No definitive evidence for a connection between autoimmune thyroid diseases and stress in women

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Abstract

The purpose of this literature review was to examine the available clinical studies performed during the last 15 years to identify if there is a causal relationship between the onset and course of autoimmune thyroid diseases (AITDs) and the hypothalamic-pituitary-adrenal (HPA) axis/sympathetic-adrenomedullary system (SAM) (dys)function in women. Using the PubMed, Web of Science and Scopus databases, a comprehensive search was performed, and 14 articles were finally identified.

The majority of selected studies suggested a causal connection between Graves’ Disease (GD) and stress, as well as between Hashimoto Thyroiditis (HT), with its variant postpartum thyroiditis, and stress. However, due to heterogeneity in the protocols, mainly based on the theoretical side effects of stress on the immune-neuroendocrine system, and the different modalities used to establish the impact of stress on individuals, no definitive conclusions could be reached to explain the mechanisms by which stress contributes to the onset of AITDs in women and to determine whether stress management could help in modifying the course of AITDs.

INTRODUCTION

Autoimmune thyroid diseases (AITDs) are the most common organ-specific autoimmune disorders (Fountoulakis & Tsatsoulis 2004), with a prevalence exceeding 5% in the general population and a significantly higher prevalence in women (Orgiazzi 2012). Although it has been shown that (unchangeable) genetic susceptibility accounts for approximately 70% of the risk of developing AITDs, the onset and course of AITDs has also been attributed to changeable environmental trigger factors, including iodine intake, drug side effects, nicotine and stress, which is a meaningful component of modern society and has become a source of significant health problems in the general population (Brent 2010; Burek & Talor 2009; Effraimidis & Wiersinga 2014; Hansen et al. 2006; Pruimel et al. 2004; Saranac et al. 2011; Weetman 2003).
Stress is a broad phenomenon that generally refers to physical and emotional challenges to which all living organisms react by the activation of complex neuroendocrine, cellular and molecular pathways, leading first to an adaptive state and ultimately to the dynamic restoration of homeostasis (Chrousos 2009; Frick et al. 2009; McEwen 2006; McEwen 2007). Daily hassles and life events may result in allostatic overload and lead to erratic neuroendocrine responses.

The two major neuroendocrine pathways involved in the allostatic adaptive stress response are the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenomedullary system (SAM) (Boutzios & Kaltzas 2015; McEwen 2007). Complex reciprocal counterbalances between the HPA axis and the SAM have been described in numerous stress-related diseases (Cortelli et al. 2012; Calandra-Buonaura et al. 2016; Ghiciuc et al. 2013). Cortisol, which is the most important steroid product of the adrenal gland, is a well-known subclinical indicator of HPA axis activity and is widely considered a biological regulator of the adaptation to physiopathological challenges (McEwen 2003; McEwen 2008; Simeoni et al. 2011). Under stress, SAM is rapidly activated, generating the “fight or flight” response through the release of epinephrine and norepinephrine from the adrenal medulla. This leads to a quick rise in an individual’s metabolic rate, blood pressure and respiratory rate, as well as increased blood flow to vital organs such as the heart and muscles (Lucassen et al. 2014).

**Purpose of this Review**

The possible role of stress as a trigger in the onset and prognosis of AITDs has been the subject of quite recent reviews (Bagnasco et al. 2006; Conte-Devolx & Vialettes 2013; Falgarone et al. 2013; Mizokami et al. 2004; Tsa-toulis 2006; Tsatsoulis & Limniati 2012). However, there still has not been any particular focus on the correlation between stress and AITDs in women, although women have a greater sensitivity to stress and a higher susceptibility to emotional-based disorders, including depression (Becker et al. 2007).

Furthermore, the mechanisms through which stress may contribute to the onset of AITDs are still not unequivocally explained. The picture is made even more complicated by the fact that AITDs are heterogeneous in their clinical presentations (Pearce et al. 2003): the organ-specific autoimmune process induces hyper-function (Graves’ Disease, GD) or hypo-function (Hashimoto Thyroiditis, HT and its variant, postpartum thyroiditis). Therefore, the purpose of the current review is to further explore the clinical studies published over the last 15 years to identify if there is a causal relationship between the course and occurrence of AITDs and the HPA axis/SAM (dys)function in women.

**METHODS**

Clinical and experimental studies from January 2000 to July 2015 were identified through the PubMed, Web of Science and Scopus databases (Arksey & O’Malley 2005; Grant & Booth 2009). The terms “autoimmune thyroid diseases,” “Hashimoto thyroiditis,” “Graves’ disease,” “thyroperoxidase antibodies,” “postpartum thyroiditis” were paired with “stress,” “stress hormones,” “cortisol,” “corticosterone,” “adrenaline,” “noradrenaline,” “Hypothalamus-pituitary-adrenal axis,” “sympathetic adreno-medullary system.” The search was conducted by the repeated use of these words in different combinations. The acquired articles were sorted by their relevance, and key articles were identified. Reference lists of publications obtained by these procedures were hand-searched for additional relevant articles. Further studies were selected by scanning the reference lists of the retrieved papers. The initial search yielded 832 titles. In addition, 46 supplementary titles were included after browsing the reference lists of the selected papers. All abstracts were independently read by each coauthor: 794 (duplicates, letters, editorials and non-English language) reports were excluded. From the remaining 84 abstracts, all full manuscripts were gathered and they were independently reviewed by each coauthor for key information; where it was unclear to someone of the coauthors whether an article met eligibility criteria, the article was discussed among the research team and full agreement was all the time reached. Seventy-one articles were excluded because not relevant to the purpose of the review, mainly because they considered the occurrence of a self-reported stressful event itself as a risk factor for the onset of AITDs. Thirteen articles were ultimately identified to be reviewed in this paper (Figure 1). Among these key articles, 8 were related to the association between stress and GD, and 5 addressed the link between stress and HT.

**RESULTS**

The connection between GD and stress (Table1). Matos-Santos et al. (2001) retrospectively evaluated the impact of stressful life events on 93 GD patients (29% male, 71% female) compared with healthy matched controls. GD patients reported significantly more negative life events than controls during the 7–12 months preceding the onset of symptoms, thus supporting the connection between stress and GD by suggesting that stressful events may be the precipitating factor of the onset of GD.

Aging has been associated with less severe Graves’ hyperthyroidism (Manji et al. 2006): a cross-sectional multicenter study of 69 males and 194 females with untreated GD explored whether reductions in the severity of Graves’ hyperthyroidism with age are actually the result of less exposure to stress with aging (Vos et al. 2009). Disease severity was ascertained by subclinical
832 titles identified from electronic literature search

46 titles added by browsing the reference list of relevant articles

878 articles selected for reading title and abstract

794 articles excluded after screening for their relevance and duplicates

84 full-text articles assessed for eligibility

71 articles excluded after reading full-text

13 papers included

8 clinical studies on stress and GD

5 clinical studies on stress and HT (with its variant: postpartum thyroiditis)

Fig. 1. Flow chart of study selection.

Tab. 1. Selected clinical studies on the connection between stress and GD.

<table>
<thead>
<tr>
<th>REFERENCES</th>
<th>SUBJECT (M/F)</th>
<th>IMMUNO-ENDOCRINE SUBCLINICAL INDICATORS OF AITDs</th>
<th>EVALUATION OF STRESS</th>
<th>STRESS – AITDs CONNECTION?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matos-Santos et al. 2001</td>
<td>93 (21/72)</td>
<td>TPO, Tg, TRAb, TSH, FT3, FT4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tsatsoulis et al. 2000</td>
<td>10 (4/6)</td>
<td>TPO, Tg, TSH, T3, T4</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fukao et al. 2003</td>
<td>69 (4/65)</td>
<td>TPO, Tg, TRAb, TSH, FT4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Vos et al. 2009</td>
<td>263 (69/194)</td>
<td>TRAb, TPO, TSH, T3, T4, FT3</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fukao et al. 2011</td>
<td>64 (10/54)</td>
<td>TRAb, TSH, FT3, FT4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Effraimidis et al. 2012</td>
<td>790 (0/790)</td>
<td>TPO, Tg, TRAb, TSH, FT3</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Agbaht &amp; Gullu, 2014</td>
<td>41 (19/22)</td>
<td>TRAb, TSH, FT3, FT4</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Vita et al. 2015</td>
<td>58 (22/36)</td>
<td>TSH, FT3, FT4</td>
<td>Yes</td>
<td>No</td>
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</table>

(thyroid hormone blood concentration) and clinical (hyperthyroid symptom scale, HSS scores) indicators. Moreover, stress levels were quantified by self-rated Dutch questionnaires on recently experienced stressful life events and by the Positive and Negative Affect Schedule (PANAS) questionnaire (Watson et al. 1988). No statistically significant correlation was found between the severity of hyperthyroidism and subjective stress perception scores, although the authors confirmed that stress perception scores decreased with
advancing age concomitantly with the decreased production of all clinical and subclinical indicators of thyroid hyper-function.

A study by Tsatsoulis et al. (2000) assessed the response of the HPA axis to low-dose ACTH stimulation after an overnight 1 mg dexamethasone-suppression test (DST) in 10 GD patients (4 male, 6 female). The results showed an attenuated response to the Adreno-corticotrophic Hormone (ACTH) stimulation test in the GD patients before treatment with anti-thyroid drugs. After 8–12 months of anti-thyroid drug therapy, the patients had returned to a stable euthyroid state, and a physiological response to ACTH stimulation test was achieved, suggesting that impaired function of the HPA axis, the main endocrine stress-related system, is associated with the onset of GD.

A significant association between subjective stress perception scores and autoimmune hyperthyroidism was reported by Fukao et al. (2003) in a cohort of 69 GD patients (4 male, 65 female). This prospective study showed that after cessation of anti-thyroid drug treatment, 41 patients (3 male, 38 female) with GD relapsed, whereas the remaining patients (1 male, 27 female) were in an euthyroid state for more than 1 year. The level of Thyroid Stimulant Hormone (TSH) receptor antibodies (TRAb) and thyroid volume were significantly higher in the relapsed GD patients than in the remitted GD patients. The daily hassles (DH) questionnaire scores were significantly higher in the GD patients who had a relapse compared with the scores of the remitted patients. Furthermore, statistically significant correlations were found between serum TRAb activity, frequency and total scores of stressful life events, suggesting that everyday stresses, as well as major life events, can aggravate the disease in patients with GD.

A few years later, the same research group confirmed the relationship between stressful life events and the prognosis of autoimmune hyperthyroidism in a prospective study (Fukao et al. 2011) involving 64 GD patients (10 male, 54 female).

Effraimidis et al. (2012) evaluated the possible relationship between life stress events and the de novo onset of autoimmune hyperthyroidism. Seven hundred and ninety euthyroid women with no previous history of thyroid disease but with at least one close relative (first/second degree) diagnosed withAITDs were followed-up for up to 5 years until the occurrence of thyroperoxidase antibodies (TPO-Ab). Subjects were also annually evaluated for the impact of stressful life events with the Dutch and PANAS questionnaires (Watson et al. 1988). During the follow-up period, 11 women developed GD. No differences were observed in stress impact perception scores between the hyperthyroid patients and the controls at baseline or at the times of the events, suggesting no connection between stress and GD.

By contrast, a clear relationship between HPA dysregulation and autoimmune hyperthyroid state was recently reported by Agbaht and Gullu (2014). The authors compared the effects of an ACTH stimulation test at baseline and after 3 months of treatment with anti-thyroid drugs in 41 GD hyperthyroid patients (19 male, 22 female). The serum cortisol and Dehydroepiandrosterone-Sulphate (DHEA-S) hormone responses to ACTH stimulation were blunted in hyperthyroid patients, indicating a dysregulation of the HPA axis, which was recovered after treatment.

A more recent survey (Vita et al. 2015) assessed the relationship between the onset/outcome of GD and stressful life events over two decades in 58 GD patients (22 male, 36 female) in which the onset of the disease was preceded by at least one stressful event. Patients who experienced an exacerbation and/or relapse had a significantly greater stress impact perception than the patients who remitted. Therefore, the authors highlighted the role of the subjective perception of stressful life events as a factor triggering autoimmune hyperthyroidism.

The connection between HT (and its variant, postpartum thyroiditis) and stress (Table 2).

Strieder et al. (2005) retrospectively evaluated a cohort of 759 euthyroid women on whether there is an association between the occurrence of TPO-Ab and self-reported measures of stressful life events. One hundred eighty-three women were found to be TPO-Ab positive, and no differences in TPO-Ab negative women were recorded in terms of their recently experienced stressful life events. TPO-Ab positive women even reported fewer pleasant events compared with the TPO-Ab negative subjects. Therefore, no significant connections were demonstrated between stressful life events and the occurrence of HT.

By contrast, a clinical observational study from Greece (Terzidis et al. 2010) showed that dysregulation of the HPA axis over several years is associated with thyroid autoimmune disease. These authors showed that among 321 subjects (114 male, 207 female), 57 apparently healthy subjects of different ages (51–95 years; 8 male, 49 female) were positive for anti-thyroid antibodies (ATA). TSH levels were higher in the ATA positive subjects compared with the ATA negative subjects. Moreover, the ATA positive subjects had baseline cortisol levels that were significantly lower than those of the ATA negative group, independent of age.

Effraimidis et al. (2012) excluded the connection between stressful life events and the de novo occurrence of autoimmune hypothyroidism in a cohort of 790 euthyroid women with no personal history of thyroid disease. During a 5-year follow-up, the subjects who developed TPO-Ab were evaluated for stress exposure through self-rated questionnaires. Eighty-one women developed TPO antibodies, 38 of which had autoimmune hypothyroidism. The authors found no differences at baseline in terms of recent stressful life events, daily hassles, or affect scale scores between the hypothyroid patients and controls among the initial cohort.
At the time of diagnosis, the hypothyroid patients reported significantly less frequent negative feelings than the control subjects, suggesting no connection between stress and HT.

By contrast, Müssig et al. (2012) found a connection between the presence of TPO-Ab and poor psychological well-being in 64 (8 male, 56 female) HT patients. The authors found that HT patients who were TPO-Ab positive had significantly poorer physical and psychological well-being compared with TPO-Ab negative HT patients. In addition, in a subgroup of HT patients (2 male, 11 female) the presence of TPO-Ab was the only factor significantly predicting poorer psychological well-being.

It has been previously shown that childhood sexual abuse results in residual psychological and physiological trauma in a substantial number of women when adult (Friedman et al. 2005; Haviland et al. 2006). Plaza et al. (2010) showed a connection between postpartum thyroiditis and stress, by investigating a group of 103 consecutive patients with postpartum major depression, evaluating whether there was a connection between stress, induced by childhood trauma, and disturbances of the thyroid axis. Among the enrolled subjects, thirty-one women with postpartum major depression had positive thyroid antibodies and 9 had thyroid dysfunction. A statistical analysis showed that the risk of developing AITDs or dysregulation of the thyroid axis was more than two fold higher in women with postpartum depression who had a history of childhood sexual abuse compared with women with postpartum depression.

**DISCUSSION**

The present review has provided up-to-date insights on the current state of knowledge about the relationship between stress and the occurrence of AITDs in women. Although there is a shortage of research available that includes women subjects, we explored the available literature to answer the question of whether there is a connection between altered thyroid autoimmune function and pathophysiological changes of the stress system.

In addition to the large amount of information on the link between stress and the onset of GD, less data are available on the relationship between stressful life events and HT.

Due to the rapid onset of hyperthyroidism in GD, symptoms are promptly reported by the patient and the disease is diagnosed early (Effraimidis et al. 2011). By contrast, hypothyroidism in HT is commonly under-diagnosed because the onset is gradual, and changes are subtle (Bagnasco et al. 2006; Mizokami et al. 2004).

The majority of the studies that we explored showed causality between AITDs and stress, although their protocols were not homogeneous and did not unequivocally explain the mechanisms through which stress may contribute (or not) to the onset and course of AITDs in women. However, some of the results could be contradictory due to general methodological problems. In our opinion, the major limitation of studies dealing with stress is the heterogeneity in objectively quantifying the impact of stressful life events among individuals, especially when the impact of the stress is quantified only by self-rated questionnaires or is based on the theoretical (obvious) effects of stress on the immune-neuroendocrine system.

Previous systematic reviews (Lichiardopol & Mota 2009; Mizokami et al. 2004) illustrated the supposed mechanism by which stress may directly or indirectly affect the immune system through the activation of the nervous and endocrine systems and the subsequent development of AITDs. A causal role of emotional stress in the pathophysiology of GD has been recently supported by an interesting review (Falgarone et al. 2013) in which the authors highlighted the significance of stress management as an important part of GD treatment.

It has been reported that there is a blunted cortisol response to ACTH stimulation in autoimmune hyperthyroidism (GD) (Tsatsoulis et al. 2000; Agbaht & Gullu

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**Tab. 2.** Selected clinical studies on the connection between stress and Hashimoto’s thyroiditis and its variant (postpartum thyroiditis*).

<table>
<thead>
<tr>
<th>REFERENCES</th>
<th>SUBJECT (M/F)</th>
<th>IMMUNO-ENDOCRINE SUBCLINICAL INDICATORS OF AITDs</th>
<th>EVALUATION OF STRESS</th>
<th>STRESS-AITDs CONNECTION?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strieder et al. 2005</td>
<td>183 (0/183)</td>
<td>TPO, Tg</td>
<td>TSH, FT4</td>
<td>Yes</td>
</tr>
<tr>
<td>Terzidis et al. 2010</td>
<td>57 (8/49)</td>
<td>TPO, Tg</td>
<td>TSH, T3, FT4</td>
<td>No</td>
</tr>
<tr>
<td>Effraimidis et al. 2012</td>
<td>790 (0/790)</td>
<td>TPO, Tg, TRAb</td>
<td>TSH, T3, FT4</td>
<td>No</td>
</tr>
<tr>
<td>Müssig et al. 2012</td>
<td>64 (8/56)</td>
<td>TPO, Tg, TRAb</td>
<td>TSH, FT4, FT3</td>
<td>Yes</td>
</tr>
<tr>
<td>Plaza et al. 2010*</td>
<td>103 (0/103)</td>
<td>TPO, Tg</td>
<td>TSH, T3, FT4</td>
<td>Yes</td>
</tr>
</tbody>
</table>
2014), which may suggest that hyperthyroidism itself, as is the case in chronic stress exposure, results in a reduced concentration of circulating glucocorticoids (Mc Ewen 2007; Pippi et al. 2014) and in an increased susceptibility to autoimmune disorders (Kassi et al. 2012). In addition, several studies have reported a blunted adrenocortical response in patients suffering from generic chronic diseases (Buske-Kirschbaum et al. 2003; Delle Chiaie et al. 2013; Ghiciuc et al. 2013), which is consistent with McEwen's allostatic load model that states that the dysregulation of the HPA axis in response to repeated challenges may manifest as a flatter diurnal pattern of cortisol production (Mc Ewen 1998; Mc Ewen 2007).

Even during the postpartum period, there is suppression of the hypothalamic Corticotropin Releasing Hormone (CRH) secretion and decreased activity of the HPA axis, resulting in a rebound reaction of the immune system, leading to a shift toward the secretion of pro-inflammatory cytokines (Tsatsoulis 2006). This may explain the high incidence of autoimmune disorders in the postpartum period after the cessation of the physiological hyper-cortisolism and in subjects with untreated or inadequately substituted adrenal insufficiency (Kassi et al. 2012; Tsatsoulis 2006).

The results of numerous experimental studies (Helmrech et al. 2005; Helmreich & Tylee 2011; Johnson et al. 2005; Johnson et al. 2013) are in favor of the fact that there is a connection between experimentally-induced hyperthyroidism and hyper-corticosteronemia in rat models. Clinically, the protocols are more heterogeneous, and we must acknowledge that most of the studies on stress involvement were based on self-reported data from questionnaires administered at the time of diagnosis; in addition, apart from the problem of recall bias, no subclinical indicators of stress system activity (more objective) are used to measure the actual level of stress. Therefore, stress-induced damages often remain in the perception of the clinicians, although inadequate reactions by the repeated or chronic activation of these pathways, stress duration, and magnitude or frequency of the stressor can cause important physical, behavioral and neuro-psychological changes, leading to disease (Conte-Devolx & Vialettes 2013; Dima-Cozma et al. 2014; Kassi et al. 2012; Lucassen et al. 2014; McEwen 2008).

It is well-documented that chronic hyper-activation of the HPA axis during prolonged stress is thought to play a key role in the clinical manifestations of neuropsychiatric (anxiety, depression, cognitive disorders), cardio-circulatory (hypertension, atherosclerotic disease), metabolic (type 2 diabetes mellitus, obesity) and autoimmune diseases associated with allostatic overload (Chrousos 2009; Kassi et al. 2012). Moreover, even thyrotoxicosis itself could be regarded as a chronic stressful condition (Fukao et al. 2003). If stress would play a provocative role in the onset of AITDs, one would expect the occurrence of the earliest immunological indicators of AITDs (i.e., TPOAb) as an after-effect of stress exposure. However, no association has been found between stressful life events, daily hassles, mood deterioration and the presence of anti-TPOAb in euthyroid women (Striedter et al. 2005).

Furthermore, there are increasing evidences that early-life stressful events can significantly increase the risk of developing depression and AITDs later in life (Friedman et al. 2005; Haviland et al. 2006; Leyhe & Müßig 2014; Plaza et al. 2012). Hyperthyroid patients may tend to exaggerate the negativity of their stressful life experiences through their symptoms. Stressful life events can indeed precipitate the onset of mood disorders, which in turn may be a trigger factor for hyperthyroidism (Lee et al. 2003; Lucassen et al. 2014). Dysphoria and mood disorders are known as common complications of hypo- or hyper-thyroidism. Hyperthyroidism is often associated with various neuropsychological and psychiatric conditions such as memory and attention impairments, depressive mood, anxiety and psychomotor deficits (Bagnasco et al. 2006; Brouwer et al. 2005; Carta et al. 2004; Giynas Ayhan et al. 2014; Radhakrishnan et al. 2013).

**CONCLUSIONS**

There are many studies that have speculated on the pivotal role of the HPA axis on the relationship between stress and autoimmune diseases. Under stress, both glucocorticoids and catecholamines may affect the onset and the course of AITDs. However, as far as we know, objective measures of maladaptive lifestyle, referred to by McEwen (1998; 2006) as allostatic overload, as well as clinical and subclinical indicators of SAM system function in AITDs, are almost completely lacking.

Therefore, further research is needed to study the possible role of stress on the course and occurrence of AITDs in genetically predisposed women.

Finally, because the current options for preventive interventions in subjects at risk for developing AITDs are very limited, there is a need for prospective studies to determine whether stress management, especially in women, could modify the course of AITDs and improve patient coping strategies for challenging life events.

**ACKNOWLEDGEMENTS**

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**Conflicts of interest**

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Lisandra Damian, et al.


