

# Hashimoto's Thyroiditis in Children and Adolescents

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## 1. Introduction

Hashimoto's thyroiditis (HT) is an autoimmune disease with genetic background. It is also named as autoimmune thyroiditis or chronic lymphocytic thyroiditis. Hashimoto's thyroiditis is the most common cause of thyroid diseases in children and adolescents and it is also the most common cause of acquired hypothyroidism with or without goiter. Hashimoto's thyroiditis was first described in 1912 by Hakura Hashimoto in a series of patients with diffusely enlarged, firm thyroid glands with distinct pathologic features, classified as chronic lymphocytic thyroiditis (1). The characteristic histologic features include diffuse lymphocytic infiltration, atrophic follicles, well-developed germinal centers, and fibrosis.

Hashimoto's thyroiditis is the most important cause of hypothyroidism in children and adolescents. In an American population with age between 11 and 18 years, five new cases were detected out of 1,000 adolescents screened every year. It is more common among girls, varying from 4:1 to 8:1 depending on the geographical region. Although the disease can be seen before three years of age, it is usually seen after six years of age and its peak ages are 10 and 11 years (2). The prevalence of Hashimoto's thyroiditis between 6-18 years old is 3% in Japan. Thirty-40% of the cases have familial history of thyroid disease. It occurs far more often in women than in men (between 10:1 and 20:1), and is most prevalent between 45 and 65 years old.

Autoimmune thyroid disease (AITD) has two clinical forms: a goitrous form more common in young age groups, in whom goiter may be the only clinical expression (3), often referred to as classical Hashimoto's disease, and an atrophic one often called atrophic thyroiditis (4). Both are characterized by circulating thyroid autoantibodies and varying degrees of thyroid dysfunction, differing only by the presence or absence of goiter.

The prognosis is not known very well, and studies reporting about long-term outcome of the disease are scarce (3,5). Thyroid function tests show variations at the time of diagnosis; mostly euthyroid or hypothyroid and rarely hyperthyroid. Hypothyroidism is thought to be a permanent sequelae of HT. Patients with overt hypothyroidism may have been recommended lifelong levothyroxine (LT4) therapy but it should be checked after puberty if LT4 therapy is still necessary or not.

## 2. Etiology

Hashimoto's thyroiditis is influenced by both genetic and environmental factors (6). Family and twin studies support the evidence for genetic susceptibility (7-9). Dittmar et al. (10) have

shown the increased familial risk especially for the first-degree relatives and females. In particular, children and siblings of patients with Hashimoto's thyroiditis had a 32-fold and 21-fold increased risk, respectively, for developing immunthyroiditis. In comparison, the risk for developing Graves' disease has been enhanced 7-fold in both children and siblings (10). The high prevalence of AITD in first degree, foremost female, and relatives of patients with AITD demonstrates the importance of family history for developing AITD. This genetic susceptibility shows necessity of familial regular screening.

Candidate gene analysis, whole-genome linkage screening, genome-wide association studies, and whole-genome sequencing are the major technologies that have advanced this field, leading to the identification of at least seven genes whose variants have been associated with AITD (11). Using these techniques, 6 AITD susceptibility genes have been identified and confirmed, HLA-DR, CD40, CTLA-4, PTPN22, Thyroglobulin (Tg) and TSH receptor. The AITD susceptibility genes identified so far can be divided into two broad groups: immune modulating genes and thyroid specific genes. The first group includes the HLA-DR, CD40, CTLA-4, and PTPN22 genes, while the second group includes the Tg and TSH receptor genes (12). In our previous study, we have studied an association of three polymorphic markers of CTLA-4 gene, namely, C(-318)T, A49G, and (AT)<sub>n</sub> dinucleotide repeat, which is known the relation with Graves' disease and we reported that A49G polymorphism may increase the susceptibility for Hashimoto's thyroiditis (13).

It is clear that additional genes contribute to the genetic susceptibility to AITD, as well as to the different phenotypes of AITD, disease severity, and, possibly, response to therapy but HLA-DR and Tg genes have stronger relation with HT than the others (14).

Several environmental and non-genetic triggers have been implicated in the etiology of HT. These include smoking, stress, iodine excess, medications, bacterial, and viral infections, irradiation, pollutants, and pregnancy. The mechanisms by which certain environmental agents induce thyroid disease could involve interference with thyroid function, direct toxic effects on thyrocytes, or immune stimulation, as well as other effects. It is often difficult to directly link an environmental exposure with thyroid autoimmunity, as disease may be associated with a combination of factors and can manifest over a long period of time. When an environmental exposure triggers HT in individuals with pre-existing thyroid autoantibodies, this may indicate gene-environment interaction, as the presence of thyroid antibodies is usually a surrogate marker of genetic susceptibility (15).

### 3. Iodine

Iodine is one of the most important precipitants of thyroid dysfunction. Although essential for normal thyroid function, excess iodine supplementation can be associated with the onset of thyroid autoimmunity. Potential mechanisms by which iodine can induce autoimmunity in the thyroid include direct stimulation of immune responses to the thyroid, increased immunogenicity of highly iodinated Tg, and direct toxic effects of iodine on thyrocytes via free oxygen radicals generation (16). A few studies have demonstrated increased incidence of autoimmune thyroiditis in regions where iodine consumption is high according to regions with low consumption (16-18).

### 4. Selenium

Selenium is a trace element that plays an essential role in thyroid hormone synthesis, because two enzymes involved in thyroid hormone production are selenoproteins: the

deiodinases and glutathione peroxidase. Selenium influences the immune system probably by enhancing plasma glutathione peroxidase and thioredoxin reductase activity and by decreasing toxic concentrations of hydrogen peroxide and lipid hydroperoxides, resulting from thyroid hormone synthesis (19,20). A deficit of selenium results in increased intrathyroidal levels of hydrogen peroxide, which possibly increase the activity and immunogenicity of Thyroid Peroxidase (TPO) (21). Low selenium blood levels cause increased thyroid volume and thyroid hypoechogenicity, a marker for lymphocytic infiltration (22).

## 5. Medication

Several medications may play a role in the development of HT. Interferon- $\alpha$ , interleukin-2, lithium, amiodarone, and highly active antiretroviral therapy are the agents most commonly associated with thyroid dysfunction (23).

## 6. Infections

Several infections have been implicated in the pathogenesis of HT including *Helicobacter pylori*, *Borrelia burgdorferi*, *Yersinia enterocolitica*, Coxsackie virus, and retroviruses. Furthermore, recent studies but not all have substantiated a strong association between HT and HCV (24,25).

Seasonal and geographic variations also support infection as a trigger of HT (11,23). Various mechanisms have been proposed to explain induction of autoimmunity by infection but it seems that three possibilities may be important in individuals susceptible to developing autoimmune disease: molecular mimicry (perhaps to retroviruses); polyclonal T cell activation (by an endogenous superantigen or an infecting organism); and MHC class II antigen induction (26). Although infections may promote HT, they can also be partially protective, as suggested by the hygiene hypothesis. According to this hypothesis, the immune system builds tolerance to repeated infectious exposures, and this may explain a lower prevalence of thyroid antibodies in those of lower socioeconomic class (27).

### 6.1 Environmental toxins

Many environmental pollutants, such as polyaromatic hydrocarbons, perfluorinated chemicals, phthalates, and bisphenol A, have been shown to be toxic to thyroid cells and promote the onset of HT (15). These chemicals are widely used in various industrial and consumer products and may specifically have thyroid-disrupting properties (28,29). Polyaromatic hydrocarbons, including polychlorinated biphenyls and polyhalogenated biphenyls, are organic compounds produced from coal and found in air and water, and they can possibly trigger thyroiditis. Polyhalogenated biphenyls are commonly used compounds in products including adhesives, lubricants, and flame retardants, while polychlorinated biphenyls are found in plasticizers. A high prevalence of hypothyroidism was observed in individuals exposed to polyhalogenated biphenyls with an associated elevation in antimicrobial antibodies and anti-Tg antibodies (30). In view of the evidence that many of these chemicals can interfere with thyroid function, there is a growing concern about their effects on neurological development during embryonic life (15,29). Exposure during pregnancy, for example, which itself is a risk factor for HT, can have hazardous effects on the developing fetus in which normal thyroid hormone levels are crucial for normal growth

and brain development. It is important, therefore, to be aware of environmental triggers of HT and to monitor thyroid functions closely in susceptible women during pregnancy (15,23).

## 7. Pathogenesis

The activation of CD4 T-lymphocytes specific for thyroid antigens is believed to be the first step in pathogenesis. Once activated, self-reactive CD4 T cells recruit cytotoxic CD8 T cells as well as autoreactive B cells into the thyroid. T cells play a crucial role in disease pathogenesis by reacting with thyroid antigens and secreting inflammatory cytokines. Besides the others, mutations in the Tg gene and CTLA-4 are associated with HT (31,32).

The three main targets of thyroid antibodies are Tg, TPO, and the TSH receptor. It is believed that these autoantibodies are secondary to thyroid follicular cell damage induced by T cells. Anti-TPO antibodies have been shown to inhibit the activity of the enzyme *in vitro*, but direct cytotoxicity by CD8 T cells is believed to be the main mechanism of hypothyroidism *in vivo*. Thyroid peroxidase is the major autoantigen and autoantibodies to TPO are closely associated with disease activity. Although this has not been proven in children, Anti-TSH receptor antibodies of the blocking type may contribute to hypothyroidism in a minority of adult patients with the atrophic form of autoimmune thyroiditis. Histologically, HT is characterized by diffuse lymphocytic infiltration with occasional germinal centers. Thyroid follicles may be reduced in size and contain sparse colloid. Individual thyroid cells are often enlarged with oxyphilic cytoplasm. In contrast, the gland of atrophic autoimmune thyroiditis is small, with lymphocytic infiltration and fibrous replacement of the parenchyma (5).

## 8. Clinical manifestation

Hashimoto's thyroiditis is one of the most common organ specific autoimmune diseases (33). Weetman (34) reported clinical HT prevalence rate at 1 in 182 or 0.55% in the US. In the UK, Tunbridge et al (35) reported an overall HT prevalence of 0.8%. However, diagnosis based fine needle aspiration biopsy study; the cytology of HT seems to be much more prevalent, at 13.4% (36). This difference may be partially explained by the fact that for diagnosing clinical HT, abnormally elevated TSH, low thyroid hormones (34,35) and the confirmatory presence of thyroid autoantibodies are usually accounted for.

The most common clinical manifestations are goiter and hypothyroidism related findings. The goiter may appear insidiously and may be small or large. In most patients, the thyroid is diffusely enlarged, firm, and nontender. In about 30% of patients, the gland is lobular and may seem to be nodular (37). Most of the affected children are clinically euthyroid and asymptomatic; some may have symptoms of pressure in the neck. Some children have clinical signs of hypothyroidism, but others who appear clinically euthyroid have laboratory evidence of hypothyroidism. A few children have manifestations suggestive of hyperthyroidism, such as nervousness, irritability, increased sweating, and hyperactivity, but results of laboratory studies are not necessarily those of hyperthyroidism (37). In one study from iodine replete area with 140 patients with HT, the most common complaint was goiter (55%). Upon admission, 18.6% of patients had complaints related to hypothyroidism (7.4% growth retardation, 4.9% weight gain and 6.3% other complaints related to hypothyroidism). Eighteen patients (11.1%) were diagnosed incidentally upon detection of

goiter during routine examination (38). Staii et al. reviewed 761 patients for which ultrasound guided thyroid fine needle aspiration biopsy were performed for nodule. The HT cohort consisted of 102 (13.4%) patients (659 out of 761 did not have cytological Hashimoto's diagnosis) for which 46 (6%) were identified as having clinical disease (i.e. diagnosed hypothyroid on thyroid hormone replacement and with cytological Hashimoto's diagnosis), 9 (1.2%) as having subclinic hypothyroidism and 47 (6.2%) as having euthyroid autoimmunity (36). Occasionally, the disorder may coexist with Graves's disease. Ophthalmopathy may occur in lymphocytic thyroiditis in the absence of Graves's disease. Hashimoto's encephalopathy is a rare condition and the estimation of incidence and prevalence is difficult. One prospective study examining cases of unexplained encephalopathy that had detectable antithyroid antibodies, estimated a prevalence of 2.1/100 000 subjects (39). Adequate information is not available about the frequency of Hashimoto's encephalopathy in children (40). The clinical picture of a relapsing and remitting encephalopathy in a female characterised by seizures, stroke-like episodes, neurological signs such as myoclonus and tremor, cognitive disturbance and hallucinations, and other psychotic symptoms is highly suggestive of Hashimoto's encephalopathy (41). Normal routine investigations, nonspecific neuroimaging and CSF findings (apart from elevated protein), and encephalopathic EEG can be supportive of the diagnosis. Thyroid hormone studies are not helpful, but may identify subclinical thyroid dysfunction (41). Detection of antithyroid (in particular anti-TPO) antibodies confirms the diagnosis. As anti-TPO antibodies are detected in as many as 10 % of the general population, (42) high titres (usually over 100-fold normal (43)) of these antibodies in conjunction with the clinical features of Hashimoto's encephalopathy are necessary before a diagnosis can be made. Thyroid antibody levels should be measured even in the setting of normal thyroid function and the diagnosis of Hashimoto encephalopathy has to be considered in patients with Down syndrome who present with rapid cognitive decline, particularly in association with myoclonus and an abnormal EEG result (44). Corticosteroid responsiveness can also support the diagnosis (45).

## 9. Related disorders

HT may be the initial presentation of an autoimmune polyglandular syndrome, and the possibility of coexisting autoimmune diseases such as type I diabetes, celiac disease, Addison's disease, and pernicious anemia must be addressed by the past medical history (46). In a study performed on 268 children with type I diabetes mellitus, the percentage of those who presented with circulating thyroperoxidase and Tg antibodies was significantly higher than those with celiac disease (47). In another study performed in Bratislava, 40-50% of patients with different types of diabetes had autoimmune thyroiditis (48). The incidence of histologic findings of autoimmune thyroid disease in diabetic patients increases with age (49). Several other studies have confirmed the coincidence of autoimmune thyroiditis and latent or overt diabetes (50) and relatives of patients with type I diabetes have an increased incidence of HT (51). In a recent study, genetic susceptibility between autoimmune thyroiditis and diabetes was investigated among 448 individuals. Three loci in chromosomes 2q, 6p and Xp were identified (52).

Hashimoto's thyroiditis sometimes may be associated with connective tissue, cutaneous, hematologic (pernicious anemia, idiopathic thrombocytopenic purpura), gastrointestinal (autoimmune liver disease, celiac disease), genetic (autoimmune polyglandular syndrome

type II/III, ovarian failure, Down syndrome, Klinefelter's syndrome, Turner's syndrome), infectious (Hepatitis C infection), neurologic (Miller Fisher syndrome, Guillain-Barre' syndrome, multiple sclerosis, myasthenia gravis) and renal diseases (minimal change glomerular disease) (53).

The coexistence of papillary thyroid carcinoma and HT is not known exactly, but it is reported to range from 10% to 58% in various studies (54,55). The prevalence of HT in patients with papillary thyroid carcinoma has been reported to be significantly higher than with benign thyroid tumours (56). Patients with HT are suggested to be at higher risk for papillary thyroid carcinoma compared with patients without HT (57)

## 10. Laboratory findings

Although the level of TSH may be slightly or even moderately raised in some individual's thyroid function tests are often normal, termed subclinical hypothyroidisms (37). In a study from iodine-replete area, twenty-four patients (21%) were euthyroid, 48 (42%) had compensated hypothyroidism, and 42 (37%) had hypothyroidism (including two patients with transient hyperthyroidism reversed to hypothyroidism within weeks). There was no difference in clinical symptoms of hypothyroidism by thyroid status, except for a higher rate of constipation in the hypothyroid group (38). The fact that many children with lymphocytic thyroiditis do not have elevated levels of TSH indicates that the goiter may be caused by the lymphocytic infiltrations or by thyroid growth-stimulating immunoglobulins.

In normal individuals, positive anti-TPO were detected in  $13.0 \pm 0.4\%$ , and positive Anti-Tg was detected in  $11.5 \pm 0.5\%$ . The prevalence of positive antibodies was lower in the disease-free population: Anti-TPO,  $11.3 \pm 0.4\%$  and Anti-Tg,  $10.4 \pm 0.5\%$ . The prevalence of positive Anti-TPO and positive Anti-Tg in the total and disease-free population was higher in females than males ( $P < 0.001$ ) and increased with age, especially among females. Approximately 18% of the disease-free population had detectable Anti-Tg or Anti-TPO of those with positive Anti-Tg, 69.9% also had positive Anti-TPO; and of those with positive Anti-TPO, 54.5% also had positive Anti-Tg. Anti-TPO was positive alone in 4.4%, and Anti-Tg was positive alone in 3.4%. Anti-TPO and Anti-Tg were detected together in 6.9% (59).

Almost all young children with HT have serum antibody titres to TPO, but the anti-Tg test for thyroid antibodies is positive in fewer than 50%. Antibodies to TPO and Tg are found equally in adolescents with HT. When both tests are used, approximately 95% of patients with thyroid autoimmunity are detected. Levels in children and adolescents are lower than those in adults with HT, and repeated measurements are indicated in questionable instances because titres may increase later in the course of the disease (37). Results about decreasing Anti-TPO under LT4 treatment have been found variable with 10% and 90% after a follow-up of 6 to 24 months (60,61). Decreasing Anti-TPO under LT4 treatment appears to depend on time, a 45 % decrease after 1 year and a 70% decrease after 5 years (62).

## 11. Imaging

Thyroid ultrasonography is a useful tool to support the diagnosis, and classical sonographic findings are present in 20-95% of affected individuals (63). Furthermore, their presence is related to subclinical hypothyroidism and levels of thyroid autoantibodies (64,65), and ultrasonography has been used for the follow-up of patients (66). Thyroid ultrasonography is usually heterogeneous because of fibrosis and hypoechoic areas, it is not necessary for

diagnosis but it is recommended to confirm the presence of a thyroid nodule, solitary or multiple nodule can be detected both hypothyroid or euthyroid patients. During disease progression, reduced echo levels develop gradually, reflecting either reduction of colloid content and increased intrathyroidal blood flow or lymphocytic tissue infiltration, which induces diffuse fibrosis (64). The appearance of thyroid gland on ultrasonography may be normal at diagnosis, but characteristic changes evolve over time. Vlachopapadopoulou et al. studied 105 children, the time needed for 30%, 50%, and 70% of children to demonstrate an abnormal thyroid sonographic pattern has been detected 4, 7, and 14 months, respectively. Important factors accelerating sonographic changes have been demonstrated as goiter, hypothyroidism, and seropositivity for both anti-TPO and anti-Tg autoantibodies (67).

## 12. Diagnosis

Hashimoto's thyroiditis is diagnosed based on findings of seropositivity for Tg autoantibodies and/or TPO autoantibodies, accompanied by at least one of the following: abnormal thyroid function; enlarged thyroid gland; morphological changes on thyroid ultrasound. If anti-TPO antibodies are absent, less common etiologies of primary hypothyroidism should be considered for example transient hypothyroidism due to postsubacute thyroiditis, hypothyroidism related to external irradiation (69) and consumptive hypothyroidism due to the inactivation of thyroid hormone by the paraneoplastic expression of type III iodothyronine deiodinase, mostly in vascular tumors (70).

The typical patient with hypothyroidism secondary to HT has an elevated TSH, a low fT4, and positive anti-TPO antibodies. In early stages of the disease, TSH may be normal and anti-TPO antibodies may be positive with or without goiter. Later, TSH elevation becomes modest (5-10 IU/mL) with a normal fT4 (biochemical or subclinical hypothyroidism). Up to 90% of patients with hypothyroidism secondary to HT have positive anti-TPO antibody (46). If HT is suggested and thyroid autoantibodies are negative, they should be controlled later. It is possible to raise in follow-up.

## 13. Treatment

Most of these patients are asymptomatic, but studies in the adult population suggest that individuals with the combined risk factors of TSH level above the normal limit and positive thyroid antibodies (anti-Tg or anti-TPO) are at high risk for progression to overt hypothyroidism. For this reason, thyroid hormone replacement is recommended in all patients with TSH values >10 IU/mL or with TSH values >5 IU/mL in combination with goiter or thyroid autoantibodies (71). Levothyroxine is the replacement therapy of choice. There are almost no adverse reactions; its good intestinal absorption and its long half life of 5-7 days allow oral administration once a day. Although very rare, the development of pseudotumor cerebri associated with the initiation of LT4 has been described in a few school-age children (72). Alternatively, a starting dose can be estimated based upon the patient's age and ideal body weight (73). The medication's long half-life insures a gradual equilibration over the course of 5 - 6 weeks, and dosing should be individualized based on biochemical monitoring (73). TSH normalization (0.5-2 micro IU/mL) is the goal of replacement. This will usually be associated with an fT4 in the upper half of the normal range. Thyroid function tests should be obtained about 6-8 weeks after the beginning or next

adjustment of the LT4 dosage. Very high TSH levels at diagnosis can be associated with thyrotroph hypertrophy and gradual suppression over the first year of treatment (74,75). Once biochemical euthyroidism has been achieved, TSH can be monitored every 4-6 months in the growing child and yearly up to the attainment of final height. If poor compliance is suspected as the cause of treatment failure, FT4 should be measured.

Levothyroxine should be administered at least 20 min, before eating or ingestion of any medication known to impair its absorption, such as calcium and iron supplements, sucralfate, potassium-binding resins, antacids containing aluminium, and bile-acids binding resins. All other medications should be checked for interactions, particularly with antidepressants and seizure medications.

Growth and sexual development should be followed systematically as in any pediatric patient. Parents of children with HT should be advised that the hypothyroidism is likely to be permanent and monitoring of thyroid function for all patients should be life long. The prognosis for recovering lost linear growth depends on the duration of the hypothyroidism as well as the age at which treatment is started. If hypothyroidism is long-standing, thyroid replacement will not recover all lost stature. Similarly, if the diagnosis is made around puberty, there may be limited time for recovering the growth spurt before attaining final height. If the onset of childhood hypothyroidism occurs after age 3 years, no permanent intellectual damage or neurologic deficit is probable.

Surgical therapy for HT most commonly is recommended in case of malignancy or for relief of compressive symptoms in patients who develop a nodular or diffuse goiter. Patients may have an associated firm nodule in the thyroid gland and the thyroid gland may be adherent to adjacent structures with associated enlarged lymph nodes, mimicking thyroid cancer. Large goiter with HT can cause local compressive symptoms such as dysphagia, coughing or choking spells, dyspnea, and hoarseness that may require surgery for relief of compression (76). Thirty-two (15%) of 216 patients with HT were referred with thyroid enlargement and compressive symptoms; 25 (78%) had an associated nodule and 12 (38%) had retrosternal extension. Symptom resolution occurred in 30 (94%) and improvement occurred in 2 (6%) patients after total thyroidectomy in 21 (66%) and thyroid lobectomy in 11 (34%) patients. The only complication was transient hypocalcemia in 12 (38%) patients. One patient had an incidental thyroid lymphoma (77).

#### 14. Follow-up

Although a percentage of patients acquire hypothyroidism gradually within months or years, most children who are euthyroid at presentation remain euthyroid. Over several years, about half of children with subclinical hypothyroidism revert to euthyroidism, while the other half develops overt hypothyroidism. In a multicentre study Radetti et al. investigated the outcome of euthyroid children with HT and showed that 64.8% of them remained euthyroid, 9.5% progressed to subclinical hypothyroidism and 25.7% to overt hypothyroidism after 5 years (78).

Few studies have examined the spontaneous evolution of the disease (80,81). A recent Italian retrospective study described the outcome of 160 children affected with HT followed for up to 32.6 years in 20 pediatric endocrine clinics (78). In compatible with other reports (80,81), TSH concentrations have showed large fluctuations overtime. The presence of associated diseases has not worsened the prognosis, because at the end of the follow-up no difference has been found in the frequency of abnormally elevated TSH between the groups with or



without associated diseases. In agreement with previous findings in children (82,83) and in contrast with adults (84), the TSH level at baseline was not a useful marker to predict disease evolution. Both thyroid antibodies were significantly higher at the last visit in the group with deteriorating thyroid function; however, whereas anti-Tg antibodies were already higher at baseline, anti-TPO antibodies increased progressively with time. This finding suggests that anti-TPO antibodies might represent a marker of deteriorating thyroid function, in agreement with a previous report showing a good correlation between anti-TPO antibodies levels and lymphocytic infiltration of the gland (85). The evaluation of patients, according to their final outcome, revealed that subjects with deteriorating thyroid function had significantly higher anti-Tg antibodies, TSH concentrations, and greater thyroid volume at presentation. Nonetheless, these findings were not helpful in individual patients. On the other hand, it should be remarked that at 5 years of followup, more than 50% of the patients remained or became euthyroid. Ikemoto investigated 199 adult patients with HT and reported a recovery rate from hypothyroidism of 40% within 10.5 years of follow-up. In the same study elevated titres for thyroid autoantibody, age above 50 years and the presence of a stony-hard goitre were the best predictive factors for permanent hypothyroidism (86). In children the presence of predictive factors for permanent hypothyroidism are controversial. In the current study, initial TSH levels and thyroid volume at presentation, duration of levothyroxine therapy and anti-TPO Ab titre were not predictive for permanent hypothyroidism (79). Previously it was shown that iodine supplementation is associated with increased incidence of HT (87,88). In addition, it has been suggested that patients with HT are prone to develop hypothyroidism following iodine administration. Daily iodine supplementation over 1 mg has been shown to potentially contribute to underlying thyroid pathology in those with HT or Graves' disease. Exacerbation of nodularities in euthyroid individuals may occur if daily intake exceeds 20 mg iodine or iodide (89,90). It is usually offered a trial of LT4 therapy to adolescents, after the completion of growth and puberty. Thyroid function is retested 6–8 weeks after the stop of medication, to determine if hypothyroidism is permanent and potentially restart therapy.

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## **Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights**

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Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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