ORIGINAL ARTICLE

Altered corneal biomechanics and autoregulation dysfunction: possible contributing factors for the development of primary open angle glaucoma in patients with elevated intraocular pressure

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Abstract

It is beyond dispute that elevated intraocular pressure (IOP) is a major risk factor for the development of primary open angle glaucoma (POAG). Nonetheless, only a minority of patients with elevated IOP generate the disease. This leads to the notion that POAG is a progressive optic neuropathy caused by added factors that may work in concert with elevated IOP. Corneal viscoelastic resistance and vascular autoregulation have been associated to the effects of elevated IOP. This article discusses investigational facts suggesting that altered corneal viscoelastic/elastic properties and vascular dysregulation may contribute to the development of POAG in patients with elevated IOP.

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KEYWORDS
Primary open angle glaucoma; Ocular hypertension; Corneal biomechanical properties; Autoregulation dysfunction; Optic nerve head; Ocular blood flow

PALABRAS CLAVE
Glaucoma primario de ángulo abierto; Hipertensión ocular; Propiedades biomecánicas de la córnea; Disfunción de la autorregulación;

Alteración de la biomecánica corneal y disfunción de la autorregulación: factores que posiblemente contribuyen al desarrollo de glaucoma primario de ángulo abierto en pacientes con presión intraocular elevada

Resumen

Es indiscutible que la presión intraocular (PIO) elevada es un factor de riesgo importante para el desarrollo de glaucoma primario de ángulo abierto (GPAA). Sin embargo, la enfermedad aparece solamente en una minoría de pacientes con PIO elevada, de lo que se deduce que el GPAA es una neuropatía óptica progresiva causada por factores añadidos que posiblemente actúan junto con la PIO elevada. La resistencia viscoelástica de la córnea y la autorregulación vascular se han associa-
Introduction

Glaucoma is a leading cause of preventable blindness in the world. The complete understanding of the pathogenesis of the disease is still very much in debate. Nonetheless, as studies have evolved, elevated intraocular pressure (IOP) has been looked at differently in regards to its contribution to the development of primary open-angle glaucoma (POAG). It is now considered by some researchers as a significant risk factor that may be influenced by viscoelastic and elastic properties of the cornea. Furthermore, corneal viscoelastic resistance and vascular autoregulation have been associated to the effects of elevated IOP. Others with a different perspective suggest that the effect of elevated IOP on the optic nerve head may be at the expense of autoregulatory mechanisms in the oculo-vascular system. Conceivably, the possible association of these two factors to elevated IOP may help clarify the reason(s) for clinical differences between patients with POAG and patients with ocular hypertension (OHT).

Ocular rigidity has been characterized in part by viscoelastic and elastic properties of the cornea. Measurement of these properties is obtained with the ocular response analyzer (ORA). This instrument is a sophisticated non-contact pneumo-tonometer (Reichert Ophthalmic Instruments, Buffalo NY, USA) that records two applanation pressure measurements from the air pulse delivered to the cornea. One at the applanation point as the cornea is moved inward and another at the applanation point as it moves outward to its original contour. The difference between these two measurements is termed corneal hysteresis (CH) (Figure 1). CH defines the viscoelastic behavior of the cornea in response to air applanation force. This viscoelastic response reflects the capacity of the cornea to dissipate air pulse energy delivered by the pneumo-tonometer, and appears to be a dynamic resistance element to the outward force exerted by IOP. CH also provides the basis for another ORA parameter called corneal resistance factor (CRF). CRF is a measurement that may better reflect the elastic properties of the cornea. Corneal elasticity relates to the resistance encountered by the air pulse of the pneumo-tonometer while deforming the corneal surface and seems to be a marker that relates more specifically to the overall ocular structural resistance.

Autoregulation is a process in which normal blood flow is maintained in response to changes in perfusion pressure. At the eye, perfusion pressure (PP) may be generally expressed as the difference between the blood pressure (BP) and the IOP. So, in essence any significant elevation in IOP will reduce perfusion pressure to the eye. This effect in turn may result in a reduction in blood flow to the optic nerve head (ONH). Nonetheless, only about 20 percent of patients that have persistent elevated IOP develop glaucomatous ONH damage. An apparent reason for this is that autoregulation impedes the process. As it occurs in other organs of the human body, ocular autoregulation maintains normal blood flow to the eye in response to changes in perfusion pressure by altering mechanical or chemical physiologic processes that influence the tone of blood vessel walls; thereby modifying vascular resistance. As the equation below shows, blood flow (BF) equals PP (PP, Pa — Pv), over vascular resistance (R).

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BF = \frac{Pa - Pv}{R}
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Figure 2  Schematic representation of the contribution of autoregulation dysfunction to glaucomatous damage in association to elevated IOP.

IOP: intraocular pressure; PP: perfusion pressure; OBF: ocular blood flow; ONH: optic nerve head; RGC: retinal ganglion cell.

Discussion

Corneal biomechanics

Statistical analysis exposing the relationship between CH and central corneal thickness (CCT), and CRF and CCT in OHT and POAG eyes revealed to be proportional. In other words, the higher the CCT, the higher the CH and CRF. Although the analysis proved to be statistically significant, the correlation coefficient was not very strong. This may imply that CH and CRF are related to CCT but are different corneal biomechanical values to assess ocular rigidity. Besides this relationship showing a positive effect, data also demonstrates that CH and CRF values tend to be greater in OHT patients. Shah et al. demonstrated that in a group of 216 eyes with POAG and 199 with OHT, the latter group had statistically significant higher CH and CRF values. Sullivan-Mee et al. also revealed in their study that OHT subjects had higher mean CH and CFR values than the POAG group.

In addition, a relationship of CH and CRF with the development and progression of glaucoma is seen. Luce and Taylor state that the Ocular Hypertension Treatment Study (OHTS), and other studies on the subject, point out the significance of CCT in diagnosing and managing the progression of glaucoma. Data of these studies rightfully imply that low CCT may be a risk factor for the development and the progression of glaucoma. Likewise, studies assessing CH and CRF values obtained with the ORA insinuate this type of relationship. Anand et al. found in their study that asymmetric POAG was associated with asymmetry in ORA measurements. Hence, lower CH values were linked to more advanced forms of POAG and had a positive correlation with advanced visual field loss. Moreover, Luce and Taylor found that compared to normal patients POAG patients had lower than average CH and CRF values. However, it is worth noting that in this study POAG eyes showed a negative correlation between CH and CRF values related to sustained elevated IOP. The eyes with severely elevated pressures had much lower than average CH values and higher CRF values. Alternatively, this may imply that a sustained elevated IOP in POAG results in a decreased dynamic resistance and stiffer elastic behavior of the cornea. Understandably, increased corneal stiffness can be expected at significantly elevated IOP since the cornea forms part of the overall structural rigidity of the eye. Utilizing Friedenwald equation for ocular rigidity in their study, Hommer et al. found that the corneal stiffness was significantly higher in POAG patients than in normal patients. It should be noted, however, that the structural rigidity of the eye cannot be attributed to corneal properties alone. Biomechanical properties of the sclera, choroid, Bruch’s membrane, and retina also play an imperative role in the overall rigidity of the eye.

Autoregulation

Albeit the precise mechanism is not fully understood, it is generally accepted that vascular autoregulation ensures adequate irrigation to the ONH. Research literature and clinical studies on OBF suggest that ocular PP decreases in response to elevated IOP and ischemic insult to the ONH may arise in the presence of autoregulatory dysfunction. Consequentially, this may lead to glaucomatous ONH damage and RGC death. Research data suggest that abnormalities in lipid metabolism, primary vasospastic syndrome, and vascular endothelial dysfunction may be responsible for ocular circulatory differences and ONH susceptibility in response to elevated IOP.

Atherosclerosis

Atherosclerosis is a chronic, progressive vascular disease that may reduce the autoregulatory capacity of the optic disc. The occurrence of atherothrombosis in this disease may lead to impediment of BF. In a study performed on monkeys, Faraci et al. found that atherosclerosis increases the response of vascular endothelial cells for the activation of leukocytes and platelets. Extracellular transduction signaling provoking abnormalities in endothelial cell function appears to be the triggering mechanism for thrombus formation. Moreover, altered serotonin released by endothelial cells seems to play an active role in the impediment of BF. Hayreh et al. demonstrated in their study on atherosclerotic monkeys that the presence of serotonin during atherothrombotic pathogenesis induced vasospasm of the central retinal artery and posterior ciliary artery, consequently impairing BF. However, a cause-effect relationship between atherosclerosis and POAG has not been proven. In fact, the prospective, population-based Rotterdam Eye Study found atherosclerosis not to be a significant risk factor for POAG.
Nevertheless, as a systemic process, atherosclerosis has recognized association with vascular conditions that have a possible correlation with POAG. For example, atherosclerosis is the most common pathologic process affecting the carotid system that leads to cerebrovascular accidents. It also shows a trend of high prevalence among patients with aortic valve stenosis that have experienced episodes of myocardial infarction. Both of these conditions have been demonstrated to have a relatively strong association with POAG. In their respective studies, encountered in females, has a well documented association with glaucoma progression. In their study, vasospasm and low BP. Ocular vasospastic episodes have been related to glaucoma. These patients often suffer from their visual field loss. Low BP has also been associated with inhibition of endothelial NO signaling in many organs including the eye. A series of studies have investigated the role of endothelial mediators in POAG. It has been demonstrated that intravenous administration of ET-1 reduces significantly retinal blood flow. From their study based on IOP increments in living isolated rat retinas, Rigosi et al. suggest that prolonged or recurrent IOP elevation may induce ET-1-mediated retinal capillary dysregulation contributing to neuronal damage overtime.

In a study evaluating glaucomatous field progression in 31 patients with POAG, specific radioimmunoessay revealed that 16 of these patients had increased ET-1 plasma levels. Another study observing the effect of dual endothelin receptor blockage on OBF reveals that oral administration of bosetan, a
dual endothelin receptor antagonist, increases ocular blood flow in patients with POAG. 16
Polak et al. 60 demonstrated in their study on NOS inhibition of the ocular vasculature that patients with POAG yielded significantly less percent reduction of blood flow to the ONH than healthy controls. Furthermore, the gene expression of NOS may be of significance in some glaucoma patients. Logan et al. 61 found in their study a statistical significant difference in the distribution of allele frequencies of a specific NOS gene isoform, between subjects with glaucoma that had a history of migraine and control subjects. Other studies on the NOS-mediated L-arginine-NO pathway in eyes of patients with POAG suggest that the pathway is genetically defective. 31,62

Altered endothelial vasoreactivity may be a determinant in the development and progression of POAG. However, the specific involvement of endothelial mediators such as ET-1, and NOS in the autoregulatory pathophysiology of POAG has yet to be completely elucidated. Nonetheless, it appears endothelial dysfunction, either primary or secondary to vascular diseases, contributes to POAG pathology.

Conclusion

Clearly, POAG is a progressive optic neuropathy that has a multi-factorial etiology, in which elevated IOP is the most important risk factor. Yet, research evidence and clinical experience clearly indicates that elevated IOP alone is not at work here. Research observations on altered corneal biomechanics and vascular dysregulation in association to elevated IOP suggest their possible contribution to the disease process. Comparing the two factors, however, it appears altered autoregulation function has a more positive correlation with POAG. A relatively strong association exists between decreased ocular PP precipitated by elevated IOP and decrease OBF in patients with vascular regulatory dysfunction. 12 However, the exact pathophysiological mechanism of how this provokes glaucomatous damage still remains uncertain. 16

Research data on corneal biomechanics appears to be a bit more contending. While results demonstrate consistent lower CH and CRF values in patients with POAG, 3,13 further longitudinal studies may be needed to determine if indeed in vivo CH and CRF values are independent predictors of glaucoma susceptibility. Besides, the possibility remains that alterations in corneal biomechanics may be a resultant of POAG rather than a risk factor. 14

In conclusion, POAG pathogenesis is a topic that warrants further pathophysiological studies to elucidate what risk factors other than elevated IOP are relevant for the development and progression of the disease. Certainly, vascular dysregulation and alterations in corneal biomechanics are factors to consider in POAG pathogenesis. Hopefully, future glaucoma research will determine more specific variables which may further clarify their correlation with the disease process.

Conflict of interests

The authors have no conflict of interests.

References
