Risk Factors for Developing Thyroid-Associated Ophthalmopathy Among Individuals With Graves Disease

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Importance Thyroid-associated ophthalmopathy (TAO) is a common and debilitating manifestation of Graves disease (GD). Presently, little is known about factors that may increase the risk of developing TAO among patients with GD.

Objective To identify risk factors associated with the development of TAO among individuals with newly diagnosed GD.

Design, Setting, and Participants In this longitudinal cohort study, all beneficiaries 18 years of age or older with newly diagnosed GD who were continuously enrolled in a large nationwide US managed care network and who visited an eye care professional 1 or more times from 2001 to 2009 were identified. International Classification of Diseases, Ninth Revision, Clinical Modification billing codes were used to identify those who developed manifestations of TAO. Multivariable Cox regression was used to determine the hazard of developing TAO among persons with newly diagnosed GD, with adjustment for sociodemographic factors, systemic medical conditions, thyrotropin levels, and medical and surgical interventions for management of hyperthyroidism.

Main Outcomes and Measures Manifestations of TAO measured by hazard ratios (HRs) with 95% CIs.

Results Of 8404 patients with GD who met the inclusion criteria, 740 (8.8%) developed TAO (mean follow-up, 374 days since initial GD diagnosis). After adjustment for potential confounders, surgical thyroidectomy, alone or in combination with medical therapy, was associated with a 74% decreased hazard for TAO (adjusted HR, 0.26 [95% CI, 0.12-0.51]) compared with radioactive iodine therapy alone. Statin use (for ≳60 days in the past year vs <60 days or nonuse) was associated with a 40% decreased hazard (adjusted HR, 0.60 [CI, 0.37-0.93]). No significant association was found for the use of nonstatin cholesterol-lowering medications or cyclooxygenase 2 inhibitors and the development of TAO.

Conclusions and Relevance If prospective studies can confirm our finding that a thyroidectomy and statin use are associated with substantially reduced hazards for TAO among patients with GD, preventive measures for this burdensome manifestation of GD may become a reality.

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raves disease (GD) is among the most common auto-
immune disorders in the United States, affecting nearly
1% of women. Some reports indicate that up to half
of patients with GD develop thyroid-associated ophthalmop-
athy (TAO), making it the most prevalent extrathyroidal mani-
festation. Debilitating components of TAO include proptosis,
diplopia, and exposure keratopathy. In rare cases, vision loss
may result from corneal ulceration or compressive optic neu-
ropathy. Currently available treatments, such as the use of cor-
ticosteroids and immune modulators, do not prevent the long-
term consequences of TAO. Identifying modifiable risk factors
that predispose patients with GD to develop TAO could dra-
matically alter the management of these patients. Thus far, the
only recognized modifiable risk factors associated with TAO
are smoking, exposure to radioactive iodine (RAI), and
dysthyroidism.3

Thyroid-associated ophthalmopathy is associated with in-
flammatory cell infiltration, accumulation of the glycosami-
nglycan hyaluronan, and expansion of extraocular muscles
and fat.4 Activating antibodies against the thyrotropin recep-
tor drives the hyperthyroidism. However, their role in TAO has
yet to be established. In fact, the proximate link between sys-
temic, antigen-specific processes in GD and the development
of TAO remains unclear.

We examined longitudinal health care claims data from
8404 individuals with newly diagnosed GD to identify risk fac-
tors for developing TAO. Specifically, our study sought to de-
termine whether the choice of management of hyperthyroid-
ism in GD (treatment with antithyroid medications, exposure
to RAI, or thyroid ablation) altered the risk of developing TAO.
In addition, the effect of elevated serum thyrotropin levels and
the effect of the use of statins (3-hydroxy-3-methyl glutaryl-
coenzyme A reductase inhibitors) and cyclooxygenase 2 (COX-2)
inhibitors were assessed. In this analysis, we find that a thy-
roidectomy or statin use significantly reduced the relative risk
of developing TAO, whereas elevations in serum thyrotropin
levels and exposure to RAI increased the risk.

Methods

Data Source

The Clinformatics database (OptumInsight) contains de-
tailed de-identified health care claims data of all beneficia-
tories in a large US managed care network. Beneficiaries receiv-
ing any form of eye care from January 1, 2001, through
December 31, 2009, were identified. This subset of beneficia-
tories comprises those with 1 or more International Classifica-
tion of Diseases, Ninth Revision, Clinical Modification
(ICD-9-CM) codes for any eye-related diagnosis (codes 360-
379.9), with the Current Procedural Terminology6 code for any
eye-related visits or for any diagnostic or therapeutic proce-
dures (codes 65901-68899 or codes 92002-92499), or with any
other claim submitted by an ophthalmologist or optometrist
during their time in the medical plan. Claims (inpatient, out-
patient, or skilled nursing facility) for ocular and nonocular con-
ditions, sociodemographic information (age, sex, race, edu-
cation, and household net worth), and all records of filled
outpatient medication prescriptions were analyzed. All indi-
viduals had dual enrollment in the medical and pharmacy
plans. This data source has been used previously to study pa-
tients with ocular diseases.7,8 The University of Michigan in-
stitutional review board approved our study as a nonregu-
lated study.

Participants and Sample Selection

The study cohort included individuals 18 years of age or older
with newly diagnosed (incident) GD who were included in the
database for at least 1 continuous year and had visited an eye
professional (ophthalmologist or optometrist) at least once
during their participation in the plan. Patients with GD were
identified using ICD-9-CM diagnostic codes 242.00 and 242.01.
We excluded those individuals who were in the plan for fewer
than 365 days, those who had noncontinuous enrollment, and
those who had received a diagnosis of GD or TAO during their
first year in the plan (nonincident cases). Enrollees who re-
ceived a diagnosis of benign or malignant neoplasms of the
orbit and orbital pseudotumor were also excluded. In addition,
to help ensure that the cohort consisted of individuals with
bona fide GD, individuals who received a diagnosis of GD but
had no record in the claims database indicating treatment for
GD (eg, exposure to RAI, a thyroidectomy, or medication) and
no record of thyrotropin testing to confirm the diagnosis were
excluded. Those with no record in the claims database of treat-
ment for GD during their time in the plan but with evidence of
GD based on laboratory testing were included in the analy-
zes. After these exclusions, 8404 patients with newly diag-
nosed GD were included in our study (Figure).

Figure. Flowchart Regarding Selection of Beneficiaries for Analysis

Note that the diagnosis or prescription was not present during the beneficiary’s
first year of enrollment in the managed care plan. CPT indicates Current
Identification of Individuals Who Developed TAO

Diagnosis of TAO was based on billing codes for Graves ophthalmopathy, eyelid retraction, restrictive strabismus, proptosis, exposure keratopathy, or compressive optic neuropathy (eTable in the Supplement).

Exposure to Medications

Individuals who filled 1 or more prescriptions for statins, COX-2 inhibitors, or antithyroid medications were identified, and medication use was quantified (eTable in the Supplement). Information regarding use of nonprescription medications was not available.

Analyses

Statistical analyses were performed using SAS version 9.3 software (SAS Institute). The characteristics of the participants were summarized using mean values and standard deviations for continuous variables and frequencies and percentages for categorical variables. A Cox proportional hazards model with delayed entry was used to estimate the hazard of developing TAO based on the predictors of interest. The first year of enrollment was used as a “look-back” period. Individuals receiving 1 or more codes for TAO during this period were excluded from the analysis in order to exclude those with preexisting TAO. All beneficiaries were observed from the date of first diagnosis of GD until they either developed TAO or were censored. Censoring occurred when the individual disenrolled from the plan or at the end of the study period (December 31, 2009). First, single-variable models were used to test potential predictors individually. Multivariable models were adjusted for age at first GD diagnosis, sex, race, level of education attained, household net worth, and geographic region of residence at the time of enrollment. Other variables included in the model were record in the claims database of thyroidectomy, exposure to RAI, hypertension, hyperlipidemia, connective tissue disease, serum thyrotropin level, Charlson Comorbidity Index (a measure of overall health), and the use of statins, other cholesterol-lowering medications, antithyroid medications, and COX-2 inhibitors. In the multivariable model, thyrotropin levels were dichotomized into 5 mIU/L or less at all measurements and greater than 5 mIU/L at any measurement. A second multivariable model was run using a thyrotropin concentration of 7 mIU/L as the cutoff instead of 5 mIU/L. In the regression model, treatment with RAI alone was the omitted reference for which other interventions were compared against. For all analyses, P < .05 was considered to be statistically significant.

Exposure to medications for a given individual frequently changes over time owing to adherence and other factors. Assuming its constancy can lead to erroneous conclusions. To address this concern, we created time-dependent covariates to quantify medication use. For each day that an individual with GD was at risk of developing TAO in the model, we determined the total number of days in the previous year the individual was prescribed each medication class. On a particular day, if the enrollee had a record of receiving a prescription for the medication of interest for at least 60 days in the past year, they were counted as a user of the medication for that day. We quantified the number of days each enrollee was prescribed each medication from the index date to the date of first diagnosis of TAO or censoring.

Results

A total of 8404 individuals were identified with newly diagnosed GD, with a mean (SD) length of medical plan enrollment of 2050 (827) days. Of these 8404 enrollees, 740 (8.8%) developed TAO during the follow-up (compared with all patients with GD, the mean [SD] total plan enrollment time for those who developed TAO was 2066 [787] days [P = .56]). The mean (SD) length of time between first GD diagnosis and first TAO diagnosis was 374 (422) days. Those who developed TAO were younger (mean [SD] age, 45.1 [11.7] years) than those without ocular manifestations (mean [SD] age, 46.6 [12.7] years) (P = .001). However, no predilection based on sex (P = .63) or race (P = .27) was identified (Table 1).

The 740 individuals who developed TAO were identified by the following codes: proptosis (602 [81.4%]), Graves eye disease (403 [54.5%]), restrictive strabismus (223 [30.1%]), eyelid retraction (191 [25.8%]), exposure keratopathy (77 [10.4%]), and compressive optic neuropathy (29 [3.9%]). Some individuals exhibited more than 1 of these ocular manifestations at initial diagnosis of TAO.

Treatment for thyroid dysfunction for individuals with GD included antithyroid medications alone (n = 4277), exposure to RAI alone (n = 2196), antithyroid medications in combination with exposure to RAI (n = 1125), and thyroidectomy alone or with antithyroid medications (n = 779). A total of 1885 patients with GD had no record in the claims database of treatment for hyperthyroidism during their time in the health plan.

Multivariable Regression Results

Sociodemographic Factors

In the multivariable models, we observed no significant association between age, race, geographical region of residence, household net worth, or level of education and the hazard of developing TAO (P > .05 for each comparison). Women with GD demonstrated a 25% decreased hazard of developing TAO relative to men (adjusted hazard ratio [HR], 0.75 [95% CI, 0.56-1.02]), a finding that was close to but not statistically significant (P = .06).

Treatments of Hyperthyroidism

In the multivariable regression model, neither medical therapy with antithyroid medications alone nor in combination with RAI appeared to alter the risk for developing TAO compared with receiving RAI alone (P > .05 for both comparisons). Individuals who received a thyroidectomy alone or who received a thyroidectomy along with antithyroid medications had a 74% decreased hazard of TAO (adjusted HR, 0.26 [95% CI, 0.12-0.51]) when compared with those receiving RAI alone. Those patients not requiring treatment for hyperthyroidism exhibited a 73% decreased hazard of developing TAO (adjusted HR, 0.27 [95% CI, 0.18-0.39]) relative to those treated with RAI alone (Table 2).
Thyroid Status

Dysthyroidism has been associated with increased incidence and worsening of TAO. Therefore, we determined the effect of elevated serum thyrotropin levels on the risk of TAO. Individuals with at least 1 measurement of the serum thyrotropin level that was greater than 5 mIU/L were found to have a 21% increased hazard of TAO (adjusted HR, 1.21 [95% CI, 0.91-1.59]) relative to those with a thyrotropin level of 5 mIU/L or less for all test measures, although this finding did not reach statistical significance (P = .19). In a separate regression model adjusting for the same comorbidities, individuals with a thyrotropin level of greater than 7 mIU/L for all test measures manifested a 31% increased hazard (adjusted HR, 1.31 [95% CI, 0.97-1.76]) relative to those with a thyrotropin level of 7 mIU/L or less for all test measures, a finding that was close to but not statistically significant (P = .07) (Table 2).
Statin Use or Other Cholesterol-Lowering Medication Use
Without adjustment for potential confounding factors, individuals with GD who were prescribed statins for at least 60 days in the year of observation had a 40% decreased hazard of developing TAO (unadjusted HR, 0.60 [95% CI, 0.47-0.75]) compared with those not similarly treated, including exposure of fewer than 60 days (P < .001). After adjustment for covariates, enrollees with GD and with 60 days or more of statin use continued to manifest a 40% decreased hazard compared with those with less exposure to statins (adjusted HR, 0.60 [95% CI, 0.37-0.93]). There was no statistically significant difference in the risk of developing TAO between those exposed to other cholesterol-lowering medications besides statins (adjusted HR, 1.00 [95% CI, 0.50-1.82]) and those not exposed to these medications (Table 2).

Use of COX-2 Inhibitors
In both the univariable and multivariable models, no significant difference in the hazard of TAO could be detected between individuals prescribed COX-2 inhibitors and individuals not receiving these medications (adjusted HR, 0.79 [95% CI, 0.28-1.73]). (Table 2)

Thyroid-Stimulating Immunoglobulin and TAO
Among the 8404 individuals with GD, 536 had at least 1 determination of thyroid-stimulating immunoglobulin (TSI). Of these 536 individuals, 275 (51.3%) had undetectable TSI levels, whereas 261 (48.7%) had detectable levels of greater than 130%. Of the 261 individuals with undetectable TSI levels, 19 (7.3%) manifested TAO. Of the 275 individuals with greater than 130% detectable levels of TSI, 50 (18.2%) developed TAO (P < .001).

Discussion
The overarching pathogenic factors shared by GD and TAO remain unidentified. Here we followed a large cohort of patients with newly diagnosed GD to identify risk factors associated with the development of TAO. Although several risk factors have been identified previously, to our knowledge, this is the first study to assess multiple, potentially modifiable risk factors in a large cohort of patients. Because both the natural history and the treatment of GD can be idiosyncratic, we determined the risk factors over several years. Our findings indicate that thyroidectomy for the treatment of hyperthyroidism or statin use may lower the risk of developing TAO. Further studies will be required to determine whether a causal relationship can be identified between these factors and TAO. In addition, assessing the effect that modifying these factors might exert on the course of TAO will also require further inquiry.

Strategies for managing GD-associated hyperthyroidism differ among practitioners. Although the therapeutic options currently used offer potentially effective control of thyroid function, each might affect the risk of developing or worsening TAO differently.11,12 Because RAI ablation can exacerbate TAO, there may be a role for prophylactic low-dose oral corticosteroids, which have been found to mitigate any negative effect.13 In the present analysis, we searched the database to see whether the enrollees given RAI had a record of prescriptions for corticosteroids in the 15-day window around the timing of the RAI and determined that very few patients (only 2) had been prescribed corticosteroids. Our findings indicate that the risk of developing TAO is substantially reduced if patients undergo a thyroidectomy compared with RAI ablation.

Elevated levels of serum thyrotropin and TSI may negatively affect TAO. Specifically, several groups have found an association between TSI levels and the incidence of TAO.14-17 Our study supports the notion that a greater proportion of patients with TAO exhibit high TSI levels.

Another issue related to the putative role of thyrotropin in TAO concerns the elevations of thyrotropin levels that sometimes occur following surgical or radioactive iodine ablation. This can result from inadequate monitoring. It has been suggested that elevated serum thyrotropin levels might trigger the activity of TAO, a suspicion that has been strengthened by reports of its worsening in patients with hypothyroidism.18,19 In the present analysis, we observed an increased risk of TAO among individuals with elevated thyrotropin levels, a finding that approached statistical significance using a cutoff of 7 mIU/L.

Another goal of our study was to identify medications that might delay or prevent TAO. Because the majority of patients with GD will not develop clinically significant TAO, any preventative strategy would need to be safe and well tolerated. Our study analyzed several classes of medications with proven or suspected anti-inflammatory activity. Among them, statins represent a widely used class of drugs that reduce low-density lipoprotein cholesterol levels. The JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial20 assessed the potential benefit of statins among healthy participants. In that study,20 rosvastatin reduced systemic markers of inflammation (eg, C-reactive protein), cholesterol levels, and the number of vascular events.21-23 The study identified the anti-inflammatory actions of statins that were independent of their cholesterol-lowering properties. Statins have been proposed as an adjuvant anti-inflammatory therapy.24-35

Of note, our cohort of individuals who received the diagnosis of GD included 22% for whom no method of treatment for hyperthyroidism could be identified in the database. Some of these patients may have manifested euthyroid or subclinical GD, and this may help explain why this group was found to have a reduced risk of TAO relative to the group treated with RAI only. Alternatively, exposure to RAI may increase the risk of TAO.

Our data analysis relied on diagnostic coding and is therefore subject to certain vagaries. Coding for GD is relatively straightforward. However, the manifestations of TAO can be subtle and may be overlooked. Thus, the individuals identified with TAO in this database are likely those with more severe disease. Although this bias is acknowledged, the goal of our study was to identify modifiable risk factors for developing TAO among patients with GD. The approach taken here ap-
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Additional analyses using other data sources will be required to tease out the contributions of these factors.

Conclusions

In conclusion, our study identifies several factors that are associated with a reduction in the risk of developing TAO among patients with GD, including thyroidectomy compared with RAI alone and statin use. A prospective study is needed to substantiate these findings and to assess whether statin use or a thyroidectomy may delay or prevent TAO in patients with GD.


