Increased depression, diabetes and diabetic complications in Graves' disease patients in Asia

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Summary

**Background:** This study aimed to evaluate the risk of depression and other cardiovascular comorbidities in Graves' disease (GD) patients in Asia.

**Methods:** The study patients were all newly diagnosed with GD (International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) 242.0) from January 1998 to December 2008. Patients aged <20 years or those with preexisting mental disorder (ICD-9-CM 290-319) were excluded from analyses. Control patients were randomly selected for the non-GD cohort, 1:4 frequency matched to the GD cohort according to sex, age and index year. The same exclusion criteria applied to the GD cohort were applied to the non-GD cohort. The GD cohort contained 4195 patients and the non-GD cohort contained 16780 patients.

**Results:** The GD patients were more likely to have diabetes (8.03% vs. 4.48%, \(P<0.0001\)), hypertension (18.1% vs. 13.5%, \(P<0.0001\)), hyperlipidemia (11.9% vs. 9.09%, \(P<0.0001\)) and coronary artery disease (10.3% vs. 5.86%, \(P<0.0001\)) than the control patients were. The GD patients were also associated with significantly higher risk of depression than the control patients were (hazard ratio = 1.69, 95% confidence interval = 1.45–1.96).

**Conclusion:** GD and GD treatment are associated with increased risk of depression diabetes and diabetic complications in Asian patients.

Introduction

Depression is a common disease and a major cause of morbidity and mortality worldwide. Previous studies have identified associations between depression and other chronic diseases. For example, Egede identified that the risk of depression was 2-fold higher in patients with diabetes (DM), hypertension (HTN) and coronary artery disease (CAD), and 3-fold higher in patients with end-stage renal failure and cerebrovascular disease than healthy control patients.\textsuperscript{1} In a World Health Organization study on the 1-year prevalence of depression among 245 400 patients in 60 countries,\textsuperscript{2} the prevalence of depression was 23% in patients with chronic physical diseases in comparison with 3.2% in healthy control patients.

Graves' disease (GD) is an autoimmune disease, typically characterized by diffused goiter and thyrotoxicosis, and can be accompanied by orbitopathy.
or dermopathy. According to studies conducted in the USA\(^3\) and in the UK,\(^4\) the prevalence of hyperthyroidism is 1–2% in women, which is 10 times higher than the prevalence of hyperthyroidism in men. Vanderpump \textit{et al.} estimated the incidence of GD in the UK as 1 case per 1000 people per year.\(^4\) GD is the most common cause of spontaneous hyperthyroidism, and its symptoms include palpitations, weight loss, hand tremors and nervousness or emotional liability. Studies have reported numerous cases of thyrotoxic periodic paralysis in Asian men;\(^5\) however, few studies have investigated GD and its association with depression or cardiovascular comorbidities in Asian patients. Therefore, our study aimed to evaluate the risk of depression and cardiovascular comorbidities in GD patients in Asia.

**Methods**

**Data source**

The National Health Insurance (NHI) is a mandatory universal health insurance program, offering comprehensive medical care coverage to 99% of the entire Taiwanese population, and is contracted with 97% of Taiwan’s hospitals and clinics.\(^6\) The National Health Research Institute (NHRI) compiles all medical claims in the NHI program and released the National Health Insurance Research Database (NHIRD) from 1996 to 2010 to the public for research purposes. Data for this study were obtained from the NHIRD, including patient demographics and clinical information on outpatient, inpatient, emergency, and traditional Chinese medicine services, prescriptions, medical expenditures, and diagnoses and procedures coded in the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) format. The details of the NHIRD have been described previously.\(^7,8\) This study analyzed the 1 million beneficiaries randomly selected from all insurants from 1996 to 2000, which have been demonstrated to be representative of the entire population. The NHIRD encrypts the patients’ personal information for privacy protection and provides researchers with anonymous identification numbers associated with the relevant claim information, which includes the patient’s sex, date of birth, registry of medical services and medication prescriptions. Patient consent is not required for accessing the NHIRD. This study was approved by the Institutional Review Board of China Medical University in central Taiwan (CMU-REC-101-012).

**Study patients**

Patients with newly diagnosed GD (ICD-9-CM 242.0) from January 1998 to December 2008 were identified. Patients aged <20 years or those with preexisting mental disorder (ICD-9-CM 290–319) were excluded from analyses. Control patients were randomly selected for the non-GD cohort, 1:4 frequency matched to the GD cohort according to sex, age and index year. The same exclusion criteria applied to the GD cohort were applied to the non-GD cohort. The GD cohort contained 4195 patients and the non-GD cohort contained 16 780 patients.

**Outcome measures and covariates**

All of the patients were followed up from the index date until the end of 2010 or the occurrence of depression (ICD-9-CM 296.2, 296.3, 300.4 and 311). Patients were censored at the end of the study follow-up, their last record, or withdrawal from the database. Major comorbidities considered as covariates, such as HTN (ICD-9-CM 401–405), DM (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), CAD (ICD-9-CM 410–414) and stroke (ICD-9-CM 430-438) were recorded.

According to the treatments provided to the GD patients, the GD cohort was divided into seven mutually exclusive groups: without treatment, propranolol, antithyroid drugs (including propylthiouracil, methimazole and carbimazole), propranolol and antithyroid drugs, iodine-131 (I-131), operations, and I-131 and operations.

**Statistical analysis**

Distributions of demographic characteristics, including age, sex and comorbidities, were compared between the GD and non-GD cohorts by using chi-square tests. The incidence densities of the two cohorts were calculated using the demographic variables. A Poisson regression was used to calculate the incidence density and incidence rate ratio (IRR) of depression according to age and sex. A survival analysis was performed using the Kaplan–Meier method to estimate the depression-free survival curve in the GD and non-GD cohorts, with the level of significance established using the log-rank test. A multivariate Cox’s proportion hazard regression was used to examine the effects of GD on the risk of depression, as indicated by hazards ratios (HR) and 95% confidence intervals (CI). A two-tailed \(P\)-value <0.05 was considered statistically significant. All analyses were performed using the SAS statistical software (version 9.2 for Windows; SAS Institute, Inc, Cary, NC, USA).
Results

Table 1 displays the demographic characteristics and comorbidities of the study cohorts. The mean age of the non-GD cohort was 41.0 ± 14.1 years and that of GD cohort was 41.3 ± 13.7 years, with 75.3% of all patients aged <50 years. Women accounted for 77.5% of the study patients (Table 1). The GD patients were more likely to have DM (8.03% vs. 4.48%, \( P < 0.0001 \)), HTN (18.1% vs. 13.5%, \( P < 0.0001 \)), hyperlipidemia (11.9% vs. 9.09%, \( P < 0.0001 \)) and CAD (10.3% vs. 5.86%, \( P < 0.0001 \)) than the non-GD cohort were.

Overall, we identified 833 newly diagnosed cases of depression (582 non-GD patients and 251 GD patients), with an incidence density of 5.01 per 1000 person-years in the non-GD cohort and 8.67 per 1000 person-years in the GD cohort (IRR = 1.73, 95% CI = 1.59–1.89) (Table 2). In multivariate analyses, after controlling for baseline characteristics, the GD patients were associated with significantly higher risk of depression than the non-GD patients were (HR = 1.69, 95% CI = 1.45–1.96). Figure 1 displays the results of the log-rank test and the cumulative incidence curve of depression, in which the GD patients were associated with a significantly higher incidence of depression than the non-GD patients were (\( P \)-value for the log-rank test < 0.001).

In a sex-stratified analysis, the adjusted HR for depression was significantly higher in women

(HR = 1.66, 95% CI = 1.41–1.96) than in men (HR = 1.81, 95% CI = 1.24–2.66) (Table 2). In an age-stratified analysis, the risk of depression was highest in the patients aged \( \geq 65 \) years (HR = 1.86, 95% CI = 1.08–3.20), followed by those aged 20–34 years (HR = 1.79, 95% CI = 1.37–2.33), 35–49 years (HR = 1.64, 95% CI = 1.29–2.08) and 50–64 years (HR = 1.47, 95% CI = 1.06–2.04).

As shown in Table 3, when we stratified the GD and non-GD patients by comorbidities, we observed that the patients without DM (HR = 1.69, 95% CI = 1.45–1.98), HTN (HR = 1.65, 95% CI = 1.39–1.95), hyperlipidemia (HR = 1.68, 95% CI = 1.43–1.97), CAD (HR = 1.73, 95% CI = 1.48–2.03), or stroke (HR = 1.65, 95% CI = 1.42–1.92) were associated with significantly higher risk of depression than the patients with the comorbidities. The risk of developing depression was particularly high in the GD patients with stroke (HR = 5.56, 95% CI = 1.73–17.9).

Table 4 displays our analyses of the treatments associated with risk of depression in the GD patients. We observed significantly higher risk of depression in the patients treated with propranolol in comparison with the GD patients without treatment (HR = 2.14, 95% CI = 1.26–3.62). Other GD treatment types were no significantly associated with depression.

Discussion

GD, diabetes and diabetic complications

As shown in Table 1, in our study sample, GD predominantly affects women in the younger age group. In the study patients, GD is no significantly associated with risk of stroke (1.24% vs. 1.07%, \( P = 0.34 \)), but is associated with significantly increased risk of DM (8.03% vs. 4.48%, \( P < 0.0001 \)), HTN (18.1% vs. 13.5%, \( P < 0.0001 \)), hyperlipidemia (11.9% vs. 9.09%, \( P < 0.0001 \)) and CAD (10.3% vs. 5.86%, \( P < 0.0001 \)). The potential risk factors for GD might explain these findings. It is well known that GD is greatly influenced by hereditary factors, such as Hashimoto's disease, insulin-dependent DM and pernicious anemia. Stress is another factor that can increase the risk of GD. Terry et al. described that a high proportion of GD patients have a history of stress in the 12 months prior to GD onset. Stress can suppress immunity through non-specific mechanisms, secondary to the effects of cortisol and corticotrophin-releasing hormone on immune cells.

Previous study mentioned that different phenotypic expression of thyroid autoimmunity is

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparisons in demographic characteristics and comorbidities in patient with and without GD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GD (N= 16 780)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>13 008 (77.5)</td>
</tr>
<tr>
<td>Men</td>
<td>3772 (22.5)</td>
</tr>
<tr>
<td>Age stratified</td>
<td></td>
</tr>
<tr>
<td>20–34</td>
<td>6376 (38.0)</td>
</tr>
<tr>
<td>35–49</td>
<td>6260 (37.3)</td>
</tr>
<tr>
<td>50–64</td>
<td>5032 (18.1)</td>
</tr>
<tr>
<td>65+</td>
<td>1112 (6.63)</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>41.0 ± 14.1</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>752 (4.48)</td>
</tr>
<tr>
<td>HTN</td>
<td>2268 (13.5)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1526 (9.09)</td>
</tr>
<tr>
<td>CAD</td>
<td>983 (5.86)</td>
</tr>
<tr>
<td>Stroke</td>
<td>179 (1.07)</td>
</tr>
</tbody>
</table>

Chi-square test. *t-Test.
dependent on the balance of T helper (Th)1 or Th2 immune response. Stress hormone may influence the differentiation of bipotential Th cells through the possible pathway to act on antigen-presenting immune cells.\textsuperscript{13} Stress hyperglycemia and stress can also induce hyperglycemia or glucotoxicity,\textsuperscript{12,14} and increase insulin resistance or induce changes in cortisol levels.\textsuperscript{15,16} Hyperglycemia can upregulate protein kinase C expression, causing endothelial dysfunction because of increased oxidation.\textsuperscript{17,18} It can also increase the risk of cardiovascular morbidities.\textsuperscript{19}

In previous studies, the factors associated with DM, HTN and CAD were the same as those associated with stroke or cerebral events. However, in our analyses, the risk of stroke in the GD and non-GD groups showed no significant differences. The causes of the discrepancies in these findings warrant further investigation. Untreated GD can lead to increased morbidity and mortality, predominantly because of increased risk of cardiovascular complications, such as atrial fibrillation, heart failure, pulmonary HTN and angina pectoris.\textsuperscript{20}

Table 2 displays the depression incidence densities in the non-GD and GD cohorts of 5.01 per 1000 person-years and 8.67 per 1000 person-years, respectively (IRR = 1.73, 95% CI = 1.59–1.89). After multivariate analyses for baseline characteristics, the GD patients were associated with significantly higher risk of depression than the non-GD patients were (HR = 1.69, 95% CI = 1.45–1.96). Our results indicated that patients in Asia are associated with higher incidence of depression (5.01 per 1000 person-years vs. 1.0 per 1000 person-years) than patients in the UK.\textsuperscript{4} Our GD patients were associated with higher incidence of depression than the patients without GD (8.67 per 1000 person-years vs. 5.01 per 1000 person-years). Li et al. identified that the HLA-B*46 allele is a risk factor for GD in Asian populations, but not in Caucasian populations,\textsuperscript{21} which might explain the high incidence of depression in Asia.

Although GD is an autoimmune disease, previous studies have demonstrated no significant associations between antithyroid antibodies and

<table>
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<tr>
<th>GD</th>
<th>No</th>
<th>Yes</th>
<th>Rate\textsuperscript{a}</th>
<th>Event</th>
<th>PY</th>
<th>Rate\textsuperscript{a}</th>
<th>Event</th>
<th>PY</th>
<th>IRR (95% CI)</th>
<th>Adjusted HR\textsuperscript{b} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>582</td>
<td>116</td>
<td>167</td>
<td>5.01</td>
<td>251</td>
<td>28</td>
<td>942</td>
<td>8.67</td>
<td>1.73 (1.59, 1.89)***</td>
<td>1.69 (1.45, 1.96)***</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>501</td>
<td>90</td>
<td>647</td>
<td>5.53</td>
<td>211</td>
<td>22</td>
<td>574</td>
<td>9.35</td>
<td>1.69 (1.54, 1.86)***</td>
<td>1.66 (1.41, 1.96)***</td>
</tr>
<tr>
<td>Men</td>
<td>81</td>
<td>25</td>
<td>521</td>
<td>3.17</td>
<td>40</td>
<td>63</td>
<td>942</td>
<td>6.28</td>
<td>1.98 (1.64, 2.38)***</td>
<td>1.81 (1.24, 2.66)***</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–34</td>
<td>175</td>
<td>44</td>
<td>814</td>
<td>3.91</td>
<td>82</td>
<td>11</td>
<td>320</td>
<td>7.24</td>
<td>1.86 (1.61, 2.13)***</td>
<td>1.79 (1.37, 2.33)***</td>
</tr>
<tr>
<td>35–49</td>
<td>232</td>
<td>44</td>
<td>169</td>
<td>5.25</td>
<td>98</td>
<td>10</td>
<td>901</td>
<td>8.99</td>
<td>1.71 (1.49, 1.97)***</td>
<td>1.64 (1.29, 2.08)***</td>
</tr>
<tr>
<td>50–64</td>
<td>134</td>
<td>20</td>
<td>602</td>
<td>6.50</td>
<td>50</td>
<td>7</td>
<td>5072</td>
<td>9.86</td>
<td>1.52 (1.24, 1.86)***</td>
<td>1.47 (1.06, 2.04)*</td>
</tr>
<tr>
<td>≥65</td>
<td>41</td>
<td>6</td>
<td>6582</td>
<td>6.23</td>
<td>21</td>
<td>16</td>
<td>942</td>
<td>12.7</td>
<td>2.04 (1.48, 2.82)***</td>
<td>1.86 (1.08, 3.20)*</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Incidence rate, per 1000 person-years. \textsuperscript{b}Multivariable analysis including sex, age and comorbidities. *P<0.05, **P<0.01, ***P<0.001.

Figure 1. Cumulative incidence comparison of depression between with and without GD.

GD and depression
depression. The relationship between hyperthyroidism and depression remains unclear. Studies have demonstrated an association between depression and hypothyroidism, but not hyperthyroidism, and identified that subclinical hypothyroidism is a risk factor for major depression. Peake suggested that prolonged hyperthyroidism might exhaust the noradrenergic system, contributing to depression. This effect might explain the similarities between the symptoms of apathetic thyrotoxicosis and those of depression, and the absence of the typical endocrine symptoms of thyrotoxicosis in apathetic thyrotoxicosis patients. Schreckenberger et al. characterized the regional metabolic changes in the major structures of the limbic and paralimbic system by using positron emission tomography, which provided direct evidence of the link between GD and depression. Spinelli et al. also provided evidence of the relationship between stress and depression. As mentioned, stress is a risk factor for GD. Therefore, stress might play a role in the association between GD and depression, although additional data are required to confirm this hypothesis. Our analyses indicated that the association between GD and depression is independent from any association with the comorbidities shown in Table 3 except for stroke. We identified a strong correlation between stroke and GD with depression in our study sample. This finding supports the results from a 9-year cohort study that demonstrated that patients with depression are associated with higher risk of developing major metabolic diseases that might lead to stroke than patients without depression. Another case–control study named INTERSTROKE mentioned 10 risk factors accounted for 90% of stroke risk and one of the 10 risk factors is psychosocial stress or depression.

**GD treatment and depression**

One studies mentioned that stress plays a role in the association between GD and depression. It may aggravate the prognosis of antithyroid drug-treated hyperthyroidism. Another study also indicated that depressive personality during antithyroid drug treatment reflects the effect of emotional stress instead of thyrotoxicosis. According to our meta-analysis on GD treatment (Table 4), the risk of depression was significantly higher in patients treated with propranolol than in GD patients without treatment (HR = 2.14, 95% CI = 1.26–3.62). Propranolol is a non-selective beta blocker (β-blocker), prescribed to reduce catecholamine surges and sympathetic hyperactivity. However, studies have described ‘β-blocker blues’ associated with the use of these compounds. A possible mechanism for β-blocker-induced depression is the inhibition of β-receptors and serotonin receptors in the central nervous system. Our another possible

### Table 3
Comparison of incidence densities of depression and HR between with and without GD by comorbidity

<table>
<thead>
<tr>
<th>GD</th>
<th>Event</th>
<th>PY</th>
<th>Ratea</th>
<th>Event</th>
<th>PY</th>
<th>Ratea</th>
<th>IRR (95% CI)</th>
<th>Adjusted HRb (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>No</td>
<td>547</td>
<td>111</td>
<td>646</td>
<td>4.90</td>
<td>228</td>
<td>26777</td>
<td>8.51</td>
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<tr>
<td></td>
<td>Yes</td>
<td>35</td>
<td>4521</td>
<td>23</td>
<td>7.74</td>
<td>2166</td>
<td>10.6</td>
<td>1.37 (0.97, 1.94)</td>
</tr>
<tr>
<td>HTN</td>
<td>No</td>
<td>472</td>
<td>101</td>
<td>4.64</td>
<td>187</td>
<td>23945</td>
<td>7.81</td>
<td>1.68 (1.53, 1.85)***</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>110</td>
<td>14420</td>
<td>64</td>
<td>7.63</td>
<td>4997</td>
<td>12.8</td>
<td>1.68 (1.37, 2.06)***</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>No</td>
<td>502</td>
<td>106497</td>
<td>4.71</td>
<td>213</td>
<td>25795</td>
<td>8.26</td>
<td>1.75 (1.60, 1.92)***</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>80</td>
<td>9670</td>
<td>38</td>
<td>8.27</td>
<td>3148</td>
<td>12.1</td>
<td>1.46 (1.13, 1.89)**</td>
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<tr>
<td>CAD</td>
<td>No</td>
<td>531</td>
<td>110121</td>
<td>4.82</td>
<td>221</td>
<td>26067</td>
<td>8.48</td>
<td>1.76 (1.61, 1.92)***</td>
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<tr>
<td></td>
<td>Yes</td>
<td>51</td>
<td>6047</td>
<td>30</td>
<td>8.43</td>
<td>2875</td>
<td>10.4</td>
<td>1.24 (0.92, 1.67)</td>
</tr>
<tr>
<td>Stroke</td>
<td>No</td>
<td>577</td>
<td>115294</td>
<td>5.00</td>
<td>242</td>
<td>28639</td>
<td>8.45</td>
<td>1.69 (1.55, 1.84)***</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5</td>
<td>873</td>
<td>5.73</td>
<td>9</td>
<td>304</td>
<td>29.6</td>
<td>5.17 (2.64, 10.1)***</td>
</tr>
</tbody>
</table>

aIncidence rate, per 1000 person-years. bMultivariable analysis including sex, age and comorbidities. **P<0.01, ***P<0.001.
mechanism is for patients with prolonged hyperthyroidism, β-blocker may aggravate the severity of depression. Our analysis to GD treatment may offer us to consider the timing of prescribing β-blocker to patients combined with GD and depression in Asia.

Study limitations

This study has several limitations that must be addressed. First, the insurance dataset used does not provide detailed information on patients' family histories, lifestyles, smoking habits, alcohol consumption, laboratory data and imaging findings, which are all potential confounding factors relevant to this study. Second, unlike prospective clinical trials, a retrospective cohort study design is subject to biases related to the adjustment for confounders. Despite the use of adequate controls, potential bias remained in our analyses because of unmeasured or unknown confounders. Third, we could not directly validate the diagnoses of GD and depression by reviewing charts. However, the diagnoses of GD and depression should be accurate because the data were strictly audited for the purpose of reimbursement.

In conclusion, our study results indicate that GD is a risk factor for depression, diabetes and diabetic complications in Asian patients. For Asian patients with GD, there are more risk factors to be screened before GD treatment. For the issue of GD and depression, we should pay more attention to the timing of prescribing β-blockers. Additional studies to fully elucidate the effects of GD and GD treatment on depression, diabetes and diabetic complications are warranted.

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Conflict of interest: None declared.

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