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REVIEW

Differences and Similarities Between Primary Open Angle Glaucoma and Primary Angle-Closure Glaucoma

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Abstract: Glaucoma is the leading cause of irreversible blindness worldwide. It is an ocular disease characterized by an increase in intraocular pressure or, in some cases, normal intraocular pressure, which leads to optic nerve damage and progressive constriction of the visual field (VF). Primary Open-Angle Glaucoma (POAG) and Primary Angle-Closure Glaucoma (PACG) represent the predominant forms of glaucoma. Numerous hypotheses have been posited to elucidate the pathogenic mechanisms underlying these conditions. There is an emerging understanding of the distinct pathological processes that differentiate the various types of glaucoma. While some similarities in the mechanisms between PACG and POAG have been suggested, evidence indicates that there are also significant differences between the two. This review synthesizes the similarities and differences in the etiology of optic neuropathy caused by POAG and PACG, considering their respective pathophysiological mechanisms, the morphology of the optic disc and surrounding tissues, genetic characteristics, optical coherence tomography angiography, optical coherence tomography, and structural and functional features from VF examinations. These characteristics may contribute to a deeper comprehension of the underlying pathogenesis of glaucoma and enhance the management of different types of this ocular condition.

Keywords: pathophysiology, lamina cribrosa, optic nerve head, visual field

Introduction

The glaucoma encompasses a collection of optic neuropathies distinguished by the gradual deterioration of retinal ganglion cells (RGCs). Based on the configuration of the anterior chamber angle, primary glaucoma can be classified into two types: primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG). It is projected that the global prevalence of glaucoma will escalate from an estimated 64.3 million individuals in 2013 to 111.8 million by the year 2040.[1] The combined worldwide prevalence of POAG is estimated to be 3.05%, whereas that of PACG stands at 0.50%.[2] Findings indicate that the incidence of POAG is significantly higher among individuals of African descent, while the incidence of PACG is most prevalent among the Asian population.[3]

PACG is categorized into two distinct forms: the acute subtype, which is characterized by a sudden closure of the anterior chamber angle accompanied by a rapid increase in Intraocular Pressure (IOP), and the chronic subtype, which involves a gradual closure of the anterior chamber angle with a slow rise in IOP or the formation of peripheral anterior synechiae.[4] These two subtypes are commonly referred to as Acute Angle-Closure Glaucoma (AACG) and Chronic Angle-Closure Glaucoma (CACG), respectively. It has been thought that there might be differences in the pattern of optic nerve damage in PACG and POAG. Normal Tension Glaucoma (NTG) is recognized as a subtype of open-angle glaucoma, where IOP measurements consistently remain at or below 21 mmHg.[5] There exists an ongoing debate regarding the classification of NTG, with some questioning whether it should be considered a variant within the spectrum of POAG or as a separate disease entity. Despite this, NTG is distinguished by several unique characteristics when

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compared to POAG. These include risk factors for the development of NTG that are independent of IOP, specific patterns of structural and functional damage, and a distinct disease progression.

It has been thought that there might be differences in the pattern of optic nerve damage in PACG and POAG. In this comprehensive review, we have delineated the comparative analysis of optic nerve damage in PACG and POAG, examining both structural and functional aspects. The discussion encompasses a detailed examination of the commonalities and disparities in the pathophysiological mechanisms leading to optic nerve injury in these two prevalent forms of glaucoma.

Methods

This review conducted a literature search on articles published before 2023 through the PubMed database and Google Scholar with one or a combination of the search terms and excluded other glaucoma types that were not part of the PACG and POAG.

Pathophysiology

The regulation of IOP relies on the equilibrium between the production and drainage of aqueous humor. Aqueous humor is generated by the non-pigmented ciliary epithelium within the ciliary processes, then it flows into the posterior chamber, passes through the pupil, and continues to the anterior chamber and the trabecular meshwork. Additionally, a portion of the aqueous humor is drained via the uveoscleral pathway.[6] It is widely recognized that elevated IOP is a significant risk factor for the development and advancement of glaucomatous optic neuropathy in both forms of primary glaucoma.[7–9] IOP reduction is the only proved clinical therapy to slow down glaucoma progression.[10,11]

Nevertheless, when it comes to the underlying pathogenic mechanisms, PACG is distinct from POAG. The traditional mechanisms of PACG can be primarily categorized into two types: pupillary block and non-pupillary block, with pupillary block being the predominant and well-known mechanism. In certain eyes, the iris and lens may come into apposition, hindering the passage of aqueous humor through the pupil into the anterior chamber. This scenario, termed pupillary block, results in an accumulation of aqueous humor behind the iris, causing it to protrude forward and make contact with the trabecular meshwork, thereby impeding the outflow (Figure 1). Non-pupillary block factors encompass a thick peripheral iris, a peripheral iris positioned anteriorly, a ciliary body that is rotated anteriorly, and a plateau iris.[12]

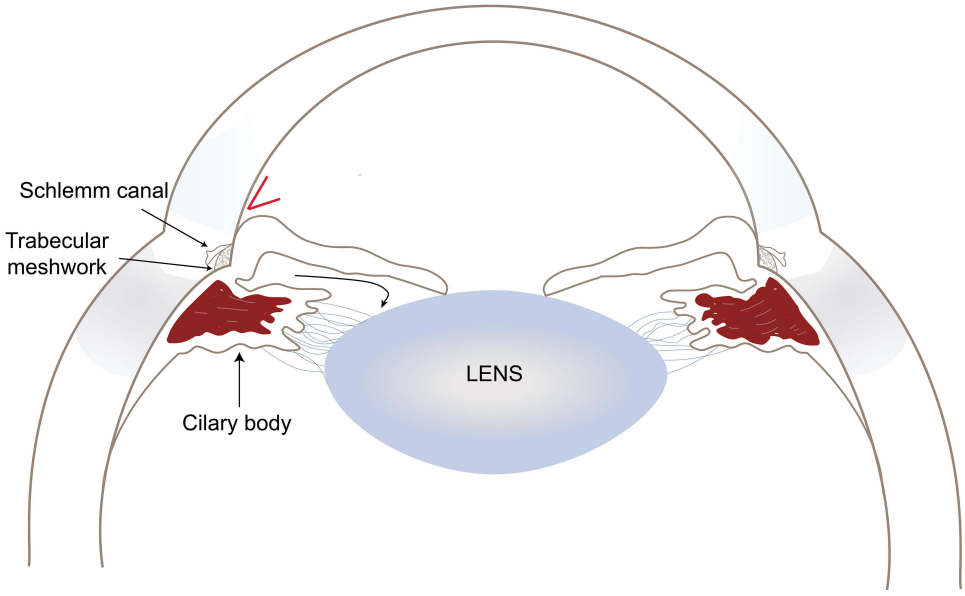

Figure 1 The Anatomical Characteristics of Primary Angle-Closure Glaucoma. In Primary Angle-Closure Glaucoma (PACG), the pupillary block mechanism is characterized by the posterior surface of the iris adhering to the lens, which impedes the circulation of aqueous humor. This leads to a forward protrusion of the iris, resulting in a narrowing or even closure of the anterior chamber angle.

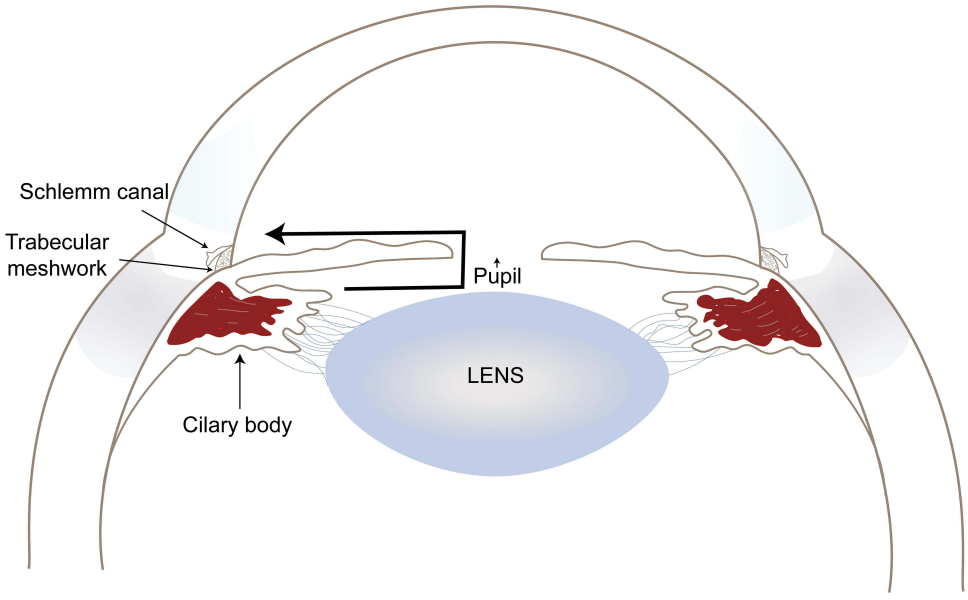

Figure 2 The Anatomical Characteristics of Primary Open Angle Glaucoma. In Primary Open-Angle Glaucoma (POAG), the anterior chamber angle remains open, with the primary resistance to aqueous humor circulation being localized at the trabecular meshwork.

There are also some hypotheses that propose choroidal expansion contributes to angle closure,[13,14] but this claim is controversial. The anterior segment of the eye, characterized by an abnormal anatomy that includes a shallow anterior chamber depth, a thicker lens, a lens positioned more anteriorly, a smaller corneal diameter, or a shorter ocular axis, leads to structural congestion in the anterior segment. This congestion augments the likelihood of PACG development.[12,15,16] Angle closure is the primary fundamental problem in PACG, while elevated IOP is secondary to angle closure.

Conversely, in the case of POAG, the resistance to the outflow of aqueous humor through the trabecular meshwork (TM) is heightened.[10] When the angle remains open but the TM is obstructed, the aqueous humor is unable to drain properly, leading to an accumulation within the anterior chamber (Figure 2). This situation results in elevated IOP, which is believed to exert pressure on the optic nerve. Such compression can lead to the death of nerve cells and a consequent, incremental deterioration of the visual field (VF). The principal site of outflow resistance in this pathway is the TM, including the inner wall of Schlemm's canal (SC)[17] (Table 1).

Structure and Function

Glaucoma, both in its POAG and PACG forms, is characterized by a reduction in retinal nerve fiber layer (RNFL) and progressive loss of VF, which are hallmark features of the disease. The relationship between functional vision loss and structural changes in the optic nerve head (ONH) and retinal ganglion cells (RGCs) is a hallmark for the diagnosis of glaucoma. Typically, functional vision loss occurs subsequent to structural alterations. It is estimated that up to 40% of the retinal nerve fibers may be damaged before discernible changes in the VF are observed.[18]

Table 1 Similarities and Differences About Pathophysiology Between PACG and POAG

	PACG	POAG
Similarity	Elevated IOP	
Differences	Narrow or closed anterior chamber angle;[9] Blockage of AH circulation[12,15,16]	Open anterior chamber angle; Increased resistance to AH outflow through TM;[10,17] NTG: IOP within the normal range[5]

Abbreviations: PACG, primary angle-closure glaucoma; POAG, primary open angle glaucoma; IOP, intraocular pressure; AH, aqueous humor; NTG, normal tension glaucoma; TM, trabecular meshwork.

Manassakorn et al[19] compared the patterns of RNFL thickness (RNFLT) loss in PACG and POAG with different severity levels. In contrast, patients with mild POAG exhibited deeper and more localized RNFL defects, while mild PACG eyes showed a more generalized reduction in RNFLT, with the PACG group having a higher average RNFLT than the POAG group. Patients with moderate or advanced stages of either condition demonstrated a similar pattern of diffuse RNFL thinning. Corresponding to the changes in the RNFL, alterations in the VF are also a certainty in glaucoma.

However, the pattern of VF loss in PACG has been reported to differ from that observed in POAG.[20,21] Lee et al[22] conducted a prospective study and found that, compared to eyes with POAG, there were fewer sectors of the RNFL with significant RNFL-VF correlations in eyes with PACG. Rao[23] also found a poor correlation of VF with the RNFL in PACG eyes as compared to POAG. Indeed, the disparity in the correlation between RNFL and VF between PACG and POAG eyes, as observed by them, may be attributed, at least in part, to differences in axial length (AL) between the two groups.

In a study conducted by Rhee et al,[20] a comparative analysis of VF was performed between patients with POAG and those with PACG in the early to moderate stages of the disease. The findings revealed that patients with CACG exhibited a more extensive pattern of VF loss in comparison to those with POAG. This observation is consistent with the conclusions drawn from other studies in the field.[24–26] Moreover, building upon their previous research, Boland et al[27] controlled for variables that can affect the appearance of the ONH, including cup area, rim area, and cup-to-disc area ratio. After performing multiple regression adjustments, the study found that at an equivalent level of mean deviation (MD), the pattern standard deviation (PSD) was significantly larger in the POAG eyes than in the PACG eyes, suggesting a greater degree of localized damage in the former.

In both POAG and PACG eyes, VF damage was more pronounced in superior hemifield than inferior hemifield. However, this tendency was more obvious in POAG eyes than in PACG eyes. Yousefi et al[28] concluded that in the early stage of POAG, three regions (central, paracentral, and peripheral) in the superior hemifield exhibited greater VF loss compared to their inferior counterparts. In the moderate and advanced stages, all glaucoma hemifield test (GHT) regions in the superior hemifield showed greater loss than those in the inferior hemifield. In contrast, PACG eyes had significantly fewer regions in the superior hemifield that were significantly worse than their inferior counterparts. Additionally, POAG eyes had larger PSD values than PACG eyes for a given mean of total deviation (TD) values. Recent comparative studies have also supported these findings.[29,30]

Furthermore, a previous study has indicated that after stratification based on MD, there are significant differences between the hemifield differences in the mild (MD ≥ -10 dB) and moderate (MD < -20 dB and ≥ -10 dB) subgroups. However, in the severe (MD < -20 dB) subgroup, such differences between the hemifield are not apparent. This suggests that as the severity of glaucoma progresses, VF damage may become more uniform, whereas in the earlier stages, damage may be more localized to specific areas.[21] The characteristic trait of the VF defect at the late PACG stage differs from POAG. PACG exhibited a more severe central VF defect, although the inferior and superior hemifield lesions in PACG are similar to those in POAG.[31]

In POAG eyes, the rate of VF decline is significantly asymmetric across the horizontal meridian; the central, paracentral, and peripheral sectors of the upper hemifield exhibit a more rapid decline in VF compared to the lower hemifield. In contrast, such a difference was not observed in PACG eyes. This distinction may reflect the differing pathophysiological mechanisms underlying the progression of these two types of glaucoma, which could have implications for the clinical management and monitoring of these conditions.[32]

The strength of the correlation between pretreatment IOP and the amount of VF damage may be an indicator of the extent to which a disease can be considered to be pressure-dependent. This association could support the belief that pathogenetic mechanisms involved in PACG are more dependent on pressure. Gazzard et al[33] compared the correlation between VF loss and pretreatment IOP in PACG and POAG. The finding demonstrated a stronger correlation between pretreatment IOP at the time of the first presentation and final VF loss severity for PACG compared with POAG. IOP may be more readily implicated as a causal factor for optic nerve damage in PACG than it is in POAG. This means that, for a given severity of VF loss, PACG subjects tended to have higher IOP. In contrast, for a given IOP, PACG level demonstrated less VF loss. In turn, these results imply that POAG subjects may have less tolerance to higher IOP levels than PACG subjects.

The diffuse nature of VF loss in PACG is currently unclear whether it is due to varying levels and durations of IOP exposure or related to differences in pathophysiology. There is evidence suggesting that in POAG, eyes with lower IOP levels exhibit more localized VF defects compared to cases of POAG with higher IOP levels. This indicates that the pattern of VF damage in glaucoma may be influenced by the level of IOP as well as other underlying pathological

mechanisms.[34,35] Despite findings by other authors that this association is not strong, it is still a factor that warrants consideration in the understanding and management of glaucoma.[36]

Structure-to-function studies reveal differences in impairment between POAG and PACG. Although there are known differences in the risk factors between the two disease types, the molecular mechanisms distinguishing PACG and POAG are not yet clear. Another possibility is that the molecular mechanisms underlying these differences are more complex (Table 2).

ONH Morphology

IOP exerts mechanical stress and strain on the eye's posterior structures, particularly the ONH and surrounding tissues. A shared characteristic across all types of glaucoma is the loss of RGCs, thinning of RNFLT, the development of focal and enlarged cupping of the optic disc, and parapapillary atrophy (PPA). Nevertheless, there is evidence indicating that there are notable differences in the morphology of the ONH between POAG and PACG.[37]

In a cross-sectional observational study, Sihota et al[38] utilized optical coherence tomography (OCT) to assess various ONH parameters in patients with CACG and POAG. The parameters evaluated included disc area, cup area, rim area, vertical integrated rim area (VIRA), rim volume (horizontal integrated rim volume), average cup/disc ratio, and both horizontal and vertical cup/disc ratios, as well as cup volume. The findings revealed that in the early stages of CACG, the eyes exhibited smaller disc areas, cup areas, and cup/disc ratios, while the rim area was larger compared to those with early POAG. These results align with the outcomes of a recent study, which suggests a distinct morphological difference between the two types of glaucoma at an early stage.[24] Additionally, they computed the respective receiver operating characteristic curves individually. The findings revealed that the VIRA, rim volume, and rim area are effective in distinguishing between normal eyes and those affected by early POAG and CACG. Moreover, the diagnostic efficacy for early POAG was found to surpass that for early CACG.

In contrast, a parallel study by Thomas et al[39] indicated that parameters derived from the Heidelberg Retinal Tomograph (HRT), including disc area, cup area, and cup volume, did not exhibit statistically significant differences, regardless of early or advanced glaucoma. This is consistent with the conclusion of a cross-sectional study in South India.[40] Meanwhile, Parikh's viewpoints on early PACG and early POAG were also different from Sihota's. Futhermore, Boland et al[27] utilized MD and average RNFLT as indicators of damage, acknowledging that eyes with glaucomatous injury may exhibit topographical variations solely due to differing extents of RGCs loss. They also accounted for disc area in their analysis, considering that a larger optic disc contains a greater number of nerve fibers.[41] Ultimately, the study's results demonstrated that there were no significant differences in any HRT parameters, such as cup depth, cup volume, rim volume, or cup shape measure, between the groups. This suggests that the fundamental appearance of the ONH does not vary between PACG and POAG.

Recently, studies have indicated that the Bruch's membrane opening minimum rim width (BMO-MRW) and the Bruch's membrane opening minimum rim area (BMO-MRA) are dependable parameters of the ONH that could be utilized for the early detection of glaucomatous progression (Figure 3). In both POAG and PACG, there is a noted reduction in both BMO-MRW and BMO-MRA.[42–45]

Table 2 Similarities and Differences About Structure and Function Between PACG and POAG

	PACG	POAG
Similarities	Thinning of RNFL thickness; Loss of VF	
Differences		
RNFL-VF correlation[22,23]	Fewer sectors	More sections
Pattern of VF loss[20,24–27]	More extensive	Localized
Hemifield asymmetric[28–30]	Fewer regions	More regions
Rate of VF loss[32]	Unobserved	Upper hemifield is faster than down hemifield
Pretreatment IOP-VF correlation[33]	Stronger	Weak

Abbreviations: PACG, primary angle-closure glaucoma; POAG, primary open angle glaucoma; IOP, intraocular pressure; VF, visual field; RNFL, retinal nerve fiber layer.

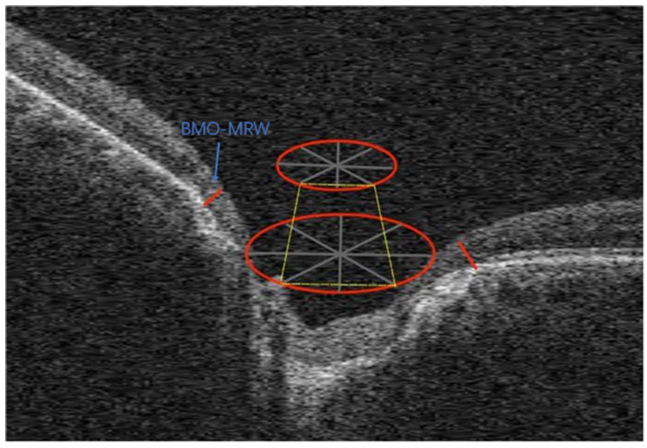

Figure 3 The Definition of BMO-MRW and BMO-MRA. The Bruch's Membrane Opening-Minimum Rim Width (BMO-MRW) is characterized as the minimal distance extending from the point of the Bruch's Membrane Opening (BMO) to the Inner Limiting Membrane (ILM). The Bruch's Membrane Opening-Minimum Rim Area refers to the smallest surface area encompassed by the ILM and any two consecutive BMOs, as demarcated by the yellow dashed arrows.

Previously, there have been reports that ONH swelling was observed at the onset of AACG.[46,47] However, it is rare in the course of POAG. Optic pallor usually means this acute angle closure, which is not only common in AACG, but also reported in CACG.[48,49] However, the optic disc is characterized by localized rim notching in POAG eyes.[40] Pale optic disc is usually a manifestation of advanced glaucoma, with reduced blood vessels or tissue atrophy.[50] Kong et al[47] compared the RNFLT, BMO-MRW, and BMO-MRA of 30 patients with AACG and 30 patients with POAG. The findings indicated that irrespective of ONH swelling, the global BMO-MRW and total BMO-MRA in AACG demonstrated comparable outcomes, with both global BMO-MRW and total BMO-MRA being significantly higher in AACG compared to the POAG group. However, this study did not rigorously control for the baseline parameters of the participants, nor did it take into account other pertinent ocular parameters. Additionally, patients with AACG and those with POAG might be at different stages of the disease, and the sample size was limited. Concurrently, the conclusions drawn by Kong et al are at odds with those of Li et al, who observed that both BMO-MRW and RNFLT were reduced in both glaucoma groups compared to the control group, yet no significant difference was found between the two glaucoma groups. A separate report utilizing the HRT highlighted differences in rim area between POAG and CACG eyes, but this study also did not strictly control for these factors.[51] Currently, there is a scarcity of research examining the distinctions between PACG and POAG in relation to BMO-MRW and BMO-MRA. Future studies should include more extensive longitudinal and cross-sectional investigations (Table 3).

The Lamina Cribrosa

The lamina cribrosa (LC) serves as an intricate network of connective tissue, offering essential structural and nutritional support to the axons of RGCs. This anatomical feature is of paramount importance, as it is recognized as the primary site

Table 3 Similarities and Differences About ONH Morphology Between PACG and POAG

	PACG	POAG
Similarities	Focal and enlarged cupping of the optic disc; Reduction of BMO-MRW and BMO-MRA.[42–45]	
Differences		
ONH parameters*[24,38–41]	Smaller parameter values	Bigger
ONH swelling and pallor[46–49]	Presence	Rare
BMO-MRW and BMO-MRA*[47,51]	Higher	Lower

Notes: The presence of " * " in the table indicates that the existing conclusion is controversial.
Abbreviations: PACG, primary angle-closure glaucoma; POAG, primary open angle glaucoma; ONH, optic nerve head; BMO, Bruch's membrane opening; BMO-MRW, BMO-based minimum rim width; BMO-MRA, BMO-based minimum rim area.

where axonal damage occurs in glaucoma.[52,53] Significantly, within the scope of glaucoma, the LC experiences morphological alterations due to strain, which manifest at both microscopic and macroscopic levels. These alterations encompass the posterior displacement of the laminar insertion point into the sclera, an increase in the cupping of the lamina cribrosa, and a reduction in the thickness of the LC (Figure 4).

Li et al[54] conducted a comparative analysis of structural characteristics within prelaminar and laminar tissues, revealing a higher prevalence of eyes with prelaminar holes in the CACG cohort as opposed to those in the POAG or control groups. The prelaminar holes observed in CACG eyes were found to be larger in size compared to those in the control group and exceeded the number detected by cross-sectional scanning in POAG eyes. The presence of multiple pores in the prelaminar region is considered a distinctive feature of the ONH injury pattern in CACG eyes (Figure 5). These findings suggest that the prelaminar pores are a significant hallmark of CACG and these pathological changes appear to be markedly different from the anterior wedge-shaped defects typically associated with the LC in POAG patients.[55] This divergence may indicate a distinct pathogenic mechanism underlying glaucomatous damage caused by CPACG.

Furthermore, in a prospective investigation, individuals suspected of having acute angle-closure underwent a 2-hour dark room prone provocative test (DRPPT) to evaluate the positional alterations of lamina cribrosa pores (LCPs) in response to acute IOP elevation. The test keeps patients parallel to the ground in a dark room for 2 hours. Within 5 minutes before and after the start and end of the DRPPT, Wang et al[56] obtained the required parameters by taking OCT and color fundus photography. Multivariate analysis revealed that the displacement of the lateral LCPs is positively correlated with an increase in IOP and the deepening of the optic cup. Among the study subjects, the LCP movement direction was upward in 12 eyes, downward in 10 eyes, temporal in 9 eyes, and nasal in 5 eyes. Consequently, the study posits that elevated IOP is associated with the movement of LCPs, and that the greater the IOP and the more profound the optic cup deepening, the more significant the LCP displacement. From these findings, it is hypothesized that elevated IOP may be a more prevalent contributing factor to the formation of pores in CACG compared to POAG. However, Li et al 's study reported no significant difference in the IOP measurements between the two groups of glaucoma patients on the day of examination. This suggests that further research is warranted to explore the relationship between IOP and the formation of prelaminar pores. Additionally, beyond the comparative methods mentioned, examining postoperative glaucoma outcomes (after IOP reduction) could provide valuable insights for making informed judgments.

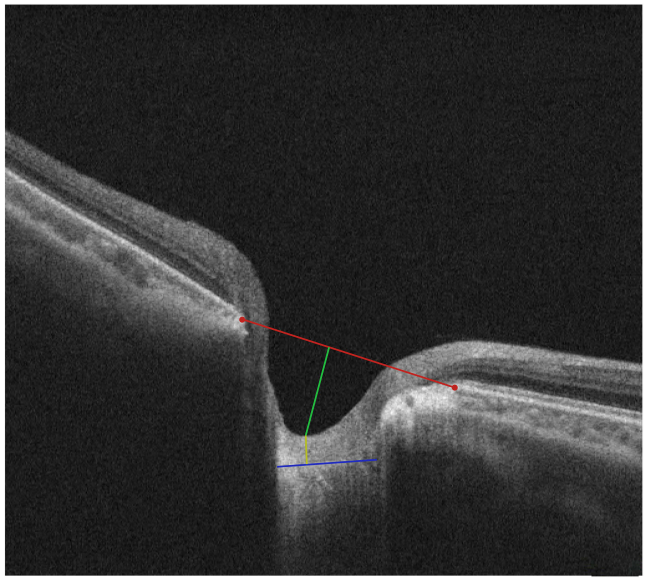

Figure 4 The B-scan Image of the Optic Nerve Head Obtained from 3D Optic Disc Pattern Scanning by Swept-Source Optical Coherent Tomographic (SS-OCT). Two red dots represent the endpoint of Bruch's Membrane Opening (BMO). The BMO reference plane (red line) can be obtained by connecting two points. Lamina cribrosa depth (LCD) is the distance (green line) of a line perpendicular to the BMO reference plane to the anterior prelaminar surface. The blue line is the anterior laminar surface. Lamina cribrosa thickness (LCT) is the distance (yellow line) from the anterior prelaminar surface to the anterior laminar surface.

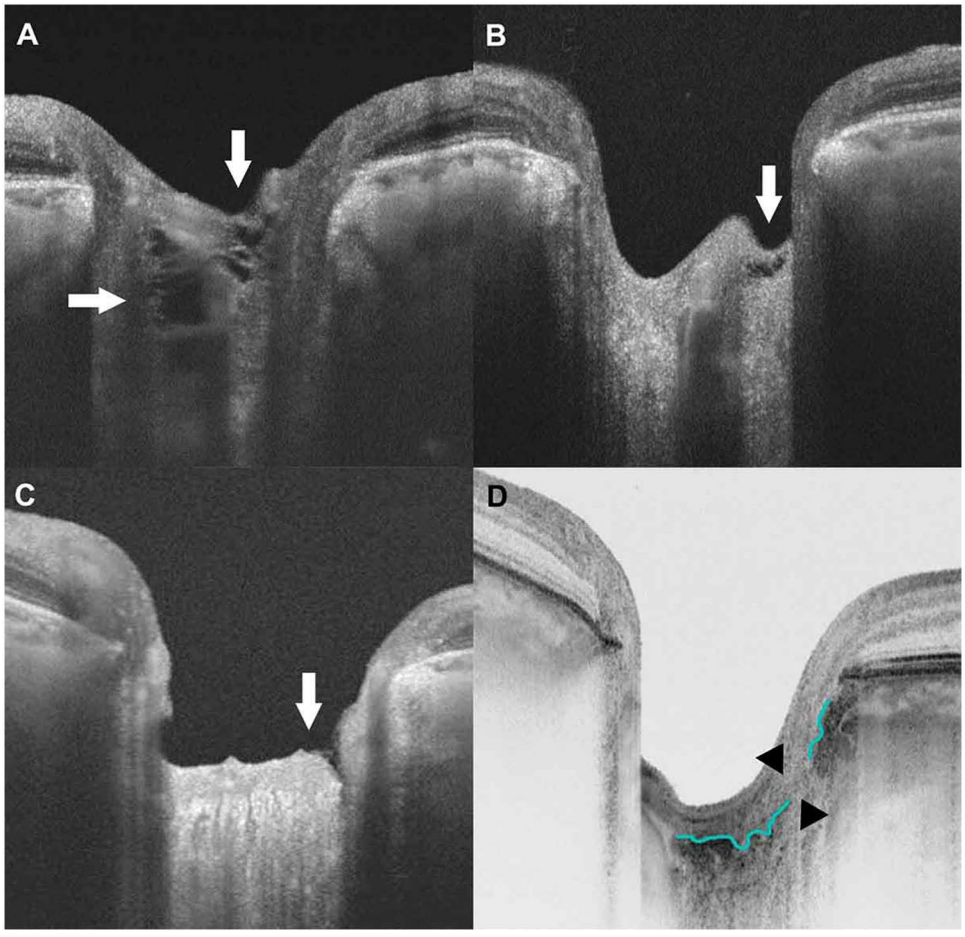

Figure 5 Examples of Prelaminar Holes. (**A**) Multiple large prelaminar holes (white arrows) in a CACG patient (**B**) A small prelaminar hole (white arrow) in a POAG patient. (**C**) Prelaminar wedge defect (white arrow) in a POAG patient. (**D**) Laminar defect (black arrow heads) in a POAG patient. The figure is sourced from: Li D, Li T, Paschalis EI et al. Optic Nerve Head Characteristics in Chronic Angle Closure Glaucoma Detected by Swept-Source OCT. *Curr Eye Res*. Nov 2017;42(11):1450–1457, with permission from Taylor and Francis. Available from: https://www.tandfonline.com/doi/full/10.1080/02713683.2017.1341535.[54]

A recent study distinguished the lamina cribrosa thickness (LCT) between patients with PACG and POAG. The findings revealed that eyes affected by glaucoma had a reduced LCT when compared to non-glaucomatous control eyes. Moreover, there was an observed inverse correlation between the maximum IOP and LCT. Notably, PACG eyes, which are characterized by higher peak IOP, demonstrated an even thinner LCT compared to POAG eyes. This observation underscores the pressure-dependent effects of PACG on the deformation of the lamina cribrosa and the amplified stress on the LC due to increased IOP, leading to greater strain.[57] The diagnostic potential of LCT has been found to be comparable to that of peripapillary RNFLT in patients with glaucoma, and it may even exceed the diagnostic value of peripapillary RNFLT in early NTG patients. This suggests that LCT measurements could be a valuable tool in the early detection and monitoring of glaucoma, particularly in cases where other parameters such as RNFLT may not show significant changes.[58] In contrast, Hao et al[59] compared the LCT and LCD of CACG and POAG using SD-OCT in a cross-sectional study. The results showed that the average LCT of CACG eyes was higher than that of POAG, but lower than that of normal eyes. The average LCD of POAG and CPACG eyes was higher than that of the normal control eye. However, there was no significant difference in the average LCD between the POAG group and CPACG group. The conclusion regarding LCD is consistent with that of another study.[54] The researchers suggested that these observations are in line with the notion that the LC in CACG eyes undergoes less deformation and compression compared to POAG eyes, which points to distinct pathological mechanisms of glaucomatous damage between the two conditions. An additional noteworthy discovery is the frequent occurrence of focal LC defects in glaucomatous eyes that exhibit

localized RNFL defects. These localized abnormalities of the LC may be associated with the occurrence of localized damage to the retinal nerve fibers. This suggests a potential correlation between structural changes in the LC and the functional impairment of the retinal ganglion cells, as indicated by RNFL defects.[60,61]

Since LCD takes into account the choroidal thickness, it results in a bias in the LCD values. Therefore, the measurement of LCD has its limitations. Recently, some scholars have calculated LCD in another way, while adding another parameter: LC curvature index (LCCI). For details on the measurement methods, the reader is referred to these two published articles.[62,63] Increased attention has been given to LCCI, because it describes the LC topography and is not affected by the choroidal thickness. LCCI was shown to have a better discriminating capability index between POAG and healthy eyes than the LCD.[64,65] However, there is a relative scarcity of comparative research on LCCI. Future research should aim to fill this gap.

Park et al[66] conducted an analysis of the prelamina and lamina alterations in 20 patients with POAG who were scheduled for glaucoma surgery and 17 patients with AACG who were to undergo laser peripheral iridoplasty, following a reduction in IOP. Their findings indicated that IOP reduction triggered distinct responses in the two patient groups. In AACG patients, a significant anterior shift of the prelamina and lamina was observed, accompanied by an increase in the thickness of the prelamina. In the POAG group, the changes in LCD and LCT were not significantly different from basic values before the reduction in IOP. Park et al have pointed out that patients with AACG showed notably greater alterations in LCT and LCD following IOP reduction, in contrast to those with POAG. Additionally, it was observed that the POAG patients demonstrated a comparatively higher LCD.

Similarly, Kadziauskienė et al[65] reported that not only does the average LCD decrease following a reduction in IOP, but the LC can exhibit both backward and forward movements post-IOP reduction. They noted that trabeculectomy results in a continuous flattening and shallowing of the LC, with stabilization occurring after approximately six months. However, they did not make a comparative analysis between POAG and PACG. Furthermore, a comprehensive comparison of the relevant parameters associated with the two types of glaucoma surgeries was not provided in their study (Table 4).

Parapapillary Atrophy

PPA β area, which is characterized by the loss of retinal pigment epithelium (RPE), has historically been linked to glaucoma.[67,68] Prior research has indicated that the mean ratio of PPA to disc area is significantly higher in POAG compared to PACG.[69] This ratio has also been confirmed to be associated with the MD in POAG patients. However, Uchida et al[48] and Xu et al[70] both did not find a significant correlation between PPA and glaucomatous damage in PACG. Uchida et al hypothesized that this might be due to a considerably lower prevalence of PPA in PACG patients (38%) as opposed to those with POAG (68%). This implies that both types of glaucoma may share some commonalities on the development of PPA in their pathogenesis.

Table 4 Similarities and Differences About Lamina Cribrosa Between PACG and POAG

	PACG	POAG
Similarities	Posterior displacement of LC; Increased cup of LC; Reduced LCT; Occurrence of focal LC defects.	
Differences		
LCT[57,59]	Thinner	Thicker
LCD[54,59]	No significant difference	
LCCI	Rare comparative research	
Prelaminar holes[54–56]	Higher prevalence	Lower prevalence

Abbreviations: LC, lamina cribrosa; LCT, lamina cribrosa thickness; LCD, lamina cribrosa depth; LCCI, LC curvature index.

Recently, it has been proposed that based on spectral-domain optical coherence tomography (SD-OCT), the conventional β region can be further divided into two regions: the γ region and the (new) β region. The γ zone is defined as the area between the edge of the temporal ONH and the beginning of Bruch's membrane, and the β zone is defined as the absence of retinal pigment epithelium in Bruch 's membrane.[71] The OCT-defined parapapillary β area is associated with aging, glaucoma, and with axial myopia. In contrast, the OCT-defined parapapillary γ area is strongly associated with axial myopia.[72–74] OCT-based classification is more relevant than the conventional photograph-based classification in distinguishing the influence of glaucoma from that of myopia on the PPA. In clinical practice, the size of the parapapillary β area in PACG patients can be used as an indicator of glaucoma severity.

Emerging evidence has increasingly indicated a predominant association between the parapapillary β zone and POAG, with a more modest correlation observed in the context of axial myopia. The majority of research endeavors have predominantly focused on POAG.[72,75] However, there is a scarcity of research on the PPA in PACG. Shang et al[76] compared the microstructural characteristics of the parapapillary γ and β zones and their influencing factors between POAG and PACG. Their findings indicate that when comparing the PACG and POAG cohorts with adjustments for age and MD values, there were no significant differences observed in the area and configuration of the OCT-defined parapapillary β zone. In contrast, the OCT-defined parapapillary γ zone was found to be larger in the POAG group. More researches concerning PACG patients and comparative researches are needed in the future.

Compromised Microvasculature

Sometimes elevated IOP alone does not explain certain clinical and experimental observations, as persistent VF deterioration occurs despite adequate control of IOP in some patients, especially in NTG. Studies suggest that vascular factors, rather than IOP-dependent risk factors, may be an important pathogenetic mechanism. The vascular theory of glaucoma suggests that inadequate blood supply to the optic nerve is a key factor in glaucoma. With the development of new techniques to study the circulation in the eye, there is increasing evidence to support the role of the microvascular system in glaucoma. A noninvasive method for examining the microvascular structure of the retina and optical disc is optical coherence tomography angiography (OCTA). By measuring the movement of red blood cells in retinal blood vessels, OCTA creates images of perfusion vessels for angiography. OCTA can evaluate the vessel density (VD) of ONH in glaucoma.[77] Numerous studies have reported a reduction in peripapillary VD and macular VD in both POAG and PACG. Moreover, the diagnostic capabilities of peripapillary VD parameters derived from OCTA have been demonstrated to be comparable to those of RNFLT measurements.[78–81]

Some existing research findings indicate that the two types of glaucoma exhibit distinct manifestations. In NTG eyes, a decrease in VD is associated with a reduction in MD, whereas in PACG eyes, it is not related to MD. Despite similar disease severity and average RNFLT in both types of glaucoma, the overall VD in early-stage NTG is lower compared to early-stage PACG.[82] In PACG eyes, VF mean sensitivity demonstrated a significant correlation with the corresponding RNFLT in four sectors, whereas VD was associated with the corresponding VF mean sensitivity in five sectors. Concurrently, in POAG eyes, the VD of all sectors exhibited a significant association with both the corresponding VF mean sensitivity and RNFLT, respectively.[83] However, there are researchers who have indicated that there were no significant differences in the OCTA parameters in the peripapillary and macular areas between the POAG and PACG groups.[84]

Hou et al[85] used OCTA to compare the VD of the ONH and macula in POAG and PACG eyes. Compared with control eyes, the whole ONH, peripapillary VD of POAG and PACG eyes were significantly reduced, suggesting impaired retinal vascular perfusion in glaucoma eyes. Although covariates were similar in the two groups, VD around the inferior temporal papilla was significantly lower in the POAG group than in the PACG group. The reduction of VD in PACG eyes was more uniform.

It has long been postulated that a reduction in ocular perfusion pressure (OPP) may elevate the susceptibility of the ONH, thereby heightening the risk of glaucoma onset and advancement.[86–88] Some studies[89,90] have shown the correlation between OPP and POAG. However, the vast majority of studies have focused on POAG, with almost no research conducted on PACG, leaving it an unexplored area (Table 5).

Table 5 Similarity and Differences About Microvasculature Between PACG and POAG

	PACG	POAG
Similarity[78–81]	Reduction of peripapillary and macular VD	
Differences		
VD-MD Correlation*[82,84]	No correlation	Decreased VD correlates with reduced MD
Pattern of MD Reduction[85]	Uniform reduction	Lower VD around the inferior temporal papillary
OPP	Rare comparative research	

Notes: The presence of " * " in the table indicates that the existing conclusion is controversial.
Abbreviations: PACG, primary angle-closure glaucoma; POAG, primary open angle glaucoma; VD, vessel density; MD, mean deviation; OPP, ocular perfusion pressure.

Genetic Susceptibility

Glaucoma has been viewed a multifactorial disease including environmental and familial factors. Several genetic regions have been elucidated to be related with glaucoma using genetic association studies or genetic linkage analyses.

Familial linkage studies of POAG have been conducted and certain likely causative genes have been identified, including MYOC (GLC1A), OPTN (GLC1E), EFEMP1 (GLC1H) and TBK1 (GLC1P).[91–94] The accumulation of mutant MYOC protein within TM cells is posited to disrupt the normal physiological functions of these cells. This disruption can impede the regular outflow of aqueous humor and result in elevated IOP.[95] The TM of PACG patients also showed similar changes as those of POAG patients.[96] However, Aung et al[97] did not find a role for MYOC mutations in the pathogenesis of PACG in Chinese. GLC1F (ASB10) and GLC1G (WDR36), which are associated with POAG but not determined to be pathogenic, have recently been identified.[98,99] Othman et al[100] performed linkage analysis of a genome scan in a large family with PACG and identified the NNO1 locus, which is localized to chromosome 11, to be associated with PACG but the causative gene at this locus has not been elucidated.

Genetic linkage studies continue to be a useful tool for the discovery of risk loci, and a recent approach is the Genome-wide association study (GWAS) that involves the detection of genome-wide genetic variation (eg SNP) polymorphisms in multiple individuals, which in turn correlates genotype with phenotype to mine trait-associated genes. GWAS identified several genes associated with POAG: CDKN2B-AS1, CAV1 and CAV2, TMCO1, ABCA1, AFAP1, GAS7, TXNRD2, ATXN2, intergenic region of chromosome 8q22, SIX1 and SIX6. The gene loci shared between high IOP and the POAG phenotype were CAV1, TMCO1, ABCA1, and GAS7, suggesting that the genetic susceptibility to POAG cannot be explained by elevated IOP alone.[6]

Recently, two large studies[101,102] have identified eight loci associated with the risk of developing PACG: PLEKHA7 rs11024102, COL11A1 rs3753841, rs1015213 located between PCMTD1 and ST18 on Chromosome 8q EPDR1 rs3816415, CHAT rs1258267, GLIS3 rs736893, FERMT2 rs7494379, and DPM2 - FAM102A, but these eight loci only explain 1.8% of the genetic basis of PACG, confirming the need for larger or more targeted studies in the future. For the first three PACG genetic susceptibility loci, preceding investigations[103,104] demonstrated that they are not correlated with anterior chamber depth (ACD), AL, MD, and PSD phenotypes, but another study[105] revealed that at least rs1015213 is associated with ACD. Additional researches[106,107] identified other loci that exhibit associations with ACD. The complexity of glaucoma phenotype is composed of diverse pathological processes.[108]

In the meantime, meta-analysis and a systematic review discovered five candidate genes for PACG risk: HGF (rs6745718)-A and rs17427817-C), heat shock protein 70 (HSP70) (rs1043618), membrane type Frizzled-related protein (MFRP) (rs2510143-C), MMP9 (rs3918249-C) and nitric oxide synthase 3 (NOS3) (rs7830-A), of which MMP9 is a collagenase thought to have an influence on intraocular extracellular matrix remodeling.[109,110] None of these candidate genes, however, has been confirmed in a large GWAS of PACG, so their magnitude in the pathogenesis of PACG is uncertain.

It has been assumed that PACG and POAG have completely different genetic profiles because no overlapping genetic markers have been identified in large GWAS. Two of the eight PACG loci (PLEKHA7 and FERMT2) are IOP-associated genes, while PLEKHA7 and FERMT2 are also associated with POAG.[111,112] These results suggest that there may be

a common pathway leading to elevated IOP in both POAG and PACG, and further studies may reveal more common genetic features. Indeed, GWAS has yielded more than 100 genetic markers associated with glaucoma risk. However, one of the drawbacks of GWAS studies is that it is difficult to identify the actual effector genes responsible for the pathogenesis of the disease. With the development of new technologies, glaucoma gene mapping has revealed the biological mechanisms that may be involved in glaucoma, revealing new therapeutic targets and prospects for individualized treatment.

Conclusion

Current theories postulate a hybrid mechanism of optic nerve injury in glaucoma. The pathogenesis of glaucoma is not a pathway but occurs as an organic continuum that ultimately leads to RGC apoptosis.

However, some research findings are contradictory, and people hypothesize several reasons for this discrepancy. Firstly, although the inclusion criteria for these comparative studies are not lax, they may not accurately control the baseline data of glaucoma patients at enrollment, particularly the severity of the condition and the basic structural parameters of the eye, which could be a major reason for the conflicting conclusions. Additionally, a small sample size may also contribute to these inconsistencies. Secondly, PACG and POAG do not exhibit substantial differences in some parameters. Despite the different pathological mechanisms underlying IOP elevation, the stress response of tissues to pressure is similar. Thirdly, it is tempting to speculate that any difference in the pattern of optic nerve damage between PACG and POAG may have to do with differences in their ONH structures or the susceptibility of RGCs to damage. Because PACG is predominantly initiated by outflow obstruction and IOP that are higher than normal, one may hypothesize that these eyes would have neither abnormally compliant disc connective tissue nor subgroups of ganglion cells with vulnerability greater than average. In POAG, on the other hand, optic nerve disease often does occur at IOP levels that are tolerated by most eyes without damage. The loss of the vulnerable VF in POAG may be in accordance with patterns that arise from idiosyncratic defects in the structure of the nerve head or the susceptibility of ganglion cells to apoptosis that are not shared by PACG. Therefore, under the influence of multiple factors, different types of glaucoma emerge. Subsequently, under varying IOP exposure states, some structures or functions exhibit consistent and distinct patterns of damage, while others show diverse yet similar damage characteristics. Future research should involve more multi-parameter, large-sample studies, either cross-sectional or longitudinal, to delve deeper into the differences between POAG and PACG, thereby enhancing our understanding of glaucoma.

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