Axial Length is a Better Predictor of Glaucoma Progression among Myopic Eyes

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Abstract

Myopia is a well-established risk factor for the development and onset of open angle glaucoma (OAG). However, the diagnosis and monitoring of myopic eyes with glaucoma are challenging due to tilted optic disc configuration and myopic retinal changes like peripapillary atrophy (PPA). Visual field (VF) defects in eyes with high myopia may not be always related to glaucoma, which can lead to misdiagnosis of the condition. Nevertheless, the risk assessment of glaucoma progression is important to determine whether patients are at risk of vision loss. Clinical studies to date have not reached any consensus regarding the nature and rate of glaucoma progression in myopic eyes in comparison to non-myopic eyes. A systematic search of Pubmed and Scopus online databases were conducted till the 1st of April 2018 to examine the structural and functional relationship between myopia, axial length and glaucoma progression. The plethora of results described in the literature is varied and extensive. Myopia, especially high myopia has been reported to be a risk factor for progressive VF damage in OAG eyes compared with mild or moderately myopic eyes. Conversely, the population based studies like the early manifest glaucoma trial (EMGT), Malmö Ocular Hypertension Study and the Advanced Glaucoma Intervention Study (AGIS) have failed to show an association between myopia and glaucomatous visual field/ photographic disc progression, and some studies even reporting myopia to be having protective characteristics, which have been addressed below. Evidences suggest that axial length is indeed a better indicator of glaucoma progression among myopic eyes than the refractive error itself. Although the results from current studies on the relationship between myopia and glaucoma progression is controversial, appropriate methodologies are warranted to assess it. Measuring the axial length is not only an important approach in identifying patients with greater risk of glaucoma progression but also in detecting glaucoma progression at an early stage.

Keywords: Myopia; Glaucoma; Progression; Axial Length; Visual Field; Structural; Functional Damage

Introduction

Glaucoma is a chronic, progressive optic neuropathy characterized by the loss of retinal ganglion cells (RGC) and their respective axons from the retinal nerve fiber layer (RNFL), narrowing of the neuroretinal rim, optic disc excavation, loss of prelaminar neural tissue, deformation and remodeling of the optic nerve head (ONH) [1,2]. The cumulative damage incurred in this progressive disease may ultimately lead to irreversible blindness. It was estimated that by 2010, one out of 15 blind people were blind due to glaucoma, and one of 45 visually impaired people were visually impaired, highlighting the increasing global burden of glaucoma [3].

Myopia has been well established to be risk factor for the development and onset of open angle glaucoma (OAG). It is expected to affect about 2.5 billion people worldwide by the year 2020. With myopia on the rise worldwide, the prevalence and incidence of OAG is also

expected to increase [4]. Glaucoma being a chronic, progressive disease, the assessment of its progression is therefore important to decide upon the treatment modality and intensity and evaluate disease prognosis. Some of the studies suggests a greater visual field progression among myopes, high myopes in particular; whereas, other studies failed to prove the association, and even reporting a protective effect from glaucoma progression. Glaucoma being a chronic progressive disease, it is even more imperative to find the rate of progression among this myopic cohort of high risk individuals. However, the findings from studies investigating visual field progression in glaucoma among myopic subjects are not consistent and less is known about the rate of retinal nerve fiber layer (RNFL) and visual field (VF) progression in myopic eyes with glaucoma. Although, studies were conducted to evaluate the relationship between myopia and glaucoma progression, few have assessed whether it can be explained by longer axial length which represents high myopia better than spherical equivalent.

Methodology

A systematic search of Pubmed and Scopus online databases were carried out till the 1st of April 2018 to examine the structural and functional relationship between myopia, axial length and glaucoma progression. Articles which maintained ethical practices and followed the guidelines of the Helsinki Declaration were only considered in this review. The literature search was performed using the medical subject headings (MeSH) and text words related to myopia and glaucoma progression. The following terms were used: myopia; shortsightedness; refractive error; axial length; spherical error; spherical equivalent; glaucoma; glaucoma progression; open angle glaucoma; angle closure glaucoma; retinal nerve fiber layer; visual field; optic disc; optic nerve head; mean deviation; visual field index. No restriction regarding study design, date or languages were imposed. The electronic database search will be supplemented by a manual search of reference lists from relevant studies. The initial search resulted in several studies from which the ones that are relevant for the review were manually selected. The references of all potentially relevant articles and our reference library were also searched to identify studies not found by the electronic searches. Retrieved studies from all the databases were downloaded and duplicate articles were manually deleted. Titles and abstracts of the remaining studies were scanned by the author. The extracted studies were compared, and inconsistencies were resolved with expert opinion. The full texts of the remaining studies were then read to determine whether they met our criteria. In addition, the reference lists from all identified studies were examined. Inclusion criteria were longitudinal studies on myopia and glaucoma progression which at least reported the refractive error/axial length, duration of follow up, definition of glaucoma progression and the conclusion.

Results

Myopia and axial length

The refractive status of the eyeball is governed by the balance between the optical power of the cornea and lens, and the axial length of the eye. The axial length is determined by its components namely the anterior chamber depth, lens thickness and vitreous chamber depth. The refractive power of the eye ascertains the posterior focus point of the eye, which lies in front of the retina among those with myopia. This may be a result of either the corneal or the lens power or both being in excess for a normal axial length; or the axial length being longer than normal or longer than what is balance for the refractive power of the eye [5].

Most infants are hyperopic at birth and in the subsequent years the eyes become less hyperopic as their axial length elongates, associated with the thinning of the lens and flattening of the cornea. Longitudinal studies have shown the increase in the axial length of children with myopia ranging from 0.38mm/year to 0.89mm/year 6. This process of forming a perfect emmetropic eye with balanced constituents is termed as emmetropization. After the emmetropization period, the cornea gets stabilized, however eyes can still grow more myopic as the axial lengths can increase for about two decades. However, the lens power of the eye has been reported to decrease up to 12 years of age, with an even slower decrease during the adult life. In general, axial length increases rapidly in the early stage of life before the onset of myopia, then the axial elongation relatively slows with stable rate of change until adulthood, followed by which it decreases slowly in old age [6].

In a cohort study, Gordon et al. showed that the axial length increases from 16.8mm in infancy to 23.6mm in adulthood [7]. The associated change in refractive status of the eyeball is offset by the corresponding change in other structures as the lens. The lens reduces its refractive power with the increase in axial length. An elongation of axial length by 1-mm alone without any other compensatory mechanism will result in a myopic shift equivalent to -2 to -2.5D [6]. Axial length has the strongest correlation with the refractive status, with longer eyes tend to be more myopic, which brings the axial length of the eye to be the most variable factor during development [6]. Most studies have agreed on axial length to be the largest determinant of refractive error [8]. Thus, balancing the axial elongation of the eyeball along with the other components mentioned above is crucial in achieving emmetropization of the eye.

Retinal nerve fiber layer arrangement in myopic eyes

The peripapillary RNFL in eyes having low to moderate (40 eyes, SE -6 D to -0.5 D) and high myopia (75 eyes, SE < -6 D) was studied by Leung et al with Stratus optical coherence tomography (OCT) fast RNFL and they reported that the average RNFL thickness were significantly smaller in high myopes compared to those with low to moderate myopia. They also reported that there is a linear correlation between RNFL thickness and axial length/spherical equivalent. A double hump pattern with peak RNFL thickness at the 11 o'clock hour (supero-temporal sector) and 7 o'clock hours (infero-temporal sector) were observed along with troughs at the 3 o'clock (nasal sector) for the myopic eyes [9]. Budenz et al. similarly reported that RNFL thickness was related significantly to both axial length and refractive error, with longer eyes and more myopic eyes had a thinner measured RNFL [10]. However, earlier report by Ozdek et al. on 85 subjects with a mean SE of -4.56±2.72 D with scanning laser polarimetry (SLP) showed there was a gradual decrease in the superior and inferior RNFL with increasing myopia (0.122 μm and 0.092 μm reductions per diopter, respectively) [11]. However, Bowd et al failed to find an association between refraction and the RNFL parameters measured by both GDx and OCT in a group of 155 subjects with refractive error ranging from -5.0 to +5.0 D [12]. Similarly, another study with OCT-1 also reported similar findings with no association between the mean peripapillary RNFL and the axial length or spherical equivalent with 132 young males with myopia (SE -0.50 to -14.25 D), using circular scans concentric with the optic disc with scan diameters of 3.40 mm, 4.50 mm and 1.75 × vertical disc diameter (VDD) [13]. Leung et al showed a temporal convergence of the superotemporal and inferotemporal RNFL bundles with increasing myopic refractive error, leaving the superior and inferior RNFL measurements relatively abnormal and resulting in false positive RNFL measurements. Owing to the antero-posterior elongation of the globe, the superior and inferior RNFL bundles are drawn closer to the macula, thus reducing the RNFL distribution angle with increasing axial length [14]. In another study, Kim et al. measured 48 myopic eyes with Stratus OCT and demonstrated that the temporal RNFL was thicker in the moderate and high myopia (SE ≤ -3.0 D) group than in the low myopia group (SE > -3.0 D) [15]. Similarly, Kang et al. found a positive correlation between the axial length and the temporal circumpapillary RNFL thickness measured in 269 young subjects (age: 19–26 years) using the Cirrus HD-OCT [16]. Likewise, Hong et al. measured the angle between the peaks of the circumpapillary RNFL profile of normal subjects (mean SE, -2.52±2.29 D and range, -10.13 to +1.5 D) and found that there is a shift in the peak RNFL thickness towards the temporal quadrant with increasing myopia [17]. Thus, myopic eyes may have thinner RNFL and a different RNFL thickness profile which may lead to abnormal diagnostic classification [18]. The frequency of occurrence of the measurement errors and the misclassification of RNFL defect has been reported to be related to the axial length [18]. However, recent studies have shown that the convergence and temporalization of RNFL is not by dragging of superior and inferior RNFL bundles, but by temporal shift of optic disc, which makes simply more nasal location of circle scan [19].

Myopia and glaucoma progression

Studies are divided when it comes to the role of myopia in glaucoma progression. Some of the studies suggests a greater visual field progression among myopes, high myopes in particular [20-28]; whereas other studies failed to show the association [29-42]. A few studies have even reported myopia to have a protective effect for glaucoma progression [36,43-48]. The studies have been summarized in table 1 based on whether myopia/spherical error/spherical equivalent or axial length was used as indicator of the glaucoma progression.

Journal, Year	Sample Size (Eyes/ Subjects)	Subject/ Study Design	Refractive Error in Dioptres, Mean ± SD (Range)	Axial Length in mm, Mean ± SD (Range)	Study Duration (years)	Definition of Progression	Outcome	Key Findings
Spherical equivalent/Spherical error as a predictor for Glaucoma progression								
1. Myopia as risk factor for Glaucoma progression								
Daubs., et al. Trans Oph-thalmolSoc U K. 1981; 101(1):121-6	1000 Eyes	Case-Control	≤ -5.0 to > +0.25	NA	-	Friedmann VF event analysis	Presence of VF defects in eyes with and with-out OHT/ myopia	**RR = 3.1 (1.6-5.8), 1.3 (1.0-1.8), 1.2 (0.9-1.5) for high (< -5D), low (> -5 to < -0.25D) and emmetropia (+0.25 to -0.25D) respectively; ǂ Interactive effect of myopia and OHT is 2.2 (1.1-3.8) times for development of glaucoma
Perkins., et al. Arch Oph-thalmol. 1982; 100(9):1464-7	487 Eyes	POAG and OHT/ Ret-rospective observational	≤ -5.0 to > +5.1	NA	7.43	Optic disc and VF event analysis	Develop-ment of POAG from OHT	Myopes with OHT have a high risk for development of VF defects, 27.4% of POAG and 16% of OHT patients were myopic (SE ≤-1D). Ratio of OAG:OHT for Hypermet-ropes, emmetropes and myopes were 1:46, 1:19 and 1:3 respectively, p < 0.01
Chihara., et al. Ophthalmo-logica. 1997; 211(2):66-71	122 Eyes/ 122 Subjects	Treated POAG/ Retrospective	-2.6 ± 4.2 (-16.0 to +2.0)	NA	5	Goldmann Kinetic pe-rimeter event analysis	# Change in VF de-fect stage	Myopia ≤ -4D is a risk factor for progressive VF loss, chi square = 5.17**, p = 0.023
Landers., et al. Clin Exp Ophthal. 2002; 30(4):242-7	739 Subjects	Treated POAG and OHT	NA	NA	6	HVF event analysis	Develop-ment of POAG from OHT	**OR = 1.5 (1.0-2.2) for myopia ≤ -1D, p < 0.05
Perdicchi., et al. Eur J Oph-thal. 2007; 17(4):534-7	208 Eyes/ 110 Subjects	Treated POAG/ Retrospective	-14.0 to +4.0	NA	4.7 ± 3.7	Octopus trend analy-sis of MD and LV	Significant decrease in the perimetric indexes vs time	36% and 34% of all eyes had MD and LV progression, of which 46% and 42% were for high myopes > -7.5D (p < 0.005)
Lee., et al. J Formos Med Assoc. 2008; 107(12):952-7	262 Eyes/ 515 Subjects	Treated POAG/ Retrospective	-5.1 ± 4.2	25.63 ± 1.90	8.7 ± 2.2	HVF event analysis	3 or more points with loss of ≥1dB mean defect in 2 consecu-tive fields	**OR = 4.69 (2.08-10.57) for myopia, p < 0.001; 15.1% Mild Myopia (> -3), 10.5% Moderate (< -3 to > -6), 34.4% High (< -6 to > -9) and 38.9% very High myopia (< -9) progressed
Han., et al. Am J Ophthalmol. 2016;169:33-45	82 non-myo-pic eyes/82 Subjects and 150 myopic Eyes/150 Subjects	Treated OAG/ Retrospective, comparative, longitudinal cohort study	NMG: -1.2 ± 2.3 (-2 to 2.5), MG: -4.5 ± 2.7 (-9.8 to -2.1)	NMG: 24.2 ± 1.0 (21.3-24.5), MG: 25.9 ± 1.4 (24.2-29.5)	NMG: 10.0 ± 2.4, MG: 9.8 ± 2.7	HVF event analysis	GPA event analysis possible progres-sion	**HR = 1.002 (0.997-1.007, p = 0.515) for progression per D of SE, Cumulative prob-ability of progression faster for myopic vs. non-myopic OAG with inferior (p = 0.038) and temporal (p = 0.002) tilted disc
						VF trend analysis of VFI	Significant decrease in slope of the VFI	
2. Myopia not a risk factor for Glaucoma progression								
Phelps. Am Oph-thalmol. 1982; 93(5):622-8	166 Eyes	Treated OAG/ Retrospective	≤-5.0 to +4.9	NA	NA	Goldmann Kinetic pe-rimeter event analysis	# # Change in VF defect stage	12% of myopes improved and 6% wors-ened vs. 6% Non-myopes improved and 18% worsened
Quigley., et al. Arch Opthal-mol. 1994; 112(5):644-9	1294 Eyes/647 Subjects	Treated OHT/ Prospective longitudinal	-12.0 to +12.0	NA	6.2	Goldmann Kinetic and static perim-eter event analysis	Develop-ment of POAG from OHT	*RR = 2.09 (0.85-5.14) for high myopia (-4.25 to -12D), 1.53 (0.70-3.34) for moder-ate myopia (-0.125 to -4D), p > 0.05

EMGT. Arch Opthalmol. 2003; 121(1):48-56	510 Eyes/255 Subjects	POAG/ RCT	≤ -1.0 to ≥ +1.0	NA	6	HVF event analysis	EMGT criteria of ≥ 3 progressing points in 3 consecutive visits from baseline	*OR = 0.97 (0.58-1.61) for myopia ≤ -1D, p = 0.99; 55% myopes vs 53% non myopes progressed
AGIS. Ophthalmology. 2004; 111(9):1627-35	509 eyes/ 401 Subjects	Treated POAG/ Multicenter RCT	-20.0 to +6.0	NA	7.4 ± 1.7	HVF event analysis	AGIS criteria of VF defect score of ≥4 from the baseline value	*OR = 0.752 (0.432-1.311) for myopia < -1 to -4D, p = 0.301
Bengtsson., *et al.* J Glaucoma. 2005; 14(2):135-8	90 Eyes/ 90 Subjects	OHT/ RCT	≤ -3.0 to ≥ +1.0	NA	10	Goldmann Kinetic perimeter event analysis	Development of POAG from OHT	*OR = 0.70 for myopia, p = 0.32; 35% of myopes vs 54% non myopes progressed
Doshi., *et al.* Ophthalmology. 2007; 114(3):472-9	32 Eyes/ 16 Subjects	Treated OAG/ Retrospective case series	-11.25 to +0.25	NA	7	HVF event analysis	CIGTS score ≥3 in 3 consecutive visits from baseline	None of the eyes progressed including the 43.8% with high myopia (< -6D)
OHTS and EGPS Groups Ophthalmology. 2007; 114(1):10-9	2533 Eyes/ 1319 Subjects	OHT/ RCT	-0.11	NA	4.8-6.6	HVF event analysis	Change in VF defect by masked observers	*OR = 0.89 (0.64-1.25) for myopia ≤ -1D, p = 0.510
						Optic disc event analysis	Increase in NRR thinning, disc excavation, RNFL defect, hemorrhage.	
Kooner., *et al.* Clinical Ophthal, 2008; 2(4):757-62	974 Eyes/ 487 Subjects	HT POAG/ Multicenter longitudinal	NA	NA	5.5	HVF event analysis	# # # Change in VF defect stage	Myopia was not significantly associated with glaucoma progression
						Optic disc event analysis	Progression of C/D ratio by ≥ 0.2, NRR notching-thinning, disk hemorrhage	
Sohn., *et al.* Am J Ophthalmol. 2010; 149(5):831-8	143 Eyes/ 143 Subjects	Treated NTG/ Retrospective case series	Emmetropia-Hyperopia (0.39 ± 0.75), Mild (-1.92 ± 0.55), Moderate (-4.57 ± 0.76) and High (-9.37 ± 0.43)	NA	> 5	HVF trend analysis of MD	Significant decrease in MD vs time	**OR = 1.34 (0.45-3.67) per D increase in myopia, p = 0.458; MD slope -1.334, -1.055, -1.113 and -0.912 db/year for emmet-hyperopia (≥-0.75), mild (-0.76 to -2.99), mod (-3 to -5.99) and high (≤-6) respectively, p = 0.255

Kim., et al. IOVS. 2012; 3;53(8):4485-9	313 Eyes/ 313 Subjects	Glaucoma/ Prospective longitudinal	-0.85 (-0.31 to -4.25)	24.9	2.7	Optic disc event analysis	Increase in NRR thinning, disc excavation, RNFL defect, hemorrhage.	*OR = 0.936 (0.873-1.003, p = 0.062) and **0.917 (0.799-1.051, p = 0.213) for predicting progression with SE; 29.4% RCS vs 27.6% non-RCS progressed, p = 0.482
						HVF event analysis	≥3 progressing points in 3 consecutive visits from baseline	
						HVF trend analysis of VFI	Significant decrease in VFI vs time	
Beijing Eye study. BJO. 2012; 96(6):811-5	222 Eyes/ 111 Subjects	OAG/ Population based prospective cohort study	-1.24 ± 3.66 (-16.25 to +5.88)	NA	5	Optic disc event analysis	Smaller NRR compared to baseline	Glaucoma progressive group and the stable group did not vary in refractive error, p = 0.69*
Hung., et al. J Chin Med Assoc. 2015; 78(7):418-23	92 Eyes/ 92 Subjects	Treated POAG (HTG + NTG)/ Retrospective	-3.10 ± 4.40	25.07 ± 1.78	5.4	HVF event analysis	CIGTS score ≥3 in 3 consecutive visits from baseline	1.289* for myopia ≤-6D, p = 0.698; 0.993* (0.869-1.135) per D of myopia, p = 0.923
Sawada., et al. Plos One. 2017; 12(1):e0170733	144 Eyes/ 72 Subjects	Treated POAG/ Retrospective	-6.31 ± 1.88	26.04 ± 1.12	8.9 ± 4.4	HVF trend analysis of MD	Significant decrease in MD (< -1 and < -2 db/year) for inner andedhe points	*OR = 0.81 (p = 0.18) for SE was not associated with faster VF progression
Song., et al. Graefes Arch ClinExpOphthalmol. 2016; 254(7): 1331-7	55 subjects	Treated POAG/ Prospective	LMG: -3.8 ± 3.3, HMG: -5.5 ± 3.1	LMG: 25.6 ± 1.7, HMG: 26.3 ± 1.7	4.5 ± 1.0	Serial VF report and HVF trend analysis	Significant change in HVF report and decrease in slope of the MD	MD progression -0.25 ± 0.34 and -0.26 ± 0.34 db/year among HMG and LMG (p = 0.91).
						Optic disc/ RNFL photograph and OCT trend analysis	Significant change in photo and decrease in slope of the RNFL thickness	RNFL progression (-0.59 ± 0.67 vs. -0.66 ± 0.72 µm/year among HMG and LMG, p = 0.68)
Yoshino., et al. Jpn J Ophthalmol. 2016; 60(2):78-85.	70 Eyes/ 70 Subjects	Treated POAG (HTG+NTG)/ Prospective	LMG: -1.62 ± 2.37, HMG: -9.77 ± 2.5	NA	LMG: 10.04 ± 4.28, HMG: 9.44 ± 4.15	HVF trend analysis of MD, upper and lower TD	Significant decrease in slope of the MD	MD progression -0.33 ± 0.33 dB/year in the HMG, and -0.38 ± 0.49 in LMG (p = 0.9565). TD progression was not signiicantly different (p > 0.05)

3. Myopia is a protective factor for Glaucoma progression								
Araie., *et al.* ActaOphthalmol. 2012; 90(5):e337-43	146 Eyes/146 Subjects	Treated NTG/ RCT	-3.5 ± 2.9 (-8.0 to +2)	NA	3	HVF event analysis	≥3 progressing points in 3 consecutive visits from baseline	**OR = 0.85, p < 0.05; 55% Myopic vs. 84% non-myopic progressed (p < 0.001)
						Optic disc/ RNFL event analysis	Worsening of RNFL defects, NRR thinning	
Sakata., *et al.* J Glaucoma. 2013; 22(3):250-4	92 Eyes/ 92 Subjects	Treated NTG/ Retrospective	-2.9 ± 2.8 (-7.9 to 3.1)	NA	7.7	HVF trend analysis of mean TD	Significant decrease in TD vs time	Moderate myopia protective for superior paracentral subfield, TD slope -0.066 ± 0.027 db, p = 0.016
Lee., *et al.* IOVS. 2015; 56(3):1775-81	369 Eyes/ 369 Subjects	Treated POAG/ Retrospective cohort study	MMG: -1.77 ± 1.45 and HMG: -9.21 ± 3.57	NA	4.4	Optic disc event analysis	Increase in NRR thinning, disc excavation, RNFL defect, hemorrhage.	*OR = MMG: 1.02 (0.67-1.55), p = 0.929 and HMG: 0.39 (0.14-1.1), p = 0.073; 25.3% NMG (> 0 D), 27.8% MMG (0 to -6D), 10% HMG (≤ -6D) progressed
						HVF event analysis or trend analysis of MD	≥3 progressing points in 3 consecutive visits from baseline or Significant decrease in MD vs time	*OR = MMG: 0.83 (0.47-1.54), p = 0.553 and HMG: 0.87 (0.30-2.51), p = 0.794; 13.5% NMG (> 0 D), 11.8% MMG (0 to -6D), 10% HMG (≤ -6D) progressed
Qiu., *et al.* Plos One. 2015; 10(7):e0133189	270 Eyes/ 270 Subjects	Treated POAG/ Retrospective	-3.72 ± 2.98	25.08 ± 1.51	5.61 ± 2.72	HVF trend analysis of MD	Significant decrease in MD (> 0.22db/ year)	**OR = 0.425 (0.292–0.620), p = 0.023 for high myopia (≤-6 to ≥-9D), 0.282 (0.193-0.411), p = 0.001 for moderate myopia (-6.0 D < to ≤-3.0 D)
Naito., *et al.* Clinical Ophthalmology. 2016; 10:1397-1403	156 Eyes/156 Subjects	Treated NTG and POAG/ Retrospective	-2.8 ± 3.7 (-16 to +2.5)	NA	7.6 ± 2.0 (4.5 to 16.5)	HVF trend analysis of MD	Significant decrease in MD vs time	Decrease in MD slope deterioration with increasing myopia severity, **OR = 1.13 (1.03-1.25, p = 0.0108) for hyperopia
Nitta K., *et al.* Clinical Ophthalmology. 2017; 11:599-604	146 Eyes/ 269 POAG Subjects	Treated POAG/ Retrospective	NMG: -0.0 ± 1.4 HMG: -8.6 ± 2.8	NMG: 23.0 ± 0.7 HMG: -27.6 ± 1.0	NMG: 12.8 ± 2.5 HMG: 13.8 ± 2.3	HVF trend analysis of MD	Significant decrease in MD vs time	MD slope in NMG (-0.383 ± 0.547) greater than HMG (-0.192 ± 0.275) in db/year (p = 0.0183), VF non-progression higher in HMG than NMG (73.7% vs. 46.3%, p = 0.0142)
Axial Length as a predictor for Glaucoma progression								
1. Myopia as risk factor for Glaucoma progression								
Georgopoulos., *et al.* Eur J Ophthal. 1997; 7(4):357-63	690 Eyes/ 345 Subjects	Untreated OHT/ Prospective longitudinal	NA	NA	7.3	HVF event analysis	Development of POAG from OHT	Axial myopia risk factor for developing glaucoma, **OR = 0.679, p = 0.028

Park., *et al.* IOVS. 2016; 57:4170-9	63 myopic and 46 non-myopic eyes	Treated POAG/ Retrospective	NMG: -0.83 ± 1.13 MG: -5.8 ± 4.2	NMG: 22.9 ± 0.5 MG: 27.4 ± 3.1; NMG: < 24, MMG: 24-26, HMG: 26-30, EMG: > 30	NMG: 6.04 ± 0.69 MG: 6.12 ± 0.68	HVF trend analysis of MD, PSD and AGIS score change	Significant decrease in slope of the variables	**OR = 1.1 (1.02-2.01) for AXL (p < 0.01), MD (-4.7 ± 3.2,p < 0.01), PSD (-1.5 ± 1.4, p < 0.01, foveal sensitivity and AGIS score (5.6 ± 1.3, p < 0.01) progressed faster among myopes
						OCT trend analysis	Significant decrease in slope of the RNFL thickness	**OR = 1.24 (1.10-1.42) for AXL (p < 0.01), temporal RNFL thickness progressed faster in myopes (-3.0 ± 3.4, p < 0.01), Mild > High > Extreme
2. Myopia not a risk factor for Glaucoma progression								
Kim., *et al.* IOVS. 2012; 3;53(8):4485-9	313 Eyes/ 313 Subjects	Glaucoma/ Prospective longitudinal	-0.85 (-0.31 to -4.25)	24.9	2.7	Optic disc event analysis	Increase in NRR thinning, disc excavation, RNFL defect, hemorrhage.	*0.942 (0.887-1.001, p = 0.053) and **0.985 (0.954-1.016,p = 0.343) for predicting progression with AXL; 29.4% RCS vs 27.6% non-RCS progressed, p = 0.482
						HVF event analysis	≥3 progressing points in 3 consecutive visits from baseline	
						HVF trend analysis of VFI	Significant decrease in VFI vs time	
Park., *et al.* Medicine. 2016; 95(21):e3500	101 and 78 Eyes with and without myopia of 179 subjects	Treated POAG/ prospective observational study	MG: -3.82 ± 3.46, NMG: 0.19 ± 1.26	MG: 25.67 ± 1.22, NMG: 23.11 ± 0.52; NMG: < 24 and MG: ≥24	MG: 6.19 ± 1.11, NMG: 6.73 ± 0.86	HVF trend analysis of MD and PSD	Significant decrease in slope of the MD and PSD	MD change -0.41 vs -0.18db/year in non-myopia vs myopia (p = 0.336), PSD change 0.92 vs 0.71, p = 0.354. AXL regression coefficient β = 0.139, p = 0.082) for all, AXL≥24 (β = 0.129,p = 0.177) and < 24 (β = 0.902,p = 0.241) respectively
Sawada., *et al.* Plos One. 2017; 12(1):e0170733	144 Eyes/ 72 Subjects	Treated POAG/ Retrospective	-6.31 ± 1.88	26.04 ± 1.12	8.9 ± 4.4	HVF trend analysis of MD	Significant decrease in MD (< -1 and < -2 db/year) for inner andedhe points	*OR = 1.07 (p = 0.12) for AXL was not associated with faster VF progression
3. Myopia is a protective factor for Glaucoma progression								
Fan., *et al.* Plos One. 2013; 8;8(7):e69772	89 Eyes/ 89 Subjects	Treated PACG/ Retrospective	NA	Progressing 22.5 ± 0.6mm vs. Non-Progressing group 23.1 ± 0.9mm	5.3	HVF event analysis	CIGTS score ≥3 in 3 consecutive visits from baseline	HR = 0.23 (0.09-0.84), p = 0.023 per mm longer AXL
Qiu., *et al.* Plos One. 2015; 10(7):e0133189	270 Eyes/ 270 Subjects	Treated POAG/ Retrospective	-3.72 ± 2.98	25.08 ± 1.51	5.61 ± 2.72	HVF trend analysis of MD	Significant decrease in MD (> 0.22db/ year)	**OR = 0.796 (0.731-0.868), p = 0.008 for AXL per mm longer, **OR for AXL > 23 to ≤24 mm (0.334, p = 0.059), > 24 to ≤25 (0.309, p = 0.044), > 25 to ≤26 (0.266, p = 0.019, > 26 (0.260, p = 0.018)

Table 1: *Details of the study design, outcome and key findings of studies pertaining to Axial length, myopia and glaucoma progression.*

*POAG: Primary Open Angle Glaucoma; OHT: Ocular Hypertensive; RCT: Randomized Clinical Trial; NMG: Non Myopic Group; MMG: Mild to Moderate Myopic Group; HMG: High Myopic Group; HTG: High Tension Glaucoma; NTG: Normal Tension Glaucoma; OR: Odds Ratio; EMGT: Early Manifest Glaucoma Treatment; HVF: Humphrey Visual Field; MD: Mean Deviation; VFI: Visual Field Index; LV: Loss of Variance; TD: Total Deviation; CIGTS: Collaborative Initial Glaucoma Treatment Study; NRR: Neuroretinal rim; C/D: Cup to Disc ratio; D: Diopter; HR: Hazard Ratio; RR: Risk Ratio; AXL: Axial Length; NA: Not Available; β: Regression Coefficient; SE: Spherical Equivalent; EMG: Extreme Myopic Group. *Univariate logistic regression **Multivariate logistic regression # Change indicates the worsening of the visual field defect stage from normal to abnormal V-4e and I-4e isopters in 1 or more quadrants to loss in central fixation # # Change indicates, the disappearance of an existing or appearance of a new defect, as well as the change of 15° in length or 5° in the width or 5° in nasal step width or depth of scotoma by ≥ 2 steps.*

 # # # Change indicates progression of stages from normal to relative scotoma outside 20°; absolute scotoma outside 20°; relative/absolute scotoma within 20°–10°; relative/absolute scotoma within 10°–5°; relative/absolute scotoma within 5° in 1 - 3 quadrants, relative/absolute scotoma within 5° in all quadrants ‡ Interactive risk ratio = observed excess RR: multiple exposure/expected excess RR: additive model

Axial length as an indicator for glaucoma progression

In the literature, high myopia is described as myopia associated with degenerative changes in the structure and function of the eye [49]. Currently, there is no universally accepted definition of high myopia. The cut off values for high or pathological myopia described in previous studies varies from spherical equivalent (SE) of atleast -5D, -6D, -8D to -10D (refractive definition) and/or axial length of atleast 25mm, 25.5, 26.0, 26.5 to 27.0mm (biometric definition) [50-53]. The most practical definition of high myopia, i.e. eyes at greater risk for glaucomatous damage and progression can be based on the study by Oku et al reporting a higher incidence of OAG (odds of 2.29, p<0.001) in patients with axial lengths ≥25.0 mm. Else, we can classify eyes into different categories of axial length (≤23, >23 and ≤24, >24 and ≤25, >25 and ≤26 and >26mm and more) in 1 mm steps [48]. Jonas et al [54] correlated the progression of VF defects and the structural changes in the lamina cribrosa and concluded that the infero-temporal region of the lamina cribrosa with the least connective tissue and the largest pores [55] is most susceptible to damage. For eyes with high myopia/longer axial length, the progression pattern was more diffused and more temporally located. There is an agreement between the faster rate of RNFL progression in eyeballs with AL≥26.0 mm and larger angular width of RNFL defect in eyeballs ≥26.0 mm. Longer eyeballs have more antero-posterior stretching and thinning of the posterior pole along with the temporal convergence of the RNFL bundles . Owing to this, the defect might shift to the temporal quadrant [14]. Moreover, tilting of the optic disc in myopic glaucoma eyes causes more distortion of the inferotemporal pore of the lamina cribrosa, generating more tensile stretch on the temporal side of lamina cribrosa [56]. Thus, the axons passing through the inferotemporal pore, i.e. the RGC axons in the papillomacular bundle may be damaged easily. This concurs with the RNFL defect pattern observed in myopic glaucomatous eyes by Chihara et al [57] where eyes with longer axial lengths had diffused type papillomacular bundled defects. Similarly, a study by Kimura et al observed using red-free fundus photographs the presence of papillomacular bundle defects in highly myopic eyes (SE<-6 D) with early glaucoma (MD<-6 dB) [56]. The findings by Ohno-Matsui et al reporting 31.6% of acquired optic nerve pits located along the temporal edge of the lamina cribrosa in high myopia further indicated the susceptibility of this area to mechanical stress [58].

Axial length can be used to define high myopia, the measurement of which can easily be done by a non-invasive technique, thus enhancing its utility to be used as a screening tool for glaucoma progression, especially in eyes with poor visibility of the optic disc due to cataractous lens. Measurement of the axial length of glaucoma subjects prior to cataract surgery can be a useful opportunity to predict glaucoma progression. Hospital based studies have found an association between longer axial length with higher grade of nuclear cataract and lower mean age of patient during surgery [59,60]. Thus, measuring the axial length is not only an important approach in identifying patients with greater risk of glaucoma progression but also in detecting glaucoma progression at an early stage. .

Discussion

Diagnosis of glaucoma in population based studies is mostly done with the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) classification which depends on the cup-to-disc ratio (CDR) asymmetry and the presence of visual field abnormality [61]. Since the myopic optic disc assumes a tilted configuration with peripapillary atrophy, the visualization of the optic disc and the measurement of the CDR is highly challenging. Thus, is it recommended to include spectral-domain OCT analysis of the RNFL and neuroretinal rim to corroborate optic disc changes detected in optic disc stereophotographs . But owing to the temporal converge of the RNFL bundles, we not only need to study the RNFL abnormalities in the RNFL thickness deviation map of the OCT generated report, but also whether there is a corresponding loss of the supero-temporal and inferotemporal RNFL bundles in the RNFL thickness map of the report [62]. Thus, including both RNFL thinning and neuroretinal rim narrowing for glaucoma diagnosis will strengthen future studies to estimate the correct prevalence, incidence and progression of glaucoma among myopic eyes. This will increase the diagnostic specificity and decrease the false positive errors as we are currently experiencing in the available OCTs.

Most studies on glaucoma progression have used VF (mean deviation) as a biomarker for progression and thus missing out on the critical examination of assessing the relationship of myopia and axial length with glaucoma and its progression. Moreover, it has been

reported that visual field defects associated with myopic changes in the ONH may appear in myopic eyes which may or may not progress [34]. Adopting stringent criteria to define glaucomatous visual field is essential. Hence, eyes with RNFL and VF abnormalities, but without glaucomatous optic disc changes need not be considered as glaucoma [62]. The application of a myopic normative database is needed to improve the specificity, without compromising the sensitivity, for the detection of glaucomatous RNFL abnormalities in eyes with myopia [63].

Several studies reported the relation based on ONH/RNFL photographic assessment which is less sensitive to detect changes compared with measurement of optic disc/RNFL parameters using digital imaging technology; this might have influenced the outcomes of those studies. The studies conducted with axial length as a predictor also has certain limitations. Most studies were retrospective studies conducted several years ago and may lack data points or contain biased data, affected by convenience sampling of study period, and which has not been randomized based on a clear protocol along with multiple-examiner related variability. Others used only event analysis did not estimate the rate of progression (trend analysis) or used axial length as a continuous variable which is actually unrelated to be glaucoma progression as the relationship between the two may not be linear. Thus, there is a need to estimate glaucoma progression among myopes with axial length as a categorical variable and the removal of the confounding factors is warranted to assess the true relation between myopia and glaucoma progression. Finally, the studies which estimated glaucoma progression among different categories of axial length were also retrospective in nature with a short duration of follow up, which might have actually decreased the structure function relationship in glaucoma progression. These studies were further limited by the underlying assumption of trend analysis that the change in RNFL/VFI/MD are linearly proportional to the duration of follow-up, which might vary with the intensity of treatment and the disease progression. However, an average of several follow up visits for each patient over several years (~5 years) provides a reasonable approach of estimating the rate of change using the linear mixed model analysis.

The RNFL progression might be detected beyond the 1.73 mm radius circle which is used to estimate the average RNFL thickness in the Cirrus SDOCT [64]. The fixed diameter circle scan might miss a considerable proportion of progressing eyes. The reason may be unclear, but have been similarly observed by Leung., *et al.* [65] in glaucoma patients with lower levels of myopia (mean SE, -2.65D). It will be worth investigating, whether the 1.73 mm radius circle is useful in detecting progression especially in highly myopic eyes, especially with the temporal convergence of the RNFL [63] and which area of the RNFL progresses faster in such cases.

It is unclear whether the pathophysiology involved in the visual field progression of myopic glaucomatous eyes is the same or different from that of the non-myopic ones [45]. Better understanding of the underlying pathology is needed in developing better tests and algorithms to confirm the diagnosis and progression of glaucoma in myopic eyes.

In conclusion, current studies reporting the relationship between myopia and glaucoma progression are limited by several factors. Although myopia is related to higher risk of glaucoma, it is still unclear whether glaucomatous eyes with longer axial lengths associated with myopia have a faster or slower rate of progressive loss in the retinal nerve fiber layer and visual field. Longitudinal studies of considerable long duration on myopia based on axial length as categorical variable, with appropriate definition of myopia (axial and/or refractive), tilted disc/PPA and the removal of the confounding factors is warranted to assess the true relation between myopia and glaucoma progression. Furthermore, the quantification of structural glaucoma progression lies not only with RNFL, but also in ONH deformation [2]. With the advent of swept-source OCT and enhanced depth imaging technology, it is possible to visualize the deformation of the lamina cribrosa and associated structures in the ONH along with the commonly known morphological changes in glaucoma namely the neuroretinal rim narrowing or optic cup excavation. This temporal relationship of the ONH deformation in eyes with myopia and glaucoma and how it is different from non-myopes would elucidate the biological basis for the development and progression of glaucoma among myopes.

Acknowledgement

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