# Hashimoto thyroiditis: an evidence-based guide: etiology, diagnosis and treatment

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# Hashimoto thyroiditis: definition and epidemiology

- Hashimoto thyroiditis (HT) is an eponym based on the description in 1912 by Haraku Hashimoto, and characterized as “struma lymphomatosa” – an enlarged thyroid gland infiltrated with lymphocytes .
- The incidence of HT is estimated to be 0.3–1.5 cases per 1000 people, with female to male predominance of 7–10: 1

- HT has an ethnic preponderance, with the white race characterized by a higher incidence than black or Asian, and Pacific Islanders being rarely affected.
- Prevalence increases with age , especially in patients diagnosed with other autoimmune conditions, such as myasthenia gravis, systemic sclerosis and other connective tissue diseases , Sjögren’s syndrome, pernicious anemia, autoimmune liver disease, and celiac disease .

- The expression of this poly-autoimmunity is likely due to an interplay

between immune defects, hormones, genetic and environmental factors.

- More rarely, HT is accompanied by other endocrinopathies of autoimmune origin thereby constituting autoimmune polyendocrine syndromes (APS): type 1 (HT with Addison's disease, hypoparathyroidism, chronic mucocutaneous candidiasis), type 2 (HT with Addison's disease and type 1 diabetes mellitus) or IPEX syndrome (HT with neonatal type 1 diabetes mellitus, autoimmune enteropathy and eczema).

- APSs are associated with certain genetic background, such as autoimmune regulator (*AIRE)* mutations for type 1 APS or X-linked forehead box P3 (*FOXO3*) pathogenic variants for IPEX syndrome .

## Pathomechanisms of Hashimoto thyroiditis

The autoimmune presentation of HT is based on the interplay between environmental factors and genetic background, such as polymorphisms in human leukocyte antigen (*HLA*), T lymphocyte-associated 4 (*CTLA-4*), protein tyrosine phosphatase, non-receptor type 22 (PTPN22) genes, and X-chromosome inactivation patterns, leading to an imbalance between self-tolerance mechanisms sustained by regulatory T and B lymphocytes[9,12-14]. In addition, genetic polymorphisms in self-antigens, cytokines and their receptors (for example, interleukin 2 receptor *IL2R*), estrogen receptors, adhesion molecules (*CD14*, *CD40)*, the promoter region of the selenoprotein S, and genes encoding for apoptosis have been linked to thyroid autoimmunity[9,15,16-18]. These genetic susceptibilities could be epigenetically modified through the methylation, histone modifications, and RNA interference of non-coding RNAs (**Figure 1**)[19].

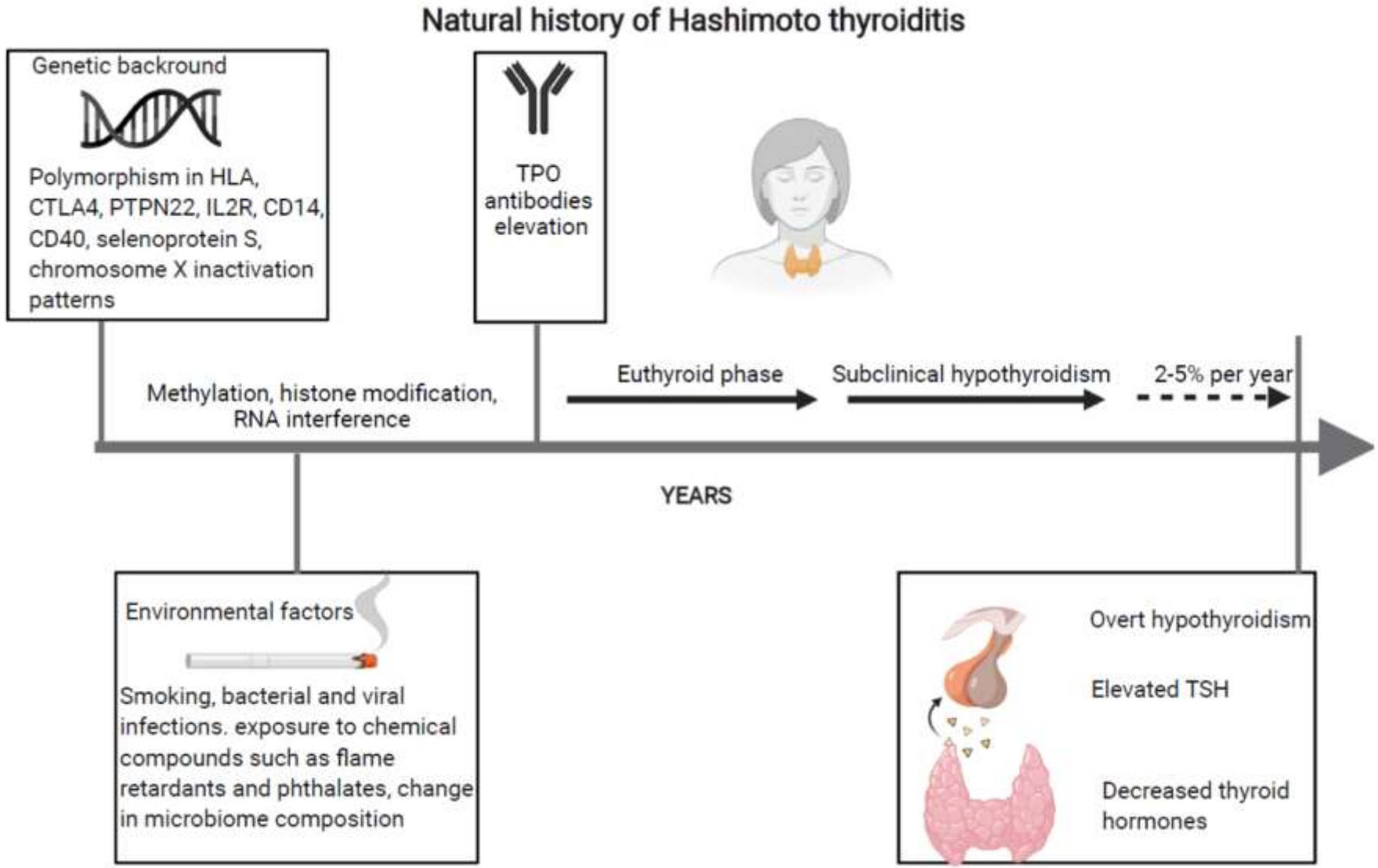



**Figure 1** The background and natural history of Hashimoto thyroiditis

Several environmental factors may trigger autoimmune disease in genetically predisposed patients. These triggers include, but are not limited to, bacterial and viral infections, cigarette smoking, maternal-fetal microchimerism, and exposure to chemical compounds such as flame retardants and phthalates [20,21]. On the other hand, limited exposure to environmental factors,

for example, living in almost sterile conditions, has also been associated with a high incidence of allergic and autoimmune diseases, including HT [22]. Microbiome composition has been associated with autoimmune thyroid disease with *Bifidobacterium* and *Lactobacillus* significantly decreased, and harmful microbiota such as *Bacteroides fragilis* significantly increased in HT as compared with control subjects without autoimmunity [23].

Dietary habits may also affect the natural history of HT, as iodine excess has been associated with up to a four-fold increment in HT incidence [24]. The mechanism behind this phenomenon could relate to an increased immunogenicity of thyroglobulin by iodine in genetically predisposed subjects [25]. While excessive iodine supplementation in HT should be discouraged, an appropriate supplementation is recommended in pregnancy and lactation to a total intake of 250 microg/day[26]. There are data suggesting that decreased selenium intake may activate HT, but selenium administration has not shown an improvement in disease course although a reduction in thyroid peroxidase (TPO) autoantibody titers was observed [27,28]. Because of an

association between HT and celiac disease, a low gluten diet has been suggested as potentially modulating HT. In a prospective study of patients with celiac disease compared to controls without celiac disease, a low-gluten diet was associated with decreased thyroid volume only in the patients with celiac disease, although TPO Abs were unaffected [29]. However, a reduction in TPOAbs was seen in another study after a low-gluten diet in patients characterized by presence of both TPOAbs and transglutaminase Abs, compared with an Abs-positive group on a gluten-containing diet [30]. The significance of this TPOAbs reduction in the context of modulating HT course is unknown.

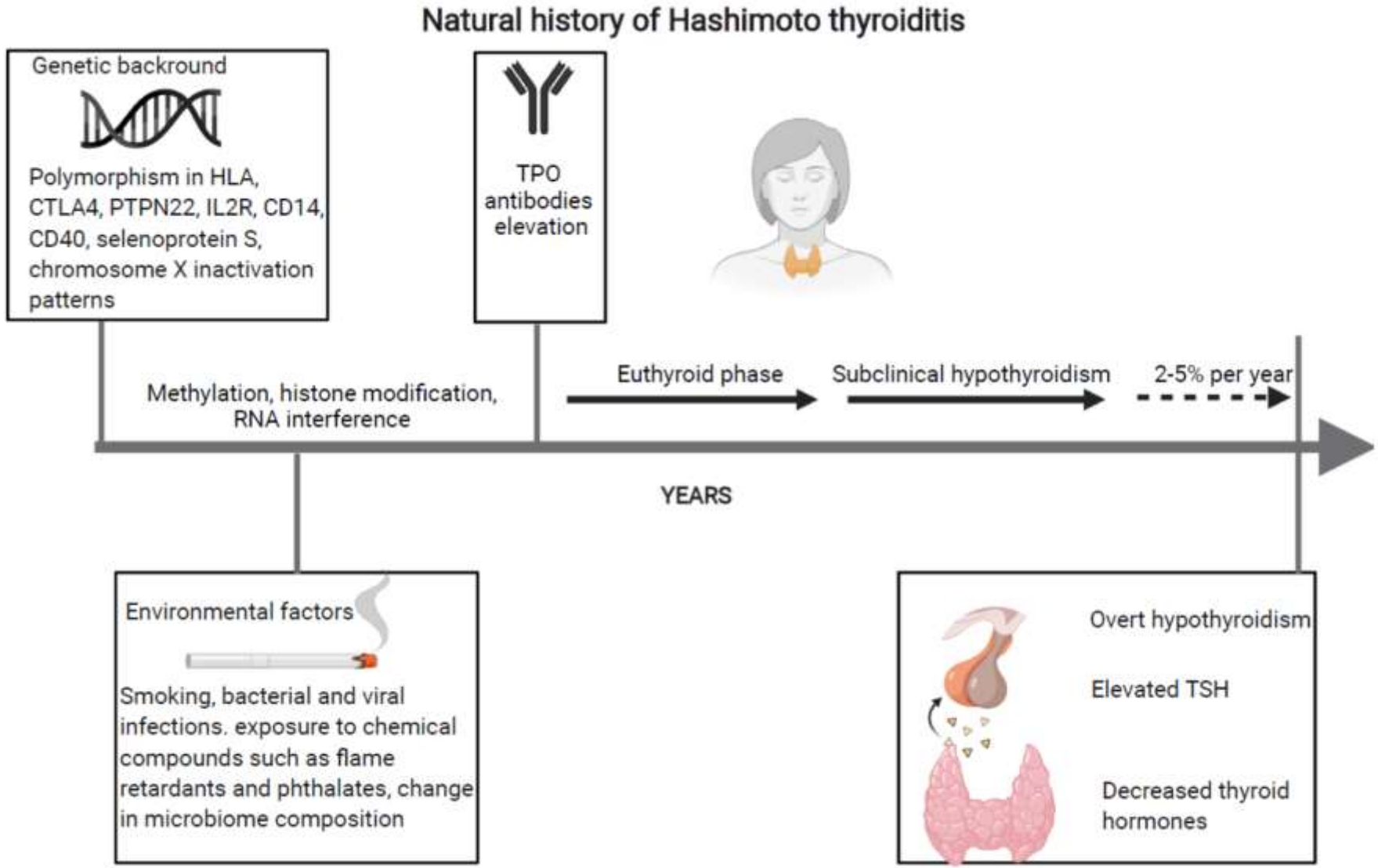



**Figure 1** The background and natural history of Hashimoto thyroiditis

- Mechanistically, HT is characterized by a direct T-cell attack on the thyroid gland, as evidenced histologically by the presence of lymphoplasmacytic infiltration, fibrosis, lymphatic follicular formation, and parenchymal atrophy.
- Several different variants of HT have been identified based upon clinical and histologic features, such as fibrotic and atrophic, Riedel thyroiditis and IG4 thyroiditis.

# Natural history of Hashimoto thyroiditis and symptomatology

The natural history of HT, evolving from genetic predisposition, through the environmental modifiers, presence of detectable TPOAbs in the euthyroid individual, subclinical and clinical disease, is depicted in **Figure 1**. Notably, in some patients with particularly pronounced thyroid destruction in the initial phase, "Hashitoxicosis" (see below) may be present as a consequence of the release of pre-formed thyroid hormones from destroyed follicles to the circulation. Primary hypothyroidism is generally considered "overt" when the thyroid stimulating hormone (TSH) level is elevated and the free thyroxine (FT4) is low. Subclinical hypothyroidism is defined biochemically as an elevated TSH, accompanied by a normal FT4 and FT3 concentrations [37, 38]. However, precise definition of the TSH reference range can be challenging due to adjusted normal ranges with age, gender, pregnancy and in certain populations. There are formulas for adjusting the TSH reference interval for age, ethnicity, and sex within the US populations, but they are not standardized nor consistently implemented[39].

The presence of symptoms in HT is linked to evolution into hypothyroidism. Signs and symptoms of hypothyroidism are consequences of thyroid hormone deficiency in target tissues and exhibit a wide spectrum of severity that include, but are not limited to, cool and dry skin, coarse hair, loss of body hair, hoarse voice, coarse facial features, facial edema, generalized edema, bradycardia, and delayed relaxation phase of the deep tendon reflexes (**Figure 2**).

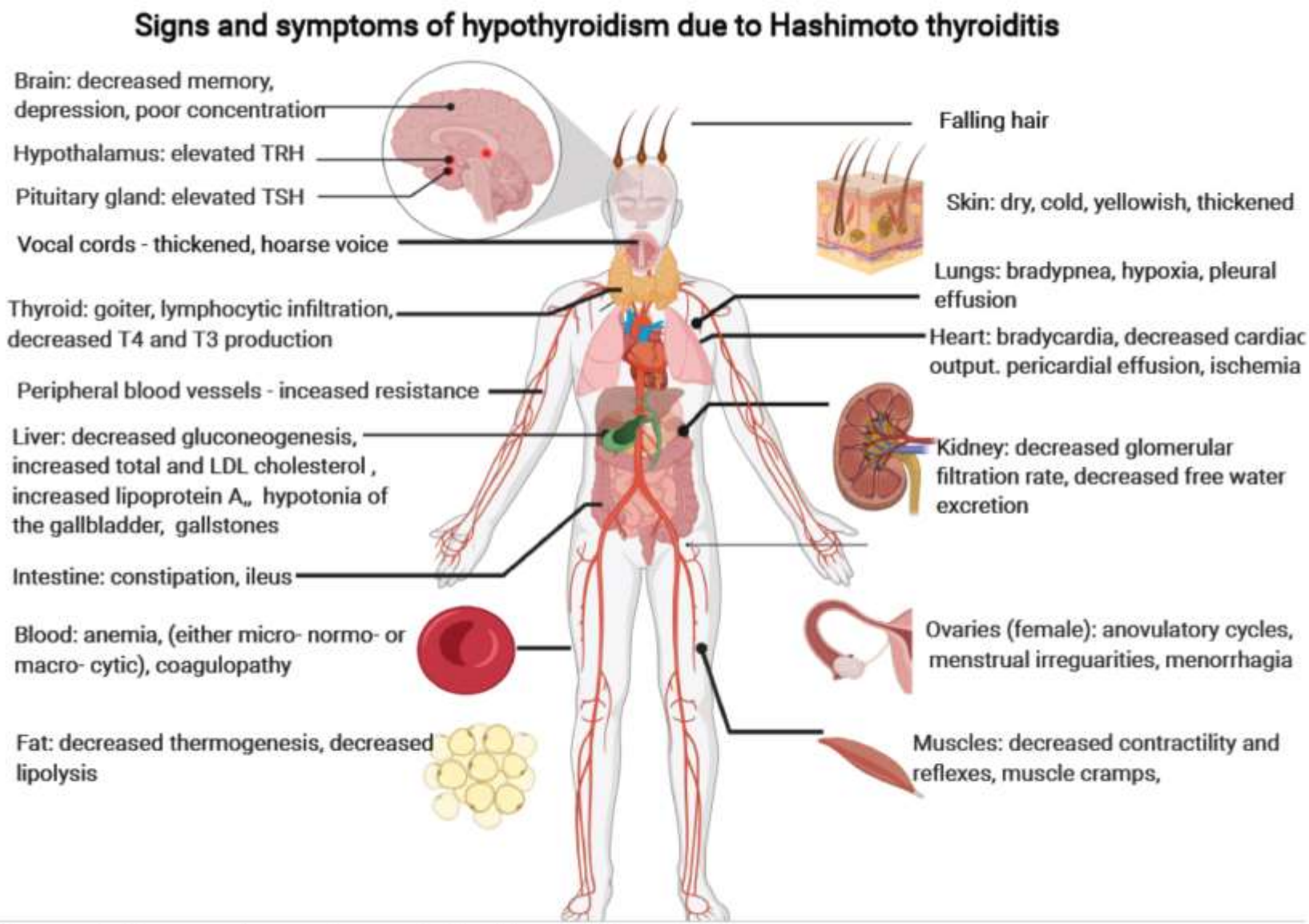



**Figure 2** Signs and symptoms of Hashimoto thyroiditis

- An extremely rare entity characterized as Hashimoto encephalopathy has been described that is marked by positive TPOAbs, elevated spinal fluid protein, non-specific cortical changes on MRI, and variable response to steroid therapy .

# Diagnosis of Hashimoto thyroiditis

- The diagnosis of HT is based on clinical symptoms of hypothyroidism, and presence of TPOAbs, although seronegative HT can be seen in 5–10% of cases.
- The ultrasound appearance of the thyroid gland may help with differential diagnosis, particularly in patients with TPOAbs-negative HT .
- The ultrasound features of HT include decreased echogenicity, heterogeneity, hypervascularity and presence of small cysts .

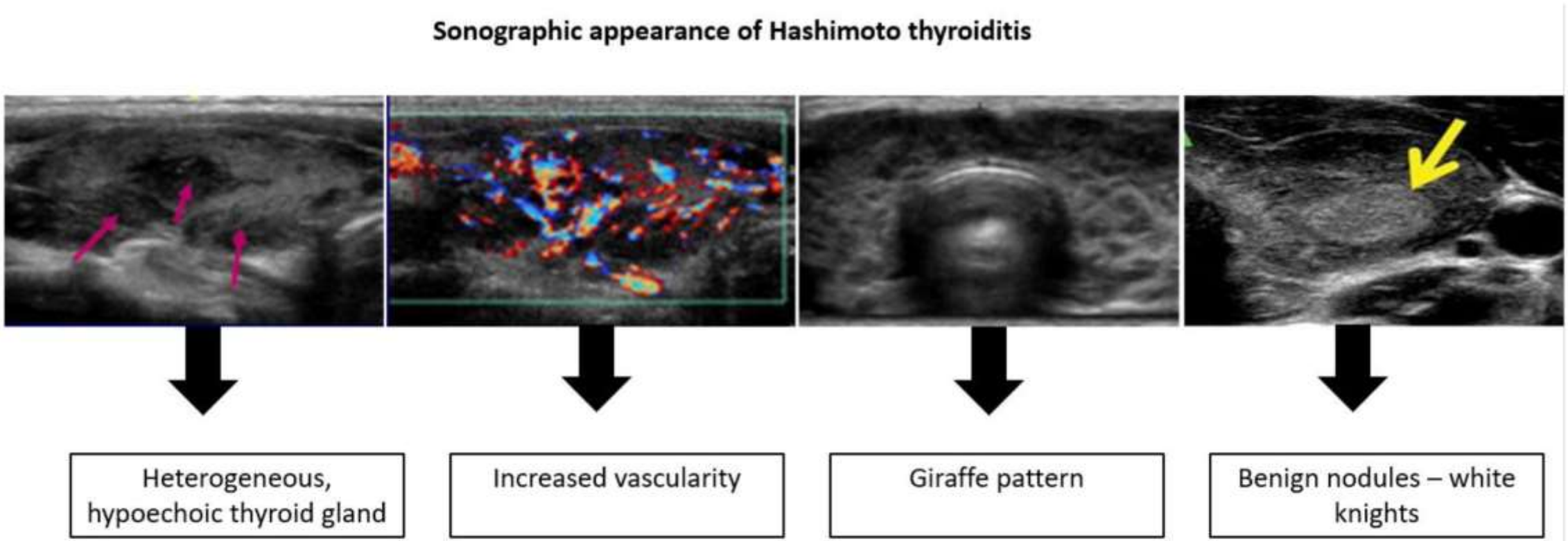
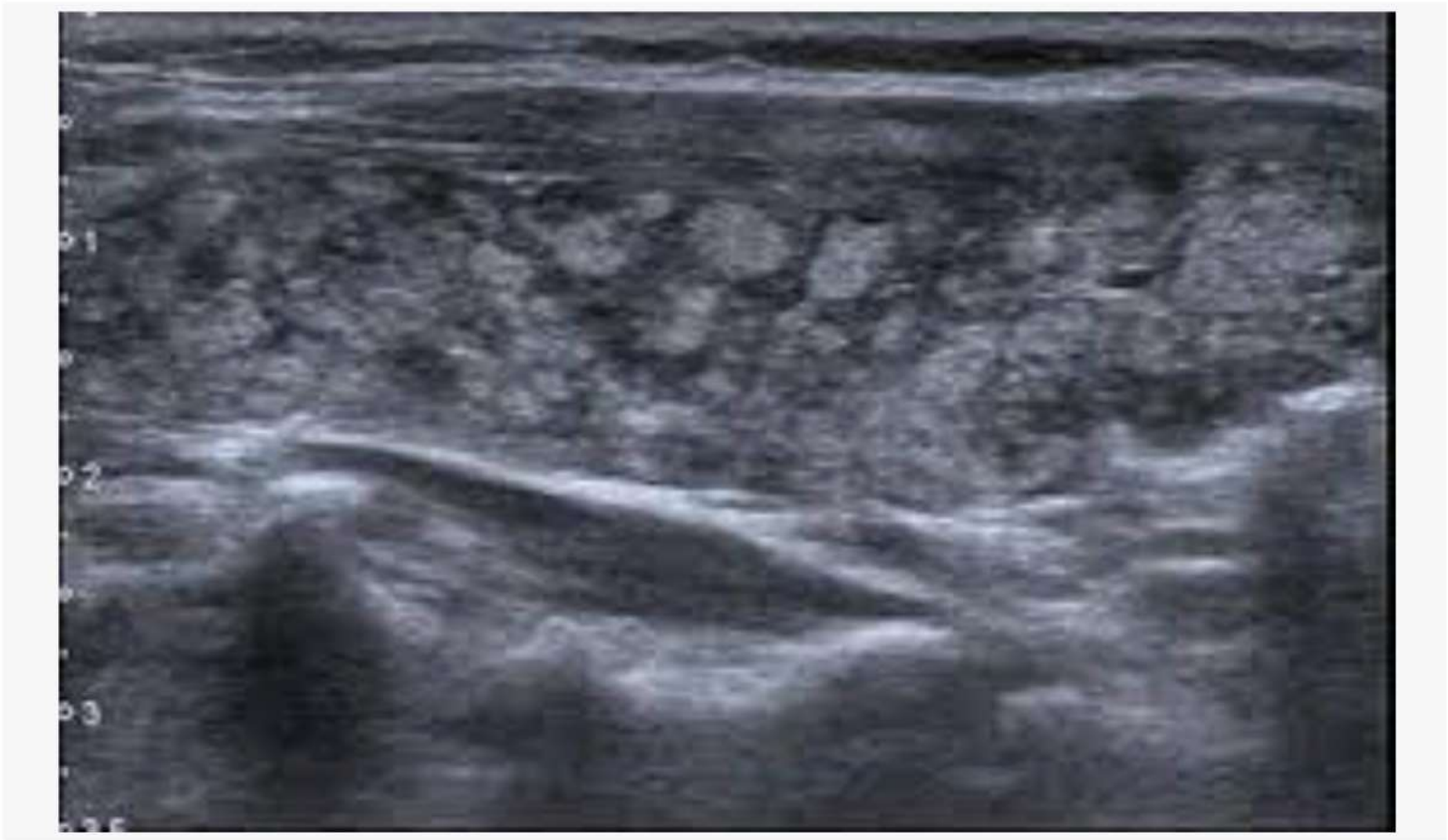



**Figure 3** The sonographic appearance of Hashimoto thyroiditis



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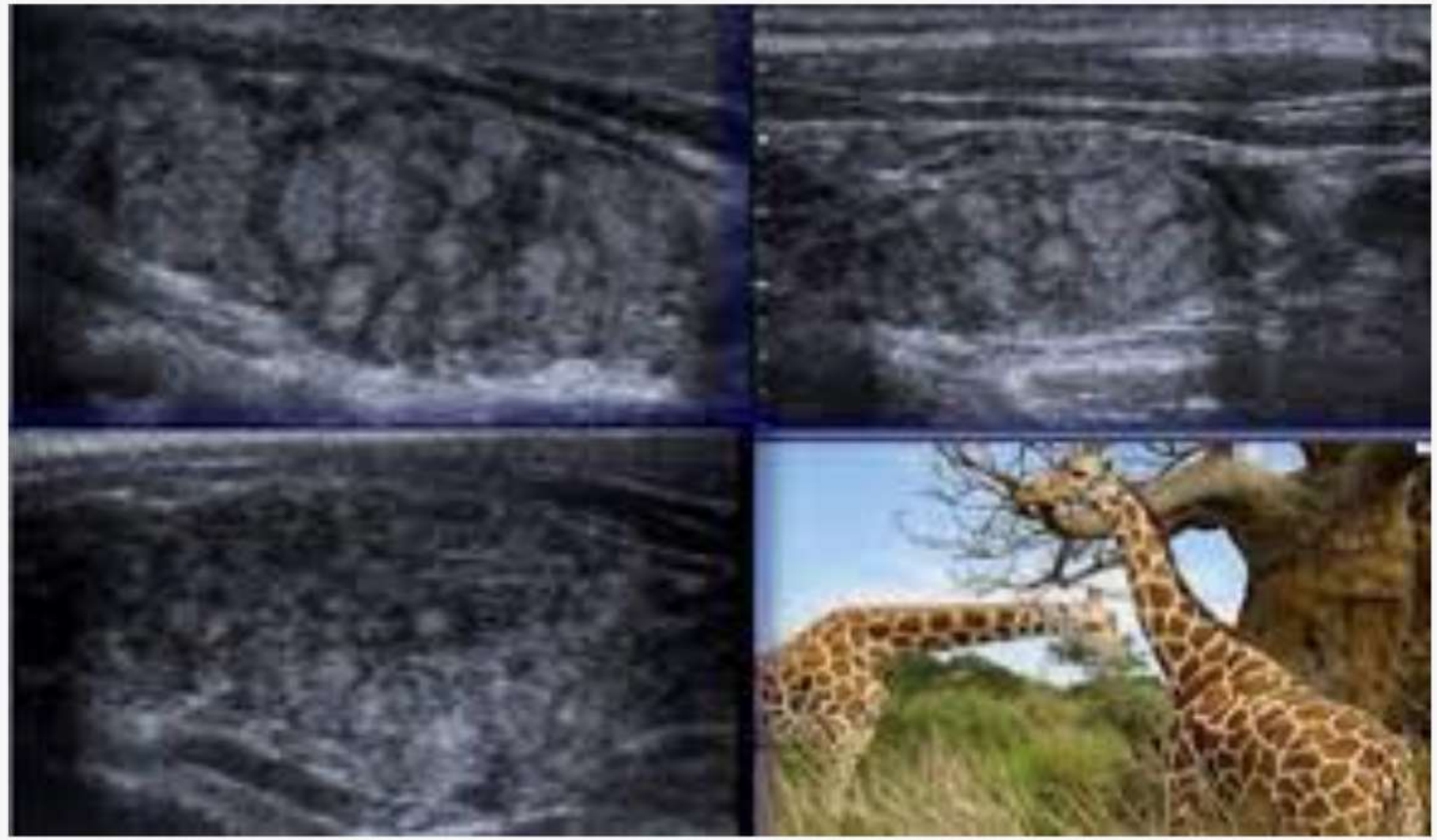

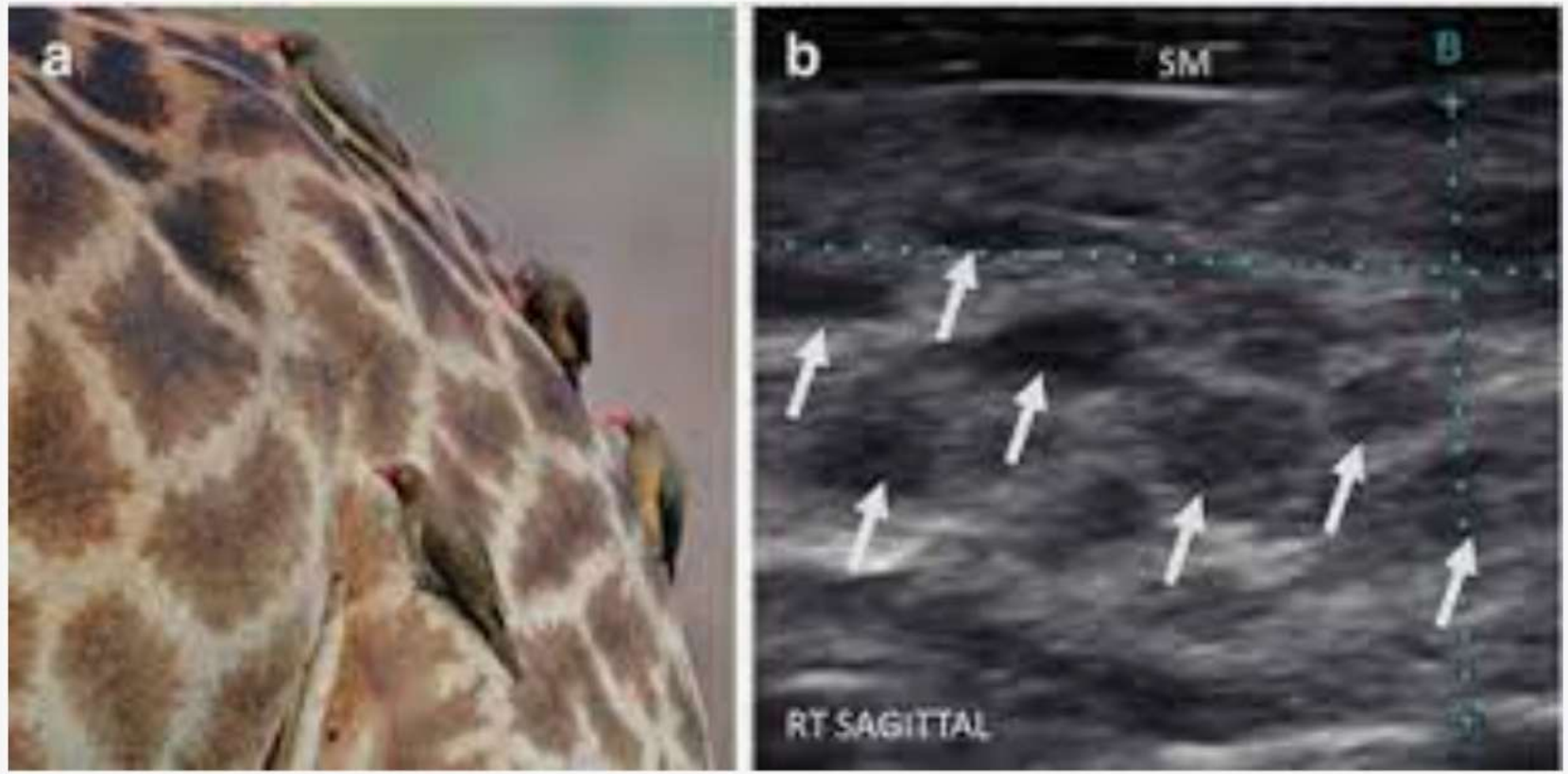
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- Serum anti-TPOAbs are present in about 95% of patients, with positive anti-TgAbs in 60- 80%.
- TPOAbs have been recognized as risk factors for progression into overt hypothyroidism over time in the general population as well as in those subjects developing hypothyroidism after exposure to amiodarone, lithium, or interferon-α.
- TPOAbs are associated with the risk of hypothyroidism during pregnancy, increased likelihood of miscarriage and the failure of *in vitro* fertilization.

# Treatment of Hashimoto thyroiditis

**Hashitoxicosis** Hashitoxicosis was first described by Fatourechi in 1971 in patients with clinical presentation of thyrotoxicosis associated with lymphocytic infiltration of the thyroid gland, typical for HT[45]. The release of stored T4 and T3 to the circulation results in transient signs and symptoms of thyroid hormone excess. As the result of thyroiditis rather than thyroid hyperfunction, the thyrotoxicosis usually requires only supportive care and implementation of beta-blockers rather than therapy with thyreostatics and subsides within 3-24 months, giving rise to usually permanent hypothyroidism[41].

This clinical picture is distinguished from those variants of HT associated with thyrotoxicosis including silent thyroiditis and postpartum thyroiditis that are characterized by transient thyrotoxicosis lasting for about a month, also not warranting therapy with thyreostatics, followed by hypothyroid phase, lasting about 2–6 months but leading to recovery to euthyroidism. However, there are some patients, particularly women with multiple pregnancies associated with post-partum thyroiditis, who may develop permanent hypothyroidism [41].

**Hashimoto thyroiditis associated with euthyroidism** The diagnosis of euthyroid HT is based on the presence of TPO Abs and / or typical sonographic appearance of the thyroid gland (**Figure 3**) but normal serum TSH and T4 levels. These patients require periodical (ie yearly) TSH measurements to screen for hypothyroidism or guide management pre-conception and during pregnancy [26]. This population of patients might be vulnerable to other autoimmune disorders, and a low threshold for further diagnostic workup should be considered, if any symptoms occur.

**Hashimoto thyroiditis associated with subclinical hypothyroidism** It is controversial whether subclinical hypothyroidism in most individuals can be observed without treatment. Initiation of treatment has been suggested for patients with subclinical hypothyroidism and serum thyrotropin levels of 10mU/L or higher, as this TSH level has been associated with increased rate

of cardiovascular events and cardiovascular mortality[38]. A lower threshold for therapy could be used for young and middle-aged individuals with subclinical hypothyroidism who are somewhat symptomatic [37, 38]. Based on the meta-analyses documenting increased rates of fatal stroke and mortality from coronary heart disease in subjects with TSH ranging from 7 to 9.9 mIU/ml, some authors postulate lowering the therapy threshold for both younger and older individuals and treating with levothyroxine when the TSH exceeds 7 mIU/ml (**Table 1**) [38,46,47]. When the decision on initiating therapy is established, levothyroxine doses ranging from 25 to 75 mcg per day are usually sufficient to achieve euthyroidism[48].

**Table 1** Indications for levothyroxine treatment considerations in patients with subclinical hypothyroidism. (Adapted from Biondi et al[38])

| **TSH concentration mIU/ml** | **Grade** | **Age <65 years** | **Age ≥65 years** |
|---|---|---|---|
| **4.5–6.9** | Grade I subclinical hypothyoidism | Annual follow up TSH measurement in asymptomatic patients.<br>Consider therapy for the following groups of patients:<br>• Positive TPOAbs<br>• Multiple symptoms of hypothyroidism<br>• Hyperlipidemia | Treatment not recommended |

| TSH concentration mIU/ml | Grade | Age <65 years | Age ≥65 years |
|---|---|---|---|
| | | increasing TSH levels<br>• A plan for pregnancy<br>• Goiter | |
| **7–9.9** | | Treat with levothyroxine to reduce the risk of fatal stroke and ischemic heart disease associated mortality | Consider treatment with levothyroxine to reduce the risk of ischemic heart disease associated mortality |
| **≥10** | Grade II subclinical hypothyoidism | Treat with levothyroxine to reduce the risk of progression to overt hypothyroidism, heart failure, cardiovascular events, and ischemic heart disease-associated mortality | |

**Hashimoto thyroiditis associated with overt hypothyroidism** Overt hypothyroidism should be treated with thyroid hormone replacement therapy[37]. Compared with untreated patients, patients treated for hypothyroidism have been shown to have decreased risk of myocardial infarction, stroke, atrial fibrillation, heart failure and cardiovascular death [49] as well as lower all-cause mortality[50,51].

The aim of optimal management based on thyroxine (T4) replacement dosage is to mimic normal physiology. Unfortunately, several studies document that therapy with levothyroxine (L-T4) is leading to over- or under-treatment in a significant proportion of patients. A large study including 162 369 patients with hypothyroidism followed for up to 23 years, revealed that 11.6% of achieved TSH values were below 0.4 mIU/L, suggesting over-treatment and 32.4% were above 4.0 mIU/L, suggesting undertreatment [52]. A smaller study supported these observations showing 19.8% overtreated and 17.4% undertreated patients over the 5-years course of follow up

The dose of L-T4 required to normalize serum TSH depends on the amount of residual endogenous thyroid function and the patient's weight, particularly lean body mass [37,55]. Notably, the intact thyroid gland is estimated to produce around 85 to 100 mcg of T4 per day and 5 to 6.5 mcg triiodothyronine (T3) per 24h, while the remaining daily production of 26.5 mcg/day of T3 results from peripheral conversion of T4 to T3 by type 1 and type 2 deiodinases [56].

Consequently, in patients with a preserved degree of endogenous thyroid function, the required initial LT4 dose ranges between 1.4 and 1.8 mcg/kg body weight [37,57,58]. Upon initiation of therapy with L-T4, there is a need for ongoing dose adjustments based on the TSH targets, with optimal management aiming for an age appropriate TSH reference range. Based on NHANES III data, for an individual in the 30- to 39-year age, the median TSH is 1.2 mIU/L, with the 2.5 and 97.5 percentiles being 0.42 to 3.56 mIU/L, respectively, while for older patients targeting TSH of 4–6 mIU/ml might be reasonable [59]. These considerations are based on a meta-analysis of 40 studies analyzing the variability within the normal TSH ranges and showing that lower TSH levels were associated with decreased bone mineral density and increased fracture risk, whereas higher TSH levels were associated with worse cardiovascular and metabolic outcomes [60].

Several studies have analyzed the effect of timing of LT4 administration, and its association with meals, on the serum TSH concentration. Despite some variability in study designs, the take home message is that post-fasting as well as bedtime regimens are acceptable, as either can be associated with normalization of TSH concentration[40].

Interestingly, normalization of TSH and biochemical euthyroidism does not always translate to improvement in perceived quality of life. Therefore, some investigators and clinicians postulated the necessity of objective evaluation of some endpoint of thyroid hormones actions on tissue levels. Potential evaluation markers include sex hormone–binding globulin, osteocalcin, cholesterol, creatine kinase, ferritin, *N*-telopeptides, and enzymes such as tissue plasminogen activator, angiotensin-converting enzyme, glutathione S-transferase, and glucose 6-phosphate dehydrogenase[37]. Physiological parameters important in evaluation of response to therapy include heart rate, pulse wave arrival time, echocardiographic parameters of left ventricular function, Achilles tendon reflex time, and basal metabolic rate[37]. There have been also attempts to quantify thyroid hormone responsive gene expression profiles in whole blood, but this approach requires validation in a larger sample size, before it could be potentially implemented as an index of thyroid status [66].

Another approach commonly brought up by patients on L-T4 who have persistent complaints is the use of combination therapy with LT4 and T3. This regimen has been addressed by 14 randomized trials of combination therapy that did not demonstrate benefit[37,44] although five

other studies[67-71] did demonstrate some benefit [40]. However, the various protocols employed differed in terms of design, including variable use of crossover or parallel groups, blinding, the ratio of T4 to T3 dosage being used, treatment duration as well as the definitions of primary and secondary outcomes. In addition, some studies were subject to carryover effects, overtreatment, and limited inclusion of men and older age groups, underpowered sample size, short duration and once daily T3 dosing. Consistently, five meta-analyses or reviews, also suggested that there is no clear advantage to combination therapy [37,72-75]. Importantly, potential long-term risks of addition of T3 such as cardiac arrhythmias, or decreased bone mineral density have not been fully investigated. Therefore, Guidelines of the American Thyroid Association have concluded that there is insufficient evidence to recommend combination

therapy. However, if such therapy is chosen, it should resemble physiology - the molar ratio of T4:T3 physiologically is 14:1 to 15:1 [37] and synthetic T4 to T3 conversion factor is 3:1 [76]. Sustained release T3 formulations under development may help achieving physiologic goals.

The role of surgery for HT has been traditionally limited to the patients presenting with either pain or compressive symptoms due to goiter or co-existing malignant thyroid nodules[84]. However, recently it has been hypothesized that thyroidectomy might be a therapeutic modality used to reduce the TPOAbs titers, as presence of such antibodies is associated with lower quality of life even in euthyroid subjects. Consequently, a clinical trial addressed this concept, randomizing highly positive TPOAb patients with continued symptoms while receiving LT4 to either thyroidectomy or continued medical management. In those who underwent thyroidectomy, TPOAbs significantly declined, quality of life and fatigue improved, and the effect was sustained at 12 to 18 months landmarks[85].

**Hashimoto thyroiditis and thyroid nodules** Based on evaluation of pathology specimens, the average prevalence of papillary thyroid cancer in patients with HT was around 27%, with an associated increased risk ratio of 1.59 as compared with the general population [86, 87]. A recent meta-analysis that combined the studies analyzing cytology and pathology specimens derived from patients with HT concluded that this association is based on low-to moderate quality evidence[88]. Apart from papillary thyroid cancer, a non-Hodgkin primary thyroid lymphoma has been strongly associated with HT, with a risk of about 60 times higher than in general population[32]. Thyroid lymphoma accounts for approximately 5% of all thyroid neoplasms. Diagnosis of thyroid lymphoma is important to be established, as it changes the first line therapy from surgery that is routinely implemented for malignant thyroid nodules to

appropriate targeted chemotherapy for lymphoproliferative disorders. Therapy of thyroid lymphoma and malignant thyroid nodules is beyond the scope of this review, but can be found in the respective guidelines[89].

# Hashimoto thyroiditis and pregnancy

The prevalence of TPOAbs in pregnant women is estimated to be 5–14% and TgAbs are seen in 3–18% of pregnant female subjects[90]. The presence of these Abs indicating thyroid autoimmunity, is associated with a two to fourfold increase in the risk of recurrent miscarriages[91,92] and two to threefold increased risk of preterm birth[91,93,94]. The mechanisms behind these adverse pregnancy outcomes in TPOAb positive euthyroid women are unclear, but some authors postulate that TPOAbs might be markers for other forms of autoimmunity that target the placental-fetal unit [95]. However, thyroid autoimmunity seems to have an additive or synergistic effect on miscarriage[93] and prematurity[96] risk, in women with maternal subclinical hypothyroidism. A recent meta-analysis including 19 cohort studies enrolling 47,045 pregnant women showed almost three-fold increased risks of preterm birth in women with subclinical hypothyroidism and 1.5-fold increased risk of preterm birth in women with isolated hypothyroxinaemia [94]. Another meta-analysis of 26 studies found significant associations between maternal subclinical hypothyroidism or hypothyroxinaemia and lower child IQ, language delay or global developmental delay compared with children of euthyroid women[97].

Overt hypothyroidism has been associated with increased rates of gestational hypertension including preeclampsia and eclampsia, gestational diabetes, placental abruption, postpartum hemorrhage, preterm delivery, low birthweight, infant intensive care unit admissions, fetal death and neurodevelopmental delays in the offspring [98,99,100]. Therefore, overt hypothyroidism

should be treated to prevent adverse effects on pregnancy and child developmental outcomes and should be started pre-conception to achieve biochemical euthyroidism.[26]. Therapy with LT4 improved success rate of *in vitro* fertilization in TPOAbs positive women with TSH>2.5 mIU/ml [26]. Importantly, women being treated for hypothyroidism typically require a 20% to 30% increase in their LT4 dose, which usually translates to addition of 2 pills per week early in the first trimester [26]. The physiologic explanation for increased thyroid hormone requirements is based upon several factors including increased hepatic thyroxine binding globulin synthesis and enhanced metabolism of thyroid hormone through its inactivation by the placental type 3

deiodinase [26,101]. The use of T3 or T4+T3 combination therapy is not indicated in pregnancy, as liothyronine does not cross the blood–brain barrier to the fetal brain[102]. LT4 replacement therapy should be monitored monthly, as over- and under- treatment lead to adverse pregnancy outcomes[26]. The suggested target TSH is within the lower half of the trimester-specific reference range or below 2.5 mIU/L, if trimester specific ranges are not available [26]. Regarding maternal subclinical hypothyroidism, the 2017 ATA guidelines recommend utilizing TPO antibody status along with serum levels of TSH to guide treatment decisions (**Table 2**)[26]. LT4 therapy is not recommended for isolated hypothyroxinaemia[26].

A 2021 systematic review and meta-analysis of six randomized controlled trials assessing the effect of LT4 treatment in euthyroid women with thyroid autoimmunity did not find any statistically significant differences in the relative risks of miscarriage and preterm delivery, or outcomes with live birth. Therefore, no strong recommendations regarding the therapy in such scenarios could be made, but consideration on a case-by-case basis might be implemented (**Table 2**)[103].

# Thank You For Your Attention