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Age, Maximum Cup Depth, Central Corneal Thickness, Disc Area and Mean Defect in Patients with Open Angle Glaucoma and Ocular Hypertension

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Abstract

Purpose: The main objective was to analyze the relationship between maximum cup depth (MCD), mean defect (MD), central corneal thickness (CCT), age and disc area, in patients with ocular hypertension (OHT) and primary open angle glaucoma (POAG). Methods: Cross-sectional study of patients diagnosed with OHT and POAG. Visual fields were obtained using an Octopus 300 analyzer, TOP strategy. MCD and disc area were obtained using a Heidelberg Retina Tomograph. Results: The study sample comprised 234 eyes of 143 patients, 91 women and 52 men, mean age 63.55 years (SD 10.49). Mean values were: MCD 0.52 mm (SD 0.27), MD 2.78 dB (SD 5.02), CCT 543.5 μm (SD 36.63), IOP 16.73 mmHg (SD 2.93), and disc area 2.01 mm² (SD 0.39). A significant correlation was observed between MCD and age in patients under 60 years, between MCD and disc area, and between MD and disc area. Conclusions: Our study showed a correlation between MCD and age which was significant in patients under 60 years of age, between MCD and disc area and between MD and disc area, suggesting that the larger the disc area, the greater the MCD and the MD in patients with OHT and POAG.

Keywords

POAG, OHT, Disk Area, Maximum Cup

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1. Introduction

The term glaucoma refers to a group of diseases of diverse etiology whose common feature is the development of optic atrophy, characterized by disc cupping, neuroretinal rim loss and impaired visual field [1]. The global prevalence of glaucoma for population aged 40 - 80 years is 3.54% [2]. Classically, the main predictor of the development and progression of glaucoma is increased intraocular pressure (IOP). Among other predisposing factors for glaucomatous damage, increased IOP produces direct compression of the axons of ganglion cells against the lamina cribrosa, interrupting blood flow and inducing cell death [3]. This association between loss of nerve fibers and IOP has been demonstrated and quantified withscanning laser polarimetry [4].

The Ocular Hypertension Treatment Study (OHTS) [5] demonstrated the important role of baseline factors other than IOP in the development of primary open-angle glaucoma (POAG). Older age, vertical and horizontal cup-to-disc ratios, greater pattern standard deviation (PSD) and thinner central corneal thickness (CCT) were independent predictors of conversion to POAG. As risk factors for progression, the Early Manifest Glaucoma Trial (EMGT) found that not only high IOP contributed to POAG but also pseudoexfoliation syndrome, more baseline damage, disc haemorrhages, thinner CCT, low blood pressure, and higher age [6]. Other risk factors for POAG include African American race, family history of glaucoma and myopia (greater than 3 diopters). Risk factors such as diabetes, systemic blood pressure, migraine, Raynaud syndrome and obstructive sleep apnea are controversial [7]-[9].

Recently published studies have described the histological and biomechanical properties of the lamina cribrosa that induce glaucoma with aging [10] [11]. The loss of compliance or increased rigidity associated with age increases susceptibility to damage of ganglion cell axons as they pass through the pores of the lamina cribrosa. Loss of compliance is more marked after the age of 40 - 50 years, with increased incidence of POAG [11]. Increased rigidity of the lamina cribrosa with aging is one of the reasons that disease progression is associated with age.

The main objective of the present work was to determine the maximum cup depth (MCD) in patients with OHT and POAG and study its relationship with mean defect (MD), age, CCT and disc area.

2. Materials and Methods

Selection of the study sample: We selected a cross-sectional sample of patients diagnosed with OHT and POAG attending the Glaucoma unit at University Hospital of the Canary Island. The diagnosis of glaucoma was based on the following criteria: 1) glaucomatous optic nerve cupping (including thinning or "notching" located in the neuroretinal rim or verticalization of the cup); 2) reproducible visual field mean defect (MD > 2 dB, SLV > 2.44 dB), or three or more contiguous points (p < 0.05) in the arcuate area on the map of pattern deviation; 3) manifest asymmetry between visual fields and optic nerve heads of both eyes (difference >0.2 in cup/disc ratio or >2 dB in MD between the two eyes). Both eyes were included when they met the inclusion criteria. Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

We excluded from the study all patients with concomitant ocular pathology other than glaucoma, and diseases or systemic treatment that could affect visual field, patients with visual acuity less than 20/40, refractive error ≥5 diopters of spherical equivalent or ≥3 diopters of astigmatism, levels of false positives, false negatives, fixation errors > 25%, and patients undergoing eye surgery during the study period. Patients with uncontrolled glaucoma and IOP > 21 mmHg measured using Goldmann applanation tonometry were also excluded.

Visual fields were obtained with an Octopus 300 analyzer (Haag-Streit, Switzerland) by two experienced practitioners, using visual stimuli on a white background, Goldmann size III, and the TOP strategy. Optical correction appropriate to the distance of observation was performed. To avoid the learning effect, the first two visual fields of each series were discarded.

The morfological analysis of cup depth and disc area was performed with a Heidelberg Retina Tomograph (HRT II, Heidelberg Engineering GmbH), which employs a diode 670 nm laser to illuminate the optic nerve. The HRT II measures the MCD in relation to a reference plane 50 mm below the temporal contour line [12]. To reduce the effect of inherent variability of HRT results, only quality tests were included.

The study variables were age, gender, IOP, CCT, MCD, MD and disc area. All study data were imported to a worksheet (OpenOfficeCalc 4.1.0). For the statistical analysis we used the PsPP 0.7.9 and the R-Commader 3.0.2 programs. Differences with a p value <0.05 were considered significant. Taking the difference between the first and third quartile as the reference value, values 1.5 times that distance in one of those quartiles were considered as outliers.

3. Results

The study sample comprised 234 eyes of 143 patients, 91 women and 52 men, mean age 63.55 years (SD 10.49). Mean values of the study variables were: MCD 0.52 mm (SD 0.27), MD 2.78 dB (SD 5.02), CCT 543.5 µm (SD 36.63), IOP 16.73 mmHg (SD 2.93) and disc area 2.01 mm^2 (SD 0.39), as shown in **Table 1**.

MCD and patient age: linear regression analysis showed a non-significant negative trend suggesting lower MCD with increasing age (r −0.08, p 0.24), **Figure 1**. However, on stratifying the sample using 60 years of age as the cutoff point, MCD showed a significant correlation with age in patients <60 years (r −0.25, p 0.02), as shown in **Table 2** and **Figure 2**. No significant correlation between MCD and age was observed in patients aged ≥ 60 years (r −0.03, p 0.75), as shown in **Figure 3**.

MCD and MD: no significant correlation (r 0.01, p 0.83) was observed between MCD and MD, (**Figure 4**) for the whole sample. Similarly, no significant correlation was found on stratifying patients according to age ≥60 years (r 0.02, p 0.79) or <60 years (r 0.01, p 0.96).

MCD, MD and disc area: a significant correlation (r 0.29, p 0.00003) was found between MCD and disc area, and between MD and disc area (r 0.16, p 0.02), suggesting that optical discs with larger area have greater MCD, (**Figure 5**) and greater MD.

MCD and CCT: no significant correlation was observed between these two parameters (r −0.05, p 0.41), (**Figure 6**).

Finally, a significant negative correlation was found between MD and CCT (r −0.26, p 0.00004).

Table 1. Descriptive statistics.

	n	Mean	SD	Minimum	Maximum
AGE (years)	234	63.55	10.49	38.00	83.68
MD (dB)	234	2.78	5.02	−2.54	25.03
MCD (mm)	234	0.52	0.27	0.02	1.30
IOP (mmHg)	234	16.73	2.93	10.00	21
CCT (µm)	234	543.50	36.63	447.00	683.00
SIZE (mm^2)	234	2.01	0.39	1.11	3.78

Table 2. Correlations of MCD with other factors, *p < 0.05.

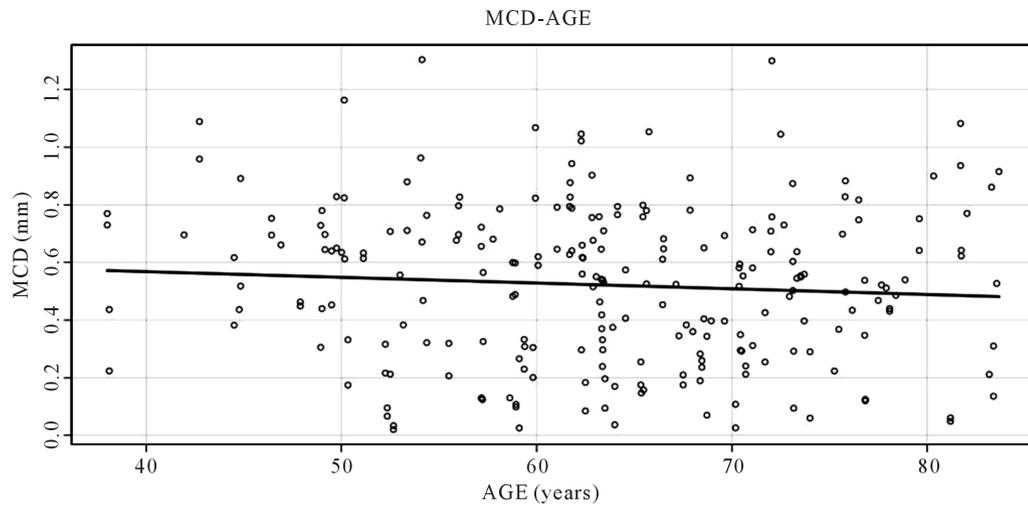|	r	p value
AGE < 60 (years)	−0.25	**0.02***
AGE ≥ 60 (years)	−0.03	0.75
MD < 60 (years)	0.01	0.96
MD ≥ 60 (years)	0.02	0.79
SIZE (mm^2)	0.29	**0.00***
CCT (µm)	−0.05	0.41

MCD-AGE

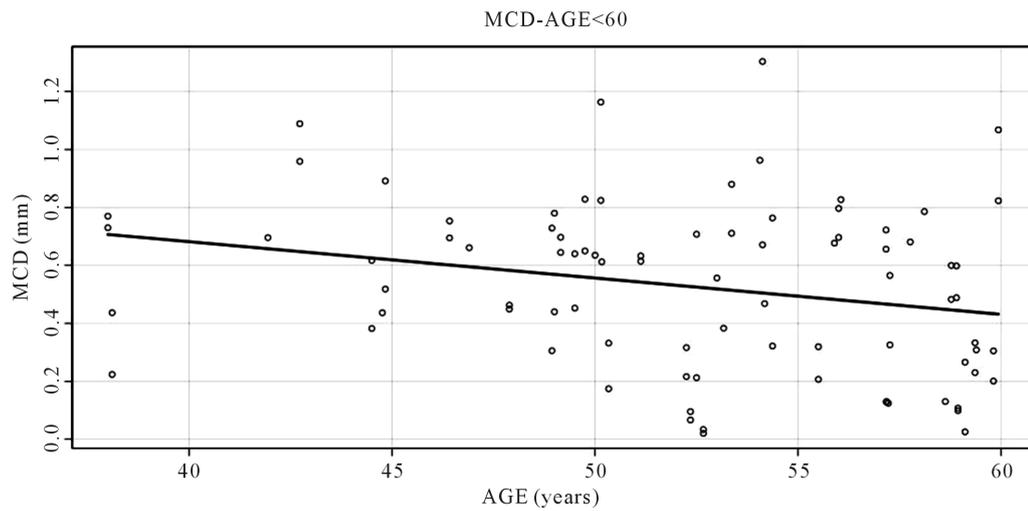**Figure 1.** Linear regression analysis: MCD and age (r −0.08, p 0.24).

MCD-AGE<60

Figure 2. Linear regression analysis: MCD and age < 60 years old, (r −0.25, p 0.02).

MCD-AGE≥60

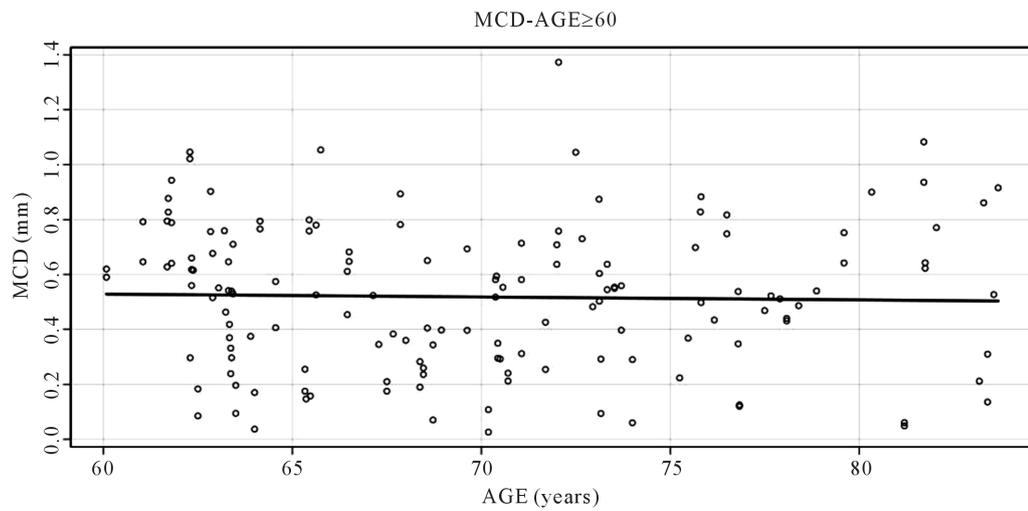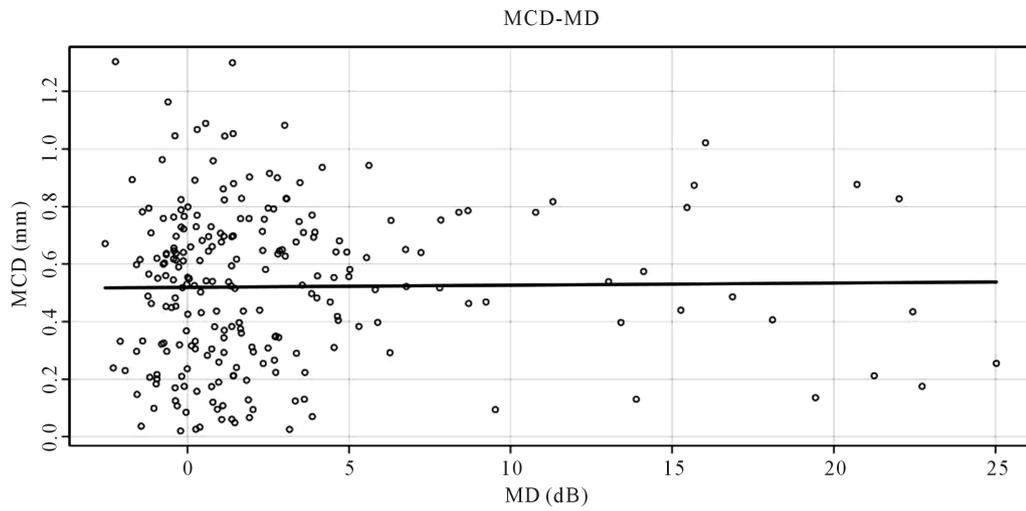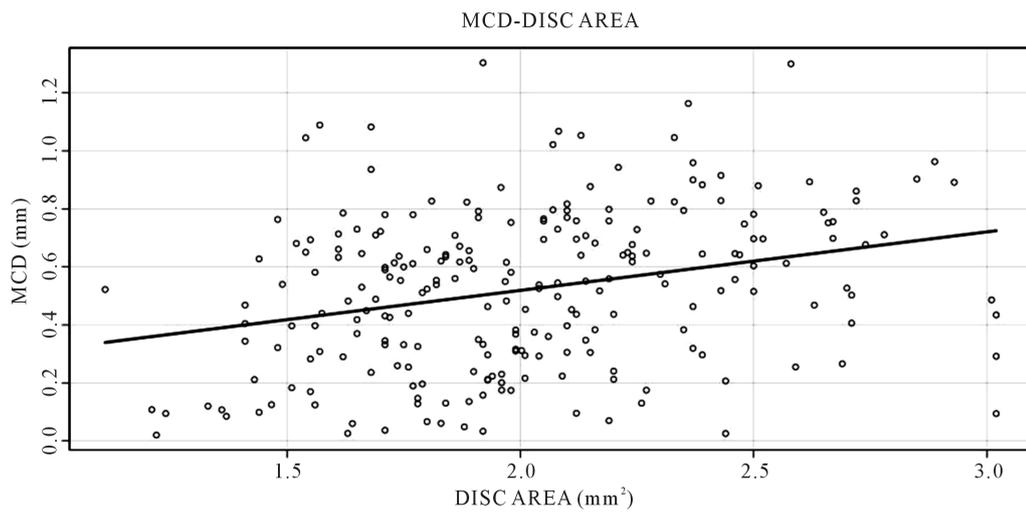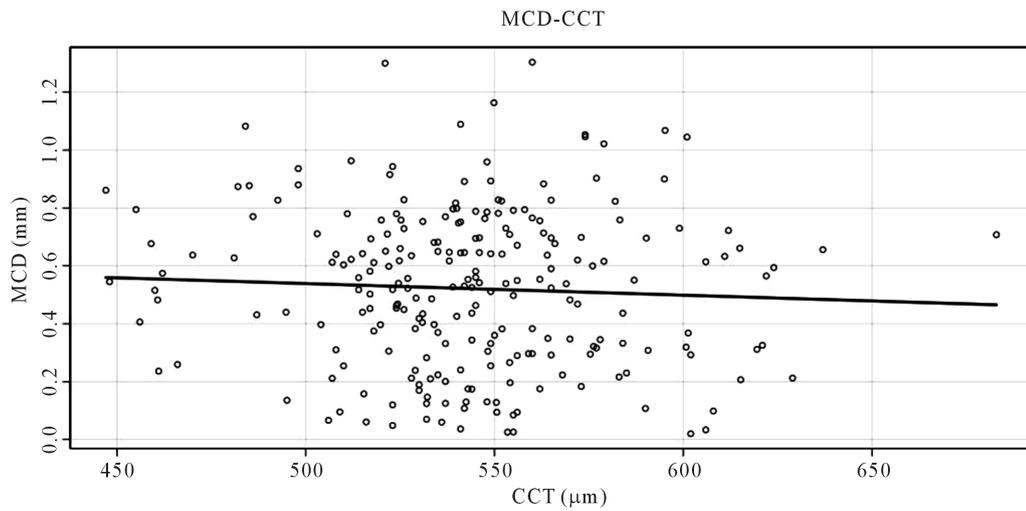**Figure 3.** Linear regression analysis: MCD and age ≥ 60 years old (r −0.03, p 0.75).

MCD-MD

Figure 4. Linear regression analysis: MCD and MD (r 0.01, p 0.83).

MCD-DISC AREA

Figure 5. Linear regression analysis: MCD and disc area (r 0.29, p 0.00003).

MCD-CCT

Figure 6. Linear regression analysis: MCD and CCT (r −0.05, p 0.41).

4. Discussion

The pathophysiology of glaucomatous damage is not yet fully understood. It seems clear that glaucoma is multifactorial and that individual susceptibility plays a role in the development and progression of the disease. Although high IOP is still the only known modifiable risk factor [13], the translaminar pressure gradient, *i.e.*, the difference between IOP and cerebrospinal fluid pressure, has been identified as a risk factor for glaucomatous damage. This gradient is important in ocular diseases where the pressure on one or both sides of the lamina cribrosa is abnormally high or abnormally low [14]. Therefore, it is important to understand the effects of IOP on the optic nerve head, lamina cribrosa and scleral canal, and how these effects vary from one individual to another, along with aging. Several authors have studied the relationship between age, lamina cribrosa and MD.

Albon *et al*. [11], in their study of the eyes of 10 human cadavers aged between 7 and 86 years, showed that increasing age correlated with increased rigidity of the lamina cribrosa and reduced deformability even at high pressures. Reduced lamina cribrosa flexibility with age is associated with greater amounts of total collagen and pentosidine and a lower proportion of type III [15] collagen. These histological changes underlie susceptibility to ganglion axon cell damage as they pass through the pores of the lamina [11].

Ruojin *et al*. [10], in a study of 221 subjects with OHT and glaucoma, obtained results suggesting that for a certain level of visual field loss, younger patients showed greater lamina cribrosa depth than older patients, and this age-related difference increased with disease severity. Their data reveal the relationship between MD, the lamina cribrosa depth and age: the depth tends to be greater with worse MD, but this effect decreases with increasing age. These authors used spectral-domain optical coherence tomography (SDOCT) to analyze the position of the lamina cribrosa.

Rho *et al*. [16], in a study of 26 eyes with POAG and 52 eyes with low tension glaucoma, observed a negative correlation (r −0.738) between lamina cribrosa depth and age in patients with POAG, as we did, but not in patients with low-tension glaucoma. According to the authors, this may be due to two factors: first, in patients with low-tension glaucoma the lamina cribrosa is sufficiently rigid to resist deformation, or second, IOP was not high enough to deform the lamina cribrosa. Other authors have found differences in the translaminar pressure gradient in patients with normal tension glaucoma and POAG, suggesting the existence of a different pathophysiological mechanism in the development of normal tension glaucoma [17].

In accord with these studies, our data suggest a correlation between MCD and age. Glaucomatous damage to the optic nerve head may be divided into two components, the prelaminar, which manifests as an extension of the cup and is due to thinning or loss of the prelaminar tissue, and the laminar component where cup elongation and deepening is due to permanent damage caused by increased IOP on the lamina cribrosa and the scleral rim [18]. As in the work by Rho *et al*. [16], our results suggest that MCD is age-dependent, with significant correlation found in the younger patients (<60 years). As age increases, the lamina cribrosa loses elasticity, it becomes less deformable and its depth ceases to correlate with age, as in our patients aged over 60 years.

We observed a significant correlation between MCD and disc area, and between MD and disc area. Our data suggest that optical discs with larger area have greater MCD and MD. The relationship between disc area and susceptibility to glaucomatous damage remains to be clarified [19]. Some authors suggest that patients with large discs have a higher incidence of glaucoma [20] [21], while others have found no such relationship [22] [23]. Recent studies suggest that, by Laplace's law, the pressure gradient across the lamina cribrosa could lead to increased deformation and posterior displacement of the center in large discs, leading to increased susceptibility to glaucoma in patients with large discs [24]. This susceptibility to posterior displacement of the center in large discs could explain the significant correlation between MCD and large discs in our work. Further analysis of this aspect is needed in future studiesto evaluate if the disc area is a risk factor of glaucoma and his role in the prevention of OHT and POAG.

Finally, we observed a negative correlation between CCT and MD in our series; patients with thinner CCT had worse MD results. The relationship between CCT and MD is already known and Leske MC *et al*. have suggested that a thinner CCT is an independent risk factor for progression of glaucoma [6].

Our work has certain limitations. We did not directly measure the depth of the lamina cribrosa, MCD depends on the lamina cribrosadepth and the amount of prelaminar tissue. Our sample comprised patients with OHT and POAG in very early stages of the disease, with an average MD of 2.78 dB (SD 5.02 dB), which may have influenced the results. Unlike Rho *et al*. [16], we found lower rates correlation between MCD and age. This was probably due to the presence of OHT patients who had not yet developed typical glaucomatous cupping. Also,

our sample had early-stage glaucoma with mild MD, which may explain why we found no significant correlation between MCD and MD. However, Ruojin *et al.* [10], in a similar sample of 221 patients with OHT and POAG with a mean MD of −0.69 dB (SD 2.94), found that the correlation between MD and the depth of the lamina cribrosa was dependent on age.

5. Conclusion

Our study showed that MCD depended on age, with MCD-age correlation being significant in patients younger than 60 years but not in older patients. Finally, MCD and MD correlated with disc area, suggesting that the larger the disc area, the greater the MCD and MD in patients with OHT and POAG. Further studies are needed to verify and interpret these results.

Conflict of Interests

None of the authors have any proprietary interests or conflicts of interest related to this submission.

References

[1] Pasutto, F., Chavarria-Soley, G., Mardin, C.Y., Michels-Rautenstrauss, K., Ingelman-Sundberg, M., Fernández-Martínez, L., Weber, B.H., Rautenstrauss, B. and Reis, A. (2010) Heterozygous Loss-of-Function Variants in CYP1B1 Predispose to Primary Open-Angle Glaucoma. *Investigative Ophthalmology & Visual Science*, **51**, 249-254.
http://iovs.arvojournals.org/article.aspx?articleid=2185823
http://dx.doi.org/10.1167/iovs.09-3880

[2] Tham, Y.C., Li, X., Wong, T.Y., Quigley, H.A., Aung, T. and Cheng, C.Y. (2014) Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040: A Systematic Review and Meta-Analysis. *Ophthalmology*, **121**, 2081-2090. http://dx.doi.org/10.1016/j.ophtha.2014.05.013

[3] Guo, L., Moss, S.E., Alexander, R.A., Ali, R.R., Fitzke, F.W. and Cordeiro, M.F. (2005) Retinal Ganglion Cell Apoptosis in Glaucoma Is Related to Intraocular Pressure and IOP-Induced Effects on Extracellular Matrix. *Investigative Ophthalmology & Visual Science*, **46**, 175-182. http://iovs.arvojournals.org/article.aspx?articleid=2163667
http://dx.doi.org/10.1167/iovs.04-0832

[4] Medeiros, F.A., Alencar, L.M., Zangwill, L.M., Sample, P.A. and Weinreb, R.N. (2009) The Relationship between Intraocular Pressure and Progressive Retinal Nerve Fiber Layer Loss in Glaucoma. *Ophthalmology*, **116**, 1125-1133.
http://dx.doi.org/10.1016/j.ophtha.2008.12.062

[5] Gordon, M.O., Beiser, J.A., Brandt, J.D., Heuer, D.K., Higginbotham, E.J., Johnson, C.A., Keltner, J.L., Miller, J.P., Parrish, R.K., Wilson, M.R. and Kass, M.A. (2002) The Ocular Hipertensión Treatment Study: Baseline Factors That Predict the Onset of Primary Open-Angle Glaucoma. *Archives of Ophthalmology*, **120**, 714-720.
http://archopht.jamanetwork.com/article.aspx?articleid=270929
http://dx.doi.org/10.1001/archopht.120.6.714

[6] Leske, M.C., Heijl, A., Hyman, L., Bengtsson, B., Dong, L. and Yang, Z., EMGT Group (2007) Predictors of Long-Term Progression in the Early Manifest Glaucoma Trial. *Ophthalmology*, **114**, 1965-1972.
http://dx.doi.org/10.1016/j.ophtha.2007.03.016

[7] Leske, M.C., Connell, A.M., Schachat, A.P. and Hyman, L. (1994) The Barbados Eye Study. Prevalence of Open Angle Glaucoma. *Archives of Ophthalmology*, **112**, 821-829.
http://archopht.jamanetwork.com/article.aspx?articleid=640727
http://dx.doi.org/10.1001/archopht.1994.01090180121046

[8] Leske, M.C., Nemesure, B., He, Q., Wu, S.Y., Fielding Hejtmancik, J. and Hennis, A. (2001) Patterns of Open-Angle Glaucoma in the Barbados Family Study. *Ophthalmology*, **108**, 1015-1022.
http://dx.doi.org/10.1016/S0161-6420(01)00566-8

[9] Mitchell, P., Hourihan, F., Sandbach, J. and Wang, J.J. (1999) The Relationship between Glaucoma and Myopia: The Blue Mountains Eye Study. *Ophthalmology*, **106**, 2010-2015. http://dx.doi.org/10.1016/S0161-6420(99)90416-5

[10] Ren, R., Yang, H., Gardiner, S.K., Fortune, B., Hardin, C., Demirel, S. and Burgoyne, C.F. (2014) Anterior Lamina Cribrosa Surface Depth, Age, and Visual Field Sensitivity in the Portland Progression Project. *Investigative Ophthalmology & Visual Science*, **55**, 1531-1539. http://iovs.arvojournals.org/article.aspx?articleid=2190060
http://dx.doi.org/10.1167/iovs.13-13382

[11] Albon, J., Purslow, P.P., Karwatowski, W.S. and Easty, D.L. (2000) Age Related Compliance of the Lamina Cribrosa in Human Eyes. *British Journal of Ophthalmology*, **84**, 318-323. http://bjo.bmj.com/content/84/3/318.long
http://dx.doi.org/10.1136/bjo.84.3.318

[12] Itai, N., Tanito, M. and Chihara, E. (2003) Comparison of Optic Disc Topography Measured by Retinal Thickness Analyzer with Measurement by Heidelberg Retina Tomograph II. *Japanese Journal of Ophthalmology*, **47**, 214-220. http://dx.doi.org/10.1016/S0021-5155(02)00699-8

[13] Díaz-Alemán, V.T., González-Hernández, M., Perera-Sanz, D. and Armas-Domínguez, K. (2015) Evaluation of Visual Field Progression in Glaucoma: Quasar Regression Program and Event Analysis. *Current Eye Research*, **19**, 1-8. http://www.tandfonline.com/doi/abs/10.3109/02713683.2015.1020169?journalCode=icey20 http://dx.doi.org/10.3109/02713683.2015.1020169

[14] Jonas, J.B., Berenshtein, E. and Holbach, L. (2003) Anatomic Relationship between Lamina Cribrosa, Intraocular Space, and Cerebrospinal Fluid Space. *Investigative Ophthalmology & Visual Science*, **44**, 5189-5195. http://iovs.arvojournals.org/article.aspx?articleid=2123836 http://dx.doi.org/10.1167/iovs.03-0174

[15] Albon, J., Karwatowski, W.S., Avery, N., Easty, D.L. and Duance, V.C. (1995) Changes in the Collagenous Matrix of the Aging Human Lamina Cribrosa. *British Journal of Ophthalmology*, **79**, 368-375. http://bjo.bmj.com/content/79/4/368 http://dx.doi.org/10.1136/bjo.79.4.368

[16] Rho, C.R., Park, H.Y., Lee, N.Y. and Park, C.K. (2012) Clock-Hour Laminar Displacement and Age in Primary Open-Angle Glaucoma and Normal Tension Glaucoma. *Clinical & Experimental Ophthalmology*, **40**, e183-e189. http://onlinelibrary.wiley.com/doi/10.1111/j.1442-9071.2011.02669.x/abstract http://dx.doi.org/10.1111/j.1442-9071.2011.02669.x

[17] Siaudvytyte, L., Januleviciene, I., Ragaukas, A., Bartusis, L., Meiliuniene, I., Siesky, B. and Harris, A. (2014) The Difference in Translaminar Pressure Gradient and Neuroretinal Rim Area in Glaucoma and Healthy Subjects. *Journal of Ophthalmology*, **2014**, Article ID: 937360. http://dx.doi.org/10.1155/2014/937360

[18] Burgoyne, C.F. and Downs, J.C. (2008) Premise and Prediction-How Optic Nerve Head Biomechanics Underlies the Susceptibility and Clinical Behavior of the Aged Optic Nerve Head. *Journal of Glaucoma*, **17**, 318-328. http://journals.lww.com/glaucomajournal/pages/articleviewer.aspx?year=2008&issue=06000&article=00012&type=abstract http://dx.doi.org/10.1097/IJG.0b013e31815a343b

[19] Enomoto, N., Anraku, A., Ishida, K., Takeyama, A., Yagi, F. and Tomita, G. (2015) Size of the Optic Nerve Head and Its Relationship with the Thickness of the Macular Ganglion Cell Complex and Peripapillary Retinal Nerve Fiber Layer in Patients with Primary Open Angle Glaucoma. *Journal of Ophthalmology*, **2015**, Article ID: 186249.

[20] Healey, P.R. and Mitchell, P. (1999) Optic Disk Size in Open-Angle Glaucoma: The Blue Mountains Eye Study. *American Journal of Ophthalmology*, **128**, 515-517. http://dx.doi.org/10.1016/S0002-9394(99)00195-6

[21] Wang, L., Damji, K.F., Munger, R., Jonasson, F., Arnarsson, A., Sasaki, H. and Sasaki, K. (2003) Increased Disk Size in Glaucomatous Eyes vs Normal Eyes in the Reykjavik Eye Study. *American Journal of Ophthalmology*, **135**, 226-228. http://dx.doi.org/10.1016/S0002-9394(02)01928-1

[22] Jonas, J.B., Fernández, M.C. and Naumann, G.O. (1991) Correlation of the Optic Disc Size to Glaucoma Susceptibility. *Ophthalmology*, **98**, 675-680. http://dx.doi.org/10.1016/S0161-6420(91)32234-6

[23] Jonas, J.B., Martus, P., Horn, F.K., Jünemann, A., Korth, M. and Budde, W.M. (2004) Predictive Factors of the Optic Nerve Head for Development or Progression of Glaucomatous Visual Field Loss. *Investigative Ophthalmology & Visual Science*, **45**, 2613-2618. http://iovs.arvojournals.org/article.aspx?articleid=2124251 http://dx.doi.org/10.1167/iovs.03-1274

[24] Hoffmann, E.M., Zangwill, L.M., Crowston, J.G. and Weinreb, R.N. (2007) Optic Disk Size and Glaucoma. *Survey of Ophthalmology*, **52**, 32-49. http://dx.doi.org/10.1016/j.survophthal.2006.10.002

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