Drusen Classification and Quantification in Eye Bank Eyes of Cataract Patients previously implanted with Intraocular Lenses with or without Blue-Light Filtration

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Abstract

Purpose

Age-related macular degeneration (AMD) is a disease that causes central vision loss and is the leading cause of blindness in the western world. A hallmark of AMD is the presence of large, soft drusen in the macular region of the retina. Drusen are lipoproteinaceous deposits found between the basal lamina of the retinal pigment epithelium (RPE) and Bruch's membrane. Although the pathogenesis of AMD is unclear, growing evidence suggests a link between drusen formation and photo-oxidative stress caused by short-wavelength blue light (BL). As such, this project aims to investigate the effect of BL-filtering intraocular lenses (IOL) on drusen formation in post-mortem eyes via histopathological analysis.

Methods

193 post-mortem pseudophakic human eyes (100 with a UV-filtering, clear IOL [cIOL] and 93 with a UV+BL-filtering, yellow IOL [yIOL]) were obtained from the Lions Gift of Sight eye bank and examined at the MUHC-McGill Ocular Pathology and Translational Research Laboratory. Clinical data was collected for each eye and included sex, age at the time of cataract surgery (age-at-surgery), age-at-death, time between cataract surgery and death (surgery-to-death time), implanted IOL model, and clinical history (smoking, diabetes, hypertension, glaucoma, cancer, AMD, and cardiovascular disease). Eyes were sectioned on their coronal and sagittal axes, and formalin-fixed, paraffin-embedded macular cross sections were obtained. The sections were then stained with hematoxylin and eosin, and scanned with the Zeiss Axio Scan.Z1 scanner. Drusen were classified by type, size or subtype, and quantity. Statistical analyses were performed using Microsoft Excel (Microsoft Corporation) and OriginPro® 9 (OriginLab Corporation).

Results

Large, soft drusen were present in 49% (n=95) of eyes, while 9% (n=17) had cuticular drusen, 16% (n=30) had hard drusen, and 26% (n=51) had no drusen. There were significantly more cIOL eyes (n=62) with large, soft drusen than yIOL eyes (n=33, $p<0.001$), and significantly more yIOL eyes (n=38) with no drusen than cIOL eyes (n=13, $p<0.0001$). No significant differences in the presence of hard or cuticular drusen were found. yIOL eyes had significantly higher mean age-at-surgery (76.5 vs. 72.2 years, $p<0.001$) and mean age-at-death (82.4 vs. 79.6 years, $p<0.05$) than cIOL eyes, and cIOL eyes had a significantly higher mean surgery-to-death time (6.96 vs. 5.41 years, $p<0.05$) than yIOL eyes. There were also significantly more yIOL eyes with a history of smoking ($p<0.01$) and hypertension ($p<0.05$), and significantly more cIOL eyes with a history of glaucoma ($p<0.05$).

Conclusion

Large, soft drusen were significantly less prevalent in yIOL eyes than in cIOL eyes and significantly more yIOL eyes had an absence of drusen. These findings suggest that yIOLs may prevent the incidence and development of AMD post cataract surgery.

Résumé

But

La dégénérescence maculaire liée à l'âge (DMLA) est une maladie qui engendre la perte de la vision centrale et constitue la cause principale de la cécité dans le monde occidental. Un signe typique de la DMLA est la présence de drusen larges et molles dans la région maculaire de la rétine. Les drusen sont des dépôts lipoprotéinés qui sont situés entre la lame basale de l'épithélium pigmenté rétinien (EPR) et la membrane de Bruch. Bien que la pathogénèse de la DMLA ne soit pas claire, il existe de plus en plus de preuves suggérant un lien entre la formation de drusen et l'exposition à la lumière bleue à courte longueur d'onde (LB). Par conséquent, ce projet vise à étudier l'effet des lentilles intraoculaires (LIO) filtrant la LB sur la formation de drusen dans les yeux post-mortem par une analyse histopathologique.

Méthodes

193 yeux post-mortem, pseudophaques et humains (100 avec une LIO transparente qui filtre la lumière UV [LIOt] et 93 avec une LIO jaune qui filtre la lumière UV et la LB [LIOj]) ont été obtenus de la banque des yeux Lions Gift of Sight et examinés au laboratoire de pathologie oculaire et de recherche translationnelle du CUSM et de l'Université McGill. Des données cliniques ont été recueillies pour chaque œil et comprennent le sexe, l'âge au moment de la chirurgie de cataracte (âge-ch.), l'âge au moment du décès (âge-déc.), le délai entre la chirurgie de cataracte et le décès (délai-ch.-déc.), le modèle de la LIO implantée et les antécédents cliniques (le tabagisme, le diabète, l'hypertension [HTN], le glaucome, le cancer, la DMLA et la maladie cardiovasculaire). Les yeux ont été sectionnés sur leurs axes coronal et sagittal afin d'obtenir des coupes transversales de la macula fixées au formol et embarquées en paraffine (FFEP). Ensuite, les coupes transversales ont été colorées à l'hématoxyline et à l'éosine et

numérisées avec le numériseur Zeiss Axio Scan.Z1. Les drusen ont été classifiées selon leur type, taille et quantité. Les analyses statistiques ont été effectuées en utilisant Microsoft Excel (Microsoft Corporation) et OriginPro® 9 (OriginLab Corporation).

Résultats

49% (n=95) des yeux avaient des drusen larges et molles, 9% (n=17) avaient des drusen cuticulaires, 16% (n=30) avaient des drusen dures et 26% (n=51) n'avaient aucune drusen. Significativement plus d'yeux LIOt (n=62) avaient des drusen larges et molles que les yeux LIOj (n=33, $p<0,001$) et significativement plus des yeux LIOj (n=38) que LIOt (n=13, $p<0,0001$) n'avaient aucune drusen. Aucune différence significative dans la présence des drusen dures ou cuticulaires a été notée. Les yeux LIOj avaient aussi une moyenne d'âge-ch. (76,5 vs. 72,2 ans, $p<0,001$) et une moyenne d'âge-déc. (82,4 vs. 79,6 ans, $p<0,05$) significativement plus élevées que celles des yeux LIOt, et les yeux LIOt avaient une moyenne de délai-ch.-déc. significativement plus élevée que celle des yeux LIOj (6,96 vs. 5,41 ans, $p<0,05$). Il y avait aussi significativement plus d'yeux LIOj avec des antécédents cliniques de tabagisme ($p<0,01$) et d'HTN ($p<0,05$), et significativement plus d'yeux LIOt avec des antécédents cliniques de glaucome ($p<0,05$).

Conclusion

Les drusen larges et molles étaient significativement moins prévalentes dans les yeux LIOj que les yeux LIOt et significativement plus d'yeux LIOj n'avaient aucune drusen. Ces résultats suggèrent que les LIOj pourraient prévenir l'incidence et le développement de la DMLA post-chirurgie de cataracte.

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Contribution of Authors

This Master's thesis is based on my original work and is formatted in accordance with the monograph format outlined in the McGill University Department of Graduate and Postdoctoral Studies thesis preparation guidelines. The entire content of this thesis was prepared and written by the author of this thesis.

List of Figures and Tables

List of Abbreviations

3-OHKG	-	3-Hydroxykynurenine Glucoside
A2E	-	Bis-retinoid N-retinyl-N-retinylidene Ethanolamine
AMD	-	Age-Related Macular Degeneration
AMP	-	Adenosine Monophosphate
AMPK	-	Adenosine Monophosphate-activated Protein Kinase
AREDS	-	Age-Related Eye Disease Study
ATP	-	Adenosine Triphosphate
cIOL	-	Clear Intraocular Lens
FFA	-	Fundus Fluorescein Angiography
H&E	-	Hematoxylin and Eosin
ICG	-	Indocyanine Green
ICGA	-	Indocyanine Green Angiography
IOL	-	Intraocular Lens
OCT	-	Optical Coherence Tomography
mTOR	-	Mammalian Target of Rapamycin
NAD+	-	Nicotinamide Adenine Dinucleotide
PARP	-	Poly (Adenosine Diphosphate-Ribose) Polymerase
PGC-1α	-	Peroxisome Proliferator-Activated Receptor-Gamma Coactivator 1 Alpha
ROS	-	Reactive Oxygen Species
RPE	-	Retinal Pigment Epithelium
SIRT1	-	Sirtuin-1
TAP	-	Treatment of AMD with Photodynamic therapy

UV	-	Ultraviolet Light
VEGF	-	Vascular Endothelial Growth Factor
yIOL	-	Yellow Filter Intraocular Lens

1. Introduction

1.1. Rationale

Current treatment options for patients with atrophic age-related macular degeneration (AMD) focus on lowering the risk of drusen formation in the macular region of the retina. These treatments consist of dietary supplementation with vitamins (A, C, and E), carotenoids (lutein, zeaxanthin, and β-carotene), and minerals (zinc and selenium). The effectiveness of these treatments, however, is contested in the existing literature.

Another factor potentially linked to drusen formation in the retina is exposure to short-wavelength blue light. Although a growing number of studies have found a positive association between blue light and drusen formation, others have not, thus calling into question the value of ultraviolet light and blue light-filtering, yellow intraocular lenses (yIOL) as a treatment option for patients at risk of developing AMD. In order to shed light on this controversy, this research investigated the effect of yIOLs on drusen formation in pseudophakic post-mortem eyes via histopathological analysis. In doing so, this work has the potential to pave the way for better treatment options for patients at risk of developing AMD.

1.2. Objectives

This research aimed to determine if yIOLs lower the risk of drusen formation and AMD progression by comparing AMD risk factors and drusen morphology between post-mortem eyes implanted with ultraviolet (UV) light-filtering, clear intraocular lenses (cIOL) and those implanted with yIOLs.

1.3. Hypothesis

Based on the current literature, I hypothesized that the presence of a yIOL implant in the post-mortem eyes would be associated with decreased drusen formation.

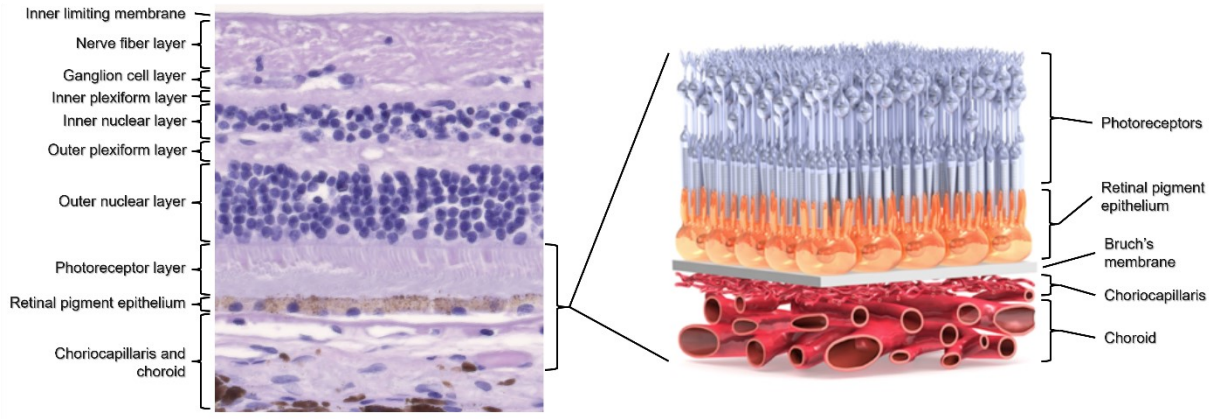
2. Literature Review

2.1. Age-Related Macular Degeneration (AMD)

2.1.1. Defining AMD

AMD is an acquired degeneration of the macular area of the retina and is the leading cause of irreversible blindness in elderly people (over 65 years of age) in the western world, accounting for 8.7% of all cases of blindness and affecting an estimated 200 million people worldwide in 2020 and 288 million people by 2040.[1,2] It is characterized by significant central vision loss due to abnormalities of the photoreceptor layer, retinal pigment epithelium (RPE), Bruch's membrane, and choriocapillaris (Figure 1), which ultimately result in geographic atrophy and/or choroidal neovascularization.[3] Individuals with AMD suffer from a decreased quality of life, as the disease will negatively affect their mobility, facial recognition, and their ability to perform tasks such as shopping, cleaning, meal preparation, and computer usage.[4] Risk factors for AMD include age[5–11], smoking[6,7,11–15], obesity[16–18], hypertension[19–21], cardiovascular disease[22,23], sunlight exposure[24], Caucasian ethnicity[16,25,26], and genetic susceptibility.[27,28]

Figure 1. Structure of the retina with labeled layers.



Left: Histological image of the retinal layers and choroid. Right: Magnification of the retinal layers and choroid; adapted from The Angiogenesis Foundation.[29]

2.1.2. Forms of AMD

There are two clinical forms of AMD: atrophic (dry) and exudative (wet). Atrophic or dry AMD is characterized by the age-dependent accumulation of drusen deposits between the RPE basement membrane and Bruch's membrane, and lipofuscin (lipid-containing residues of lysosomal digestion) within RPE cells, resulting in geographic atrophy of photoreceptors and RPE cells.[3,30,31] Drusen are yellow, lipoproteinaceous residues that can form either between the RPE and its basement membrane (basal laminar deposits) or within the inner collagenous aspect of Bruch's membrane (basal linear deposits). They can be hard, cuticular, or soft. Hard drusen are small in size (<63 μm in diameter), clearly demarcated, and common with aging.[30] Cuticular drusen are also small in size (25-75 μm in diameter) but are more numerous than hard drusen and often aggregate.[30] Soft drusen are medium (63-125 μm in diameter) to large (>125 μm in diameter) in size, placoid or dome shaped, poorly demarcated, and pathognomonic for AMD, being associated with progression towards late stage AMD and geographic atrophy of the retina.[6,12,30,32] Soft drusen may also merge into larger drusen which may lead to drusenoid RPE detachments.[33] As for lipofuscin, it is a pigmented byproduct of lysosomal digestion that, when in overabundance, can lead to cellular instability through its inhibition of RPE cell phagocytosis and sensitization of lysosomes to the visible light spectrum.[34,35] Atrophic AMD can progress to exudative AMD as roughly 10% of patients with atrophic AMD will develop choroidal neovascularization and, among them, 79-90% will become legally blind due to associated complications.[36]

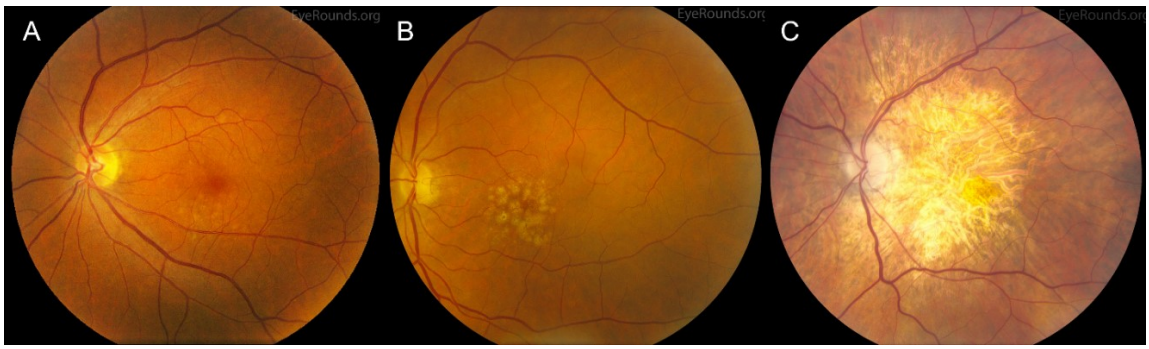
Wet or exudative AMD is characterized by the presence of choroidal neovascularization, where newly formed blood vessels from the choroid invade through Bruch's membrane and proliferate either between Bruch's membrane and the RPE or in the subretinal space.[37] These

newly formed blood vessels are also called choroidal neovascular membranes. On examination, patients with exudative AMD will often have decreased visual acuity and will report visual distortion or blurring of their central vision, while other patients may also report metamorphopsia, micropsia, or scotoma, and some patients may report vague complaints or no symptoms.[38] On dilated funduscopic examination, there may be presence of blood, lipid, or subretinal fluid, subretinal hemorrhage with central vision loss, vitreous hemorrhage with peripheral vision loss, RPE tears, and RPE detachment.[39] This form of AMD, although less common than its dry counterpart (10-15% vs. 85-90% of cases, respectively)[40], accounts for roughly 90% of severe vision loss associated with AMD.[41]

2.1.3. Stages of AMD Progression

Four stages of dry AMD progression have been defined based on the presence of drusen, geographic atrophy, and choroidal neovascularization. Stage 1 (no AMD/normal aging) is characterized by the presence of no drusen or 5-15 small drusen (<63 μm in diameter) with no other retinal abnormalities.[42] Stage 2 (early AMD) is characterized by the presence of more than 15 small drusen, less than 20 medium-sized soft drusen (63-124 μm in diameter), or less than 20 areas of pigment abnormalities in the macula.[42] Stage 3 (intermediate AMD) is characterized by the presence of either more than 20 medium-sized soft drusen, at least one large soft drusen (>125 μm in diameter), or non-central geographic atrophy (not involving the fovea).[42] Finally, stage 4 (advanced AMD) is defined by the presence of central geographic atrophy (involving the fovea) or choroidal neovascularization (Figure 2).[42]

Figure 2. Fundoscopic photos of patient retinas showing different stages of AMD progression.



(**A**) Early atrophic AMD with small drusen. (**B**) Intermediate atrophic AMD with poorly demarcated medium-sized drusen. (**C**) Advanced atrophic AMD with areas of geographic atrophy with involvement of the fovea. Adapted from Scruggs et al.[43]

2.1.4. Diagnostic Evaluation of AMD

Clinical diagnosis of AMD is performed via an assessment of patient clinical history and through the use of imaging techniques such as fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT). Symptoms reported by patients that may be indicative of AMD include acute or insidious vision loss in one or both eyes, blurred vision, distorted near vision, scotoma (blind spot in vision), and visual distortions such as metamorphopsia and micropsia in one or both eyes.

FFA is an invasive imaging technique where sodium fluorescein, a fluorescent dye with an activation peak between 465-490 nm and an excitation peak between 520-530 nm, is injected intravenously in order to cause the blood vessels of the retinal and choroidal circulations to fluoresce and to facilitate their assessment.[44] A fundus camera equipped with a cobalt blue excitation filter (transmits light between 465-490 nm) and a barrier filter (transmits light between 520-530 nm) is used to capture the fluorescence images. Since the retinal vascular endothelium and RPE prevent diffusion of the dye, the resulting fluorescent light emissions allow for

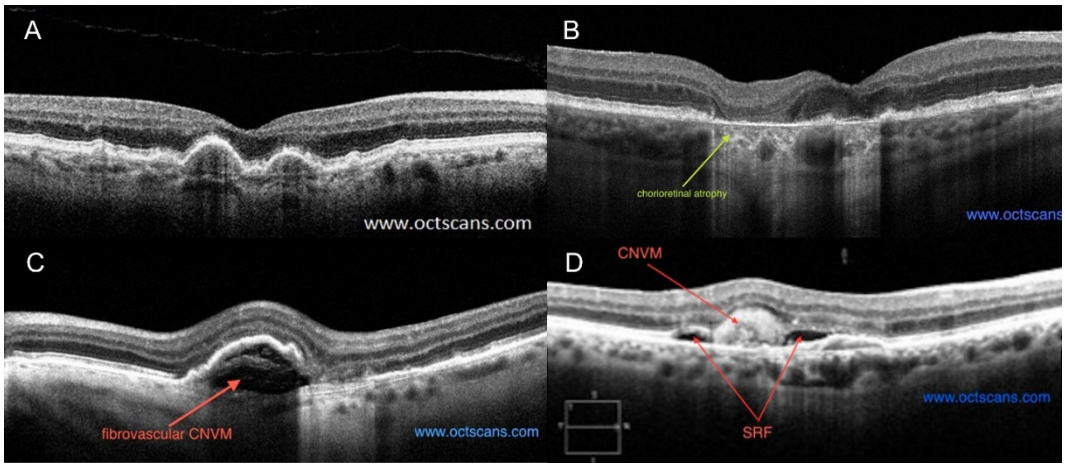
assessment of the retinal vasculature.[45] However, due to the choriocapillaris allowing fluorescein to diffuse freely under the RPE and fluorescein's poor transmittance through the RPE, assessment of the choroidal vasculature with FFA is suboptimal, although it can still be useful to detect choroidal neovascular membranes.[46]

ICGA is a similarly invasive imaging technique that relies on a fundus camera with excitation and barrier filters to capture the emitted fluorescence of intravenously injected indocyanine green (ICG), a dye with an absorption peak at 790-805 nm and an emission peak at 835 nm.[47] Compared to FFA, ICGA is better for assessing the choroidal vasculature due to the higher wavelengths of ICG's absorption and emission spectra (compared to those of fluorescein), which allow for better penetration through the RPE, and because 98% of serum ICG is protein-bound, thereby limiting its diffusion from the choriocapillaris.[48,49] These differences avoid the blurring of the choroidal anatomy seen with FFA, resulting in much clearer fundoscopic images.

Opposite to FFA and ICGA, OCT is a non-invasive imaging technique that uses low-coherence interferometry to produce high-resolution cross-sectional images of the retinal layers.[50] In the case of atrophic AMD, this technique allows for more precise measuring of drusen area and volume underneath the retina, as well as a better assessment of areas of geographic atrophy by noting the absence of the inner and outer segments of the photoreceptor layer, the RPE and Bruch's membrane complex, and the retina's external limiting membrane (Figure 3A-B).[51] For cases of exudative AMD, retinal OCT can be used to define the type of choroidal neovascular membrane involved based on whether it is located below (type 1) or above (type 2) the RPE and to differentiate between the different types of RPE detachment (serous, fibrovascular, drusenoid, and hemorrhagic) (Figure 3C-D).[52] Other prognostic markers for

exudative AMD defined via OCT include outer retinal tubulations (round structures within the outer retina with hyperreflective borders and hyporeflective lumina) and hyperreflective dots.[53,54]

Figure 3. OCT images of patient retinas with atrophic or exudative AMD.



(**A**) Atrophic AMD with large drusen. (**B**) Atrophic AMD with subfoveal atrophy of the retina and choroid. (**C**) Exudative AMD with a fibrovascular RPE detachment secondary to a sub-RPE type 1 choroidal neovascular membrane. (**D**) Exudative AMD with a type 2 choroidal neovascular membrane above the RPE with adjacent subretinal fluid. OCT scans adapted from Vien.[55] Abbreviations: CNVM, choroidal neovascular membrane; SRF, subretinal fluid.

2.1.5. Treatment Options for AMD

Treatment for AMD depends on the progression of the disease and whether the patient is suffering from the atrophic or exudative form. Across all forms of the disease, however, elimination of modifiable risk factors is paramount. Smoking is among the more significant risk factors to curtail since many studies have reported its effects on AMD progression despite the timing of diagnosis and treatment.

Patients with early atrophic AMD in one or both eyes do not require any intervention while those with intermediate or advanced atrophic AMD in at least one eye can benefit from treatment with antioxidants such as zinc, vitamins C and E, and carotenoids (lutein, zeaxanthin,

β-carotene) due to their potential to reduce the risk of drusen formation.[42,56,57] The specific formulation and clinical effectiveness of these antioxidants were established in the landmark Age-Related Eye Disease Study (AREDS) and AREDS2.[58,59]

Most recently, intravitreal injections of pegcetacoplan, a compliment factor 3 inhibitor, is undergoing clinical phase 3 trials for the treatment of geographic atrophy. Phase 2 trials revealed efficacy in the reduction of the growth rate of geographic atrophy lesions after 12 months of monthly injections.[60] While pegcetacoplan shows promise, its role in the clinical management of patients with geographic atrophy remains to be seen when considering cost-effectiveness and the clinical value of reducing atrophy growth to patients.

For exudative AMD, treatment methods have evolved over the last two decades. The Treatment of AMD with Photodynamic therapy (TAP) study established potential benefit of photodynamic therapy in predominantly classic choroidal neovascularization[61], although this treatment modality is rarely used to treat AMD currently. Argon laser photocoagulation has also been used to treat exudative AMD but is no longer the modality of choice.[62] In the early 2000s, the VISION study established the superiority of anti-vascular endothelial growth factor (VEGF) in the treatment of exudative AMD by comparing pegaptanib intravitreal injections with photodynamic therapy.[63] Subsequent studies established the efficacy of intravitreal injections of anti-VEGF monoclonal antibodies in the treatment of exudative AMD.[64,65] In the present, anti-VEGF therapy is the mainstay of treatment of exudative AMD.

2.1.6. Metabolic Pathways Underlying AMD Pathogenesis

One of the main metabolic pathways associated with AMD pathogenesis is the adenosine monophosphate-activated protein kinase (AMPK)/sirtuin-1 (SIRT1)/peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) pathway.[66] In the AMD RPE, the

AMPK/SIRT1/PGC-1α pathway has been found to be dysfunctional, leading to impairments in autophagy, mitochondrial biogenesis and degradation, lysosomal lipid trafficking, and scavenging of reactive oxygen species (ROS).[66] This dysfunction ultimately leads to an increase in sensitivity to oxidative stress and neurotoxicity. Other enzymes or pathways that either affect or are affected by the AMPK/SIRT1/PGC-1α pathway include poly(adenosine diphosphate-ribose) polymerases (PARP) 1 and 2, and the mammalian target of rapamycin (mTOR) signaling pathway.[66]

AMPK is an energy-sensing enzyme that is activated by an elevated ratio of adenosine monophosphate (AMP) to adenosine triphosphate (ATP) in order to upregulate ATP-producing mechanisms such as fatty-acid oxidation and glucose transport, and to downregulate ATP-consuming mechanisms such as cell growth and proliferation, protein synthesis, and lipid synthesis.[67,68] AMPK regulates SIRT1 and PGC-1α activity either by directly binding to them or through its ability to increase the production of nicotinamide adenine dinucleotide (NAD+), a co-substrate of SIRT1.[69] In primary RPE cells derived from donor eyes with AMD, AMPK phosphorylation was found to be increased compared to normal RPE cells, resulting in reduced AMPK activity, and, consequently, reduced SIRT1 and PGC-1α activation.[66]

SIRT1 is an NAD+-dependent protein deacetylase that regulates various mechanisms such as autophagy (via deacetylation of autophagy proteins) and mitochondrial biogenesis (via deacetylation and activation of PGC-1α)[70,71], and who's expression is negatively regulated by PARP2.[72] SIRT1 has also been found to upregulate AMPK activity[73] and downregulate the mTOR signaling pathway[74], potentially resulting in an increase in autophagy (via AMPK-mediated phosphorylation of mammalian autophagy-initiating kinase Ulk1)[75] and dysfunction of cellular growth and proliferation mechanisms regulated by mTOR complexes 1 and 2.[76] AMD

RPE cells have been found to contain higher PARP2 expression levels, resulting in lower levels of SIRT1 activity, overactivation of the mTOR pathway, and downregulation of AMPK and PGC-1α activity.[66] Due to impairment of the mTOR pathway, patients with AMD may be more susceptible to neurological disorders and neurodegenerative diseases.[77]

PGC-1α is a regulator of mitochondrial biogenesis and degradation[78,79], fatty acid oxidation[80], lysosomal lipid trafficking[81], and ROS scavenging for oxidative stress detoxification.[82,83] Its activation is controlled by AMPK and SIRT1.[69] Highly expressed in the retina[84], PGC-1α has been found to regulate light sensitivity and normal or pathological angiogenesis in the retina[84,85], and oxidative metabolism and antioxidant capacity in the RPE.[86] In the AMD RPE, PGC-1α activity is reduced due to decreased activity of AMPK and SIRT1, resulting in dysfunctional mitochondrial biogenesis and turnover, and increased ROS production.[66] The resulting increase in oxidative stress can potentially trigger chronic inflammation and subsequent cellular damage in the RPE through the activation of proteins in the complement system[87], thereby contributing to drusen formation and the general pathophysiology of AMD.[88,89] Working in parallel with the AMPK/SIRT1/PGC-1α pathway, exposure to blue light has also been found to increase ROS production and inflammation in the RPE.[90]

2.2. Blue Light

2.2.1. Defining Blue Light

A growing domain of ocular research is concerned with the potential effects of blue light exposure on ocular health. Blue light characterizes the spectrum of visible light between wavelengths of 400-500 nm. It is able to bypass the light absorption thresholds of the cornea

(below 295 nm) and crystalline lens (in between 295 nm and 390 nm), directly affecting the retina and subjacent tissues as a result.[91]

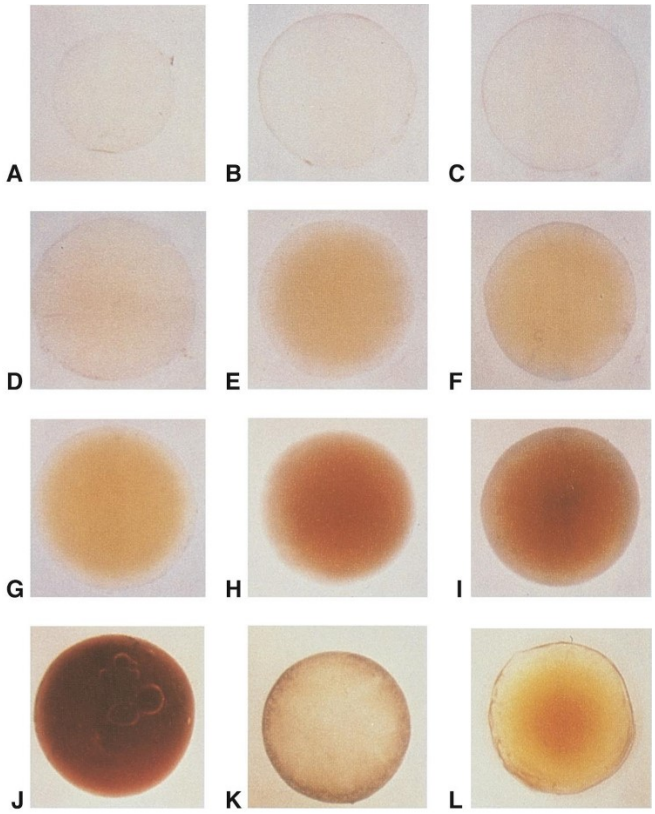
2.2.2. Effects of Blue Light Exposure

Studies have found that exposure to short-wavelength blue light (415-455 nm) can induce photo-oxidative stress and damage in murine retinal cells[92–94] and human retinal epithelial cells.[95–97] Blue light has also been found to induce RPE cell senescence and death through the oxidation of bis-retinoid *N*-retinyl-*N*-retinylidene ethanolamine (A2E) and subsequent production of mitochondrial ROS, making it a risk factor for AMD.[96–98]

2.2.3. Age-Dependent Lens Coloration

With age, the natural crystalline lens becomes progressively more yellow due to an accumulation of yellow chromophore deposits that allow for better absorption of blue light radiations (Figure 4A-I).[99] This change in lens coloration is caused by the interaction between crystallins of the natural lens with 3-hydroxykynurenine glucoside (3-OHKG), a UV-filtering compound, which results in the deamination of the amino acid side chain of 3-OHKG.[100] The subsequent nucleophilic attack of the deaminated 3-OHKG by cysteine, histidine, and lysine residues in the lens contributes to the yellow coloration of the aged natural lens.[100] Although the mechanisms that allow for progressive yellow coloration of the natural lens may be beneficial due to their ability to mitigate the harmful effects of blue light exposure on the retina, they can also lead to opacification and hardening of the natural lens (nuclear sclerosis), and eventual formation of a nuclear sclerotic cataract (Figure 4J).[101]

Figure 4. Age-dependent yellow coloration of the natural crystalline lens.



Progressive yellow coloration of the natural human lens at various age timepoints: (**A**) 6 months, (**B**) 8 years, (**C**) 12 years, (**D**) 25 years, (**E**) 47 years, (**F**) 60 years, (**G**) 70 years, (**H**) 82 years, and (**I**) 91 years. Yellowing can result in hardening of the natural lens, leading to the formation of a (**J**) nuclear cataract, (**K**) cortical cataract, or (**L**) mixed nuclear and cortical cataract. Adapted from Lerman.[102]

2.3. Intraocular Lens (IOL)

2.3.1. Definition and Function

An intraocular lens (IOL) is an artificial lens that replaces the opacified natural crystalline lens during cataract surgery.[103] A cataract is a clouding of the natural lens that can result in decreased central vision and eventual blindness if left untreated. The main treatment for cataract is phacoemulsification cataract surgery, where an ultrasound probe is used to dissolve

the opacified lens before its removal by suction and replacement with an IOL. Eyes that have been implanted with an IOL are referred to as pseudophakic (Latin for “false lens”) while eyes that still possess their natural lens are referred to as phakic. Although all IOLs have the capacity to filter UV light, only blue light-filtering IOLs contain a yellow chromophore that enables filtration of high-energy, short-wavelength blue light.[104,105]

2.3.2. Blue Light-Filtering Intraocular Lenses (yIOL)

yIOLs are an alternative to traditional cIOLs that are designed to mimic the blue-light filtration of the healthy aged natural lens and protect the retina from damage induced by exposure to blue light.[106] In the literature, there have been many different types of studies that have investigated the potential benefit of yIOLs in protecting against AMD disease progression. These include animal studies, cell culture studies, case-control studies, cohort studies, and randomized controlled trials.

2.3.2.1. yIOL Animal Studies. A 1989 study by Nilsson et al. compared photochemical light injury in pigmented rabbits by exposing them to light for 3.5 hours while protecting each eye with either a cIOL or yIOL.[107] After 4-6 days of exposure, they found significantly more RPE and neuroretina damage in the cIOL-protected eyes. They also found that significantly more cIOL-protected eyes had pathological changes to their fundus than the yIOL-protected eyes.[107]

A later 2006 study by Tanito et al. evaluated retinal damage in albino rats that were exposed to 4.5 k lux fluorescent lights emitting either short-wavelength (380-500 nm, peak at 420 nm) or long-wavelength (400-540 nm, peak at 446 nm) blue light while having either clear or yellow soft acrylic IOLs attached to their eyes.[108] After short-wavelength exposure, they found that retinal damage was significantly reduced in the eyes with a yIOL compared to those with a cIOL. After long-wavelength exposure, however, they found that there were no significant

differences in retinal damage between cIOL and yIOL eyes. As such, they concluded that yIOLs were more effective at protecting the retina from acute short-wavelength blue light exposure than cIOLs.

2.3.2.2. yIOL Cell Culture Studies. Earlier cell culture studies compared light-induced damage to human RPE cells in the presence of a cIOL or yIOL. First, Sparrow et al. found in their 2004 study, that there was a significant reduction in RPE cell death when the cells were protected by a yIOL while being exposed to blue, green, and white light.[109] Second, Yanagi et al. similarly found in their 2006 study that the presence of a yIOL significantly reduced light-induced cell damage in ARPE-19 cells that were exposed to white light in comparison with those that were protected by a cIOL.[110] Third, Rezai et al. found in their 2008 study that yIOLs significantly lowered blue light-induced apoptosis of cultured RPE cells.[111] Finally, Kernt et al. found in their 2009 study that yIOLs reduced significantly more light-induced cell damage in primary RPE cells than cIOLs.[112]

In a more recent study, Abdouh et al. aimed to determine the effect of blue light exposure on oxidative stress in human retinal pigmented epithelial cells and the potentially mitigating effect of yIOLs.[113] To accomplish this, they exposed primary human RPE cells to blue light for 30 minutes while protected by either no intraocular lens, a cIOL, or a yIOL, and recorded the levels of total cellular and mitochondrial ROS. They found that exposure to blue light significantly increased the levels of ROS in the RPE cells and that protection by the yIOL managed to decrease the levels of ROS. They also found that the increased RPE cell death from the production of ROS was significantly decreased in cells protected by the yIOL, thereby concluding that yIOLs had a protective effect on RPE cells by mitigating photo-oxidative damage from exposure to blue light.

2.3.2.3. yIOL Case-Control Studies. In their 2021 retrospective case-control study, Hamel et al. aimed to investigate if yIOLs had a protective effect on the onset of exudative AMD.[114] They accomplished this by comparing the proportion of yIOLs in exudative AMD patients with that of the general North American population of pseudophakic patients. After completing their assessment, they found no significant correlations between the presence of yIOLs and the incidence of exudative AMD. They also reported significantly later initial anti-VEGF treatments in normal patients compared to exudative AMD patients. They concluded that their findings contradicted the potential clinical benefit of blue light filtration.

2.3.2.4. yIOL Cohort Studies. There have been many cohort studies in the literature investigating the effect of yIOLs on AMD progression, with earlier studies reporting a protective effect against the incidence of advanced AMD and later studies reporting no discernable effect.

First, a 2015 study by Pipis et al. aimed to clinically evaluate the effect of yIOLs on disease progression in geographic atrophy patients by measuring atrophic legion size via spectral-domain OCT and the advanced RPE analysis tool.[115] They assessed 66 eyes from 40 patients, with 39 eyes being implanted with a cIOL and 27 being implanted with a yIOL. They found that, after a 1-year follow-up, progression of geographic atrophy was significantly faster in the cIOL eyes. Within the same year, a later study by Nagai et al. observed changes in fundus autofluorescence between 79 cIOL and 52 yIOL eyes from cataract patients, while also recording the presence of newly formed drusen, geographic atrophy, and choroidal neovascularization.[116] They reported a significant increase in abnormal fundus autofluorescence, as well as a significantly higher incidence of new drusen, geographic atrophy, neovascularization, and AMD, in the cIOL eyes.

Later, in 2021, a study by Achiron et al. aimed to assess the ability of yIOLs to prevent post-cataract surgery exudative AMD.[117] They evaluated 5,972 cIOL and 5,425 yIOL eyes from 11,397 patients. They found that yIOLs had no effect on the development of exudative AMD and that there were no significant differences between IOL types in any of the secondary outcomes associated with advanced AMD (best corrected visual acuity, foveal thickness, and the number and interval of anti-VEGF treatments). Finally, in 2022, a study by Lee et al compared incidence rates of atrophic and exudative AMD between cIOL and yIOL eyes after a 10-year follow-up.[118] After examining 186,591 patients that had received cataract surgery between 2008 and 2013, they found no significant differences in the incidence rates of atrophic or exudative AMD between patients with a cIOL implant and those with a yIOL implant.

2.3.2.5. yIOL Randomized Controlled Trials. A 2018 literature review by Downie et al. assessed the reported effects of yIOLs on ocular health from 51 randomized controlled trials with a combined sample size of over 5000 eyes.[119] After performing their review, they were able to conclude with moderate certainty that there was no significant difference in best corrected visual acuity between cIOL and yIOL eyes at 6-18 months post-cataract surgery and, with a lower level of certainty, that there was no significant difference in short-term contrast sensitivity. These findings led Downie et al. to conclude that the questionable protective effect of yIOLs on macular health remained unclear.

2.3.2.6. yIOL Post-Mortem Studies. While these studies have managed to assess the effect of yIOLs on the progression of AMD in live patients, there nevertheless remains a gap in the surrounding literature. As of yet, there does not seem to be any studies that have investigated the effect of yIOLs on AMD progression in post-mortem eye samples. Given the analytical opportunities allowed by the use of post-mortem tissue, such a study may allow for more precise

assessment of the retinal anatomy and a better understanding of the potential influence of yIOLs on AMD progression. As such, this work consists of a novel approach to AMD research that may lead to a better understanding of AMD pathogenesis and may offer a new avenue of approach for physicians to better treat patients at risk of developing AMD.

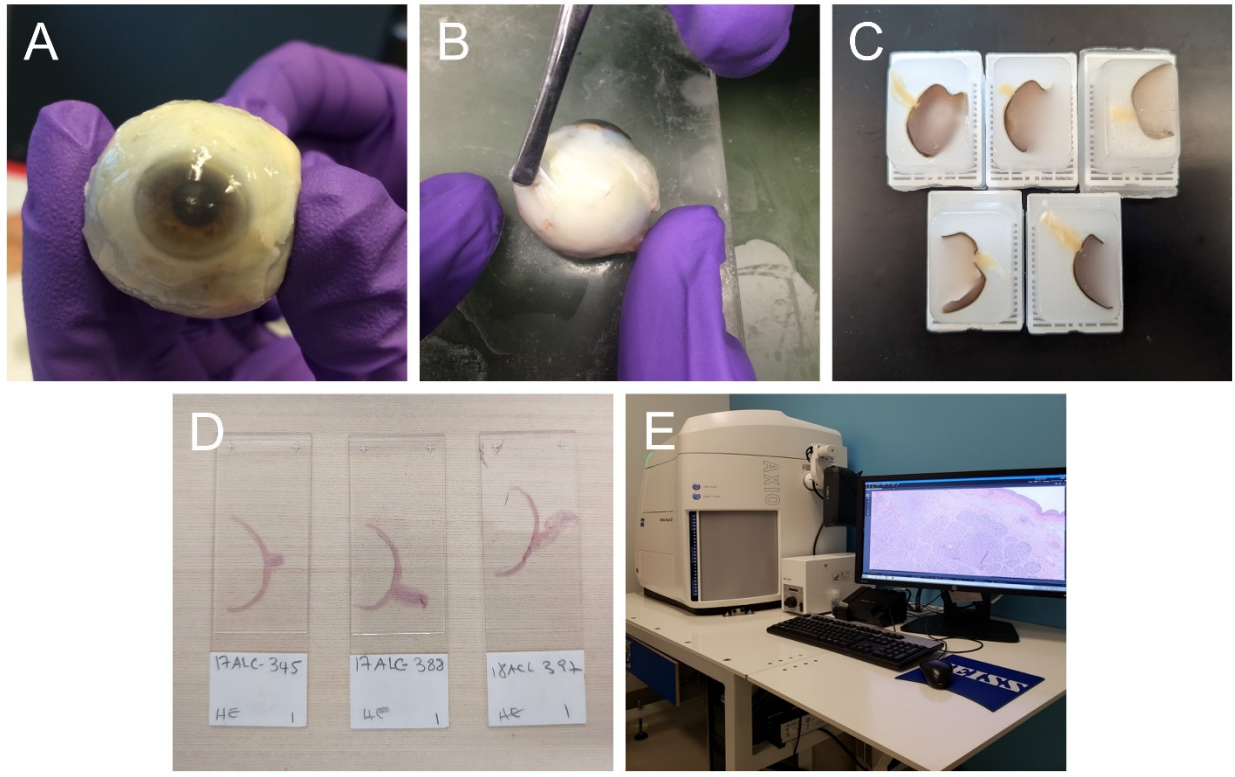
3. Methodology

One hundred and ninety-three post-mortem pseudophakic human eyes were obtained from the Lions Gift of Sight eye bank (Saint Paul, MN, USA) from September 2015 to April 2018 and examined at the MUHC-McGill University Ocular Pathology & Translational Research Laboratory. All data collection was performed in accordance with the legislation of Canada and Province of Quebec, and the tenets of the Declaration of Helsinki. Clinical data was collected for each eye and included the donor's sex, date of death, age at the time of death (age-at-death), date of cataract surgery, and clinical history, and the model number of the implanted IOL. The donor's date of death, age-at-death, and date of surgery were used to determine the age of the donor at the time of their cataract surgery (age-at-surgery) and the time between the donor's cataract surgery and death (surgery-to-death time). The IOL model numbers were used to categorize the eyes based on whether they were implanted with a cIOL or a yIOL. The clinical history of the eyes was used to determine if the donors had a history of smoking, diabetes, hypertension, glaucoma, cancer, AMD, or cardiovascular disease. Eyes from donors who had been smokers for any number of years, were former smokers, or had a tobacco dependence were noted as having a history of smoking. Eyes from donors with clinical histories mentioning any type of cancer were marked as having a history of cancer. Eyes from donors with clinical histories mentioning heart disease, coronary artery disease, or peripheral vascular disease were noted as having a history of cardiovascular disease.

The eyes were received at room temperature in a 10% buffered formalin fixative solution to prevent significant post-mortem changes, with a mean death to fixation time of 18 hours and 32 minutes (Figure 5A). Eyes were sectioned on their coronal and sagittal axes, and the posterior halves were kept in a 70% ethanol solution before being sent to the Histopathology Platform of

the RI-MUHC for paraffin wax embedding (Figure 5B-C). Cross sections of the macula were subsequently obtained from the formalin-fixed paraffin-embedded samples (Figure 5D). The macular cross sections were then stained with hematoxylin and eosin (H&E), and scanned with the Zeiss Axio Scan.Z1 scanner (Figure 5E).

Figure 5. Processing of post-mortem eyes.

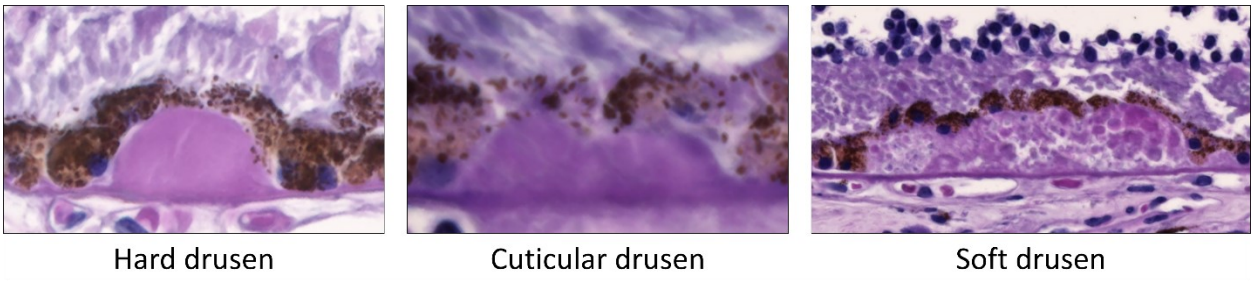


(**A**) Formalin-fixed post-mortem eye before sectioning. (**B**) Post-mortem eye sectioned on sagittal axis. (**C**) Formalin-fixed paraffin-embedded post-mortem tissue blocks. (**D**) H&E-stained macular cross sections. (**E**) Zeiss Axio Scan.Z1 digital scanner.

Drusen were classified and quantified from the scanned H&E-stained sections via the Zen 3.6 (blue edition) microscopy software (ZEISS Group). Drusen classification was based on type, size or subtype, and quantity. Type classifications included no drusen, hard, cuticular, and soft (Figure 6). Size classifications were based on the measured diameter of drusen within the Zen

software and included small (<20 μm in diameter), medium (20-50 μm in diameter), and large (>50 μm in diameter). All drusen recorded as soft had a diameter larger than 125 μm. Subtype classifications referred specifically to soft drusen and included basal linear deposits and basal laminar deposits. Quantity classifications for hard and cuticular drusen included none (0 drusen), few (<5 drusen), and multiple (≥5 drusen). For soft drusen, quantity classifications included zonal (<500 μm in diameter), multiple zonal (more than a single zonal soft drusen), and extensive (≥500 μm in diameter).

Figure 6. Drusen types on H&E-stained cross sections.



Statistical analyses were performed using Microsoft Excel (Microsoft Corporation) and OriginPro® 9 (OriginLab Corporation). To compare frequency counts between both IOL types (sex, drusen quantification, clinical history incidences), chi-squared test was used. To compare mean values of clinical data (age-at-surgery, age-at-death, surgery-to-death time), two-tailed t-test was used. F-test for equality of two variances was used to determine if variances between cIOL and yIOL data groups were significantly different and, therefore, if Welch's t-test (two-tailed t-test assuming unequal variances) should be used. $P<0.05$ was considered statistically significant.

4. Results

4.1. Demographic Data

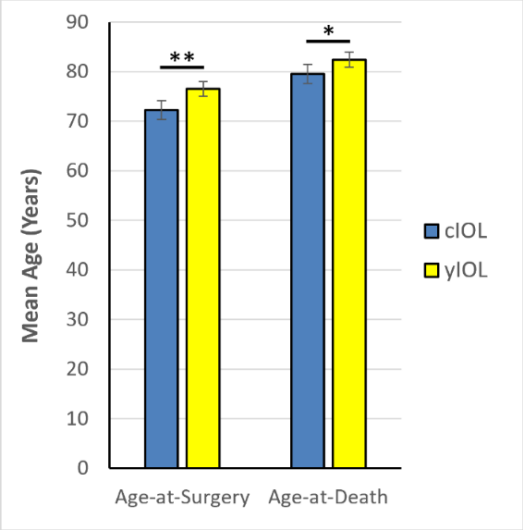
Demographic information for all post-mortem eyes is shown in Table 1. Out of the 193 post-mortem eyes, 100 were implanted with a cIOL and 93 were implanted with a yIOL. Comparing demographic data between both IOL types, yIOL eyes had a significantly larger proportion of female donors (52.69%) than cIOL eyes (38%, p=0.0404). yIOL eyes also had a significantly higher mean age-at-surgery (76.52 years, p=0.000524), with a mean difference of 4.30 years, and higher mean age-at-death (82.40 years, p=0.0234), with a mean difference of 2.83 years, than cIOL eyes (72.22 and 79.57 years, respectively) (Figure 7). cIOL eyes had a significantly higher mean surgery-to-death time than yIOL eyes (6.96 years vs. 5.41 years, p=0.0424), with a mean difference of 1.55 years (Figure 8).

Table 1. Demographic information of all post-mortem eyes.

Factor	**Sample size**	**Value**
Percentage of Males	193	106 (54.92%)
Mean Age-at-Surgery (SD)	193	74.29 (8.78)
Mean Age-at-Death (SD)	193	80.93 (8.76)
Range of Years of Cataract Surgery	193	1986-2017
Median Year of Cataract Surgery	193	2011
Mean Surgery-to-Death Time in Months (SD)	193	74.59 (64.83)

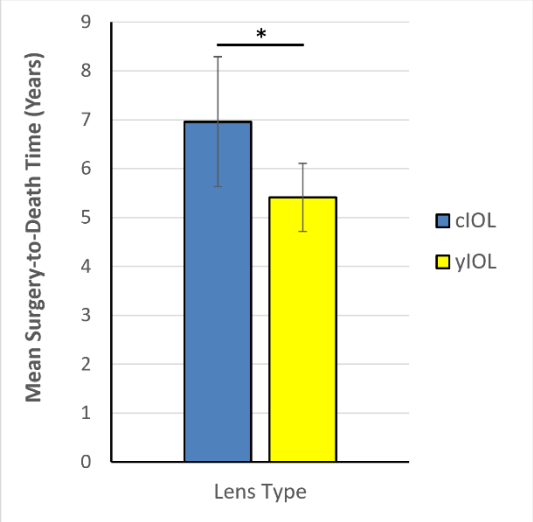
Abbreviations: SD, standard deviation.

Figure 7. Welch's t-test comparing mean age-at-surgery and age-at-death by IOL type.



* = p<0.05; ** = p<0.001.

Figure 8. Welch's t-test comparing mean surgery-to-death time by IOL type.

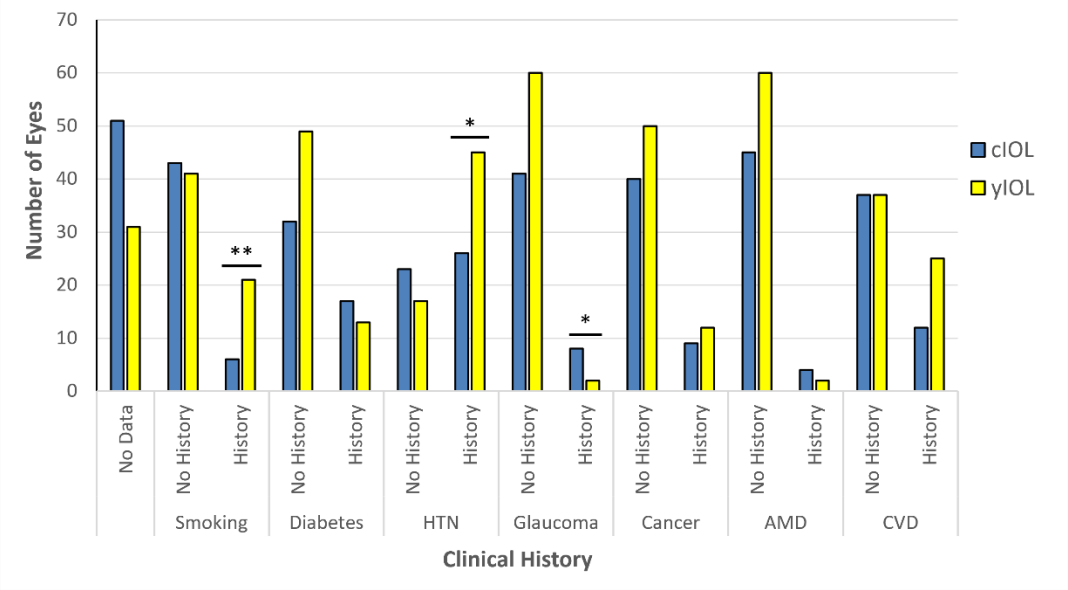


* = p<0.05.

As for the clinical history of the eyes, only 49 cIOL and 62 yIOL eyes had clinical history data. History of hypertension (n=71) was the most common clinical history found among all eyes, followed by history of cardiovascular disease (n=37), diabetes (n=30), smoking (n=27), cancer (n=21), glaucoma (n=10), and AMD (n=6) (Figure 9). Between both IOL types, there

were significantly more yIOL eyes with a history of smoking (p=0.00836) and hypertension (p=0.0334), and significantly more cIOL eyes with a history of glaucoma (p=0.0167) (Figure 9). No significant differences in the number of eyes with a history of diabetes, cancer, or AMD were found (Figure 9).

Figure 9. Chi-squared tests comparing clinical history of post-mortem eyes by IOL type.



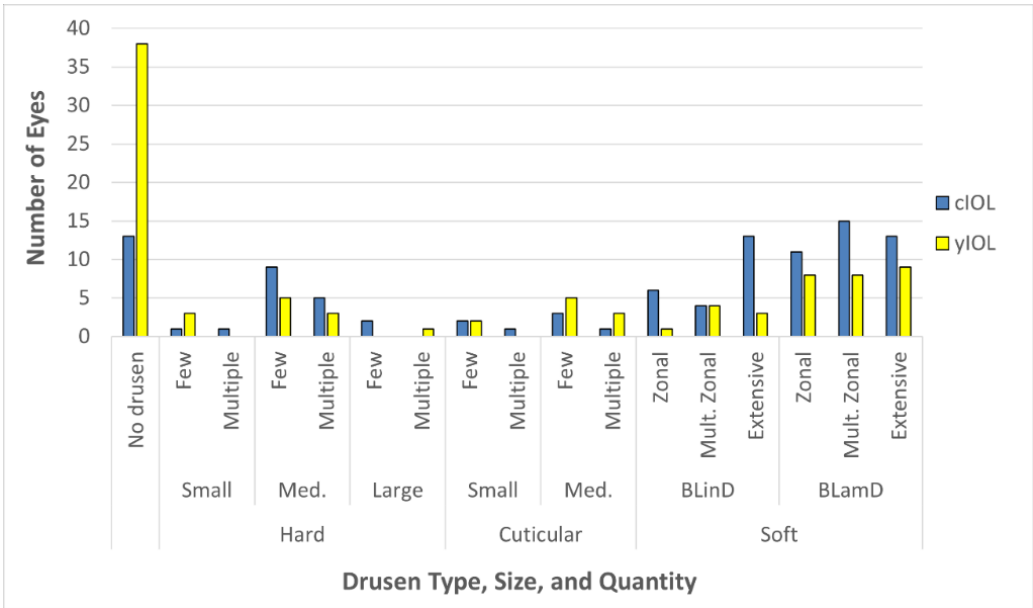
Abbreviations: AMD, age-related macular degeneration; cIOL, clear intraocular lens; CVD, cardiovascular disease; HTN, hypertension; yIOL, yellow intraocular lens. * = p<0.001; ** = p<0.0001.

4.2. Drusen Classification and Quantification

Across all post-mortem eyes, 26% (n=51) had no drusen present, 16% (n=30) had hard drusen, 9% (n=17) had cuticular drusen, and 49% (n=95) had soft drusen (Figure 10). Medium-sized drusen were most common among eyes with hard drusen (73.33% of eyes) and cuticular drusen (70.59% of eyes) (Figure 10). Between both types of soft drusen, basal laminar deposits were more common (67.37% of eyes) (Figure 10). Comparing the proportion of drusen types by 10-year age groups, the 90-99 age group (n=29) was found to have a significantly higher

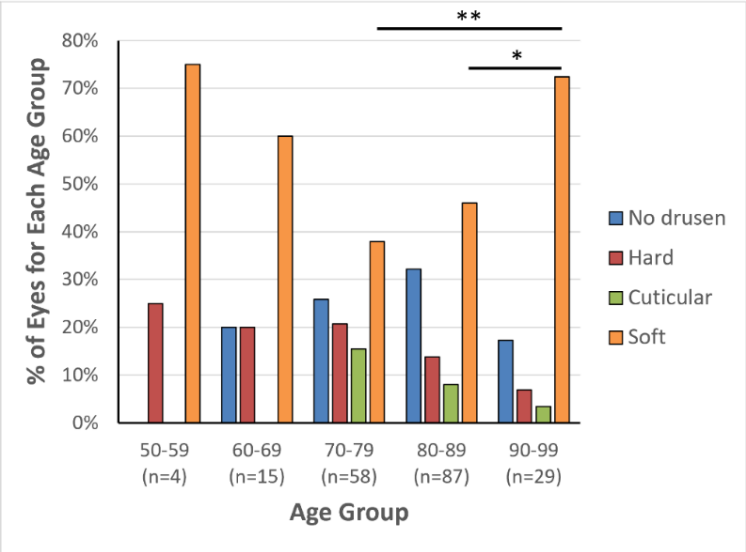
proportion of eyes with soft drusen (72%) than the 80-89 age group (n=87, 46% soft drusen, p=0.0319) and 70-79 age group (n=58, 38% soft drusen, p=0.00632) (Figure 11).

Figure 10. Distribution of drusen type, size, and quantity by IOL type.



Abbreviations: BLamD, basal laminar deposit; BLinD, basal linear deposit; cIOL, clear intraocular lens; Med., medium; Mult., multiple; yIOL, yellow intraocular lens.

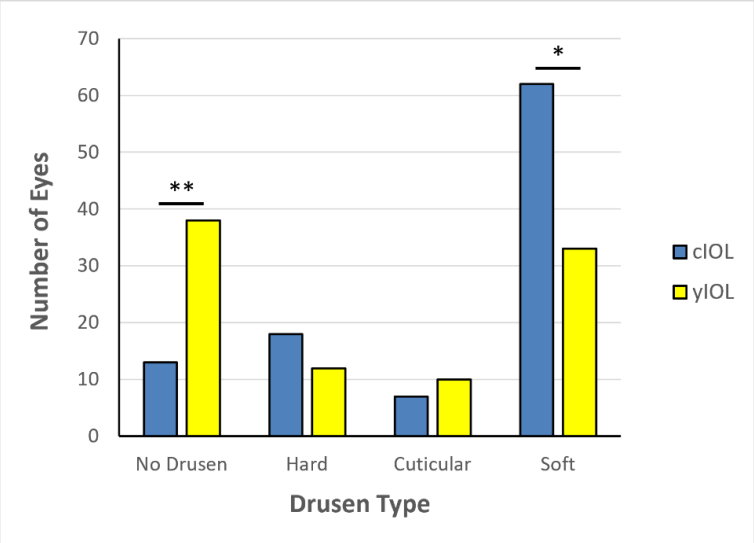
Figure 11. Chi-squared tests comparing proportions of drusen types by 10-year age group.



* = $p<0.05$; ** = $p<0.01$.

Comparing drusen types between IOL types, soft drusen were found to be significantly more prevalent in cIOL eyes (n=62) than in yIOL eyes (n=33, p=0.000232) (Figure 12). There was also significantly less cIOL eyes (n=13) with no drusen than yIOL eyes (n=38, p=0.0000115) (Figure 12). No significant differences between cIOL and yIOL eyes in the presence of hard (n=18 vs. n=12, p=0.329) or cuticular drusen (n=7 vs. n=10, p=0.358) were found (Figure 12).

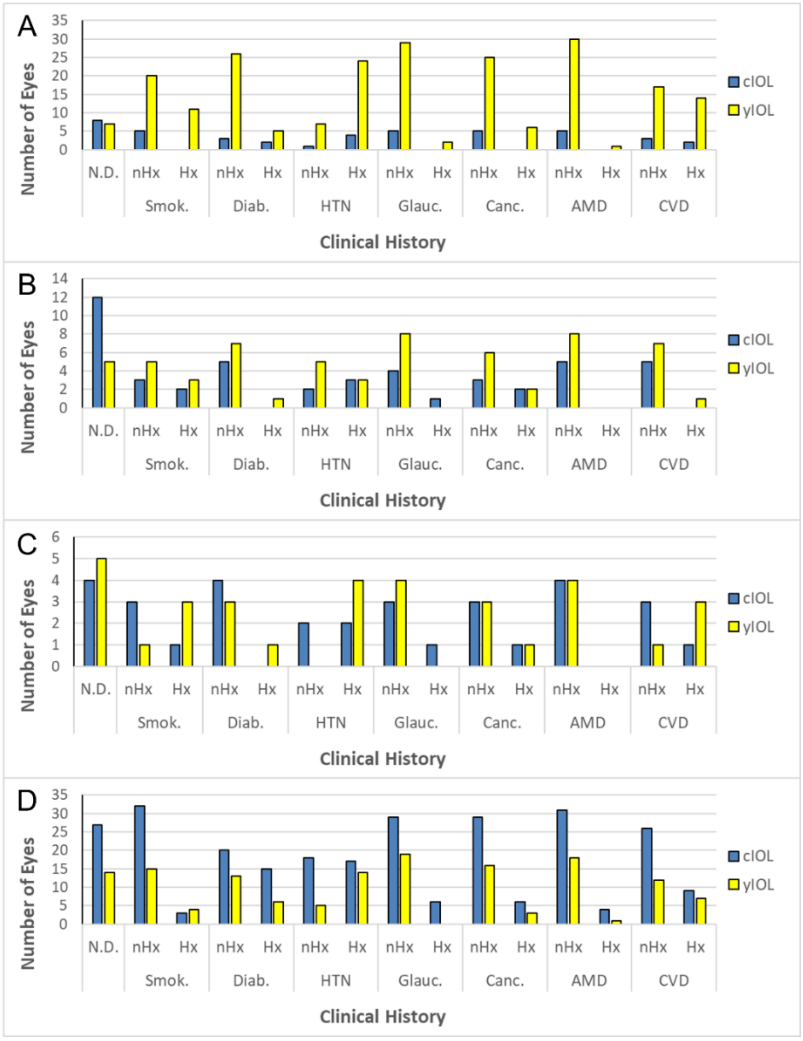
Figure 12. Chi-squared tests comparing distribution of drusen types by IOL type.



* = p<0.001; ** = p<0.0001.

Clinical history data was also compared via Chi-squared test between IOL types and by drusen type (Figure 13). No significant differences in any of the assessed clinical histories were found, although there was a trend for more history of glaucoma in cIOL eyes with soft drusen (p=0.056).

Figure 13. Chi-squared tests comparing clinical history of post-mortem eyes by IOL type, within drusen type subgroups.



Clinical history data from post-mortem eyes with (**A**) no drusen (n=51), (**B**) hard drusen (n=30), (**C**) cuticular drusen (n=17), and (**D**) soft drusen (n=95). Abbreviations: AMD, age-related macular degeneration; Canc., cancer; cIOL, clear intraocular lens; CVD, cardiovascular disease; Diab., diabetes; Glauc., glaucoma; HTN, hypertension; Hx, clinical history; nHx, no clinical history; Smok., smoking; yIOL, yellow intraocular lens.

Afterwards, the comparison of drusen types between cIOL and yIOL eyes was repeated while controlling for the clinical history of the eyes in order to better ascertain the effect of IOL

type on drusen formation. Single and combined exclusions of clinical histories were applied to the sample group of eyes with clinical history data. For each exclusion, chi-squared tests comparing the prevalence of eyes with soft drusen and no drusen between both IOL types were performed (Table 2). After controlling for any single clinical history or for a combination of any two clinical histories, soft drusen and no drusen significant differences were maintained in all exclusion combinations. After controlling for any combination of three clinical histories (35 combinations), significant differences were maintained in 24 exclusion combinations, partially lost (loss of one or the other) in 7 combinations, and completely lost (loss of both) in 4 combinations. Among combinations resulting in partial or complete loss of significant differences, the exclusion of history of hypertension was the most common (9/11 combinations), followed by history of diabetes (6/11 combinations) and cancer (5/10 combinations). After controlling for any combination of four clinical histories (35 combinations), significant differences were maintained in 7 exclusion combinations, partially lost in 14 combinations, and completely lost in 14 combinations. Among combinations resulting in partial or complete loss of significant differences, the exclusion of history of hypertension was the most common (19/28 combinations), followed by history of diabetes (17/28 combinations). When controlling for any combination of five clinical histories (21 combinations), significant differences were partially lost in 2 combinations, and completely lost in 19 combinations. Among combinations resulting in partial or complete loss of significant differences, all clinical history exclusions were each included in 15/21 combinations. Finally, after controlling for any combination of six (7 combinations) or for all clinical histories, significant differences were completely lost in all combinations.

Table 2. Chi-squared tests comparing the prevalence of soft or no drusen between cIOL and yIOL eyes while controlling for various combinations of clinical history.

	Sample Size		P values				Sample Size		P values	
Excluded Hx	cIOL	yIOL	Soft drusen	No drusen		**Excluded Hx**	cIOL	yIOL	Soft drusen	No drusen
All Hx	11	8	0.552	0.348						
1 Hx Excluded						**4 Hx Excluded**				
s	43	41	<0.001	<0.001		s / d / h / g	15	9	0.157	0.265
d	32	49	<0.01	<0.001		s / d / h / c	17	8	0.317	0.170
h	23	17	<0.01	<0.01		s / d / h / a	13	11	0.219	0.085
g	41	60	<0.001	<0.001		s / d / h / v	17	11	0.074	<0.05
c	40	48	<0.001	<0.001		s / d / g / c	22	23	0.051	<0.05
a	45	60	<0.001	<0.001		s / d / g / a	20	30	0.063	<0.05
v	37	37	<0.01	<0.001		s / d / g / v	22	19	<0.05	<0.05
2 Hx Excluded						s / d / c / a	20	23	0.172	<0.05
s / d	28	32	<0.01	<0.001		s / d / c / v	22	18	0.064	<0.05
s / h	21	13	<0.01	<0.05		s / d / a / v	20	21	0.087	<0.05
s / g	37	39	<0.01	<0.01		s / h / g / c	17	9	0.102	0.215
s / c	36	28	<0.05	<0.01		s / h / g / a	13	11	0.107	0.200
s / a	39	39	<0.01	<0.001		s / h / g / v	17	11	<0.05	0.114
s / v	31	26	<0.01	<0.01		s / h / c / a	17	9	0.192	0.215
d / h	17	13	<0.05	<0.05		s / h / c / v	17	9	0.091	0.144
d / g	26	47	<0.01	<0.001		s / h / a / v	17	13	<0.05	<0.05
d / c	26	39	<0.01	<0.01		s / g / c / a	28	26	0.059	<0.05
d / a	28	49	<0.01	<0.001		s / g / c / v	22	17	<0.05	0.051
d / v	28	30	<0.05	<0.01		s / g / a / v	23	24	<0.05	<0.05
h / g	19	15	<0.01	<0.05		s / c / a / v	22	19	<0.05	<0.05
h / c	23	13	<0.05	<0.05		d / h / g / c	15	10	0.096	0.119
h / a	19	17	<0.01	<0.01		d / h / g / a	11	11	0.201	0.269
h / v	23	17	<0.01	<0.01		d / h / g / v	15	11	0.059	0.150
g / c	36	48	<0.001	<0.01		d / h / c / a	13	10	0.305	0.162
g / a	37	58	<0.001	<0.001		d / h / c / v	17	10	0.118	0.088
g / v	31	35	<0.01	<0.01		d / h / a / v	13	13	0.116	0.063
c / a	36	46	<0.001	<0.01		d / g / c / a	18	39	<0.05	<0.05
c / v	30	29	<0.01	<0.01		d / g / c / v	20	24	<0.05	<0.05
a / v	33	37	<0.01	<0.001		d / g / a / v	20	28	0.113	<0.05
3 Hx Excluded						d / c / a / v	20	26	0.087	<0.05
s / d / h	17	11	0.074	<0.05		h / g / c / a	15	13	0.063	0.097
s / d / g	24	30	<0.05	<0.01		h / g / c / v	19	13	<0.05	0.051
s / d / c	24	23	0.059	<0.01		h / g / a / v	15	15	<0.05	0.068
s / d / a	24	32	<0.05	<0.01		h / c / a / v	19	13	<0.05	0.051
s / d / v	24	21	<0.05	<0.01		g / c / a / v	20	27	<0.05	<0.05
s / h / g	17	11	<0.05	0.114		**5 Hx Excluded**				
s / h / c	21	9	0.091	0.144		s / d / h / g / c	15	8	0.263	0.214
s / h / a	17	13	<0.05	<0.05		s / d / h / g / a	11	9	0.391	0.413
s / h / v	21	13	<0.01	<0.05		s / d / h / g / v	15	9	0.157	0.265
s / g / c	32	28	<0.05	<0.05		s / d / h / c / a	13	8	0.604	0.271
s / g / a	33	37	<0.01	<0.01		s / d / h / c / v	17	8	0.317	0.170
s / g / v	27	24	<0.01	<0.05		s / d / h / a / v	13	11	0.219	0.085
s / c / a	32	26	<0.05	<0.05		s / d / g / c / a	18	23	0.162	<0.05
s / c / v	26	19	<0.05	<0.01		s / d / g / c / v	20	16	0.112	0.056
s / a / v	27	26	<0.01	<0.01		s / d / g / a / v	18	19	0.140	0.091
d / h / g	15	11	0.059	0.150		s / d / c / a / v	18	18	0.182	<0.05
d / h / c	17	10	0.118	0.088		s / h / g / c / a	13	9	0.245	0.329
d / h / a	13	13	0.116	0.063		s / h / g / c / v	17	9	0.102	0.215
d / h / v	17	13	<0.05	<0.05		s / h / g / a / v	13	11	0.107	0.200
d / g / c	22	39	<0.01	<0.01		s / h / c / a / v	17	9	0.192	0.215
d / g / a	22	47	<0.05	<0.01		s / g / c / a / v	18	17	0.130	0.109
d / g / v	24	28	<0.05	<0.05		d / h / g / c / a	11	10	0.279	0.223
d / c / a	22	39	<0.05	<0.01		d / h / g / c / v	15	10	0.096	0.119
d / c / v	24	26	<0.05	<0.01		d / h / g / a / v	11	11	0.201	0.269
d / a / v	24	30	0.073	<0.01		d / h / c / a / v	13	10	0.305	0.162
h / g / c	19	13	<0.05	0.051		d / g / c / a / v	16	24	0.121	0.079
h / g / a	15	15	<0.05	0.068		h / g / c / a / v	15	13	0.063	0.097
h / g / v	19	15	<0.01	<0.05		**6 Hx Excluded**				
h / c / a	19	13	<0.05	0.051		s / d / h / g / c / a	11	8	0.552	0.348
h / c / v	23	13	<0.05	<0.05		s / d / h / g / c / v	15	8	0.263	0.214
h / a / v	19	17	<0.01	<0.01		s / d / h / g / a / v	11	9	0.391	0.413
g / c / a	30	46	<0.01	<0.01		s / d / h / c / a / v	13	8	0.604	0.271
g / c / v	24	27	<0.01	<0.05		s / d / g / c / a / v	16	16	0.288	0.127
g / a / v	27	35	<0.05	<0.01		s / h / g / c / a / v	13	9	0.245	0.329
c / a / v	26	29	<0.05	<0.01		d / h / g / c / a / v	11	10	0.279	0.223

Abbreviations: a, age-related macular degeneration; c, cancer; cIOL, clear intraocular lens; d, diabetes; g, glaucoma; h, hypertension; Hx, clinical history; s, smoking; v, cardiovascular disease; yIOL, yellow intraocular lens.

5. Discussion

5.1. Summary of Findings

This project aimed to investigate the effect of yIOLs on drusen formation and AMD progression in pseudophakic post-mortem eyes by comparing AMD risk factors, classifying and quantifying drusen, and comparing drusen types, sizes, and quantities in post-mortem eyes implanted with a cIOL or a yIOL. It was found that yIOL eyes had a larger percentage of eyes from female donors, a higher mean age-at-surgery and mean age-at-death, and more yIOL eyes had a history of smoking and hypertension, while cIOL eyes had a higher mean surgery-to-death time and prevalence of a history of glaucoma (Figures 4.1-4.3). After classifying and quantifying the drusen present in the post-mortem eyes, it was found that soft drusen was the most common type of drusen in all post-mortem eyes, that basal laminar deposits were the more common form of soft drusen, and that roughly a quarter of the post-mortem eyes had no drusen present in their retinas (Figure 10). It was also found that, when comparing drusen types by 10-year age groups, the 90-99 age group had a significantly larger proportion of eyes with soft drusen than the 80-89 and 70-79 age groups (Figures 4.5). Finally, when comparing drusen types between cIOL and yIOL eyes, it was found that significantly more cIOL eyes had soft drusen present in the retina while significantly more yIOL eyes had no drusen (Figure 12). Repeating these comparisons while controlling for the clinical history of the eyes, it was found that the significant differences in the prevalence of eyes with soft drusen and no drusen were conserved when controlling for different combinations of one or two clinical histories, but became less conserved with larger combinations. Across all combinations excluding three or more clinical histories, history of hypertension was the clinical history that, when excluded, most commonly resulted in a loss of

statistical significance for the comparisons of soft drusen and no drusen prevalence between cIOL and yIOL eyes.

5.2. Effect of Gender Differences on Drusen Formation

The larger female-to-male ratio observed in the eyes implanted with a yIOL may indicate that these eyes are subject to a higher risk of developing AMD than the cIOL eyes, although there are conflicting reports in the literature. A 2012 meta-analysis by Rudnicka et al. investigating age and gender-specific differences in AMD prevalence within Caucasian populations from 25 studies published between 1978-2008 found that there was evidence pointing to a higher risk of exudative AMD development in females but that this increased risk was more prominent in studies not using fundus imaging or international classification systems to define cases of AMD.[120] Newer studies outside the scope of Rudnicka et al.'s meta-analysis have also suggested an association between female sex and faster AMD progression rates.[13–17,121] However, a 2018 report by Sasaki et al. that investigated gender-specific associations of AMD in a Japanese population of participants from the Tsuruoka Metabolomics Cohort Study found that both the early and late stages of AMD were more prevalent in male participants than female participants, with male participants being more likely to have large drusen and pigmentary abnormalities in their retina.[122] There are also many studies that have reported a lack of association between sex and AMD progression.[6–11,123] It is possible that the significantly larger female-to-male ratio in the yIOL eyes may have resulted in more soft drusen being observed in these eyes than what would have been observed with a more equal spread of male and female eyes across both IOL types. However, given the conflicting evidence in the literature surrounding gender as a risk factor for AMD progression, the effect of the difference in gender ratios between cIOL and yIOL eyes on the formation of drusen remains unclear.

5.3. Effect of Age Differences on Drusen Formation

Regarding the findings on mean age-at-surgery and mean age-at-death, the significantly higher values of the yIOL eyes indicate that these eyes were at a higher risk of having more advanced drusen formation and AMD progression by the time of enucleation since age is the main risk factor for AMD.[6–11] Compared to the donors of cIOL eyes, the yIOL eye donors were on average 4.30 years older at the time of cataract surgery and 2.83 years older at death (Figure 7). In the literature, time delays shorter than these differences in age have been found to allow for early-to-advanced progression of atrophic AMD in cataract patients. A 2011 study by Yehoshua et al. analyzed 143 eyes from 100 patients with drusen secondary to atrophic AMD across 6-24 months of follow-up in order to track the progression of drusen morphology over time.[124] They found that there was a tendency for mean drusen area and volume to significantly increase by the 12-month and 24-month follow-up assessments.[124] They also reported that, after 24 months, 19 of the 143 assessed eyes had developed late-stage AMD, with 5 eyes developing neovascular disease and 14 developing geographic atrophy.[124] Given that both the age-at-surgery and age-at-death mean differences between the cIOL and yIOL eyes were longer than 24 months, it is possible that these differences may have led to an increased prevalence of soft drusen in the yIOL eyes and decreased prevalence of yIOL eyes with no drusen, which may have not been the case if both IOL sample groups had similar mean age values. The use of a more closely age-matched cohort of post-mortem samples may help in minimizing the influence of age on study findings.

5.4. Effect of Cataract Surgery Timing Differences on Drusen Formation

The significantly higher mean surgery-to-death time of the cIOL eyes may have led to an increased prevalence of soft drusen in the cIOL eyes due to the potential for cataract surgery to

increase AMD progression and risk of developing advanced AMD. Currently, there is conflicting evidence in the literature surrounding the association between cataract surgery and AMD. Reports from the Beaver Dam Eye Study, a large epidemiological study based in the United States, found an association between previous history of cataract surgery, increased AMD progression, and increased risk of developing advanced AMD based on five-year and ten-year follow-up results.[125,126] Other epidemiological studies, such as the Blue Mountains Eye Study, Rotterdam Study, and Copenhagen City Eye Study, have reported similar results.[127–129] However, the AREDS study, a more recent epidemiological study, found little evidence to support the association between cataract surgery and risk of developing advanced AMD.[130] Furthermore, in their clinic-based cohort study assessing 1178 participants over a three-year follow-up, Wang et al. found no increased risk of early or advanced AMD in unilaterally operated eyes when compared to fellow eyes.[131] As such, given the conflicting evidence in the literature, it is unclear if the additional mean surgery-to-death time of the cIOL eyes influenced the prevalence of soft drusen in a significant manner.

5.5. Effect of Clinical History Differences on Drusen Formation

Concerning the clinical history findings, the significant differences in history of smoking and hypertension between IOL type groups may have had an impact on drusen formation in the yIOL eyes since both factors have been associated with AMD progression in the literature[6,7,11,13–15,19–21], although some studies have found no association between hypertension and AMD.[13,16,121,123] However, the effect of these factors on the differences in drusen classification and quantification between cIOL and yIOL eyes may not have been significant, since no significant IOL type-specific differences in the prevalence of history of smoking or hypertension were found within the groups of eyes with drusen (Figure 13B-D) and because the majority of

eyes with a history of smoking or hypertension had no drusen in their retina (Figure 13A). As for the cIOL eyes, their larger prevalence of history of glaucoma is less likely to have impacted the drusen quantification results since there has not been many studies in the literature that have reported an association between glaucoma and AMD, although both diseases have been shown to be affected by similar morphological and functional changes in the central nervous system.[132] Additionally, since there was no significant differences found in the prevalence of smoking, hypertension, or glaucoma between the cIOL and yIOL eyes within any of the drusen type subgroups (Figure 13), it is possible that these clinical histories had no influence on the differences in drusen morphology found between both IOL types. This lack of influence is somewhat reflected in the repeated analyses comparing the prevalence of eyes with soft drusen and those with an absence of drusen in the post-mortem eyes while controlling for various combinations of clinical histories (Table 2). Although all histories, save for glaucoma, have been associated with AMD progression in the literature, it was only after excluding four or more clinical histories that the majority of combinations resulted in a loss of the significant differences in the prevalence of soft drusen and no drusen eyes between the cIOL and yIOL sample groups (Table 2). Additionally, although the exclusion of history of hypertension led to the highest number of combinations that resulted in a loss of significance, hypertension was also the most common history among all post-mortem eyes (Figure 9). As such, the effect of its exclusion on the comparison between cIOL and yIOL eyes with soft or no drusen may have been due to the resulting loss of sample size and not its inherent influence on drusen formation. Furthermore, although excluding all clinical histories led to complete loss of the significant differences in soft and no drusen prevalence between IOL types, it also resulted in a severe loss of sample size within both cIOL and yIOL eyes (Table 2). Therefore, because of the low sample sizes of the

clinical history data in this research, it is likely that the assessed clinical histories did not significantly influence drusen formation in either IOL type sample group.

5.6. Implications of Age Group Differences in Drusen Morphology

Pertaining to the comparison of drusen types across 10-year age groups, the larger proportion of eyes with soft drusen in the 90-99 age group falls in line with the current literature, since age is the most important risk factor for AMD progression. Although younger age groups also had a large proportion of soft drusen eyes, this is could have been caused by the smaller sample sizes of these groups. Therefore, acquiring a larger sample of post-mortem eyes in the younger age groups may add more statistical power to these findings and may lead to a better approximation of real-world trends.

5.7. Implications of IOL-Specific Differences in Drusen Morphology

Finally, we found that there were more cIOL eyes with soft drusen and more yIOL eyes with no drusen. These differences could be explained by the effect of blue light exposure on RPE health, since many studies have reported a photo-oxidative and damaging effect on photoreceptors and the RPE.[90,93,94] Despite there being a myriad of factors involved in the formation of drusen and the pathogenesis of AMD, our findings and the surrounding literature suggest that, within the context of this work, the observed differences in drusen types between cIOL and yIOL eyes were not likely to be overtly influenced by these confounding factors. Although the yIOL eyes had a higher mean age-at-surgery and age-at-death, they also ended up having a lower prevalence of eyes with soft drusen and higher prevalence of eyes with no drusen. In contrast, the cIOL eyes had a lower mean age-at-surgery and age-at-death, and ended up with a higher prevalence of eyes with soft drusen and lower prevalence of eyes with no drusen. Although cIOL eyes also had a larger mean surgery-to-death time, the association between

cataract surgery and AMD disease progression is not clear in the literature, with many studies reporting conflicting evidence. However, because the cIOL eyes became pseudophakic at an earlier timepoint than the yIOL eyes and, as a result, lost the blue light filtering capability of their natural crystalline lens much earlier, it is possible that they were exposed to blue light for a longer period of time than if there were no differences in mean surgery-to-death time. Nevertheless, given that the cIOL eyes were already implanted with a cIOL and that their mean surgery-to-death time was 6.96 years, the extra 1.55 years post-cataract surgery may not have significantly increased the amount of blue light that the cIOL eyes were ultimately exposed to. Furthermore, while controlling for different combinations of clinical histories did result in losing the significant differences in soft drusen and no drusen prevalence between the cIOL and yIOL eyes, it is possible that this loss of significance was due to the small sample sizes that resulted from the clinical history exclusions, since it took controlling for four or more clinical histories for the majority of combinations to result in a loss of significance. As such, it would be beneficial to acquire larger sample sizes in order to better assess the influence of these factors on drusen formation. However, aside from these factors, there are also many limitations that may have influenced the findings of this research.

5.8. Research Limitations

When considering the limitations of this project, there are a few notable considerations. First, enucleation of the post-mortem eyes by the technicians at the eye bank could be very traumatic since it can result in rapid increases in intraocular pressure and lateral compression of the eye, both of which could result in damage to the retina and warping of the retinal anatomy. Since this project relies on objective visualization of the retinal layers and subretinal drusen through histopathological analysis, changes to the architecture of the retina could severely

impact findings on drusen size and morphology. Second, it is possible that the eyes were slightly deteriorated due to the delay between enucleation and fixation, a factor that may have influenced the appearance of the retinal anatomy and, as a consequence, the findings from the histopathological analysis of the samples. Third, due to the use of post-mortem tissue, there was a potential for anatomical warpage from tissue handling when the eyes were sectioned. Specifically, the sectioning may have caused damage to the retina and choroid, potentially resulting in detachment of the retina. Fourth, since there is a lack of pre-cataract surgery clinical data, it was not possible to assess the state of drusen development or AMD progression in the post-mortem eyes before they received their respective IOL implants. Because of this lack of data, it is not clear if any of the eyes that were found to have drusen in their retinas did not already have drusen before IOL implantation. It is similarly unclear if any of the eyes with no drusen in their retinas actually benefited from having a yIOL implanted over a cIOL or vice versa. Fifth, because of a lack of data on family history and genotyping of the eyes, the potential effect of donor-specific family history of AMD or genetic predisposition to AMD on drusen development and AMD progression could not be controlled for. Finally, because the post-mortem eye samples only represented a fixed timepoint of disease progression, earlier timepoints could not be assessed within the same sample population or within any individual sample.

6. Conclusion

This research aimed to determine if blue-light filtering intraocular lenses decrease the risk of drusen formation and AMD progression by comparing AMD risk factors and drusen morphology in 193 post-mortem pseudophakic eyes implanted with either a cIOL or a yIOL. Based on the current literature, it was hypothesized that the eyes implanted with yIOLs would have less drusen formation. After evaluating the risk factors in both the cIOL and yIOL eyes, it was found that significantly more cIOL eyes had a history of glaucoma, while the yIOL eyes had significantly higher mean age-at-surgery and mean age-at-death, and significantly more eyes with a history of smoking and/or hypertension. No significant differences in the number of eyes with a history of diabetes, cancer, cardiovascular disease, or AMD were found. After comparing drusen morphology between the cIOL and yIOL eyes, it was found that significantly more cIOL eyes had large soft drusen (>125 μm) in their macula, while significantly more yIOL eyes had an absence of drusen. No significant differences in the number of eyes with hard or cuticular drusen were found. As such, these findings suggest that yIOLs decrease the risk of drusen formation in the macula and are protective against the incidence and development of AMD post-cataract surgery.

In order to further explore the potential protective effect of yIOLs against AMD progression, future research may include an assessment of RPE cell viability via immunohistochemical analysis in post-mortem eyes implanted with cIOLs or yIOLs, or an in-vivo evaluation of the RPE and choroid via optical coherence tomography in cataract patients with cIOL or yIOL implants.

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