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REVIEW ARTICLE

Ultraviolet radiation oxidative stress affects eye health

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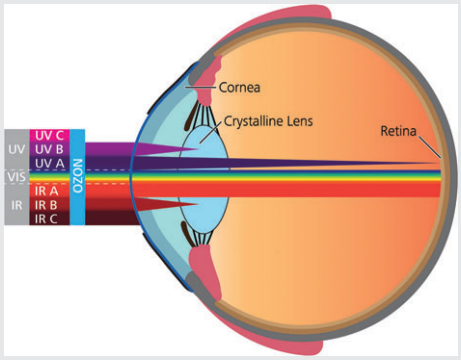
In the eye, ultraviolet radiation (UVR) is not known to contribute to visual perception but to mainly damage multiple structures. UVR carries higher energy than visible light and high dose exposure to UVR causes direct cellular damage, which has an important role in the development of cancer. This review provides an overview on the most recent knowledge on the role of UVR in oxidative stress (OS) in relation to noncancer ocular pathologies: various corneal pathologies, cataract, glaucoma and age-related macular degeneration. Possible OS signaling streams and mechanisms in the aging eye are discussed. Excessive exposure to UVR through live may seriously contribute to increase in OS of various eye tissues and thus lead to the advancement of serious ocular pathologies. Children are especially vulnerable to UVR because of their larger pupils and more transparent ocular media: up to 80% of a person's lifetime exposure to UVR is reached before the age of 18. Therefore, efficient everyday protection of the sensitive tissues of the eye by wearing of sunglasses, clear UVR-blocking spectacles or contact lenses should be considered from early age on. Many initiatives are taken worldwide to inform and raise the population's awareness about these possible UVR hazards to the eye.



KEYWORDS
eye health, oxidative stress, ultraviolet radiation, UVA, UVB

1 | INTRODUCTION

Visual perception is a complex phenomenon that is initiated when electromagnetic radiation from the sun reaches the retina and the visible spectrum is converted from radiant energy into sensation by the phototransduction in the retinal photoreceptors. The ability to translate electromagnetic radiation into usable visual information relies on a complex interaction between the different structural and functional components of the eye and the brain. Electromagnetic radiation has a dual wave-particle nature, but when it is absorbed by a photoreceptor at the retina, its particle nature is dominant. The portions of the electromagnetic spectrum that interact with the eye are shown in Figure 1. They are referred to as optical radiation and include wavelengths from ultraviolet (100-400 nm, UVR), visible light (400-760 nm, VIS) to infrared (above 760 nm, IR) [1]. The International Commission on Non-Ionizing Radiation Protection (ICNIRP) defines [2] several subgroups of ultraviolet or invisible radiation classified into UVA (315-400 nm), UVB (280-315 nm) and UVC (100-280 nm). Infrared radiation has also been subdivided into 3 groups depending on the

Abbreviations: OS, oxidative stress; UVR, ultraviolet radiation

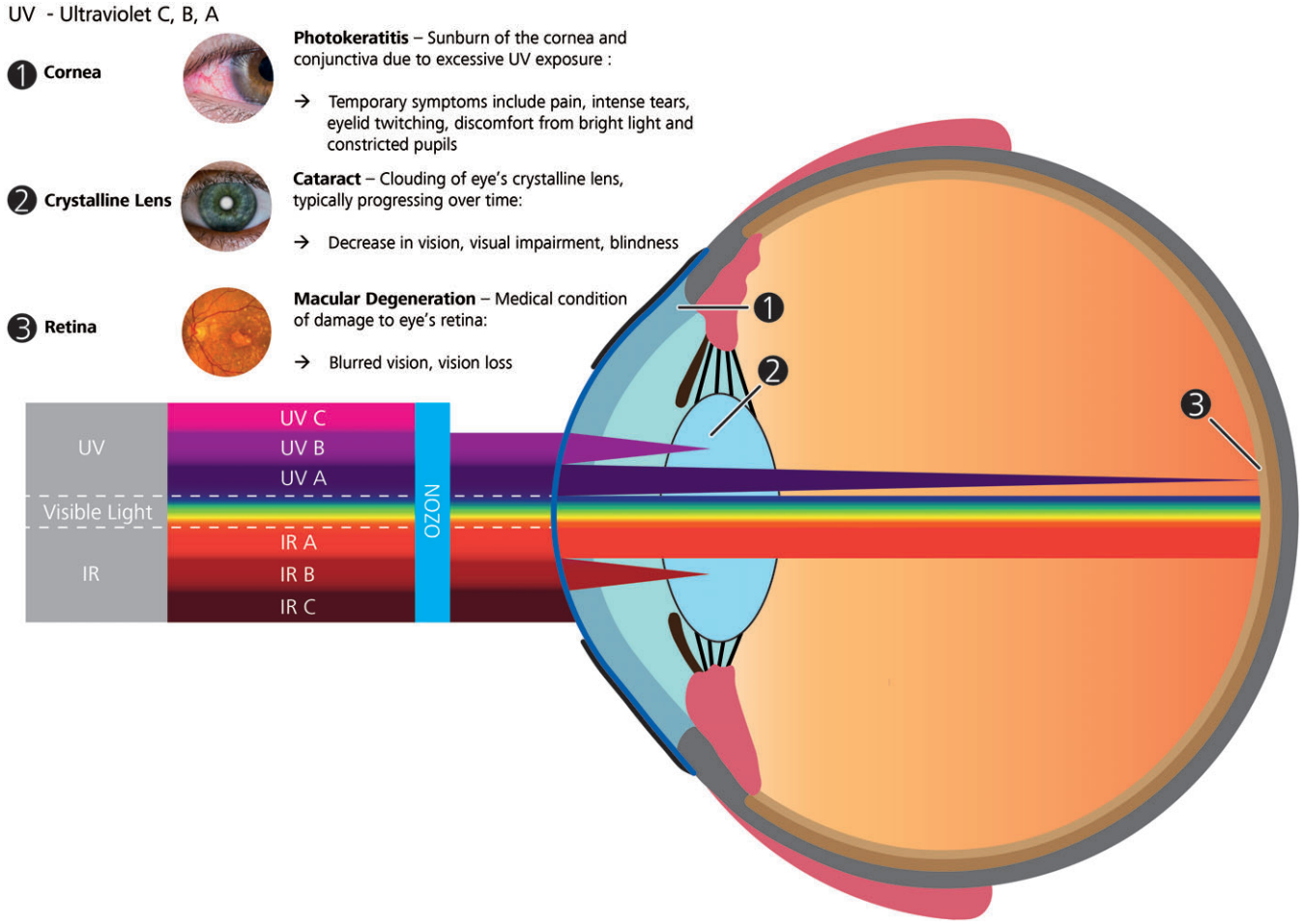


FIGURE 1 A schematic diagram of the eye showing the relative propagation of the different optical radiation bands through the ocular tissue. The optical media (cornea lens, aqueous humor and vitreous humor) are generally transparent only to wavelengths in the visible and IRA bands. UVC and UVB are mostly absorbed by the nucleotide bases and aromatic amino acids and therefore do not propagate past the cornea and the lens, respectively. The IR bands beyond 1400 nm (IRB and IRC) are increasingly absorbed by water molecules and do not penetrate past the superficial cornea. UVA and UVB radiation reaching the retina varies with age but it is estimated that in adulthood less than 2% UVA and 1% UVB radiation (not illustrated) reaches the retina. Under certain circumstances the different structures of the human eye and the retina may be damaged by solar or coherent laser radiation

wavelength: IRA (700-1400 nm), IRB (1400-3000 nm) and IRC (3000-10 000 nm) [1]. We follow these subdivisions as they are useful for safety and hazard evaluations. They separate the wavelengths into bands of roughly similar photon energy, tissue penetration and general classes of bio-effects. Visible light is referred to as short ($\lambda = 420$ nm), medium ($\lambda = 530$ nm) and long wavelength ($\lambda = 560$ nm) corresponding to the peak absorption spectra of the cone visual pigments. Light is transmitted through the eye and then after absorption, scattering and transduction, the signals are compressed and send via the optic nerve to the brain directing both visual perception and circadian rhythm. Because of its function and structure, the eye is most susceptible to light damage; it is designed to focus incoming light rays to form images on the neural retina. This has the effect of concentrating the light or increasing the power density of light on the retina. Thus, light delivering a radiant exposure insufficient to produce skin damage may indeed cause injury when focused on the retina. The absorption spectrum of each ocular tissue [3, 4] must be taken into account to understand its differential sensitivity with respect to wavelength (Figure 1). The primary factors that determine whether ambient radiation will injure the human eye outside of defined laboratory conditions are: (1) the intensity of the light, (2) the wavelength received by ocular tissues and (3) the age of the recipient [4]. In the eye, UVR is not known to contribute to visual perception and there are strong evidences that acute high dose exposure to UVR causes photokeratitis and photoconjunctivitis, while even low dose chronic exposure to UVR is a risk factor for cataract, pterygium and squamous cell carcinoma of the cornea and conjunctiva [5–7]. There is weaker evidence in relation to other, noncancer eye conditions, related with the oxidative stress (OS) induced by UVR exposure.

The aim of this review is an overview of the most recent knowledge on the role of the UVR in eye health and its aging process with a main focus on OS-induced noncancer diseases. Highlighted are endogenous and exogenous mechanisms to protect the retina from different type of injuries caused by the invisible bands of the electromagnetic

spectrum. Most prevalent ocular diseases are analyzed in relation to OS and solar UVR exposure, such as cataract, glaucoma and age-related macular degeneration (AMD). Possible OS signaling streams and mechanisms related to the various diseases in the aging eye are discussed.

2 | TYPES OF LIGHT-INDUCED DAMAGE TO THE OCULAR TISSUES

Three main types of tissue light damage are distinguished [8]: thermal (inflammatory response), photomechanical (stress confinement) and photochemical (photo-oxidation). Important differences among these photic damages are related not only to their damaging mechanism but also to their primary absorbers, thresholds and light inducing spectrum [8]. One of the main differences between the photochemical and the other damages is their light-inducing sources [8]. While thermal and photomechanical damages occur only due to coherent light sources, for example, lasers, photochemical damage may also be produced by exposure to solar radiation. Solar light reaching the eye is essential for visual perception but despite that the eye has several UVR protective mechanisms, discussed in detail in section 3.1, it is easy to expose it to levels that exceed these natural defense limits. We continue with a brief description of the damaging mechanisms in the thermal and photomechanical types and discuss in detail the role of UVR in the photochemical damage, which is thought to be the most common mechanism by which light exposure causes cellular damage. An overview of the different types of damage is given in Table 1.

TABLE 1 Mechanisms of light damage to the eye

Mechanism	Spectra	Exposure time (short pulses)	Temperature increase
Photothermal	upper end VIS; near IR	~100 ms	$10°C < \Delta T < 100°C$
Photomechanical	near IR	~10 ns	ΔT ~10 000°C
Photochemical		linear	
Ablative	UVC	~1 μs	$\Delta T < 10°C$
Oxidative	UVA and VIS	long ~s, min	$\Delta T < 10°C$
Photosensitized			
Type I and type II	UVA	~months, years	$\Delta T < 10°C$
Delayed effects	UVA and UVB	~months, years	$\Delta T < 10°C$

The type of tissue light damage (first column) depends on the spectra of the exposing light (second column), the duration of the exposure (third column) and the type of tissue being exposed, which in turn determines the exposure temperature (last column). Example of photothermal damage to the retina is in the form of the clinical usage of lasers for the treatment of various diseases in the retina. Pulsed lasers produce photomechanical damage via stress confinement in tissues when used for producing precise holes or cuts, particularly in the anterior segment. The most familiar example of human photochemical damage is the sunburn of the skin.

2.1 | Photothermal damage

In thermal damage, the structure of proteins is corrupted by strong oscillations that break bonds between molecules [9]. For example, when boiling an egg the protein changes from transparent to opaque.

Photothermal damage occurs by the transfer of radiant energy, photons, from light to the retinal tissue. A photon can be absorbed by a molecule only if its energy is equivalent to the energy difference between the molecule's current energy state and an allowed higher energy level known as an excitation state. For wavelengths of light at the upper end of the visible spectrum, as well as wavelengths of light near infrared, vibrational and rotational energy states predominate over the excitation states. Therefore, rather than attaining their excitation states, molecules in the tissue tend to gain both rotational and vibrational energy. This increase in mean kinetic energy is dissipated as molecules collide with each other and their temperature increases. The ability of light to cause an increase in mean kinetic energy is inversely proportional to the wavelength of the light. The relationship between light and energy is described by the equation: $E = hc/\lambda$, where energy (E) equals Planck's constant (h) multiplied by the speed of light (c) divided by the wavelength of light (λ). Therefore, the shorter the wavelength, the greater the potential increase in kinetic energy and the greater the rise in temperature for a fixed exposure time. In a closed system, there is a proportional relationship between exposure time and thermal effect. In an open system, the amount of energy required to produce a given thermal effect increases for longer exposure times as energy in the form of heat dissipates to the surrounding environment during the exposure. Therefore, dependent on the duration of thermal exposure, irreversible thermal damage in the retina typically occurs after the ambient temperature in the tissue is raised by at least 10°C [10]. On cellular and molecular levels, increase in temperature cause the denaturing of proteins, loss of molecular tertiary structure and fluidization of membranes.

2.2 | Photomechanical damage

Photodisruption occurs when the laser exposure deposits energy into the optical zone in a pulse that is shorter than the relaxation time required to relieve the mechanical stress produced in the tissue by thermoelastic expansion [8]. The local temperature in the optical zone during the laser exposure may reach up to 10 000°C. Tissue damage results from actual mechanical compressive or tensile forces. Tensile forces resulting in the formation of microcavitation bubbles, in particular, are lethal for retinal pigment epithelium (RPE) and other cells of the retina (Figure 2).

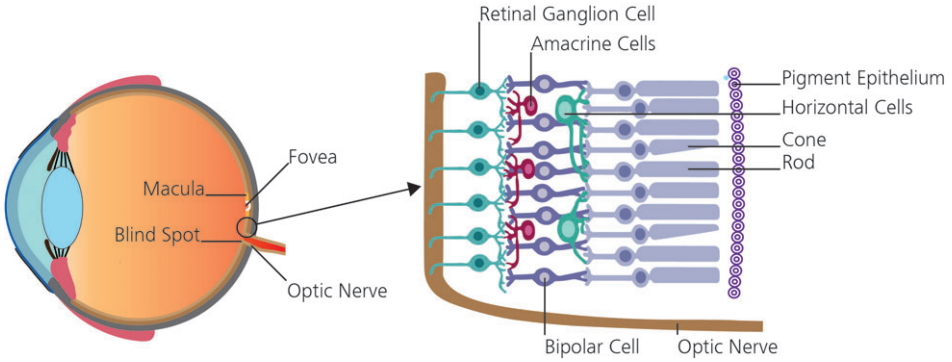


FIGURE 2 Morphological structure of the retina

2.3 | Photochemical damage and UVR (solar and laser)

Photochemical damage involves cellular damage by supercharged molecules [11]. By definition, it is damage to the tissue that is independent of either mechanical or thermal damage. Three types of photochemical damage are known: ablation, photo-oxidative damage and photosensitized reaction. Among them, the last 2 are the most common damages in tissue caused by solar energy and UVR in particular.

2.3.1 | Photochemical ablation

Photochemical ablation results when high-energy UVC and UVB photons interact with molecules [12]. At wavelengths below 200 nm, photons are sufficiently energetic to break chemical bonds, for example, these photons possess greater than 6 eV/photon compared to the average covalent bond strength of 2 to 4 eV. If these UV photons are delivered to the tissue in short pulses, tissue may be removed precisely. Tissue removed through this mechanism is ejected at high velocities, with little apparent thermal damage to the remaining tissue, although there is continuing concern about the degree of risk to the remaining tissue from recoil shock produced by the high-velocity ejection of molecules [12]. However, photochemical ablation is used extensively in ophthalmology for refractive surgery, where the cornea is reshaped to change its refractive power by application of the ArF excimer laser, which emits light at 193 nm.

2.3.2 | Photo-oxidative damage

Photo-oxidative, or commonly referred to as photochemical damage, occurs when incident light interacts with an endogenous chromophore in the ocular tissue, causing a chemical change that is not related to a thermal increase in the irradiated tissue. Candidates for intraocular chromophores excitable by UVA and visible wavelengths are photoreceptor visual pigments, proteins, flavoproteins and the naturally occurring pigment granules of melanin and lipofuscin in the RPE [8, 11]. Photochemical damage is associated with long-duration exposure, wavelength of 550 nm or shorter (including blue light) and low to moderate tissue irradiance [8, 11]. The short visible wavelengths are also strongly absorbed by the RPE pigments, melanin and lipofuscin, both of which are photoexcitable. Photochemical damage is generally a linear process: their extent depends on the amount of light absorbed in a chromophore. When the chromophore absorbs a photon, it is typically excited to a triplet state. Triplets are reactive species and readily undergo chemical reactions with other molecules.

A well known example of photochemical damage is the retinopathy produced by prolonged sungazing. Solar retinopathy has been studied in detail and a thermal contribution has been ruled out by an analysis showing that the temperature increase in the retina during sungazing is at most only 2 to 4°C [13] which is less than the 10°C increment required for permanent thermal damage [10, 14]. This indicates that a photochemical process is responsible for solar retinopathy. Retinal damage can also be incurred by prolonged exposure to artificial light sources.

2.3.3 | Photosensitized UVR reactions

The previous discussion was primarily concerned with photochemical damage resulting from the direct interaction of light with endogenous tissue chromophores. In contrast, in the photosensitization process oxygen and photosensitizers are required to absorb the UVR, although sometimes longer wavelengths can also be involved. Some sensitizers are natural compounds but most are synthetic. A photosensitizer may be defined as a chemical which, on activation by radiation, causes another component of a cellular system to react. Two basic mechanisms for photosensitized reactions have been distinguished (Figure 3). It is important to note that these reactions are significant sources of reactive oxygen species (ROS) due to the constant exposure of the eyes to solar UVR. While it is known that both the UVA and UVB components of the solar radiation are strongly implicated in the etiology of most skin [16, 17] and eyelid [18] cancers and in the generation of reactive free radicals, [19] their role and contribution to noncancer diseases in the eye is less clear cut [20].

3 | UVR TYPE AND REACTIVE OXYGEN SPECIES

Here, our focus is on the involvement of the UVA and UVB solar bands in the different photosensitized reactions (Table 2), rather on giving detail description of the complex

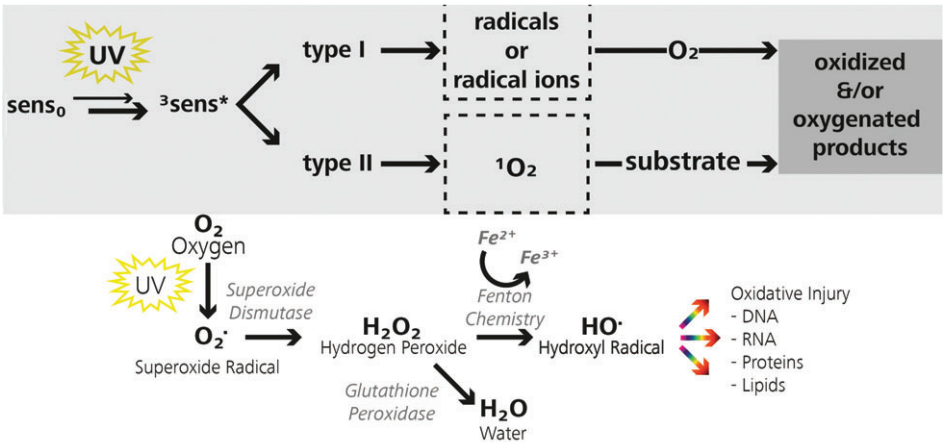


FIGURE 3 A schematic diagram of ROS generation due to UVR exposure. On the top, type I and II reactions are shown. In type II, a chromophore is excited by light to a triplet state, and undergoes a direct electron or hydrogen exchange with a substrate, creating a free-radical intermediate. This free radical reacts with additional substrate or with oxygen to create peroxidation reaction products. In the case of lipid peroxidation, the reactions proceed as a self-propagating chain. In the type II photodynamic reaction, there is an energy transfer from the excited chromophore directly to oxygen (O_2), creating a reactive singlet oxygen, which is a triplet in its ground state and it is abandon especially in the retina. Singlet oxygen $^1O_2$ in turn reacts with lipids to create peroxides without a free-radical intermediate, or it can react with other substrates to generate reactive free radicals. At the bottom, a schematic diagram of a delayed reaction is shown. It is characterized by the generation of the electric neutral hydrogen peroxide, which can cross through specific cell membranes and appear in other compartments of a cell different from those where it was generated [15]. In the presence of some metal ions the H_2O_2, a nonradical oxygen species, forms the highly reactive and most powerful free radical HO..

processes underlying the different reactions, described elsewhere [19, 21]. Both type I and type II reactions, presented schematically in Figure 3, are known to be induced by UVA and give rise to carbon-centered radicals, the likely precursors of peroxyl radicals through subsequent O_2 addition. Superoxide radical anion $O_2^{\cdot-}$ is typically the final result of type I reactions. The toxic $O_2^{\cdot-}$ is highly reactive and may also dismutate biologically to form the electric neutral hydrogen peroxide (H_2O_2) and singlet oxygen in a secondary reaction. The second major photosensitization mechanism is mostly related with energy transfer to molecular oxygen giving rise to singlet oxygen $^1O_2$, which is specifically reactive towards biomolecules exhibiting double bonds rich in electrons. Confirmation for the occurrence of the sensitized reactions to UVA radiation was gained from a noninvasive detection of $^1O_2$ and $O_2^{\cdot-}$ in UVA-exposed skin of mice [22, 23]. This was achieved using a specific and a sensitive chemiluminescence probe and ultra low light imaging device with a Charge-Coupled Device (CCD) camera.

TABLE 2 Contribution of UVA and/or UVB radiation to the different photosensitized reactions, oxidative and cancer damage to the eye

	UVA	UVB
Reaction		
Type I	✓	
Type II	✓	
Delayed	✓	✓
Oxidative damage		
Direct DNA damage	✓	
Other molecules damage	✓	✓
Cancer	✓	✓

More specific information concerning the involvement of the UVB radiation in photosensitized delayed reactions was gained from real-time chemiluminescence imaging measurements with a time-dependent increase within the few minutes following the end of the irradiation [24, 25] and using noninvasive Fourier-transform Raman spectroscopy analysis of the epidermis [26]. It is also known that UVB radiation is a more efficient generator of H_2O_2 than UVC photons [15]. Similarly, it is now known that exposure to UVA photons may also lead to the generation of ROS as delayed biochemical reaction. Evidence is showing that UVA-induced inflammation reactions are mediated by initially generated H_2O_2 that are likely to initiate signal transduction processes [27].

It is worth noting that UVA radiation is more efficient than UVB in inducing oxidatively generated damage to the deoxyribonucleic acid (DNA) in isolated cells and skin [19, 21]. The UVA-induced damage is mostly explained in terms of selective oxidation by singlet oxygen generated through type II photosensitization mechanism. However, while both UVB and UVA radiation bands are able to trigger delayed oxidative responses that may persist after the irradiation is stopped, there is no evidence for the implication of delayed oxidative degradation pathways of cellular DNA.

Once generated, the free radicals ($HO^{\cdot}$, $O_2^{\cdot-}$) that belong to the ROS and the nonradical oxygen species (H_2O_2, $^1O_2$), beside DNA, can attack many other molecule types causing damage and rendering them inactive. Tissues in which there is a large concentration of cell membranes and oxygen are particularly vulnerable to free radicals; the attack of free radicals on polyunsaturated fatty acids results in lipid peroxidation that breaks down membranous structures. Lipid

peroxidation is propagated as a chain reaction and can cause extensive damage. Retinal photoreceptors, particularly the outer segments, possess large amounts of membrane and are, therefore, thought to be especially susceptible to this type of free radical-induced damage. Free radicals are also thought to induce protein oxidation in much the same way as lipid oxidation, hence also causing injury to both the neurosensory retina and RPE.

3.1 | Exogenous and endogenous UVR protective mechanisms and oxidative stress in the retina

The retina is probably the tissue that contains the highest endogenous photosensitizers that can be excited by light and, as a consequence, it is highly sensitive to oxidative damage. The proximity to choroidal blood vessels in the outer retina favors photoreceptor cells and RPE cells to be highly oxygenated and consequently more sensitive to oxygen imbalance (Figure 4) and photochemical damage. Although, the retina has a system that protects cells and tissues against OS, aging or deficient nutritional conditions, these mechanisms could fail and the pathologic symptom of retinal degeneration begins. There are several layers in and outside the human eye that protect the retina from OS induced by direct exposure to UVR.

Ozone is a gas present in the upper layers of the atmosphere and serves as the first exogenous protection layer against harmful UVR. Its molecules are formed by 3 atoms of oxygen and have the ability to absorb UVR from the sunlight. The major natural source of ultraviolet radiation is the sun and when solar UVR passes through the atmosphere, it undergoes scattering and absorption. Absorption is mainly in the stratosphere and is mediated by molecular oxygen and ozone. The ozone layers prevent almost all UVC from reaching the eye. They also absorb about 70% to 90% of the UVB. Thinning of the protective ozone layers has led to an increase in solar UVB radiation reaching the Earth's surface, with many consequences for human health.

As already outlined in section 1, the absorption spectrum of each ocular tissue determine the effect of light on the retina and the manner in which light traverses the ocular media to reach the retina (Figure 1). Beside the upper eye lids and to a lower extent the eyebrows that shield the eye, tear film is the first protective layer of the eye that absorbs UVR. Although the eye is designed to focus light specifically on the central retina, some of the light entering the eye is either absorbed or scattered by the tissue and media between the front of the eye and the retina. The 2 most important sources of tissue absorption of UVR are the cornea and the lens. The cornea is transparent to visible light but absorbs a significant portion of the UVB radiation, variously noted as 22% to 73% for the 300 to 320 nm band or up to 92%, and a very small amount of UVA radiation [28, 29]. The next layer of defense against UVR is the aqueous humor. Ultraviolet wavelengths from 295 to 317 nm are absorbed in the

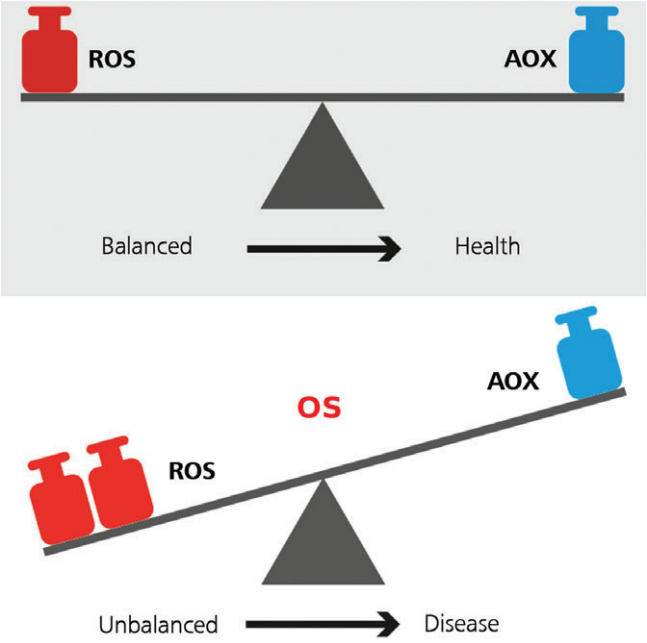


FIGURE 4 Top, equilibrium between reactive oxygen species production and antioxidant defense mechanism. Bottom, imbalanced situation between ROS and AOX, which is associated with many pathologies. All biomolecules can be attacked by ROS: DNA, lipids, proteins and nucleic acids. Among them, lipids are probably the most susceptible to undergo oxidation. All cell membranes are rich in polyunsaturated fatty acids, which are easily injured by oxidizing agents. Oxidative stress and its biomarkers are the biochemical end point of the imbalance between ROS production and the ability of AOX to counteract the effects of ROS metabolites. Cells maintain a reducing environment by the corresponding enzymes and the constant supply of metabolic energy. The OS effects depend on the intensity of such abnormalities and the cellular response. If the cell is unable to overcome and to recover its function, the exogenous and endogenous AOX defenses cannot counter it, and the cell can become extinct

aqueous humor but absorption decreases with increasing wavelength, such that the aqueous humor is transparent to visible light, that is, there is no absorption of wavelengths greater than 400 nm. Ascorbic acid in the aqueous humor is believed to be responsible for UV absorption and also provides antioxidant protection from UVR-induced damage to the lens surface. The human lens is cloudless at birth and transmits both UVA and UVB radiation, allowing these wavelengths to reach the retina, the choroid, and the ciliary body. As the lens ages, changes in the lens proteins and yellowing of the lens decreases transmission of UV wavelengths, so that tissues beyond the lens are believed to be protected from UVR in adulthood. Although a considerable proportion of UVR reaching the lens is absorbed (36% absorbance at 320 nm and 48% absorbance at 340 nm), it is estimated that in adulthood less than 1% of UVR below 340 nm and 2% of UVR between 340 and 360 nm reaches the retina [3, 4]. The lens is also rich in antioxidants, peroxidase and vitamin C. Transmission through the vitreous humor, comprised of approximately 98% water, increases with increasing wavelength, to approximately 80% at

350 nm and greater than 90% in the visible range, while UVR and most of the IR bands are almost entirely absorbed. Macular pigments are thought to confer protection to the retina through their ability to absorb relatively high-energy blue light. With an absorption spectrum peaking at 460 nm, these macular pigments are estimated to filter approximately 40% of visible blue light.

The life-long build-up of oxidative damage induced by the solar UVA and UVB radiation, can overcome these protective layers and contribute to age-related changes and degenerations observed in the adult retina. There is strong evidence in literature that acute high dose exposure to UVR causes photokeratitis and photoconjunctivitis, while even low dose chronic exposure to UVR is a risk factor for cataract, pterygium, and squamous cell carcinoma of the cornea and conjunctiva. Retinal damage models are in general done in the spectrum of the visible light range. Here, we demonstrate evidence of retinal degenerations related to UVR-induced OS. It is well established that UVA is directly inducing oxidatively generated damage to the DNA and other molecules in the cells [19]. In the following, we mainly focus on the recently discovered dual role of UVA- and UVB-induced hydrogen peroxide [19] in intercellular membrane transport and OS of biological systems.

4 | THE ROLE OF HYDROGEN PEROXIDE AS SIGNALING MOLECULE IN THE EYE

On one side, ROS and H_2O_2 have long been known with their potential to damage proteins, lipids and nucleic acids. On the other side, more recently the picture of H_2O_2 as a threat to cellular homeostasis has changed towards seeing it as a signaling molecule controlling different essential processes in plants and mammals [30, 31]. Therefore, hydrogen peroxide appears to be both potentially toxic and a central signaling compound. While it is shown that free diffusion of H_2O_2 across membranes is limited, there are evidences that selected aquaporin homologs have the capacity to channel it across membranes. Aquaporins (Figure 5) are selective channels in the cell membrane and mainly facilitate the transport of water in response to osmotic gradients [32, 33].

The first evidence about H_2O_2-mediated intercellular signaling was striking. In one study [34], it was demonstrated that hydrogen peroxide produced by human epidermal keratinocytes regulates melanogenesis of neighboring melonocytes and contributes to the progression of lesions. In another study [35], H_2O_2 secretion of myofibroblasts induced cell death in adjacent lung epithelial cells. In both studies [34, 35], coculture systems were used to demonstrate that H_2O_2, produced from one cell type, was perceived as a signal in the other cell type, though both cell types were physically separated via a transwell system.

The existence of aquaporin-9 (AQP-9) in various structures of the human eye is important, as this aquaporin is

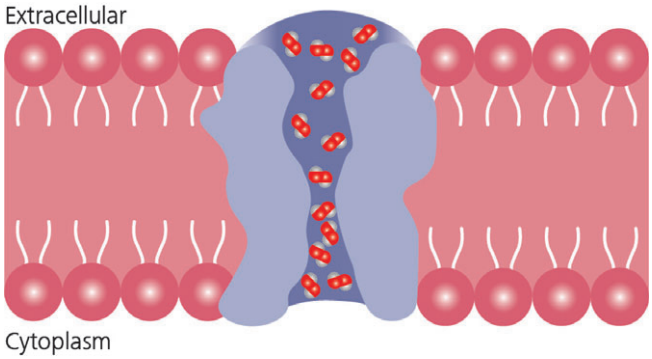


FIGURE 5 A model of aquaporin-9-mediated intercellular signaling of H_2O_2. In humans, the aquaporin family contains several isoforms divided into classic aquaporins transporting water molecules only, aquaglyceroporins, comprising AQP-3, AQP-7, AQP-9 and AQP-10, which besides water also allow the passage of small molecules like H_2O_2

capable of transporting molecules other than water, hydrogen peroxide in particular. AQP-9 has been localized to specific and important regulatory sites within the human eye where the transport of both water and other solutes with metabolic properties occurs. In a study using immunofluorescence technique [36], it was investigated the expression of the more recently discovered AQPs 6-12 in the human eye. AQP-9 was detected in the choroid, ciliary body, corneo-limbal tissue, retina and sclera. The AQP-9 facilitated membrane transport of hydrogen peroxide in mice and human cells was also recently demonstrated by Watanabe et al. [37].

These findings highlight ways of H_2O_2 generation and transport substrate in different layers of the human eye and show that OS is not confound only to tissues directly exposed to the harmful UVR. Therefore, high concentration levels of H_2O_2 in an exposed eye tissue are likely via aquaporin water channels to increase OS levels in surrounding tissues where H_2O_2 concentration is lower. The H_2O_2 concentration in the eye usually range from 30 to 70 μmol/L with high concentration of UVR-induced oxidant occurring in the anterior uvea and aqueous humor. It is therefore plausible that H_2O_2, due to its ability to diffuse in aqueous medium across cell membranes, to produce harmful $HO^{\cdot}$ radicals, which imbalance retinal ROS and contribute considerably to the epithelial cell death. Additionally, throughout the life chronic exposure of the retina to varying low levels of both UVA and UVB radiation [3, 4] also contributes to the accumulation of OS. We will conclude this paper by discussing ocular pathologies known to be related with increased OS and thus influenced by prolonged eye exposure to harmful solar UVA and UVB radiation.

5 | NONCANCER OCULAR PATHOLOGIES

There is growing evidence and general agreement for the OS theory of aging. The theory of aging proposes that

damage to DNA, lipids and proteins from ROS generated by both the exogenous and endogenous sources, accumulates during the cycle of life and its rate increases with age. This process has been observed in several ocular disease pathologies (see Table 3). Reported experimental studies indicate that DNA damage does occur in noncancer ocular diseases. Such a damage results from exposure to genotoxic agents of both exogenous and endogenous origins and targets nuclear and mitochondrial DNA and also results from alteration of DNA repair processing. The most frequently reported criteria for the involvement of OS in the ocular diseases pathology include the increased levels of biomarkers of oxidative damage of DNA, proteins and lipids, as well as decreased antioxidant levels. These criteria are fulfilled in several ocular pathologies (Table 3) among which, AMD, glaucoma and cataract are the main cause of blindness in the world. Since the cornea absorbs approximately 80% of the incident UVB radiation, it is especially prone to OS and hence several corneal conditions are also discussed.

5.1 | Age-related macular degeneration

The pathogenesis of AMD, which is the main cause of blindness in the adult population of the developed countries, is complex and multifactorial, involving various genetic loci and environmental factors. There is considerable evidence in the literature that the OS is an important factor in the disease process [38, 39]. For instance, a recent study [38] on a large cohort of participants evaluated the effects of current and past sunlight exposure, as well as the iris color on early and late AMD. They investigated the amount of self-reported sun exposure the participants had in their past and more currently. It was found that past and prolonged sunlight exposure was significantly associated with early and late AMD development. It was concluded that sunlight-induced OS is an important risk factor for AMD, but in the study was not investigated whether its effect on the retina was due to UVR or short-wavelength blue light.

There are direct evidences supporting the involvement of OS in the development of changes and death in RPE cells: for instance, exposure of RPE to H_2O_2 leads to damage and death of these cells [40, 41]. Indirect evidence for the role of UVR-induced OS in AMD comes from a histological cross-sectional study [42]. Loeffler et al. [42] examined the association between AMD and other ocular changes possibly induced by UVR: pinguecula and scleral plaque. What they found was a significant association between scleral plaque and AMD. This finding provides in turn support for a causative role of exposure to solar radiation in the development of AMD, given that solar radiation has a causative role in the development of scleral plaque. Similarly, Klein et al. [43] found that cataract was associated with incidence of early AMD and progression of AMD. Therefore, the role of both UVA and UVB radiation in the development of AMD should be seriously considered and proper prevention throughout the life against harmful UVR must not be underestimated.

There is currently a scientific debate on the effect of blue light on the development of eye conditions such as AMD and there is a evidence that the use of digital devices that emit visible blue light may impact sleep [44]. In an in vitro study [45], the response of RPE cells to a non-lethal dose of blue light was evaluated. In a model system, blue light irradiation of RPE cells induced mild stress without causing cell death. This effect that otherwise do not affect cell viability is consistent with the early stages of AMD where widespread RPE cell death is not generally seen. In another study [46], the hypothesis that there is a link between blue light oxidation-induced events and the onset of AMD was demonstrated in mice exposed to blue light.

TABLE 3 OS-related noncancer ocular pathologies of the eye and the affected tissues, respectively

Disease	Targeted tissues
Glaucoma	Trabecular meshwork
AMD	Retinal pigmented epithelial cells; choroid
Cataract	Lens
Dry eye syndrome	Tear film; ocular surface
Pterygium	Cornea
Fuch's endothelial corneal dystrophy	Cornea
Keratoconus	Cornea

Diseases that are among the main causes of blindness in the world are highlighted in bold.

5.2 | Glaucoma

Glaucoma is the second most relevant cause of blindness worldwide. The disease is a progressive optic neuropathy, often caused by elevated intraocular pressure (IOP) consequent to abnormal high resistance to aqueous humor drainage via the trabecular meshwork and Schlemm's canal [47]. Regulation of IOP depends on the balance of complex mechanisms involved in the production and outflow of aqueous humor, including the stability and survival of cellular phenotypes responsible for correct maintenance of homeostasis [48]. The most frequent glaucoma type is the chronic clinical manifestation known as the primary open-angle glaucoma (POAG) [47]. In spite of elevated IOP, apoptosis has been recognized as the end point for retinal ganglion cells (RGC) in any glaucoma type [48]. Oxidative UVA and UVB damage was found in the DNA of POAG patients [49]. Moreover, a significant correlation between oxidative DNA damage and IOP was described in glaucomatous patients. It was shown that POAG patients display a genetic background rendering them susceptible to ROS-induced damage because of a more frequent deletion of specific genes pivotal for the antioxidant defense (AOX)

mechanism (Figure 4). OS has also been linked to POAG by increasing flow resistance in the aqueous humor of the eye in the presence of high levels of hydrogen peroxide. These reports implicate that OS is a critical factor involved in RGCs apoptosis in glaucomatous patients [50]. While, RGC loss in glaucoma is still a mystery to scientists, the contribution of OS is unequivocal and therefore chronic exposure of the eye to UVR in daily life must be minimized.

5.3 | Cataract

It is a commonly considered hypothesis that OS is a key factor in the development of cataract, the most common cause of blindness in the world [51, 52]. The disease is characterized by damage of crystalline proteins, nucleic acids, lipids and polysaccharides with consequent opacity of the eye lens [53, 54]. The main factors leading to cataract are UVR-induced ROS formation and reduction in the activity of an enzyme family that catalyzes the reductase of hydrogen peroxide to water and oxygen, as well as catalyzing the reduction of peroxide radicals to alcohols and oxygen. It has been observed that the concentration of H_2O_2 in aqueous humor is strongly increased when this oxidant concentration is high in the lens. The role of H_2O_2 in cataract development also found a confirmation in the reduction of the defense enzymes activities and antioxidant reductase in the lens of patients with cataract. Importantly, an increased concentration of lipid peroxidation products in aqueous humor of age-related cataract has been observed. It was demonstrated that an accumulation of products of the lens oxidation, the decreasing potential of antioxidants with age and weaker repair mechanisms are relevant to the development of age-related cataract.

5.4 | Dry eye syndrome

Dry eye is defined as a multifactorial disease of the tears and the ocular surface that is characterized by symptoms of discomfort, visual disturbance and tear-film instability that may cause potential damage to the ocular surface [55]. OS can be involved in dry eye disease or keratoconjuctivitis sicca, a high impact ocular pathology that affects 20% to 30% of the population worldwide [56–58]. Although the detailed mechanisms operating in this disease have not been fully elucidated, the body of evidence available from basic and clinical research [56, 57] indicates that inflammation and ocular surface immunology play a key role in the initiation and development of dry eye disease. The tear-film layer is responsible for the homeostasis of the ocular surface and antioxidant protection against OS. In dry eye syndrome, the expression of various antioxidant enzymes is significantly lower as compared to healthy controls [59]. OS is highly involved in the disruption in the homeostasis, which causes a disorder in the integrity of the ocular surface and damage in extracellular DNA [58, 60]. Thus, the inflammatory reactions are initiated and become the key mechanism in dry eye syndrome and ocular surface injury. These tear-film alternations and their effects on the ocular surface result in reduced visual quality and in rear cases may lead to visual impairment. The ocular surface inflammation and dry eye syndrome are frequently seen in pterygium patients [61].

5.5 | Pterygium

The corneal epithelium acts as a UV filter to protect internal eye structures through absorption of UVB rays as well as through fluorescence-mediated ray transformation and reduction [62]. Key role in these processes involves the high ascorbate concentration in the corneal epithelium [62]. UVB radiation modulates expressions of antioxidants and pro-inflammatory mediators by corneal epithelium cells [63]. Alternations in the expression of these important protecting mediators, by UVR-induced OS, may result in pterygium [64]. Thus, pterygium is inflammatory and degenerative ocular surface disease attributed to chronic UVB exposure. Clinically, the condition involves invasive centripetal growth with associated inflammation and neovascularization [49, 65]. When it extends to the central optical zone, visual function can be severely impaired [49, 65]. While genetic components may also be involved in pathogenesis of pterygium, chronic exposure to UVB is the determining factor in promoting the development of pterygium [65]. For instance, the prevalence of pterygium is high and is a significant health issue in Australia and surrounding territories [66], where extreme levels of solar UVR exposure may be reached in outdoors. Conjunctival ultraviolet autofluorescence is a biomarker of ocular sun exposure and can be associated with increased time spent outdoors [66]. Increased prevalence of pterygium is associated with increased time spent outdoors and autofluorescence [66], which in turn suggests a relation between UVR exposure, induced OS and development of pterygium. Further evidence for the involvement of UVR in pterygium pathogenesis comes from the finding that it is usually found at sites in the eye where peripheral light is focused by the anterior eye [61]. By using computer simulations of ray—tracing, it was demonstrated the pathways by which the anterior eye, acting as a side—on lens focuses light onto the opposite side of the eye, to the nasal limbus [61]. In particular, light rays proceed across the anterior eye by traversing the aqueous humor in the anterior chamber and the degree of limbal focusing is determined in part by the corneal shape and anterior chamber depth. The peak light intensity at the distal limbus is approximately 20 times that of the incident light intensity and the light focus is not a spot but rather a complex arc shape [61], which coincides with the typical shape of the bulbar conjuctiva that grows on the ocular surface in pterygium.

5.6 | Keratoconus

Although keratoconus (KCN) is not among the main diseases that may cause blindness in the world, it is important from a clinical and epidemiological aspect. In a recent nationwide registration study [67] on more than 4 million patients from a mandatory insurance database in the Netherlands, the prevalence and incidence of KCN were estimated to be 5- to 10-fold higher than previously reported. The prevalence, the number of given cases at a given time point, that is cited most often is 1:2000 [68], while the newly estimated was 1:375 [67]. The big difference between the 2 estimations may be accounted for by the advent of new imaging techniques, leading to more sensitive diagnosis [67]. KCN is a progressive corneal disease, characterized with corneal protrusion and thinning, which result in irregular astigmatism that may lead to decrease in vision: the thinning results in shape alternations and ultimately the cornea assumes conical shape. Although in most cases the loss in visual acuity can be restored through the use of glasses or contact lenses, complex corneal transplantations are indicated in approximately 10% to 20% of KCN patients [67, 69].

While KCN is a multifactorial disease with several biochemical processes contributing to its development, OS plays a critical role in both its development and progression [70, 71]. OS involvement in KCN is indicated by the accumulation of cytotoxic byproducts and mitochondrial DNA damage [70, 71]. OS is induced in response to direct cornea exposure to UVA and UVB radiation that leads to decrease in keratocyte density, a reduction in the number of lamellae, and a degradation of fibroblasts in the stroma. In addition, changes occur in the gross organization of the lamellae, and an uneven distribution of collagen fibrillar mass, especially around the apex of the cone is observed. OS also causes failure of catalyzes [72] that reduces the lipid hydroperoxides to water and alcohol, and H_2O_2 to water and O_2. KNC corneas exhibit higher levels of mitochondrial DNA damage and increased number of mitochondrial DNA rearrangements, deletions and mutations [71, 73]. Mitochondrial DNA is more prone to damage, as it has a less efficient repair system than nuclear DNA. Thus, mitochondrial damage induces an increase in OS and may alter gene expression, induce apoptosis and loss of cell viability [71, 73].

5.7 | Fuch's dystrophy

In a healthy cornea, endothelial cells keep the tissue from excess fluid absorption, pumping it back into the aqueous humor. When oxidative damage occurs, the premature corneal endothelial cell loss is permanent and if cell number is too low, the fluid absorption pump starts to fail [49]. This causes the fluid to move anterior into the epithelium, which in turn leads to swelling of the cornea. As fluid accumulates between the basal epithelium cells, blisters form and they may undergo painful ruptures releasing their fluid content to the surface. Changes in Descemet membrane, a layer adjacent to the corneal endothelium, coincide with primary failure of the endothelial cells and are integral component of the process of loss of corneal endothelial function [74]. These characteristic malformations produce corneal clouding that disrupts vision and creates pain sensations: this condition is known as Fuch's endothelial corneal dystrophy [49, 74]. Decreased ability to resist OS in the corneal endothelium is known to play a key role in alternation of gene expressions in the antioxidant response element mitochondrial DNA damage [49, 75, 76]. In Fuch's dystrophy, the premature endothelial cell loss, due to their decreased ability to resist OS and increased susceptibility to apoptosis [74], is associated with pathways throughout the corneal layers [74].

6 | UVR PROTECTION HIGHLIGHTS

In the end, we want to highlight that the invisible thread caused by solar UVA and UVB radiation to the human eye should not be underestimated. Unfortunately, some ophthalmic lens standards still ignore this invisible hazard of UVR wavelengths, especially the ones longer than 380 nm, thus creating an UVR protection void. However, UVR between 380 and 400 nm is abundant in the solar UVR spectrum [77], and UVR hazard from these wavelengths have been reported in numerous recent works [78–82]. Therefore, we adopted the most widely used definition of UVR extending up to 400 nm, first described by the ICNIRP [2]. The ICNIRP document is a guideline to evaluate specific exposure levels by measuring the expected amount of UVR exposure and determining whether an individual might be exposed to a daily dose that exceeds permissible levels. This adoption is in line with the recommendations adopted by the World Health Organization (WHO) [83], while other organizations like the American National Standards Institute [84] still keep the 380 nm limit. The adoption of UVR limit is important since in a study by Latimer et al. [78] it was shown that when the ICNIRP-UVR action spectrum was weighted by the solar UVR spectrum adopted in ISO 8980-3 [77], where the 380 nm limit is also considered, the results (Figure 6) suggested that a much larger threat exists from the wavelengths ignored by the ISO and ANSI standards. The adoption of a proper UVR definition seems to be critical, considering the fact that most nonglass spectacle lens materials possess high transmittance in the UVA band of wavelengths above 350 nm.

There are reliable evidences that excessive exposure to UVR through live, especially until teenager age, may seriously contribute to increase in OS of various eye tissues and thus lead to the advancement of serious ocular pathologies, such as AMD, glaucoma and cataract later in life. Children are especially vulnerable to UVR because of their larger

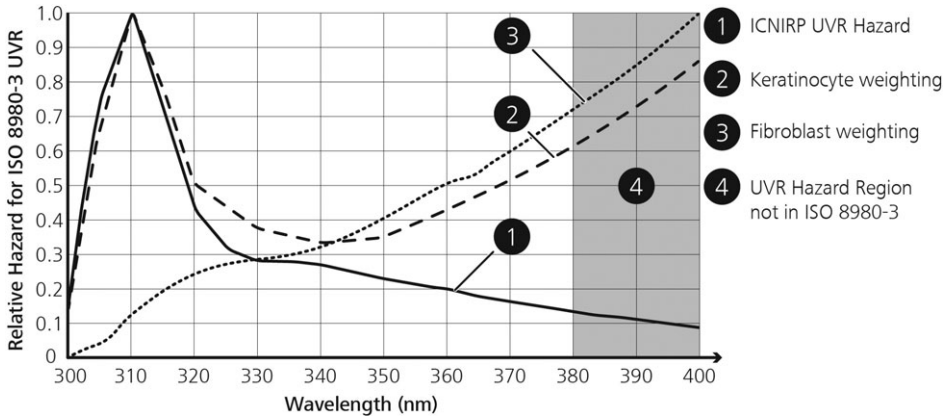


FIGURE 6 Application of the results of Latimer et al. [78] suggests that long wavelength UVR (horizontal axis) may be much more harmful than expected when ICNIRP-UVR action spectrum is weighted ① by the solar UVR spectrum adopted in ISO 8980-3 (vertical axis). Wavelengths between 380 and 400 nm were equally as damaging as wavelengths between 350 and 380 nm. Because of the greater penetration of long wavelengths, the region between 380 and 400 nm (shaded area ④) may actually be more hazardous to skin: deep fibroblasts ③ are more susceptible to damage than shallow keratinocytes ②

pupils and more transparent ocular media. WHO has estimated that up to 80% of a person's lifetime exposure to UVR is reached before the age of 18. A study [85] using fluorescence photography has demonstrated this point and showed examples of early UVR damage to young eyes that are not visible under normal light viewing, for example, direct ophthalmoscopy. We also want to stress that exposure to UVR has a cumulative effect over lifetime. Considering that the life expectancy is rising, this increases the chance for the accumulated effect in the tissues to develop and result in age-related pathologies. It is clear that provision and sustained UVR protection from a young age is extremely important.

Therefore, options for solar protection, including sunglasses, clear spectacles or contact lenses, wide brim hats, absorbing films for side windows in cars [86], blocking UV below 400 nm should be seriously considered. To that end, several initiatives have already been started. For instance, in Australia sunglass standards are the common UV protection bench mark, where light below 400 nm is defined as harmful [87] and is blocked by the lenses. WHO has presented information to form a knowledge base for the prevention of adverse effects of UV exposure that is achievable with known and accessible interventions. They acknowledge the global burden of disease from solar ultraviolet radiation and the special care needed to protect kids from the harm associated with overexposure of the eye to UVR. In addition, the European Medicine Agency has adopted a Guidance on photosafety evaluation of pharmaceuticals, since certain UV-excited drugs, like antibiotics, antidepressants and topically applied anti-inflammatories may represent a likely phototoxic risk to the retina, lens and other structures in the eye.

7 | DIGITAL AGE AND EYE HEALTH

Low energy lighting and the extensive use of computer and mobile devices in modern society expose our eyes to ever-increasing light emissions containing blue light. Consequently, the question of whether radiation emitted by these digital devices may cause eye damage is frequently circulated in the media and raises concerns in the public. In a recent study comparing natural exposures with the reasonably estimated exposure to optical radiation from low-energy lighting, computer screens and mobile devices, it was shown that the actual spectrally weighted irradiance is lower than the natural exposures [88]. In the ICNIRP guidelines light radiation levels below which adverse health effects are unlikely are calculated. To assess an exposure condition from the different devices investigated, the spectrum of light at a specific location was measured and the value at each wavelength was weighted by a relevant factor at that wavelength. Finally, the weighted values were summed to give the irradiance for comparison with the guideline exposure limit. It was found that under even extreme long-term viewing conditions, none of the assessed sources exceeded the guideline limits and therefore extensive exposure to digital device-emitted radiation should not raise concerns for public eye health [88]. However, these devices are known to emit strongly in the short-wavelength part of the visible spectrum and blue light is currently considered to have the strongest effect in synchronizing human circadian rhythm [89, 90]. In the long run, exposure to even low-level blue light during night or before bed time may disrupt the circadian rhythm with severe general health implications. Therefore, if use of digital devices in the evenings can not be avoided, their detrimental effect on the circadian rhythm can be reduced, for instance, by wearing blue light blocking glasses.

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Conflict of interest

I.V.I. and S.W. are scientists at the University of Tuebingen; T.M., P.S., C.L. and S.W. are employed by Carl Zeiss Vision International GmbH, manufacturing spectacle lenses and sunglasses. There is no conflict of interest regarding this study.

Author contributions

I.V.I. and S.W. did the literature study and analysis, I.V.I. wrote, P.S. and C.L. designed the illustrations, T.M. reviewed the illustrations, and T.M. and S.W. critically reviewed the manuscript.

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REFERENCES

[1] D. H. Sliney, S. L. Trokel, *Medical Lasers and Their Safe Use*, Springer Science & Business Media: New York, **2012**.
[2] International Commission on Non-Ionizing Radiation Protection, *Health Phys.* **2004**, *87*, 171.
[3] D. H. Sliney, *Int. J. Toxicol.* **2002**, *21*, 501.
[4] D. H. Sliney, *Progress in Lens and Cataract Research*, Vol. 35, Karger Publishers: Freiburg, **2002**, p. 40.
[5] M. S. Oliva, H. Taylor, *Int. Ophthalmol. Clin.* **2005**, *45*, 1.
[6] J. Pe'er, *Ophthalmol. Clin.* **2005**, *18*, 1.
[7] M. Pastor-Valero, A. E. Fletcher, B. L. de Stavola, V. Chaqués-Alepúz, *BMC Ophthalmol.* **2007**, *7*, 18.
[8] R. D. Glickman, *Int. J. Toxicol.* **2002**, *21*, 473.
[9] K. Schulmeister, B. E. Stuck, D. J. Lund, D. H. Sliney, *Health Phys.* **2011**, *100*, 210.
[10] Z. Yu, K. Schulmeister, N. Talebizadeh, M. Kronschläger, P. G. Söderberg, *J. Biomed. Opt.* **2014**, *19*, 105008.
[11] J. J. Hunter, J. I. W. Morgan, W. H. Merigan, D. H. Sliney, J. R. Sparrow, D. R. Williams, *Prog. Retin. Eye Res.* **2012**, *31*, 28.
[12] R. R. Krueger, T. Seiler, T. Gruchman, M. Mrochen, M. S. Berlin, *Ophthalmology* **2001**, *108*, 1070.
[13] J. J. Vos, *Bull. Math. Biol.* **1962**, *24*, 115.
[14] T. J. White, M. A. Mainster, P. W. Wilson, J. H. Tips, *Bull. Math. Biol.* **1971**, *33*, 1.
[15] M. Davies, *Aust Biochem* **2012**, *43*, 8.
[16] F. R. de Gruijl, H. J. van Kranen, L. H. F. Mullenders, *J. Photochem. Photobiol. B* **2001**, *63*, 19.
[17] F. R. De Gruijl, H. Rebel, *Photochem. Photobiol.* **2008**, *84*, 382.
[18] J. D'Orazio, S. Jarrett, A. Amaro-Ortiz, T. Scott, *Int. J. Mol. Sci.* **2013**, *14*, 12222.
[19] J. Cadet, T. Douki, J.-L. Ravanat, *Photochem. Photobiol.* **2015**, *91*, 140.
[20] R. M. Lucas, *Eye Contact Lens* **2011**, *37*, 168.
[21] M. S. Baptista, J. Cadet, P. Di Mascio, A. A. Ghogare, A. Greer, M. R. Hamblin, C. Lorente, S. C. Nunez, M. S. Ribeiro, A. H. Thomas, M. Vignoni, T. M. Yoshimura, *Photochem. Photobiol.* **2017**, *93*, 912.
[22] H. Yasui, H. Sakurai, *Biochem. Biophys. Res. Commun.* **2000**, *269*, 131.
[23] H. Sakurai, H. Yasui, Y. Yamada, H. Nishimura, M. Shigemoto, *Photochem. Photobiol. Sci.* **2005**, *4*, 715.
[24] H. Yasui, T. Hakozaki, A. Date, T. Yoshii, H. Sakurai, *Biochem. Biophys. Res. Commun.* **2006**, *347*, 83.
[25] T. Hakozaki, A. Date, T. Yoshii, S. Toyokuni, H. Yasui, H. Sakurai, *Arch. Dermatol. Res.* **2008**, *300*, 51.
[26] K. U. Schallreuter, J. M. Wood, *J. Photochem. Photobiol. B* **2001**, *64*, 179.
[27] A. Valencia, I. E. Kochevar, *J. Invest. Dermatol.* **2008**, *128*, 214.
[28] D.-N. Hu, J. D. Simon, T. Sarna, *Photochem. Photobiol.* **2008**, *84*, 639.
[29] H. L. Chandler, K. S. Reuter, L. T. Sinnott, J. J. Nichols, *Invest. Ophthalmol. Vis. Sci.* **2010**, *51*, 172.
[30] S. Neill, R. Desikan, *Curr. Opin. Plant Biol.* **2002**, *5*, 388.
[31] R. Mittler, S. Vanderauwera, N. Suzuki, G. Miller, V. B. Tognetti, K. Vandepoele, M. Gollery, V. Shulaev, F. Van Breusegem, *Trends Plant Sci.* **2011**, *16*, 300.
[32] A. S. Verkman, J. Ruiz-Ederra, M. H. Levin, *Prog. Retin. Eye Res.* **2008**, *27*, 420.
[33] A. Rojek, J. Praetorius, J. Frøkiaer, S. Nielsen, R. A. Fenton, *Annu. Rev. Physiol.* **2008**, *70*, 301.
[34] E. Pelle, T. Mammone, D. Maes, K. Frenkel, *J. Invest. Dermatol.* **2005**, *124*, 793.
[35] M. Waghray, Z. Cui, J. C. Horowitz, I. M. Subramanian, F. J. Martinez, G. B. Toews, V. J. Thannickal, *FASEB J.* **2005**, *19*, 854.
[36] M.-H. Yang, A. Dibas, *Biosci. Rep.* **2013**, *33*, e00035.
[37] S. Watanabe, C. S. Moniaga, S. Nielsen, M. Hara-Chikuma, *Biochem. Biophys. Res. Commun.* **2016**, *471*, 191.
[38] T. Schick, L. Ersoy, Y. T. E. Lechanteur, N. T. M. Saksens, C. B. Hoyng, A. I. Den Hollander, B. Kirchhof, S. Fauser, *Retina* **2016**, *36*, 787.
[39] S. C. Tomany, K. J. Cruickshanks, R. Klein, B. E. K. Klein, M. D. Knudtson, *Arch. Ophthalmol.* **2004**, *122*, 750.
[40] G.-F. Jin, J. S. Hurst, B. F. Godley, *Curr. Eye Res.* **2001**, *22*, 165.
[41] C. S. Alge, S. G. Priglinger, A. S. Neubauer, A. Kampik, M. Zillig, H. Bloemendal, U. Welge-Lussen, *Invest. Ophthalmol. Vis. Sci.* **2002**, *43*, 3575.
[42] K. U. Loeffler, S. M. Sastry, I. W. McLean, *Curr. Eye Res.* **2001**, *23*, 33.
[43] R. Klein, B. E. K. Klein, T. Y. Wong, S. C. Tomany, K. J. Cruickshanks, *Arch. Ophthalmol.* **2002**, *120*, 1551.
[44] J. G. Lawrenson, C. C. Hull, L. E. Downie, *Ophthalmic Physiol. Opt.* **2017**, *37*, 644.
[45] C. Roehlecke, A. Schaller, L. Knels, R. H. W. Funk, *Mol. Vis.* **2009**, *15*, 1929.
[46] B. S. Winkler, M. E. Boulton, J. D. Gottsch, P. Sternberg, *Mol. Vis.* **1999**, *5*, 32.
[47] R. N. Weinreb, P. T. Khaw, *Lancet* **2004**, *363*, 1711.
[48] W. Huang, A. Dobberfuhl, T. Filippopoulos, M. Ingelsson, J. B. Fileta, N. R. Poulin, C. L. Grosskreutz, *Am. J. Pathol.* **2005**, *167*, 673.
[49] S. C. Saccà, A. Izzotti, *Prog. Brain Res.* **2008**, *173*, 385.
[50] G. Tezel, *Prog. Retin. Eye Res.* **2006**, *25*, 490.
[51] M.-C. Kim, F.-J. Cui, Y. Kim, *Asian Pac. J. Cancer Prev.* **2013**, *14*, 3625.
[52] F. Shang, L. Minyi, E. Dudek, J. Reddan, A. Taylor, *Free Radic. Biol. Med.* **2003**, *34*, 521.
[53] M.-C. Ho, Y.-J. Peng, S.-J. Chen, S.-H. Chiou, *J. Clin. Gerontol. Geriatr.* **2010**, *1*, 17.
[54] H. Shichi, *Expert Opin. Investig. Drugs* **2004**, *13*, 691.
[55] N. A. Listed, *Ocul. Surf.* **2007**, *5*, 75.
[56] Y. Ogawa, K. Tsubota, *Inflamm. Regen.* **2013**, *33*, 238.
[57] S. Nakamura, M. Shibuya, H. Nakashima, R. Hisamura, N. Masuda, T. Imagawa, M. Uehara, K. Tsubota, *Invest. Ophthalmol. Vis. Sci.* **2007**, *48*, 1552.
[58] T. H. Wakamatsu, M. Dogru, K. Tsubota, *Arq. Bras. Oftalmol.* **2008**, *71*, 72.
[59] J. Cejkova, T. Ardan, Z. Simonova, C. Cejka, J. Malec, D. Dotrelová, *Histol. Histopathol.* **2008**, *23*, 1477.
[60] C. K. M. Choy, P. Cho, I. F. F. Benzie, *Optom. Vis. Sci.* **2011**, *88*, 507.
[61] M. Coroneo, *Eye Contact Lens* **2011**, *37*, 214.
[62] A. Ringvold, *Acta Ophthalmol.* **1998**, *76*, 149.
[63] A. T. Black, M. K. Gordon, D. E. Heck, M. A. Gallo, D. L. Laskin, J. D. Laskin, *Biochem. Pharmacol.* **2011**, *81*, 873.

[64] J. Čejková, T. Ardan, Č. Čejka, J. Luyckx, *Graefes Arch. Clin. Exp. Ophthalmol.* **2011**, *249*, 1185.
[65] J. C. Bradley, W. Yang, R. H. Bradley, T. W. Reid, I. R. Schwab, *Br. J. Ophthalmol.* **2010**, *94*, 815.
[66] C. M. McKnight, J. C. Sherwin, S. Yazar, H. Forward, A. X. Tan, A. W. Hewitt, E. Smith, D. Turton, P. Byrd, C. E. Pennell, M. T. Coroneo, D. A. Mackey, *Clin. Experiment. Ophthalmol.* **2015**, *43*, 300.
[67] D. A. Godefrooij, G. Ardine De Wit, C. S. Uiterwaal, S. M. Imhof, R. P. L. Wisse, *Am. J. Ophthalmol.* **2017**, *175*, 169.
[68] R. H. Kennedy, W. M. Bourne, J. A. Dyer, *Am. J. Ophthalmol.* **1986**, *101*, 267.
[69] M. O. Gordon, K. Steger-May, L. Szczotka-Flynn, C. Riley, C. E. Joslin, B. A. Weissman, B. A. Fink, T. B. Edrington, H. E. Olafsson, K. Zadnik, *Am. J. Ophthalmol.* **2006**, *142*, 923.
[70] E. Arnal, C. Peris-Martínez, J. L. Menezo, S. Johnsen-Soriano, F. J. Romero, *Invest. Ophthalmol. Vis. Sci.* **2011**, *52*, 8592.
[71] S. R. Atilano, P. Coskun, M. Chwa, N. Jordan, V. Reddy, K. Le, D. C. Wallace, M. Cristina Kenney, *Invest. Ophthalmol. Vis. Sci.* **2005**, *46*, 1256.
[72] L. R. Atalla, A. Sevanian, N. A. Rao, *Curr. Eye Res.* **1988**, *7*, 1023.
[73] R. Buddi, B. Lin, S. R. Atilano, N. C. Zorapapel, M. Cristina Kenney, D. J. Brown, *J. Histochem. Cytochem.* **2002**, *50*, 341.
[74] A. O. Eghrari, J. D. Gottsch, *Expert Rev. Ophthalmol.* **2010**, *5*, 147.
[75] U. V. Jurkunas, M. S. Bitar, T. Funaki, B. Azizi, *Am. J. Pathol.* **2010**, *177*, 2278.
[76] U. V. Jurkunas, I. Rawe, M. S. Bitar, C. Zhu, D. L. Harris, K. Colby, N. C. Joyce, *Invest. Ophthalmol. Vis. Sci.* **2008**, *49*, 2956.
[77] ISO 8980-3, Ophthalmic optics-uncut finished spectacle lenses. Part 3: Transmittance specification and test methods; **2013**.
[78] J. A. Latimer, J. J. Lloyd, B. L. Diffey, P. J. Matts, M. A. Birch-Machin, *J. Invest. Dermatol.* **2015**, *135*, 2512.
[79] T. Gomez, *J. Environ. Health* **2015**, *77*, 8.
[80] M. Linetsky, C. T. Raghavan, K. Johar, X. Fan, V. M. Monnier, A. R. Vasavada, R. H. Nagaraj, *J. Biol. Chem.* **2014**, *289*, 17111.
[81] S. Seite, F. Christiaens, C. Bredoux, D. Compan, H. Zucchi, D. Lombard, A. Fourtanier, A. R. Young, *J. Eur. Acad. Dermatol. Venereol.* **2010**, *24*, 219.
[82] A. R. Young, G. E. Orchard, G. I. Harrison, J. L. Klock, *J. Invest. Dermatol.* **2007**, *127*, 975.
[83] WHO, *Solar Ultraviolet Radiation*. Environmental Burden of Disease Series 13, World Health Organization, Geneva **2006**.
[84] American National Standards Institute. ANSI Z80.3-2015, Ophthalmics—Nonprescription sunglass and fashion eyewear requirements. American National Standards Institute.
[85] J.-L. Ooi, N. S. Sharma, D. Papalkar, S. Sharma, M. Oakey, P. Dawes, M. T. Coroneo, *Am. J. Ophthalmol.* **2006**, *141*, 294.
[86] B. S. Boxer Wachler, *JAMA Ophthalmol.* **2016**, *134*, 772.
[87] S. J. Dain, *Clin. Exp. Optom.* **2003**, *86*, 77.
[88] J. B. O'Hagan, M. Khazova, L. L. A. Price, *Eye* **2016**, *30*, 230.
[89] S. W. Lockley, G. C. Brainard, C. A. Czeisler, *J. Clin. Endocrinol. Metabol.* **2003**, *88*, 4502.
[90] G. Vandewalle, P. Maquet, D.-J. Dijk, *Trends Cogn. Sci.* **2009**, *13*, 429.

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