Graves’ disease: Introduction, epidemiology, endogenous and environmental pathogenic factors

Maladie de Basedow : introduction, épidémiologie, facteurs pathogéniques endogènes et environnementaux

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Abstract

Graves’ disease is the most frequent cause of hyperthyroidism. Many questions remain about the choice of diagnostic evaluations and treatment strategy according to clinical context (age, gender, pregnancy, etc.) and about the best management of the main extrathyroidal complication that is Graves orbitopathy. The exact pathogenic mechanisms are not fully clear. They associate genetic factors, interactions between endogenous and environmental factors, and immune system dysregulation. Graves orbitopathy is one of the consequences of this partial understanding. Iatrogenic Graves’ disease induced by the new targeted therapies are described and could help to better understand the molecular pathways involved in the disease and to develop new therapeutic approaches.
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Keywords: Graves’ disease; Epidemiology; Pathophysiology

1. Introduction

Graves’ disease is the most frequent etiology of hyperthyroidism, with the most spectacular semiology. In German and French-speaking countries, it is known as “Basedow’s disease”, in homage to Karl von Basedow who described an exophthalmic goiter in 1840 [1]; in English-speaking countries, it is named “Graves’ disease” after its description by Robert Graves from Dublin, in 1834 [2,3]. Mechanisms remained unknown for a long time, but the auto-immune origin is now admitted, related to the appearance of auto-antibodies stimulating thyroid growth and secretion. However, its characterization is not perfectly understood.

1.1. Definition

Graves’ disease is typically defined by a diffuse hyperfunctional goiter, usually of recent onset, related to an immunological thyroid stimulation factor. It may be accompanied by extrathyroid manifestations, especially orbital and pretibial. It does not involve a thyrotoxic condition due to release of vesicular contents in an inflammatory cytolytic process implicating drug or radiation therapy, but is rather a strictly “autoimmune hyperthyroidism”, related to thyroid hyperfunction rather than thyrotoxicosis [4]. Even so, ambiguities of definition and difficulties of diagnosis persist, especially in forms
1.2. Etiology
ANDO-1089; thyroiditis; • variant localization); Other Iatrogenic Toxic Thyrotropic hormone (TSH) excess: • hypersecretion by pituitary • exogenous administration of TSH (block-replace or excess) • autonomous glandular hyperfunctioning goiter (Graves’ hyperthyroidism)

- Toxic adenoma
- Subacute thyroiditis
- Other

Graves’ (1st episode) 802 81/19 43 ± 14 23 ± 4 23/77 732 (91) 69 (9)
Graves’ (recurrence) 350 89/11 44 ± 15 24 ± 4 22/78 292 (83) 54 (15)
Toxic adenoma 121 83/17 64 ± 16 26 ± 5 15/85 75 (62) 44 (36)
Toxic adenoma 69 78/22 59 ± 14 25 ± 5 12/88 44 (64) 25 (36)
Iatrogenic 112 28/72 67 ± 13 26 ± 5 3/97 53 (47) 58 (52)
Subacute thyroiditis 40 88/12 43 ± 14 23 ± 4 21/79 33 (83) 7 (17)
Other 52 67/33 58 ± 19 25 ± 5 2/98 42 (81) 10 (19)

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* Mean ± SEM (standard error of the mean).

without goiter: isolated Graves’ orbitopathy, or Means’ syndrome that occurs without goiter or hyperthyroidism; nodular variant of Graves’ disease (Graves’ disease developing on a pre-existing goiter, sometimes already showing nodular organization); Hashitoxicosis involves hyperfunction related to thyroid-stimulating auto-antibodies developing in Hashimoto thyroiditis; and finally, there are forms with no biologically detectable thyroid-stimulating immunologic factor.

1.2. Issues

Definition is not the only outstanding issue in Graves’ disease [5,6]:
- epidemiology: worldwide, in Europe and in France;
- progression and pathogenesis;
- homogeneous criteria for positive diagnosis and prognosis;
- choice of the best management strategy: choice of the antithyroid drugs, the starting dose and the best schedule (block-replace or decreased dose);
- role of total or subtotal thyroidectomy;
- role of radioiodine metabolic treatment (131I); indication, calculated or standard dose, target: euthyroid status or abolition of hyperthyroidism by hypothyroidism; role of glucocorticoids and systematic early levothyroxine; and monitoring modalities;
- assessment and treatment methods for Graves’ orbitopathy;
- management of Graves’ disease during pregnancy;
- specificities of pediatric management;
- respective roles of general practitioner, endocrinologist, nuclear physician, surgeon, et al.

All of the above will be dealt with here, to draw up a consensus and put forward recommendations.

2. Epidemiological data

2.1. Hyperthyroidism

Prevalence of hyperthyroidism is 0.5–2% in females, in geographical areas not featuring iodine deficiency [7]. Males show 10 fold lower prevalence. Prevalence is higher in geographical areas affected by iodine deficiency [8–10]. The most frequent cause is Graves’s disease, followed by toxic multinodular goiter. In Sweden, which is not affected by iodine deficiency, incidence is 27.6/100,000 persons per year [11,12], with 86% symptomatic and 14% subclinical forms. Graves’ disease accounts for 77.5% of cases, toxic multinodular goiter for 15.6% and toxic adenoma for 6.5% [11].

2.2. Graves’ disease: general considerations

In Goichot et al.’s study (Tables 1 and 2) of 1,572 hyperthyroid patients living in France, 73.3% had Graves’ disease (either primary or recurrence), of whom 85% were female, with a mean age of 43 years (primary onset) to 44 years (recurrence). The prevalence of the main clinical symptoms, according to the etiology of hyperthyroidism, is summarized in the Table 2. Only 4.3% of Graves’ disease cases were subclinical, compared to 10.4% of hyperthyroidisms as a whole [13].

In Sweden, the lifetime risk of Graves’ disease is 1.7%, with a 5–6 fold greater risk for females. Mean age at diagnosis is around 48 years, with no significant difference according to gender. Orbitopathy is found in 20% of cases [11].

Epidemiographic data are sparse, but Graves’ disease would seem to be more frequent in Asian populations and less frequent in Sub-Saharan Africans [14,15].

2.3. Graves’ disease: particular situations

2.3.1. Graves’ disease and pregnancy

Gestational immune tolerance improves many auto-immune diseases, including Graves’ disease [16]. In 30 year-old women beginning pregnancy, the rate of past Graves’ disease is 0.5%, and 1.3% in 40 year-olds [17].

Five to eighteen percent of pregnant women have antithyroid auto-antibodies, but only 0.1–0.4% develop clinical hyperthyroidism [18]. The risk of onset of Graves’ disease during pregnancy is 0.05–0.4% [19], with a first trimester peak followed by lower rates in the second half of pregnancy and a second post-partum peak due to immune rebound [20,21]. The relative risk of postpartum Graves’ disease is 2.1, but may exceed 5.5 in 35–39 year-olds [20,22]. Incidence peaks are observed between 7 and

Table 2
Prevalence of main symptoms according to etiology of hyperthyroidism in 1,572 French hyperthyroid patients.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Graves' disease</th>
<th>Toxic HMNG</th>
<th>Toxic adenoma</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>802</td>
<td>121</td>
<td>69</td>
</tr>
<tr>
<td>Palpitations</td>
<td>618 (78%)</td>
<td>58 (52%)</td>
<td>47 (71%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weakness</td>
<td>619 (78%)</td>
<td>71 (63%)</td>
<td>37 (56%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digestive disorder</td>
<td>257 (32%)</td>
<td>20 (18%)</td>
<td>8 (12%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thermobobia, polydipsia</td>
<td>471 (60%)</td>
<td>39 (35%)</td>
<td>17 (26%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>343 (43%)</td>
<td>35 (31%)</td>
<td>17 (26)</td>
<td>0.002</td>
</tr>
<tr>
<td>Other symptoms&lt;sup&gt;a&lt;/sup&gt;</td>
<td>300 (38%)</td>
<td>40 (36%)</td>
<td>13 (20%)</td>
<td>0.01</td>
</tr>
<tr>
<td>(AF) Cardiac arrhythmia</td>
<td>82 (11%)</td>
<td>23 (24%)</td>
<td>6 (12%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Weight loss</td>
<td>513 (70%)</td>
<td>51 (54%)</td>
<td>19 (37%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>546 (75%)</td>
<td>39 (41%)</td>
<td>27 (53%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visible goiter</td>
<td>251 (34%)</td>
<td>39 (41%)</td>
<td>20 (39%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Other clinical signs&lt;sup&gt;b&lt;/sup&gt;</td>
<td>94 (13%)</td>
<td>7 (7%)</td>
<td>13 (26%)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

By kind permission from Goichot et al. [13].

<sup>a</sup> Trembling, anxiety, dyspnea, irritability, mood disorder.

<sup>b</sup> Trembling, orbitopathy.

9 months after delivery [20], although one study found no such postpartum peak [23].

2.3.2. Graves’ disease in children

Graves’ disease is rare in childhood and especially in early childhood, but is more severe, as seen from the elevated anti-TSH-R antibody (TRAB) levels, in children under 5 year-olds [24,25]. Under the age of 4 years, sex-ratio is 1.

Incidence increases with age, from 0.1/100,000 patient-years in children to 3/100,000 in adolescents [26]. Prevalence is 106.9/100,000 between 10 and 19 years of age in the USA [27]. In Hong-Kong, the iodine intake is increased, and the incidence of Graves’disease in childhood is high and still increases, especially in girls, with a sex-ratio of 1/9.7 [28].

2.3.3. Graves’ disease in the elderly

In all, 2.1% of elderly subjects show subclinical hyperthyroidism [29]. Toxic multinodular goiter underlies 25–66% of cases of hyperthyroidism in subjects over-65 year-olds in the UK, compared to 5–10% in subjects under 40 year-olds [30]. Graves’ disease underlies only 21.4% of cases of hyperthyroidism in over 55 year-olds [31]. In the elderly population, inaugural symptoms are attenuated (Table 2) [13]. Thermophobia and sleep disorder are less frequent; so are palpitations, which may seem paradoxical given the higher risk of arrhythmia due to atrial fibrillation in this age-group. Complications related to atrial fibrillation show the same prevalence in clinical and subclinical forms [13].

3. Pathogenic factors

3.1. Pathophysiology

Onset of Graves’ disease involves a breakdown of immune tolerance toward thyroid structures. Development of this auto-immune process is multifatorial, with endogenous and environmental factors in a predisposing genetic context.

In Graves’ disease, auto-immune reaction induces production of anti-TSH-receptor (anti-TSH-R) auto-antibodies by B-cell clones infiltrating the thyroid gland. The antibodies target the extracellular domain of the TSH-receptor, most exerting a stimulating but some a so-called blocking action. The functional result of their intra-thyroid presence depends on concentration and valence (stimulating or blocking). In the majority of cases, the stimulating action predominates, leading to unregulated thyroid hyperfunctioning. Sometimes, either initially or after a hyperthyroid period, the blocking action takes over, inducing hypothyroidism.

In parallel, the immune tolerance breakdown extends to other thyroid antigens, accounting for the presence of thyroid peroxidase (TPO) and/or thyroglobulin (Tg) antibodies in 50–70% of cases of Graves’ disease.

3.2. Genetic factors

The 35% rate of familial cases suggested a role of genetic factors since a long time [32,33], reinforced by mono- and dizygotic twin studies [34]. After data modelization, Brix et al. were able to attribute a 75–80% role to genetic factors in Graves’ disease, vs. 20–25% for environmental factors [35]. This genetic susceptibility could explain the ethnic differences in prevalence of Graves’ disease [36].

Predisposition of Graves’ disease seems to be polygenic. The co-expression of several genes, each with weak impact, is needed to seriously affect the genetic risk of Graves’ disease in one subject. The first predisposing genes were identified on a “candidate gene” linkage or association approach guided by knowledge of pathophysiological stages and agents. More recently, panegemonic analyses, enabled by next-generation sequencing (NGS) and bioinformatics, identified many other predisposing genes, some concerning various auto-immune diseases, others concerning thyroid auto-immune diseases as a whole, and others again more specifically involved in Graves’ disease or Hashimoto’s thyroiditis.

3.2.1. Immunomodulatory genes

3.2.1.1. Major histocompatibility complex. In Asian populations, 4 class II HLA susceptibility genes were identified:
HLA-B*35:01, -B*46:01, -DRB1*14:03, and -DPB1*05:01, with a relative risk of Graves’ disease between 2 and 3. A leucine in HLA-DPB1 protein position 35, induces a maximum relative risk [37].

In Caucasian populations, the implicated genes are HLA-C*07, HLA-DR3, HLA-DQB1*03:01, HLA-DQA1*05 and HLA-DQB1*02 [38]. An arginine in position 74 of DPB1 is associated with high risk of Graves’ disease in Caucasian but not in Asian populations [39].

There are far fewer studies of Black populations. They identify DRB3*01:01 in Jamaicans [40], and DRB3*02:02 and DQA1*05:01 in African Americans [40,41]. Of these haplotypes, only DRB1*14:03 and DRB1*05:31 are specific to risk of Graves’ disease, the others predisposing equally to Hashimoto’s thyroiditis [42].

Protective genes have also been identified: HLA-DRB1*07, HLA-C*03, and HLA-C*16. Epistatic mechanisms have been demonstrated between the various HLA haplotypes and may account for regulation of the intensity and expression of Graves’ disease by T-cells recognizing a protective HLA motif on antigen-presenting cell surfaces, such as DRB1*13:02, or interfering with anti-TSH-R production [42].

The predisposing role of class I HLA molecules implies that the predisposing variants can bind to TSH-R auto-antigens with greater affinity, thus interfering with negative selection of auto-reactive T-cell clones.

Class I HLA variants may be involved in antigen presentation: microbial antigens activating auto-reactive T-cell clones by their molecular similarity, or superantigens produced by non-specific immune reaction following viral infection. Class I expression induced by viral infection or presence of soluble class I molecules might also explain the predisposition mechanism [43].

3.2.1.2. CTLA4. CTLA4 is a T-cell activation down-regulator, reducing the adhesion time between the T-cells and antigen-presenting cell and thereby halting T-cell activation and multiplication. Down-regulation may also involve T-cell regulator stimulation by the soluble fraction of CTLA4, or stimulation of trans-endocytosis of CD86 on antigen-presenting cells.

CTLA4 polymorphisms are associated with an increased risk of Graves’ disease, Hashimoto’s thyroiditis and other auto-immune diseases. Two polymorphisms were identified for Graves’ disease: CT60 (rs3087243) and A49G (rs231775), in different ethnic populations, but with small cohorts. The meta-analysis by Kavvoura et al. showed an odds ratio (OR) of about 1.5 for each; however, haplotype analysis suggests that the two variants show linkage disequilibrium. OR is higher in double heterozygotes (CT60-CT60), suggesting a dose effect [44]. The mechanism of these associations remains unclear: CTLA4 glycosylation and processing defect, lengthened (AT)n sequence impairing CTLA4 mRNA stability, or reduced sCTLA4 level [45].

These polymorphisms may act synergistically with MHC polymorphisms such as HLA-A*02 or HLA-DPB1*05:01 [46].

3.2.1.3. PTPN22. PTPN22 encodes a lymphocyte tyrosine phosphatase that inactivates the kinases associated with T-cell receptors, thus reducing T-cell activation. PTPN22 variants (rs2476601 or R620W) were shown to be associated with Graves’ disease (OR: 1.5–1.9) in several studies, but exclusively in Caucasians [47]. The mechanism remains poorly understood. Association of a PTPN22 variant with an HLA-DRB1*03 phenotype seems to be of especially poor prognosis in under 30 year-olds [48].

3.2.1.4. CD40. CD40 is expressed on antigen-presenting cells and acts as co-regulator of T-cell activation, and contributes to B-cell activation and proliferation and to B-cell memory formation. It is present in the thyroid within germinal centers and on thyroid epithelial cells [49] and orbital fibroblasts [50]. Variants of CD40 can be expected to impact onset of Graves’ disease and orbitopathy.

The rs1883832 C>T variant in a sequence involved in initiation of C allele translation, was associated with increased risk of Graves’ disease in most studies and ethnic groups, with OR of 1.22 according to a meta-analysis [51].

Other polymorphisms were associated with an increased risk of recurrence after antithyroid drug withdrawal [52].

3.2.1.5. CD25. CD25 (IL-2 receptor alpha sub-unit) is mainly expressed by regulatory T-cells. This locus on chromosome 10p15.1 was associated with Graves’ disease in Caucasians [53,54].

3.2.1.6. FOXP3. FOXP3, carried by the X chromosome (Xp11, coding for scurfy) is an important regulator of regulatory T-cells. In young boys, FOXP3 mutations induce IPEX syndrome, which is lethal and includes immune deregulation, poly-endocrinopathy (notably hypothyroidism) and enteropathy [55]. Polymorphisms were associated with Graves’ disease [56,57]. The X chromosome location of FOXP3 may contribute to the female predominance seen in Graves’ disease.

3.2.1.7. FCRL3. FCRL3 belongs to the superfamily of immunoglobulin receptors involved in B-cell response regulation. Several studies, in both Caucasian and Asian subjects, reported association with various auto-immune conditions, including Graves’ disease [58,59].

3.2.2. Thyroid-specific genes

3.2.2.1. Thyroglobulin. Thyroglobulin (TG) is a large dimeric protein, with numerous post-translational sequence variants and variable iodination. Thus, many isotypes are to be expected, with a high likelihood of some being considered as auto-antigens. Many studies reported association between TG polymorphisms and onset of thyroid auto-immune disease [45,60]; for Graves’ disease, they are also associated with recurrence after antithyroid drug withdrawal.

The polymorphism WI1999R (exon 33) is a special case of TG variants associated with thyroid auto-immune disease: when associated with the HLA-DRB1*03 allele, it increases the OR for Graves’ disease to 16.1, which is the highest OR ever reported.
The *TG* gene promoter region is subject to a Single Nuclear Polymorphism, -1623A/G, in which the G allele increases risk of Graves’ disease [61]; this is a very particular variant, increasing promoter activity when bound to a transcription factor induced by interferon (IRF-1). This example highlights the interaction between genetic factors and epigenetic mechanisms and matches the thyroid effects observed under interferon treatment, supporting the hypothesis of viral involvement in the pathogenesis of Graves’ disease.

3.2.2.2. *TSH-receptor*. Once the role of anti-TSH-R antibodies in Graves’ disease became clear, the temptation was to cast them in the role of both victim and culprit. The first linkage studies were disappointing, focusing on *TSH-R* gene coding regions [45]; later, non-coding regions were also studied. Variants associated with Graves’ disease were mainly found on intron 1: rs179247, rs2284720, rs12101255, rs12101261, rs2268458, rs2239610 and rs2268474; most of these variants affect exclusively Caucasian subjects [47,62–64]. In contrast intron 7 variants were identified in Asian populations [65].

Colobran et al. showed that the genotype of variant rs 179247, associated with Graves’ disease, and itself in strong linkage disequilibrium with rs 12101261, reduced TSH-R expression in the thymus [66].

Subsequently, exploration of a relation between these polymorphisms and epigenetic changes induced by interferon-alpha showed that the TT genotype of variant rs12101261 interacted with a transcriptional repressor, PLZF (promyelocytic leukemia zinc-finger protein), which also reduced TSH-R expression in the thymus; this effect could impair the efficacy of negative selection of anti-TSH-R auto-reactive T-cell clones in the thymus, thereby increasing risk of Graves’ disease [67].

3.2.2.3. Other genes. A very large number of other genes have been identified on genome-wide linkage or association studies as predisposing to or on the contrary protective against Graves’ disease [45,68]. More recently, even more genes were identified, including the genes coding for cytokines, TLR or TPO [69–73].

These studies need replicating before all of these genes can be confirmed and the mechanisms of the predisposing or protective effects be analyzed.

3.2.3. Other genetic effects

Graves’ orbitopathy: genetic predisposition has been less fully studied in this thyroid auto-immune disease [74].

Pretibial myxedema is rare, making it difficult to study possible genetic susceptibility. However, Khalizadeh et al. showed that Graves’ orbitopathy could be associated with a polymorphism in position 49 of the gene coding for CTLA4 [75].

Several studies sought to identify genetic prognostic factors for Graves’ disease [45], but without agreement, although allele A49G of CTLA4 was the most frequently associated with severe or severely recurrent disease.

Two studies reported possible genetic susceptibility for the antithyroid drug-induced side effect agranulocytosis [76–78]. None focused on antithyroid drug-induced hepatitis. However, Graves’ disease and ANCA-associated vasculitis, sometimes found under antithyroid drug therapy, share certain susceptibility variants of CTLA4 and PTPN22 [79].

Genes so far identified as predisposing for Graves’ disease are only a small part of the genetic contribution to the disease. High throughput sequencing and bioinformatic methods need applying in cohorts of highly homogeneous phenotype, to identify other implicated genes; these findings should then be validated in other cohorts and for other ethnic groups. The genetic data are yet to have any clinical impact, and do not suggest any preventive measures or genotype-tailored individual therapies. Further light may be shed by transcriptome studies on tissue from Graves’ disease patients [80]. Moreover, the relatively low penetrance of Graves’ disease in case of genetic predisposition (in twins or first-degree relatives) suggests that endogenous and environmental factors are determining.

4. Endogenous and environmental risk factors

As well as genetic susceptibility, environmental factors are involved in onset of Graves’ disease in 30% of cases [81]. They induce reversible or irreversible epigenetic changes: DNA methylation, histone modification, X chromosome inactivation, etc. Endogenous factors are also largely involved.

4.1. Endogenous factors

4.1.1. Estrogen impregnation

Graves’ disease shows female predominance, suggesting a role of estrogen in its pathophysiology. Estrogen variation can explain disease fluctuation over the menstrual cycle, in pregnancy and with the menopause [82]. Of the 2 types of estrogen receptor, ESR2 is closer to the susceptibility locus [83]. ESR2 polymorphisms are frequent in Graves’ disease [82]. Estrogen α receptor expression was reported on orbital fibroblasts, and can be affected by glucocorticoids [84].

4.1.2. X-inactivation

Estrogens and X-inactivation in females impair the immune system and may account for female predominance in Graves’ disease. Female tissues are mosaics of maternal and paternal cell lines with activated X chromosome [85]. Asymmetric X-inactivation, arbitrarily defined by inactivation of the same X chromosome in 80% of cells [86], contributes to female predominance in thyroid auto-immune disease. A recent meta-analysis confirmed the importance of X-inactivation in onset of Graves’ disease in females (OR, 2.54; 95%CI: 1.58–4.10) [87,88].

4.1.3. Fetal microchimerism

During pregnancy, there is early exchange of cells between fetus and mother between 4 and 6 weeks’ gestation. Passage from fetus to mother is fetal cellular microchimerism, and passage from mother to fetus is maternal microchimerism [88]. Persistent fetal microchimerism was reported at onset of thyroid auto-immune disease, but with contradictory findings [89,90].
4.2. Environmental factors

4.2.1. Iodine

In some subjects, iodine excess increases intra-thyroid infiltration of Th17 T-cells and inhibits Treg development. It promotes overexpression of TNF-alpha, inducing apoptosis and parenchymal destruction. Iodine intake does not seem to affect the risk of Graves’ disease; the relation between iodine intake and thyroid dysfunction forms a U-curve, both iodine deficiency and excess impairing thyroid function [91,92].

4.2.2. Selenium

Selenoproteins are involved in anti-oxidation, redox and anti-inflammatory processes [93,94]. Selenium contributes to immune system balance. It activates T-cell receptors and induces differentiation of CD4+ T cells into regulatory CD25+FoxP3+ and Treg cells. Deficiency induces a Th1 type immune response, with cytokine elevation (IL-2, TNF-α, IFN-γ) and lower regulatory cell levels [95,96]. Selenium replacement reduces antithyroid antibody levels, without affecting thyroid function as such, and improves Graves’ orbitopathy [95,96].

4.2.3. Vitamin D status

Low concentrations of 25(OH) vitamin D are observed in Graves’ disease, and the deficiency should be corrected before the initiation of antithyroid drug therapy [97]. There is as yet no evidence to determine whether vitamin D deficiency is a cause or a consequence of Graves’ disease.

4.2.4. Seasonal variation

Recurrence of Graves’ disease is more frequent in spring and summer, in line with allergic rhinitis episodes [98].

4.2.5. Smoking

Smoking has long been identified as a risk factor for Graves’ disease, with OR 3.30 (95%CI, 2.09–5.22) in active smokers vs. non-smokers; in Graves’ ophthalmopathy, the OR is even higher, at 4.40 (95%CI, 2.88–6.73). The risk disappears within a few years of cessation [99,100]. However, the impact of smoking is complex, because the cessation has also been associated with an increased frequency of thyroid auto-immune disease [101].

4.2.6. Alcohol

Dutch and Danish epidemiological studies reported a protective effect of alcohol against Graves’ disease (6.7 vs. 23.7%) [102]. On the other hand, excessive consumption reduces Natural Killer cells activity and antibodies production, and induces hyper-gammaglobulinemia with impaired cytokine production, disturbing the Th1/Th2 immune balance [103].

4.2.7. Stress

A role of stress in Graves’ disease pathophysiology was suggested in World War I. Some studies reported stress in 62–85% of cases [104,105]. A recent study correlated degree of stress, symptom intensity (HSS hyperthyroid symptom score) and biological status (T4, T3, serum TBII antibodies) in 263 patients with first episode of Graves’ disease [106]. Stress modulates immune response, inhibiting cell response and activating humoral response [106,107].

4.2.8. Ionizing radiation

Even low-dose external radiation treatment of the thyroid leads to nodules and thyroid carcinoma. Higher doses are associated with hypothyroidism. External irradiation induces thyroid hyperplasia, associated with increased rates of auto-immune thyroid disease such as Graves’ disease (0.1–2% of cases), although pathophysiology is unknown [108,109].

4.2.9. Infection

Several infectious agents show involvement in Graves’ disease: Yersinia enterolitica, Coxsackie B, Retrovirus, Helicobacter pylori and hepatitis C virus [110–114]. In the study by Valtonen, recent infection confirmed on serology, was found in 36% of newly diagnosed cases of Graves’ disease, vs. 10% of healthy controls [110]. Some bacteria, such as Yersinia, show cross-immunogenicity with TSH receptor epitopes; this is the antigen mimicry hypothesis [52,114]. Genetic predisposition and certain HLA groups form the link between these retroviral infections and Graves’ disease, especially in familial forms [115].

4.2.9.1. Medication.

4.2.9.1.1. Cytokines. One mechanism involved in onset of Graves’ disease has been suggested to be the loss of pro- vs. anti-inflammatory cytokine function balance, promoting lymphocyte infiltration of the thyroid and activation of antibody-producing B-cells. Pro-inflammatory cytokine serum levels (IL-2, 8, 6, 17, 22 and TNF-alpha) are elevated in Graves’ disease. Thryocytes also produce pro-inflammatory cytokines (TNF-alpha, IL-αγ, IFN gamma), stimulating lymphocyte reaction in the thyroid [116–119]. In hepatitis C, IFN-alpha treatment triggers an immune reaction within the thyroid in 2–8% of cases. Interferon exerts and immune-modulation effect on the thyroid, but also an inhibitory effect on thyroid hormone synthesis. Risk factors for thyroid dysfunction under interferon are known: female gender, history of thyroid pathology and pre-existing thyroid auto-immunity [120].

4.2.9.1.2. Ipilimumab. Ipilimumab is an anti-CTLA-4 monoclonal antibody used in oncology (metastatic melanoma, small-cell lung cancer, etc.). Blocking CTLA4 abolishes down-regulation following activation of T-cells, inducing an immune response [42]. Some very rare cases of Graves’ disease or Graves’ ophthalmopathy were reported under ipilimumab [42,43]. Other immunotherapy drugs (anti-PD1/PDL-1) used in or under development for cancer treatment have the same risk of induced auto-immune dysthyroidism, most often of inflammatory thyroiditis with a thyrotoxicosis phase followed by hypothyroidism.

5. Conclusion

The many etiological pathogenic factors that may account for or contribute to Graves’ disease and the advent of targeted
immunomodulation therapies provide opportunities to shed new light on and design new therapeutic approaches for thyroid autoimmune diseases.

Disclosure of interest

The authors declare that they have no competing interest.

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