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REVIEW ARTICLE

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; Prummel *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 sympathetic-adrenomedullary system (SAM) (Boutzios & Kaltsas 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; Tsatsoulis 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

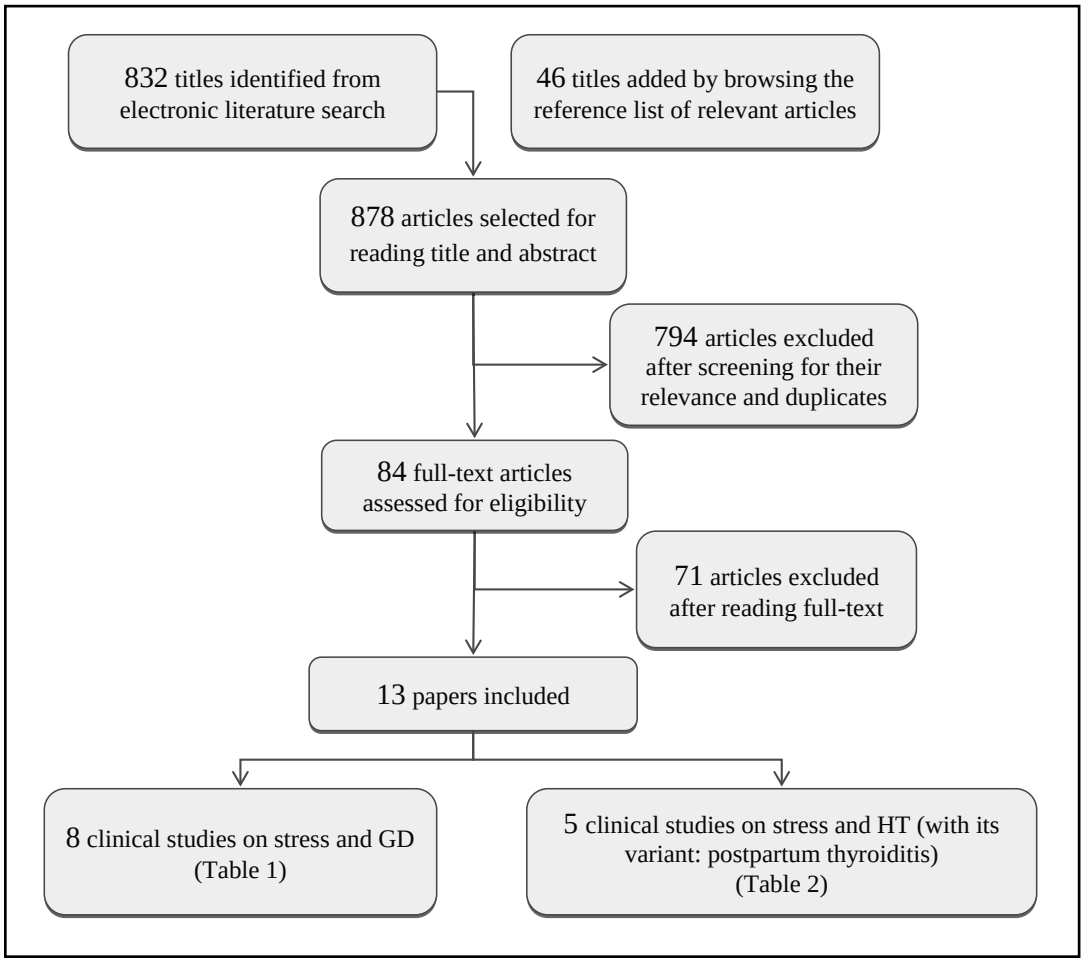

Fig. 1. Flow chart of study selection.

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

REFERENCES	SUBJECT (M/F)	IMMUNO-ENDOCRINE SUBCLINICAL INDICATORS OF AITDs		EVALUATION OF STRESS			STRESS – AITDs CONNECTION?
		Antibodies	Hormones	Self-reported questionnaires	HPA axis subclinical indicators	SAM subclinical indicators	
Matos-Santos *et al.* 2001	93 (21/72)	TPO, Tg, TRAb	TSH, FT3, FT4	Yes	No	No	Yes
Tsatsoulis *et al.* 2000	10 (4/6)	TPO, Tg	TSH, T3, T4	No	Yes	No	Yes
Fukao *et al.* 2003	69 (4/65)	TPO, Tg, TRAb	TSH, FT4	Yes	No	No	Yes
Vos *et al.* 2009	263 (69/194)	TRAb, TPO	TSH, FT4, FT3	Yes	No	No	No
Fukao *et al.* 2011	64 (10/54)	TRAb	TSH, FT3, FT4	Yes	No	No	Yes
Effraimidis *et al.* 2012	790 (0/790)	TPO, Tg, TRAb	TSH, T3, FT4	Yes	No	No	No
Agbaht & Gullu, 2014	41 (19/22)	TRAb	TSH, FT3, FT4	No	Yes	No	Yes
Vita *et al.* 2015	58 (22/36)	No	TSH, FT3, FT4	Yes	No	No	Yes

(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-supression test (DST) in 10 GD patients (4 male, 6 female). The results showed an attenuated response to the Adrenocorticotropic 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 a 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 with AITDs 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 an 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.

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

REFERENCES	SUBJECT (M/F)	IMMUNO-ENDOCRINE SUBCLINICAL INDICATORS OF AITDs		EVALUATION OF STRESS			STRESS-AITDs CONNECTION?
		Antibodies	Hormones	Self-reported questionnaires	HPA axis subclinical indicators	SAM subclinical indicators	
Strieder *et al.* 2005	183 (0/183)	TPO, Tg	TSH, FT4	Yes	No	No	No
Terzidis *et al.* 2010	57 (8/49)	TPO, Tg	TSH, T3, FT4	No	Yes	No	Yes
Effraimidis *et al.* 2012	790 (0/790)	TPO, Tg, TRAb	TSH, T3, FT4	Yes	No	No	No
Müssig *et al.* 2012	64 (8/56)	TPO, Tg, TRAb	TSH,FT4, FT3	Yes	No	No	Yes
Plaza *et al.* 2010*	103 (0/103)	TPO, Tg	TSH, T3, FT4	Yes	No	No	Yes

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 underdiagnosed 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

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 (Helmreich *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 (Strieder *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. Hypothyroidism 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.

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Conflicts of interest

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