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Associations Between Thyroid Eye Disease and Glaucoma Among Those Enrolled in the National Institutes of Health *All of Us* Research Program

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Abstract

Purpose: To assess the association between thyroid eye disease (TED) and glaucoma.

Methods: Patients aged 18 and over enrolled in the NIH *All of Us* Research Program, a nationwide cohort, were extracted. Those with conditions relating to TED were identified and compared with 2020 US Census matched controls without a diagnosis of TED in a 1:4 ratio. We used Pearson's chi-square tests to study demographics by TED status, and logistic regression to generate odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the association between TED and glaucoma (any type, including glaucoma suspect), using those without TED as the reference group. Multivariable models were adjusted for age, gender, race/ethnicity, eye doctor visits, and smoking status.

Results: A total of 393 cases of TED were identified, as well as 1572 US Census-matched controls. The median age of the cohort was 63 years (interquartile range: 48–73 years). Age, gender, and race/ethnicity varied by TED status ($p<0.001$). Overall, 114 (29.0%) of TED cases had a diagnosis of glaucoma, compared to 94 (6.0%) of non-TED controls. On bivariate logistic regression models, those diagnosed with TED were significantly more likely to be diagnosed with glaucoma compared to controls (OR: 6.42; 95% CI: 4.76–8.70; $p<0.001$). This trend persisted on

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multivariable logistic regression controlling for confounding factors (OR: 3.37; 95% CI: 1.85–6.20 p<0.001).

Conclusion: Individuals with TED were significantly more likely to be diagnosed with glaucoma. Clinicians caring for patients with TED should be aware of this elevated risk and arrange glaucoma evaluation, accordingly. \

Précis:

In this nationwide study, we found that those diagnosed with thyroid eye disease were significantly more likely than controls to be diagnosed with glaucoma, even after adjusting for potential confounders.

INTRODUCTION

Thyroid eye disease (TED) is group of ophthalmic manifestations often associated with autoimmune disorders of the thyroid gland.[1] TED is most commonly associated with Graves' disease, but may also include other thyroid disorders including Hashimoto's thyroiditis and may occur in euthyroid patients.[1,2] It results from autoantigens shared between the thyroid and tissues in the orbit.[1,3] Several biologic factors result in the expansion of orbital contents and proptosis.[1,4,5]. These include lymphocytic infiltration of orbital tissues, cytokine secretion and associated inflammation and edema, excess glycosaminoglycan secretion by fibroblasts, and enhanced fibroblast differentiation into either myofibroblasts or adipocytes.[1,3–5]

TED has been postulated to cause higher intraocular pressure and glaucoma since at least the early 1900s.[6] There are several proposed mechanisms in the literature that attempt explain this connection. First, direct pressure on the globe from expansion of tissues in the orbit may increase intraocular pressure.[6] Second, outflow of aqueous humor in some patients may be impeded by increased episcleral venous pressure resulting from external pressure on the globe.[6–8] In other patients, there may be mucopolysaccharide deposition in the trabecular meshwork with increased outflow resistance.[9–11] Third, TED is associated with chronic surface and anterior chamber inflammation and formation of peripheral anterior synechiae, which may cause outflow resistance and secondary angle closure.[6,12–14] Lastly, since many patients are treated with ocular and systemic steroids in the acute phase of TED, steroid-induced intraocular pressure spikes may occur.[6,15] Though many mechanisms have been proposed, the extent of the clinical relationship between TED and glaucoma still remains to be elucidated.

Betzler *et al.* published a systematic review of studies looking at the association between TED and glaucoma from 1991 to 2021.[6] Overall, they reported the prevalence of glaucoma among those with a diagnosis of TED ranged from 0.4%–13.5%,[6] and concluded that those with TED are at higher risk for glaucoma.[6,16–18] Notably, all studies were performed at a single center. However, one Danish study with a broader definition for the exposure variable (Graves' disease and toxic nodular goiter without orbitopathy) and not included in this systematic review on TED patients did utilize EHR data from multiple centers, and found no association with glaucoma.[19] Further, there has been only one study[18] that has compared

glaucoma prevalence rates with a control group, while the others subjectively compared rates with those found in prior publications.

In this study, we assess the relationship between TED and glaucoma among individuals enrolled in the NIH *All of Us* Research Program, a multicenter nationwide dataset, in order to compare prevalence of glaucoma among TED patients with a control group. Understanding the extent of any association can help inform future practice guidelines aiming to promote appropriate care for this population.

METHODS

Study Population

We obtained data from the National Institutes of Health (NIH) *All of Us* Research Program, a nationwide database with an emphasis on diversity.[20] Participants provided written informed consent at enrollment in the study, which was approved by the NIH *All of Us* IRB. *All of Us* collects a wide range of data from participants, including electronic health record (EHR) data.[20] *All of Us* data undergo de-identification processes prior to becoming available to researchers, and according to data sharing policies results with less than 20 respondents are suppressed in this study.[20] Secondary analyses of de-identified data, such as those evaluated for our study, are considered non-human subjects research, which was verified by the University of California San Diego IRB. The study adhered to the Health Insurance Portability and Accountability Act (HIPAA) and the tenets of the Declaration of Helsinki.

Our case group consisted of US-based adults aged 18 and over with a diagnosis of TED. We defined TED as those with a relevant thyroid disease and diagnosis of proptosis or lid retraction on International Classification of Diseases (ICD) codes. Glaucoma status was defined as any type of glaucoma on ICD codes, including glaucoma suspect. Open-angle glaucoma status included both primary and secondary definitions. Names for diagnoses used to create our study cohort can be found in Supplemental Digital Content 1. At the time of our analysis, 372 380 participants had enrolled in the *All of Us* Research Program, and a total of 393 individuals were identified with a diagnosis of TED. These patients were derived from at least 14 states – with state information not available for some patients due to privacy.

Our control group consisted of US-based adults aged 18 and over without a diagnosis of TED using the definition described above. We selected a sample from the non-TED cohort that matched gender and racial/ethnic demographics from the 2020 US Census. We then randomly selected 1572 of these individuals, representing a control cohort four times the size of our case cohort. Prior studies have shown that control-to-case ratios exceeding 4:1 do not confer any additional statistical benefit.[21]

Variables

Demographic information was extracted from participants' survey responses in the *All of Us* Basics survey.[22] Gender was categorized as male, female, and other/skipped. Age in years was categorized as <40, 40–64, 65–74, 75–84, ≥85. Racial and ethnic categories were coded

as non-Hispanic (NH) White, NH African American, NH Asian, and Hispanic (any race) individuals. To characterize smoking status, we studied the following question in the *All of Us* Lifestyle survey:[22] "Have you smoked at least 100 cigarettes in your entire life?" Further, to understand engagement with eye care clinicians, we studied the following question in the *All of Us* Healthcare Access and Utilization survey:[22] "During the past 12 months, have you seen or talked to an optometrist, ophthalmologist, or eye doctor (someone who prescribes eyeglasses)?" Prior glaucoma surgery was defined using specific procedures listed in Supplemental Digital Content 1.

Data Analysis

Demographic information and survey responses were stratified by TED status and analyzed using Pearson's chi-squared tests to generate unadjusted p-values, using the Holm-Bonferroni adjustment for multiple comparisons. We used bivariate and multivariable logistic regression to generate odds ratios (ORs) and 95% confidence intervals (CIs) to characterize the association between TED and glaucoma. Potential covariates were identified using a directed acyclic graph[23] of known and suspected confounders for the association between TED and glaucoma (Supplemental Digital Content 2). Age, gender, race/ethnicity, education, income, insurance status, pregnancy, smoking, cardiovascular disease, diabetes, and eye doctor visits were considered. Paths between the exposure and outcome were identified using the back-door criterion.[23] We found that adjusting for age, gender, race/ethnicity, smoking status, and eye doctor visits in the prior year provided the minimal sufficient adjustment for estimating the relationship between TED and glaucoma (Supplemental Digital Content 2). Statistical tests were two-sided, and p-values were considered statistically significant at the $\alpha = 0.05$ level. Analyses were conducted on the NIH *All of Us* Researcher Workbench using R software version 4.1.0 on cloud based Jupyter notebooks.

RESULTS

A total of 393 cases of thyroid eye disease were identified, as well 1572 controls. The median age of the entire cohort was 63 (interquartile range: 48–73). Female gender accounted for 78.1% of cases and 50.8% of controls, which significantly differed on unadjusted chi-square tests ($p<0.001$). Cases were also more likely to be NH African American (28.0% vs 10.9%) and less likely to be NH Asian (1.8% vs. 4.8%) than controls ($p<0.001$). Further, cases were more likely to have a diagnosis of glaucoma (29.0% vs 6.0%, $p<0.001$), have a history of open-angle glaucoma (7.9% vs 2.4%, $p<0.001$), have a history of glaucoma surgery (2.5% vs 0.4%, $p<0.001$), and to have seen an eye doctor in the previous 12 months (29.5% vs 17.8%, $p<0.001$). No difference was found for smoking status between cases and controls (44.0% vs. 42.6%, $p=0.42$) (Table 1).

Overall, 114 (29.0%) of TED cases had a diagnosis of glaucoma, compared to 94 (6.0%) of non-TED controls. On bivariate logistic regression models, those with a diagnosis of TED were significantly more likely to have a diagnosis of glaucoma (OR: 6.42; 95% CI: 4.76–8.70; $p<0.001$). This trend persisted even after controlling for age, gender, race/ethnicity (OR: 5.72; 95% CI: 4.08–8.04; $p<0.001$) and smoking status (OR: 5.39; 95% CI: 3.82–7.64;

p<0.001) in our models. Trends were attenuated but were significant on our DAG-informed models which included eye doctor visits as a variable (OR: 3.37; 95% CI: 1.85–6.20; p<0.001) (Figure 1).

DISCUSSION

In this multicenter nationwide study assessing the association between TED and glaucoma, we found that those with TED were more likely to be diagnosed with glaucoma of any type. These results are in line with several prior studies demonstrating similar associations.[16,17] However, other studies have reported[24–26] that glaucoma rates did not differ from those found in the general population. Further, a Danish study of Graves' disease and toxic nodular goiter without orbitopathy found no association with glaucoma,[19] which may be due to the lack of orbital changes in these patients.[19]

We found that our prevalence rate of glaucoma among TED patients (29.0%) is considerably higher than the highest prevalence previously reported (13.5%),[17] which studied open-angle glaucoma. This discrepancy may be due to differences in definition of glaucoma. In the current study, glaucoma was defined broadly to include all types of glaucoma based on diagnostic ICD-9 and ICD-10 codes. In contrast, other studies defined glaucoma based on history or examination findings, including intraocular pressure (measured using a variety of techniques), prescribed glaucoma medications, and glaucomatous visual field defects, among others.[6,16,24,27]

Betzler *et al.* described how understanding the epidemiological connection between TED and glaucoma is challenging, as anterior segment disease among TED patients can make imaging and diagnosis of visual field defects difficult.[6] Moreover, the comorbidity of dysthyroid optic neuropathy, which can affect 3%–7% of TED patients,[28] can be mistaken for glaucomatous visual field defects and obfuscates the diagnosis.[6] These potential biases may be partially mitigated by studying TED patients who are treated at a variety of institutions, as was done in this study. However, as this is the first US-based study to use multicenter EHR data, it is difficult to draw direct comparisons with prior literature. More evidence is needed to understand the true magnitude of the clinical relationship between TED and glaucoma, which may be possible with the NIH *All of Us* Research Program as enrollment increases or with other large population-based datasets. Further, more research is needed to understand potential effect modification of this association by glaucoma type. Though we had access to glaucoma type in our dataset, including open-angle glaucoma, we were unable to perform regression modeling due to a small sample size.

Nevertheless, those who provide care for patients with TED should be aware of its association with all types of glaucoma in order to facilitate early detection and treatment, and reduce the possibility of permanent vision loss. Current clinical practice guidelines from the European Group on Graves' Orbitopathy (EUGOGO) do not specifically recommend glaucoma evaluations for TED patients.[29] Presentation to an eye doctor for management of TED provides an opportunity to examine a potentially high-risk group for glaucoma. As the exact glaucoma risk associated with a TED diagnosis is being delineated, clinicians should assess their patients' optic nerves and refer them for further management, as necessary.

Other than associations between TED and glaucoma, we found significantly greater representation of females in our TED group compared to the control group. Female gender is a well-established risk factor for the development of TED, which is thought to be related to females having higher risk of autoimmune disease generally and Graves' disease specifically.[30] However, among Graves' disease patients, males are thought to be at higher risk for more severe TED, which is likely related to differences in smoking prevalence by gender.[30,31] However, it should be noted that we did not observe any significant difference in smoking prevalence by TED status, though this finding is unadjusted for confounding factors such as gender.

We also found significant differences in the prevalence of TED by race and ethnicity, which has been reported in the literature.[30] In particular, NH Africans Americans in our study had nearly a threefold greater representation in the TED group than the control group, while NH Asians had nearly a threefold reduced representation. Of note, we sampled the control group to be consistent with US demographics based on US Census statistics. This is consistent with prior studies showing that those of African descent have the highest risk of TED, followed by Caucasians, and Asians having the lowest risk.[32,33] Further research is needed to understand genetic risk factors associated with race and ethnicity among those with TED.

We also observed significantly greater engagement with eye specialists in the prior year among TED patients compared with controls. This is an expected finding as those with a diagnosed eye disorder are naturally more likely to utilize more eye care related services. This makes visits to an eye specialist an important confounding variable in our analysis, as greater engagement with eye specialists increases surveillance bias and the likelihood that someone with glaucoma will be diagnosed. Though we controlled for this variable in our analysis, it is possible that residual confounding may have occurred, as is true for any observational research study.

Our study must be understood in the context of a few additional limitations. First, the eye specialist visits in the prior year survey question may be influenced by social desirability bias. This may have led to an overestimation among TED patients in particular compared to controls, which may have biased our models towards the null. Second, as we used ICD codes and clinical notes were not available in this database, we were thus unable to determine TED or glaucoma severity with optic nerve health or visual field examinations. This is particularly relevant for glaucoma suspect cases. However, glaucoma suspects comprised <20 of our cases, and sub-analyses of logistic regression models with suspect cases removed were largely unchanged (results not shown). Further, as ICD codes were determined by a variety of different clinicians from different institutions, there is potential for interobserver variability and misclassification of diagnoses.

Third, there may have been some selection bias, as most of the *All of Us* participants who elected to participate in the NIH *All of Us* Research Program, like other longitudinal research cohorts that require participation on part of enrollees, are of higher socioeconomic status than the general US population. We do not expect this bias to affect our case and control groups differently. Still, it is possible that generalizability may be affected, though to a lesser degree than other study cohorts that do not emphasize diverse enrollment

like the NIH *All of Us* Research Program. Finally, because ophthalmic examination data such as intraocular pressure is currently limited in *All of Us*, we have limited ability to understand the pathophysiological underpinnings mediating the association between TED and glaucoma.

In conclusion, we found that those with TED were significantly more likely to have been diagnosed with glaucoma. In light of this study's findings in the context of previous literature, clinicians should be suspicious of glaucoma development among TED patients, which requires further evaluation with baseline structural and function testing, as well as close follow-up. Future studies should take advantage of emerging EHR-based data to help quantify this relationship for this relatively rare disease. As vision loss from glaucoma is irreversible, understanding the extent of this relationship is essential for clinicians who care for TED patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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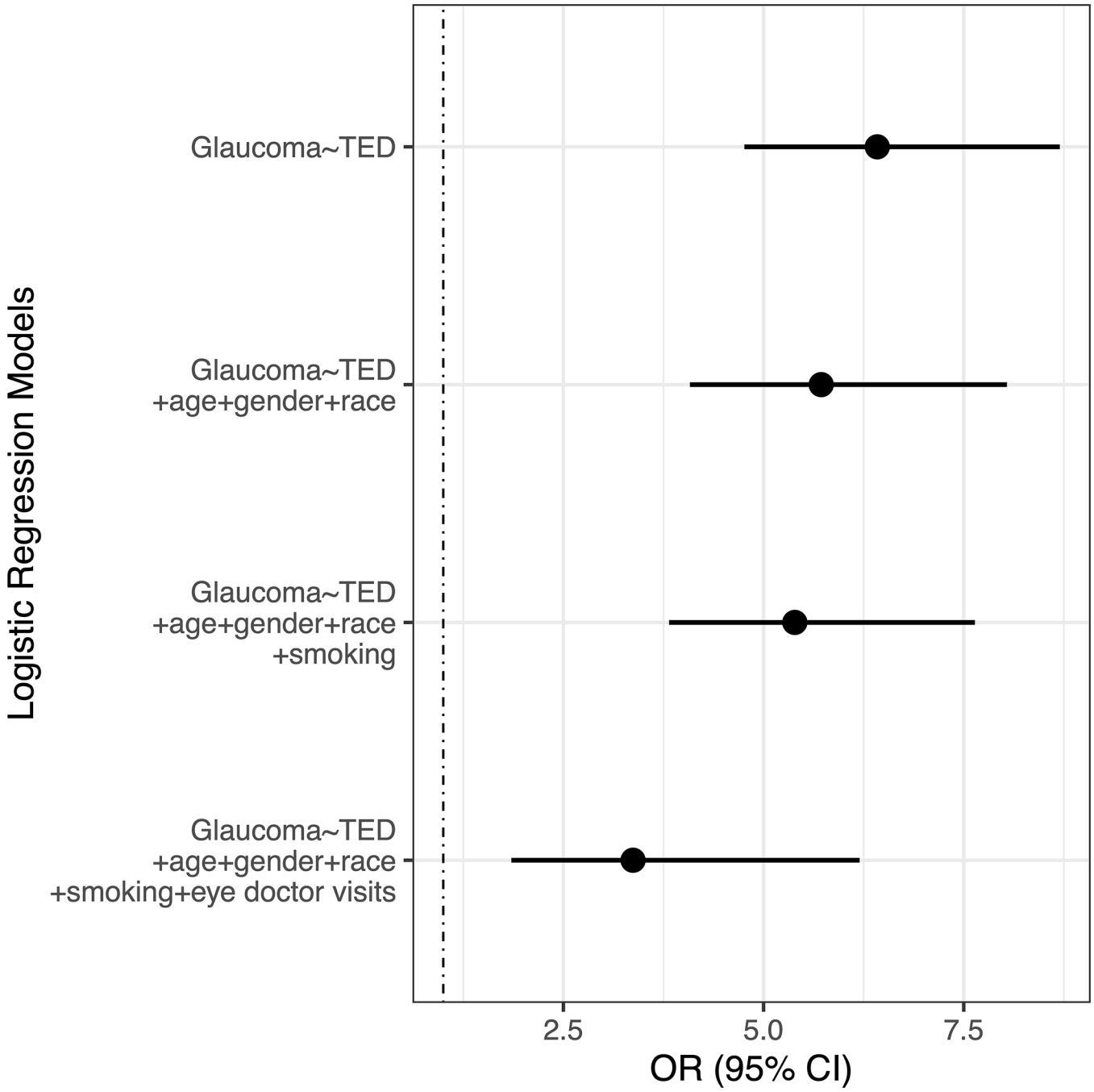

Figure 1.

Forest plot illustrating odds ratios (OR) and 95% confidence intervals (CI) calculated from bivariate and multivariable logistic regression models for the association between thyroid eye disease (TED) and glaucoma, with those without TED as the reference group. Final models were adjusted for age category, gender, race/ethnicity, smoking status, and eye doctor visits in the prior year.

Table 1.

Select characteristics among those with and without thyroid eye disease enrolled in the NIH *All of Us* Research Program.

Characteristics[a]	TED diagnosis	No TED diagnosis	P-value[b]
Total, No. (%)	393 (20.0)	1572 (80.0)	
Median age (IQR)	66 (56–74)	62 (46–73)	
Age category, No. (%)			<0.001
<40	21 (5.3)	280 (17.8)	
40–64	160 (40.7)	601 (38.2)	
65–74	116 (29.5)	355 (22.6)	
75–84	81 (20.6)	261 (16.6)	
≥85	<20	75 (4.8)	
Gender, No. (%)			<0.001
Female	307 (78.1)	798 (50.8)	
Male	79 (20.1)	774 (49.2)	
Other/Skipped	<20	<20	
Race/Ethnicity			<0.001
NH White	200 (50.9)	978 (62.2)	
NH African American	110 (28.0)	172 (10.9)	
NH Asian	<20	75 (4.8)	
Hispanic (any race)	59 (15.0)	282 (17.9)	
Other/Skipped	<20	65 (4.1)	
Smoked ≥100 cigarettes in life, No. (%)			0.42
Yes	173 (44.0)	670 (42.6)	
No	211 (53.7)	740 (47.1)	
NA	<20	162 (10.3)	
Seen eye doctor in prior 12 months, No. (%)			<0.001
Yes	116 (29.5)	280 (17.8)	
No	25 (6.4)	141 (9.0)	
NA	252 (64.1)	1151 (73.2)	
Glaucoma diagnosis, No. (%)			<0.001
Yes	114 (29.0)	94 (6.0)	
No	279 (71.0)	1478 (94.0)	
Open-angle glaucoma diagnosis, No. (%)			<0.001
Yes	31 (7.9)	37 (2.4)	
No	362 (92.1)	1535 (97.6)	
Glaucoma surgery, No. (%)			<0.001
Yes	<20	<20	
No	383 (97.5)	1566 (99.6)	

Abbreviations: TED, thyroid eye disease; No., number; IQR, interquartile range; NH, non-Hispanic.

[a]Per the *All of Us* Research Program data sharing policies, cells with less than 20 respondents are suppressed.

[b] P-values were generated from Pearson's chi-squared tests using the Holm-Bonferroni adjustment for multiple comparisons.