharmaceutical compounds, nutritional deficiencies, and environmental factors.

Deficiency of nutrients, in particular micronutrients, results in various non-specific physiological effects including metabolic disorders, suppressed immune responses, and altered endocrine functioning—including that of the thyroid gland. Micronutrients play a key role in enzyme synthesis, immune function, and regulating cellular homeostasis [6, 7]. Optimum levels of iodine intake have long been associated with thyroid health, it is, however, important to consider the optimal supply of other micronutrients that aid in thyroid function as well.

Recent studies have demonstrated the early diagnosis of autoimmune thyroid diseases could reduce the severity of the consequent thyroid disease and reduce its effect on the resulting comorbid conditions. Autoimmune thyroid disease is the most common thyroid disorder affecting the reproductive system in both males and females resulting in infertility. The current chapter details the most important causes of thyroid dysfunction and also discusses recent advances in thyroid research covering various aspects. The application of anti-TPO as an early predictor of various thyroid disorders and the effect of thyroid alteration on human reproductive health is also discussed [8, 9].

2. The pathology of hyperthyroidism

Hyperthyroidism is characterized by exceedingly high secretions of free thyroxine (T4), triiodothyronine, or both. The elevated levels of thyroid hormone in tissues result in systemic clinical manifestations such as weight loss, palpitations, and heat intolerance that result in thyrotoxicosis [10]. Graves' disease, toxic multinodular goiters, and toxic adenomas are the most common causes of hyperthyroidism resulting from mutations in genes that regulate the TSH receptor causing familial or non-autoimmune hyperthyroidism (FNAH) [11]. In FNAH the disease-causing mutations are inherited in an autosomal dominant manner and distinguished by a positive history of inherited non-autoimmune hyperthyroidism exhibiting variable onset symptoms. With FNAH, patients are clinically presented with goiter with no signs of autoimmune responses. Iodine-induced hyperthyroidism is one of the major nutritional causes of hyperthyroidism. Others include germ cell tumors, thyroid cancer, trophoblastic, struma ovarii, TSH-producing pituitary tumors, and medications such as lithium or pregnancy. Hyperthyroidism resulting from these reasons is generally self-limited for a period of time and does not require any medications [12, 13].

3. Etiology and epidemiology

Hyperthyroidism is a clinical state resulting from the disproportionate secretion of thyroid hormones. The most common causes include Graves' disease and toxic nodular goiter and other less common causes include factitious thyroiditis, iodine-induced hyperthyroidism, subacute thyroiditis, and postpartum thyroiditis [14]. Graves' disease is the most common cause of hyperthyroidism in the United States

and other western countries. The etiology of Graves' disease remains multifactorial, as it arises by the loss of immunotolerance resulting in the development of autoimmune responses this induces the thyroid follicular cells by binding to TSH receptors, Graves' disease is the most common cause of hyperthyroidism in the young population. Deficiency of vitamin D and selenium, thyroid damage, immunomodulating drugs, beta-blockers, and infections also account for the development of Graves' disease [15]. Toxic multinodular goiter was found to be the most common cause of hyperthyroidism in the older population [16]. The use of excessive pharmaceutical thyroid hormones or inappropriate intake of external hormones results in factitious thyroiditis. Due to a well-received side effect of weight loss, thyroxine has the potential for abuse, and any history of a hyperthyroid patient should include a medication list and an assessment of possible misuse (whether intentional or unintentional). Struma ovarii, metastatic follicular thyroid cancer, and TSH-secreting pituitary adenoma are the other less common causes of hyperthyroidism [16].

The global epidemiology of hyperthyroidism can be defined in correspondence to the population in iodine-deficient regions and iodine-sufficient regions. In Europe, the dietary intake of iodine is the major cause of hyperthyroidism, whereas in a few cases autoimmune disease results in hyperthyroidism. In the US, Grave's disease is the most common factor of hypothyroidism in the younger population, whereas toxic nodular goiter is more common among the older. The overall prevalence of hyperthyroidism is 0.8% and 1.3% in Europe and the USA respectively. The prevalence of overt hyperthyroidism rates 0.1 per 1000 men and 0.4 per 1000 women in Europe, whereas overt hyperthyroidism accounts for 0.5% of the total US population.

4. Forms of thyroid diseases

4.1 Graves' disease

Graves' disease is seen as the prime cause of hyperthyroidism and accounts for more than 70% of all hyperthyroid cases. Annually over 2% of women and 0.2% of men were reported with Graves' disease globally [17]. Graves' disease was found to be much more frequent in females, particularly during childhood, and more prevalent during puberty. The pathology of Graves' disease remains unclear, the genetic predisposition of the disease in concordance with additional environmental factors can be given as the most common cause of Graves' disease [18, 19]. The infiltration of the thyroid gland by autoreactive T and B cells synthesis of cytokines results in producing TSH-receptor Ab. The production of auto-antibodies and the preexistence of genetic predisposition of Graves' along with external factors including a recurring infection, stress, smoking, or oral iodine results in Graves' mediated hyperthyroidism. The most common first-line therapy includes antithyroid drugs (ATD) [20, 21]. The lower liver toxicity makes thiamazole as most preferred ATD. The suboptimal remission rate limits the use of thiamazole therapy and offers the use of radioiodine therapy as primary treatment. Carbimazole and its active metabolite such as propylthiouracil (PTU) and methimazole (MMI) are other commonly used ATD for Graves'.

4.2 Thyroiditis (Hashimoto's disease)

Hashimoto thyroiditis is presented as an autoimmune disease that results from the self-destruction of thyroid cells by auto-antibody-mediated immune responses [22].

Progressive fibrosis resulting from damaged thyroid tissue by antithyroid antibodies is the most common pathology of Hashimoto's disease. Based on the pathology Hashimoto's can also be termed as chronic lymphocytic thyroiditis or autoimmune thyroiditis. Hashimoto's disease is most prevalent among women than men, particularly among women aged between 30 and 50 years [23]. Diagnosis remains a constraint in Hashimoto's as it still takes time even after the disease progression. Monitoring elevated levels of antithyroid peroxidase along with depleted levels of free thyroxine and elevated TSH is the most common diagnostic method [24]. Levothyroxine is the most common medication which acts by converting T4 to T3, the active form of thyroid hormone [25].

4.3 Thyrotoxicosis

The physiological malfunctions in the expression of excessive levels of thyroid hormones are characterized as thyrotoxicosis. Thyrotoxicosis refers to the release of excess thyroid hormone resulting from the rapid distraction of thyroid tissue and it is not associated with hyperfunction of the thyroid gland [26]. Viral infection or autoimmune malfunctions resulting in the inflammation of the thyroid gland is the prime cause of thyrotoxicosis [27]. High levels of circulating thyroid hormones exhibit a direct inotropic effect by increasing α- to β-myosin heavy chain expression which affects cardiac contraction. Increased appetite, heat intolerance, and increased basal metabolic rate results in metabolism and increased food intake [28, 29]. Based on the degree of the increased rate of metabolism, nutritional deficiency and chronic caloric inadequacy ensue. The increased basal metabolic rate results in increased synthesis and degradation of the protein. Increased protein metabolism results in severe thyrotoxicosis and a radical decrease in net protein content can be evidenced by muscle wasting, proximal muscle weakness, and loss of weight [30].

4.4 Toxic nodular goiter

Toxic nodular goiter is a hormonally heterogeneous disorder, goiter is a multinodular hyperthyroidism characterized by multifunctional thyroid nodules with normal, increased, or decreased thyroid hormone production [31]. The functional heterogenicity of normal follicular cells through genetic factors and also through accruing new inheritable qualities by replicating thyroid cells are the two major primary factors of nodular goiter [32]. Secondary factors include external aspects such as smoking, stress, high levels of TSH, pharmaceutical agents, TSF (IGF-1), and other exogenous factors. Iodine plays a pivotal role development of nodular goiters. Iodine deficiency results in hyperplasia with increased TSH levels, with raise in iodine to a normal level hyperplasia, go into the resting phase [33]. These physiological alterations result in the development of diffuse hyperplasia with a higher risk of developing uni-nodule or multi-nodular goiter. Toxic multinodular goiter exhibits characteristic precursors such as single toxic adenomas or nontoxic multinodular goiter. The other complications include congestive heart failure, rapid heart rate, and atrial fibrillation, which might also result in osteoporosis [34].

5. Causes of hyperthyroidism

Hyperthyroidism is a multifactorial hormonal disorder that varies according to the patient's age, degree of hormone synthesis, the incidence of similar health conditions, and extent of the illness. The clinical presentation of hyperthyroidism

differentiates with each of the conditions given above [35]. Grave's disease and thyroiditis are the most common causes of hyperthyroidism. Grave's is commonly characterized as an autoimmune disease with an overproduction of thyroid hormone and this can be inherited or mostly associated with other autoimmune diseases. Thyroiditis is also an autoimmune condition resulting from inflammation of the thyroid gland [36]. An onset of thyrotoxic symptoms results from a hormone leak from the inflamed gland in subacute thyroiditis. Lymphocytic thyroiditis results from transient inflammatory causes and is difficult to distinguish from Graves at the early acute stage.

Various other factors influence the cause of hyperthyroidism which includes, but not limited to, such as excess thyroid hormone supplementation, iodine-induced hyperthyroidism, noncancerous tumor of the pituitary gland, and drugs associated with hyperthyroidism.

5.1 Exogenous thyroid hormone (acute or chronic)

The excessive intake of liothyronine, levothyroxine, or desiccated thyroid either intentionally or inadvertent may result in exogenous hyperthyroidism. Prevalence of exogenous hyperthyroidism is more common in elderly people than endogenous hyperthyroidism due to an intentional overdose of thyroid hormone [37]. Levothyroxine is the most common suppressive dose of thyroxine administered to treat patients with goiter and to suppress tumor growth. Drugs used for treating depression, infertility, and obesity were also known to cause exogenous hyperthyroidism. Overdose of thyroid hormones may result in bone loss, cardiac dysfunction, and myocardial infarction. Exogenous hyperthyroidism typically exhibits symptoms of thyrotoxicosis [38, 39].

5.2 Iodine-induced hyperthyroidism

Iodine-induced hyperthyroidism was first stated in 1821 and has been recurrently observed in patients when introduced to iodine in iodine-deficient areas. It was also observed in patients without a history of thyroid disease in iodine-sufficient areas. The disorder has been reported later in relatively low iodine intakes regions such as western Europe and regions with iodine-deficient goiter. Iodine-induced hyperthyroidism has been reported in iodine-sufficient areas such as the United States where iodine intake was far above the minimum daily requirement (50 to 100μg). The syndrome was commonly reported in iodine-sufficient areas without any other sign of thyroid diseases. This might result from pharmacological doses of iodine from common drugs such as Betadine, Iodo-Niacin, amiodarone, and various other radiographic dyes. Globally 800 million people are at risk of iodine deficiency (ID) and related disorders. Iodine supplementation is the most preventable approach to eliminating the risk of ID disorders. The term iodide refers to the biological form of the free element (inorganic), while iodine includes both inorganic iodides (I-) and iodine covalently bound to tyrosine [40]. The thyroid adopts several mechanisms to compensate for the iodine deficiency and to maintain sufficient thyroid production. Prolonged compensatory mechanisms result in the development of multifunctional autonomous growth and function of the thyroid with induced mutation of TSH receptors by harboring scattered cell clones [12, 41]. A high prevalence of multinodular goiter and nodular hyperthyroidism may be associated with mild prolonged ID (**Figure 1**) [42].

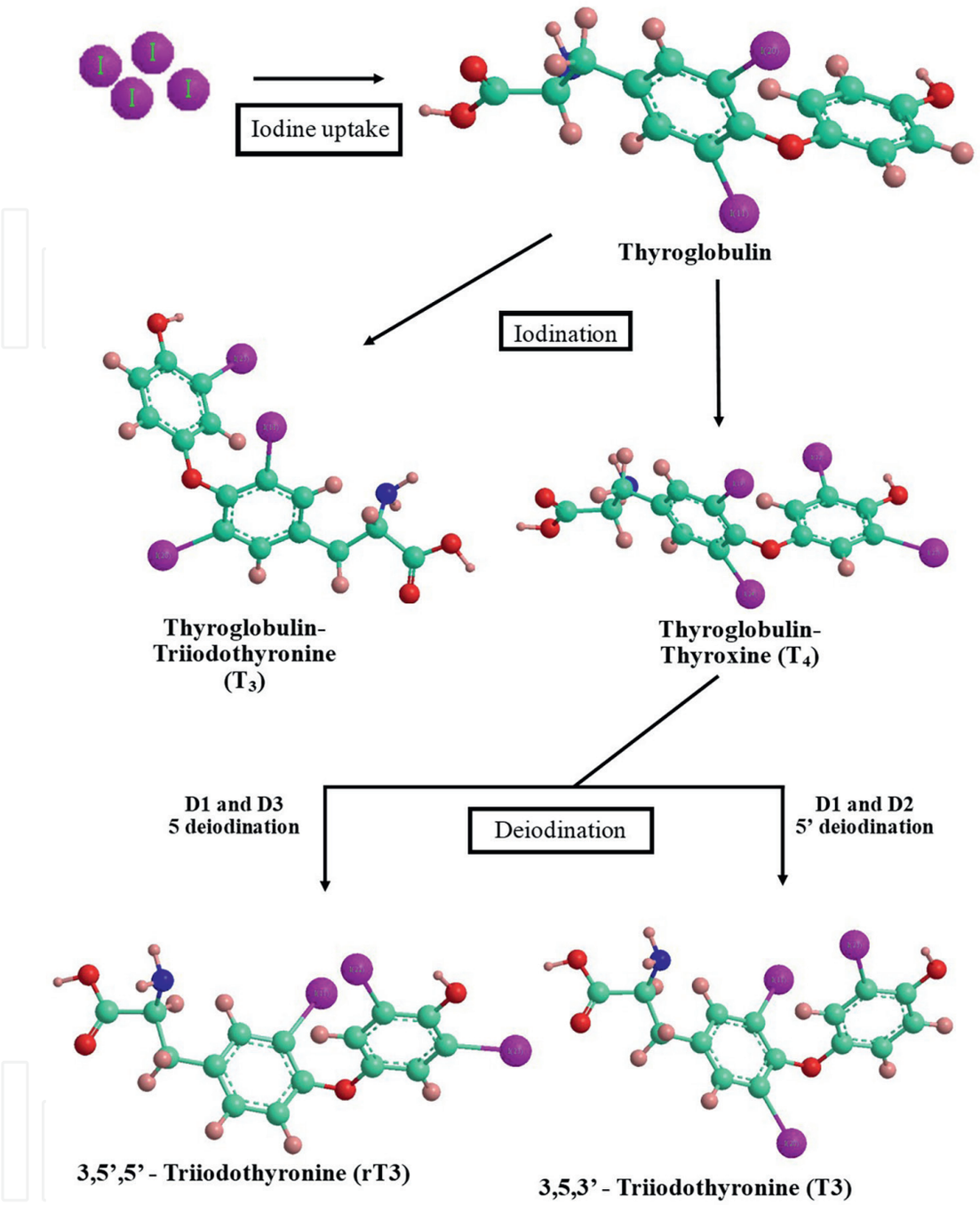

Figure 1.
Metabolic pathway of thyroid iodination and deiodination mediated by iodine deiodinases.

5.3 Noncancerous tumors of the pituitary gland

Thyrotroph adenomas are pituitary tumors that induce overproduction of thyroid-stimulating hormone resulting in hyperthyroidism. Among pituitary adenomas, thyrotropic adenomas account for less than 1% and are a rare cause of hyperthyroidism [43]. Pituitary adenomas are mostly benign and localized in the pituitary gland. Tumors spread to nearby tissues by expansion or invasion of their surroundings or tissue displacement and usually do not spread to other body parts [31]. TSH- secreting adenomas widely produce TSH (72%) alone where in certain cases, elevated secretion

of TSH by adenomas results in activating various other hormones such as gonadotrophins, prolactinoma, and growth hormone which results in various physiological functioning of the brain by affecting cavernous sinus. Most of the thyroid-adenomas are macroadenomas (<10 mm) [44]. Hyperthyroidism along with thyrotroph adenomas are frequently associated with loss of vision, headache, visual defects, and loss of anterior pituitary functioning. Atrial fibrillation, thyrotoxic failure, and vertebral fracture are the few deleterious effects of thyrotroph adenomas [45].

5.4 Drug-associated hyperthyroidism

Drug-associated hyperthyroidism is commonly referred to as factitious hyperthyroidism resulting from inappropriate intake of thyroid hormones. Molecular-targeted agents, thyroid hormone, interferon, and amiodarone are the most common drugs associated with hyperthyroidism [45]. Amiodarone is a common drug used to treat heart rhythm disorder. The high iodine content of the drug accelerates the thyroid gland to secrete excessive amounts of thyroid hormones [46]. Alemtuzumab an anti-cancerous drug induces hyperthyroidism in patients by producing autoantibodies against the thyroid gland and resulting in the development of Graves' disease. Another cancer drug PD-1 inhibitor used in cancer immunotherapy to boost the body's innate immune system results in the development of hyperthyroidism in patients by producing antibodies against thyroid hormones [47]. Highly active antiretroviral therapies, lithium, tyrosine kinase, and interferon α are other pharmaceutical compounds associated with drug-induced hyperthyroidism [48].

6. Micronutrients in hyperthyroidism

Nutritional factors are closely associated with regular physiological activities and optimal metabolic functioning. Dietary micronutrients are one of the predominant sources of essential micronutrients such as vitamins, minerals, trace elements, and amino acids [49]. Deficiency in these micronutrients results in great health concerns and according to the WHO, around 2 billion people are affected by micronutrient deficiency-related health disorders. Micronutrients mediate optimal metabolic functioning through the production of hormones, enzymes, and various biomolecules for optimal growth and development [50]. Despite being required in a small amount, a sensible deficiency of micronutrients results in detrimental effects on various physiological functioning such as regulating membrane permeability, enzymatic reactions, etc. [51]. Nutritional alterations are highly related to thyroid dysfunctions as the normal functioning of the thyroid is derived from optimal supplementation of various essential micronutrients.

The role of iodine and selenium in optimal production and proper metabolism of the thyroid is remarkable. Selenium-containing deiodinases play a pivotal role in the conversion of circulating T4 into physiologically active thyroid. The affinity of selenium-containing deiodinases toward specific receptors allows them to bind to receptors in nuclei, which in turn regulate gene expression. Selenium exists in the form of selenoproteins as functionally active. Glutathione peroxidase (GPX) and iodothyronine deiodinase are the two major enzymes with selenocysteine as an integral protein. Deiodinases generally exist in three forms, where 5′DII mediates the conversion of active thyroid hormone T3 from prohormone T4 and 5′DI catalyzes the degradation of rT3. The selenocysteine-containing deiodinase is involved in the

feedback and inactivates both thyroid hormones T4 and T3. Selenocysteine containing GPX protects the thyroid tissues from oxidative damage caused by hydrogen peroxide during the synthesis of thyroid hormone. The precursor of selenocysteine, monoselenium is also involved in the cellular defense mechanism.

The efficacy of iodine can be improved by supplementation of vitamin A, which results in vitamin A-mediated TSH-β suppression. The patients with severe iodine deficiency were observed with increased levels of TSH, thyroglobulin, and goiter size due to a deficiency of vitamin A [52]. Fluorine inhibits iodine transport and exhibits an anti-thyroid effect. Dietary intake of fluorine results in severe iodine deficiency and at higher concentrations, it might lead to goitrogenic [53]. The iodine transportation to the thyroid gland is inhibited by bromine, which results in physiological changes in the cellular architecture and affects the thyroid secretions [54]. Cobalt at higher concentrations results in goiter and affects thyroid hormone production, whereas cobalt deficiency reduces T3 levels. The function of selenium in thyroid functioning is well-studied in iodine transport [55]. Metal ions like cadmium, zinc, mercury, and rubidium tend to mimic the role of selenium or impart with selenium in iodine transport. Where these metals have various negative effects on thyroid functioning, as cadmium in rats has proven to increase levels of T3 and T4, and it also affects the activity of hepatic D1 [56]. Rubidium has been reported with inducing goiter in rats. Calcium has been reported to interfere with thyroid functioning, where excess dietary calcium results in goiter and is associated with low iodine clearance. Calcium also inhibits thyroxine adsorption [57, 58]. Asparagine and serine have been found to be positively correlated with the expression of TSH. Synthesis of T4 and FT4 were correlated with certain amino acids namely valine, leucine, and arginine, and the same was reported by Krishnamurthy *et al*., 2021.

7. Antinuclear antibodies (ANA) in early diagnosis of hyperthyroidism

Among the spectrum of autoimmune diseases, autoimmune thyroid diseases are the most common and are frequently associated with various organ-specific and non-organ-specific autoimmune disorders. Ani-thyroid peroxidase (Anti-TPO) and anti-thyroglobulin (Anti-Tg) are common markers of AITD. The prevalence of these anti-nuclear antibodies has been widely reported in AITD adult patients. ANA and other extractable antibodies are identified as novel diagnostic markers for predicting various autoimmune diseases. Over 90% of the patients with a multifactorial autoimmune disease such as systemic lupus erythematosus was detected with ANA. Various cross-sectional studies have reported the presence of ANA in healthy populations. A cross-sectional study by Satoh et al. [59] on 4754 individuals above 12 years reported the prevalence of ANA in 13.8% of the population. Another study by Hilário et al. [60] on healthy children reported the prevalence of ANA in 12.6% of the population. The rationale for the occurrence of these ANA remains unclear, but the assessment of these autoantibodies can be an early predictor of future autoimmune disorders.

Graves' disease and chronic lymphocytic thyroiditis are the most common organ-specific autoimmune disorders resulting from lymphocytic infiltration of autoantibodies and thyroid hormones. A retrospective analysis by Siriwardhane et al. [61] evaluated the association of thyroid hormones TSH, FT4, and anti-TPO antibodies and anti-Tg. In this study, the presence of ANA and anti-ENA were evaluated in subjects with systemic autoimmune disease markers such as thyroid, anti-TPO, and anti-Tg. They reported a strong prevalence of ANA in 20.4% of thyroid positive subjects,

18.0%, and 17.6% in anti-TPO and anti-Tg positive subjects respectively. In their retrospective study, they exhibited a strong association between ATID markers and systemic autoimmune markers and the prevalence of anti-TPO and ANA and anti-ENA as specific markers for autoimmune thyroid disorders. This also suggests that periodical evaluation of ANA and other autoimmune antibodies would assist in the early detection of autoimmunity among individuals who have anti-TPO antibodies.

8. Hyperthyroidism in human reproductive health

Thyroid hormones are vital endocrine enzymes in maintaining regular metabolism and healthy reduction in both males and females. Alterations in thyroid synthesis have adverse effects on reproductive health. Sex steroids and sex-hormone-binding globulins are the prime metabolites associated with thyroid disorders. Both hyperthyroidism and hypothyroidism have considerable effects on reproductive health, whereas overactive thyroid is associated with various reproductive dysfunctions. In males, hyperactive thyroid results in impaired sexual behavior, a decrease in morphologically normal sperm, reduction in sperm motility and count. In females, thyroid imbalance mainly results in menstrual disturbances and reduced fertility. Hyperthyroidism is also associated with polymenorrhea and hypomenorrhea. A sharp increase in estrogen levels can be observed in hyperthyroid women and levels of SHBG were also found to increase. The production rate of testosterone and androstenedione was found to significantly increase in hyperthyroid women along with changes in androgen metabolism.

Hyperthyroidism in men is primarily characterized by elevated levels of SHBG resulting in increased levels of circulating total testosterone. Studies have reported that concentrations of free testosterone remain stable whereas the circulating levels of bioavailable testosterone were found to be depleted. Both total and free estradiol concentrations were found to decrease in hyperthyroid subjects. Overactive thyroid had adverse effects on semen quality, a study by Clyde et al. reported marked oligospermia resulting in low motility in two out of three hyperthyroid patients, where one was reported with low sperm count. A similar study by Kidd et al. in five hyperthyroid patients reported low sperm counts in all subjects.

A comprehensive retrospective analysis by Siriwardhane et al. analyzed the effects of altered thyroid hormones on vital sex hormones. The study with 15,043 subjects between the reproductive age of 15–49 years reported elevated levels of total testosterone and SHBG in hyperthyroid women. Anti-TPO seropositive women reported elevated testosterone and low cortisol. Whereas hyperthyroid men were reported with low DHEA-S and elevated estradiol, FSH, and prolactin. The study reported an inverse direction of SHBG levels in hyperthyroid and hypothyroid subjects in women. The positive correlation between SHBG with thyroid hormones FT3 and FT4 has been reported in various studies. The reduction in the metabolic clearance rate of testosterone due to the increased affinity between SHBG and testosterone increases the circulating levels of testosterone. This study also suggested that thyroid hormones could activate steroidogenesis in hyperthyroid patients resulting in increased levels of DHEA-S.

9. Role of anti-TPO in early detection of hyperthyroidism

Thyroid-specific auto-immune disorders are the second most organ-specific autoimmune disorder next to rheumatoid arthritis. Graves' disease and Hashimoto's

thyroiditis are the most common thyroid-specific auto-immune disease. The pathogenesis of AITD includes various environmental and genetic factors. Anti-thyroid peroxidase is an antibody that synthesizes against a transmembrane of thyrocyte and is related to the levels of TSH which can be used to predict thyroid abnormalities. Over 90% of the cases with Hashimoto's thyroiditis and 80% of cases with Graves' disease are reported with the presence of anti-TPO. Anti-TPO antibodies in AITD subjects act as competitive inhibitors of thyroid activity and destroy thyrocytes. Anti-TPO antibodies highly belong to the IgG1 and IgG4 class of autoantibodies. Anti-TPO is an effective indicator of thyroid disease and also could indicate oxidative stress, advanced glycation, and oxygen metabolites in blood. Several studies have reported the presence of anti-TPO in Graves' disease, the recurrence of Graves' disease can be predicted by systemic evaluation of anti-TPO after anti-thyroid treatment [62].

A retrospective analysis by siriwardhane et al. reported the prevalence of anti-TPO as a selective marker for the early prediction of thyroid diseases. The results revealed the presence of anti-TPO prior to the onset of thyroid disease in both hyperthyroid and hypothyroid patients. The study also reported the occurrence of anti-TPO antibodies lacking any alterations in thyroid hormone levels. The study also reported that the anti-Tg antibody is a less specific marker for thyroid disease. A similar study by Hutfless et al. reported the prevalence of anti-TPO and anti-Tg antibodies 7 years prior to the diagnosis of Hashimoto's and Graves' disease. In summary, the thyroid system has a complex interplay with various factors including nutrition, autoimmunity, and reproductive function. Though some of these associations have been highlighted in the past decades, novel biochemistry and better diagnostic capabilities are unraveling novel associations that are leading to a more nuanced understanding of thyroid functions. This chapter explores some of these novel associations and sheds light on exciting outcomes that may arise in the years to come.

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Conflict of interest

The authors declare no conflict of interest.

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