Statins and Thyroidectomy May Reduce the Risk of Orbitopathy Developing in Patients with Graves’ Disease

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SUMMARY

Background
Graves’ orbitopathy (GO) is a component of Graves’ disease (GD) that is difficult to treat and may be very debilitating for the patient. Orbitopathy (ophthalmopathy [harder to pronounce]) is a significant problem for about 5% to 10% of patients with Graves’ disease. The factors that cause a predisposition to it are not clear. The current study examines a database of patients with Graves’ disease in order to determine what factors predispose to orbitopathy.

Methods
The Clinformatics database (Optum) contains detailed deidentified health care claims data of all beneficiaries in a large U.S. managed-care network. It was examined for eye disease–related claims. The study cohort included individuals 18 years of age or older with newly diagnosed GD who were in the database for at least 1 continuous year and reviewed those who had visited an eye care professional (ophthalmologist or optometrist) at least once during their participation in the plan. Patients who were in the plan for fewer than 365 days and those who had received a diagnosis of GD or GO during their first year in the plan were excluded in order to exclude patients with preexisting GD. Medication use was identified for antithyroid drugs, cyclooxygenase 2 (COX-2) inhibitors and statins. An appropriate statistical analysis was performed.

Results
A total of 8404 patients with newly diagnosed GD were identified with a mean (±SD) length of medical plan enrollment of 2050±827 days. Orbitopathy developed in 740 of the 8404 patients (8.8%). The mean length of time between the first diagnosis of GD and the first diagnosis of GO was 374±422 days. Those in whom GO developed were younger (mean age, 45.1±11.7 years) than those without orbitopathy (mean age, 46.6±12.7 years) (P = 0.001), but there was no predilection based on sex or race. Demographic factors such as region of residence, household net worth, or level of education did not correlate with orbitopathy.

The treatment for hyperthyroidism was antithyroid drugs alone in 4277 patients (51%), RAI in 2196 (26%), antithyroid drugs in combination with RAI in 1125 (13%), and thyroidectomy alone or with antithyroid medications in 779 (9%). Patients who underwent thyroidectomy alone or in combination with antithyroid medications had a 74% decreased hazard of orbitopathy (adjusted HR, 0.26; 95% CI, 0.12 to 0.51), as compared with those receiving RAI alone (the reference group).

Patients with a TSH level >7 mU/L had a 31% increased hazard (adjusted HR, 1.31; 95% CI, 0.97 to 1.76) as compared with those with a TSH of ≤7 mU/L for all test measures, a finding that was not statistically significant (P = 0.07). Only 536 had at least one measurement of thyroid-stimulating immunoglobulin (TSI). Orbitopathy developed in 50 (18.2%) of the 275 patients with levels of TSI of >130% (P<0.001).
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Patients who were prescribed statins for at least 60 days during the year of observation had a 40% decreased hazard of developing GO (unadjusted HR, 0.60; 95% CI, 0.47 to 0.75) as compared with those not similarly treated (P<0.001), but this was not the case with the use of other lipid-lowering drugs. COX-2 inhibitors did not reduce the hazard of developing orbitopathy.

Conclusions

Among patients with Graves disease, thyroidectomy and the use of statins are associated with reduced hazard for developing orbitopathy.

ANALYSIS AND COMMENTARY

The most striking finding is that thyroidectomy reduced the chance of the development of GO as compared with treatment with RAI. However, this form of treatment was used in only 9% of patients, and the basis for selecting it is unclear. Also, in patients with even mild orbitopathy, glucocorticoids may prevent its worsening following RAI (1). In this study, only 2 patients had received prescriptions for corticosteroids at the time of receiving RAI. If they had received corticosteroids, the results may have been different.

Another limitation is that 1885 patients (22%) had no record of treatment in the database, although the authors report a form of treatment for nearly all of the 8404 patients. The basis for obtaining the record of treatment for the 1885 patients is unclear.

Elevated levels of serum thyrotropin and TSI may negatively affect GO. In this study, elevated TSH was weakly associated with GO. Most endocrinologists avoid hypothyroidism in patients with active GO because current data indicate that TSH and TSI are involved in the pathogenesis of the orbital inflammation (2,3). Specifically, several groups have found an association between TSI levels and the incidence of GO. This study supports the notion that a greater proportion of patients with GO exhibit high TSI levels compared with Graves patients without GO.

A very interesting novel finding is that statins significantly reduced the hazard for the development of orbitopathy. This could be attributed to the antiinflammatory effect of statins (4).

The data analysis was also limited because smoking, a factor known to predispose to orbitopathy, was not assessed.

References