THE ROLE OF BLUE LIGHT IN THE PATHOGENESIS OF AGE-RELATED MACULAR DEGENERATION

Blue light exposure is one of the modifiable risk factors involved in the pathogenesis of Age-Related Macular Degeneration (AMD). Several studies have evaluated the relationship between light exposure and AMD, as well as clinical trials evaluated the visual function effect of blue filtering IOLs versus conventional IOLs. However, the authors encourage further clinical trials to assess the preventive filtering effect of ophthalmic lenses, particularly those with narrow bandwidth filters, in the development and/or progression of AMD.
Age-related Macular Degeneration (AMD) is the most common cause of blindness in the elderly population in developed countries and accounts for 8.7% of all the blindness worldwide. In the future, the prevalence of AMD is likely to increase as a consequence of exponential population aging. The early stages of AMD are characterized by yellowish deposits (drusen) and/or pigmentary changes of retinal pigment epithelium (RPE) but without overt functional loss of vision. In advanced stages of AMD, there is dysfunction and death of photoreceptors secondary to an atrophic (geographic atrophy, GA) and/or a neovascular (choroidal neovascularization, CNV) event leading to irreversible loss of central vision.

The early stages of AMD, compared to its later stages, affect a significantly larger proportion of the population and increase the risk for visually significant advanced AMD by 12- to 20-fold over 10 years. There have been significant advances in the management of neovascular AMD and the introduction of anti-angiogenesis therapy can now prevent blindness and in many cases restore vision. However, the treatment modalities are expensive and not available to patients in many countries. Therefore, identification of modifiable risk factors that may inform disease prevention programmes is of priority. This review evaluates the long held belief that blue light exposure has a role in the pathogenesis of AMD.

"Light is necessary for vision but it can damage the sight organ itself." Light is necessary for vision but it can damage the sight organ itself – a property that has long been recognized. The human retina is exposed to the "visible component" of the electromagnetic spectrum from 400 to 700 nm and some short wavelength infrared because ultraviolet radiations are naturally filtered by ocular tissues located in front of the retina, particularly the cornea (295 nm) and the crystalline lens (less than 400 nm). Therefore, high-energy visible light, the blue-violet light renamed "blue light" for simplification, between 400 and 500 nm wavelength reaches the retina.

Blue light may damage the retina in a number of ways involving different chromophores and cellular events; however, retinal damage by photochemical mechanism is most likely to be of relevance in the development of AMD. Photochemical reactions occur in normal ambient conditions and involve a reaction between energetic photons and an absorbing molecule in the presence of oxygen leading to the generation of reactive oxygen species (ROS) that are highly toxic to the retina.

Short-term exposure (up to about 12 hours) to relatively intense blue light, referred to as "blue light hazard", can produce damage at the level of RPE in primates. The dependence of this type of damage on the oxygen concentration and on the level of various antioxidants to reduce the light damage confirms its oxidative nature. Furthermore, lipofuscin in the RPE is the most likely chromophore for this type of damage because lipofuscin is a potent generator of ROS, and more importantly, the action spectra for photochemical damage to the RPE correspond to the aerobic photoreactivity of the lipofuscin. The key component likely to contribute to lipofuscin’s photoreactivity is A2E (N-retinyldene-N-retinylethanolamine), a photosensitizer that has been demonstrated to produce ROS, trigger RPE cell apoptosis and lead to RPE cell death.

Long term exposures (typically 12-48 hrs) to less intense exposures produce damage at the level of the photoreceptors. The photopigments absorb the blue light and act as photosensitizer resulting in photoreceptor damage. It is believed that deep blue light is 50-80 times more efficient at causing photoreceptor damage than green light due to rhodopsin photo reversal. Blue light promotes the photoisomerization of all-trans-retinal...
that leads to the regeneration of rhodopsin and an increase phototransduction signaling in turn leads to photoreceptor apoptosis. Photoreceptor damage may also take place from liberation of ROS by all-trans-retinal, which is a well-known photosensitizer.  

Blue light damage increases substantially with aging and may play a role in the pathogenesis of AMD. Phototoxicity contributed by lipofuscin increases substantially with age because of substantial increase in the concentration of photoreactive elements. Past studies have shown that aging significantly increased the potential for blue light hazard by nine-fold over a life span. Lipofuscin is of particular importance because of several reasons: first, the chronology of lipofuscin accumulation within RPE cells is coincident with the development of AMD; second, in-vivo autofluorescence studies have shown that degenerative changes in the retina corresponds with the areas of highest autofluorescence; thirdly, RPE cells are retained throughout life and their repair system operates at a molecular level and this type of closed-system is more prone to ROS induced damage.

**TABLE I**

List of studies that have evaluated the relationship between light exposure and Age-Related Macular Degeneration (AMD)

<table>
<thead>
<tr>
<th>INVESTIGATOR</th>
<th>TYPE OF STUDY</th>
<th>SAMPLE SIZE</th>
<th>TYPE OF AMD</th>
<th>ASSESSMENT OF LIGHT EXPOSURE</th>
<th>CONCLUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor H.R. et al. (1992)*</td>
<td>Cross-sectional</td>
<td>838</td>
<td>Late AMD (GA+CNV)</td>
<td>Blue light exposure at leisure and working time for the previous 20 years</td>
<td>High levels of exposure to blue and visible light in late life may play a role in the pathogenesis of late AMD (OR: 1.35, 95%CI: 1.0-1.81)</td>
</tr>
<tr>
<td>Cruckshanks K. J. et al. (1993)*</td>
<td>Population-based</td>
<td>4926</td>
<td>Early AMD</td>
<td>Time spent outdoors in summer</td>
<td>The amount of time spent outdoors in summer was associated with an increased risk of early AMD (OR: 1.44, 95%CI: 1.01-2.04)</td>
</tr>
<tr>
<td>Darzins P. et al. (1997)</td>
<td>Case-control</td>
<td>409/286**</td>
<td>Any type of AMD (early+GA+CNV)</td>
<td>Annual sun exposure</td>
<td>Sun exposure was relatively greater in control subjects than in cases with AMD (p &lt; 0.01)</td>
</tr>
<tr>
<td>Delcourt C. et al. (1997) POA study</td>
<td>Population-based</td>
<td>2584</td>
<td>Early AMD</td>
<td>Annual ambient solar radiation</td>
<td>A decreased risk of early AMD was observed in subjects exposed to high ambient solar radiation (OR:0.73, 95%CI:0.54-0.98)</td>
</tr>
<tr>
<td>Tomany S.C. et al. (2004)* Beaver Dam Eye Study</td>
<td>Population-based</td>
<td>3684</td>
<td>Early AMD</td>
<td>Leisure time spent outdoors aged 13–19 years and aged 30–39 years</td>
<td>Significant associations were observed between extended exposure to the summer sun and the 10-year incidence of early AMD (RR:2.09; 95%CI:1.19-3.65)</td>
</tr>
<tr>
<td>Khan J.C. et al. (2006)</td>
<td>Case-control</td>
<td>446/283**</td>
<td>Late AMD (GA)</td>
<td>Sun exposure index (per unit increment)</td>
<td>No associations between late AMD (GA) and sun exposure or related factors were observed (p = 0.44)</td>
</tr>
<tr>
<td>Hirakawa M. et al. (2007)</td>
<td>Case-control</td>
<td>148/67**</td>
<td>Late AMD (GA+CNV)</td>
<td>Facial wrinkle length (direct correlation with sunlight exposure)</td>
<td>Significantly more facial wrinkling was found in patients with late AMD (p = 0.047, OR: 3.8; 95% CI: 1.01 - 13.97)</td>
</tr>
<tr>
<td>Vojinovic B. et al. (2007)</td>
<td>Population-based</td>
<td>1300</td>
<td>Any type of AMD (early+GA+CNV)</td>
<td>Exposure of sunlight</td>
<td>Significant correlation was observed between chronic exposure to sunlight and prevalence of any type of AMD</td>
</tr>
<tr>
<td>Pletina-Borjan I. et al. (2007)</td>
<td>Cross-sectional</td>
<td>623</td>
<td>Any type of AMD (early+GA+CNV)</td>
<td>Mean daily exposure (in hours) to solar radiation</td>
<td>A positive relationship was observed between long-term sunlight exposure and increased risk of any type of AMD</td>
</tr>
<tr>
<td>Fletcher A.E. et al. (2008)*</td>
<td>Population-based</td>
<td>4753</td>
<td>Late AMD (CNV)</td>
<td>Blue light exposure</td>
<td>Significant associations were found between blue light exposure and neovascular AMD in patients with lowest antioxidant levels (OR:1.09,95%CI:0.84-1.41)</td>
</tr>
</tbody>
</table>

*significant and positive association; ** no. of controls; GA: Geographic atrophy; CNV: Choroidal neovascularization; OR: Odds ratio; RR: Relative risk; CI: Confidence interval
Several studies in the past have evaluated the role of blue light on the development of AMD (Table 1). A study by Taylor et al. on 838 watermen of the Chesapeake Bay demonstrated that patients with advanced AMD had significantly higher exposure to blue or visible light over the preceding twenty years. Similarly, the Beaver Dam Eye Study observed that visible light rather than UV light might be associated with AMD. Furthermore, the EUREYE study found a significant association between blue light exposure and AMD. Recently, a systematic review and meta-analysis included fourteen studies that evaluated the association between sunlight exposure and AMD. In this review article, twelve out of fourteen studies identified an increased risk of AMD with greater sunlight exposure, six of which reported significant risks. The pooled odds ratio was 1.379 (95% confidence interval 1.091 to 1.745). The subgroup of non-population-based studies revealed a significant risk (odds ratio 2.018, confidence interval 1.248 to 3.265, p=0.004). The authors concluded that individuals with more sunlight exposure are at significantly increased risk of AMD. It is important to note that epidemiological studies evaluating light exposure and risk of AMD have several limitations. The pathogenesis of AMD is very complex and lifetime light exposure cannot be measured accurately. Also, there are notable dif-

<table>
<thead>
<tr>
<th>PRINCIPAL INVESTIGATOR (YEAR OF PUBLICATION)</th>
<th>TYPE OF STUDY SUBJECTS</th>
<th>SAMPLE SIZE (N° OF EYES)</th>
<th>VISUAL FUNCTION</th>
<th>CONCLUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuan Z. et al. (2004)</td>
<td>Healthy</td>
<td>30* 30*</td>
<td>Colour vision, contrast sensibility</td>
<td>Blue filtering IOLs are preferable over conventional IOLs in preserving spatial contrast sensitivity and cause less photophobia and cyanopsia in the early postoperative period</td>
</tr>
<tr>
<td>Marshall J. et al. (2005)</td>
<td>Healthy</td>
<td>150 147</td>
<td>Photopic, scotopic &amp; colour vision</td>
<td>No significant difference between blue filtering IOLs and conventional IOLs in terms of visual performance</td>
</tr>
<tr>
<td>Raj S.M. et al. (2005)</td>
<td>Congenital color blind (partial red-green)</td>
<td>30 30</td>
<td>Colour vision</td>
<td>No significant difference between blue filtering IOLs and conventional IOLs in terms of visual function in subjects with congential partial colour blindness</td>
</tr>
<tr>
<td>Rodriguez-Galietero A. et al. (2005)</td>
<td>Diabetes</td>
<td>22 22</td>
<td>Colour vision, contrast sensitivity</td>
<td>Blue filtering IOLs improved color vision in the blue-yellow chromatic axis in diabetic patients</td>
</tr>
<tr>
<td>Kara-Júnior N. et al. (2006)</td>
<td>Healthy</td>
<td>56 56</td>
<td>Photopic &amp; colour vision</td>
<td>No significant difference between blue filtering IOLs and conventional IOLs in blue-yellow perception</td>
</tr>
<tr>
<td>Vuori M.L. et al. (2006)</td>
<td>Healthy</td>
<td>25 27</td>
<td>Colour vision</td>
<td>No significant difference between blue filtering IOLs and conventional IOLs in color vision</td>
</tr>
<tr>
<td>Miftuqulu O. et al. (2007)</td>
<td>Healthy</td>
<td>38 38</td>
<td>Photopic, scotopic &amp; colour vision and contrast sensitivity</td>
<td>No significant difference between blue filtering IOLs and conventional IOLs in terms of visual performance</td>
</tr>
<tr>
<td>Landers J. et al. (2007)</td>
<td>Healthy</td>
<td>93 93**</td>
<td>Colour vision, contrast sensitivity</td>
<td>No significant difference between blue filtering IOLs and conventional IOLs in terms of visual performance</td>
</tr>
<tr>
<td>Schmidinger G. et al. (2008)</td>
<td>Healthy</td>
<td>31* 31*</td>
<td>Colour vision, contrast sensitivity</td>
<td>No significant difference between blue filtering IOLs and conventional IOLs in color contrast sensitivity</td>
</tr>
<tr>
<td>Kiser A.K. et al. (2008)</td>
<td>AMD</td>
<td>22 22</td>
<td>Photopic, scotopic &amp; colour vision</td>
<td>No significant difference between blue filtering IOLs and conventional IOLs in scotopic vision but detection of navy colour may be impaired</td>
</tr>
<tr>
<td>Wirtitsch M.G. et al. (2009)</td>
<td>Healthy</td>
<td>48* 48*</td>
<td>Colour vision, contrast sensitivity</td>
<td>Blue filtering IOLs negatively affect contrast acuity and blue/yellow foveal threshold when compared with conventional IOLs</td>
</tr>
<tr>
<td>Kara-Júnior N. et al. (2011)</td>
<td>Healthy</td>
<td>30 30</td>
<td>Photopic, scotopic &amp; colour vision and contrast sensitivity</td>
<td>No significant difference between blue filtering IOLs and conventional IOLs in terms of visual performance</td>
</tr>
<tr>
<td>Espíndola R.F. et al. (2012)</td>
<td>Healthy</td>
<td>27 27</td>
<td>Photopic, scotopic &amp; colour vision</td>
<td>Contrast sensitivity was better under mesopic conditions with conventional IOLs; however, no significant difference was observed between blue filtering IOLs and conventional IOLs in terms of color vision</td>
</tr>
</tbody>
</table>

Blue filtering intraocular lens (IOLs) refer to Alcon SN60AT except * corresponding to Hoya UV AF-1 and ** corresponding to other conventional IOLs.
difficulties in such studies that depend on the patients’ own recall about cumulative exposure to blue light. Moreover, other factors including variability in genetic susceptibility or diet may obfuscate the true relationship between light exposure and AMD.

The nature of the blue light induced damage is dependent not just on the photoreactivity of a variety of chromophores but also on the capacity of the defense and repair systems. One of the defense systems that deserve special mention is macular pigment (MP). MP is composed of two dietary carotenoids, lutein (L) and zeaxanthin (Z), and has peak concentration within the central 1-2 degrees of the fovea.23 MP carotenoids are natural protective filters attenuating short-wavelength light prior to photoreceptor light capture with absorbance spectra ranging from 400 to 500 nm (lutein = 452 nm; zeaxanthin = 463 nm). It is therefore particularly effective at reducing the potential damaging effect of lipofuscin whose photoreactivity peaks at 450 nm in elderly population. MP acts, uniquely as an antioxidant, both passively and actively, the former mechanism being dependent on its ability to limit photo-oxidative damage by filtering short wavelength light at a pre-receptorial level and the latter mechanism attributable to its capacity to quench ROS.24, 25

Implantation of blue-light filtering intraocular lens (IOLs) following cataract surgery may have the potential to protect the retina from oxidative damage secondary to blue light and slow the progression of AMD. In experimental studies, these IOLs have been demonstrated to significantly reduce the death of RPE cells from light induced damage mediated by lipofuscin fluoropore A2E.26 Furthermore, blue light filtering IOLs may provide additional visual benefit for AMD patients because blue light is selectively scattered by the ocular media and its attenuation has been associated with improvements in contrast sensitivity and a reduction in glare sensitivity.27

There have been theoretical speculations about the potential negative ramifications of filtering blue light. Blue light provides 35% of scotopic vision, 53% of melanopsin, 55% of circadian and 32% of s-cone photoreception. Blue light filtering IOLs eliminate 27-40% of incident blue light depending on their dioptic power.28 The decrease in blue light photoreception therefore may result in impairment of color vision, scotopic vision, and circadian rhythm. Several randomized clinical trials have been conducted to compare visual performance using blue filtering IOLs and conventional IOLs in healthy volunteers and in patients with AMD (Table 2). The results from these trials suggest that there are no clinically significant effects on various measures of visual performance, including color vision, photopic and scotopic sensitivities and contrast sensitivity with blue filtering IOLs.29 Also, given the great improvement in light transmission achieved simply by removing the cataract, it seems unlikely that blue filtering IOLs cause any significant disruptions to the circadian rhythm. However, there is a current lack of evidence that demonstrates that blue filtering IOLs have any effect on AMD. No randomized prospective studies have been conducted to prove claims of macular protection against progressive disease.

Furthermore, a recent study in animal model suggested that the 415-455 nm spectral range might be the most damaging light for patients at risk of AMD.30 The authors suggest that filters in this narrow bandwidth would not occlude light in the 460-500 nm range, not only essential for color vision but also for circadian rhythm regulation mediated by melanopsin-sensitive retinal ganglion cells. However, it remains to be evaluated if new selective ophthalmic filters in the defined bandwidth could provide macular protection in patients at risk of AMD.

Similarly, another proposed option is to use eyeglasses that attenuate short-wavelength light in bright environments for effective photo-protection. Crizal® Prevencia® No-Glare clear lenses represent the first application of new patent-pending technology.
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that enables selective attenuation of harmful light, both UV and blue-violet, while allowing beneficial light to pass through and maintaining exception- al transparency at all other visible-light wavelengths. The goal is to enable patients to enjoy the best vision with significant protection against UV and high-energy blue-violet wavelengths. The advantage of eye- glasses (c.f. IOLS) lies in the fact that there is freedom to remove sunglasses for optimal scopic and circadian photoreception, if necessary.

In summary, there is persuasive theor- etical and experimental evidence suggesting that blue light exposure may damage the retina and possibly play a role in the pathogenesis of AMD; however, there is a paucity of clinical evidence to support this notion. In the future, well-designed clinical trials should be undertaken to evaluate the effect of blue light filtration, particularly those with narrow bandwidth, in the development and/or progression of AMD.

**KEY TAKEAWAYS**

- Blue light provides 35% of scotopic vision, 53% of melanopsin, 55% of circadian and 32% of s-cone photoreception. Yet blue-violet light may damage the retina.

- The nature of the blue-violet light induced damage is dependent on the photoreactivity of a variety of chromophores and on the capacity of the defense-repair systems.

- A systematic review and meta-analysis indicates that people with more sunlight exposure are at significantly increased risk of AMD.

- However, individual patients’ cumulative exposure to blue-violet light is complex to measure. Several other individual factors involved in AMD pathogenesis can vary, including genetics, diet, etc.

- Implantation of blue-light filtering intraocular lens (IOLS) following cataract surgery may have the potential to protect the retina from oxidative damage secondary to blue light and slow the progression of AMD.

- Blue light filtering IOLS eliminate 27-40% of incident light depending on their dioptic power.

- It remains to be evaluated if new selective opthalmic filters in the defined bandwidth could provide macular protection in patients at risk of AMD and/or patients operated on cataracts.

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**REFERENCES**