Collagen: A potential factor involved in the pathogenesis of glaucoma

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Source of support: This article was supported by the grants from the National Natural Science Foundation of China (81170849), Guangdong Provincial Natural Science Foundation (S2011020002401), and the Fundamental Research Funds of State Key Laboratory of Ophthalmology (2011C02)

Numerous studies have been completed on glaucoma pathogenesis. However, the potential and controversial interaction between ocular biomechanical properties and the glaucomatous diseases process has received much more attention recently. Previous studies have found that collagen tissues gain mutation change in glaucoma patients. This study was conducted to determine the role of collagen in the biomechanics of glaucoma in humans. Its changes may be the result of mechanical modifications brought on by intraocular pressure (IOP) fluctuations. More importantly, biomechanics and genetic evidence indicate that the mutation of collagen may play a role in the process of glaucoma. Alteration of collagen in the outflow pathway may alter mechanical tissue characteristics and a concomitant increase of aqueous humor outflow resistance and elevation of IOP. The variations of collagen, leading to inter-individual differences in scleral and lamina cribrosa properties, result in different susceptibility of individuals to elevated IOP. Therefore, this study hypothesized that collagen mutations may be an original cause of glaucoma.

Key words: collagen • glaucoma • pathogenesis

Full-text PDF: http://www.basic.medscimonit.com/download/index/idArt/889061

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Background

Glaucoma, an optic neuropathy affecting over 60 million people, is the second cause of global blindness and draws intensive attention because of the irreversibility of glaucomatous optic nerve damage [1]. However, its underlying mechanism still remains unclear. Previous studies have found that collagen tissues create changes in glaucoma patients, such as biomechanics changes of trabecular meshwork (TM) [2], thinner sclera, and laminar cribrosa [3–5]. However, are these changes the result of elevated intraocular pressure (IOP) or are they the primary original factors causing glaucoma?

Elevated IOP is generally considered as the main risk factor in glaucomatous pathogenesis, which is primarily caused by increased aqueous humor outflow resistance. The TM constitutes the major regulated ocular outflow pathway in adult human eyes [6]. Its changes may participate in the development of increased outflow resistance. Previous studies hypothesized that one of the main causes of this is biomechanical and molecular changes of the extracellular matrix (ECM) in the TM [7,8]. This study assumes that changes in collagen, as the main component of ECM in the TM, may be involved in increased aqueous humor outflow resistance and elevation of IOP.

The ocular response to elevated IOP varies depending on the individual. In clinical data we can find that patients have variable susceptibility to glaucomatous optic neuropathy, which presents with high-tension glaucoma, normal-tension glaucoma (NTG), or ocular hypertension. Sclera and lamina cribrosa, known as the load-bearing tissues, may be responsible for that. Collagen plays structural roles and contributes to mechanical properties, organization, and shape of tissues [9]. Collagen changes can result in a weaker structure, including changes in elasticity and compliance of collagen tissues, and decreased density and thickness of these tissues, which may be more sensitive to elevated IOP.

Based on the above, this study hypothesized that primary change of collagen is an original factor in the pathogenesis of glaucoma.

Change of TM Collagen Leads to Elevated IOP

ECM in TM is believed to be essential for maintenance of the normal outflow system [10]. Changes in biomechanics of ECM, caused by dysfunction and structural alteration of collagen, affect the TM function and the aqueous humor outflow. Comparing the stiffness of TM in normal tissue and glaucomatous tissue, Last et al. found that the stiffness of glaucomatous TM significantly increased, which resulted from dysregulation of ECM [2]. Increased stiffness of the tissue, in turn, decreases outflow from the eye. Studies also found that glaucomatous eyes have different forms of ECM deposited within the cribiform layer to increase the outflow resistance [11,12]. Hence, changes in TM elasticity and mechanical load may have a significant role in glaucoma.

Several alterations in collagen expression and transcription have been characterized in the TM of primary open-angle glaucoma (POAG). Type I collagen is the major component of structures within the TM collagen beams and uveoscleral aqueous humor outflow pathways. Aihara et al. targeted type I collagen mutation and induced an elevation of IOP in mice, and their results suggested an association between IOP regulation and collagen turnover [13]. The turnover of collagen causes difficulty in hydrolyzation by matrix metalloproteinases (MMPs), leading to accumulation of type I collagen. Excess synthesis of type IV collagen has also been found in glaucomatous TM [2]. Another collagen, type VI, also increases, which is associated with sheath-derived plaques in the cribiform meshwork [14]. Thus, collagen abnormality in the outflow pathway appears to play an important role in the elevation of IOP and may be one of the significant original factors of glaucoma.

Inter-Individual Differences of Sclera and Lamina Cribrosa

A variety of cellular and molecular changes can occur that modify the connective tissues of the optic nerve and surrounding sclera in aging, ocular development, and glaucomatous disease. These changes remodel the microenvironment of the optic nerve, and presumably change the susceptibility to axonal injury in this region.

Sclera

Many experimental and clinical studies have found that the biomechanical properties of sclera shift to being less elastic and stiffer in glaucoma [15–17]. Some scientists indicate that these changes may be related to the development of glaucoma.

Sclera has a collagen-rich ECM, and collagen constitutes 90% of scleral dry weight [18]. Its material properties strongly depend on the distribution and composition of collagen. Collagen fibers in sclera are organized into irregularly arranged and somewhat interwoven lamellae; the lamellae varying in thickness [19]. The variations of collagen may lead to inter-individual differences in scleral material properties. Previous detailed modeling studies found that scleral material properties were varied over physiologic ranges [20], suggesting that there could be significant inter-individual differences. Inter-individual variations in sclera, particularly peripapillary scleral thickness, can result in vastly different biomechanical responses to IOP [16]. Thinner sclera
is more sensitive to developing glaucoma. For example, decreased density of collagen in the peripapillary sclera was found in glaucoma [3]; and in high myopia eyes, sclera is elongated and thinned, which increases risk of developing POAG [21].

**Lamina cribrosa**

The region of laminar cribrosa in the optic nerve head (ONH) is the principal site of retinal ganglion cells (RGCs) axonal insult in glaucoma [22,23]. The lamina cribrosa provides structural and functional support to the RGCs axons while passing from the relatively high-pressure environment in the eye to a low-pressure region in the retro bulbar cerebrospinal space. However, because of discontinuity in the corneal-scleral shell, lamina cribrosa is often considered a weak spot in mechanically loaded systems, and is the site of substantial stress concentration. The characteristics of the lamina cribrosa render it biomechanically sensitive to IOP elevation.

Collagen types I, III, IV, V, and VI constitute the main composition in the lamina cribrosa, and these macromolecules change with age. As this tissue ages, individual differences, leading to more or less of a particular macromolecule of the extracellular matrix, may alter the support function of the lamina cribrosa and influence the degeneration of the optic nerve associated with glaucoma [24]. The inter-individual variations in lamina cribrosa thickness are responsible for ability to resist damage. Recently, using spectral domain optical coherence tomography (SD-OCT), Park et al. found that lamina cribrosa thickness was significantly thinner in NTG than in POAG [25]. Thin lamina cribrosa provide less biomechanical support for the optic nerve. On the other hand, thin lamina cribrosa leads to a decreased distance between the intraocular space and the space of the retrobulbar cerebrospinal fluid compartment – at a given trans-lamina cribrosa pressure difference between both compartments, the pressure gradient gets steeper due to the reduced distance between both compartments [26]. Hence, one may assume that even at the same IOP level, individuals with thinner lamina cribrosa will have increased susceptibility to glaucomatous optic neuropathy. The density of the lamina cribrosa also plays a role in glaucoma susceptibility. A recent study strongly claimed that the lower and upper quadrants of ONH are indeed lower density [22], and that if exposed in increased IOP, this region is an area of vulnerability and may be the first site to become damaged. This may help understand the selective visual field loss observed in the initial stages of glaucoma. Besides thickness and density, ocular developmental differences and mechanical properties changes with aging form the inter-individual variations of susceptibility to developing glaucoma [27].

Laboratory evidence has also demonstrated the potential role for collagens in glaucomatous optic neuropathy. In glaucomatous monkey eyes, alterations in the three-dimensional organization of collagen fibrils were observed in the optic nerve head, suggesting that these architectural changes may affect the flexibility and resilience required of the lamina cribrosa in supporting optic nerve fibers [28]. In glaucoma and suspected glaucoma, the content and/or the composition of the collagen molecules in the lamina cribrosa is significantly changed, and differs from that of normal eyes [29]. One can therefore speculate that a primary collagen disturbance might be involved in the pathogenesis of glaucoma.

Evidence, as mentioned above, indicates that the inter-individual differences of sclera and lamina cribrosa will affect susceptibility to glaucoma. This may explain the individual variation to elevated IOP seen clinically. During rises in IOP, if these tissues are strong enough to resist elevated IOP and to prevent the optic nerve from being damaged, ocular hypertension occurs. In contrast, if these tissues are weak, normal-tension glaucoma is presented. Based on this evidence, this study hypothesizes primary changes in collagen molecules results in a weaker structure, which increases susceptibility to glaucoma.

**High myopia and glaucoma**

Evidence from a meta-analysis strongly indicates that individuals with myopia have an increased risk of developing POAG [21]. People with moderate and especially high myopia have a two-fold to three-fold increased risk of glaucoma compared with that of non-myopic subjects, and this risk is independent of other glaucoma risk factors and IOP [30]. Myopia is a complex pathology of ocular structure with elongated axial length. Increasing axial length results in many structural changes such as thinner sclera and lamina cribrosa and weakness of the fibroglial matrix of the nerve fibers at the optic disc. The explanation is thought to be that variation of collagen structure and amounts leads to weakness of these tissues, which could contribute to the high susceptibility of the optic disc to IOP fluctuations and to the increasing risk of glaucomatous neuropathy.

Collagen undergoes significant changes during the development of myopia [18]. In regard to the development of myopia, previous studies found a significant loss of scleral tissue weight and subsequent scleral thinning associated with a narrowing and disconnection of collagen fiber bundles and a reduction in the number of bundles [31]. Reduction of collagen amounts in sclera is a result of both decreased collagen synthesis and increased collagen degradation [32]. Thinning of existing collagen fiber bundles is also found in myopic eyes. These ultrastructural variations suggest a derangement of the organization and growth of the collagen fibers, which result in the thinning of sclera. Moreover, the thinning of the peripapillary sclera is an additional biomechanical factor that increases tension in the lamina cribrosa beams, leading to increased glaucoma susceptibility [26].
Conclusions

Until now, the mechanism of the development of POAG has remained unclear. In addition, recent theories about glaucoma-tous optic neuropathy cannot effectively explain the different susceptibility of individuals to elevated IOP. This article hypotheses that glaucoma is a disorder disease with a series of characteristic pathological alterations of collagen in its content, distribution, ultrastructure, and metabolism. Abnormality of collagen in the outflow pathway tissues results in elevation of IOP. Inter-individual differences in scleral and lamina cribrosa caused by variations of collagen contribute to interindividual variation in susceptibility to elevated IOP. Collagen, as an original cause of glaucoma, plays an important role in glaucoma pathogenesis. Some changes in eye collagen may occur before the development of glaucoma or glaucomatous optic neuropathy.

Conflict of interest

The authors declare no conflict of interest with respect to this research.

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