Stress and Thyroid Disease

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1 Introduction

Graves’ disease (GD) is one of the most frequently seen thyroid disorders characterized by hyperthyroidism, goiter and extrathyroidal manifestations such as exophthalmos. Various genetic factors and environmental factors affect pathogenesis of GD (Akamizu, 1997). In particular, the role of emotional stress including psychosocial strain, trauma and stressful life events has been the subject of considerable debate since Caleb Parry (1825) who first described the syndrome of hyperfunction of the thyroid gland attributed the disorder in his young female patient to the fear she had experienced when thrown out of her wheelchair when coming down a hill, fast. Graves, Basedow and others reported similar debates. There are many reports on the association between stress and the onset of GD or thyrotoxicosis. However, most early reports were anecdotal and various epidemiologically problems. Recently, many epidemiologically improved study have demonstrated that GD patients had more stress than controls subjects prior to the onset of hyperthyroidism and stress had an unfavorable effect on the prognosis of GD. If stress affect the prognosis of GD, psychosomatic therapeutic approaches may improve the disease.

This review described the role of psychosocial factors including personality traits as well as stresses on the etiology of thyroid diseases for physicians to be able to utilize in the clinical setting. Our recent studies in GD were also included in this paper. Because there are some studies about the relationship between stress and other thyroid diseases including Hashimoto’s thyroiditis, Plummer’ disease and benign thyroid nodule, we introduced these reports.

2 Stress and GD

2.1 Emotional Stresses on the Onset of GD

To this day, many research efforts are still directed at exploring the possible role of stress on the onset of GD. These early reports were followed by epidemiological observations of an increase of GD or thyrotoxicosis during major wars, a condition named “Kriegbasedow”. Indeed, the incidence of GD significantly increased in Scandinavian countries during WW II (1939-1945) and returned to normal rates after the war (Gorman, 1990). Bram (1936) found that 2842 patients in 3343 GD patients (85%) had experienced trauma before disease had occurred. But this study and other early studies (Lids & Whitehorn, 1949; Mandelbrote & Wittkower, 1955; Hadden & McDevitt, 1974) were uncontrolled and more recent authors have used unstandardized research instruments or inadequate epidemiological method, small size, improper controls, poor differential diagnosis within thyrotoxicosis.

Winsa et al (1991) has reported the first large population-based case-control study demonstrating a relationship between stress and GD. 208 (95%) of 219 eligible patients with newly diagnosed GD and 372 (80%) of all selected matched controls answered an identical mailed questionnaire about marital status, occupation, drinking and smoking habits, physical activity, familial occurrence of thyroid disease, life events, social support and personality. Compared with controls, GD patients claimed to have had more negative life events in 12 months preceding the diagnosis, and negative life-event scores were also significantly higher (odds ratio 6.3, 95% confidence interval 2.7-14.7, for the category with the highest negative score). When results were adjusted for possible confounding factors in multivariate analysis, risk estimates were almost unchanged. After this report, many case control studies were reported. Sonino et al (1993) reported by structured interview that 70 GD patients had reported significantly more life events
compared to 70 controls. They also have had more independent events on thyrotoxicosis that had an objective negative impact according to an independent rater, unaware whether the events had occurred in patients or controls. Kun (1995) reported by questionnaires that 95 GD patients had reported more daily hassles as well as negative life events compared to 95 controls. Radosaljevic et al (1996) reported by structured interview that 100 GD patients had reported more independent life events and potentially dependent life events on illness compared to 100 controls. Yoshiuchi et al (1998) reported by questionnaires that 182 female GD patients had reported more life events compared to 228 controls but daily hassles were not significant different. Matos-Santos et al (2001) reported by structured interview that 31 GD patients had reported more stressful life events compared to 30 toxic nodular goiter (Plummer’s disease) patients and 31 controls, and no significant differences were found between toxic nodular goiter patients and controls. Paunkovic et al (1998) also reported that the incidence of GD significantly increased in eastern Serbia during the civil war from 1992 to 1995, and the incidents of Plummer’s disease did not increase for the same period. These retrospective data suggest the positive relationship between stress and the onset of GD.

Conversely, some authors obtained contradictory findings. Gray and Hoffenberg (1985) found no association between stressful life events in 50 thyrotoxic patients by structured interview. However, this study have some methodological problems that the date of onset of symptoms was uncertain, thyrotoxic patients include GD and toxic nodule and 50 control subjects were not healthy subjects but non toxic goiter. Chiovato et al (1998) could not find past or present GD patients in 87 patients with panic disorder encompassing a total of 478 patient-years of exposure to recent endogenous stress unrelated to life events. Martin-du Pan (1998) evaluated the role of major stress and pregnancy in triggering autoimmune thyroid disease in 98 GD patients and 97 patients with benign thyroid nodules. There were no significant differences of stress factors between two groups, and generally the role of stress in triggering GD seemed weak and dubious compared to the role of pregnancy and the postpartum period. Effraimidis et al (2011) reported a prospective cohort study on the association between stress and the onset of autoimmune thyroid disease (AITD) in 521 euthyroid women who were 1st or 2nd degree relatives of AITD patients. They could not find that stress factors (stressful life events, daily hassles and negative feeling) involved in the onset of GD including development of TPOAb and hyperthyroidism.

Some criticisms of case-control studies were proposed (Chiovato & Pinchera, 1996; Mizokami, et al, 2004). There are some general methodological problems and limitations in studies dealing stress, especially preceding retrospective studies based on the assessment of life events preceding thyrotoxicosis or the diagnosis of GD. Firstly, the main scientific problem is the difficulty in defining “stress” and objectively quantifying individual stressors. Second, the recall bias cannot be avoided in retrospective studies. GD patients may be more prone to recall stressful life events than healthy controls. Third, it is impossible to date the onset of GD precisely. Thus stressful life events may occur after the onset of GD. Some studies investigated life events in the 12 months before diagnosis, rather than before the first symptoms or signs. However, some events could have occurred between the onset and diagnosis. Finally, thyrotoxicosis itself can cause psychological disturbance and behavioral changes such as anxiety and depression, which may have an effect on life events. So, some stressful life events may be the consequence rather than the trigger for disease development. Though each above-mentioned study was planned with various devices, some problems remained. So the role of stress on the onset of GD is still controversial.
2.2 Emotional Stresses on the Clinical Course of GD

2.2.1 Previous Studies

On the other hand, there are case reports in which emotional stress induced an exacerbation and relapse of hyperthyroidism. Ferguson-Rayport (1956) reported that the course of thyrotoxicosis in 20 patients during antithyroid drug (ATD) treatment had seemed to be related to the patient’s ability to cope with life stress psychologically, especially when confronted with loss or bereavement. If successful solutions were found, the illness subsided; if not, the exacerbation progressed. Voth et al (1970) reported that among 239 women the hyperfunctioning regions on thyroid scintiscans had appeared to wax and wane in a direct relationship with life stress followed for 12 years, and some women developed clinical thyrotoxicosis during conditions of severe or prolonged life strain. Yoshiuchi et al (1998) investigated the association between the short term outcome of 230 newly diagnosed GD patients, assessed 12 months after the ATD therapy, and stressful life events. They reported that daily hassles at 6 months after beginning therapy were associated with continued hyperthyroid state 12 months later in female patients.

It seems that a therapeutic approach to the patients’ psychology such as stress management is effective in improving the prognosis of hyperthyroidism. Indeed, there is a brief interesting report (Benvenega, 1996) in which administration of minor tranquilizer (bromazepam) together with ATD increased the remission rate of hyperthyroidism.

2.2.2 Our Studies on Psychiatric Abnormality and Stress

We (2003) have determined three psychological tests including the Minnesota Multiphasic Personality Inventory (MMPI) for personality traits, the Natsume’s Stress Inventory for stressful life events and the Hayashi’s Daily Life Stress Inventory for daily life stress in 69 GD patients who had been a euthyroid state after ATD medication for more than two years and 32 healthy subjects (Table 1). When the patients were divided according to prognosis (41 with relapse and 28 with remission), depressive personality traits including hypochondriasis, depression and psychasthenia were significantly more common in the relapsed GD group than those of the remitted group and control group (Table 2). The scores of daily hassles were also significantly greater in the relapsed GD group than in the remitted GD group and control group (Figure1). In the GD patients, stress scores of life events correlated significantly with serumTSH receptor antibody (TRAb) activity ($r = 0.424, P < 0.001$) and thyroid volume ($r = 0.480, P < 0.001$) (Table 3). The scale scores of depression and psychasthenia showed a positive correlation with scores of daily hassles ($r = 0.535, P < 0.001$; $r = 0.580, P < 0.001$, respectively), while an inverse correlation with scores of daily uplifts ($r = -0.0373, P < 0.05$; $r = -0.322, P < 0.05$, respectively) (Table 3).

We (2011) also determined the MMPI for personality traits, the Natsume’s Stress Inventory, and the Hayashi’s Daily Life Stress Inventory before and during ATD treatment in 64 untreated GD patients. In the untreated thyrotoxic state, depressive personality (T-scores of hypochondriasis, depression or psychasthenia greater than 60 points in MMPI) were found for 44 patients (69%) (Figure 2). For 15 (23%) (group C) of these patients, the scores decreased to the normal range after treatment. However, depressive personality persisted after treatment in the remaining 29 patients (46%) (group A). Normal scores before treatment were found for 20 patients (31%), and the scores were persistently normal for 15 patients (23%) (group D). The remaining 5 patients (8%) (group B) had higher depressive personality after treatment. Such depressive personality was not associated with the severity of hyperthyroidism before treat-
### Table 1: Clinical profiles and thyroid function tests in two groups of GD patients on ATD and normal controls. The data are shown as mean±SD.

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of Subjects</th>
<th>Male / Female</th>
<th>Age (years)</th>
<th>Duration of Therapy (years)</th>
<th>FT₄ (pmol/l)</th>
<th>TSH (mU/l)</th>
<th>TRAb (%)</th>
<th>Thyroid Volume (ml)</th>
<th>MCPA (percent positive) (%)</th>
<th>TGPA (percent positive) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed Graves' disease</td>
<td>41</td>
<td>3/38</td>
<td>39.3±14.6</td>
<td>3.1±0.9 (2.0–5.0)</td>
<td>16.86±4.63</td>
<td>0.76±1.21*+</td>
<td>24.9±21.9§</td>
<td>43.8±22.8§</td>
<td>93**</td>
<td>29**</td>
</tr>
<tr>
<td>Remitted Graves' disease</td>
<td>28</td>
<td>1/27</td>
<td>43.4±12.4</td>
<td>2.9±1.0 (2.0–4.7)</td>
<td>16.86±3.60</td>
<td>1.86±2.07 3.8±3.9†</td>
<td>24.4±6.2§</td>
<td>89**</td>
<td>39**</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>32</td>
<td>1/31</td>
<td>36.7±12.6</td>
<td>--</td>
<td>16.22±3.22</td>
<td>1.57±1.23 0.7±2.3</td>
<td>10.2±2.5 4.8±3.9¶</td>
<td>24.4±6.2¶</td>
<td>89**</td>
<td>39**</td>
</tr>
</tbody>
</table>

* P < 0.05, vs. controls by Fisher’s PLSD test.  
+ P < 0.05, vs. remitted Graves’ disease by Fisher’s PLSD test.  
# P < 0.001, vs. controls by Mann-Whitney’s test.  
§ P < 0.001, vs. remitted Graves’ disease by Mann-Whitney’s test.  
¶ P < 0.05, vs. controls by Mann-Whitney’s test.  
** P < 0.001, vs. controls by χ² test for independence.

### Table 2: Comparison of clinical scales of MMPI among the three groups of subjects. The data are shown as mean±SD of T-scores in MMPI. T-scores express the psychiatric tendency by each clinical scale.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Hypochondriasis</th>
<th>Depression</th>
<th>Conversion Hysteria</th>
<th>Psychopathic deviation</th>
<th>Masculity / Feminity</th>
<th>Paranoia</th>
<th>Psychosclerosis</th>
<th>Social Introversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed Graves' disease</td>
<td>53.7±10.7*#</td>
<td>57.8±13.7**#</td>
<td>55.6±9.7**</td>
<td>55.0±12.4*</td>
<td>50.3±8.9 54.4±12.5§</td>
<td>57.5±15.3§</td>
<td>53.6±14.9†</td>
<td>49.0±10.2 53.9±10.8</td>
</tr>
<tr>
<td>Remitted Graves' disease</td>
<td>48.2±8.6</td>
<td>50.0±9.9</td>
<td>51.6±8.1</td>
<td>51.0±8.0</td>
<td>50.4±9.7 48.1±10.1</td>
<td>50.3±10.9</td>
<td>49.4±9.7</td>
<td>47.3±9.9 51.4±8.5</td>
</tr>
<tr>
<td>Controls</td>
<td>46.2±7.9</td>
<td>46.6±8.1</td>
<td>49.5±9.0</td>
<td>48.6±8.6</td>
<td>48.3±6.6 52.6±6.5</td>
<td>46.8±8.6</td>
<td>46.5±7.8</td>
<td>48.1±10.5 48.9±10.0</td>
</tr>
</tbody>
</table>

* P < 0.001, vs. controls by Fisher’s PSD test.  
† P < 0.05, vs. controls by Fisher’s PLSD test.  
# P < 0.05, vs. remitted Graves disease by Fisher’s PLSD test.
## Table 3: Correlation between psychological factors and thyroid-related parameters in 69 GD patients.

<table>
<thead>
<tr>
<th></th>
<th>Frequency of life events</th>
<th>Stress scores of life events</th>
<th>Daily hassles score</th>
<th>Daily uplifts score</th>
<th>MMPI depression</th>
<th>MMPI psychasthenia</th>
<th>Serum TRAb activity</th>
<th>Thyroid volume</th>
<th>Serum FT4 concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of life events</td>
<td>-</td>
<td>0.933**</td>
<td>0.189</td>
<td>0.173</td>
<td>0.150</td>
<td>0.013</td>
<td>0.396**</td>
<td>0.419*</td>
<td>-0.059</td>
</tr>
<tr>
<td>Stress scores of life events</td>
<td>-</td>
<td>0.225</td>
<td>0.194</td>
<td>0.103</td>
<td>0.031</td>
<td>0.424**</td>
<td>0.480*</td>
<td>0.077</td>
<td></td>
</tr>
<tr>
<td>Daily hassles score</td>
<td>-</td>
<td>0.193</td>
<td>0.535**</td>
<td>0.580**</td>
<td>0.009</td>
<td>0.083</td>
<td>0.009</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Daily uplifts score</td>
<td>-</td>
<td>-0.373*</td>
<td>-0.322*</td>
<td>0.054</td>
<td>0.144</td>
<td>-0.088</td>
<td>0.054</td>
<td>0.144</td>
<td></td>
</tr>
<tr>
<td>MMPI depression</td>
<td>-</td>
<td>0.784**</td>
<td>0.063</td>
<td>0.293</td>
<td>0.042</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMPI psychasthenia</td>
<td>-</td>
<td>-</td>
<td>0.032</td>
<td>0.032</td>
<td>-0.162</td>
<td>0.086</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum TRAb activity</td>
<td>-</td>
<td>0.527**</td>
<td>0.012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid volume</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum FT4 concentration</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Significant difference: *P < 0.05; **P < 0.001.

### Figure 1: Stressors and subjective appraisal on stress in the three groups of subjects. The data from each group are shown as mean ± SD. Significant differences (P < 0.05) between groups are represented by asterisks. Relapsed Graves’ disease; Remitted Graves’ disease; Controls, *P < 0.05 by Mann-Whiney’s test. **P < 0.05 by Fisher’s PLSD test.
Figure 2: Changes of the depressive personality of Graves’ disease patients before and during treatment. Depressive personality show the patients whose T-scores of hypochondriasis, depression or psychasthenia are greater than 60 points in MMPI. Group A: depressive personality was present before and persisted after treatment. Group B: depressive personality scores became higher after treatment. Group C: depressive personality was present before treatment and decreased to within the normal range after treatment. Group D: depressive personality did not appear either before or after treatment.

These findings suggest that in ATD treated GD patients, depressive personality during treatment when patients are euthyroid reflects the effect of emotional stresses rather than thyrotoxicosis and that it aggravates hyperthyroidism. So antidepressant may improve the prognosis of GD patients with depression. Indeed, the authors have experienced three cases of first remission after long term ATD treatment together with antidepressants (paroxetine) in GD patients with depression (Fukao, 2010).

2.2.3 Our Studies on Ego States, Depression and Alexithymia

We (2000a) determined three types of questionnaires in 61 ATD-treated GD patients for more than two years (37 with relapse and 24 with remission) and 21 healthy subjects to examine which patterns to cope with patients’ feeling and thinking relate to either prognosis of hyperthyroidism or accompanied psychiatric symptoms. The Toronto Alexithymia Scale-20 (TAS-20) including factor 1 (difficulty of identifying feeling), factor 2 (difficulty of describing feeling) and factor 3 (externally oriented thinking) was used for assessment of alexithymic personality relating to psychosomatic disorder. The Tokyo University Egogram (TEG) including terms of critical parent (CP), nurturing parent (NP), adult (A), free child (FC) and adapted child (AC) was used for assessment of ego state. Self-rating Depression Scale (SDS) was also used for assessment of depression.
Figure 3: Comparisons of thyroid functions and severity of hyperthyroidism among four groups. The data from each group are shown as mean ± SD. Group A (29): depressive personality was present before and persisted after treatment. Group B (5): depressive personality scores became higher after treatment. Group C (15): depressive personality was present before treatment and decreased to within the normal range after treatment Group D (15): depressive personality did not appear either before or after treatment. There were no significant differences in any parameters among the four groups by ANOVA.

Figure 4: Comparisons of emotional stresses between the depression and non-depression groups. The closed bar express the depression group (34), even in the euthyroid state (group A and B) and open bar express the remaining non-depression group (30) without depressive personality (group C and D). The data from each group are shown as mean±SD. Significant difference: *P < 0.005 by Mann-Whitney’s test.
Figure 5: Comparison of the prognosis of hyperthyroidism between the depression and non-depression groups. The data from each group are shown as mean±SD. The gray zone expresses the normal ranges. Significant difference: *P < 0.05 by Student t-test. Remission rate: depressive group 22% (5/23) vs non-depressive group 52% (13/25) (P < 0.05 by chi-square test).

In TAS-20, total scores, scores of factor 1 and factor 2 were significantly (P < 0.05) greater in the relapsed GD group than in the remitted GD group. In TEG, scores of A scale, showing ability of rational consideration, and FC scale, showing ability of describing feeling, were significantly (P < 0.05) greater in the remitted GD group than in the relapsed GD group. Scores of AC scale, showing tendency of suppressing feelings, were significantly (P < 0.05) lower in the remitted GD group than in the relapsed GD group. Scores of SDS were significantly (P < 0.001) greater in the relapsed GD group than in the remitted GD group. In total patients, total scores of TAS-20, scores of factor 1, factor 2, AC scale and SDS significantly (P < 0.001) correlated each other. On the other hand, scores of A and FC scales significantly (P < 0.05) correlated with total scores of TAS-20, factor 2 and SDS negatively. The results suggest that difficulty of identifying and describing feeling relate to both aggravation of hyperthyroidism and depressive state. Conversely, the ability of describing feeling and rational consideration relate to the good prognosis of hyperthyroidism.

Then, we (2002) carried out a prospective study to confirm the relationship between ego states of GD patients evaluated by TEG and prognosis of hyperthyroidism. Seventy three GD patients were divided into two groups; high A group (44 patients) whose A at euthyroid state after ATD treatment were greater than 50 percentile and low A group (29 patients) whose A were lower than 50 percentile. The relationships between ego states of these groups and prognosis of disease at three years were investigated. Additionally, similar relationships were investigated in another two groups; FC predominant group (40 patients) who’s FC was greater than AC and AC predominant group (33 patients) who’s AC were greater
than FC conversely. Age, sex, rates of smoking, serum FT4, FT3 concentrations, serum TBII (TRAb), TSAb activities, 131I-uptake, goiter size before treatment were not significant different between each groups (Table 4). Serum FT4 and TSH concentrations were not significant different between high A group and low A group during treatment (Figure 6). But serum TBII activity and diameter of thyroid were significantly ($P < 0.05 \sim 0.001$) higher in low A group than in high A group and remission rate at three years were significantly ($P < 0.01$) lower in low A group than in high A group (10% vs 41%). Remission rate at three years were also significantly ($P < 0.05$) lower in AC predominant group than in FC predominant group (18% vs 40%) (Figure 7).

<table>
<thead>
<tr>
<th></th>
<th>Number (male / female)</th>
<th>Age (years old)</th>
<th>Rate of smoking</th>
<th>Serum thyroid concentration</th>
<th>Serum TSH receptor antibody activity</th>
<th>$^{123}$I – uptake (%)</th>
<th>Thyroid volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High A group</strong></td>
<td>44/44 (7/37)</td>
<td>39.7 ±14.3</td>
<td>10/44 (23%)</td>
<td>5.08 ±1.98</td>
<td>16.37 ±7.05</td>
<td>45.8 ±22.8</td>
<td>48.8 ±11.3</td>
</tr>
<tr>
<td><strong>Low A group</strong></td>
<td>29/29 (4/25)</td>
<td>34.6 ±13.2</td>
<td>9/29 (31%)</td>
<td>5.29 ±1.63</td>
<td>16.04 ±6.46</td>
<td>48.7 ±24.4</td>
<td>52.5 ±6.07</td>
</tr>
<tr>
<td><strong>FC predominant group</strong></td>
<td>40/33 (7/33)</td>
<td>37.6 ±13.5</td>
<td>10/40 (25%)</td>
<td>5.17 ±1.93</td>
<td>16.81 ±6.97</td>
<td>47.0 ±22.5</td>
<td>49.1 ±11.6</td>
</tr>
<tr>
<td><strong>AC predominant group</strong></td>
<td>33/33 (4/29)</td>
<td>37.8 ±14.9</td>
<td>9/33 (27%)</td>
<td>5.15 ±17.6</td>
<td>15.44 ±6.58</td>
<td>46.7 ±24.6</td>
<td>51.1 ±7.00</td>
</tr>
</tbody>
</table>

Table 4: Comparison of pretreatment clinical profiles and thyroid function tests between each groups of GD patients.

These results confirm that ability of rational consideration and expressing feeling of ATD treated GD patients are important to get early remission. It can be concluded that psychotherapies for patients to think rationally, to express feeling and to cope with the stress in the positive manner may be useful in improving the disease prognosis. Indeed, the authors had two cases of patients with successful outcome by conventional medication and psychotherapy (Fukao, 2000b). Recently, Tanaka et al (Tanaka, 2013) reported that the remission rate of ATD treated GD patients was significantly higher in the patients group with longer (over than 31 times) psychotherapy than in the patients group with shorter (less than 5 times) psychotherapy.
Figure 6: Comparison of prognosis of hyperthyroidism between high A group and low A group. The data from each group are shown as mean±SD. The gray zone express the normal ranges. Significant difference: *P < 0.05; **P < 0.01; ***P < 0.001.

Figure 7: Comparison of prognosis of hyperthyroidism between the FC predominant group and the AC predominant group. The data from each group are shown as mean±SD. The gray zone expresses the normal ranges. Significant difference: *P < 0.05
3 Stress and Hashimoto’s Thyroiditis

In contrast to GD, there are few studies on the relationships between stress and Hashimoto’s thyroiditis (HT). Two case-control studies (Martin-du Pan, 1998; Oretti et al, 2003) evaluated the role of stressful life events in HT or postpartum thyroiditis. They concluded that stress was not a trigger in either condition. Because the onset and clinical course of HT are often insidious and the diagnosis may be delayed until the patients develop overt hypothyroidism, it is difficult to assess the role of stress on the onset and clinical course of disease. A population study (Strieder, 2005) also did not find a relationship between stress and the presence of anti-TPOAb. Effraimidis et al (2011) reported a prospective cohort study on the association between stress and the onset of AITD in 521 euthyroid women who were 1st or 2nd degree relatives of AITD patients. They could not find that stress involved in the development of TPOAb and hypothyroidism.

On the other hand, painless thyroiditis often occurs after cure from Cushing’s syndrome or discontinuation of glucocorticoid therapy. These situations are similar to the situations after activation of hypothalamic-pituitary-adrenal axis by stress. So that future studies about the role of stress in HT or autoimmune thyroiditis are needed.

4 Stress and Thyroid Nodule

There are also few studies about the relationships between stress and thyroid nodule. All studies were determined stress as control groups in benign thyroid nodule or toxic nodular goiter compared to GD patients. Gray and Hoffenberg (1985) found no association between stressful life events and 50 thyrotoxic patients and 50 non toxic goiters. Martin-du Pan (1998) evaluated the role of major stress in 98 GD patients and 97 patients with benign thyroid nodules. There were no significant differences of stress factors between two groups. Matos-Santos et al (2001) reported that 31 GD patients had reported more stressful life events compared to 30 toxic nodular goiter patients and 31 controls, and no significant differences were found between toxic nodular goiter patients and controls. Paunkovic et al (1998) also reported that the incidence of GD significantly increased in eastern Serbia during the civil war from 1992 to 1995, and the incidents of Plummer’s disease did not increase for the same period. These data suggest that stress is not associated with the etiology of thyroid nodule.

5 Stress and Thyroid Autoimmunity

Mechanism of effects of stress on the pathogenesis of GD is still controversial. Volpe (1991) proposed that a defect of antigen-specific suppressor T-lymphocytes is partially responsible for the initiation of GD. Stress may cause a generalized suppressor T-lymphocytes defect and TRAb may be produced as a result of a specific defect in immunologic surveillance though the relationships are still not established. Some reports (Paschke et al, 1990; Harsch et al, 1992) that GD patients with depression and anxiety exhibit abnormal peripheral helper/suppressor T-lymphocyte ratios support this hypothesis. GD is generally considered to be a Th2-predominant disease. Both endogenous glucocorticoids and cathecholamines at concentrations observed during periods of stress cause a selective suppression of Th1 response and a shift toward Th2-mediated immunity (Elenkov & Chrousos, 1999; Elenkov et al, 2000). This Th2 shift may
affect the onset or course of GD (Chrousos & Gold, 1992). On the other hand, HT is generally considered to be a Th1-predominant disease. OS chickens, which are an animal model of autoimmune thyroiditis is influenced by a reduced glucocorticoid tonus and painless thyroiditis often occur after cure from Cushing’s syndrome or discontinuation of glucocorticoid therapy (Ader et al., 1995; Chrousos, 1995). These situations have been associated with increased susceptibility to Th1-mediated immune disorders. This might also include the period that follows cessation of chronic stress or a rebound reaction upon relief of various stressors. Tsatoulis (2006) proposed hypothesis shown in Figure 8. Genetic and environmental factors may induce an aberrant immune response against thyroid autoantigens and render an individual susceptible to develop thyroid autoimmunity. If an individual is under stress, the stress hormones will influence the antigen-presenting cell (APC) to steer the balance toward Th2-type activity. Effector Th2 cells and type 2 cytokines will induce antigen-specific B lymphocytes to produce TRAb. Under these circumstances, the clinical outcome is GD. Conversely, if a susceptible individual is recovering from stress response or the immune suppressive effect of pregnancy, a rebound reaction may create the potential for APCs to activate the Th1-mediated pathway, leading to cellular immunity and destruction of thyroid follicular cells. The likely outcome then will be autoimmune or postpartum thyroiditis respetively. Further researches are needed to confirm the relationship between stress and thyroid autoimmunity.

![Figure 8: Role of stress in the clinical expression of AITD by Tsatsoulis](image)

6 Conclusion

Although there are many epidemiological and clinical reports on the relationship between stress and the onset of GD, it is still controversial. However, stress affects the prognosis of GD certainly. If further study sample would be enough large, the problems could be solved. Psychosomatic therapeutic approaches including antipsychiatric drugs and/or psychotherapy appear to be useful for improving the prognosis of hyperthyroidism. Stress may influence immune system both directly and indirectly through
the activation of the neural and endocrine systems. Further researches are needed to confirm the relationship between stress and thyroid diseases.

References


Paukovic, N., Paukovic, J., Palvovic, O. et al. (1998). The significant increase in incidence of Graves’ disease increased in eastern Serbia during the civil war in the former Yugoslavia (1992 to 1995). Thyroid, 8, 37-41.