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The Correlation between Myopia and Pathological Progression in Glaucoma

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Abstract

In recent years, myopia and glaucoma have become two major threats to eye health and are also hot topics in ophthalmic disease research. Among the various areas of investigation, exploring the correlation between myopia and glaucoma lesions has become a core and high-priority research direction, given the growing clinical observation of their comorbidity. This paper systematically classifies and analyzes a large body of relevant studies published in recent years, aiming to synthesize the latest research progress. The analysis reveals that current research on the myopia-glaucoma correlation spans multiple dimensions, including epidemiological risk quantification, ocular structural changes, intraocular pressure regulation, genetic associations, and even racial differences. Relatively mature and consistent results have been obtained in key areas: for instance, how different degrees of myopia (especially high myopia) increase glaucoma risk, and what specific alterations myopia induces in ocular structures to promote glaucomatous damage. However, significant gaps persist in understanding genetic-level influences-only a handful of genes (e.g., SOX21, GSAP) have been preliminarily linked to both diseases, and the shared genetic pathways and regulatory mechanisms remain largely unelucidated. These findings not only help clarify the current state of research in this field but also provide clear guidance for future studies on the myopia-glaucoma correlation. Additionally, they offer valuable clinical clues for optimizing the early screening, diagnosis, and comprehensive management of patients with myopia-glaucoma comorbidity, ultimately contributing to better preservation of patients' visual function.

Keywords

Myopia; Glaucoma; Correlation.

1. Introduction

Myopia is the most widespread, common and extensively studied eye health issue globally. The current global prevalence of myopia is approximately 28.3%. Over the past decade, the prevalence of myopia has continued to rise, especially in East Asia, where the rate of increase is difficult to predict. If no effective intervention is taken, it is estimated that nearly half of the global population will suffer from myopia to varying degrees by 2050. About 10% of the others will develop high myopia[1]. The problems caused by myopia are not only the decline in visual acuity, but also a series of ocular complications and more serious eye diseases brought about by the elongation of the eye axis and damage to the ocular structure. As the degree of myopia deepens, common complications such as retinal defects and myopic macular degeneration occur. These diseases can severely damage the patient's vision and even lead to serious consequences such as blindness[2]. Glaucoma is a general

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term for blinding ophthalmic diseases caused by optic nerve damage due to elevated intraocular pressure. There are two forms of glaucoma: primary open-angle glaucoma (POAG), in which the drainage channel is anatomically open; and angle-closure glaucoma (ACG), in which the aqueous humor outflow in the eye is blocked. This article focuses on adult primary open-angle glaucoma, as it is the most prevalent and common type among all types of glaucoma[3]. Glaucoma is generally more harmful than myopia. However, in clinical practice, it is often seen that myopia patients develop glaucoma and that glaucoma is combined with high myopia. Therefore, it is particularly important to explore the relationship between the two and the mechanism causing such situations. At present, many studies have clearly confirmed that myopia has an impact on the occurrence of glaucoma. In-depth research has been conducted on various aspects such as the degree of influence of different degrees of myopia on the occurrence of glaucoma, the structural correlation between the two, and the genetic correlation. In a analysis, the probability of myopic patients developing glaucoma is approximately twice that of the general population, which similar association patterns have also been discovered in studies conducted in countries such as the Netherlands and Italy[4]. Therefore, this article is based on relevant research in the past five years, summarizes and organizes research from different perspectives, starting from the degree of influence, different directions of correlation and the complexity brought by correlation, in order to provide certain clues and assistance for the prevention and treatment of glaucoma caused by myopia in the future.

2. Correlation between Myopia and Glaucoma

2.1 Influence of Myopia Degree on Glaucoma Incidence

The degree of myopia is mainly measured by two clinical standards: the length of the eye axis and the refractive power. Clinically, it is generally believed that an axial length of the eye greater than 24 mm indicates myopia, while a refractive power greater than -0.50D is also defined as myopia. The conversion standard between the two is approximately 300 degrees of myopia for every 1mm increase in axial length. Clinically, myopia of 600 degrees or more is generally classified as high myopia.

Studies have shown that all degrees of myopia can increase glaucoma incidence, with a more pronounced effect in high myopia-a clinical phenomenon supported by frequent observations of glaucoma coexisting with high myopia. For instance, a meta-analysis by Ahnul HA et al. on myopia and glaucoma risk found that for every 1-diopter (1-D) increase in myopia degree, the risk of glaucoma lesions rises by approximately 20%. Notably, this risk shows a non-linear, sharp increase in high myopia patients, presenting an additional independent correlation[5]. Another meta-analysis involving 24 countries reported a pooled odds ratio (OR) of 1.77 for glaucoma in patients with low-to-moderate myopia (after excluding confounding factors), while the OR reached 2.46 in high myopia patients[6]. Additionally, from the perspective of axial length, each 1mm increase in axial length raises the risk of glaucoma in myopia patients by approximately 26%[2]. These findings collectively confirm that myopia progression significantly elevates glaucoma risk, with a non-linear rapid increase observed in high myopia (defined as ≥600 degrees or axial length ≥25-26mm), substantially increasing the likelihood of glaucoma comorbidity.

2.2 Multi-dimensional Correlation Mechanisms

In recent years, numerous studies have explored the correlation between myopia and glaucoma lesions, covering multiple directions that can be roughly categorized into four aspects: intraocular pressure, ocular structure, genetics and other factors.

2.2.1 Intraocular Pressure(IOP)

Elevated IOP is the most common and direct cause of glaucoma, leading to irreversible optic nerve damage. Myopia can impair the function of the trabecular meshwork (a key structure in aqueous humor circulation), increasing aqueous humor outflow resistance and thereby raising IOP[7]. Generally, IOP shows a positive correlation with myopia degree; however, IOP elevation in glaucoma is not primarily caused by myopia. Thus, IOP is not the main pathway through which myopia

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increases glaucoma risk. Studies have further found that the association between myopia and glaucoma is more pronounced in glaucoma cases with lower IOP, which also confirms that IOP is not the most critical factor driving the myopia-glaucoma correlation[8].

2.2.2 Ocular Structure

The most significant change in the eye structure due to myopia is the elongation of the eye axis. However, the elongation of the eye axis can cause many changes in the eye's structure, thereby increasing the incidence of glaucoma.

First, from the perspective of the outermost layer of the eyeball, the sclera, the thickness of the eyeball wall directly affects the degree of retinal microcirculation. Relevant studies have found that the length of the eye axis has a significant impact on the thickness of the eyeball wall. When patients experience elongation of the eye axis due to myopia, the thickness of the eyeball wall decreases, leading to a reduction in retinal microcirculation[9]. Eventually, this results in ischemic damage to the retina and an increased risk of glaucoma.

Secondly, there are changes in the sclera. A series of clinical studies have already demonstrated that in the ocular structure of myopic patients, due to the elongation of the eye axis, the posterior part of the anterior segment of the sclera undergoes remodeling, becoming more brittle and thinner. Collagen and proteoglycans in the sclera are lost to varying degrees. The consequence of this loss of scleral material is that the optic nerve head (ONH) becomes more vulnerable to intraocular pressure, leading to damage of the optic nerve axons at the location of lamina cribrosa ((LC), and ultimately resulting in glaucomatous lesions[10].

Then there are the most directly related structural changes to glaucoma - the retina and optic nerve. In the comparison between patients with myopia combined with glaucoma and those with simple glaucoma, it was found that the reduction rate of the peripapillary retinal nerve fiber layer (pRNFL) in patients with myopia combined with glaucoma was faster. Through analysis, it was concluded that the increase in axial length would accelerate the thinning rate of the retinal nerve fiber layer, increase the susceptibility to optic nerve damage, and raise the risk of glaucoma[11]. At the same time, the research also found that the deformation of the central layer of the retina (LC) and the enlargement of the opening of the neural tube caused by myopia play a certain role in low intraocular pressure glaucoma[12]. On the other hand, some research shows that the morphology of the optic disc is closely related to the pathogenesis of glaucoma. During the process of axial elongation of the eye, the shape of the sclera will be distorted, and the shape of the optic disc will also change accordingly, such as presenting an elliptical form. This process is called optic disc tilting. During the process of optic disc tilting, the axons of the optic nerve in patients are more prone to damage. At the same time, glaucoma patients with optic disc tilting are more likely to suffer from central visual field loss due to retinal defects, resulting in serious consequences[13]. Beyond these changes, myopia may also cause glaucoma through optic disc atrophy, retinal atrophy and subretinal atrophy brought about by axial elongation. However, these changes may also occur simultaneously in patients with high myopia or glaucoma, making it difficult to distinguish. This also leads to certain challenges in diagnosing glaucoma in patients with high myopia[1].

2.2.3 Gene Factors

Genetic alterations have become a focal direction in exploring disease correlations, as identifying shared genetic changes between two diseases can deepen understanding of the mechanisms driving their mutual influence. While research on the genetic links between myopia and glaucoma has made some progress, it remains less extensive compared to studies on intraocular pressure or ocular structure.

The SOX21 gene, a member of the SOX gene family, primarily regulates the differentiation of the nervous system and epidermal tissues by controlling downstream gene expression. Located on chromosome 13q14, it was first associated with congenital microcornea. Patients with this condition often show recombination in the 13q region, leading to ectopic SOX21 expression, and they have a high likelihood of developing both myopia and glaucoma simultaneously. Post-mortem examinations

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of these patients revealed that ectopic SOX21 expression can cause potential ocular muscle dysplasia, including iris thinning, stromal atrophy, and absence of anterior iris epithelium processes. Further analysis of gene pathways identified TGFB2 as a target gene of SOX21, and ectopic SOX21-mediated TGFB2 secretion was found to play a key role in disease development. TGFB2, mainly secreted by periocular mesenchyme, is critical for the mid-stage development of various ocular structures. On one hand, TGFB2 accumulation in aqueous humor (driven by SOX21) promotes the expression of active TGF receptor complexes in iris and corneal cells; these receptors respond to exogenous TGFB2, increasing the synthesis of extracellular matrix proteins, which in turn raises aqueous humor outflow resistance, elevates intraocular pressure, and boosts glaucoma risk. On the other hand, abnormal SOX21 expression can also cause abnormal eye axis elongation, accelerating myopia progression and significantly increasing the risk of high axial myopia[14].

The GSAP gene has been closely linked to pigmentary glaucoma, a special type of glaucoma. In this condition, abnormal pigment granules shed from the iris pigment epithelium deposit on the trabecular meshwork, blocking aqueous humor drainage and increasing intraocular pressure. Studies have shown that GSAP overexpression impairs amylin function, leading to abnormal deposition of eye pigments and incorrect expression of the tyr gene, which ultimately induces pigmentary glaucoma. Experiments also confirmed that GSAP overexpression may cause abnormal amyloid-β expression, and the neurotoxicity of amyloid-β can promote optic nerve damage and glaucoma occurrence. Additionally, research found that the baseline expression level of GSAP in myopic patients is significantly higher than in non-myopic patients, indicating that GSAP overexpression contributes to some cases of myopia-induced glaucoma, particularly pigmentary glaucoma[15].

Other genes related to both diseases include ZNF644 and MYOC. The ZNF644 gene, located on chromosome 19p13.3, is associated with the progression of axial myopia. Recent studies discovered that its rs13382811 polymorphism increases glaucoma risk by regulating scleral collagen synthesis. The MYOC gene, located on chromosome 1q24.3-q25.3, is a well-known glaucoma-causing gene. Its p.Gln368Stop mutation not only leads to primary open-angle glaucoma but also correlates with accelerated eye axis elongation in myopic patients, though the specific mechanism behind this association still requires further verification.

2.2.4 Other Perspectives

Beyond intraocular pressure, ocular structure and genetics-three commonly studied aspects in ophthalmic research-scholars have also explored the correlation between myopia and glaucoma from additional angles, uncovering unique influencing factors.

Racial and ethnic differences have been found to affect the correlation between myopia and glaucoma. A study focusing on primary open-angle glaucoma compared two populations: Latinos and Chinese Americans. Researchers observed that myopia increases the risk of primary open-angle glaucoma through different pathways in these two groups. With the same degree of myopia, Latinos have a risk of developing primary open-angle glaucoma nearly 1.6 times higher than Chinese Americans. However, in terms of refractive myopia and axial myopia, Chinese Americans face a higher risk of developing moderate to high myopia compared to Latinos. After calculating the combined incidence of glaucoma among myopic patients and the overall incidence of myopia, the results showed that the prevalence of primary open-angle glaucoma is very close between Latinos and Chinese Americans[16]. These findings confirm that racial differences do impact the correlation between myopia and glaucoma, but the specific mechanisms underlying these differences remain unclear and require further investigation.

Biomechanical susceptibility is another important perspective. It refers to the changes that occur in biological tissues when exposed to pressure; higher biomechanical susceptibility means the tissue is more prone to damage. In the context of eye health, this mainly refers to damage caused by intraocular pressure. Researchers compared the tensile resistance of the optic nerve between patients with high myopia and those with non-high myopia. They found that the optic nerve of patients with high myopia is more likely to undergo distortion and damage when subjected to pulling forces. This increased

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biomechanical susceptibility is widespread in patients with high myopia, and researchers speculate it may be related to the changes in the sclera and retina caused by excessive eye axis elongation[10]. These research results provide a valuable direction for understanding why high myopia increases the incidence of glaucoma to a greater extent than mild or moderate myopia.3. Clinical Complexity of Myopia-Glaucoma Association

3. The Complexity between Myopia and Glaucoma

3.1 Diagnostic Complexity

The strong correlation between myopia and glaucoma introduces complexity into the clinical diagnosis and treatment of both diseases. This complexity is a major challenge in managing myopia-glaucoma comorbidity. Clinically, glaucoma patients-especially those with POAG-exhibit high individual variability in symptoms, with approximately 50% of patients remaining unaware of their glaucoma until experiencing significant visual loss[3]. Myopia-induced visual quality deterioration further masks the mild visual function decline caused by early glaucoma. For example, a survey of patients undergoing myopia refractive surgery found that the proportion of glaucoma patients among them was much higher than in the general population; 5.1% of patients seeking refractive surgery were unaware of existing glaucoma lesions, and an even higher proportion had already experienced significant pRNFL thinning and optic nerve head narrowing[11]. The overlapping symptoms of myopia and glaucoma complicate disease diagnosis, requiring more precise clinical methods to identify comorbid patients.

3.2 Ocular Structural Complexity

The correlation between myopia and glaucoma also manifests in overlapping ocular structural changes. Studies have found that peripapillary and optic nerve lesions caused by excessive axial elongation in high myopia are highly similar to glaucoma lesions, and the resulting visual field defects closely resemble glaucoma symptoms[6]. This overlap in structure and function increases the complexity of the myopia-glaucoma relationship, highlighting the importance of clarifying their specific correlation.

4. Conclusion

This paper systematically classifies and analyzes recent studies on the myopia-glaucoma correlation to summarize current research progress and identify future directions. The analysis reveals that research on the myopia-glaucoma correlation covers multiple perspectives, with relatively comprehensive conclusions reached in areas such as the impact of myopia on glaucoma incidence and ocular structural changes. However, genetic research remains scarce: only the functions of certain characteristic genes in specific cases have been thoroughly studied and interpreted, and further research is needed to explore associations between core myopia-related genes and glaucoma-causing genes. Additionally, many mechanisms through which myopia induces glaucoma (from different perspectives) remain unclear-these gaps represent key directions for future research in this field. Current studies confirm a strong correlation between myopia and glaucoma across dimensions including IOP, ocular structure, genetics, racial differences and biomechanical susceptibility, clarifying their close connection. Future research should further explore the mechanisms underlying this correlation along existing directions. The value of this paper lies in helping researchers understand current progress, identify future directions through multi-dimensional classification and organization, promote research on the myopia-glaucoma correlation, and provide clues for the clinical management of both diseases. The main limitation of this review is that, as a summary of existing research, it only compiles relevant findings from recent years without conducting original experimental research. Additionally, due to time and resource constraints, this review only classifies and analyzes literature from PubMed published in the past five years, limiting the scope of coverage. In the future, it is hoped that original experimental research can be conducted on the myopia-

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glaucoma correlation, or that a more detailed analysis of literature over a longer time frame can be performed to further enrich understanding of this topic.

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