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Original article

Baseline characteristics predictive of structural and functional progression in open-angle glaucoma patients with different demographic characteristics

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Abstract

Purpose: The aim of this study was to examine ocular blood flow parameters that may predict structural and functional disease progression in open-angle glaucoma (OAG) patients of different diabetic status, gender, ethnicity, and body mass index (BMI).
Methods: One hundred twelve patients with OAG were assessed for systemic blood pressure (BP), ocular perfusion pressure (OPP), retrobulbar blood flow, capillary blood flow, and optic nerve head morphology at baseline and every six months for a five-year period. Structural progression was monitored with optical coherence tomography and Heidelberg retinal tomography-III. Functional disease progression was monitored with automated perimetry using Humphrey visual fields. Factors associated with OAG structural and functional progression were analyzed using Cox proportional hazards models.
Results: The following were associated with shorter time to structural progression: In diabetic patients, larger area of avascular space; in males, lower central retinal artery peak systolic velocity and end diastolic velocity; in patients of African

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descent, higher systolic BP and OPP; in obese patients, lower ophthalmic artery end diastolic velocity. The following were associated with shorter time to functional progression: In diabetic patients, cup area, cup volume, cup/disc area ratio, linear cup/disc ratio, mean cup depth, cup shape; in males, systolic BP, diastolic BP, mean arterial pressure, systolic PP, diastolic PP, OPP, mean PP; in overweight patients, higher ophthalmic artery and central retinal artery resistive indices; in obese patients, lower central retinal artery resistive index.
Conclusions: Structural and functional OAG disease progression may be influenced differently in patients based on diabetic status, gender, ethnicity, and BMI. Mathematical modeling of risk variables that takes into account demographic characteristics may assist in better identifying OAG progression risk.

Key words: body mass index, demographic, diabetes, ethnicity, gender, glaucoma, blood flow

1. Introduction

Open-angle glaucoma (OAG) is a multifactorial optic neuropathy that remains the second leading cause of blindness worldwide.[1] Elevated intraocular pressure (IOP) is recognized as a main risk factor for OAG progression and is the primary modifiable risk factor focused on for management.[2] However, despite aggressive treatment, a high percentage of patients with normal IOP continue to experience visual field loss.[3] Over the past few decades, studies have investigated other risk factors for OAG that may contribute to disease progression. Additional risk factors identified include exfoliation, bilateral disease, advanced age, disc hemorrhages, thinner central corneas, lower systolic perfusion pressure, lower systolic blood pressure (BP), cardiovascular disease, history of migraine, female gender, vertical and horizontal cup-disc ratios, and pattern standard deviation, all of which have been linked to early predictors for the development of glaucoma.[3-6] Furthermore, findings indicate that ocular blood flow may contribute to OAG progression, but the exact nature of the relationship remains elusive.[7] In addition, African descent is a known risk factor for the development and progression of OAG, and more than six times as many people of African descent develop OAG.[8,9] The purpose of this analysis was to examine the relationship between baseline measurements that may predict structural and functional disease progression in OAG patients of different diabetic status, gender, ethnicity, and body mass index (BMI).

2. Methods

One hundred twelve patients with OAG were assessed for systemic BP, ocular

perfusion pressure (OPP), retrobulbar blood flow as measured by color Doppler imaging, capillary blood flow as measured by Heidelberg retinal flowmetry, and optic nerve head morphology as measured by Heidelberg retinal tomography III (HRT III) and optical coherence tomography (OCT) at baseline and every six months for a five-year period. The following subgroups were considered: Diabetic status, gender, ethnicity (African descent and European descent), and BMI (normal weight: BMI < 25, overweight: BMI 25 to 30, obese: BMI > 30). Structural progression was monitored with OCT and HRT III and was defined as two consecutive visits with retinal nerve fiber layer thickness decrease ≥ 8% and/or horizontal or vertical cup/disc ratio increase ≥ 0.2 compared to baseline. Functional disease progression was monitored with 24-2 Swedish interactive thresholding algorithm visual field exam using Humphrey automated perimetry and was defined as two consecutive visits with mean deviation decrease ≥ 2 and/or advanced glaucoma intervention study increase ≥ 2 compared to baseline. Analysis of covariance (ANCOVA) was used to test for statistical difference between groups from baseline to five-year follow-up. Time to structural and functional progression was analyzed using Cox proportional hazards models.

3. Results

In patients with diabetes mellitus (DM), a higher number of superior zero pixels (indicating increasing avascular area) was associated with shorter time to structural progression ($p = 0.0352$) (Table 1). The baseline optic nerve head parameters were associated with shorter time to functional progression in diabetic patients

Table 1. A summary of the factors associated with shorter time to structural progression from each demographic.

Factors in DM patients	
Increased superior zero pixels	$p = 0.0352$
Factors in male patients	
Lower CRA peak systolic velocity	$p = 0.0113$
Lower CRA end diastolic velocity	$p = 0.0020$
Factors in ED patients	
Higher systolic blood pressure	$p = 0.0217$
Higher systolic perfusion pressure	$p = 0.0306$
Factors in obese patients	
Lower OA end diastolic velocity	$p = 0.0289$

CRA: central retinal artery; OA: ophthalmic artery

compared to patients without DM (cup area: p = 0.0254; cup volume: p = 0.0089; cup/disc area ratio: p = 0.0382; linear cup/disc ratio p = 0.0437; mean cup depth: p = 0.0013; cup shape: p = 0.0160) (Table 2).

The following factors in males were associated with shorter time to structural progression compared to females: Lower central retinal artery (CRA) peak systolic velocity (PSV) (p = 0.0113) and lower CRA end diastolic velocity (EDV) (p = 0.0020) (Table 1). In males only, higher systemic BP and OPP were associated with shorter time to functional progression, leading to a significant gender difference (systolic BP: p = 0.0178; diastolic BP: p = 0.0230; mean arterial pressure: p = 0.0156; systolic PP: p = 0.0060; diastolic PP: p = 0.0066; OPP: p = 0.0061; mean PP: p = 0.0035) (Table 2).

The following were associated with shorter time to structural progression in patients of European descent as compared to African descent: Higher systolic BP (p = 0.0217) and higher systolic PP (p = 0.0306) (Table 1). No significant associations were found regarding the influence of ethnicity on functional disease progression.

A lower ophthalmic artery (OA) end diastolic velocity (EDV) was associated with shorter time to structural progression in obese patients (p = 0.0289) (Table 1). This was not observed in the cohorts of normal weight or overweight patients. In addition, higher ophthalmic artery (OA) resistivity index (RI) and central retinal artery (CRA) RI were predictive of functional progression in overweight patients (OA RI: p = 0.0483; CRA RI: p = 0.0148), but lower CRA RI was predictive of functional progression in obese patients (CRA RI: p = 0.0439). Baseline inferior mean capillary blood flow was associated with shorter time to functional progression in obese patients, leading to a significant difference between groups (p = 0.0317) (Table 2).

4. Discussion

4.1. Diabetes

The role of diabetes in glaucoma currently remains unclear. Some studies have established a positive relationship between the presence of diabetes and glaucoma progression.[10,11] Alternatively, others found no evidence or show evidence of a relationship between DM and IOP rather than DM and glaucoma.[12-15] Previous findings reported in the Indianapolis Glaucoma Progression Study found changes in retinal capillary blood flow to be correlated with optic nerve head changes in DM patients[16] and that DM patients showed impaired vascular regulation.[17] Our data demonstrated a shorter time to both structural and functional progression in OAG patients with DM based on certain optic nerve head and retinal capillary blood flow findings measured at baseline.

4.2. Gender

Discrepancies exist regarding the influence of gender on glaucoma progression as

Table 2. A summary of the factors associated with shorter time to functional progression from each demographic.

Factors in DM patients	
Cup area	p = 0.0254
Cup volume	p = 0.0089
Cup/disc area ratio	p = 0.0382
Linear cup/disc ratio	p = 0.0437
Mean cup depth	p = 0.0013
Cup shape	p = 0.0160
Factors in males	
Systolic blood pressure	p = 0.0178
Diastolic blood pressure	p = 0.0230
Mean arterial pressure	p = 0.0156
Systolic perfusion pressure	p = 0.0060
Diastolic perfusion pressure	p = 0.0066
Ocular perfusion pressure	p = 0.0061
Mean perfusion pressure	p = 0.0035
Factors in overweight patients	
Higher OA resistive index	p = 0.0483
Higher CRA resistive index	p = 0.0148
Factors in obese patients	
Lower CRA resistive index	p = 0.0439
Baseline inferior mean capillary blood flow	p = 0.0317

OA: ophthalmic artery; CRA: central retinal artery

well.[18,19] The Indianapolis Glaucoma Progression Study previously showed a positive association between retinal microcirculation and OPP in females but a negative association between these two factors in males.[20] The current study revealed that in males, lower retrobulbar blood flow velocity and higher systemic BP and OPP correlated with shorter time to structural and functional disease progression. These findings suggest that vascular involvement may be more strongly implicated in male patients in terms of risk for experiencing functional vision loss.

4.3. Ethnicity

OAG disproportionately affects individuals of African descent compared with

persons of European descent. Ocular structural differences have been found between patients of African and European descent, and systemic vascular diseases such as hypertension, cardiovascular disease, stroke, and DM also disproportionately affect individuals of African descent.[21,22] The Indianapolis Glaucoma Progression Study previously demonstrated that in persons of African descent, changes in retrobulbar blood flow velocities and vascular resistivity indices were correlated to retinal nerve fiber layer thickness.[23] Changes in retinal blood flow were correlated with glaucomatous morphological changes in optic nerve head in patients of African descent.[24] The present study found that higher systolic BP and OPP were associated with shorter time to structural progression in patients of European descent, while no significant differences were found between patients of African and European descent regarding functional disease progression.

4.4. Body Mass Index

The majority of studies have shown a positive association between increased BMI and glaucoma risk.[25-30] However, one study indicated that cerebral spinal fluid pressure showed a positive linear relationship with BMI, suggesting that higher BMI could reduce glaucoma risk.[31] The Singapore Malay Eye Study found that decreased BMI was associated with decreased optic rim area and increased cup/disc ratio, suggesting an inverse relationship.[32] Results from the current study revealed that in obese patients, lower OA EDV and lower CRA RI were associated with shorter time to structural and functional progression, respectively. In overweight patients, increased OA RI and CRA RI were predictive of functional progression, suggesting a stronger vascular influence in patients with higher BMI.

5. Conclusion

This study demonstrated that structural and functional disease progression may be influenced by differing demographic factors. Important considerations may include diabetic status, gender, ethnicity, and BMI. These findings suggest the establishment of mathematical modeling to allow for inclusion of demographic characteristics may increase specificity of risk assessment. Such models have previously been used to describe mechanical responses to changes in glaucoma risk factors such as IOP, scleral tension, and cerebral spinal fluid pressure.[33] Current models also aim to determine the methods by which ocular blood flow is regulated and the relative importance of these mechanisms.[33] Incorporating demographic differences may provide a more complete understanding of glaucoma progression and allow a more individualized, evidence based approach to disease management.

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