Thyroid autoimmunity

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Summary

This overview of the thyroid autoimmunity in human presents the various facets of a very common pathology. Focus is rather on fundamental than clinical aspects, although some specific clinical situations are discussed. Epidemiology, pathophysiology and pathology ofAITD are detailed. One of the peculiarities ofAITD is that they express two opposed phenotypes, hypothyroid thyroiditis and hyperthyroid Graves’ disease. The latter is characterised by the presence of a unique type of autoantibodies, the anti-TSH receptor antibodies. Those are capable to activate the TSH receptor leading to the gland hypertrophy and hyperfunction. On the contrary, the autoimmune thyroiditis processus progressively and slowly tends to the necrosis/apoptosis of thyroid cells and their functional impairment. Other forms of autoimmune thyroiditis, postpartum thyroiditis and silent thyroiditis are also described. This review, which is not exhaustive, aims at providing a wide scope on the AITD, a basis from which the interested reader or the specialist will be able to find routes towards deeper knowledge.

Autoimmune thyroid diseases (AITD) result from a deregulation of the immune system leading to an immune attack on the thyroid gland. AITD have several peculiarities. AITD are T cell-mediated organ-specific. In a given patient, the immune dysfunction often selectively affects the thyroid gland only. However, in many cases, AITD may be associated in the same individual with one or several other organ-specific autoimmune attacks such as in the case of type II autoimmune polyglandular syndrome (type II APS), an association more common than the one of AITD with systemic autoimmune syndromes. The more frequent association of AITD is with type 1 diabetes mellitus [1]. In human, AITD are the more common autoimmune disorders, affecting women...
predominantly. Also, together with nodules, AITD are the more frequent pathological conditions of the thyroid gland. Although appearing as a single pathologic entity, the AITD comprise two main clinical presentations: Graves’ disease and Hashimoto’s thyroiditis. Both conditions are characterized by lymphocytic infiltration of the thyroid parenchyma. In Graves’ disease, the infiltration is mild and induces the production of anti-TSH receptor antibodies that stimulate the growth and the function of thyroid follicular cells, ultimately leading to hyperthyroidism. In Hashimoto’s thyroiditis, the lymphocytic infiltration is more severe and causes the destruction of the thyroid follicles and subsequent hypothyroidism. It is a typical T cell-mediated autoimmune disease, characterized by the ectopic formation of tertiary lymphoid follicles within the thyroid gland.

**Historical vignette**

Is it pure hazard that the three publications which launched not only the concept but the experimental reality of thyroid autoimmunity appeared in the same year of 1956 [2]? These works came from three different places: University of Buffalo in the New York state, Oxford and London, and Dunedin, New Zealand. These researchers, N. Rose and E. Witebsky, I. Roitt, D. Doniach and their collaborators, and D. Adams and H. Purves, discovered respectively the existence of experimental or spontaneous auto-reactivity of the organism against the thyroid, as well as the first hints about what would come to be known, after many years of hard research work, as the stimulating anti-TSH receptor antibodies (TRAB). H. Purves had been on the trail of a circulating thyroid stimulator in Graves’ disease since 1948. Despite the long way covered since that time, it is clear that AITD, as well as autoimmunity, still hide much to be discovered and understood, a stimulating challenge for the present generation.

**Epidemiology of autoimmune thyroid diseases**

AITD epidemiology has to be considered of public health significance. Since susceptibility to AITD appears to depend on genetic and environmental factors, it is clear that epidemiology may vary from area to area and from population to population. Unfortunately, geographical comparisons of the prevalence of AITD are not available so that only the results of selected studies can be recorded. Overall, the AITD affect up to 5% of the general population, [3,4]. The annual incidence of Graves’ disease in different populations living in areas of iodine sufficiency ranges from 0.22 to 0.27/1000 [5]. In a recent 3-year period exhaustive survey of 1,457,036 inhabitants in Sweden the incidence of Graves’ disease was 24.5/100,000 per year, with a female: male ratio of 3.4:1, and a peak age of 30–39 years [6]. The prevalence of hyperthyroidism in women is between 0.5 and 2%, 10 times more frequent in women than in men in areas without iodine deficiency where Graves’ disease is the leading cause of hyperthyroidism. In the Whickham study, one of the more informative, comprehensive and long-term epidemiologic survey of thyroid dysfunction, the prevalence of hyperthyroidism was 4.7/1000 women [3]. A prevalence of 1–2% of spontaneous hypothyroidism is generally observed in areas without iodine deficiency, more common in older women and 10 times more common in women than in men [7]. In the Whickham study, the prevalence of spontaneous hypothyroidism—resulting from lymphocytic thyroiditis—was 15/1000 in women, with mean age at diagnosis of 57 years, and less than 1/1000 in men [3]. As to the mean incidence of spontaneous hypothyroidism, it was 3.5/1000 in women and 0.6/1000 in men. Similar figures have been recorded in other geographical areas [5]. Interestingly, while a longitudinal study from the Mayo Clinic showed no significant change in the incidence of Graves’ disease over the 33 years (1935–1967) of the study [8] there was a significant increase in the incidence of Hashimoto’s thyroiditis during the same period. In contrast, another Swedish study found an increased incidence of Graves’ disease during the 1970/74–1988/90 period [9]. Therefore, environmental factors might affect differently Graves’ disease and lymphocytic thyroiditis expression as well as the expression of Graves’ disease in certain populations.

**Epidemiology of antithyroid antibodies**

Presence of thyroid antibodies is observed in up to 10% of the general population in the United States [4] and in approximately 25% of US women over 60 years of age [10]. The prevalence of high serum concentrations of thyroid antibodies varies according to race and ethnic background. In the third US National Health and Nutrition Examination Survey of persons 12 years of age or older, high serum concentrations of thyroid antibodies were present in 14.3% of whites, in 10.9% of Mexican Americans, and in only 5.3% of blacks [4]. The majority of subjects with measurable thyroid antibody concentrations have normal thyroid function. In studies in England, 10% of postmenopausal women with high serum thyroid antibody concentrations had subclinical hypothyroidism and 0.5% had overt hypothyroidism, although euthyroid patients with high serum thyroid antibody concentrations had progression to overt hypothyroidism at a rate of 2 to 4% a year [11]. In a 10-year prospective study conducted in Switzerland, high serum thyroid peroxidase antibody concentrations predicted the progression of subclinical hypothyroidism to overt hypothyroidism [12].

**Spectrum of the autoimmune thyroid diseases**

The various clinical presentations of AITD are listed in table 1 [13].
Table I
Presentation of the main types of autoimmune thyroid diseases (AITD)

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Thyroid gland: volume</th>
<th>Thyroid gland: function</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal thyroiditis</td>
<td>Variable</td>
<td>Normal or subclinical</td>
<td>P+++; presence of TAb; may progress to overt hypothyroidism</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>Nontender, firm</td>
<td>Normal or hypothyroid (overt or subclinical)</td>
<td>P+++; US: hypoechoic; presence of TAb; includes the “adolescent goitre”</td>
</tr>
<tr>
<td>Atrophic thyroiditis (primary myxoedema)</td>
<td>Atrophic</td>
<td>Hypothyroid</td>
<td>P+; presence of TAb</td>
</tr>
<tr>
<td>Postpartum thyroiditis</td>
<td>Small (nontender, firm)</td>
<td>Transient thyrotoxicosis and/or hypothyroid</td>
<td>P±; US: hypoechoic</td>
</tr>
<tr>
<td>Silent thyroiditis</td>
<td>Small (nontender, firm)</td>
<td>Transient hyperthyroid and/or hypothyroid</td>
<td>P+++; US: hypoechoic</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>Variable</td>
<td>Hyperthyroid</td>
<td>P++; presence of pathogenic anti-RTSH receptor Ab in addition to TAb; extrathyroidal manifestations: a systemic disease?</td>
</tr>
</tbody>
</table>

Modified from [13].
P: prevalence; TAb: thyroid autoantibodies; US: ultrasonography.

Focal thyroiditis is defined as the presence of spotty lymphocytic infiltration of the thyroid tissue usually fortuitously observed at pathology examination after thyroidectomy for thyroid nodule or multinodular goitre. The association of focal thyroiditis and thyroid papillary might have a physiopathological meaning. Spots of thyroid autoimmunity around thyroid nodules in multinodular goitre are frequent, even in areas of mild iodine deficiency. Focal thyroiditis may be observed in up to 40% of autopsies of women [14]. The marker of focal thyroiditis is usually the presence of circulating antithyroid antibodies. Table II shows the serum levels of anti-TPO-Ab in a group of 261 normal subjects selected as having no familial, personal and clinical history of thyroid disease and whose TSH and thyroid hormones were within the normal range [15]. Anti-TPO-Ab were positive in 14.91% of them, and in 6.1% at significant levels. In the latter group, female predominance, parity, mean TSH and circulating thyroglobulin (Tg) levels, either markers of susceptibility to thyroid autoimmunity or of functional impact on the thyroid, as well as the presence of anti-Tg antibodies (Tg-Ab), were significantly greater than in the two other groups [15].

Two variants of hypothyroid autoimmune thyroiditis have been identified: the atrophic variant described in the late 1890s by Ord as “dependent on a destructive affection of the thyroid gland” [16] and the hypertrophic variant, named Hashimoto’s disease after the author who described the pathology of this condition [17]. However, whether atrophic and goitrous thyroiditis are distinct diseases in terms of humoral and cellular immunity, involvement of antibody-dependent cell-mediated cytotoxicity or blocking TSH receptor antibody, is debated. Also, that the atrophic form be the end stage of Hashimoto’s disease does not appear as a rule. A recent study, on the contrary, suggests that in patients with primary autoimmune hypothyroidism, thyroid atrophy and goitre do not represent separate disorders [18]. Patients had a more dispersed distribution of thyroid volumes than controls, nearly all patients had thyroid autoantibodies, but titres were correlated with thyroid volume. No difference between groups was observed in prevalence of TSH receptor autoantibody. Patients with the smallest thyroid

Table II
Detection of anti-TPO antibodies in a group of 261 normal subjects without any familial and personal history of thyroid disease and selected on normal clinical and biological thyroid status

<table>
<thead>
<tr>
<th>Subjects’ characteristics</th>
<th>Anti-TPO-Ab (IU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Number</td>
<td>232</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>42.2</td>
</tr>
<tr>
<td>Female/Male</td>
<td>1</td>
</tr>
<tr>
<td>Parity</td>
<td>2.3</td>
</tr>
<tr>
<td>Mean TSH (mU/l)</td>
<td>1.20</td>
</tr>
<tr>
<td>Tg (μg/l)</td>
<td>10.3</td>
</tr>
<tr>
<td>Anti-Tg-Ab + (%)</td>
<td>6</td>
</tr>
</tbody>
</table>

From [15].
*P < 0.05 as compared to both “< 100” and “100–175” groups.
volumes were biochemically more hypothyroid at diagnosis. Therefore, the authors even propose to follow Davies’ suggestion to rename autoimmune thyroiditis Ord-Hashimoto’s disease [18,19].

Postpartum thyroiditis and silent thyroiditis are similar manifestations of autoimmune thyroiditis at the only difference of the context of pregnancy. The latter is much more uncommon than the former.

Postpartum thyroiditis is defined as the occurrence of de novo autoimmune thyroid disease, excluding Graves’ disease, in the first year postpartum [20]. The incidence of postpartum thyroiditis ranges from 1.1 to 18.2%, averaging about 5%. This incidence is about triple in type 1 diabetes patients. The clinical presentation of postpartum thyroiditis is variable. Classically, it follows a two-phase evolution: first, a transient destructive (or cytolytic) thyrotoxicosis one, 2–4 months postpartum, second, a transient hypothyroid one 6–8 months postpartum with, in most cases, spontaneous restoration of euthyroidism by the end of the first year postpartum. The biphasic presentation occurs in only 22% of the cases and other presentations include either isolated thyrotoxicosis (30%) or isolated hypothyroidism (48%) [20]. Postpartum thyroiditis is usually transient but permanent hypothyroidism is observed in 20–30% of women in the subsequent 5 years. Women positive for thyroid autoantibodies before or during the 1st trimester of pregnancy have a risk of 30–50% of developing postpartum thyroiditis. In essence, as stated by Muller et al., “…postpartum thyroiditis is ‘just’ an aggravation of an existing autoimmune thyroiditis after an amelioration of the inflammation during pregnancy…” [21]. In other words, the pre-existing thyroid autoimmune disorder is exacerbated along with the rupture of the relative immune tolerance state of pregnancy. It can be considered that the mechanism of some of the cases of silent thyroiditis arising as untoward effects of immunomodulating cytokine treatments is reminiscent of that of postpartum thyroiditis.

The presentation of spontaneous silent thyroiditis is typically biphasic, as that of postpartum thyroiditis, but often incomplete. The diagnosis, then, relies on the combination of a firm painless non-goitrous thyroid gland, hypoechogetic at ultrasonography, with lymphocytic infiltration would a fine needle biopsy aspiration be performed, low or absent thyroid uptake at scintigraphy contrasting with suppressed TSH in the absence of iodine contamination, and presence of circulating thyroid autoantibodies in the absence of signs of systemic inflammation. Graves’ disease contrasts sharply with the other presentations of AITD. Due to the unique presence of anti-TSH receptor autoantibodies (TRAb) capable of stimulating both the function and growth of the thyroid gland, the disease is characterised by hyperthyroidism and goitre. Extrathyroidal manifestations are also part of the disease, raising the issue of Graves’ disease as a systemic disease. These include Graves’ orbitopathy, present in more than 50% of the patients, frequent enough to be part of the typical presentation of the disease, a dermopathy in the leg area known as pretibial myxoedema, a relatively uncommon manifestation, and a very rare inflammation of the hands and fingers known as acropachy. However, links are obvious between Graves’ disease and lymphocytic thyroiditis as shown by their inheritance intertwining, the presence of thyroid antibodies in Graves’ disease, the occasional presence of TRAb in patients with thyroiditis, the observation of anecdotic cases of biphasic or even triphasic cases spontaneously shifting from hypo to active hyperthyroidism and, finally, the spontaneous evolution towards hypothyroidism of GD patients conservatively treated with antithyroid medication only.

Pathological characteristics of autoimmune thyroid diseases

Whatever the presentation of the AITD, the common pathological feature is the presence of lymphocyte infiltrates within the gland. Histologically, autoimmune thyroiditis is characterized by lymphocytic infiltration composed mainly of T cells that may progressively replace thyroid follicles. Lymphoid infiltrates are also present in Graves’ disease glands, but in this condition most of the thyroid remains intact except for the signs of hyperfunction. Most AITD glands contain typical secondary lymphoid follicles, large and tonsil-like in lymphocytic thyroiditis, smaller and lymph node-like in Graves’ disease [22]. Intrathyroidal secondary lymphoid follicles possess a mantle zone and well-formed germinal centres containing B cells with obvious signs of activity such as lymphoblasts in mitosis. The germinal centres appear in areas of heavy infiltration, but, alternatively, they may also be relatively isolated. Dendritic cells are present in the germinal centres and plasma cells are scattered all over the infiltrate. Specific aspects differ in thyroiditis and Graves’ disease. Variable thyroid follicular cell reduction and fibrosis are characteristic of thyroid atrophy while, in Graves’ disease, thyroid follicles are hypertrophied although antithyroid drug treatment may reverse completely the follicles mainly to a colloid appearance.

“Immunological partners’’ and consequences on the thyroid

Thyroid autoantigens

Although sera from patients with AITD may react with a number of antigens, specific or not, AITD involve three main thyroid antigens: Tg, thyroid peroxidase and the TSH receptor.

Thyroglobulin

Thyroglobulin (Tg) is a homodimeric 660-kDa glycosylated iodoprotein, synthesised by the thyroid follicular cells, transported to the apical pole of the cells. The Tg molecule is the matrix of the synthesis of the thyroid hormones. Among the 100 tyrosine residues of the molecule, about 1/4 are iodinated.
depending on iodine availability and functional activity. The Tg molecule provides spatial arrangement allowing the hormonogenic sites localised at each extremity of the molecule to interact at the apical pole of the cell with the iodination system (iodide-thyroid peroxidase-H2O2 generating system DUOAx2) to generate mono- and di-iodo-tyrosines and to complete the process through the intra-molecular iodo-tyrosine coupling to iodo-thyronines, tri-iodo- and tetra-iodo-thyronines (T3, T4 or thyroxine). The pro-hormone iodinated Tg, stored in the follicular colloid space, is subsequently internalised at the apical pole in order to undergo lysosomal proteolysis which frees T4 and T3 for secretion in the blood. Some Tg reaches the circulation through an unregulated passage grossly correlated with thyroid volume. It has been shown in animal models of thyroiditis that the level of iodination of the Tg molecule affects its antigenicity [13]. Although there is no direct proof for such a mechanism in human, the link between iodine status and prevalence of AITD (see below) might fit with this view, an interesting one as far as the question of the major antigen in AITD is concerned.

Tg-Ab preferentially recognize native Tg and a restricted range of conformational epitopes on Tg molecule; there are two major antigenic regions. One of them, region II, an immunodominant domain located in the central part of the human Tg molecule is principally recognized by anti-Tg-Ab from patients with Graves’ or Hashimoto’s diseases [23].

**Thyroid peroxidase**

**Thyroid peroxidase (TPO)** is a large (107 kDa) globular glycosylated haemoprotein which catalyses both the iodination of Tg and the coupling of the iodotyrosyl residues to generate the thyroid hormones T3 and T4. Human TPO (hTPO) is a 933 amino acid type I integral apical membrane protein that contains a large extracytoplasmic domain oriented towards the follicular lumen, a short membrane-spanning region, and a 61 amino acids cytoplasmic tail. The extracellular region consists of 848 amino acids and contains five potential glycosylation sites. hTPO is formed, from the N to the C-terminus, of three distinct domains: a myeloperoxidase (MPO)-like, a complement control protein (CCP)-like, and an epidermal growth factor (EGF)-like domain [23]. TPO-Abs recognise conformational epitopes. These epitopes are restricted to an immunodominant region consisting of two overlapping regions A and B [24]. Four distinct regions distributed between the MPO- and CCP-like domains have been identified and it has been shown that the MPO-like and CCP-like domains have to be close within the three-dimensional structure of hTPO to form an immunodominant binding surface recognized by the majority of TPO-Abs [25]. The majority of the human TPO-Abs are directed against the immunodominant region B [26] which might be the first immunodominant epitope generated during the development of AITD.

**TSH receptor**

The TSH-R, expressed on the basolateral membranes of thyroid epithelial cells, is the primary regulator of thyroid hormones synthesis thyroid and cell growth. It is a member of the G-protein-coupled receptor family with an extracellular domain of 398 amino acids with nine leucine-rich repeats and an N-terminal tail, a seven loop transmembrane domain of 266 amino acids and an intracellular domain of 93 amino acids [27]. The mature TSH-R contains two subunits A (55 kDa), extracellular, and B (40 kDa), transmembrane, joined by disulphide bonds [28]. The two subunits can be cleaved leading to the shedding of the A subunit from the cell surface, a characteristic which can have immunological consequences [29,30]. The TSH receptor has low-level extrathyroidal expression, notably in adipocytes, more specifically pre-adipocytes, which provides the basis for a current working hypothesis for the pathophysiology of the Graves’ orbitopathy.

TRAbs interact with highly conformational binding sites on TSH receptor. The precise description of the interaction of the TRAbs with the TSH receptor is still in progress as much concerning the comparison with that of TSH as the one between interaction modalities of stimulating and blocking TRAbs. One of the most recent salient contribution, taking advantage of the analysis of the crystal structure of the TSH receptor bound to a monoclonal stimulating TRAB or a blocking-type TRAB, has shown that the blocking autoantibody (K1-70) binds more N-terminally on the TSH receptor concave surface than either the stimulating autoantibody M22 or the hormone TSH, and this may reflect its different functional activity [31]. It is obvious that the elucidation of the modalities of interaction of the TRAbs with the TSH receptor will open new routes towards the emergence of differential assays for stimulating or blocking TRAbs and, possibly, innovative treatments of GD and Graves’ orbitopathy.

**T and B cell functions in autoimmune thyroid diseases**

**T cells**

It has been known for long that the number of CD8+ T cells is decreased in peripheral blood of patients with Graves’ disease, Hashimoto’s thyroiditis and postpartum thyroiditis, just as in patients with other autoimmune diseases. Consequently, the CD4/CD8 ratio is increased. Also, activated T cells expressing HLA-DR are increased. In the thyroid tissue, T cell infiltrates associate CD4+ and CD8+ cells, often in the activated state. CD4+ may be predominant in Hashimoto glands. No restriction of intrathyroidal T cell receptor V alpha/beta family gene usage could be observed in Hashimoto’s and Graves’ diseases, even in the activated T cell population [32]. This lack of clonality among committed activated intrathyroidal T cells indicates the occurrence of a prompt epitope spreading during the immune response, especially in the presence of multiple antigens.
The presence of circulating T cells reactive to the various thyroid antigens has been studied through proliferation or cytokine production experiments. Positive results have been obtained, but stimulation indexes are weak, as expected with blood cells. As to the pattern of cytokine production, studied either in cell cultures or in situ within the thyroid, no sharp picture has emerged. The trend for a Th1 pattern in Hashimoto’s thyroiditis has been confirmed, but a typical Th2 pattern is not so apparent in Graves’ disease.

The basic interaction remains the classical one which involves the ‘‘immunological synapse” between autoreactive T cells and antigen-presenting cells through appropriate MHC class II molecules with the help of the co-stimulatory molecules. InAITD, this interaction does not depart from the classical scheme. That γ-interferon stimulated thyroid cells express class II molecules is no longer understood as the initiating event in thyroid autoimmunity but either as a perpetuating phenomenon or, rather, as a T cell tolerance inducer since thyroid cells do not express co-stimulators [33,34].

**B Cells**

B cell numbers are normal in the blood circulation in AITD. As described above, B cells are found within the thyroid tissue, typically organised in secondary lymphoid follicles sometimes with germinal centres, especially in Hashimoto’s thyroiditis. Intrathyroid B cells have been shown to produce antibody spontaneously suggesting that the thyroid is the main source of the autoantibodies in vivo. Bone marrow and juxta-thyroid lymph node B cells are also a source of antibodies. In some cases, the sustained production of TRAB after the radical treatment of Graves’ disease with thyroidectomy and/or ablative dose(s) of radioactive iodine may represent a challenging difficulty in a patient planning a pregnancy, for instance. These cases raise the question of the site of the antibody production. The spectrum of the actions of B cells in autoimmunity, antigen presentation and cytokine production in addition to antibody secretion, has recently been challenged through the use of rituximab, an anti-CD20 monoclonal antibody that depletes B cells but not plasmocytes. In the thyroid field, some beneficial effects have been observed in Graves’ orbitopathy [35,36].

**Thyroid antibodies**

**Tg-Abs**

Although Tg could possibly represent a dominant or early antigen in the course of AITD, Tg-Ab diagnostic value is not as strong as that of TPO-Abs. Indeed, the prevalence of Tg-Abs in patients with Hashimoto’s thyroiditis is 25–50% as compared to 90% for TPO-Abs [14]. In the young patients with thyroiditis, however, in whom the prevalence of thyroid antibodies is less than in adults, Tg-Abs may be present in the absence of TPO-Ab.

In a prospective study of the spontaneous course of subclinical hypothyroidism Tg-Abs, contrarily to TPO-Abs, were not predictive of the occurrence of subsequent overt hypothyroidism [12]. Tg-Abs, predominantly IgG1 and 4, do not activate complement and are not pathogenic. However, it cannot be excluded that they might be involved, although much less than TPO-Abs, in mediating antibody-dependent cell-mediated cytolysis (ADCC). Independently of the AITD, low affinity IgM and IgG Tg-Abs appear to be present in normal subjects. These may be part of the “natural antibodies” with potential physiological role in body homeostasis including the scavenging of metabolic waste and senescent cells, a first line of protection against viral and bacterial infection and the control of autoimmune diseases [37,38]. Whether Tg-Abs often detected during the follow-up of patients with thyroid papillary carcinoma are “natural antibodies” is not settled. In these patients the presence of Tg-Abs in the circulation may interfere with the assay of Tg leading to false negative serum Tg determination. Tg-Abs will decrease and disappear in patients in complete remission. Thus, the persistence or reappearance of circulating Tg-Abs may be regarded as an ‘indicator’ of disease [39].

**TPO-Abs**

Formerly known as anti-microsomal Abs, TPO-Abs are a sensitive marker of AITD, both thyroiditis and Graves’ disease. TPO-Abs are markers of thyroid dysfunction [40]. Their presence is predictive of the subsequent occurrence of thyroid failure in subjects with subclinical hypothyroidism. In the context of pregnancy, prior to the onset of pregnancy or during the first trimester, they are predictive of the risk of postpartum thyroiditis. TPO-Abs may be involved in thyroid cell necrosis through either complement dependent cytotoxicity or the ADCC-natural killer cell mechanism [41,42]. However, it is of general observation—and this should be made clear to pregnant women—that whatever the pathogenic potential of Tg- or TPO-Abs neither are harmful to the foetal thyroid.

**TRAb**

TRAbs are the hallmark of Graves’ disease. These autoantibodies are pathogenic. Indeed, the stimulating TRAbs are responsible for the hyperthyroidism of Graves’ disease. TRAbs are present in more than 90% of the patients. However, about 5% of patients with authentic Graves’ disease, even positive for TPO-Abs, are TRAb-negative. A prospective study has shown these patients to have biochemically less severe hyperthyroidism and no Graves’ orbitopathy, possibly corresponding to a disease of recent onset [43]. It might be that the sensitivity of even the current assays of TRAbs is still too low to pick up minute amounts of antibodies, or that the production of TRAbs is confined to the thyroid gland and adjacent lymph nodes, still without spill-over of antibodies into the circulation [43]. It is known that, on a quantitative basis, the production and blood concentration of TRAbs are much lower than that of TPO-Abs, for instance [44]. The methods of detection of TRAb have been
reviewed extensively [45]. TRab radioimmunometric competition assays are the more common, using various forms of TSH receptor and monoclonal TRAB as reagents. These methods detect TRAbs through their capacity to bind to the TSH receptor. They provide no indication on the biological activity of the antibodies, stimulating, blocking or, even, neutral. So far, identification of the bioactivity of TRAbs requires a bioassay using cellular systems carrying functional TSH receptors based on the activation of the cAMP pathway assessed either by the direct measurement of the production of cAMP or the activation of a cAMP responsive reporter gene system [46]. Blocking antibodies are detected using the same bioassay, modified to assess the inhibition of the stimulation induced by a fixed concentration of bovine TSH co-incubated with the sample to be tested [47,48]. Blocking TRAbs, are mostly detected in a fraction of patients with autoimmune thyroiditis, and appear to be operative in these patients withAITD who spontaneously fluctuate from hypo-to hyperthyroidism. For clinical purposes, competition assays are used most often. More demanding and costly, the bioassays are restricted to clinical research or special diagnostic situations.

The practical contribution of the assay of TRAbs to the diagnosis of Graves’ disease is restricted only to a minority of cases in which the clinical picture is unclear e.g., in the nodular variant of Graves’ disease that must be differentiated from toxic nodular goitre, in patients with exophthalmos without thyrotoxicosis (“euthyroid Graves’ disease”) and in the differential diagnosis of hyperemesis gravidarum. Two other conditions in which TRAB assay is useful or mandatory are patient’s evaluation at the end of an antithyroid drug course and because of the risk of transplacental foetal hyperthyroidism, the association of Graves’ disease, current or antecedent, with current or planned pregnancy.

Main mechanisms of the autoimmune thyroid alterations

While the pathophysiological concept is reasonably clear for the hyperthyroidism of Graves’ disease, the types and mechanisms of the destructive lesions observed in autoimmune thyroiditis are still incompletely understood so that no integrated general picture still emerges.

There is a combination, likely in variable proportions along the evolution of the disease and from one patient to another, of cellular, humoral (thyroid antibodies) and cytokine effects. The impact of specific cytotoxic perforin-expressing CD8+ T cells is relatively poorly documented in human AITD [49]. As to the implication of the Fas-Fas-ligand system in thyroid cell apoptosis, it remains so far unclear. The demonstration of the abnormal expression by thyroid cells in Hashimoto’s thyroiditis of Fas-ligand capable of inducing apoptosis through interaction with the ubiquitously expressed Fas [50] could now be interpreted either as deleterious or protective since CD4+ and CD8+ cells express also Fas. In addition, soluble Fas has also been identified, which competes with Fas-ligand for interaction with Fas.

Aside the potential destructive effects of thyroid Abs through complement activation and ADCC the extent of which is unevaluated, cytokines released locally by infiltrating lymphocytes and macrophages may exacerbate thyroid injury both morphologically and functionally [13]. Gamma-interferon induces thyroid cell expression of MHC class II molecules. Adhesion molecules facilitate reactive cells aggregation within the tissue and contribute to enhance the pro-inflammatory environment. Thyroid cells themselves are induced to produce a whole array of cytokines with local exacerbating and self-perpetuating effects. In addition, cytokine actions affect also the intrathyroidal vascular bed which, together with the locally produced chemokines and adhesion molecules, increases the recruitment of immune cells.

On the clinical grounds, the natural history of the transition from euthyroidism to dysthyroidism has been recently confirmed a slow process in two prospective studies of 790 and 522 women, respectively. Progression toward overt autoimmune hypothyroidism has been gradual over several years but, in contrast, overt autoimmune hyperthyroidism developed faster, in a matter of months [51]. Antibodies to Tg and TPO have been confirmed to precede by years the development of the diagnostic autoimmune thyroid disease phenotypes, thyroiditis or Graves’ disease, while TRAbs have been found to be positive only a few months before, or at diagnosis of Graves’ disease indicating that the presence of thyroid antibodies in apparently healthy individuals should not be neglected [52].

Susceptibility factors to autoimmune thyroid diseases

As schematically depicted in figure 1, occurrence of AITD is logically considered as resulting from the interaction between environmental factors, which are therefore acquired, and genetic individual susceptibility [53].

Genetic susceptibility

Epidemiological evidence for a genetic susceptibility to AITD has been supported by several observations, the familial clustering of the disease (20–30% of AITD in siblings of affected patients), sibling risk ratio of 16.9 for AITD and presence of thyroid Abs in 50% of siblings of affected subjects [5]; the shape of the age-incidence of AITD which decreases sharply after the peak occurring in the fifth decade indicating that most of the susceptible individuals have developed the disease by that time; and more recently, the results of the twin studies with a concordance rate for AITD of 0.29–0.55 for monozygotic as compared to 0.00–0.07 for dizygotic twins [54]. From the twin studies, the heritability of Graves’ disease has been calculated to be 79% of the presence of thyro Abs 73% [54]. An important
undertaking, then, is to identify the various genes contributing to this overall heritability. 

Table III lists the genes which have been so far identified as significantly associated with the AITD and the presence of thyroid antibodies [55]. Interestingly, most of these genes encode proteins which are involved in the economy of the immune system. Graves’ disease is strongly associated with HLA-DR3, Hashimoto’s thyroiditis less so. HLA-DR3 is associated with all the major autoimmune endocrinopathies. It is well known that HLA class II molecules are not only operative in the presentation of autoantigen to CD4+ cells, but also involved in the thymic deletion of autoreactive T cells during foetal life. CTLA-4 is a powerful down-regulator of T cell activation. Several variants of CTLA-4 are associated with AITD. Protein tyrosine phosphatase, non-receptor type 22, is also a potent inhibitor of T cell activation. CD40 molecule, a member of the TNF receptor family is expressed on B cells and other antigen-presenting cells. Its expression plays an important role in B cell activation and functions. The Fc receptor-like protein 3 gene may also play a role in immune regulation. IL-2 receptor alpha is the specific component of the high affinity IL-2 receptor system involved in the immune response and in the control of autoimmunity. It is emerging as a general susceptibility gene for autoimmune diseases.

The thyroid specific Tg gene is strongly associated with AITD susceptibility. Variants of the Tg gene could affect the interaction of Tg with the HLA-DR molecule, a fruitful research hypothesis [56]. As to the TSHR gene, the variants associated with Graves’ disease are intronic which suggests that the presentation of the receptor could be altered in some way. A recent Chinese report of the genome-wide association study in 1536 individuals with Graves’ disease and 1516 controls confirmed four previously reported loci, in the MHC, TSHR, CTLA-4 and FCRL3, and identified two new susceptibility loci on chromosomes 6q and 4p. The same study identified also strong associations of TSHR and MHC class II variants with the persistence of TRAb-positive hyperthyroidism after a ≥ 1-year antithyroid drug course [57].

The involvement of other gene variants in the genetic susceptibility to AITD is under study. It should be noted that, currently, the variants already identified represent not more than 20% of the total genetic contribution to the susceptibility to AITD. Multiple genes with low contribution statistical value (LOD score) are likely to be involved in the occurrence of AITD and major genes have not been found. It could be that multiple-gene polymorphisms be needed to develop AITD, but the combination modalities between environmental factors and the genetic background are still not known [55].

Table III

Genes associated with Autoimmune thyroid diseases (AITD). The respective Odds Ratio is rather weak, ranging from 2.0-4.0 for HLA class II to 1.1-2.6 for the others. Many other genes await for confirmation

<table>
<thead>
<tr>
<th>Genes</th>
<th>Chromosome</th>
<th>Gene symbol</th>
<th>Gene name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoregulatory genes</td>
<td>6p</td>
<td>HLA class II</td>
<td>Major histocompatibility complex</td>
</tr>
<tr>
<td></td>
<td>2q</td>
<td>CTLA-4</td>
<td>Cytotoxic T-lymphocyte-associated protein 4</td>
</tr>
<tr>
<td></td>
<td>2p</td>
<td>PTPN22</td>
<td>Proteine tyrosine phosphatase, non-receptor type 22</td>
</tr>
<tr>
<td></td>
<td>20q</td>
<td>CD40</td>
<td>CD40 molecule, TNF receptor superfamily member 5</td>
</tr>
<tr>
<td></td>
<td>10p</td>
<td>IL-2RA/CD25</td>
<td>Interleukin 2 receptor, alpha</td>
</tr>
<tr>
<td></td>
<td>1q</td>
<td>FCRL3</td>
<td>Fc receptor-like 3</td>
</tr>
<tr>
<td>Thyroid-specific genes</td>
<td>8q</td>
<td>Tg</td>
<td>Thyroglobulin</td>
</tr>
<tr>
<td></td>
<td>14q</td>
<td>TSHR</td>
<td>TSH receptor</td>
</tr>
</tbody>
</table>

Adapted from [55].
Environmental factors

Aside the genetic factors, the remaining 20% or so contribution to the occurrence of AITD is thought to be due to environmental factors. Several factors have been identified and proposed. These include radiation, iodine status, smoking, infection, stress and drugs such as lithium and interferon [58].

Radiation

External radiation for Hodgkin’s disease triggers the subsequent occurrence of antithyroid antibodies and AITD, hypothyroid thyroiditis as well as Graves’ disease. Similarly, radioiodine treatment of toxic goitre may be followed, years later, by the occurrence of Graves’ disease, even Graves’ ophthalmopathy [59]. In a different context, children exposed to radiation from Chernobyl showed a greater incidence of thyroid autoantibody positivity, with no increase in the incidence of hypothyroidism [60].

Iodine

As a general rule, AITD tend to be more prevalent in areas with iodine sufficiency. Likewise, iodine supplementation of populations previously iodine deficient is associated with a transient rise in the incidence of both autoimmune subclinical hypo and hyperthyroidism [61]. The studies performed in Denmark are of the utmost interest in that connection. Indeed, iodine supplementation has been extremely cautious, avoiding iodine excess, and the follow-up of the populations extensive and close. Overall, it is clear that the long-term many benefits of the optimisation of the iodine status far outweigh the thyroid ill-effects of the iodine supplementation. However, while thyroid abnormalities are transient at the population level, it remains to be seen whether the same is true at individual level.

Smoking

Cigarette smoking has been associated with GD and, more strongly, with Graves’ ophthalmopathy [62,63]. However, on the contrary, smoking decreases the risk of overt hypothyroidism as well as the prevalence of thyroid antibodies [64,65]. These apparently contradictory effects are unexplained. The exacerbation of the autoimmune manifestations observed after quitting smoking could be reminiscent of a rebound effect which could therefore suggest some kind of smoking-induced immunosuppression.

Infection

There is very little evidence linking infection to AITD in human. Despite extended work, no convincing role for retroviruses in AITD has been demonstrated. On the contrary, subacute “viral” thyroiditis, likely caused by viruses of several types, does not, or exceptionally, lead to autoimmune thyroiditis. Epidemiological and serological surveys have suggested the possibility of a link between *Yersina enterocolitica* infection and Graves’ disease, a link for which molecular mimicry had been considered [66]. In contrast, within the frame of the “hygienist hypothesis”, it has been shown that the prevalence of thyroid antibodies is lower in areas with relatively poor standard of hygiene which suggests that infections could in some way protect from the emergence of autoimmunity [67].

Stress

As early as one of the first description of the disease, stress has been considered as a trigger factor for Graves’ disease onset. An abundant literature is devoted to that question [68], the approach of which remains relatively uncertain in the absence of objective markers.

Drugs

Lithium treatment is associated with an increased prevalence of thyroid antibodies, hypothyroidism and, to a lesser extent, of Graves’ disease. However, lithium-induced AITD must be differentiated from the inhibitory effect of lithium on thyroid secretion [69]. One of the commonest side-effects – up to 40% of the patients – of interferon-alpha, used notably for the treatment of chronic hepatitis C virus infection, is thyrotoxicosis. Interferon-induced thyroiditis can manifest as classical autoimmune thyroiditis or, rarely, Graves’ disease, but also as non-autoimmune thyroiditis. Whether the hepatitis C virus itself plays a role in the disease remains questionable [70]. Two other iatrogenic conditions associated with Graves’ disease onset appear to provide some clues to the pathophysiology of the disease. The so-called “reconstitution Graves’ disease” has been observed, in patients treated with the predominantly anti-T cell anti-CD52 Campath monoclonal antibody for multilocular sclerosis, in AIDS patients treated with highly active antiretroviral therapy [71]. In both case, Graves’ disease occurred during the lymphocyte reconstitution phase suggesting the existence, at this point, of an imbalance towards a Th2-mediated immune response with deregulation of autoreactive lymphocytes.

Role of innate immunity

A link between innate immunity, or non-specific immunity, and autoimmunity has become obvious in many conditions and is a matter of active research in AITD. The basic principle is that any injury resulting from any aggression, infectious, chemical, radiological, etc., may contribute to the activation of innate immune response and, in susceptible individuals, to the development of AITD [72].

Endogenous factors

These are only to be mentioned since the demonstration of their role and the mechanisms of their impact are still under study. One of the main items, in this category, is the marked predominance of AITD in female [73]. Estrogens have a significant role in that predominance. The skewed inactivation of the X chromosome might also have an impact. Additionally, the complex immunological changes associated with pregnancy and their postpartum reversion, together with the thyroid stress.
imposed to the thyroid by pregnancy, are obviously important factors. However, the female predisposition toAITD is also apparent in nulliparous women.

Microchimerism, the presence of small populations of cells from one individual in another genetically distinct individual, has also been considered as one of the potential endogenous factors linked toAITD. Interestingly, this hypothesis has recently gained some support not from studies in women with previous pregnancies, the usual model so far, but in dizygotic twins, which may widen the meaning of the concept [54]. The immunoregulatory role of endogenous glucocorticoids is clearly suggested by the exaggerated condition of the endogenous Cushing’s syndrome. The cure of endogenous hypercortisolism may trigger, in susceptible patients, the onset of anAITD or the mere increase of the blood level of thyroid antibodies [74].

Clinical corner: remarks on specific patients’ approach and management

Autoimmune thyroiditis

L-thyroxine treatment of the goitre of Hashimoto’s thyroiditis, especially in children and adolescents

Often clinically presenting as a simple goitre, the disease, in this age group, has nevertheless the usual characteristics of thyroid autoimmunity (table 1). The natural history of Hashimoto’s thyroiditis has been studied in 160 children (43 boys, 117 girls, aged 9.1 ± 1.6 years) followed-up for 5 years [75]. Among the 105 children with a normal initial TSH, TSH remained normal in 68, increased up to 10 mU/l in 10 and doubled in 27 reaching overt hypothyroid level in 9. Among the 55 with initial TSH at the upper limit of normal range, TSH normalised in 16, remained unchanged in 16 and doubled in 23. Initial risk factors were the presence of Tg-Ab, the only antithyroid Ab in 6% of the cohort, and the presence of a euthyroid goitre [75]. In another study of the effect of the L-thyroxine treatment of 90 patients with Hashimoto’s thyroiditis aged 6–17 years with a follow-up of 0.5–10.2 years (median: 2.8 years), the decrease in thyroid volume was correlated with the initial TSH level, more marked in overt hypothyroidism than in subclinical hypothyroidism and euthyroidism [76]. In a third study of 611 type 1 diabetics aged 2.5–20 years, among the 89 (14%) patients positive for Tg-or TPO-Ab, 15 were treated with l-thyroxine for 2 years and 15 with placebo with the following outcomes: reduction of the thyroid volume in the treated versus augmentation in the placebo group, absence of effect on the titres of antibodies, absence of prevention of the subsequent risk of hypothyroidism which was around 9%/year [77]. As a general rule, in patients with Hashimoto’s thyroiditis and a large goitre, TSH-suppressing doses of l-thyroxine can be given over the short term i.e., 6 months, to decrease the size of the goitre. In most patients with Hashimoto’s thyroiditis, whether euthyroid or hypothyroid, goitre size will decrease by 30% after 6 months of therapy. Replacement doses should be resumed if the size of the goitre does not decrease [14].

Subclinical hypothyroidism

Defined as the combination of supranormal TSH level and normal free thyroid hormone blood levels, subclinical hypothyroidism is extremely frequent as detailed in the first part of this review. More than three-quarters of individuals with subclinical hypothyroidism have serum TSH concentrations between 5 and 10 mU/l. Although treatment of the mild thyroid failure with l-thyroxine would seem to be a logical approach to management, only a minority of individuals with subclinical hypothyroidism have symptoms of hypothyroidism. Overall, while L-thyroxine treatment would seem a reasonable treatment option for many patients with subclinical hypothyroidism, the evidence for benefit, either in terms of symptom or outcome improvement, is marginal.

The reasons not to treat systematically subclinical hypothyroidism are the following [78]:

- uncertainty on the clinical meaning of serum TSH (not a marker of general thyroid hormone action, serum concentration somewhat variable, normal values still insufficiently defined for given population groups eg, extreme longevity is associated with increased serum TSH);
- uncertainty on the morbidity of subclinical hypothyroidism (only few patients progress to overt hypothyroidism, no evidence for distinct symptoms or a worse prognosis);
- uncertainty on a clear benefit from L-thyroxine treatment in general, and even during pregnancy because of confounding factors (iodine status, associated autoimmune disorders, older age of parturient women);
- therapy with L-thyroxine is not free of inconvenience and risks.

On the contrary, treatment with L-thyroxine must be considered if [78]:

- TSH > 10.0 mU/l;
- pregnancy or pre-pregnancy (normal mean TSH during pregnancy: 1.03–1.35 mU/l [79]);
- age < 65 years;
- presence of symptoms or signs of hypothyroidism;
- high vascular risk (ischaemic heart disease, diabetes, dyslipidaemia, cigarette use);
- positive TPO-Ab and/or goitre.

Painful Hashimoto’s thyroiditis

Thyroid pain and tenderness are uncommon in Hashimoto’s thyroiditis and suggest an alternative diagnosis of subacute granulomatous thyroiditis. In the absence of any relief from L-thyroxine replacement or steroid treatment, surgical intervention may be required for unremitting pain [80].

Postpartum thyroiditis

Symptoms are more common in the hypothyroid phase. The question of the causal relationship between postpartum
Thyroid autoimmunity

Goitres and postpartum depression remains unsettled. Long-term follow-up of women who had an episode of postpartum thyroiditis reveals a 20–40% incidence of permanent primary hypothyroidism. In a single study, selenium administration significantly decreased the incidence of postpartum thyroiditis. However, confirmation is required before the administration of selenium be recommended to all pregnant women positive for anti-peroxidase Abs. As far as treatment is concerned, the hyperthyroid phase requires only the control of symptoms, whereas l-thyroxine treatment of the hypothyroid phase is indicated for symptomatic relief as well as in women who are either breastfeeding or attempting to conceive [20].

**Graves’ disease**

**General treatment strategy**

Two opposite treatment modalities may be proposed to patients with hyperthyroid Graves’ disease, the medical/conservative with antithyroid drugs and the radical/destructive with radioactive iodine or surgery with subsequent definitive hypothyroidism. Antithyroid drugs restore euthyroidism in all patients in a few weeks but, even after a 12–18 months treatment course, ~50% of the patients will relapse. There is no specific way to identify initially those who will relapse, hence some subjectivity in the selection of the treatment strategy, combined with obvious cultural/educational regional biases worldwide. With this background, the selection of the treatment strategy, in the case of the “average patient”, requires a clear and comprehensive outline presentation of the therapeutic programme and the patient’s informed cooperation [81,82]. In a pivotal prospective randomized study, 179 patients were allocated randomly to an 18-month antithyroid drug treatment (71 patients), near-total thyroidectomy (67 patients), or radioactive iodine (120 Grays; 41 patients) [83]. Only patients over 35 years of age were randomized to radioactive iodine, the proportion of ‘young’ (20–34) and ‘old’ (35–55) patients allocated to medical or surgical treatment was comparable; cigarette smoking was similar in each group. Patients with large goitres were excluded from the study. Patients were followed-up for 4 years after treatment.

The main results from this study were as follows:

- the risk of relapse was higher in the medically treated ‘young’ (42%) than ‘old’ (34%) patients; relapse was 21% after radioiodine treatment and 3 to 8% after surgery;
- patients’ satisfaction with the randomly allocated treatment was excellent (95–98%); only 8 to 11% feared adverse effects from their treatment while 14% were concerned about receiving radioactivity; 68%, 74% and 84% allocated to medical, surgical, or 131I treatment, respectively, would recommend it to a friend;
- relapse was considered a point of major disappointment by 57% of the patients treated medically, 75% surgically and only by 40% of those who received 131I;
- of major importance was the time taken to return to a state of well-being: 48% of those operated on felt they had recovered in less than 3 months as compared with 24% for the other two treatment groups; at 1 year, 61% of those treated surgically, and 39% and 48% of the patients in the medical and radioactive groups, respectively, felt well;
- sick leave was comparable (62–74 days) in the three groups;
- occurrence or worsening of ophthalmopathy during or after treatment was observed exclusively in patients in the radioactive group, mainly in those who had received more than one dose of 131I.

The study raises the following points regarding selection of treatment: no difference in satisfaction related with the treatment, the feeling of strong disappointment associated with relapse, the concern about receiving radioactive iodine and the delay before full recovery, longer for the medical and radiation treatments than for surgery. In addition, longer follow-up (14–21 years) of the same cohort of patients showed that it was Graves’ disease itself, but not the treatment modality, which has negative consequences on the health-related quality of life, especially with regard to mental performance and vitality [84].

**Graves’ disease and pregnancy**

During pregnancy incidence of Graves’ disease is lower than in the general population and approximates 0.1%. Hyperthyroidism is deleterious to the mother and impairs the normal evolution of pregnancy. Graves’ disease, after a transient exacerbation likely related to the first trimester peak of hCG, usually tends to spontaneously improve or even remit in the second half of pregnancy. The primary therapeutic objectives are restoration of maternal euthyroidism, avoidance of foetal hypothyroidism and evaluation of the risk of foetal hyperthyroidism due to the transplacental transfer of maternal stimulating TRAb. Antithyroid drugs at a dose sufficient to maintain maternal T4 levels within the normal range may induce a mild hypothyroidism in the foetus. Therefore, management of thiouamide therapy during pregnancy should aim at maintaining the maternal free T4 in the upper normal range through periodic titration. Antithyroid treatment can be withdrawn in the majority of the cases near mid-pregnancy. In contrast, in rare cases, usually with large hypervascular goitre and high T3 and TRAb concentrations, restoration of euthyroidism requires prolonged full-dose antithyroid drug treatment. Tight management is mandatory in these difficult cases to ensure treatment compliance. This usually allows thyroidectomy during pregnancy, an option which does not protect from the risk of foetal hyperthyroidism [85]. In these cases there is a risk of foetal hyperthyroidism or, on the contrary, of iatrogenic foetal hypothyroidism (vide infra).

The teratogenicity of antithyroid drugs is a matter of controversy. Multiple case reports associating aplasia cutis and carbimazole or methimazole have been reported. Also, some
instances of choanal or oesophageal atresia have been associated with exposure to carbimazole or methimazole in the first trimester of pregnancy. Although epidemiological data are not conclusive, it is recommended to use PTU, despite a risk of hepatotoxicity, rather than carbimazole or methimazole, during the first trimester of pregnancy [86]. Hyperthyroidism occurs in 2 to 10% of babies born to women with active Graves’ disease. It may also occur in women previously treated with radioactive iodine or thyroidectomy euthyroid on L-thyroxine treatment. In more than 95% of the cases, foetal/neonatal hyperthyroidism can be predicted by determining maternal TRAb at the beginning of the third trimester. Women who must be screened for TRAb include patients with ongoing Graves’ disease, patients previously treated for Graves’ disease either by surgery or radioiodine whatever their current thyroid status, and patients with a previous child with neonatal transient hyper- or hypothyroidism [87]. If the test is positive for TRAb activity, a biological assay could be performed to assess the stimulating potency of the autoantibody. Foetal thyroid status may be assessed indirectly through clinical signs of hyperthyroidism. Foetal thyroid is enlarged at ultrasonography to be performed after the 23–25th week of pregnancy [88]. However, depending on the serum concentration of stimulating TRAb and on the dose of antithyroid drug in the mother, foetal thyroid enlargement may reflect either foetal hyper or hypothyroidism the differentiation of which may require, especially when the goitre is large, TSH and thyroid hormone determination in foetal blood through cordocentesis. Neonatal hyperthyroidism, although self-limited, may be immediately fatal if unrecognized or poorly managed. Antithyroid drugs, β-blocker, and supportive measures should be started even before the exacerbation of thyrotoxicosis that follows clearance of the maternally transferred antithyroid drugs.

**Extrathyroidal manifestations of Graves’ disease**

**Orbitopathy**

Graves’ orbitopathy, present in 50% of the patients overall, constitutes a major clinical and therapeutic challenge. Graves’ orbitopathy is an autoimmune disorder representing the commonest and most important extrathyroidal manifestation of Graves’ disease, but it may occur in patients without current or prior hyperthyroidism (euthyroid or ophthalmic Graves’ disease) or in patients who are hypothyroid due to chronic autoimmune thyroiditis. The etiopathology of Graves’ orbitopathy is still unclear but a key point is the antigenic link between thyroid and orbit, possibly the TSH receptor expressed by the orbit pre-adipocytes. Active immuno-inflammatory reactions develop within the orbit involving autoreactive T and B cells, macrophages and the resident fibroblasts and pre-adipocytes with local production of cytokines and hydrophilic glycosaminoglycans. In many cases, clinical ophthalmopathy begins or grows worse during or after the treatment of hyperthyroidism. It has been shown that radioiodine treatment might favour the development of ophthalmopathy more than antithyroid drugs or thyroid surgery, especially in the more severely hyperthyroid patients. But two other risk factors of orbitopathy have been identified: cigarette smoking and iatrogenic hyperthyroidism. Administration of radioiodine can be considered in cases of orbitopathy since glucocorticoid treatment (0.4–0.5 mg prednisone/kg/day, starting 2–3 days post-dose for 1 month, then tapered over 2 months) prevents the potentially deleterious effect of radioiodine treatment on the orbit. Whether medical or radical treatment of hyperthyroidism is more appropriate in cases of severe or malignant ophthalmopathy remains unsettled. Antithyroid drugs treatment is appropriate when management of ophthalmopathy is urgent. Management of Graves’ orbitopathy has been recently reviewed in detail [89].

**Thyroid dermopathy and acropachy**

Dermopathy, an uncommon immuno-inflammatory non-pitting symmetrical thickening of the skin in the pretibial area, appears similar to Graves’ orbitopathy as far as etiopathogenesis is concerned [90,91]. The two lesions are usually associated although dermopathy develops later. Pretibial myxoedema may sometimes extend to the toes. Usually moderate, it can be hypertrophic, of the elephantiasis type, preventing shoeing. Rarely, it is associated with similar lesions affecting the hands, fingers and digits, with clubbing. In some cases, plain radiographs show a periosteal reaction in the area of skin involvement [90,91]. The usual treatment of thyroid dermopathy is topical corticosteroids.

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Thyroid autoimmunity


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