Characteristics of Diabetic and Nondiabetic Patients With Thyroid Eye Disease in the United States: A Claims-Based Analysis

Vishal K. Patel, PharmD 1, 2, Lissa Padnick-Silver, PhD 2, *, Sherwin D’Souza, MD 3, Rajib K. Bhattacharya, MD 2, Megan Francis-Sedlak, PhD 2, Robert J. Holt, PharmD, MBA 2

1 Rosalind Franklin University of Medicine and Science, College of Pharmacy, North Chicago, Illinois
2 Horizon Therapeutics plc, Deerfield, Illinois
3 St. Luke’s Health System, Boise, Idaho

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A B S T R A C T

Objective: Thyroid eye disease (TED) is a debilitating autoimmune disease characterized by ocular and periorbital tissue inflammation, proptosis, and visual impairment. The known risk factors for TED include radioactive iodine therapy, female sex, and smoking. The risk factors for severe TED include hyperthyroidism, male sex, smoking, and diabetes; however, little is known about how diabetes mellitus (DM) influences TED. This claims-based analysis examined TED characteristics in patients with and without diabetes.

Methods: Symphony database (2010-2015 U.S. claims) was mined for patients with ≥1 Graves’ disease diagnosis code and ≥1 TED-associated eye code, including proptosis, strabismus, diplopia, lid retraction, exposure keratoconjunctivitis, and optic neuropathy (ON). DM status was determined based on type 1 or type 2 diabetes coding. Sight-threatening TED was defined as ≥1 ON or exposure keratoconjunctivitis code.

Results: A total of 51,220 patients were identified. Of them, 2618 (5.1%) and 12,846 (25.1%) had type 1 and type 2 DM, respectively. Patients with and without DM had similar characteristics, but patients with DM were more often men (type 1: 30.3%, type 2: 28.7% vs no DM: 20.5%; both P < .001) and older at the first TED code. In patients with DM, strabismus (25.4%, 22.6% vs 19.9%) and diplopia (38.6%, 37.9% vs 29.9%) occurred more often but proptosis occurred less often (42.3%, 46.3% vs 58.5%; all P < .001). Sight-threatening TED occurred more often in patients with DM because of higher ON rates.

Conclusion: Patients with TED and DM may have more extraocular muscle involvement. Furthermore, the higher prevalence of severe TED stemmed from higher ON rates, possibly associated with diabetes-related vasculopathies. These hypothesis-generating data warrant further exploration.

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Introduction

Thyroid eye disease (TED) is a debilitating autoimmune condition most often associated with Graves’ disease.1 In its initial, active, progressive phase, TED is characterized by ocular surface inflammation, periorbital tissue inflammation, and retro-orbital fat and muscle expansion. As a result, patients often present with eyelid retraction, proptosis, eyelid swelling, conjunctival redness and swelling, strabismus, and/or diplopia. After inflammation subsides, patients may experience some improvement, but residual clinical symptoms often persist.2 TED can be classified as mild, moderate, severe, or sight-threatening depending on the severity of lid retraction, soft tissue involvement, proptosis, diplopia, corneal exposure, and optic nerve status.3,4 Sight-threatening TED, which requires urgent intervention, occurs when a patient develops compressive optic neuropathy (ON) and/or corneal breakdown.

The known risk factors for TED development include a history of radioactive iodine therapy, thyroid dysregulation, smoking, high serum concentrations of thyroid-stimulating hormone receptor (TSHR) antibodies, and vitamin D deficiency.5-10 TED is 5 to 6 times more prevalent in women than in men, but men with Graves’...
disease are more likely to develop TED than their female counterparts. The risk factors for more severe disease include higher levels of stimulating TSHR autoantibody immunoglobulin, male sex, older age, and smoking. Case reports have suggested that diabetes is also a risk factor for both TED development and more severe disease. More specifically, Ramamurthy et al found that among patients with TED, the prevalence of severe TED was much higher in patients with type 2 diabetes. Of 18 patients with severe TED, 10 patients had dysthyroid ON (of whom 9 had diabetes) and 8 patients had corneal decompensation (of whom 5 had diabetes). Proptosis and extraocular muscle involvement were more frequently seen in patients with diabetes than in those without. However, differences between TED patients with and without diabetes have not yet been studied in a very large patient population. The current study used a large insurance claims database of patients in the United States to examine the prevalence of diabetes in a population of patients with TED and compare characteristic differences in TED patients with and without diabetes.

Methods

PearlDiver software (PearlDiver, Inc) was used to mine the Symphony insurance claims database for patients with both Graves’ disease and TED. The database contained medical claims, reported between 2010 and 2015, for both private-pay and Medicare patients. This study used only aggregate, deidentified patient data that was obtained from an existing database and did not involve the collection, use, or transmission of individually identifiable data. Therefore, institutional review board approval for this study was not needed.

All patients included had ≥1 International Classification of Disease-9 (ICD-9) diagnosis code for Graves’ disease (ICD-9-242.*), ≥1 ICD-9 diagnosis code associated with TED, and data in the Symphony database for ≥2 years after the first Graves’ disease diagnosis code. The following codes for TED signs and symptoms were used to identify TED because there is no specific TED diagnosis code. The following codes for TED signs and symptoms were used to identify TED because there is no specific TED diagnosis code used in the United States: proptosis (ICD-9-D-376.*), diplopia (ICD-9-D-368.2), lid retraction (ICD-9-D-374.41), strabismus (ICD-9-D-378.*), exposure keratopathy (corneal damage from a dry ocular surface; ICD-9-D-370.34), and ON (ICD-9-D-377.49). Diabetes mellitus (DM) status for each patient was determined based on the presence or absence of diabetes-ICD-9 codes (ICD-9-D-242.*). The patients were stratified based on the DM codes identified: no DM, type 1 DM, and type 2 DM groups. Patient and TED characteristics in each group were examined and compared.

TED severity was investigated in each diabetes status group to better understand the influence of diabetes on sight-threatening TED. Based on the European Group on Graves’ Orbitopathy and American Thyroid Association guidelines, sight-threatening TED was defined as patients with ≥1 diagnosis code for ON or exposure keratopathy. Procedural codes for TED-associated surgeries were also examined by searching for the following codes: orbital decompression (CPT-674.*), strabismus surgery (CPT-673.*), eyelid surgery (CPT-158.*), CPT-678.*, CPT-679.*), and full-thickness corneal transplant (CPT-657.*).

Data are presented as mean or number (%), as appropriate. Differences between the groups in terms of diagnosis and procedural coding were examined using 2-tailed X² tests. This study was meant to be hypothesis-generating regarding TED differences in patients with and without diabetes. Because our patient cohort was divided into 3 groups (no DM, type 1 DM, and type 2 DM), resulting in 3 different hypotheses, the critical P value was adjusted from <.05 to <.017 using Bonferroni correction.

Results

Patient Characteristics

A total of 51,220 patients with ≥1 Graves disease and ≥1 TED sign or symptom code were identified and included in the analyses. Furthermore, ≥1 type 1 DM code was found in 2618 patients (5.1%), and ≥1 type 2 DM code was found in 12,846 patients (25.1%) (Fig. 1). The groups had similar patient characteristics, but on average, patients with DM were older at the first TED diagnosis code (type 1 DM: 59.0 years, type 2 DM: 59.6 years vs no DM: 51.4 years) and more often men (30.3%, 28.7% vs 20.5%; both P < .001).

Sight-Threatening TED

Sight-threatening TED was identified in 5976 (11.7%) of included patients, with a higher prevalence in patients with DM (type 1 DM: 13.3%, type 2 DM: 12.8%) than in those without DM (no DM: 11.2%; both P < .001). The higher prevalence of sight-threatening TED in patients with DM resulted from higher rates of ON in both the DM groups (Fig. 2). Exposure keratoconjunctivitis was similarly coded in patients with and without diabetes.

The proportion of male and female patients with sight-threatening TED was also examined. A total of 1236 men (10.5%) and 4740 women (12.0%) had sight-threatening disease. Sight-threatening TED occurred significantly more often in female patients than in male patients in all DM status groups. Women with type 1 DM (14.2%) had the highest prevalence of sight-threatening TED, and men without DM (10.1%) had the lowest.

TED-Related Surgeries

One or more TED-related surgery codes were identified in 6926 patients (13.5%) (Table 2). The no DM group (14.0%) had a similar surgical rate as both the type 1 (12.8%) and type 2 (12.3%) DM groups. The small difference between the type 2 DM and no DM groups was statistically significant (P < .001), but the difference between the type 1 and type 2 DM groups was not (P = .483).

The proportion of surgical patients who underwent orbital decompression (36.5%-38.1%) and a strabismus procedure (39.1%-40.8%) were similar among the diabetes status groups (all P > .269). However, full-thickness keratoplasty accounted for a higher proportion of surgeries in the type 2 DM group than in the no DM group (1.8% vs 0.7%, respectively, P < .001), and eyelid surgery accounted for a lower proportion in the type 2 DM group than in the no DM group (54.9% vs 58.8%, respectively, P = .007). The total number of procedures per patient were similar among the groups, with an average of 2.16, 2.04, and 1.98 procedures per patient in the no DM, type 2 DM, and type 1 DM groups, respectively.

Overall, the proportion of men and women who had undergone ≥1 TED-related surgery was the same (both 13.5%, P = .986), but fewer men and women with type 2 DM had been treated with surgery than their counterparts without DM (men: 12.1% vs 14.5%,
and type 2 DM groups were not statistically significantly related surgery at a similar rate as women without DM (13.7% vs 14.5%, P = 0.904). The differences between the type 1 and type 2 DM groups were not statistically significant.

Discussion

The current study included >50 000 patients with Graves’ disease and TED. The vast majority of patients included were women (76.9%), which was expected based on prior characterizations of TED populations.11,13 The proportion of patients who were men was higher in both the type 1 and type 2 DM groups than in the no DM group (type 1 DM: 30.3%, type 2 DM: 28.7% vs no DM: 20.5%). This was not surprising, given that both type 1 and type 2 DM are more prevalent in men.20-22 In agreement with prior studies, our findings suggest that patients with TED and DM develop sight-threatening TED more often than nondiabetic patients with TED (type 1 DM: 13.3%, type 2 DM: 12.8% vs no DM: 11.2%).14,17-19 The higher proportion of men in both diabetes groups cannot explain the observed increase in the prevalence of sight-threatening TED, which was highest in women with type 1 DM (14.2%) and lowest in men without DM (10.1%). The difference in the sight-threatening disease rate was largely attributable to a higher coding of ON in the DM groups, potentially suggesting that the optic nerve is more vulnerable to compression in patients with TED and DM. This finding is in agreement with a prior study that showed that patients with compressive ON were more likely to have diabetes.23 Furthermore, DM has been shown to be a risk factor for nonarteritic ischemic ON (odds ratio: 1.64), ganglion cell dysfunction, and glaucoma-associated optic nerve dysfunction.24-26 This might stem from diabetes-associated vasculopathies, metabolic imbalances, and/or impaired retrograde transport in optic nerve axons.27-29 As has been suggested for both glaucoma and nonarteritic ischemic ON, patients with coincident DM and TED seem to have optic nerves that are more vulnerable to nondiabetic causes of optic nerve insult.24,30 Furthermore, TED may manifest differently in patients with and without DM, as indicated by the higher prevalence of diplopia and strabismus and lower prevalence of proptosis in patients with DM.

**TED and Type 1 DM**

Type 1 DM was identified in 5.1% of patients with TED—approximately 10 times higher than the rate in the general U.S. population (2016-2017 statistic: 0.5%).31 Similarly, Kalmann and Mourits18 and Le Moli et al19 reported the prevalence of type 1 TED populations.11,14 The proportion of patients who were men was not surprising, given that both type 1 and type 2 DM are more prevalent in men.20-22 In agreement with prior studies, our findings suggest that patients with TED and DM develop sight-threatening TED more often than nondiabetic patients with TED (type 1 DM: 13.3%, type 2 DM: 12.8% vs no DM: 11.2%).14,17-19 The higher proportion of men in both diabetes groups cannot explain the observed increase in the prevalence of sight-threatening TED, which was highest in women with type 1 DM (14.2%) and lowest in men without DM (10.1%). The difference in the sight-threatening disease

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DM in European TED populations to be 5 to 7 times higher than that in the general population (TED population: 1.1%-1.7%, general population: 0.22%-0.26%). Given that patients with Graves disease also have a higher prevalence of type 1 DM, this finding was not surprising. Hyperglycemia has been reported in patients receiving some current TED treatments (eg, glucocorticoids and teprotumumab). In a patient with pre-existing type 1 DM, this is likely to manifest as worsening glycemic control, necessitating insulin adjustments. The association between type 1 DM and TED has not been fully elucidated, but these seem to have related etiologies; both are T-cell mediated autoimmune diseases that target a specific organ. Furthermore, they have common susceptibility gene variants that influence antigen presentation to T cells, T cell activation, and regulatory T cell differentiation.

Our data strongly suggest that patients with type 1 DM are more likely to develop severe or sight-threatening TED (type 1 DM: 13.3% vs no DM: 11.2%). This finding is in agreement with that of Kalman and Mourtis, who reported that patients with type 1 DM and TED had a significantly higher prevalence of ON (20%) than the general population (3.9%). The higher rate of ON observed in their study versus that observed in the current study is likely related to methodologic differences in the studies (retrospective chart review vs claims-based analysis). Patients with TED and DM tend to have poorer outcomes following an orbital decompression surgery, possibly because of insufficient optic nerve vascularization. Graves disease and type 1 DM are both autoimmune disorders, with their coincidence known as autoimmune polyglandular syndrome 3A. Both are associated with thyroid peroxidase and thyroglobulin autoantibodies, and both types of patients have a genetic susceptibility of the human leukocyte antigen system. Therefore, it is not unreasonable to theorize that autoantibodies from both diseases act synergistically in TED pathogenesis, increasing autoimmune inflammation. In patients with Graves disease, the TSHR is targeted by stimulating autoantibodies. This uncontrolled TSHR activation, in orbital fibrocytes of patients with TED, in conjunction with insulin-like growth factor-1 receptor (IGF-1R)-mediated inflammation, underlies TED development. Additionally, glutamic acid decarboxylase antibodies, markers of islet cell autoimmunity, can be present before type 1 DM onset; moreover, glutamic acid decarboxylase antibodies have been identified in nondiabetic patients with Graves' disease.

**Table 2**

<table>
<thead>
<tr>
<th>TED-related surgery parameter</th>
<th>No DM</th>
<th>Type 1 DM</th>
<th>Type 2 DM</th>
<th>P value</th>
<th>No DM versus type 1 DM</th>
<th>No DM versus type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 TED surgery code identified, n (%)</td>
<td>5008 (14.0%)</td>
<td>336 (12.8%)</td>
<td>1582 (12.3%)</td>
<td>.101</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Type of surgery, n (% surgical patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbital decompression</td>
<td>1906 (38.1%)</td>
<td>127 (37.8%)</td>
<td>577 (36.5%)</td>
<td>.970</td>
<td>.269</td>
<td></td>
</tr>
<tr>
<td>Strabismus surgery</td>
<td>1982 (39.6%)</td>
<td>137 (40.8%)</td>
<td>618 (39.1%)</td>
<td>.706</td>
<td>.739</td>
<td></td>
</tr>
<tr>
<td>Eyelid surgery*</td>
<td>2944 (58.8%)</td>
<td>186 (55.4%)</td>
<td>869 (54.9%)</td>
<td>.239</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td>Full-thickness corneal transplant</td>
<td>35 (0.7%)</td>
<td>3 (0.9%)</td>
<td>30 (1.9%)</td>
<td>.731</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Number of surgeries per patient</td>
<td>2.16</td>
<td>1.98</td>
<td>2.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By sex, n (% of male or female patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1064 (14.5%)</td>
<td>85 (10.7%)</td>
<td>447 (12.1%)</td>
<td>.004</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>3944 (13.9%)</td>
<td>251 (13.7%)</td>
<td>1135 (12.4%)</td>
<td>.904</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DM = diabetes mellitus; TED = thyroid eye disease.

* Includes blepharoplasty, eyelid repair, lid retraction correction, lagophthalmos correction, temporary eyelid closure, ptosis reduction, and canthoplasty.
also had type 2 DM. In contrast to type 1 DM, an association between Graves' disease and type 2 DM has not been demonstrated.\(^{19}\) However, based on the clinical literature, the severity of TED seems much higher in patients with type 2 diabetes, regardless of glycemic control or pre-existing retinopathy.\(^{14,15,19}\) Therefore, there is likely an association between type 2 DM and TED, albeit more indirect than type 1 DM.

In patients with TED, TSHR- and IGF-1R-positive fibrocytes are created in the bone marrow. They then circulate in the blood and eventually get deposit in the orbit, where they differentiate into fibroblasts. These fibroblasts can further differentiate into adipocytes and myofibroblasts, contributing to orbital fat and extracellular muscle expansion, respectively.\(^{42}\) The IGF-1R is heavily involved in TED pathogenesis, and IGF-1R inhibition can interrupt TED disease processes and reverse inflammatory sequelae.\(^{43}\) The TSHR and IGF-1R form a physical and functional receptor complex, synergistically upregulating inflammatory pathways and hyaluronan production. Furthermore, IGF-1R expression is upregulated in orbital fibroblasts, B cells, and T cells in patients with TED.\(^{44-46}\) In patients with type 2 DM, insulin resistance results in compensatory hyperinsulinemia, which leads to a reduction in insulin-like growth factor-1 (IGF-1) binding protein and a subsequent increase in IGF-1 bioavailability.\(^{47}\) It is reasonable to speculate that together, the TED-associated IGF-1R increase on orbital fibroblasts and immune cells and the hyperinsulinemia-associated IGF-1 bioavailability increase amplify the already abnormal IGF-1R activation involved in TED pathogenesis. Additionally, diabetes-induced vasculopathy involving the optic nerve may make patients with type 2 DM and TED more susceptible to ON, as has been previously suggested.\(^{19}\) Therefore, patients with TED and type 2 DM should be referred to an ophthalmologist early in the course of TED for coordination of care.

Extraocular Muscle Involvement in Patients With and Without DM

Differences seen in this analysis of TED signs and symptoms suggest that TED pathogenesis differs between diabetic and nondiabetic patients. Although propotis was common among all the diabetes status groups (42%-59%), it was coded most often in patients without diabetes. Furthermore, higher rates of strabismus and diplopia in both the DM groups suggest that muscle involvement is more common in patients with diabetes and that fat involvement is more common in patients without diabetes. Ramamurthy et al\(^{14}\) and Le Moli et al\(^{19}\) found that both propotis and muscle involvement occurred more frequently in patients with TED and type 2 DM than in nondiabetic patients, who acted as controls. In contrast, the differences in propotis rates were not observed between patients with type 1 DM and patients without DM.\(^{40}\) Discrepancies between these studies and the current analysis might have resulted from differences in patient populations, study size, and/or data type (medical chart vs claims data). However, increased muscle involvement in diabetic patients was a common finding among all studies. TED can predominantly involve fat or muscle, with phenotype associated with differences in orbital fibroblast populations (Thy-1\(^+\) or Thy-1\(^-\)).\(^{32}\) It may be that diabetes influences orbital fibroblast populations in patients with TED; however, further investigation is needed.

Study Limitations

Our study had several limitations. First, claims data cannot be used to determine causality between TED and diabetes. Second, the accuracy of claims data relies on physician coding of patient signs, symptoms, and procedures. For example, lid retraction, a more subtle TED sign, was reported in approximately 15% of the current study population but is known to occur in approximately 90% of patients with TED.\(^{30}\) Coding errors related to hyperglycemia or diabetes could have also influenced our patient grouping. For instance, impaired glucose tolerance (“prediabetes”) might have been inadvertently coded using a type 2 DM code. Third, our data relied on ICD-9 coding. Unfortunately, there is no specific ICD-9 diagnosis code for TED used in the United States. Therefore, patients with more obscure coding for TED, or those with mild TED, might have been unintentionally omitted from our data set; however, it is unlikely that those included did not TED given the imposed coding constraints. Fourth, TED can also develop in patients with Hashimoto thyroiditis, who were not included in our analyses. Lastly, we did not examine the presence of other ocular disease (eg, diabetic retinopathy, cataracts, glaucoma), which might have influenced our findings.

Conclusion

This study identified unique differences between diabetic and nondiabetic patients with TED, including a higher diplopia and strabismus prevalence and a lower proptosis prevalence in those with diabetes. Furthermore, sight-threatening TED was identified more often in diabetic patients, but TED-related surgical rates were similar in diabetic and nondiabetic patients. These data demonstrate that TED may manifest differently in diabetic and nondiabetic patients with TED. Furthermore, early detection of TED is crucial for patients with comorbid diabetes, who may be more susceptible to TED-associated optic nerve damage than their nondiabetic counterparts. These data are intriguing and lead to additional questions about the association of concomitant diabetes in patients with TED, which requires further investigation.

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Disclosure

V.P. is a post-doctoral fellow at Horizon. L.P.-S., R.B., M.F-S., and R.H. are employees of and current stockholders at Horizon. S.D. is a consultant for Horizon. Horizon Therapeutics plc was involved in the study design, data analysis and interpretation, report writing, and the decision to submit the article for publication.

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