

EXPERT REVIEWS

Hashimoto's thyroiditis: TGAb, TPOAb, TRAb and recovery from hypothyroidism

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Hashimoto described four patients with goiter. The histology of the goiter was characterized by diffuse lymphocytic infiltration, fibrosis and epithelial cell destruction. Thyroglobulin antibody (TGAb) and thyroid peroxidase antibody (TPOAb) have been used to diagnose Hashimoto's thyroiditis. Patients with positive TGAb and/or TPOAb have been assumed to have Hashimoto's thyroiditis. Approximately 10% of those with positive TGAb and/or TPOAb have hypothyroidism. There are two types of autoimmune thyroiditis: goitrous Hashimoto's thyroiditis and atrophic thyroiditis. The latter patients have blocking antibody (thyroid-stimulating hormone [TSH]-stimulation blocking antibody [TSBAb]). TSBAb is a TSH-receptor antibody (TRAb). TSBAb causes thyroid atrophy and hypothyroidism. TGAb and/or TPOAb do not necessarily cause hypothyroidism. Hypothyroid patients with Hashimoto's thyroiditis usually receive life-long L-thyroxine therapy. However, spontaneous recovery from hypothyroidism has been reported. Patients who had Hashimoto's hypothyroidism and then Graves' hyperthyroidism (and vice versa), have also been reported. Hashimoto's hypothyroidism and Graves' hyperthyroidism could be the opposite spectrums of one disease.

KEYWORDS: autoimmune atrophic thyroiditis • autoimmune goitrous thyroiditis • autoimmune thyroid disease • autoimmune thyroiditis • Graves' disease • Hashimoto' thyroiditis • hyperthyroidism • hypothyroidism • TBII • thyroglobulin antibody • thyroid peroxidase antibody • TSH-receptor antibody • TSH-stimulating antibody

In 1912, Hashimoto described four patients with goiter (struma lymphomatosa), which is the painless enlargement of the thyroid gland [1]. The histology of the goiter was characterized by diffuse lymphocytic infiltration, fibrosis and epithelial cell destruction. This disease has been called Hashimoto's thyroiditis, chronic thyroiditis, autoimmune chronic thyroiditis, lymphocytic thyroiditis, lymphadenoid goiter or autoimmune thyroiditis. Patients with Hashimoto's thyroiditis have a painless, diffuse enlargement of the thyroid gland. Hashimoto's thyroiditis can cause hypothyroidism. Thyroid antibodies (thyroglobulin antibody [TGAb] and thyroid peroxidase antibody [TPOAb]) have been used to diagnose Hashimoto's thyroiditis [2,3]. Hashimoto's thyroiditis is now one of the most common thyroid diseases. Hashimoto's thyroiditis has been diagnosed on the basis of histology. However, histological examinations of the goiter have not always been done. Patients with positive TGAb and/or positive TPOAb have

been thought to have Hashimoto's thyroiditis. Approximately 10% of those with positive TGAb and/or TPOAb have hypothyroidism.

There are two types of autoimmune thyroiditis [4]:

- Autoimmune goitrous Hashimoto's thyroiditis
- Autoimmune atrophic thyroiditis

Patients with autoimmune goitrous Hashimoto's thyroiditis have goiter and patients with autoimmune atrophic thyroiditis do not have goiter. The thyroid glands of the latter patients are atrophic. Patients with autoimmune atrophic thyroiditis may have blocking antibody (thyroid-stimulating hormone [TSH]-stimulation blocking antibody [TSBAb]). This TSBAb is a TSH-receptor antibody (TRAb). This TSBAb causes atrophy of the thyroid glands, as well as hypothyroidism.

In patients with autoimmune thyroiditis, whether with goitrous thyroiditis or atrophic thyroiditis, the autoimmune process gradually reduces thyroid function. There is a phase of

compensation when normal thyroid hormone levels are maintained by a rise in TSH (subclinical hypothyroidism). In this phase, the patients are asymptomatic. Subclinical hypothyroidism is defined as a normal serum-free thyroxine (T₄) concentration and a slightly high TSH concentration (usually TSH 4.5–10 mU/l) [5,6]. Patients with subclinical hypothyroidism do not have symptoms. This compensated phase is called subclinical hypothyroidism. Later, free T₄ levels fall and TSH levels rise further. Symptoms become more readily apparent at this stage (usually TSH >10 mU/l), which is referred to as clinical hypothyroidism or overt hypothyroidism. Some of the patients with subclinical hypothyroidism develop into overt hypothyroidism, some continue to be in a subclinical hypothyroid state and the others regain a euthyroid state.

Prevalence

We studied 2506 women and 2468 men, aged 30 years or over, in Okinawa, Japan. Approximately 14% of the women (350 out of 2506 subjects) had positive TGAb and/or TPOAb and 10% of them (36 out of 350 subjects with positive TGAb and/or TPOAb) had hypothyroidism. Approximately 7% of the men (173 out of 2468 subjects) had positive TGAb and/or TPOAb and 6% of these (ten out of 173 subjects with positive TGAb and/or TPOAb) had hypothyroidism. Approximately 1.4% of women (36 out of 2506), 0.4% of men (ten out of 2468) and 0.9% of the subjects (46 out of 2506 women and 2468 men) had hypothyroidism. In the patients with hypothyroidism due to Hashimoto's thyroiditis, the men:women ratio was 1:3.6. In a Japanese study, serum triiodothyronine (T₃), T₄, TSH and thyroid antibody (TGAb or TPOAb) were measured in 1251 samples from the general population (546 men and 705 women) aged 40 years or over in Hisayama, a Japanese rural town [7]. TGAb or TPOAb was positive in 7.7% of men and 15.0% of women, and the men:women ratio was 1:2 for Hashimoto's thyroiditis. This ratio was markedly different from those in hospital patients with thyroid disorders, where the ratio was 1:8. Among the study subjects, overt hypothyroidism was 0.3% and latent hypothyroidism was 4.2%. Hypothyroidism was more evident in women than in men [7]. The prevalence of thyroid disease and dysfunction, including thyroid autoimmunity, was studied in 94,009 inhabitants, aged 20 years and older in Nord-Trøndelag, Norway [8]. The prevalence of former diagnosed hypothyroidism was 4.8% in females and 0.9% in males. In both sexes the prevalence increased with age. The prevalence of positive TPOAb (>200 U/ml) was 13.9% in women and 2.8% in men.

The number of cases of hypothyroidism due to Hashimoto's thyroiditis have been thought to be approximately 1% of the population (1.4% of women and 0.4% of men) [3,9,10]. Women are more affected than men [3,7,8,10,11]. In patients with hypothyroidism due to Hashimoto's thyroiditis, the ratios of women to men have been reported to be 1:3–20 [3,7,8,10,11]. In both sexes, the prevalence increased with age [8–10].

Hypothyroidism is more common in certain populations, such as the Japanese, probably because of genetic factors and chronic exposure to a high-iodine diet. Excess iodine intake may affect the development of Hashimoto's thyroiditis. Kelp consumption is very high in Okinawa (Japan) and we expected a high prevalence of Hashimoto's thyroiditis. We studied the amount of iodine intake and the frequencies of positive TGAb and TPOAb in the residents of a small town in Okinawa, Yamagata in Yamagata, Kobe in Hyogo, and Hotaka in Nagano, Japan [3]. TGAb and/or TPOAb were positive in 142 (13.7%) out of 1039 subjects in Okinawa, in 16 (16.0%) out of 100 subjects in Yamagata, in 31 (13.4%) out of 232 subjects in Kobe, and in 35 (13.9%) out of 252 subjects in Nagano; no differences of the frequencies of positive TGAb and/or TPOAb were noted among these four areas. In total, 10% of the subjects with positive TGAb and/or TPOAb had hypothyroidism; no differences in the frequencies of hypothyroidism in those with positive TGAb and/or TPOAb were noted among these four areas. Differences in iodine intake were noted, however, the differences in dietary iodine intake do not affect the frequencies of positive TGAb and/or positive TPOAb in Japanese subjects. This is probably due to the fact that, throughout the country, the Japanese are taking enough iodine.

The mean age at diagnosis of Hashimoto's thyroiditis is 30–50 years and the prevalence of overt hypothyroidism increases with age. Subclinical hypothyroidism with slightly high TSH concentrations (TSH 4.5–10 mU/l) is found in the patients with positive TGAb and/or positive TPOAb [6]. Some of them develop into overt hypothyroidism.

The frequency of autoimmune goitrous Hashimoto's thyroiditis is higher than that of autoimmune atrophic thyroiditis [4]. We have seen 21 patients with autoimmune atrophic thyroiditis and 1032 patients with autoimmune goitrous Hashimoto's thyroiditis from 1993 to 2007; the ratio of the patients with autoimmune atrophic thyroiditis and those with autoimmune goitrous Hashimoto's thyroiditis is 1:49. However, the exact frequency of the patients with autoimmune atrophic thyroiditis is not known.

Pathology, pathogenesis & pathophysiology

The histology of Hashimoto's thyroiditis (autoimmune goitrous thyroiditis) was characterized by diffuse lymphocytic infiltration, fibrosis and epithelial cell destruction [1]. There is a marked lymphocytic infiltration of the thyroid with germinal center formation, atrophy of the thyroid follicles accompanied by oxyphil metaplasia, absence of colloid and mild-to-moderate fibrosis. In autoimmune atrophic thyroiditis, the fibrosis is much more extensive, lymphocytic infiltration is less pronounced and thyroid follicles are destroyed [12]. Some of these histopathological features of autoimmune atrophic thyroiditis are caused by TSBAb [12]. It is not known whether autoimmune atrophic thyroiditis is a distinct disorder or a stage of Hashimoto's goitrous thyroiditis. Patients with autoimmune atrophic

thyroiditis may have TSBAb [4]. TSBAb causes the atrophy of thyroid glands [12] and also causes hypothyroidism in patients with autoimmune atrophic thyroiditis [4].

Hashimoto's thyroiditis is an autoimmune disease. Susceptibility to Hashimoto's thyroiditis is determined by a combination of genetic and environmental factors. The risk of Hashimoto's thyroiditis is increased in individuals with a family history of autoimmune thyroid diseases (ATDs). In a Danish twin study, the concordance rates for Hashimoto's thyroiditis were 38% for monozygotic (MZ) twins and 0% for dizygotic (DZ) twins [13]. A twin study in California (USA) confirmed these results, demonstrating concordance rates of 55 and 0% in MZ and DZ twins, respectively [14]. These data suggest that patients with Hashimoto's thyroiditis have a substantial inherited susceptibility. Hashimoto's thyroiditis seems to be a polygenic disease with a complex mode of inheritance. Immunomodulatory genes play an important role in the development of Hashimoto's thyroiditis. *HLA-DR* polymorphisms are the best-documented genetic risk factors for Hashimoto's thyroiditis, especially *HLA-DR3*, *-DR4*, and *-DR5* in Caucasians [15]. *HLA-DR5* was said to be a genetic risk factor for goitrous Hashimoto's thyroiditis and *HLA-DR3* for autoimmune atrophic thyroiditis [16]. However, the results do not support a difference between goitrous and atrophic thyroiditis based on respective associations with *HLA-DR5* and *-DR3* [15]. HLA may increase susceptibility to ATDs but the major genetic influence on the inheritance of ATDs may be at another locus [17]. A weak association also exists between polymorphisms in *CTLA-4*, a T-cell-regulating gene, and Hashimoto's thyroiditis [18]. These genetic associations are shared by other autoimmune diseases. This may explain the relationship between Hashimoto's thyroiditis and other autoimmune diseases, including Type 1 diabetes, Addison's disease, pernicious anemia and vitiligo vulgaris. *HLA-DR* and *CTLA-4* polymorphisms may explain the genetic susceptibility to Hashimoto's thyroiditis. The other contributory loci remain to be identified.

The female preponderance of Hashimoto's thyroiditis is probably due to the effects of sex steroids on the immune response and possibly due to an X chromosome-related genetic factor as well. This X chromosome-related genetic factor may explain the high frequency of Hashimoto's thyroiditis in Turner syndrome [19]. A gene on chromosome 21 may be responsible for the association between Hashimoto's thyroiditis and Down's syndrome [20]. Other genes may also play some role in susceptibility to Hashimoto's thyroiditis.

The higher concordance rate in MZ compared with DZ twins indicates that genetic factors play a role in the etiology of Hashimoto's thyroiditis among Caucasian women living in areas with borderline iodine deficiency [13]. However, the fact that the concordance rate among MZ twins was below 1 suggests that environmental factors are also of etiological importance [13]. Environmental susceptibility factors are poorly defined. A high iodine intake may increase the risk of Hashimoto's thyroiditis [21]. Iodine causes thyroid cell damage and

thyroid follicle destruction [22], and induces hypothyroidism [23]. However, the differences in dietary iodine intake do not affect the frequencies of positive TGAb and/or TPOAb in Japanese individuals [3]. There is no convincing evidence for a role of infection, except for the congenital rubella syndrome (CRS). In CRS, there is a high frequency of Hashimoto's thyroiditis and Type 1 diabetes [24,25]. People with certain immune and organ-specific genes are predisposed to developing ATDs when they are exposed to certain environmental triggers. Iodine deficiency [26], iodine excess [21,23], lithium [27], selenium deficiency [28,29], smoking [30], sex steroids [31], IFN [32], *Yersinia* infection [24,33], adult T-cell leukemia (ATL) virus [11] and other viruses [24] infection, iodine-rich medications, such as amiodarone [34] and iodine contrast dyes [35] may be environmental triggers. Soybean has been reported to be goitrogenic [36–38].

Hashimoto's thyroiditis was characterized by diffuse lymphocytic infiltration. Activated CD4⁺ and CD8⁺ T cells, as well as B cells, infiltrate the thyroid [39]. Thyroid cell destruction is primarily mediated by the CD8⁺ cytotoxic T cells. The CD8⁺ cytotoxic T cells destroy thyroid cells by either cell necrosis or apoptosis. Local T cells produce cytokines, such as TNF, IL-1 and IFN- γ . These cytokines impair thyroid cell function and induce the expression of other proinflammatory molecules by the thyroid cells themselves, such as cytokines, HLA class I and class II molecules, adhesion molecules, CD40 and nitric oxide. Thyroid cells may become more susceptible to apoptosis mediated by death receptors, such as Fas and programmed cell death (PD)-1 [40], which are activated by their respective ligands on T cells. Administration of IFN- α is associated with ATD [32].

TGAb and TPOAb are clinically useful markers for the diagnosis of Hashimoto's thyroiditis [41]. However, neither TGAb or TPOAb has been shown to inhibit thyroid functions. Transplacental passage of TGAb or TPOAb has no effect on the fetal thyroid [42]. This suggests that T-cell-mediated injury is required to initiate autoimmune damage to the thyroid.

Transplacental passage of TSBAb may cause transient neonatal hypothyroidism [43,44]. TSBAb inhibits TSH-stimulated cAMP responses. TSBAb blocks TSH-stimulated responses of thyroid glands and causes hypothyroidism.

Iodine

Iodine deficiency is the most common cause of hypothyroidism worldwide [26]. Iodine-induced hypothyroidism has been documented [23]. A high iodine intake may increase the risk of Hashimoto's thyroiditis [21]. However, the mechanisms for this iodine-induced development of autoimmune disease in Hashimoto's thyroiditis have not been clearly demonstrated. Iodine causes thyroid cell damage and thyroid follicle destruction [22]. This iodine-induced thyroid cell damage and thyroid follicle destruction may be associated with the development of Hashimoto's thyroiditis.

Iodine has both acute and chronic inhibitory effects on thyroid function:

- Acute iodine effects (Wolff–Chaikoff effect) [45]
- Chronic iodine effects

Both acute and chronic iodine effects cause hypothyroidism:

- Acute iodine-induced hypothyroidism
- Chronic iodine-induced hypothyroidism

Acute iodine effects; acute iodine-induced hypothyroidism (Wolff–Chaikoff effect)

Iodine is an essential element for thyroid hormone synthesis. The thyroid gland has the capacity and holds the machinery to handle the iodine in iodine deficiency, as well as in iodine excess. In the latter situation, excess iodine acutely inhibits the iodine organification in the thyroid. This acute inhibitory effect of iodine on iodine organification has been called an acute iodine effect or Wolff–Chaikoff effect [45]. Plasma inorganic iodide is a homeostatic regulator of thyroid function. This acute iodine effect is an effective means to reject iodide and, therefore, to prevent the thyroid from excess thyroid hormone-synthesis. Ingestion of a large amount of iodine causes Wolff–Chaikoff effect. This acute iodine effect is an autoregulatory phenomenon; iodine acutely inhibits thyroid hormone release from the thyroid gland and also acutely inhibits formation of thyroid hormones in the thyroid gland. This acute iodine effect causes hypothyroidism and lasts several days, after which it is followed by an ‘escape phenomenon’ [46]. Through the escape phenomenon, the organification of intrathyroidal iodide resumes and the normal synthesis of T4 and T3 resumes. Escape from the acute iodine effect is associated with a decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein [46]. The escape phenomenon may be due to decreased inorganic iodine concentration, secondary to downregulation of sodium–iodide symporter on the basolateral membrane of the thyroid follicular cell.

When ‘escape’ does not occur, the acute iodine-induced hypothyroidism develops into a chronic form.

In iodine-induced hypothyroidism, the hypothyroidism is transient and thyroid function returns to normal in 2–3 weeks after iodide withdrawal but transient levothyroxine (L-thyroxine [L-T4])-replacement therapy may be required in some patients. The patients who develop transient iodine-induced hypothyroidism must be followed long term thereafter because many will develop permanent primary hypothyroidism.

Chronic iodine effects; chronic iodine-induced hypothyroidism

As mentioned previously, when escape does not occur, the acute iodine-induced hypothyroidism develops into chronic iodine-induced hypothyroidism. Iodine inhibits thyroid

hormone secretion and also inhibits iodine uptake and iodine organification and thyroid hormone synthesis [22]. Ingestion of a large quantity of iodine inhibits thyroid hormone-release from the thyroid gland and also inhibits iodine organification and decreases thyroid hormone synthesis in the thyroid gland. Iodine induces hypothyroidism. Chronic ingestion of kelp, which contains iodine, induces hypothyroidism. This is a chronic iodine effect. Iodine causes thyroid cell damage and thyroid follicle destruction. Iodine inhibits thyroid hormone secretion and also inhibits iodine uptake, iodine organification and thyroid hormone synthesis [22].

Iodine-induced hypothyroidism can be treated with iodine restriction. Patients with iodine-induced hypothyroidism recover from hypothyroidism with iodine restriction. Transient L-T4-replacement therapy may be required in some patients.

Amiodarone

Amiodarone may cause thyroid dysfunction [34]. Amiodarone is a benzofuranic-derivative, iodine-rich drug used widely for the treatment of tachyarrhythmias. Amiodarone increases serum T4 and reverse T3 (rT3) and decreases serum T3 concentrations; it inhibits 5′-deiodinase activity, resulting in a decrease in the generation of T3 from T4 and a decrease in the clearance of rT3. In 14–18% of amiodarone-treated patients, there is overt thyroid dysfunction, either amiodarone-induced hypothyroidism (AIH) or amiodarone-induced thyrotoxicosis (AIT) [47]. Both AIH and AIT may develop either in apparently normal thyroid glands or in glands with pre-existing, clinically silent abnormalities. Pre-existing Hashimoto’s thyroiditis is a definite risk factor for the occurrence of AIH [48]. Due to the iodine content of amiodarone (iodine 37.3 mg/100 mg), a major part of the amiodarone effects is iodine effects on thyroid hormonogenesis. In the patients with AIH, amiodarone can be continued in association with L-T4 replacement, if it is necessary for the underlying cardiac disorder. L-T4 is the drug of choice, particularly in these patients with cardiac problems, because it requires only once-daily administration and is not associated with the spikes in serum T3 concentrations. L-T3 requires three- to four-times administration per day. L-T3-administration gives spikes of serum T3 increases. The serum TSH concentration is the most important parameter to monitor therapy. AIT is primarily related to excess iodine-induced thyroid hormone synthesis in an abnormal thyroid gland (type I AIT) or to amiodarone-related destructive thyroiditis (type II AIT).

We have had 128 amiodarone-treated patients between 2005 and 2007. We have seen 17 patients with AIH. All of the 17 patients with AIH had Hashimoto’s thyroiditis. We have seen two patients with type I AIT, but we have not seen any patients with type II AIT. In total, 19 (15%) out of 128 amiodarone-treated patients have had amiodarone-associated thyroid dysfunctions. AIH is more frequent in iodine-sufficient areas and AIT appears to occur more frequently in geographical areas with low iodine intake [34,47–50].

After the discontinuation of amiodarone, AIH disappears. Patients with AIH recovered from hypothyroidism after amiodarone discontinuation. In type I AIT, the main medical treatment consists of the simultaneous administration of thionamides and potassium perchlorate, while in type II AIT, glucocorticoids are the most useful therapeutic option [34,47–50].

Soybean

Soybean, an important protein source in many areas, including Japan, is goitrogenic and may cause goiter when iodine intake is limited. Soybean may induce hypothyroidism. Soybean interrupts the enterohepatic cycle of thyroid hormone [36] and causes excess fecal loss of thyroid hormones [36–38]. In humans, goiter has been seen in infants fed soy formula; this is usually reversed by changing to cow milk or iodine-supplemented diets [36,51–56]. After the 1960s, manufacturers reportedly began adding iodine to formulas to mitigate thyroid effects. A retrospective epidemiologic study was conducted on teenage children diagnosed with ATD (Hashimoto's thyroiditis or Graves' disease) [57]. The subjects, consuming soy formula as infants, had twice the prevalence of ATD (18 out of 59 [31%]) of healthy siblings (nine out of 76 [12%]) or of controls (seven out of 54 [13%]). Soybean allergy might be associated with ATD development. Goiter and high normal TSH levels in healthy iodine-sufficient adults occurred as early as 1 month ($n = 37$) after commencing a diet that included 30 g of pickled soybeans per day [58]. Although it was not measured, dietary iodine content may have been insufficient to protect against the anti-thyroid effect of soybean. Furthermore, no changes in serum thyroid hormone T3 and T4 levels were found. After 1 month off the soybean diet, TSH decreased to the pretreatment levels and goiters were diminished in size. Soybean may cause goiter when iodine intake is limited. Soybean increases fecal loss of thyroid hormones [38]. Japanese individuals usually eat soybean with kelp (seaweed), which contains iodine.

Antibodies: thyroglobulin antibody, thyroid peroxidase antibody & TSH-receptor antibody

Thyroglobulin antibody & thyroid peroxidase antibody

Hashimoto's thyroiditis has been diagnosed on the basis of histology. However, patients with positive TGAb and/or positive TPOAb, have been assumed to have Hashimoto's thyroiditis, and histological examinations of the goiter have not been always done. Thyroid-function tests should be performed in all patients suspected of having Hashimoto's thyroiditis. Hashimoto's thyroiditis is characterized by the presence of specific thyroid autoantibodies (TPOAb and/or TGAb). Humoral and cellular immune responses are both involved in autoimmune disorders of the thyroid gland. TGAb and TPOAb are not responsible for initial thyroid damage and the pathogenic importance of TGAb and TPOAb is not known. TGAb or TPOAb do not induce

hypothyroidism. TGAb and TPOAb have been used for many years to diagnose Hashimoto's thyroiditis. Their diagnostic importance is well known.

The histological findings (presence or absence of Hashimoto's thyroiditis) and the values of TGAb and TPOAb were studied and compared in each patient. We obtained thyroid tissue around the thyroid nodule at surgical removal of thyroid nodule. When diffuse lymphocytic infiltration, fibrosis and/or epithelial cell destruction were histologically observed in thyroid tissues, definitive diagnosis of Hashimoto's thyroiditis was made. Blood samples were obtained just before the surgery to measure TGAb and TPOAb. TGAb and TPOAb were measured, using commercial kits (Cosmic Co., Tokyo, Japan). We studied sensitivity and specificity of TGAb and TPOAb measurements for the diagnosis of Hashimoto's thyroiditis. We studied the TGAb and TPOAb values and the histology in the surrounding thyroid tissues, obtained by surgical removal of the thyroid nodule. We performed receiver operating characteristic (ROC) curve analysis of TGAb and TPOAb measurements for diagnosis of Hashimoto's thyroiditis (definitive diagnosis of Hashimoto's thyroiditis was made on histology). ROC analysis of TGAb and TPOAb was performed on the basis of histology (FIGURE 1). We had studied 454 patients with thyroid adenoma. Histological examinations of the surrounding tissues were performed in all 454 patients. Of these 454 patients, 341 showed normal thyroid histology, but 113 showed Hashimoto's thyroiditis, characterized by diffuse lymphocytic infiltration, fibrosis and/or epithelial cell destruction. FIGURE 1 shows ROC analysis. High diagnostic efficiency was obtained at 1.6 U/ml in TGAb (sensitivity: 72.1%; specificity: 71.4%) and in TPOAb (sensitivity: 65.1%; specificity: 68.6%). For comparison, ROC analysis of TSH-binding inhibitory immunoglobulin (TBII) in Graves' patients is shown (FIGURE 2). High diagnostic efficiency was obtained at 10% with high sensitivity and high specificity (sensitivity: 95.7%; specificity: 98.7%). In both TGAb and TPOAb measurements, sensitivities and specificities were not so high. Patients with TGAb at least 2.6 U/ml and/or TPOAb at least 6.7 U/ml may be followed cautiously. We performed ROC analysis of TPOAb and TGAb values for the diagnosis of Hashimoto's thyroiditis. Definitive diagnosis of Hashimoto's thyroiditis was made on thyroid histology. Sensitivities of TGAb and TPOAb are not as high. TGAb and/or TPOAb are associated with Hashimoto's thyroiditis. Positive TGAb and/or positive TPOAb are suggestive of the presence of Hashimoto's thyroiditis. However, negative TGAb and negative TPOAb do not necessarily deny the presence of Hashimoto's thyroiditis.

Thyroid-function tests indicate the presence of hypothyroidism. The hypothyroid patients should be treated with L-T4. Euthyroid patients with positive TGAb and/or TPOAb do not require L-T4 therapy but require the evaluations of their thyroid-function tests, including T3 (free T3), T4 (free T4) and TSH once a year. We recommend measuring TGAb and TPOAb activities once a year. Subclinical hypothyroidism will be discussed later.

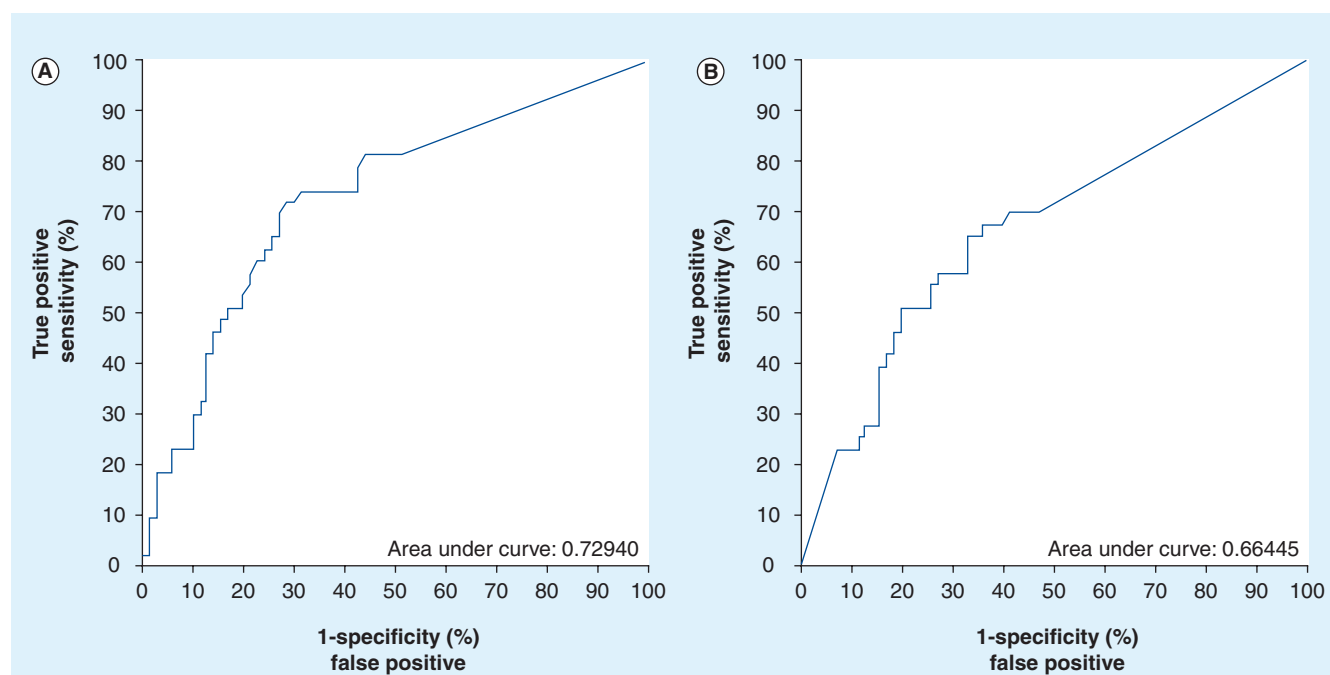


Figure 1. Receiver operating characteristic (ROC) curve analysis of (A) thyroglobulin antibody (TGAb) and (B) thyroid peroxidase antibody (TPOAb). The sensitivity and specificity of TGAb (A) and TPOAb (B) for the diagnosis of Hashimoto's thyroiditis are figured in the ROC curve. We performed ROC analysis of TGAb and TPOAb measurements for diagnosis of Hashimoto's thyroiditis (definitive diagnosis of Hashimoto's thyroiditis was made on histology). We have studied 454 patients with thyroid adenoma. Histological examinations of the surrounding tissues were done in these 454 patients. Of these 454, 341 showed normal thyroid histology but 113 showed Hashimoto's thyroiditis, characterized by diffuse lymphocytic infiltration, fibrosis, and/or epithelial cell destruction. High diagnostic efficiency was obtained at 1.6 U/ml in TGAb (sensitivity: 72.1%; specificity: 71.4%) and in TPOAb (sensitivity: 65.1%; specificity 68.6%). TGAb and TPOAb do not have high sensitivity or high specificity.

TSH receptor antibody, thyroid-stimulating antibody & TSH-stimulation blocking antibody

There are two types of TRAb; TSAb and TSBAb [4,44,59,60]. TSAb stimulates thyroid cells and causes Graves' hyperthyroidism. TSBAb blocks TSH stimulation of thyroid cells and causes hypothyroidism. Both TSAb and TSBAb block TSH binding to thyroid cells as TRAb, which have been measured as TBII [60]. TBII does not distinguish between TSAb and TSBAb. TBII reflects both TSAb and TSBAb activities and is measured by a radioreceptor assay.

TBII measures the binding of antibody to TSH receptors by competition with radiolabeled TSH. TSAb is measured as a stimulator assay, and TSBAb as a TSH-stimulation blocking assay. The former TRAb is a stimulating antibody (TSAb), and the latter TRAb is a blocking antibody (TSBAb) [61]. TSAb causes Graves' hyperthyroidism. TSBAb causes hypothyroidism.

TSAb activities are expressed as percentage of Graves' IgG-stimulated cAMP compared with that in the presence of normal IgG. TSAb is calculated as follows [61]; $TSAb (\%) = (a/b) \times 100$, where a: cAMP generated in the presence of test IgG and b: cAMP generated in the presence of normal IgG. Normal IgG does not stimulate cAMP synthesis. Thus, normal control values of TSAb distribute normally (mean: 100%; cut-off value: 180%).

TSBAb activities are expressed as percentage inhibition of bovine TSH-stimulated cAMP production by test IgG. TSBAb is calculated as follows [61]; $TSBAb (\%) = (1 - [c-b]/[d-b]) \times 100$, where b: cAMP generated in the presence of normal IgG, c: cAMP generated in the presence of test IgG and bTSH, and d: cAMP generated in the presence of normal IgG and bTSH. Normal IgG does not inhibit TSH-stimulated cAMP responses. Thus, normal control values of TSBAb distribute normally (mean: 0%; cut-off value: 40%).

We studied TSBAb and TSAb in 43 TSBAb-positive patients with hypothyroidism and in 55 untreated Graves' patients with hyperthyroidism [61]. TSBAb-positive patients with hypothyroidism (TSBAb-positive autoimmune atrophic thyroiditis) have very strong positive TSBAb (80–103%) and negative-to-very weakly positive TSAb (100–240%) (FIGURE 3) [61]. Their TSBAb activities are 80–103% (80–103% inhibition of TSH-stimulated cAMP response). Their TSAb activities are negative-to-very weakly positive.

In general, TSBAb-positive hypothyroid patients have very strong TSBAb (80–103% inhibition of TSH-stimulated cAMP responses) and Graves' patients have very strong TSAb (180–3000%). TSBAb-positive hypothyroid patients have very strong TSBAb (80–103% inhibition of TSH-stimulated cAMP responses) and negative-to-very weakly positive (100–240%)

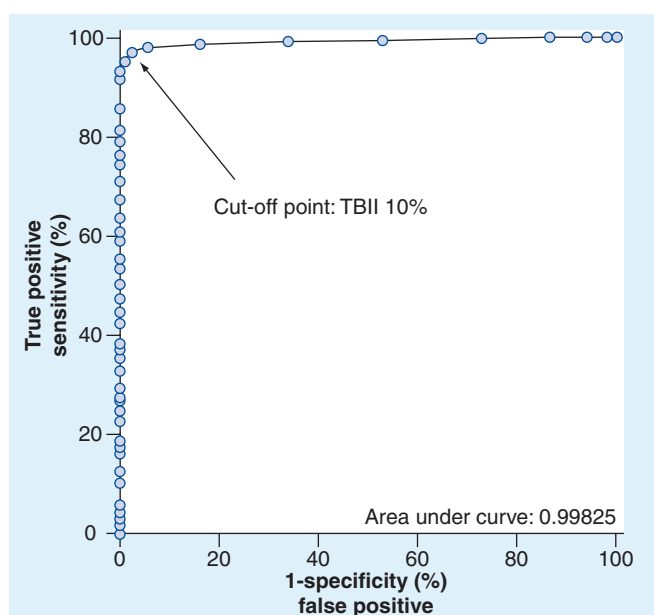


Figure 2. Receiver operating characteristic (ROC) curve analysis of TBII. The sensitivity and specificity of TBII for the diagnosis of Graves' disease are figured in the ROC curve. High diagnostic efficiency was obtained at 10% with high sensitivity and high specificity (sensitivity: 95.7; specificity: 98.7%). TBII: TSH-binding inhibitory immunoglobulin.

TSAb. Graves' patients have strongly positive TSAb and have negative-to-very weakly positive TSBAb. Some TSBAb-positive patients with hypothyroidism and some Graves' patients with hyperthyroidism may have both TSBAb and TSAb. However, it should be noted that TSBAb-positive patients with hypothyroidism have very strong blocking antibodies (80–103% inhibition of TSH-stimulated cAMP responses).

TRAb has been measured as TBII and TSAb [60]. TSAb is a bioassay using thyroid cells. TSAb activities are expressed as a percentage of Graves' IgG-stimulated cAMP compared with that in the presence of normal IgG. We usually measure TBII with a commercially available kit (R.S.R. Ltd., Cardiff, UK). The cut-off value for TBII was 10% [60]. We also measure TSAb using a commercially available kit (Yamasa, Chiba, Japan) [62]. The cut-off value for TSAb was 180% [62]. In Japan, a TSAb-assay kit is available [62] but a TSBAb kit is not. When a patient has hypothyroidism with elevated TSH levels and positive TBII, this TBII could be TSBAb. In a hypothyroid patient with positive TBII, we usually measure TSAb. If this TSAb-activity is not so high (less than 240%), we consider that this patient may have TSBAb. This patient has TSBAb-positive hypothyroidism (autoimmune atrophic thyroiditis). TSBAb activities could be measured, if indicated.

Patients may have both TSBAb and TSAb simultaneously or sequentially. Thyroid function can oscillate between hypothyroidism and hyperthyroidism as one or the other antibody becomes dominant (FIGURE 4) [60]. Predicting the course of disease in such individuals is difficult and they require close monitoring

of thyroid function. Bioassays (TSAb and TSBAb) can be used to document the changes of TRAb function [60]. TSBAb-positive patients with hypothyroidism have very strong TSBAb (80–103% inhibition of TSH-stimulated cAMP responses) [61] and are hypothyroid.

Practically, when a patient with hypothyroidism has positive TBII, this TBII may be TSBAb. When a patient with hyperthyroidism has positive TBII, this TBII may be TSAb. Assays that measure the binding of antibodies to the receptor by competition with radiolabeled TSH (TBII) do not distinguish between TSAb and TSBAb, but a positive TBII result in a patient with spontaneous hypothyroidism is suggestive of the presence of blocking antibodies (TSBAb). The use of these bioassays (TSAb and TSBAb) does not change clinical management; however, these bioassays are useful to detect transient neonatal hyperthyroidism and also to detect transient neonatal hypothyroidism [44]. These bioassays are important to confirm the causes of hyperthyroidism and hypothyroidism [61].

Laboratory evaluation

To evaluate thyroid function, we usually measure blood levels of T4 (free T4), T3 (free T3) and TSH. TSH is more sensitive than the others to detect hypothyroidism. A normal TSH level excludes primary (but not secondary) hypothyroidism. By definition, subclinical hypothyroidism refers to biochemical evidence of thyroid hormone deficiency (high TSH levels with normal free T4) in patients who have no apparent clinical features of hypothyroidism [63,64]. Typical patients with subclinical hypothyroidism may have slightly increased TSH levels (TSH 4.5–10 mU/l) [5]. Patients with overt clinical hypothyroidism have clinical symptoms and signs of hypothyroidism and decreased levels of serum T4 (free T4) and T3 (free T3), and increased levels of serum TSH (>10 mU/l).

Once overt clinical or subclinical hypothyroidism is confirmed, the etiology is usually easily established by demonstrating the presence of anti-thyroid antibodies (TGAb and TPOAb). Positive TBII can be found. This positive TBII may be blocking antibody (TSBAb). If there is any doubt regarding the cause of goiter associated with hypothyroidism, fine-needle aspiration biopsy can be done to confirm the presence of Hashimoto's thyroiditis.

Other abnormal laboratory findings in hypothyroidism may include increased creatine phosphokinase (CPK), and elevated cholesterol and triglycerides (hyperlipidemia). Elevated serum prolactin (PRL) levels might be observed. These abnormalities gradually resolve with L-T4-replacement therapy.

Diagnosis

Clinical manifestations of hypothyroidism have been described elsewhere [65]. Thyroid functions and thyroid antibodies should be evaluated in a patient with symptoms and signs of hypothyroidism, and also in a patient with goiter. To evaluate thyroid function, we usually measure blood levels of T4 (free T4), T3

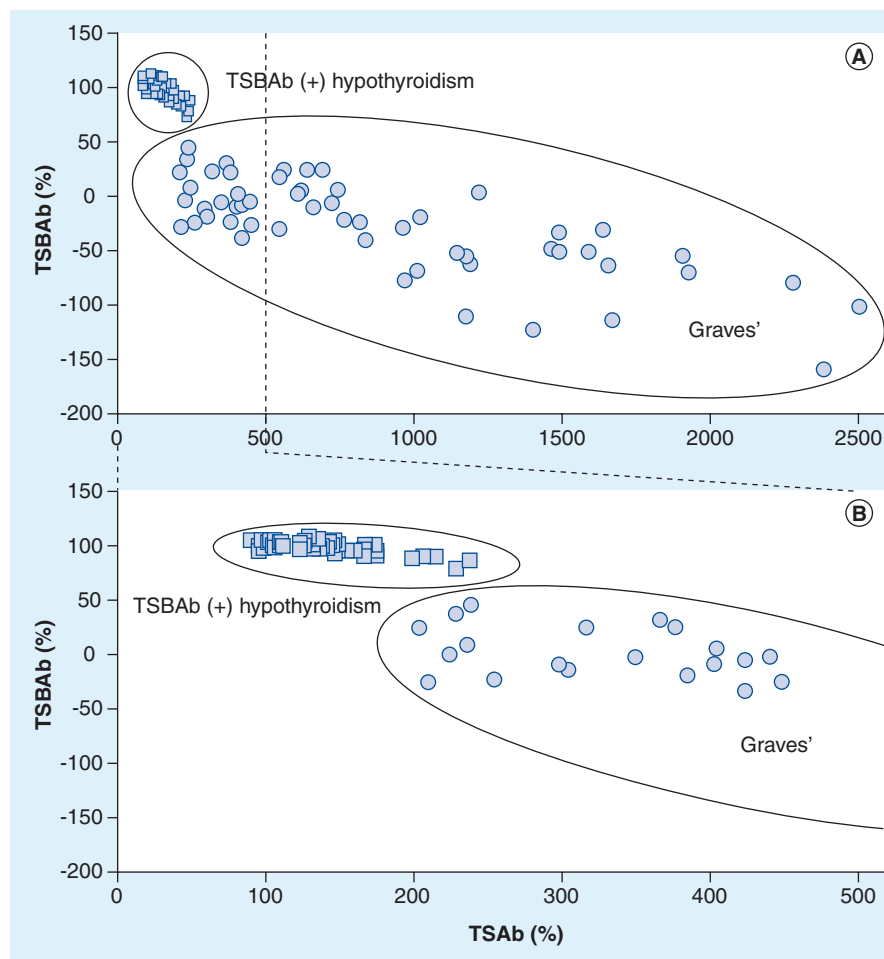


Figure 3. TSBAb and TSAb on 43 TSBAb-positive patients with hypothyroidism (squares) and 55 Graves' patients with hyperthyroidism (circles). (A) TSBAb and TSAb activity in 43 TSBAb-positive patients with hypothyroidism and 55 Graves' patients with hyperthyroidism. **(B)** TSBAb and TSAb activity of the 43 TSBAb-positive patients with hypothyroidism and 20 of the 55 Graves' patients, whose TSAb activity was less than 500%. All of the 43 TSBAb-positive patients with hypothyroidism (squares) had strongly positive TSBAb (75–103%, mean $\pm$ SD = $94 \pm 6\%$). Some of them had weakly positive TSAb (<240%).

TSAb: Thyroid-stimulating receptor antibody; TSBAb: Thyroid-stimulating hormone-stimulation blocking antibody.

(free T3), and TSH. TSH is more sensitive than the others to detect hypothyroidism. The patients with elevated TSH levels (10 mU/l TSH) usually have clinical symptoms and signs (overt clinical hypothyroidism). TGAb, TPOAb and TBII are thyroid antibodies. Positive TGAb and/or positive TPOAb suggest the presence of Hashimoto's thyroiditis. In autoimmune atrophic thyroiditis, TBII may be positive.

Treatment

Clinical hypothyroidism

Overt clinical hypothyroidism (TSH > 10 mU/l) should be treated with L-T4. The daily replacement dose of L-T4 is 1.5–2.5 μ g/kg bodyweight daily. It is usually 1.5 μ g/kg

bodyweight (75–100 μ g/day) daily, in Japanese individuals, and 1.7 μ g/kg bodyweight daily in the USA [66]. There is often some residual thyroid tissue and the replacement dose of L-T4 is less than 1.5–1.7 μ g/kg bodyweight daily.

Young-to-middle-aged adult patients without heart disease can be started on the maintenance dose of L-T4. The dose is adjusted on the basis of TSH levels. The goal of treatment is a normal TSH level (0.3–0.45 mU/l). Serum TSH levels change gradually and TSH response is usually delays. Serum TSH should be measured every month after instituting treatment or after any subsequent change in L-T4 dosage. Adjustment of L-T4 dosage is made in 25 μ g increments if the TSH is high; decrements of the same magnitude should be made if the TSH is suppressed. Patients with a suppressed TSH of any cause, including L-T4 overtreatment, have an increased risk of atrial fibrillation and reduced bone density; adjustment of L-T4 dosage is made in 25 μ g increments if the TSH is suppressed.

Elderly patients with heart disease may be started on a low dose of L-T4 (12.5–25 μ g/day), since maintenance doses of L-T4 may induce angina pectoris or myocardial infarction. Adjustment of L-T4 dosage is made in 12.5 or 25 μ g increments to obtain normal TSH levels.

Once full replacement is achieved and TSH levels are stable, follow-up measurement of TSH is recommended at every 3–6 months. It should be noted that some patients may recover from hypothyroidism spontaneously.

Schmidt's syndrome is an autoimmune polyglandular syndrome first used to describe patients with both Addison's disease (autoimmune adrenal insufficiency) and Hashimoto's thyroiditis (autoimmune hypothyroidism) [67]. Today, the term Schmidt's syndrome is used synonymously with autoimmune polyglandular syndrome type II to describe conditions of adrenal insufficiency occurring in conjunction with one or more of the following conditions; Type 1 diabetes, Hashimoto's thyroiditis, hypoparathyroidism (parathyroid hormone deficiency) or gonadal failure [67]. In patients with Schmidt's syndrome (Addison's disease and Hashimoto's thyroiditis), hydrocortisone should be administered first and then 1–2 weeks later, L-T4 could be administered. Adrenal crisis could be precipitated by T4 therapy in Schmidt's syndrome [68]. Hypothyroidism is a common condition. Rarely, it may occur

in combination with Addison's disease (autoimmune polyendocrinopathy syndrome type 2, previously known as Schmidt's syndrome). In such cases, T4 administration may precipitate adrenal failure. Clinicians should have a high index of suspicion for this condition in patients with Addison's disease, those with a family history of autoimmune endocrine gland failure, patients with one autoimmune endocrine disease who develop nonspecific or serious illness.

In pituitary hypothyroidism, hydrocortisone should be administered first, and then 1–2 weeks later L-T4 could be administered. The patients with pituitary hypothyroidism may have decreased adrenocorticotrophic hormone (ACTH) secretion and may have adrenal insufficiency. In the presence of adrenal insufficiency, administration of L-T4 may induce adrenal crisis.

Subclinical hypothyroidism

Patients with subclinical hypothyroidism can develop overt hypothyroidism, some continue to be in a subclinical hypothyroid state and the others regain a euthyroid state. They should be followed every 3 months. When patients progress to overt hypothyroidism (10 mU/l TSH), they should be treated by starting with a low dose of L-T4 (25–50 µg/day). The goal is to normalize serum TSH levels. When a patient continues to have subclinical hypothyroidism over 1 year, they should be treated by starting them on a low dose of L-T4 (25–50 µg/day), with the goal of normalizing TSH.

Subclinical hypothyroidism is relatively prevalent in the general population, especially among women and the elderly. The main cause of subclinical hypothyroidism is Hashimoto's thyroiditis. Several studies have demonstrated that subclinical hypothyroidism may affect both diastolic and systolic cardiac function. It may also worsen many risk factors for cardiovascular disease, including abnormal endothelial function, and elevated low-density lipoprotein cholesterol concentrations [69]. Furthermore, subclinical hypothyroidism may cause symptoms or progress to symptomatic overt hypothyroidism. Prompt treatment of subclinical hypothyroidism in pregnant women is mandatory to decrease risks for pregnancy complications and impaired cognitive development in offspring [70]. Children with subclinical hypothyroidism should be treated to prevent growth retardation [71]. Whether nonpregnant adult patients with subclinical hypothyroidism should be treated and at what TSH values is debatable [72].

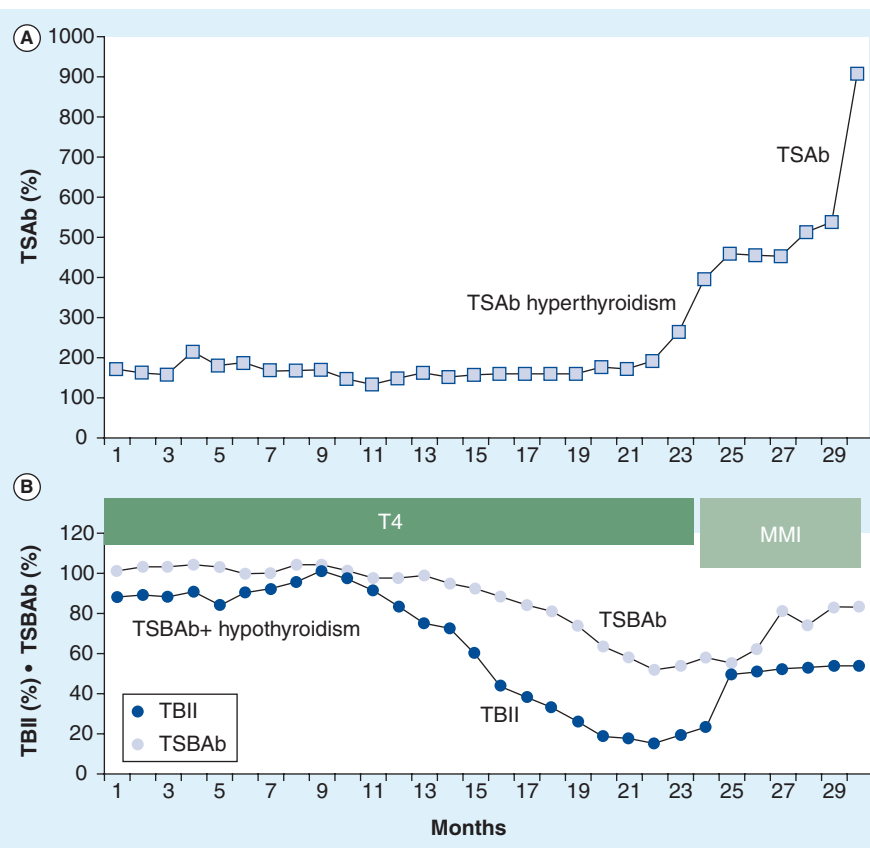


Figure 4. TSAB-positive hypothyroidism and then TSAb-positive Graves' hyperthyroidism. A 44-year-old woman with TSAB-positive hypothyroidism developed into TSAb-positive Graves' hyperthyroidism. MMI: 1-methyl-2-mercapto-imidazol; TBII: Thyroid-stimulating hormone binding inhibitory immunoglobulin; TSAb: Thyroid-stimulating antibody; TSAB: Thyroid-stimulating-stimulation blocking antibody.

Low-T3 syndrome is seen in severe illness. Low thyroid hormone concentrations, in particular low serum T3 concentrations, are a common finding in patients with severe illness (e.g., starvation, sepsis, surgery, myocardial infarction, bypass and bone marrow transplantation) [73]. Low-T3 syndrome is the most commonly encountered abnormality in severe illness. T3 levels fall rapidly within 30 min to 24 h of onset of illness, while rT3 levels increase [74]. TSH and total and free T4 levels are usually normal. Low-T3 syndrome is thought to be due to a decrease in T4 conversion to T3 by the hepatic deiodinase system. The finding of increased rT3 levels differentiates low-T3 syndrome from true hypothyroidism. In true hypothyroidism, rT3, T3 and T4 levels would be low. In patients who are moderately ill, low T3 levels are accompanied by low T4 levels. In patients with the most severe illness, low TSH, low T3 and low T4 levels may be observed. Although most of these patients have TSH levels at the low end of normal, some may have undetectable TSH. The finding of low TSH and low total T4 and T3 levels suggests altered pituitary or hypothalamic responsiveness to serum T3 and T4 levels. During the recovery period, serum TSH levels return to normal or may even rise transiently before returning to normal.

The role of low-T3 syndrome is not well understood. Low-T3 syndrome is an adaptive mechanism to preserve energy and a strong association between the T3-reduction and mortality has been demonstrated in hospitalized patients [75]. A highly significant increase in the incidence of deaths has been shown in patients with low T3 compared with patients with normal T3 levels. Whether patients with low-T3 syndrome should be treated with L-T3, is debatable.

Spontaneous recovery from hypothyroidism (reversible hypothyroidism)

Hypothyroid patients with Hashimoto's thyroiditis usually receive life-long L-T4 therapy; when a patient is diagnosed to have hypothyroidism due to Hashimoto's thyroiditis, they are recommended to take L-T4 for the rest of their life. However, we have reported spontaneous recovery from hypothyroidism in some patients with Hashimoto's thyroiditis [76]. We studied 92 patients with hypothyroidism due to Hashimoto's thyroiditis [76]. The diagnosis of Hashimoto's thyroiditis was made on histology. When patients with Hashimoto's thyroiditis, who had been taking L-T4 over years, discontinued L-T4, 70 patients developed hypothyroidism but the other 22 (24%) patients continued to be euthyroid. This indicates that these 22 patients, who had been taking L-T4 over years under the diagnosis of Hashimoto' hypothyroidism, recovered from hypothyroidism spontaneously. Hypothyroidism is therefore reversible in some patients with Hashimoto's thyroiditis.

Spontaneous recovery from hypothyroidism has been seen in patients with Hashimoto's thyroiditis in some occasions as follows.

Disappearance of TSH-blocking antibodies

Thyroid-stimulating hormone-blocking antibodies cause hypothyroidism. Patients usually do not have goiter, but have autoimmune atrophic thyroiditis. Patients with hypothyroidism due to TSBAb recover from their hypothyroidism with the disappearance of TSBAb [59]. Spontaneous recovery from hypothyroidism with the disappearance of TSBAb in autoimmune thyroiditis has been reported in Japan [59]. We have seen 72 patients who had TSBAb-induced hypothyroidism. The disappearance of TSBAb had been noted in 29 (40%) of the 72 patients with TSBAb-induced hypothyroidism; 18 (62%) of these 29 patients with TSBAb-disappearance had recovered from hypothyroidism. The other 43 (60%) of the 72 patients continued to have TSBAb and continued to have hypothyroidism. These 43 patients continue to have strong TSBAb and continue to have hypothyroidism. They continue to take L-T4. Spontaneous recovery from hypothyroidism is noted with the TSBAb-disappearance [59]. Hypothyroidism in some patients is due to TSBAb. TSBAb production may subside, producing remissions of hypothyroidism. TSBAb may cause transient as well as permanent hypothyroidism. Spontaneous recovery from hypothyroidism is noted with the TSBAb disappearance.

Exacerbation of autoimmune thyroid dysfunction after unilateral adrenalectomy in patients with Cushing's syndrome

Little is known about the factors that cause exacerbations of autoimmune thyroid dysfunction. Postpartum thyroiditis is exacerbation of Hashimoto's thyroiditis after delivery. However, the mechanism for the development of postpartum thyroiditis is not known. One possibility is an alteration in steroid hormone levels, since steroid hormones are known to alter both pituitary-thyroid and immunologic function. Exacerbation of autoimmune thyroid dysfunction after unilateral adrenalectomy in patients with Cushing's syndrome due to an adrenocortical adenoma is noted [77]. Glucocorticoids are known to alter immunologic function. We encountered three patients in whom overt ATD developed after unilateral adrenalectomy for Cushing's syndrome due to an adrenocortical adenoma. After unilateral adrenalectomy, one of the three patients had transient thyrotoxicosis and a low thyroid radioactive iodine uptake, indicative of silent thyroiditis. After the same surgical procedure, the second patient had hypothyroidism, whereas the third patient had transient thyrotoxicosis at first, and then hypothyroidism. All three patients had positive serum antithyroid antibodies (TGAb and/or TPOAb). We conclude that reductions in the secretion of glucocorticoid may exacerbate subclinical ATD. Patients with Cushing's syndrome due to adrenocortical adenoma, who have thyroid antibodies, should be followed closely after treatment, because thyroid dysfunction may develop. Exacerbations of autoimmune thyroid dysfunction were also noted after Hardy's operation in Cushing's syndrome with ACTH-producing pituitary adenoma [78].

Most patients recover spontaneously and no treatment is needed. Some may require L-T4-replacement therapy.

Postpartum thyroiditis

Postpartum thyroiditis is exacerbation of Hashimoto's thyroiditis after delivery [79]. Patients with postpartum thyroiditis may have thyrotoxicosis or hypothyroidism. They may have thyrotoxicosis initially and then hypothyroidism. Exacerbation of autoimmune thyroid dysfunction after unilateral adrenalectomy in patients with Cushing's syndrome [77] explains the exacerbation of Hashimoto's thyroiditis after delivery (postpartum thyroiditis). Postpartum thyroiditis has been shown to follow three sequential phases; thyrotoxicosis, hypothyroidism and recovery. The first phase, thyrotoxicosis, appears 1–3 months after delivery. During this time, the patients may have symptoms and signs of thyrotoxicosis; sweating, palpitation, insomnia and anxiety. Subsequently, approximately 3–6 months after birth, a phase of hypothyroidism appears. This is a slowing down of production by the gland and results in weight gain, sluggishness, and intolerance to cold. Postpartum thyroid dysfunction typically resolves without treatment when the mother's body goes through a recovery phase and returns to a normal thyroid

(euthyroid) state. Some believe that most patients recover spontaneously and no treatment is needed. It is when symptoms are significant and impair daily living that treatment should be considered. Symptoms of postpartum thyroiditis are goiter, dry skin, constipation, weight gain and cold intolerance, with goiter being the most common physical sign. Some hypothyroid patients with postpartum thyroiditis may require L-T₄-replacement therapy. Their thyroid functions recover spontaneously and they are, therefore, usually able to stop L-T₄.

Iodine-induced hypothyroidism

Iodine-induced hypothyroidism has been documented [23]. Iodine is an essential element for thyroid hormone synthesis. The thyroid gland has the capacity and holds the machinery to handle iodine in iodine deficiency as well as in iodine excess. In the latter situation, excess iodine acutely inhibits iodine organification [45]. This acute iodine effect on iodine organification is an effective means of rejecting the large quantities of iodide and therefore preventing the thyroid from synthesizing large quantities of thyroid hormones. This acute iodine-effect lasts for a few days to weeks and then, through the so-called escape phenomenon, the organification of intrathyroidal iodide resumes. The hypothyroidism is transient and thyroid function returns to normal in 2–3 weeks after iodide withdrawal, but transient L-T₄ replacement therapy may be required in some patients. Patients who develop transient iodine-induced hypothyroidism must be followed long term thereafter because many will develop permanent primary hypothyroidism.

Rifampin-induced hypothyroidism

Rifampin is often used to treat tuberculosis. We reported on three euthyroid patients with Hashimoto's thyroiditis who became frankly hypothyroid after the administration of rifampin [84,85]. Some drugs accelerate the clearance of T₄ from the bloodstream. They include rifampin, which is used to treat tuberculosis, and phenytoin and carbamazepine, which are used to treat epilepsy. In most people treated with these drugs, thyroid hormone secretion increases sufficiently to maintain normal serum T₄ concentrations. However, the hormone secretion may not increase enough in patients with thyroid disease. We described three patients with Hashimoto's thyroiditis in whom treatment with rifampin was associated with hypothyroidism. One case was of a 62-year-old man who was hospitalized because of cough (FIGURE 5). His serum TSH concentration was normal but he had positive TPOAb and positive TGAb. He was found to have pulmonary tuberculosis and was treated with rifampin. A total of 3 months after starting rifampin, his serum TSH concentration became high (170 mU/l) and his serum T₄ concentration became low. He was treated with L-T₄. After rifampin was stopped, L-T₄ was also stopped and he remained in a euthyroid state.

Hypothyroidism developed within 2 weeks following administration of rifampin in these patients but resolved in each once rifampin was discontinued. Rifampin increases T₄ clearance, possibly because of enhanced hepatic T₄ metabolism and biliary excretion of iodothyronine conjugates. Studies in normal volunteers indicate that rifampin decreases circulating thyroid hormone levels without affecting TSH levels, suggesting that rifampin has a direct downward effect on thyroid hormone levels. Rifampin-induced hypothyroidism is reversible [84,85].

Interferon-induced hypothyroidism

Thyroid disease is a frequent side effect of IFN therapy for HCV and other disorders [32]. Before patients undergo IFN therapy, we suggest that serum TSH, T₄ (free T₄), T₃ (free T₃), TGAb and TPOAb concentrations and perhaps a thyroid echography could be studied to identify pre-existing thyroid dysfunction and autoimmunity. Given the fundamental importance of IFN therapy in HCV patients, prior thyroid dysfunction is not a contraindication to the antiviral therapy. IFN treatment should be started after adequate correction of the existing thyroid dysfunction. During IFN treatment, measurement of serum TSH concentrations should be done every 2–3 months. This is adequate to identify patients with hypothyroidism. In patients developing hypothyroidism during IFN-treatment, L-T₄ should be administered, and IFN-therapy should be continued. At the termination of IFN therapy, L-T₄ therapy may be discontinued because hypothyroidism may be reversible. However, in some patients with positive TGAb and/or positive TPOAb, permanent hypothyroidism is more likely and, therefore, L-T₄ therapy must be continued. A re-evaluation of thyroid function should be performed 1 month after IFN discontinuation.

Other drugs

Bexarotene-induced hypothyroidism has been reported [86]. Bexarotene stimulates the peripheral metabolism of thyroid hormones. Increased peripheral degradation of thyroid hormones by a nondeiodinase-mediated pathway contributes to bexarotene induced-hypothyroidism.

Ethionamide was also reported to induce hypothyroidism [87]. Ethionamide is an antimycobacterial drug used as a second-line agent in the treatment of multidrug-resistant tuberculosis. It is structurally similar to methimazole and has been shown to inhibit thyroid hormone synthesis.

Unknown

Hypothyroid patients with Hashimoto's thyroiditis usually receive life-long L-T₄ therapy. Some are known to recover thyroid function. We have reported spontaneous recovery from hypothyroidism in the patients with Hashimoto's thyroiditis [76]. When 92 patients with Hashimoto's thyroiditis (diagnosis made on histology), who had been taking L-T₄ over years, discontinued L-T₄, 70 patients developed into hypothyroidism but the

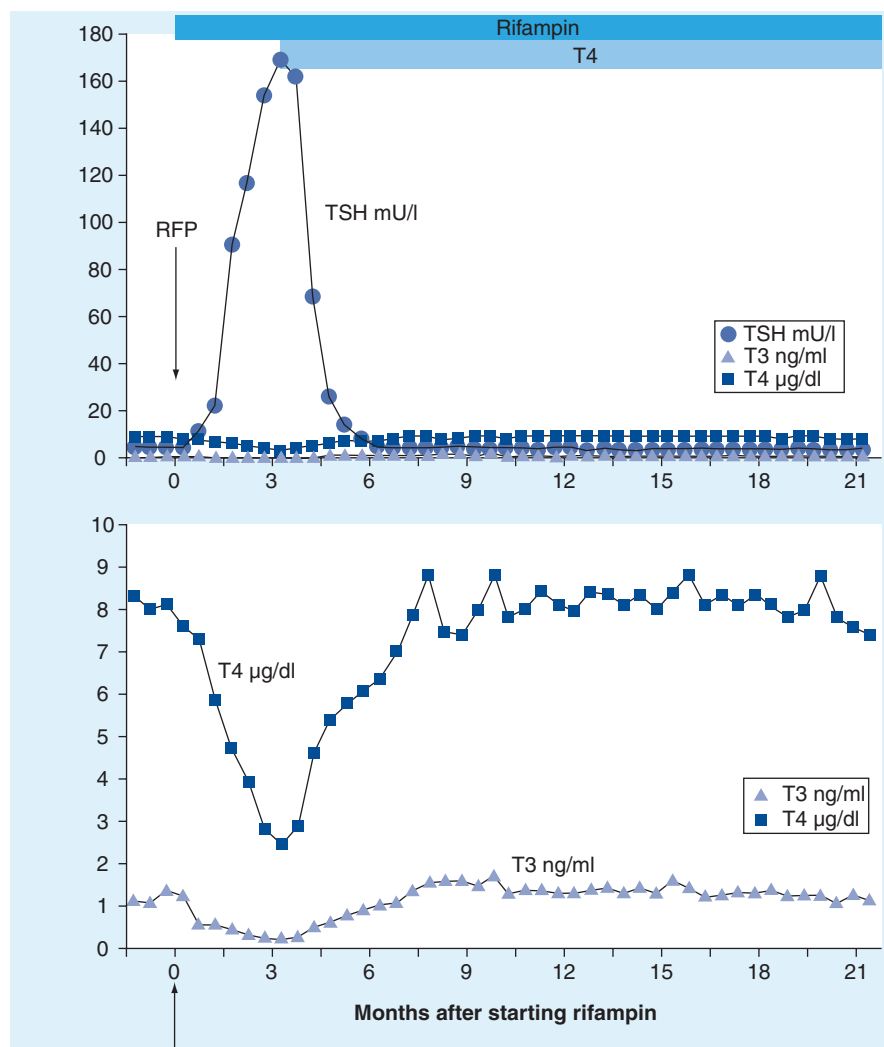


Figure 5. Rifampin-induced hypothyroidism. A 62-year-old man with lymphoma had pulmonary tuberculosis. After the administration of rifampin, he developed hypothyroidism (TSH 170 mU/l), and received. He had euthyroid Hashimoto's thyroiditis. Arrows indicate the time when rifampin was started (0 time). T3: Triiodothyronine; T4: thyroxine; TSH: Thyroid-stimulating hormone

other 22 patients continued to be euthyroid. This indicates that the 22 patients, who had been taking L-T₄ over years under the diagnosis of Hashimoto' hypothyroidism, recovered from hypothyroidism spontaneously.

Spontaneous recovery from hypothyroidism has been seen in the patients with Hashimoto's thyroiditis on some occasions. The 22 of 92 patients, who had been taking L-T₄ over years under the diagnosis of Hashimoto' hypothyroidism, recovered from hypothyroidism spontaneously [76]. In many cases, the mechanism of spontaneous recovery from hypothyroidism has not been known. In these cases, new mechanisms will be found. To study the mechanism of the spontaneous recovery from hypothyroidism will reveal new aspects of the development of Hashimoto's thyroiditis. Little is known about the factors that cause exacerbations of autoimmune thyroid dysfunction. These factors should be identified.

From Hashimoto's hypothyroidism to Graves' hyperthyroidism & vice versa

Hashimoto's thyroiditis and Graves' disease represent the two main types of ATD. The combination of these two is well known. However, occurrence of Graves' disease after primary hypothyroidism due to Hashimoto's thyroiditis is rare. We reported patients with hypothyroidism due to Hashimoto's disease, who had developed Graves' disease with hyperthyroidism [88]. We also reported one patient with hypothyroidism due to Hashimoto's disease who continued to be hypothyroid even in the presence of TSAb [88]. These patients were divided into several groups according to the changes in thyroid function and clinical course:

- Hyperthyroidism due to Graves' disease following hypothyroidism due to Hashimoto's thyroiditis (*vice versa*);
- Persistent hypothyroidism due to Hashimoto's thyroiditis, even in the presence of positive TSAb;
- Patients may have TSAb (Graves' hyperthyroidism) and TSBAb (hypothyroidism) sequentially and *vice versa* (FIGURE 4);
- Hashimoto's hypothyroidism (transient or permanent) and Graves' hypothyroidism (transient or permanent) and *vice versa*;
- And others.

Such changes in thyroid function and clinical course seem to be decided by four factors: TSAb activity; TSBAb activity; the responsiveness of the thyroid gland to TSAb and/or TSBAb; and the changes of the thyroid gland.

A patient had TSBAb during the hypothyroid state and TSAb during the hyperthyroid state, indicating that the alterations in the thyroid state were related to the balance between the activities of TSAB and TSBAB (FIGURE 4) [60]. Another patient continued to be hypothyroid despite the presence of TSAb [88]; his thyroid gland was not palpable and could not respond to TSAb.

In ATDs (Graves' disease and Hashimoto's thyroiditis, thyroid functions and clinical courses are decided by the four factors mentioned previously. TGAb and/or TPOAb have not been reported to inhibit thyroid function directly.

The relationship between Graves' disease and Hashimoto's thyroiditis has been debated for decades. Although initially considered to be two separate diseases, the present view is

that they might represent opposite sides of one disease. On the other hand, whole-genome scanning studies in humans have revealed distinct differences between loci linked to, or associated with, these two ATDs [89]. A role for Tregs in the natural progression of hyperthyroid Graves' disease to Hashimoto's thyroiditis and hypothyroidism in humans was reported [90].

Other recent topics

Low-grade systemic inflammation was reported to cause endothelial dysfunction in patients with Hashimoto's thyroiditis [91]. Association between hypothyroidism and small intestinal bacterial overgrowth was reported [92]. The history of overt hypothyroidism is associated with bacterial overgrowth development. Excess bacteria could influence clinical gastrointestinal manifestations.

Expert commentary

Hashimoto described four patients with goiter (struma lymphomatosa). The histology of the goiter was characterized by diffuse lymphocytic infiltration, fibrosis and epithelial cell destruction. Thyroid antibodies (TGAb and TPOAb) have been used to diagnose Hashimoto's thyroiditis. Patients with positive TGAb and/or TPOAb have been assumed to have Hashimoto's thyroiditis, and thyroid functions should be followed. Approximately 10% of the patients with positive TGAb and/or TPOAb have hypothyroidism.

There are two types of autoimmune thyroiditis: autoimmune goitrous Hashimoto's thyroiditis and autoimmune atrophic thyroiditis. The latter patients with autoimmune atrophic thyroiditis may have blocking antibody (TSBAb). This TSBAb is a TRAb. This TSBAb causes hypothyroidism. TGAb and TPOAb do not necessarily cause hypothyroidism.

Spontaneous recovery from hypothyroidism has been seen in patients with Hashimoto's thyroiditis in some occasions as follows:

- Disappearance of TSH-blocking antibodies (TSBAb)
- Exacerbation of autoimmune thyroid dysfunction after unilateral adrenalectomy in patients with Cushing's syndrome
- Postpartum thyroiditis
- Iodine-induced hypothyroidism
- Rifampin-induced hypothyroidism
- Unknown causes

Hashimoto's thyroiditis and Graves' disease represent the two main types of ATD. The combination of these two has been reported. Patients, who had Hashimoto's hypothyroidism and then Graves' hyperthyroidism (vice versa), have been also reported. Hashimoto's hypothyroidism and Graves' hyperthyroidism could be the opposite sides of one disease. In ATDs (Graves' disease and Hashimoto's thyroiditis), thyroid functions and clinical courses are decided by four factors:

- TSAb activity

- TSBAb activity
- The responsiveness of the thyroid gland (the destruction of the thyroid gland or its histological changes) to TSAb and/or TSBAb. TGAb and/or TPOAb have not been reported to inhibit thyroid function directly
- The changes of the thyroid gland

Five-year view

Hypothyroid patients with Hashimoto's thyroiditis usually receive life-long L-T4 therapy. When a patient is diagnosed to have Hashimoto' hypothyroidism, they are recommended to take L-T4 for the rest of their life. We have reported spontaneous recovery from hypothyroidism in the patients with Hashimoto's thyroiditis [76]. When 92 patients with Hashimoto's thyroiditis, who had been taking L-T4 over years, discontinued L-T4, 70 patients developed hypothyroidism but the other 22 patients continued to be euthyroid. This indicates that these patients, who had been taking L-T4 over years under the diagnosis of Hashimoto' hypothyroidism, recovered from hypothyroidism spontaneously. In many cases, the mechanism of spontaneous recovery from hypothyroidism has not been known. In these cases, new mechanisms will be found. To study these cases will reveal new aspects of the mechanisms of the development of Hashimoto's thyroiditis. Little is known about the factors that cause exacerbations of autoimmune thyroid dysfunction. These factors should be identified.

Over 20% of patients with hypothyroidism after Hashimoto's thyroiditis may recover satisfactory thyroid function, and can be identified during L-T4 treatment by their thyroid response to TSH in a TSH-releasing hormone (TRH) test [76]. However, TRH tests is difficult to perform. Now we are trying to find the patients with Hashimoto's thyroiditis, who recover from hypothyroidism spontaneously using other methods. One method is to decrease the replacement doses of L-T4 to 50 µg/day. Then we measure serum TSH levels at 1 month after the L-T4 decrease to 50 µg/day. If serum TSH levels continue to be normal, the patient can discontinue L-T4. If serum TSH levels increase over 4 mU/l, the patient cannot discontinue L-T4 and continue to take maintenance doses of L-T4.

Another issue may be how to prevent the development of Hashimoto's thyroiditis. Hashimoto's thyroiditis is caused by a combination of genetic and environmental factors. People with certain immune and organ-specific genes are predisposed to developing ATDs when they are exposed to certain environmental triggers. Iodine deficiency, iodine excess, lithium, selenium deficiency, cigarette smoke, sex steroids, trauma, IFN-α, infection with *Yersinia*, ATL virus and other viruses, iodine-rich medications, such as amiodarone, and iodine contrast dyes may be environmental triggers. We should be aware of these facts. However, it is most important to follow the patients with Hashimoto's thyroiditis. It is easy to treat hypothyroidism.

It is also important to diagnose patients with Hashimoto's thyroiditis. We recommend that every individual should have annual physical and laboratory examination, as in Japan. Physical examination will reveal the goiter. Annual examination should include serum TSH and T4 measurements. Early diagnosis and early treatment are required. Hashimoto's thyroiditis is not a serious disease, as long as it is diagnosed early and treated properly.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- The histology of Hashimoto's thyroiditis is characterized by diffuse lymphocytic infiltration, fibrosis and epithelial cell destruction.
- Thyroid antibodies (thyroglobulin antibody [TGAb] and thyroid peroxidase antibody [TPOAb]) are positive in patients with Hashimoto's thyroiditis.
- Patients with goiter, who have positive TGAb and/or TPOAb, have been assumed to have Hashimoto's thyroiditis. Their thyroid functions should be followed. Approximately 10% of the patients with goiter, who have positive TGAb and/or TPOAb have hypothyroidism or will develop hypothyroidism.
- There are two types of autoimmune thyroiditis; autoimmune goitrous Hashimoto's thyroiditis and autoimmune atrophic thyroiditis. The latter patients with autoimmune atrophic thyroiditis may have blocking antibody (thyroid-stimulating hormone(TSH)-stimulation blocking antibody [TSBAB]). This TSBAb is a TSH-receptor antibody (TRAb).
- This TSBAb causes hypothyroidism, whereas TGAb and TPOAb do not necessarily cause hypothyroidism.
- It is important to find patients with Hashimoto's thyroiditis. Every individual should have annual physical and laboratory examination. Annual examination should include serum TSH and thyroxine (T4) measurements.
- Spontaneous recovery from hypothyroidism has been seen in the patients with Hashimoto's thyroiditis on some occasions as follows: disappearance of TSBAb; exacerbation of autoimmune thyroid dysfunction after unilateral adrenalectomy in patients with Cushing's syndrome; postpartum thyroiditis; iodine-induced hypothyroidism; rifampin-induced hypothyroidism and unknown causes.
- Hashimoto's thyroiditis and Graves' disease represent the two main types of autoimmune thyroid disease. The combination of these two has been reported. Patients who had Hashimoto's hypothyroidism and then Graves' hyperthyroidism and *vice versa*, have been also reported. Hashimoto's hypothyroidism and Graves' hyperthyroidism could be opposite spectrums of one disease.
- In autoimmune thyroid diseases (Graves' disease and Hashimoto's thyroiditis), thyroid functions and clinical courses are decided by four factors: TSAb activity; TSBAb activity; the responsiveness of the thyroid gland (the destruction of the thyroid gland or its histological changes) to TSAb and/or TSBAb; and the changes of the thyroid gland.

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