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# The Prevalence of Autoimmune Diseases in Primary Open Angle Glaucoma Patients Undergoing Ophthalmic Surgeries

**Maltish M. Lorenzo, MD**[1], **Julia Devlin, BS**[1], **Chhavi Saini, MD**[1], **Kin-Sang Cho, PhD**[1,2], **Eleftherios I. Paschalis, PhD**[1,2], **Dong Feng Chen, MD, PhD**[1,2], **Rafaella Nascimento e Silva, MD, PhD**[1], **Sherleen H. Chen, MD**[1], **Milica A. Margeta, MD, PhD**[1], **Courtney Ondeck, MD, MPhil**[1,3], **David Solá-Del Valle, MD**[1], **James Chodosh, MD, MPH**[1], **Joseph B. Ciolino, MD**[1], **Roberto Pineda, MD**[1], **Louis R. Pasquale, MD**[4], **Lucy Q. Shen, MD**[1]

[1.]Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, United States.

[2.]Schepens Eye Research Institute of Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, United States.

[3.]VA Boston Hospital, Boston, MA, United States.

[4.]Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, NY, United States.

## Abstract

**Purpose—**To assess the prevalence of autoimmune diseases (AiD) in patients with primary open angle glaucoma (POAG) undergoing ophthalmic surgery.

**Design—**Retrospective cross-sectional study.

**Participants—**POAG patients undergoing any ophthalmic surgery and control subjects undergoing cataract surgery at the Massachusetts Eye and Ear from March 2019 to April 2020.

**Methods—**All available medical records with patient demographics, ocular and medical conditions were reviewed. Differences in AiD prevalence were assessed and adjusted for covariates using multiple logistic regression. Additionally, a subgroup analysis comparing the POAG patients with and without AiD was performed.

**Main Outcome Measures—**To assess prevalence of AiD based on the American Autoimmune Related Diseases Association list.

**Results—**172 POAG patients and 179 controls were included. The overall prevalence of AiD was 17.4% in the POAG group and 10.1% in the controls (p=0.044). 6.4% of POAG patients

**CORRESPONDING AUTHOR:** Lucy Q. Shen, MD, Massachusetts Eye and Ear, 243 Charles Street, Boston, MA 02114, Phone: 617-573-3569, Fax: 617-573-3707, lucy_shen@meei.harvard.edu.



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and 3.4% of controls had more than one AiD (p = 0.18). The most prevalent AiDs in POAG group were rheumatoid arthritis (4.6%) and psoriasis (4.1%), which were also the most common in controls (2.8% each). In a fully adjusted multiple logistic regression analysis accounting for steroid use, having an AiD was associated with 2.62-fold increased odds of POAG relative to controls (95% confidence interval: 1.27–5.36, p = 0.009); other risk factors for POAG derived from the analysis included age (odds ratio [OR] = 1.04, p = 0.006), diabetes mellitus (OR = 2.31, p = 0.008) and non-White ethnicity (OR = 4.75, p < 0.001). In a case-only analysis involving the eye with worse glaucoma, there were no statistical difference in visual field mean deviation or retinal nerve fiber layer thickness (RNFLT) in POAG patients with (n = 30) and without AiD (n = 142, p > 0.13, for both).

**Conclusions—**A higher prevalence of AiD was found in POAG patients compared to control patients undergoing ophthalmic surgery. The presence of AiD was associated with increased risk for POAG after adjusting for covariates. Additional factors may have prevented a difference in RNFLT in POAG patients with and without AiD. Autoimmunity should be explored further in the pathogenesis of POAG.

## Précis:

Autoimmune disease (AiD) prevalence was higher in primary open angle glaucoma (POAG) patients undergoing ophthalmic surgery compared to cataract controls. Multivariable analysis showed that AiD was independently associated with increased odds of POAG.

### Keywords

POAG; autoimmune disease; inflammation; glaucoma; prevalence

## Introduction

Glaucoma is characterized by progressive degeneration and apoptosis of retinal ganglion cells (RGCs) resulting in permanent loss of peripheral or central vision.[1] Despite extensive research conducted in the field of glaucoma, the exact pathogenesis is not fully understood, and glaucomatous damage of the optic nerve can occur even with normalization of intraocular pressure (IOP).[2,3] Wax *et al.* explored the autoimmune etiology and reported elevated antibody titers against heat shock protein 27 (HSP27) and HSP60 in glaucoma patients.[4,5] Subsequently, several other studies have detected humoral deviations in glaucoma patients, such as antibodies against alpha-fodrin, vimentin, phosphatidylserine and glycosaminoglycans, most of which are prevalent in patients with autoimmune disorders.[6–10] Additionally, our group has shown a low anion gap with high serum chloride levels indicative of high IgG in patients with primary open angle glaucoma (POAG), supporting a possible underlying antibody-mediated mechanism.[11]

Apart from humoral immunity, recent laboratory studies by Chen *et al.* provided support for a T-cell mediated response in glaucoma by demonstrating a systemic increase of T cells specific to HSP27 and HSP60 after IOP elevation in a murine model; subsequently, RGC and axonal loss occurred in immunocompetent but not in T-cells deficient mice.[12] In addition to the adaptive immune response, there is growing evidence that the innate immune

response, mediated by reactive glial cells and increased production of cytokines such as tumor necrosis factor alpha (TNF-α) can cause optic nerve degeneration in glaucoma.[13–15]

The purpose of this retrospective study is to investigate whether POAG is associated with autoimmune diseases. Specifically, we evaluated patients undergoing ophthalmic surgeries, because these patients are more likely to have complete documentation of their non-ophthalmic conditions as part of their preoperative evaluation than patients followed in clinic only. Finding an association between autoimmune diseases and POAG can provide clinical evidence to support the laboratory findings and improve our understanding of autoimmunity in the pathogenesis of POAG.

## Methods

A retrospective, cross-sectional study was conducted on patients undergoing ophthalmic surgery at Massachusetts Eye and Ear (MEE). It was approved by the MEE institutional review board (IRB) in accordance with Health Insurance Portability and Accountability Act regulations. The IRB granted a waiver of informed consent as this was a retrospective study and the risk to the study subjects was minimal. The study adhered to the tenets set forth by the Declaration of Helsinki.

### Study Design and Study Population

All adult subjects, who underwent any ophthalmic surgery by 8 surgeons at MEE between March 2019 and April 2020, were identified and consecutively included in this study.

Inclusion criteria for the POAG group were: being scheduled to undergo glaucoma surgery, cataract surgery or both, open angles on gonioscopy and no evidence of secondary open angle glaucoma or peripheral anterior synechiae indicative of uveitic[16] or angle closure glaucoma; glaucomatous optic neuropathy, defined as thinning or notching of the neuroretinal rim; and corresponding visual field (VF) loss, such as arcuate defect, nasal step, paracentral loss or temporal wedge defect.[17] We excluded any patients with non-glaucomatous VF loss, which consisted of patterns localizing to retinal tissue damage or damage to the optic nerve or higher visual pathways from neuro-ophthalmic etiologies (6.7% of POAG patients).[18,19] Furthermore, VFs of POAG patients with autoimmune diseases which can potentially cause VF loss, such as giant cell arteritis, were carefully examined to confirm the glaucomatous VF defect patterns as listed above with correspondent optic nerve changes consistent with glaucoma.[17]

For control subjects, inclusion criteria were: being scheduled to undergo routine cataract surgery, intraocular pressure (IOP) < 22 mm Hg, cup-to-disc ratio (CDR) ≤ 0.6 in both eyes and CDR asymmetry < 0.2. Exclusion criteria were any history of retinal and neuro-ophthalmic pathologies (14.9% of control subjects), a family history of glaucoma or a diagnosis of glaucoma suspect, use of any glaucoma medications or history of glaucoma surgery.

The presence of autoimmune disease (AiD) was determined based on all available medical records. The American Autoimmune Related Diseases Association (AARDA) disease

list (www.aarda.org) was used to determine whether a diagnosis was autoimmune or autoimmune related.[20] Only diagnoses that were definitive and explicit were included in our study; generalized diagnoses without clear autoimmune etiologies such as hypothyroidism or arthritis were not included. Additionally, the diagnoses of seronegative arthropathy and lichen planus were not considered as autoimmune diseases.[21,22] We did not exclude patients with non-infectious anterior uveitis given the association and high prevalence of systemic autoimmune diseases with non-infectious anterior uveitis.[23,24]

### Data Collection and Outcome Measures

A thorough chart review was conducted for all eligible subjects. Demographic and ophthalmic information at the preoperative visit was collected. Any history of systemic steroid use for > 4 weeks in duration, inhaled steroid use for > 3 months in duration and topical steroid use for > 4 weeks in duration was also recorded.[25–27] For POAG patients, clinical information about both the operated eye and the more affected eye, if it was not the operated eye, was collected for subgroup analysis comparing POAG patients with AiD and without AiD. Humphrey visual field test (HVF, Carl Zeiss Meditec, Dublin, CA) mean deviation (MD) from reliable VFs within 1 year of preoperative visit were collected. A reliable VF was defined as one with fixation losses ≤ 33%, false-positive and false-negative rates ≤ 20%.[28] Retinal nerve fiber layer (RNFL) thickness values were obtained from Cirrus HD-OCT (Carl Zeiss Meditec, Inc. Dublin, CA, USA) performed within 1 year of the pre-operative visit, with signal strength of 6 or better.[29,30]

Main outcome measure was the prevalence of AiD in POAG and control groups. A secondary outcome measure was glaucoma severity of the more affected eye in POAG patients with and without AiD. Severity of the eye was based on reliable HVF when it was available, or based on average RNFL thickness, as prior laboratory studies have shown loss of ganglion cell axons from immune response in animal models of glaucoma.[12,31] In cases where neither was available, CDR was used to determine the more severely affected eye.

### Statistical Analysis

Data analysis was performed using the statistical software STATA 16.1 (StataCorp LLC, College Station, Texas, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables were compared with independent sample t-test or Mann-Whitney test and categorical variables with chi-square test or Fisher exact test when appropriate. Multiple logistic regression model was used to assess the effect of covariates on the primary comparison. All tests were two-tailed, and statistical significance was determined at $p < 0.05$.

## Results

A total of 351 patients with 172 POAG patients and 179 control subjects were included in the study. POAG patients were older than controls (72.9 ± 9.0 years vs 70.3 ± 8.3 years, $p = 0.005$). The control group had a higher percentage of White subjects than the POAG group (82.1% vs 52.3%, $p < 0.001$). Both the groups had similar gender distribution (45.3% male

in POAG vs 40.8% in controls, p = 0.39) and body mass index (BMI) (27.2 ± 4.9 kg/m$^2$, 26.8 ± 5.4 kg/m$^2$, respectively, p = 0.41, Table 1).

Of the POAG patients, 17.4% underwent cataract surgery only, 18.0% minimally invasive glaucoma surgery (MIGS) with cataract surgery, 32.6% penetrating glaucoma surgery (including trabeculectomy and tube shunt surgery) or cyclodestructive procedures (including cyclophotocoagulation and endoscopic cyclophotocoagulation) only, while 28.5% underwent penetrating glaucoma surgery or cyclodestructive procedures combined with cataract surgery. All control subjects underwent cataract surgery. Pre-operative best corrected visual acuity (BCVA) in the operated eye was similar for POAG patients (logarithm of minimum angle of resolution [LogMAR] 0.3 ± 0.5) and control subjects (LogMAR 0.4 ± 0.4, p = 0.07, Table 1). Pre-operative IOP of the operative eye was significantly higher for POAG group than the control group (16.5 ± 5.4 mm Hg vs 14.8 ± 2.6 mm Hg, p < 0.001). Likewise, the maximum IOP was significantly higher in POAG patients than controls (25.8 ± 7.3 mm Hg vs 16.0 ± 2.7 mm Hg, p < 0.001). 96.5% of POAG patients were treated with IOP lowering medications, while the remaining 1.7% had previous surgery and 1.2% laser. The CDR differed significantly between POAG patients (0.8 ± 0.1) and controls (0.3 ± 0.1, p < 0.001). For the operated eye, the most recent reliable HVF's within 12 months of pre-op were available for 66.3% of POAG subjects. The mean time from HVF to pre-op date was 2.8 ± 3.2 months and the MD was −11.1 ± 8.2 dB. The control subjects did not have HVFs available.

The overall prevalence of autoimmune diseases was 17.4% in the POAG group and 10.1% in the controls (p = 0.044, Table 1). 6.4% of POAG patients had more than one AiD compared to 3.4% of controls (p = 0.18). The two groups did not differ in patients with a known diagnosis of uveitis (2.9 vs 0.6%, respectively, p=0.11). 14.5% of POAG patients and 17.9% of controls had a history of steroid use (p=0.40). Systemic steroid use (> 4 weeks), including intravenous or oral, was 5.2% in POAG and 7.3% in controls (p = 0.43), while history of inhaled steroid use (> 3 months) was 6.4% in POAG patients and 12.0% in controls (p = 0.04). Indications for steroid treatment in all subjects without AiD included asthma, COPD, lymphoma and bronchitis. 4.1% of the POAG patients and 3.9% of controls had a history of topical steroid use for more than 4 weeks (p = 0.94). Indications for topical steroid usage comprised of blepharitis, ocular allergies and postoperative mediations for previous eye surgeries such as corneal transplantation and cataract surgery.

The most prevalent AiD in the POAG group was rheumatoid arthritis (4.6%), followed by psoriasis (4.1%), non-infectious anterior uveitis (2.9%) and Graves' disease (1.7%). In control subjects, psoriasis and rheumatoid arthritis were the most prevalent (2.8% for each) followed by Raynaud's syndrome, Sjogren syndrome and Hashimoto's thyroiditis (1.7% for each, Table 2). Based on the predominant immune mechanism of the autoimmune disease, prevalence of T-cell mediated disease[32–39] was higher in POAG patients (11.6%) than in controls (5.0%, p = 0.02). The prevalence of B-cell mediated disease[40–44] was 2.9% in POAG patients and 2.8% in controls (p > 0.99), while the prevalence of combined T-cell and B-cell mediated autoimmune disease[45–54] was 9.9% in POAG group and 7.3% in controls (p = 0.38).

The association between POAG and AiD was further analyzed using a multiple logistic regression analysis adjusted for age, BMI, gender, ethnicity, type 2 diabetes and any history of steroid use (systemic, inhaled or topical) with control subjects as the reference group. Having an AiD was associated with 2.62-fold increased odds of POAG relative to controls (95% confidence interval [CI]: 1.27–5.36, p = 0.009, Table 3). Older age (odds ratio [OR] =1.04; CI = 1.01–1.07, p = 0.006), diabetes (OR = 2.31; CI = 1.24–4.29, p = 0.008) and non-White ethnicity (OR = 4.75; CI = 2.76–8.16, p < 0.001) were also associated with increased risk of POAG. Gender, BMI and steroid use did not show a significant effect on the odds of POAG (p > 0.21, for all).

## Subgroup Analysis amongst POAG Patients

Additional analysis was performed to compare POAG patients with and without AiD to assess for any effect of AiD on glaucoma severity. A total of 30 POAG patients had a diagnosis of autoimmune disease while 142 patients did not (Table 4). 13.3% of POAG patients with AiD and 31.7% of POAG patients without AiD underwent penetrating glaucoma surgery or cyclodestructive procedure combined with cataract surgery (p = 0.05). The subgroups did not differ in other types of surgeries received (p ≥ 0.07). POAG with AiD and without AiD did not differ in age (72.3 ± 9.1 years vs 73.1 ± 9.0 years, p = 0.65), gender distribution (30.0 % vs 48.6% male, p = 0.06) and BMI (27.0 ± 5.5 kg/$m^2$ vs 27.3 ± 4.8 kg/$m^2$, p = 0.81). A history of steroid use was present in 26.7% of POAG patients with AiD versus 11.9% of POAG patients without AiD (p = 0.04). The presence of any history of systemic steroid use (> 4 weeks), either intravenous or oral, was significantly higher in POAG with AiD, 16.7% versus 2.8% in POAG without AiD (p = 0.002). None of the POAG patients with AiD had any history of inhaled steroid use (> 3 months) while 7.7% of POAG patients without AiD did (p = 0.11). 10.0% of the POAG patients with AiD had a recorded history of topical steroid use of 4 weeks or more while 2.8% of the POAG patients without AiD did (p = 0.07). Indications for systemic and inhaled steroids in POAG patients without AiD included gout, asthma, and steroid therapy adjunctive to chemotherapy; indications for topical steroids included post-operative mediations for previous eye surgeries.

The more affected eye, rather than the operated eye, was chosen to represent glaucoma severity for each POAG patient. POAG patients with AiD had similar BCVA (logMAR 0.3 ± 0.3) compared to POAG without AiD (0.3 ± 0.5, p = 0.77, Table 4). POAG patients with and without AiD did not differ in treated IOP (15.0 ± 3.8 mm Hg vs 16.0 ± 6.7 mm Hg, p = 0.42) and maximum IOP (27.1 ± 7.1 mm Hg vs 26.1 ± 8.8 mm Hg, p = 0.58). HVFs were available for 66.7% of POAG patients with AiD and 65.5% of POAG patients without AiD, dated 2.0 ± 3.3 and 3.0 ± 3.4 months before pre-op visit; HVF MD was similar for both the groups (−11.0 ± 7.7 dB vs −13.5 ± 8.6 dB, respectively, p = 0.23). The average RNFL thickness, which was available in 60.0% of the POAG patients with AiD and 61.9% of the POAG patients without AiD, dated 4.6 ± 3.7 and 2.9 ± 3.1 months before the pre-op visit, did not differ in the two subgroups (67.8 ± 6.6 μm, 63.9 ± 10.4 μm, respectively, p = 0.13). Similarly, POAG patients with and without AiD did not differ in CDR (0.8 ± 0.1 vs 0.8 ± 0.1, p = 0.94).

## Discussion

In this study, we investigated the relationship between POAG and autoimmunity by assessing the prevalence of AiD in POAG patients versus cataract controls undergoing ophthalmic surgeries. Our results support the association between POAG and autoimmunity; specifically, we found a significantly higher prevalence of AiD in POAG compared to cataract controls (17.4% vs 10.1%; p=0.044), with more POAG patients having T-cell mediated autoimmune diseases[32–39] than controls (11.6% vs 5.0%, p = 0.02). The association between AiD and POAG was confirmed in the multiple logistic regression analysis after adjusting for covariates such as steroid use.

Our findings were in agreement with a previous study by Cartwright *et al.*, who conducted a retrospective chart review including 67 normal tension glaucoma (NTG) patients and 67 matched patients with ocular hypertension (OHT).[55] The authors found a higher prevalence of immune-related diseases in NTG patients than OHT patients. Compared to their study, we studied a larger group of subjects (172 POAG patients and 179 controls), used cataract patients as controls instead of OHT patients, had more stringent definition of AiDs and included steroid use as a covariate to assess the association between POAG and AiD. We selected POAG patients instead of NTG patients to be consistent with laboratory studies, which showed that IOP elevation initiated the immune response leading to RGC degeneration.[12] We selected cataract patients as controls rather than OHT patients, as the latter are at higher risk for developing POAG than normal controls.[56] We used a definition of AiD based on published information and excluded diagnoses listed without clear autoimmune etiologies, such as arthritis and hypothyroidism, as they can have non-autoimmune etiologies.[57,58] We further assessed the types of AiD in our study population and reported higher incidence of AiD mediated by T-cell mediated mechanism in POAG patients. We also assessed steroid use as a potential confounder, because IOP elevation can occur with steroid use.[26] We considered topical, inhaled and systemic steroid use of certain duration based on prior studies which demonstrated an increase in IOP associated with duration of steroid use and route of administration.[25–27] Hence, our study provides more robust evidence of autoimmunity in patients with POAG.

Autoimmune responses mediated by T-cell and B-cell targeting HSPs have been implicated in glaucomatous neurodegeneration in previous laboratory and clinical studies. HSPs are chaperone proteins essential to protein homeostasis, but can stimulate antigen presentation to mediate T cell responses.[59–61] Laboratory studies have shown that elevated IOP induces HSP expression in retinal ganglion cells as well as HSP-specific $CD4^+$ T cell infiltration into the retina. This subsequently leads to continuous neurodegeneration, which is dependent on the presence of HSP-specific $CD4^+$ T cells.[12] HSP70 genes have been mapped within the major histocompatibility complex class III region that lies between human leukocyte antigen (HLA) class I and II loci, and a recent genetic study demonstrated that certain HLA associated single nucleotide polymorphisms (SNPs), particularly HLA-G and HLA-H SNPs, are associated with POAG.[62,63] The role of T-cell mediated RGC loss is further supported by studies in human immunodeficiency virus (HIV) positive patients, who are deficient of $CD4^+$ cells. HIV patients with a low CD4 count have thicker RNFL, suggesting protective effect of T cell deficiency.[64] On the other hand, increased prevalence of glaucoma

medication use is found in certain HIV patient populations on antiretroviral therapy, which increases $CD4^+$ T cell count.[65] These findings are consistent with our results, which showed that more POAG patients had AiDs, which are mediated by T cells, than control subjects. In addition to T-cell mediated response, various anti-HSP antibodies have been demonstrated in patients with psoriatic arthritis, rheumatoid arthritis and ulcerative colitis.[66,67] Similarly, autoantibodies against HSPs have been detected in patients with POAG and have been shown to lead to death of RGCs.[31,68] This is consistent with our study, which showed that the most prevalent AiD in the POAG patients was rheumatoid arthritis.

In order to assess if glaucoma severity is affected by AiD, we also conducted a subgroup analysis of the POAG patients in our study. When comparing the more affected eye of each POAG patient, we did not find a difference in glaucoma severity in patients with and without AiD. A higher proportion of POAG patients with AiD had a history of steroid use, which has been shown to prevent RGC loss in experimental models of glaucoma.[69,70] Furthermore, steroid administration decreases $CD4^+$ T cell infiltration into the retina.[71] Hence, higher prevalence of steroid use in our POAG patients with AiD may have modulated disease severity and prevented the difference between POAG patients with and without AiD. In addition, non-White ethnicity was more prevalent in the POAG group without AiD than with AiD, and may have contributed to severity of disease in the former group.[72]

Our study has several limitations due to the retrospective design: potential sources of bias are present, particularly in collection of medical information, although we only included patients undergoing surgery, who are more likely to have a comprehensive list of systemic diseases; we were unable to determine the onset or duration of both POAG and AiD, and hence could not establish a cause and effect relationship; similarly, information about the use and duration of any systemic immunosuppressive therapy for the treatment of autoimmune diseases could not be uniformly collected, although we were able to assess the use of steroid medications; the POAG patients in our study were older than control subjects, although we tried to account for the age difference in the multiple regression analysis. This study took place at a tertiary care center and it is possible that the patient population at our hospital does not represent the general population. On the other hand, the incidence of AiD among our control subjects was similar to those reported in the literature.[73,74] In addition, we included AiD which can potentially affect the visual field, such as giant cell arteritis, but carefully examined the visual fields of POAG patients to ensure that only patients with glaucomatous loss were included. Similarly, we included patients with non-infectious anterior uveitis given the association and high prevalence of systemic autoimmune diseases with non-infectious anterior uveitis.[23,24] We carefully reviewed the charts of POAG patients to ensure that patients with uveitic glaucoma and peripheral anterior synechiae on gonioscopy were excluded. Finally, the role of autoimmunity in patients with POAG may be more complex than demonstrated by laboratory studies. It is possible that immune-mediated mechanisms can play a role even in glaucoma patients without a diagnosis of a systemic autoimmune disease. Hence, we are conducting a prospective study to assess the role of autoimmunity in greater detail.

In conclusion, we showed in a relatively large retrospective study the higher prevalence of autoimmune diseases in POAG patients undergoing ophthalmic surgery compared to control

subjects undergoing cataract surgery. AiD is associated with higher risk for POAG after adjusting for steroid use and other co-variates. These findings are consistent with laboratory studies demonstrating a role of autoimmunity in the pathogenesis of POAG and support additional clinical studies to identify immunologic targets for the treatment of POAG.

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### CONFLICT OF INTEREST

Dr. D. F. Chen is a consultant for PriMed (Boston, MA) and Boston Pharma (Cambridge, MA). Dr. R. Pineda is supported by Alcon and Sanofi-Genzyme (Cambridge, MA). Dr. L. R. Pasquale is a consultant for Eyenovia, Twenty Twenty, and Skye Biosciences. Dr. L. Q. Shen received research funding from Topcon.

## ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| **AiD** | autoimmune disease |
| **AARDA** | The American Autoimmune Related Diseases Association |
| **BCVA** | best corrected visual acuity |
| **BMI** | body mass index |
| **CDR** | cup to disc ratio |
| **dB** | decibels |
| **HLA** | human leukocyte antigen |
| **HIV** | human immunodeficiency virus |
| **HSP** | heat shock protein |
| **HVF MD** | Humphrey visual field mean deviation |
| **IRB** | institutional review board |
| **IOP** | intraocular pressure |
| **LogMAR** | logarithm of the minimum angle of resolution |
| **MD** | mean deviation |
| **MEE** | Massachusetts Eye and Ear |
| **mmHg** | millimeters of mercury |
| **MIGS** | minimally invasive glaucoma surgery |

| | |
|---|---|
| **MS** | multiple sclerosis |
| **NTG** | normal tension glaucoma |
| **OHT** | ocular hypertension |
| **POAG** | primary open angle glaucoma |
| **RGC** | retinal ganglion cell |
| **RNFL** | retinal nerve fiber layer |
| **SLE** | systemic lupus erythematosus |
| **SNP** | single nucleotide polymorphism |
| **SSA [Ro]** | Sjogren's syndrome A antigen |
| **TNF-α** | tumor necrosis factor alpha |
| **VF** | visual field |

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**Table 1:**

Comparison between primary open angle glaucoma patients and controls

| Demographic and Ophthalmic Information | POAG (n = 172) | Controls (n = 179) | p-value |
|---|---|---|---|
| Age (years) | 72.9±9.0 | 70.3±8.3 | **0.005** |
| Gender (% male) | 45.3 | 40.8 | 0.39 |
| Race (% White) | 52.3 | 82.1 | **<0.001** |
| BMI (kg/m$^2$) | 27.2±4.9 | 26.8±5.4 | 0.41 |
| Type 2 diabetes (%) | 31.6 | 14.0 | **<0.001** |
| Autoimmune disease (%) | 17.4 | 10.1 | **0.044** |
| Diagnosis of > 1 autoimmune disease (%) | 6.4 | 3.4 | 0.18 |
| Known diagnosis of non-infectious uveitis (%) | 2.9 | 0.6 | 0.11 |
| Any history of steroid use[a] (%) | 14.5 | 17.9 | 0.40 |
| BCVA (LogMAR) | 0.3±0.5 | 0.4±0.4 | 0.07 |
| HVF MD (decibels)[b] | −11.1±8.2 | - | - |
| IOP (mm Hg) | 16.5±5.4 | 14.8±2.6 | **<0.001** |
| IOP max (mm Hg) | 25.8±7.3 | 16.0±2.7 | **<0.001** |
| Cup to disc ratio | 0.8±0.1 | 0.3±0.1 | **<0.001** |

All values are expressed as mean ± standard deviation unless otherwise specified. Significant p-values are in bold.

[a]Any history of systemic steroid use for > 4 weeks in duration, inhaled steroid use for > 3 months in duration and topical steroid use for > 4 weeks in duration.

[b]Available for 66.3% of POAG patients.

**Abbreviations**: BCVA, best corrected visual acuity; BMI, body mass index; HVF MD, Humphrey visual field mean deviation; IOP, intraocular pressure; LogMAR, logarithm of the minimum angle of resolution; POAG, primary open angle glaucoma.

**Table 2:**

Type of autoimmune diseases present in primary open angle glaucoma and control patients undergoing ophthalmic surgery

| Predominant Immune Mechanism | POAG % (n = 172) | Controls % (n = 179) | p-value |
|---|---|---|---|
| **T-cell mediated** | 11.6 | 5.0 | **0.02** |
| • Psoriasis | 4.1 | 2.8 | |
| • Non-infectious anterior uveitis | 2.9 | 0.6 | |
| • Alopecia areata | 1.2 | 0 | |
| • Giant cell arteritis | 0.6 | 0 | |
| • Polymyalgia rheumatica | 1.2 | 0.6 | |
| • Multiple sclerosis | 0.6 | 0 | |
| • Psoriatic arthritis | 0.6 | 1.1 | |
| • Ankylosing spondylitis | 0.6 | 0 | |
| **B-cell mediated** | 2.9 | 2.8 | >0.99 |
| • Graves' disease | 1.7 | 0 | |
| • Raynaud's syndrome | 1.2 | 1.7 | |
| • Systemic lupus erythematosus | 0 | 0.6 | |
| • Meniere's disease | 0 | 0.6 | |
| **Combined T-cell and B-cell mediated** | 9.9 | 7.3 | 0.38 |
| • Rheumatoid arthritis | 4.6 | 2.8 | |
| • Juvenile rheumatoid arthritis | 1.2 | 0 | |
| • Inflammatory polyarthropathy (ANA+) | 0.6 | 0 | |
| • Immune thrombocytopenic purpura | 0.6 | 0 | |
| • Hashimoto's thyroiditis | 0.6 | 1.7 | |
| • Autoimmune hepatitis | 0.6 | 0 | |
| • Rheumatic fever | 0.6 | 0 | |
| • Inflammatory bowel disease | 0.6 | 1.1 | |
| • Sjogren syndrome | 0.6 | 1.7 | |

Significant p-values are in bold.

Note: % Autoimmune diseases add up to higher % than the overall prevalence as some patients had multiple autoimmune diseases.

**Abbreviation:** ANA, anti-nuclear antibody; POAG, primary open angle glaucoma.

**Table 3:**

Multivariable analysis of risk factors for primary open angle glaucoma

| | | 95% Confidence Interval | | |
|---|---|---|---|---|
| **Dependent variable: POAG** | **OR** | **Lower Bound** | **Upper Bound** | **p-Value** |
| Age (years) | 1.04 | 1.01 | 1.07 | **0.006** |
| Gender (reference=female) | 1.24 | 0.76 | 2.03 | 0.39 |
| Race (reference=White) | 4.75 | 2.76 | 8.16 | **<0.001** |
| BMI (kg/m$^2$) | 1.01 | 0.96 | 1.06 | 0.69 |
| Type 2 diabetes | 2.31 | 1.24 | 4.29 | **0.008** |
| Autoimmune disease | 2.62 | 1.27 | 5.36 | **0.009** |
| Any history of steroid use[a] | 0.65 | 0.33 | 1.27 | 0.21 |

Significant p-values are in bold.

Control subjects were the reference.

[a]Any history of systemic steroid use for > 4 weeks in duration, inhaled steroid use for > 3 months in duration and topical steroid use for > 4 weeks in duration.

**Abbreviations**: BMI, body mass index; OR, odds ratio; POAG, primary open angle glaucoma.

**Table 4:**

Comparison between primary open angle glaucoma patients with and without autoimmune diseases

| Demographic and Ophthalmic Information | POAG with autoimmune disease (n = 30) | POAG without autoimmune disease (n = 142) | p-value |
|---|---|---|---|
| Age (years) | 72.3±9.1 | 73.1±9.0 | 0.65 |
| Gender (% male) | 30.0 | 48.6 | 0.06 |
| Race (% White) | 73.3 | 47.9 | **0.01** |
| BMI (kg/m$^2$) | 27.0±5.5 | 27.3±4.8 | 0.81 |
| Type 2 diabetes (%) | 26.7 | 32.6 | 0.52 |
| Any history of steroid use[a] (%) | 26.7 | 11.9 | **0.04** |
| BCVA (LogMAR) | 0.3±0.3 | 0.3±0.5 | 0.77 |
| HVF MD (decibels)[b] | −11.0±7.7 | −13.5±8.6 | 0.23 |
| IOP (mm Hg) | 15.0±3.8 | 16.0±6.7 | 0.42 |
| IOP max (mm Hg) | 27.1±7.1 | 26.1±8.8 | 0.58 |
| Cup to disc ratio | 0.8±0.1 | 0.8±0.1 | 0.94 |
| Average RNFL thickness (μm)[c] | 67.8±6.6 | 63.9±10.4 | 0.13 |

All values are expressed as mean ± standard deviation unless otherwise specified. Data from the more affected eye are presented.

[a]Any history of systemic steroid use for > 4 weeks in duration, inhaled steroid use for > 3 months in duration and topical steroid use for > 4 weeks in duration.

[b]Available for 66.7% patients with autoimmune disease and 65.5% of patients without autoimmune disease.

[c]Available for 60% patients with autoimmune disease and 62% of patients without autoimmune disease.

**Abbreviations**: BCVA, best corrected visual acuity; BMI, body mass index; CDR, cup to disc; HVF MD, Humphrey visual field mean deviation; IOP, intraocular pressure; LogMAR, logarithm of the minimum angle of resolution; POAG, primary open angle glaucoma; RNFL, retinal nerve fiber layer thickness.