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Review

Understanding Factors Contributing to Glaucoma in Populations of African Descent

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Abstract: Glaucoma is the leading cause of irreversible blindness globally, with the commonest subtype being primary open angle glaucoma (POAG). POAG is characterised by an increase in intraocular pressure (IOP), optic nerve damage and irreversible visual field loss. People of African descent (AD) are significantly more susceptible to POAG when compared to people of European descent (ED), and the reasons for this are complex and multifaceted. The vast level of genetic diversity in AD populations has allowed, through genome-wide association studies (GWAS), for the identification of several single nucleotide polymorphisms (SNPs) as well as differences in mitochondrial haplogroups, which could explain the pathophysiology underlying the increased susceptibility of AD populations to POAG. The altered expression of genes such as MYOC as well as the expression of inflammatory mediators influencing reactive astrocytes have also been implicated. There are also several differences in morphology between AD and ED eyes which must be considered, including differences in central corneal thickness (CCT) and corneal hysteresis (CH) as well as variation in properties of optic discs. The link between all the aforementioned factors and the increased prevalence of POAG in AD populations will be explored in this review.

Keywords: glaucoma; African descent; corneal thickness; oxidative stress; reactive-astrocytes; myocilin; filtration surgery

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1. Introduction

Glaucoma is a group of optic neuropathies involving the degeneration of retinal ganglion cells (RGC) with loss of the retinal nerve fibre layer (RNFL) and is the second leading cause of blindness worldwide. The most common type of glaucoma is primary open angle glaucoma (POAG), which affects an estimated 57.5 million people worldwide [1]. Raised intraocular pressure (IOP) is the most important modifiable risk factor for RGC loss [2], and lowering IOP has been proven to slow down or arrest the progression of glaucoma [3].

Previously conducted population-based studies reveal that glaucoma is six times as prevalent in populations of African descent (AD) compared to those of European descent (ED) and is also six times more likely to result in blindness in AD populations compared to ED [4]. The prevalence of POAG worldwide is projected to reach up to 79.8 million by 2040, an estimated 51.4% increase since 2020, which is largely attributed to Asian and African individuals [5]. Developing a better understanding of the underlying pathophysiological mechanisms resulting in the increased susceptibility of AD populations will facilitate the development of appropriate interventions to mitigate the risk of visual loss.

This review will highlight the current state of knowledge in relation to the pathological mechanisms underlying the increased susceptibility of AD populations to glaucoma, the higher propensity of blindness and the florid scarring reaction to surgical intervention. This includes exploring racial variation relating to genetic differences, such as specific mutations or varying levels of expression of particular genes, as well as the significance of mitochondria and the effect that oxidative stress responses may have on the development of POAG in AD individuals. The impact of various morphological differences in the cells and tissues surrounding the eyes of AD individuals will also be discussed with regards to their relevance to the pathogenesis of glaucoma.

2. Cellular Pathophysiology

2.1. Myocilin Mutations Within the Trabecular Meshwork Are More Prevalent in African Populations Compared to European Populations

The myocilin (MYOC) gene encodes for the protein myocilin, which is expressed in the sclera, choroid, cornea and trabecular meshwork (TM) [6–8]. Mutated variants of MYOC cannot be properly secreted from TM cells into aqueous humour [9], which can thus lead to the intracellular build-up of myocilin, subsequently blocking the flow of aqueous humour in the TM. This can therefore lead to increased IOP and consequent optic nerve damage (Figure 1) [10]. It has been established that MYOC mutations follow a mendelian pattern of inheritance in several populations of varying ethnic backgrounds [11–14]; however, whether these mutations are more likely to occur in AD populations is not completely clear. Some studies suggest that MYOC mutations are more prevalent in individuals of AD ancestry compared to ED [15], whilst other studies show a lower incidence of MYOC mutations in other AD population samples [16]. Though more data is required to develop firm conclusions regarding the relevance of MYOC mutations in increasing the predisposition of AD populations to glaucoma, it should be noted that these mutations only make up a minor percentage of POAG cases, ranging between 2% to 4% as demonstrated by several prevalence studies conducted in populations worldwide [17,18].

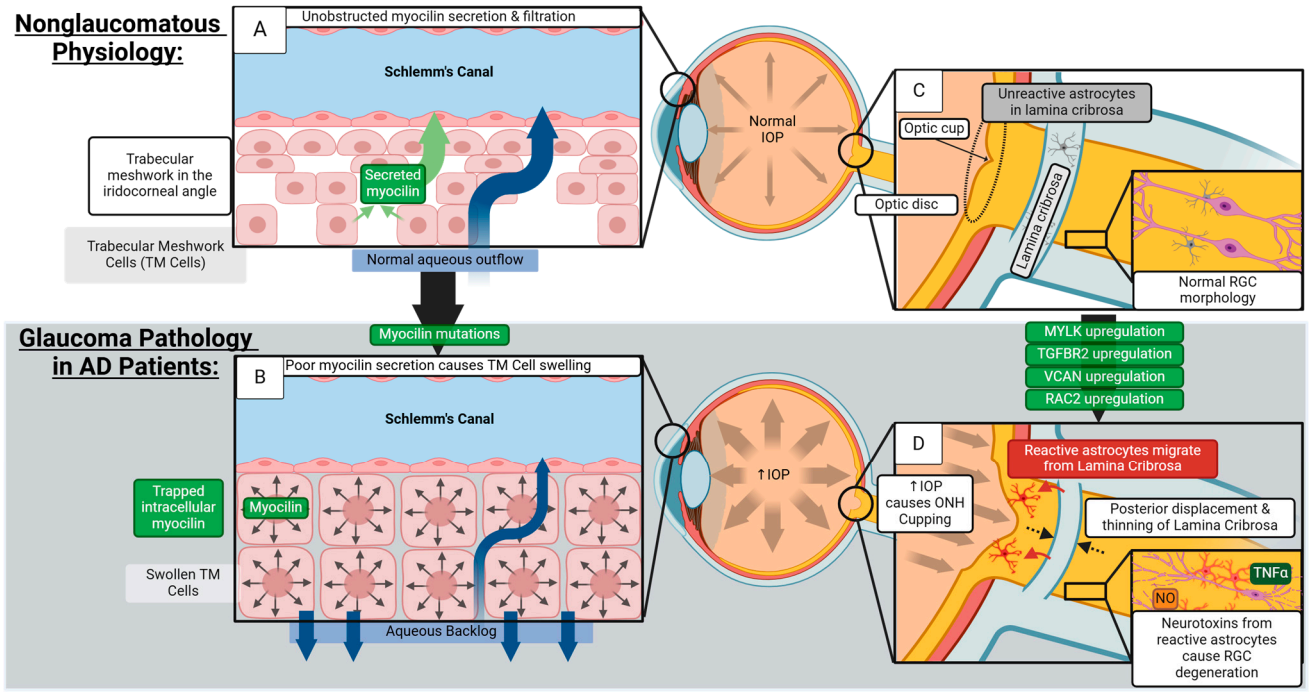

Figure 1. Comparing cellular morphology and pathological features between healthy and glaucomatous eyes in patients of African Descent (AD). (**A**) Cellular morphology of a non-glaucomatous

eye demonstrating normal myocilin secretion and filtration. Aqueous humour flows unobstructed into Schlemm's canal through the healthy TM cells. (**B**) Cellular morphology of the trabecular meshwork in a glaucoma patient of AD. The intracellular accumulation of myocilin leads to TM cell swelling, obstructing aqueous outflow, resulting in increased IOP. (**C**) ONH in a healthy patient showing unreactive astrocytes in the lamina cribrosa and normal RGC morphology. (**D**) ONH in a glaucomatous patient of AD. Increased IOP causes the cupping of the optic nerve head. Reactive astrocytes migrate from the lamina cribrosa to the ONH and release neurotoxins such as nitric oxide (NO) and TNF-α, leading to RGC degeneration. Figure produced on biorender.com (accessed on 20 May 2024).

2.2. Higher Rates of Reactive Astrocyte-Mediated Optic Nerve Head (ONH) Degeneration Are Found in African Populations Compared to European Populations

Upon an examination of the data, glaucomatous ONH astrocytes have been found to be similar to reactive astrocytes in the central nervous system [19]. The migration of reactive astrocytes is a key part of ONH remodelling in glaucoma [20,21], as reactive astrocytes migrate from the lamina cribrosa into nerve bundles [22,23] and synthesise neurotoxic mediators such as nitric oxide and tumour necrosis factor (TNF)α near axons, which can lead to neuronal damage [24,25]. In vitro studies show that human ONH astrocytes respond to elevated pressure with increased migration, which may be related to axonal damage in glaucoma-related optic neuropathy [26]. AD patients with glaucoma displayed a significantly faster rate of reactive astrocyte migration compared to ED glaucoma patients (Figure 1). Findings from cultured glaucomatous ONH astrocytes attribute this difference in their rate of migration to modified gene expression that favours cell motility, migration and the downregulation of cell adhesion, which can contribute to neural degeneration. Several genes including myosin light chain kinase (MYLK), transforming growth factor-β receptor 2 (TGFBR2), versican (VCAN) and rho-family GTPase-2 (RAC2) were identified as being upregulated, causing the aforementioned altered cellular functions (Figure 1) [19]. MYLK upregulation points towards an increased responsiveness of the myosin regulatory system towards activation by second messenger signalling systems such as Ca^{2+} [27]. Likewise, the differing expression of RAC2 suggests that other Rho family signalling networks are altered in AD glaucoma patients' astrocytes. Therefore, it is possible that myosin-regulated motility is prone to activation by signals from Ca^{2+}, rho GTPase and growth factors coupled to the activation of phosphotinides [19]. PIK3R1, part of the phosphotinide pathway, is upregulated in AD glaucomatous astrocytes [28], which is relevant as the pathway mediates astrocytes' response to increased hydrostatic pressure [26]. Actin-dependent astrocyte migration is associated with networks involving the Rho GTPase signalling pathway [19]. Rho activity was demonstrated to be increased in astrocytes exposed to elevated hydrostatic pressure, contributing to the increased rate of astrocyte migration in Acute Angle Glaucoma (AAG) [29]. RAC2, among other TGFβ signalling proteins such as TGFBR2, and the downstream signalling protein SMAD3 are upregulated in AAG astrocytes, suggesting a link between glaucomatous pathology and an increased responsiveness of this signalling pathway [19]. SMAD3 was also upregulated in ONH astrocytes exposed to hydrostatic pressure, indicating that pressure activates the TGFβ pathway [29]. TGFβ regulates cell motility through the expression of extracellular matrix (ECM) proteins as well as the regulation of cell polarity, which can contribute to controlling polarised cell migration and actin remodelling [30], thus explaining why AD individuals may have a greater susceptibility to increases in IOP leading to glaucoma.

3. Oxidative Stress Within the TM Is Increased in African Populations Compared to European Populations

Oxidative stress is a significant factor in the pathogenesis of glaucoma, especially in individuals of AD. Mitochondria provide ATP for cellular functions, a process which also requires an appropriate oxygen supply in order to sustain cells, tissues and organs. The process of oxidation of fats and carbohydrates involves the removal of electrons and H^+

ions, which are passed through the electron transport chain (ETC), after which electrons are transferred to molecular O_2. 1–2% of O_2 undergoes incomplete reduction by mitochondria, generating reactive oxygen species (ROS) such as superoxide and hydrogen peroxide (H_2O_2) [31], which are highly unstable molecules. ROS endogenously formed from the mitochondrial respiratory chain can induce cell and tissue damage [31] and have been implicated in several ophthalmic diseases including glaucoma [32,33]. This imbalance of ROS is referred to as oxidative stress [34]. There are 11 known sites in the ETC which act as sources of H_2O_2 or superoxide or both [31]. On examination of the 11 sites of electron leakage in the ETC, the flavin mononucleotide group, iron–sulphur clusters and Coenzyme Q binding sites in complex I and complex III have all been shown to play a noteworthy role in ROS production [35,36]. Higher complex I activity was detected in the TM cells of AD populations. Other reports show that TM cells transfected with L mitochondrial haplogroup, which is associated with African origin, showed a significantly increased expression of five mitochondrial DNA-encoded mitochondrial complex I subunits, including NADH dehydrogenase subunits 1–3 and NADH dehydrogenase subunits 5 and 6 [37]. Overall, this points towards a trend of elevated complex I activity, which could, in part, explain the higher ATP levels and elevated ROS production in the TM cells of AD populations [37]. Increased activity at complex III, which is another common site of electron leakage, may also be increased in TM tissue from AD compared to ED populations, although more research is needed to establish this. The summative effect of elevated complex I activity and complex III activity and higher mitochondrial content in TM cells from AD may lead to increased ATP production, resulting in higher ROS levels [37]. Oxidative stress markers have been associated with a high risk for POAG, and antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase have been found to be significantly increased in POAG patients [31]. Oxidative stress has been suggested to be a factor leading to the degeneration of TM cells in glaucoma patients. This is supported by research showing that primary human umbilical vein endothelial cells from healthy AD population donors had higher levels of intracellular ATP levels than ED population donors. Elevated ATP levels imply enhanced oxidative phosphorylation in TM cells from AD people compared to TM from ED people, which would therefore generate additional mitochondrial-associated ROS through the process of ATP production [38]. This is in concordance with the finding that a higher PO_2 environment is a source of oxidative stress and damage to porcine TM cells [39]. There has also been evidence for oxidative damage and reduced resistance to oxidative stress in the outflow pathway leading to RGC degeneration. With regards to the increased susceptibility of AD individuals to oxidative stress [40], it is thought that it may be linked to a higher molecular oxygen level in the anterior chamber in AD eyes compared to ED eyes [41]. There was a correlation discovered between PO_2 in the anterior chamber angle and thinner central corneas, which is a known risk factor for POAG that AD individuals tend to possess [42]. The greater oxygen concentration in the aqueous humour may be a source of ROS, depleting antioxidant defences [43]; however, its contribution to the risk of developing glaucoma requires further elucidation. Interestingly, oxidative damage to the DNA of TM cells is also greater in glaucoma patients and correlates with IOP levels and visual field loss [44]. Oxidative DNA damage can be represented by elevated levels of urinary and plasma 8-hydroxy-2′-deoxyguanosine (8-OHdG) [45–47], and a study found higher levels of 8-OHdG in the aqueous humour of AD patients with severe-stage POAG compared to ED patients [48]. Additionally, it has been hypothesised that progressive RGC death in glaucoma involves a non-apoptotic programmed cell death known as paraptosis which may be accompanied by apoptosis or autophagy in the latter stages. Paraptosis in glaucomatous RGCs may be triggered by damaged cellular mitochondria [49], and it has also been demonstrated that oxidative stress can induce autophagy in response to noxious stimuli in RGCs [50].

4. Genetic Differences That Increase POAG Susceptibility

African populations are known to be amongst the most genetically diverse populations, possessing more haplotypes and weaker linkage disequilibrium compared to other populations [51–54]. There is also a greater degree of admixing found in populations with African heritage [55], so much so that the modern AD population has an average of 20% European ancestry, though proportions may significantly vary between individuals [56]. Several studies have proposed genetic ancestry to be a potential risk factor for AD populations' increased susceptibility to POAG.

Genome-wide association studies (GWAS) have presented promising evidence in favour of the impact of genetics on the pathogenesis of glaucoma. The first POAG GWAS of AD populations was carried out in 2018, confirming the presence of POAG loci previously found in ED populations: CDKN2B-AS1, TMCO1 and TXNRD2 [57]. There was also an SNP (rs141186647) at the novel locus EX04. Analysis of the gene CDKN2B-AS1, which is associated with cardiovascular disease [58–61] but has also demonstrated strong pleiotropy with other conditions including glaucoma [62–65], revealed an association between single nucleotide polymorphism (SNP) rs10120688 and POAG. An association between CDKN2B-AS1 SNP rs10965245 and 1/SIX6 SNP rs11849906 and high-tension glaucoma was also established [10]. Retrespo et al. attempted to further clarify the relationship between POAG in African populations and genetic factors (Table 1) [66]. Despite not finding a direct association with POAG at the CDKN2B-AS1 locus using SNP analysis, evidence suggests that the percentage of African ancestry in an AD cohort correlates with POAG at the CDKN2B-AS1 locus [66]. Another GWAS conducted on POAG patients of African ancestry revealed that "APBB2 rs59892895T > C" was associated with POAG (Table 1) [67]. Notably, this SNP was primarily present in AD populations, with a frequency of <0.1% in European or Asian populations [67]. The African Descent and Glaucoma Evaluation Study (ADAGES), specifically ADAGES III, attempted to outline the specific underlying genetics behind POAG through comparing AD and ED POAG populations, identifying the novel locus EN04, which was associated with POAG in AD populations [68].

Table 1. Summary of relevant loci and SNPs.

Gene Loci	SNP	Study
CDKN2B-AS1	rs10120688	Retrespo et al. [66]
	rs10965245	Retrespo et al. [66]
1/SIX6	rs11849906	Retrespo et al. [66]
TMCO1		
TXNRD2		
EX04	rs141186647	Bonnemaijer et al. [57]
APBB2	rs59892895T	Hauser et al. [67]
EN04		
ROCK1p1	rs34957764	Verma et al. [69]
DBF4P2	rs1666698	Verma et al. [69]
ARHGEF12	rs4938802	Springelkamp et al. [70]
	rs11824032	Springelkamp et al. [70]

Furthermore, a GWAS of African ancestry populations identified 46 genome-wide significant risk loci whereby three loci were implicated in POAG pathogenesis (Table 1) [69]. Two loci mapped to the Rho Associated Coiled-Coil Containing Protein Kinase 1 Pseudogene (ROCK1p1) and DBF4 Pseudogene 2 (DBF4P2) genes, and one to the Rho Guanine Nucleotide Exchange Factor 12 (ARHGEF12) gene. The previously undiscovered variant rs34957764 mapped to the ROCK1P1 gene region. This is a pseudogene that is responsible for cellular processes including growth, proliferation and apoptosis. The rs1666698 variant mapped to the DBF4P2 gene. The minor allele frequency (MAF) score for variant rs34957764 was found to be 0.25 in AD individuals compared to 0.12 in ED individuals, whereas for rs1666698 the MAF for AD populations was 0.4 compared to 0.02 in ED populations, showing a significant difference [69]. Whilst the exact mechanisms explaining the impact of

these SNPs are not clear, the MAF data highlight potential avenues for further research to understand the association between these disparities and POAG susceptibility.

Another previously unknown variant, rs4938802, was found alongside the known variant rs11824032, which both map to the gene ARHGEF12. This gene has been known to be associated with raised IOP in ED individuals [70]; however, the locus reported in this study is in a different region from the locus impacting ED individuals. In human TM cells, ARHGEF12 tended to be overexpressed under stressful conditions. A similar trend was observed in induced pluripotent stem cell-RGCs but was not deemed significant. There are trends in the overexpression of both ARHGEF12 and ROCK1P1 in retinal tissue from POAG patients, but they did not reach statistical difference when compared to controls. It has been suggested that this could be partially due to the process of retinal biopsy obscuring the expression of genes in the RGC layer. A novel association was identified between rs11824032 and cup to disc ratio, although the influence of other unknown factors was acknowledged [69]. A proposed mechanism for this association involves ARHGEF12 activating RhoA leading to ROCK activation, which causes a reduction in the outflow of aqueous humour and Schlemm canal cell permeability [71], which leads to an increased IOP, which contributes to an increased cup to disc ratio in individuals of AD.

Though GWAS studies based on previously neglected African populations are being conducted more frequently than before, it is apparent that more GWAS studies with larger population samples would be beneficial to improving understanding of the role of genetics in the pathogenesis of glaucoma in AD populations. There is also evidence to suggest family history plays a significant role in predicting the development of POAG in AD populations. The Primary Open-Angle African American Glaucoma Genetics (POAAGG) study is the largest case-control GWAS of AD patients with POAG to date [72]. Studies focused on the POAAGG cohort revealed that individuals with a positive family history of POAG tended to be younger than those without it, indicating that a positive family history could result in an earlier onset of POAG [73]. Maximum IOP was also found to be higher in cases with positive family history alongside higher rates of past glaucoma surgery. The proposed explanation was that younger patients with higher IOP may have been considered for surgical intervention more readily, therefore indicating a higher level of severity of POAG in those individuals with a positive family history [73].

Mitochondrial haplogroups of AD populations with POAG, when compared to controls, displayed novel findings with regards to susceptibility to POAG. A study identified 13 major haplotypes within an AD population, which were all represented in the POAAGG cohort. In cases of POAG, there were higher proportions of L1c and L2 haplogroups relative to controls. Additionally, MT-RNR2, which encodes mitochondrial ribosomal 16s RNA gene, harboured two variants at position m.2220: an L1c2b1a'b-associated A > G transition and a L4b2b1-associated A > T transversion [74]. m.2220A > G was approximately four times more common than m.2220A > T, meaning that the affiliation between m.2220 and POAG primarily originated from L1c2b1 haplogroups as opposed to L4b2b1 [74]. Further comparisons of mitochondrial haplogroups from individuals of ED (haplogroup "H") compared to those of AD (haplogroup "L") suggest a difference in functional effects because of variations in mitochondrial DNA. Experiments on cybrids (cell lines with identical nuclei but mitochondria from different individuals, expressing either H or L mtDNA) demonstrate varying expression in respiratory genes and ATP turnover rates and differences in the expression of inflammation-related signalling genes [75]. While these heritable variants are not enough to significantly impair normal neurological function, it has been proposed that they may increase the rate of somatic mtDNA mutations, limiting mitochondrial energy production. Tissues with relatively higher energy demands such as RGCs would therefore be more adversely affected, resulting in individuals possessing these variants being more sensitive to elevated IOP [74].

5. Morphological Differences That Increase POAG Susceptibility

Several morphological differences between the cells and tissues that form or interact with the eye have been hypothesised to be responsible for the increased prevalence of POAG in individuals of AD. Greater African ancestry has been associated with thinner central corneal thickness (CCT) [76], and it is commonly understood that AD patients have a thinner CCT than ED patients in cases of healthy individuals [77,78]. A study comparing sub-Saharan and European populations found that IOP was 5–7 mmHg higher and CCT was more than 20 µm thinner in the sub-Saharan group [79]. There appears to be a lack of consensus in the literature as to whether thinner CCT by itself is a predictive factor for the development of POAG [80–82]. There are some reports of thinner CCT leading to the underestimation of IOP as a result of the Goldman applanation tonometry techniques assuming little variation in CCT thickness between individuals [76], therefore leading to the undertreatment of the disease [78]. Several correlations between CCT and previously mentioned structures have also been identified. An inverse correlation was found between CCT and PO_2 in the anterior chamber angle, supporting the theory of more oxidative damage occurring due to more trabecular O_2 exposure as a consequence of the thinner CCT [42]. A thinner CCT was also linked to a smaller rim area and greater cup to disc ratio in subjects with POAG [83], whereas some population-based studies refute any association of CCT with optic disc parameters [84]. There have also been proposed associations between a thin CCT and thin lamina, whereby a thin lamina is less rigid than a thicker one and so is more susceptible to displacement by IOP fluctuations [85]. Some studies demonstrate that lamina cribrosa displacement was greater in patients with thinner CCT [86]; however, others have found no relationship between CCT and the lamina cribrosa [87,88], so it is evident that further research is required in order to establish conclusions regarding the relevance of CCT to glaucoma.

An alternative property of the cornea that has been investigated is corneal hysteresis (CH), which has been established as a potential risk factor for glaucoma which is independent of corneal thickness [89]. CH determines the viscoelastic properties of the cornea and was found to be lower in healthy Africans compared to healthy Caucasians [90] and consequently could lead to the underestimation of IOP [91,92]. Lower CH also leads to a higher risk of visual field progression [93] and optic nerve damage [94]. It has also been observed in a study by Leite et al. [95] that optic disc compliance is associated with CH not CCT, so it is possible that CH is related to changes in mean optic disc depth, as it is representative of properties of the rest of the structures of the eye rather than just the cornea. In this study, a relationship between optic nerve surface compliance and hysteresis was only present in glaucoma patients, indicating the presence of discrepancies in ocular tissue biomechanics in glaucoma patients [96]. There is growing evidence to suggest that low CH is a more effective predictor for progression than thin CCT; however, it is more accurate to consider it a strong association rather than a confirmed risk factor [97]. There is also some contention in the literature as to the degree of independence of CH from CCT in the context of African ancestry populations, as Leite et al. argue that the lower CH measurements can be attributed to differences in corneal thickness in AD individuals compared to ED individuals, therefore making it unlikely that CH would have an independent role in the varying susceptibility to glaucoma between racial groups [95].

An evaluation of findings from optic disc photography carried out as part of the Baltimore Eye Survey showed that the mean optic disc area was 12% larger in AD individuals compared to ED individuals [98]. Therefore, there was a decrease in rim/disc area, suggesting a decrease in rim thickness and nerve fibres relative to disc size [98]. This is relevant because there is evidence indicating optic disc area can impact the diagnostic precision of the confocal scanning laser ophthalmoscope (cSLO) leading to more patients being incorrectly identified as glaucomatous who, in actuality, had larger optic nerves [99]. Little is known about the effect that the anatomy of the optic disc has on the pathogenesis of glaucoma, but the preliminary computational modelling of the lamina cribrosa and posterior sclera indicates that laminar connective tissue is prone to experiencing greater

IOP-related stress and more IOP-induced deformation in eyes with a larger optic disc area [100]. Therefore, the larger optic nerve generally found in AD individuals would make them more susceptible to greater strain at similar levels of IOP [101]. A larger optic nerve has a larger scleral canal and hence has larger optic cups for the same rim volume and number of retinal nerve fibres. This greater cup depth has been consequently linked to a thinner lamina cribrosa or a more posterior insertion of the lamina within the scleral wall [102]. Few histological studies have been carried out to examine morphological differences in the lamina cribrosa and ONH of AD individuals compared to ED individuals, though current histological data confirm a larger and more oval optic disc in cohorts of AD [103]. There have also been differences found in the RNFL, primarily that a thinner RNFL is present in the papillomacular bundle in populations of AD as well as a thinner inner macula [104], implying differences in the number of retinal nerve fibres in that region amongst individuals of AD [105]. RNFL loss was found to occur at a faster rate in AD cohorts compared to ED cohorts at almost three times the standard age-related rate of change [106].

It has been suggested that black populations exhibit a greater degree of TM pigmentation when compared to Caucasians [107], which could explain their greater likelihood of developing pigment dispersion syndrome which progresses to pigmentary glaucoma (PG) [108]. Pigment dispersion decreases phagocytosis and migration in trabecular cells and increases actin stress fibre formation. Sustained deposition leads to trabecular cell overload and thus TM cell structural dysfunction [109]. Although the degree of pigmentation is not directly associated with developing PG, it is a risk factor for PG severity [110]. It still remains to be investigated whether greater pigmentation contributes to PDS–PG conversion as well as the role racial factors have to play.

Previous studies show an association between retrobulbar blood flow and glaucomatous disease. Siesky et al. reported that AD POAG patients had a significantly lower retrobulbar blood flow compared to ED patients despite both groups demonstrating similar IOP levels, indicating the contribution of reduced ocular circulation to disease progression in AD patients [111]. Additionally, there is a higher incidence of systemic vascular diseases such as hypertension, stroke and cardiovascular disease in AD populations which are associated with an increased susceptibility to POAG [112]. However, the precise relationship between systemic vascular health, ocular vascular health and POAG development is not clearly defined and should be considered a target for future investigation [112].

6. The Role of the Lens

The increasing size of the lens due to cataract or ageing is an important pathophysiological factor in glaucoma. With an increasing lens volume, the trabecular outflow pathway is impacted. An increase in the lens volume also results in increase contact between the lens zonules and the posterior pigment epithelium of the iris. This can increase pigment release, which can further obstruct outflow pathways. Lens extraction has a powerful effect on IOP lowering in both angle closure and open angle glaucoma [113].

There are differences in the lens morphology in patients of AD and Caucasians. In normal populations the mean lens thickness is thinner in AD populations compared to Caucasian; this may explain the fact that AD populations have a lower incidence of acute primary angle closure [114]. In AD patients who develop angle closure, the lens is thicker but still less so compared to Caucasian populations. It has been shown that the PTPRM locus harbours genetic polymorphisms that may contribute to an increased lens thickness resulting in narrower angles [115]. This study was performed in a predominantly Indian population; therefore, further work is required in other cohorts to ascertain the role of this locus in the pathophysiology of angle closure glaucoma. Early cataract surgery followed by use of the Hydrus stent has proven to be a promising alternative option for sustainably lowering IOP in AD glaucoma patients, as Laroche et al. reported a 4.2% decrease in IOP in a black and Afro-Latino patient sample with 82.8% of patients being medication-free after 1 year with no additional surgeries required and minimal complications [116].

7. Filtration Surgery Failure Rates Are Increased in Patients from African Populations

Morphological differences also impact scarring in individuals with African ancestry, particularly in the aftermath of trabeculectomy procedures. AD patients' eyes have been proven to display more episcleral scarring compared to ED patients in instances of failed filtration surgeries [117]. This process of excessive wound healing response is thought to be responsible for the increased risk of failure in AD patients [118]. A study examining the differences in the cellular profile of AD and ED skin tissues reported that AD skin contained more fibroblasts, macrophages and multinucleated giant cells [119]. Additionally, another study corroborated these findings, specifically examining the conjunctiva of AD patients to reveal that they contained more macrophages and fibroblasts [120]. Notably, macrophages and fibroblasts were extensively present in the eyes of patients who underwent failed filtration surgery [120], demonstrating a relationship between these pro-inflammatory cells and the risk of filtration surgery failure, which could explain why populations of AD may experience a higher rate of failure. Though fibroblasts are the primary cells involved in wound healing, macrophages also play a vital role in wound healing. Macrophages remove damaged and exogenous material in early phases of wound healing and are significantly involved in tissue remodelling in later phases of healing [121,122]. Macrophages also release enzymes that mediate tissue degradation, recruit inflammatory cells, produce cytokines and are responsible for the proliferation of fibroblasts and endothelial cells [123–125]. Angiogenic and fibrogenic cytokines are produced by macrophages, such as macrophage and platelet derived growth factors, so the activation of these cells is crucial for normal wound healing [120], but amplified macrophage activity can cause excessive wound healing responsible for the altered scarring response in AD individuals. It has been argued that filtration failure could also be more common in AD patients due to a thicker tenon's capsule [126], whilst some studies argue that the tenon's capsule is of normal thickness but is capable of a greater reaction after surgical trauma [118]. This has caused some debate regarding the benefit of partial tenectomies being performed alongside glaucoma filtration surgeries in AD patients [120], though there are few comparative, case-controlled studies comparing the efficacy of such tenectomies in AD and ED patients undergoing filtration surgeries, so an immediate verdict cannot be reached.

8. Discussion

Glaucoma is fundamentally a multifactorial disease, and it has been established that AD populations are disproportionately affected. A key consideration when approaching the underlying factors involved in the pathogenesis of glaucoma in populations of AD is developing a clear understanding and definition of the phrase "populations of African descent". Many of the studies that were reviewed describe using a form of a self-reported questionnaire in order to appropriately classify the race of the individuals involved; however, self-reports have been found to correlate poorly with true racial origins, leading to potentially skewed results, particularly in the process of linking the genomic assessment of loci to the prediction of outcomes of disease [127]. This effect is most prominent within populations with African ancestry in non-African countries, as was demonstrated by a study in Missouri whereby the mean African ancestry of self-reported AD subjects is only 75–80% [128].

Current research confirms that there are various genetic differences between AD populations and ED populations, as well as altered mitochondrial function and levels of oxidative stress in AD populations. Several pathophysiological and morphological differences such as variation in optic disc parameters and CCT thickness have also been proposed. Together, all of these differences could contribute to an increased prevalence of POAG in AD populations. However, much of the current data surrounding morphological variants in AD individuals only highlight potential associations between differences in properties of the structure of the eye and increased susceptibility to POAG.

As regards the failure of filtration surgery, there is some useful information around tissue structure; however, information is lacking as to differences at a cellular and molecular level which may underpin the clinical observations.

Whilst this review discusses factors contributing to the increased prevalence of Glaucoma in populations of AD primarily from a biological perspective, it is vital to develop a holistic understanding of the topic. There is evidence to suggest social determinants of health could be a significant factor in the observed disparities. A US study found screening for glaucoma to be correlated with several markers of poverty, such as living in a deprived neighbourhood and the lack of ownership of a personal vehicle as well as identifying as black. Black participants without a personal vehicle had a greater likelihood of screening for glaucoma than white participants with a personal vehicle but not greater than white participants without a personal vehicle [129]. There are also observable wealth disparities, as the average white household in the US was found to be worth $171,000 compared to the average black household at $17,000 [130], consequently resulting in black populations having potentially restricted access to healthcare services, healthcare education and screening programs, contributing to the increased disease burden that AD populations face. There is evidence to support the link between glaucoma and low socioeconomic status, with several studies finding that low socioeconomic status is a risk factor for presentation with advanced glaucoma [131–133]. The interactions between race, socioeconomic background and disease incidence represent a complex, multifactorial issue which requires further investigation.

9. Conclusions

The exact pathophysiological mechanisms which increase risk, severity and response to surgery in populations of AD are not clearly understood. Furthermore, there are many gaps within the current understanding of the pathophysiological consequences of mutations at several gene loci that correlate with an increased prevalence of POAG in AD populations.

10. Future Directions

Future research should focus on identifying key molecular differences in physiological and pathophysiological tissues taken from black populations. Correlating these biological differences with clinical and genetic parameters will enable us to better understand the pathological processes. This will impact the development of targeted therapies to reduce blindness in these unfortunate individuals.

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