·Review·

High myopia as a risk factor in primary open angle glaucoma

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Abstract

• Glaucoma, one of the leading causes of irreversible blindness in the adult population worldwide, is a progressive optic neuropathy. Primary open angle glaucoma (POAG) is the most commonly reported type of glaucoma in population based prevalence studies worldwide. Elevated intraocular pressure is a well-known major risk factor for POAG. In addition, there is growing evidence that other risk factors like age, gender, race, refractive error, heredity and systemic factors may play a role in glaucoma pathogenesis. Many studies found that high myopia has been associated with POAG, however, direct and convincing evidences are still lacking. The aim of this review is to summarize the evidences implicating high myopia as a risk factor in the pathogenesis of POAG.

• KEYWORDS: high myopia primary open angle glaucoma; risk factor

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INTRODUCTION

Glaucoma is a group of diseases, and is one of the leading causes of irreversible blindness in the adult population worldwide [1]. Glaucoma is characterized by the loss of retinal nerve fiber tissues, recognized clinically as visual field defect and loss of the neuroretinal rim of the optic nerve head, termed glaucomatous optic neuropathy (GON) [2]. The global prevalence of glaucoma is estimated to be 80 million in 2020 [3]. Primary open angle glaucoma (POAG) is a chronic progressive optic neuropathy, direct and convincing evidences for primary mechanisms of glaucoma are still lacking and early detection or predicting progression of POAG remains difficult and challenging [4].

Many studies have investigated and reported risk factors associated with glaucoma [5]. Elevated intraocular pressure (IOP) is a well-known major risk factor for POAG [6]. Evidence shows that lowering IOP reduces the risk of development or slows the progression of glaucoma [5]. In addition, there is growing evidence that other risk factors like age, gender, race, refractive errors, heredity and systemic factors may play a role in glaucoma pathogenesis [7]. Many studies found that high myopia has been associated with POAG. It is possible that myopic individuals may be at increased risk for the development of glaucoma [8]. Epidemiologic evidence suggests that high myopia is a risk factor for the development and the progression of glaucomatous optic neuropathy [4].

The aim of this review is to summarize the evidence implicating high myopia as a risk factor in the pathogenesis of POAG.

PATHOGENESIS OF POAG

The pathogenesis of POAG is still poorly understood, an increase in ocular pressure can be caused by an increase in the secretion of aqueous humour or a reduction in its outflow [9]. There are two major theories have been proposed: 'the mechanical theory' and 'the vascular theory' for the initiating mechanisms of POAG [10].

The mechanical theory hypothesizes that an elevated IOP compresses the structure in and around the optic nerve head, disturbing the axoplasmic transport within the nerve fibers. This leads to the death of RGCs and their axons, resulting in thinning of the neuroretinal rim and excavation of optic nerve head [11]. Based on this theory, lowering IOP would be an efficient treatment to prevent further damage of optic nerve system [12,13]. Current available evidence has shown that pharmacologic and surgical interventions to lower IOP can slow the progression of visual field loss. In the vascular theory, glaucomatous optic neuropathy is considered to be a consequence of insufficient blood supply because of either increased IOP or other causes that reduce ocular blood flow,

such as elevated systemic blood pressure or vasospasm [14]. Thus, although elevated IOP is still considered as the major risk factor of glaucoma, there has been an increase in evidence supporting significant roles for vascular risk factors in the pathogenesis of glaucoma.

Although the mechanisms responsible for the link between glaucoma and myopia are poorly understood, it has been postulated that the optic nerve head in myopic eyes may be structurally more susceptible to glaucomatous damage because of the changes in connective tissue structure and arrangement [4]. The increased risk of development of glaucomatous change may be related to the already reduced retinal nerve fiber layer (RNFL) thickness in myopic eyes or the reduced RNFL thickness in myopia may itself represent a risk factor for development of glaucoma [15].

High Myopia Myopia is a complex trait including both genetic and environmental factors as well as gene-environment interactions [16,17]. High myopia is associated with an increased risk of pathological ocular complications and may lead to blinding disorders such as premature cataracts, glaucoma, retinal detachment, and macular degeneration [18]. Thus, high myopia is a major cause of legal blindness in many developed countries [19]. The prevalence of myopia varies across populations of different regions and ethnicities. In population-based studies on children, the prevalence of myopia has been reported to be higher in urban areas and Chinese ethnicity [20]. High myopia is especially common in Asia; the prevalence of myopia is significantly higher in Asian populations than in populations of European descent, especially in the younger generations in recent decades [21,22].

The Handan eye study showed the prevalence rate of myopia and high myopia (myopia in excess of 6 diopters [D]) in a rural Chinese adult population was 26.7% and 1.8% separately [23], and a study of the Singapore adult Chinese population showed the prevalence rate of myopia and high myopia was 38.7% and 9.1% separately [24]. However, effective treatment methodology and preventive strategies for high myopia have not yet been fully established.

High Myopia and POAG Population-based studies indicate that the risk of glaucoma increases with the increasing degree of myopia. Most studies have suggested that moderate to high myopia is associated with increased risk of POAG. The Blue Mountains Eye Study, one of the more frequently cited studies when discussing the association between myopia and glaucoma, after adjusting for age, sex, and other risk factors, found a strong relationship between POAG and myopia, with an odds ratio of 2.3 in eyes with low myopia (between -1.0 and -3.0D) and 3.3 in eyes with moderate-to-high myopia (>-3.0D) [25]. In the Barbados Eye Study, a myopic refraction was one of several risk factors for POAG in adult black people [26]. The Beaver Dam Eye Study showed that, after taking into account the effects of age, sex, and other risk factors, persons with myopia were 60% more likely to have glaucoma than those with emmetropia [27]. In Asian populations, the Singapore Malays Eye Study showed an association between moderate or high myopia (worse than -4D) and POAG. Persons with moderate or high myopia had an almost 3 times higher risk of POAG compared with those with emmetropia [28]. In Beijing Eye Study in China, a population study, marked to high myopia with a myopic refractive error exceeding -6D may be a risk factor associated with glaucomatous optic neuropathy [29]. One of the largest screening surveys of myopia and glaucoma was performed in preparation for the Early Manifest Glaucoma Trial, covering 32 918 individuals aged 57 to 79 years examined for glaucoma with refraction measured by auto refractors and glaucoma defined as reproducible perimetric disease in Sweden, and found that the prevalence of newly detected glaucoma increased with increasing myopia ($P<0.0001$) across all age groups [30].

However, not all studies have found significant relationships; for example, no association between myopia and POAG was found in the Ocular Hypertension Treatment Study [31]. Chao *et al* [32] studied twenty myopic patients of Chinese ancestry (Myopia >6.00 diopters was also found in 30 out of 40 eyes), and did not find axial length to be a risk factor for visual field loss ($P>0.99$, Freeman-Halton extension of the Fisher exact test) in this patient population. These findings suggest that factors other than progressive lengthening of the eye play an important role in the etiology of glaucomatous appearing optic nerve damage and visual field loss in this specific subset of patients [32]. Cross-sectional studies have their limitations. Ideally, longitudinal cohort data is best as the onset of glaucoma can be variable and delayed compared with the onset and stabilization of myopia [15].

Several theories have been put forward to explain a link between myopia and POAG. The association between myopia and POAG has been thought to be due to a variety of mechanisms, including increased susceptibility of the optic nerve head to damage by raised IOP and the increased effect of shearing forces in optic nerve head damage. One of the potentially blinding ocular diseases associated with

myopia is glaucoma, which is characterized by progressive degeneration of retinal ganglion cells. An important approach to detecting early structural change in glaucoma is based on assessment of the RNFL. Numerous studies have confirmed that RNFL measurement is sensitive for detection of glaucoma, and the extent of RNFL damage correlates with the severity of functional deficit in the visual field. Shoji *et al* [33] studied 93 glaucoma and 86 non-glaucoma patients with high myopia, the macular ganglion cell complex (GCC) and circumpapillary retinal nerve fiber layer (cpRNFL) measurements were compared, and found macular GCC parameters showed good ability to detect glaucoma, also all cpRNFL measurements were significantly related to both refractive errors and glaucoma, they believe that assessment of GCC parameters is a useful technique complementary to cpRNFL thickness assessment, for clinically evaluating patients with concomitant glaucoma and high myopia. This risk has been proven to be independent of other glaucoma risk factors and IOP. Myopic eyes have slightly although probably not clinically relevant, higher IOPs than emmetropic or hyperopic eyes [34]. Another cross-sectional analysis of 4 926 Beaver Dam Wisconsin white population aged 43 to 86 years demonstrated that a myopic refraction was correlated with increasing IOP at baseline (P<0.001) [27].

Studies showed that, for a given IOP in eyes with POAG, optic nerve damage appears to be more pronounced in highly myopic eyes with large optic discs than in non-highly myopic eyes [35]. This may suggest a higher susceptibility for glaucomatous optic nerve fiber loss in highly myopic eyes compared with non-highly myopic eyes.

CONCLUSION

Increasing evidence indicates that high myopia is important in the pathogenesis of glaucoma, especially for POAG, although increased IOP remains the major risk factor for this condition. Myopia as a risk factor for glaucoma is supported by population based surveys, but for the individual, the link between myopia and increased susceptibility to, or progression of glaucoma remains controversial [15]. Population-attributable risk estimates are best used to prioritize medical and public health interventions based on the magnitude of the potential effect of a risk factor on the disease outcome in the community [28]. It is important to investigate factors of refractive errors associated with glaucoma in longitudinal studies. Further prospective, clinical and epidemiological studies will improve our understanding of the pathogenesis of glaucoma. High myopic subjects should be screened for glaucoma at closer intervals.

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