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Review

The Role of Ultraviolet Radiation in the Ocular System of Mammals

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Abstract: With decreasing levels of ozone in the atmosphere, we are being exposed to higher levels of ultraviolet radiation (UVR) than ever before. UVR carries higher energy than visible light, and its effects on tissues include DNA damage, gene mutations, immunosuppression, oxidative stress and inflammatory responses. In the eye, UVR is strongly associated with the development of basal and squamous cell carcinoma of the eyelid, pterygium, photokeratitis, climatic droplet keratopathy, ocular surface squamous neoplasia, cataracts, and uveal melanoma, and is weakly associated with age-related macular degeneration. Despite overwhelming evidence regarding the deleterious effects on UVR, public health measures to encourage UV protection of the eyes is generally lacking. Options for photoprotection include sunglasses, wide brim hats, windshields, plastic films for side windows in cars, UV blocking contact lenses, and following the UV Index report daily. The American National Standards Institute currently has regulations regarding properties of UV blocking sunglasses; however, compliance in the US is not mandatory. On the other hand, UVR does have therapeutic applications in the eye, particularly, riboflavin activated by ultraviolet A light (UVA) radiation is used clinically to slow the progression of keratoconus, post-LASIK keratectasia, and bullous keratopathy by crosslinking corneal collagen fibers.

Additionally, riboflavin activated by UVA has been shown to have antibacterial, antiviral, and antiparasitic effects. This is clinically relevant in the treatment of infectious keratitis. Finally, exposure to low levels of light in the UV spectrum has been found to regulate the growth of the eye and lack of adequate exposure may increase the risk of development and progression of myopia.

Keywords: ultraviolet radiation; ocular effects of UVR; cornea; sunglasses; therapeutic ultraviolet radiation

1. Introduction

Aside from the skin, the eye is the organ that is the most susceptible to damage induced by ultraviolet radiation (UVR). While eyebrows, eyelashes and pupillary constriction create some defense against extreme light, the eye is still susceptible to damage. The main UVR source is the sun, but UVR can also be produced artificially by tools such as sunlamps and welding arcs.

UVR is electromagnetic radiation in the waveband 100–400 nm. Visible light ranges from 400 to 700 nm, and infrared light ranges from 700 to 1200 nm. UVR contains more energy than visible or infrared light and consequently has more potential for biological damage.

The UV spectrum can be further divided into three bands: UV-A (315–400 nm), UV-B (280–315 nm) and UV-C (100–280 nm) [1]. The shorter wavelengths of light carry greater energy and thus have the greatest potential for biological damage.

As sunlight passes through the atmosphere, all UV-C and approximately 90 % of UV-B radiation is absorbed by ozone, water vapor, oxygen and carbon dioxide. Solar radiation that reaches the earth's surface constitutes approximately 95% UVA and 5% UVB [2]. Due to ozone depletion, there has been an increase in the amount of UVR reaching the earth. UV-B fluxes increase with increasing altitude and decreasing latitude, except in proximity to areas of ozone depletion at lower latitudes [3]. UV-B levels vary between hemispheres, with some sites in the Southern hemisphere receiving up to twice the UV observable at comparable latitude in the Northern hemisphere [3]. Ozone levels drop in the austral spring; the ozone hole over the Antarctic in an annual event that persists through spring, though the exact etiology of this phenomenon is unknown [4]. UVA is of longer wavelength than UVB and is less affected by altitude or atmospheric conditions. UVA radiation can penetrate deeper through the skin and is not filtered by window glass [5]. UVB radiation carries higher energy, thus has a higher potential for damage. The intensity of UVB radiation in the environment varies; it has greater intensity in the summer, at midday, at places closer to the equator, and at higher altitudes. Sand, snow, concrete, and water can reflect up to 85% of sunlight, which further intensifies exposure [6].

Exposure to UVR produces DNA damage, gene mutations, immunosuppression, oxidative stress and inflammatory responses in tissues [7]. Evidence suggests formation of ROS following UV irradiation results in severe damaging effects due to higher ROS concentrations [8]. A majority of single stranded breaks in DNA are generated by production of reactive oxygen species from UVR exposure [9]. UVR can also cause direct mutagenesis of epidermal DNA. Most DNA breakage is repaired by proteins in the cell’s nucleus. Failure or delay in DNA repair leads to errors in DNA synthesis and somatic mutations,

which may contribute to development of cancerous cells in the context of active cell proliferation [10,11]. In addition to this, UVR creates mutations in the p53 tumor suppressor gene [12]. The p53 gene mediates mitochondria-dependent apoptosis through the BCL-2 family of regulatory proteins. P53 directly interacts with nucleotide excision repair regulatory proteins. Mutations in nucleotide excision repair proteins can cause xeroderma pigmentosum and early development of skin cancers [11] Additionally, studies have demonstrated that DNA repair is impaired in the absence of functional p53 [11]. UVB is also thought to cause DNA damage via the formation of pyrimidine dimers. Some studies have indicated that UVA radiation is even more immunosuppressive than UVB [13,14].

Sun exposure in ocular tissues can lead to photochemical reactions that result in acute and chronic damage to the structures in the eye [15]. A study examining the phototoxicity of UVR on lens cellular function revealed that high-dose UVA alone and relatively low dose UVA in combination with low UVB radiant exposure can impair lens cellular and optical functions [16]. UVA causes DNA damage by an oxidative process in the epithelium of the lens, which results in lens cell damage and opacity [17,18].

2. Ocular Effects of UVR

In the eye, the proportion of UV radiation absorbed by different structures depends on the wavelength of the beam [19]. The first structure which absorbs UV radiation is the tear film [1]. The cornea and the lens cortex are major UV filters and absorb primarily the shorter, more active UVB range wavelengths [20]. The human cornea absorbs all UVR below around 280 nm [21]. Above this threshold, there is a rapid increase in transmission to 320 nm, then a steady increase to a maximum in the visible spectrum. Longer wavelengths of UVR pass better through the anterior portion of the eye; these reach the lens and retina. The lens absorbs wavelengths below 400 nm [19]. The lens nucleus and retina in young eyes absorb UVA, and the retina absorbs visible light. UVR that is not absorbed by the various structures of the eye is transmitted to the tissues, and it can induce photooxidative damage. Eyes of infants and juveniles transmit a higher amount of UVR and visible radiation than eyes of elderly persons [20].

2.1. Eyelid

Studies show that ultraviolet radiation (UVR) exposure is associated with the formation of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the eyelid. UVR exposure is the strongest environmental risk factor for developing these cancers. There is a strong relationship between SCC and occupational sun exposure [22–24] and continuous, lifelong sun exposure is important in development of SCC. Increased childhood sun exposure and intermittent sunlight exposure resulted in an increased risk of BCC [25–27]. Studies have shown that protection from UV exposure can lower the incidence of subsequent skin cancer [28].

Melanin plays an important role in photoprotection by functioning as a free radical scavenger and physical barrier that can scatter UV rays. There is an epidemiological inverse correlation between skin pigmentation and sun-induced skin cancers. However, a study has shown that increased melanin content along without protection against UVR was not sufficient to protect completely against DNA damage [29], thus care should be taken to avoid exposure and minimize risk of developing BCC and SCC of the eyelid.

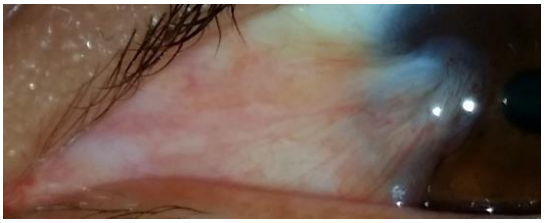
Melatonin has recently been indicated to be a skin protectant via free radical scavenging and DNA repair mechanisms [30]. Melatonin is a strong scavenger of UV-induced ROS, preventing potential DNA damage that would lead to carcinoma [31]. Melatonin is synthesized in the pineal gland and has classically been thought to regulate the circadian day/night rhythm and more recently has been found to be also synthesized cutaneously [30,31]. Melatonin up-regulates mRNA levels for several antioxidant enzymes and has an even higher reduction potential than Vitamin C. In the skin, melatonin has been reported to be involved in the regulation of seasonal hair growth and pigmentation. Topical administration of melatonin 0.5% reduces UV irradiation induced erythema when applied before UV exposure [30]. Topically applied melatonin may be used as a potent defense system against cutaneous photodamage and many other conditions that produce oxidative stress (*i.e.*, atopic dermatitis) in the future.

Certain phototoxic or photoallergic medications can increase the skin's susceptibility to UVR, which potentially increases the risks of skin cancers. There have been reports a significant increase in the risk of squamous cell carcinoma, basal cell carcinoma, and early-onset basal cell carcinoma in individuals who had used photosensitizing medication [32,33]. They show a 1.3 increase in odds of SCC with diuretic use, supporting a previously quoted 1.6 odds increase of SCC with diuretic use. However, other studies show no relation, thus CV disease may be a confounding variable. Robinson *et al.* reported a link with tetracycline use and BCC risk [33]. The link needs to be further studied, but the consensus is to take special care in patient education with use of these agents.

2.2. Pterygium

Pterygium has long been believed to be an environmental disease, with UVR playing a large role in its development [34]. Pterygium is a hyperplasia of the bulbar conjunctiva that can extend over the cornea, obstructing vision (Figure 1). A pterygium involves basophilic degeneration of the subepithelial stroma in the bulbar region of the conjunctiva [35]. There is a strong positive correlation in the literature between the quantity of UVR exposure and the prevalence of pterygium [34,36,37]. The incidence of pterygium in areas near the equator with areas of higher UVR exposure approaches 50%. A pterygium rarely affects vision, but it can be cosmetically significant and may require surgery. Pterygium predominately occurs at the nasal side of the eye and is thought to be secondary to tangentially incident UVR focused onto the nasal limbus, which induces the tissue changes that predispose to pterygium formation. One theory that explains the nasal preference and supports the UVR relationship of pterygium formation is that UVR beams reflect off of the skin of the nose and the facial regions and onto the nasal side of the eye [35].

Figure 1. The predominance of pterygium on the nasal side is thought to be predominantly due to focusing of the sun rays onto this location.



2.3. Pinguecula

Pinguecula is a degenerative change in the bulbar conjunctiva within the palpebral aperture [38]. Histopathologically, pinguecula are within the same spectrum of diseases as pterygium and actinic keratosis, which may predispose to squamous cell carcinoma [39]. One study reported a high prevalence of pinguecula among people who live in the Red Sea region [40]. Pinguecula is thought to be contributed to by environmental exposures such as UVR, but evidence of the link between UVR and development of pinguecula is less convincing than that for pterygium. Immunological and chronic irritative mechanisms have been proposed [39].

2.4. Ocular Surface Squamous Neoplasia (OSSN)

OSSN is a term for precancerous and cancerous epithelial lesions of the conjunctiva and cornea. It includes dysplasia, carcinoma *in situ*, and SCC. While the human papilloma virus and human immunodeficiency virus play a role in the development of OSSN, in many studies it was found that exposure to solar UVR has also been identified as a major contributing factor to OSSN development [41]. Some studies study reported a high incidence of conjunctival SCC in an African population living in Uganda near the equator [42], in sub- Saharan African countries [42,43] and Australia where people are more exposed to sunlight [44]. In comparison, another study showed low incidence in Europe and North America [45]. One study reported that outdoor exposure in childhood contributes to the development of OSSN, although there are other risk factors including fair skin, pale irises, and the propensity to burn on exposure to sunlight [46]. There is strong evidence in the literature supporting a relationship between UV exposure and OSSN [46–49].

Squamous intraepithelial neoplasms of the conjunctiva or cornea have been shown to be more common in people with fair skin [50].

2.5. Cataract

A number of epidemiological studies have determines that the amount of sun exposure is directly correlated with incidence and prevalence of cataracts in the population [51–69]. Opacification of the crystalline lens that causes reduced passage of light is called a cataract. High sunlight exposure has consistently been associated with an increased risk of cataract formation [70]. Oxidative damage is an important etiological factor for nuclear and cortical cataracts. UVR catalyzes the generation of ROS, which causes oxidative stress in the lens. This leads to caspase-3 activation followed by apoptosis in the lens epithelial cells, which creates a disturbance of transmittance of the lens [71]. With increasing age, the lens nucleus becomes more susceptible to oxidation and less able to repair oxidative damage [70].

Cataracts have been shown to have a direct correlation with amount of sun exposure [51]. Approximately 20.5 million Americans over age 40 have a cataract in at least one eye, and rates are expected to rise to over 30 million by 2020 [72]. In Australia, two studies noted a dose–response relationship between the prevalence of cataracts and levels of UV-B radiation [64,65]. A country-wide survey of Nepal in which 30,565 lifelong residents were examined also found a positive correlation between the prevalence of cataracts and the average hours of sunlight across different zones of the country [66]. In a study examining 367 fishermen in Hong Kong, it was found that the risk for

cortical cataracts among men aged 40–50 years who spent 5 or more hours per day outdoors was increased compared with that of men who spent less time outdoors [67]. Calculated attributable risk of cortical cataract in an Australian study for average UVB exposure was 10% [73], meaning that 10% of cortical cataracts can be prevented by protecting against UVR exposure. This is very significant from a public health standpoint.

2.6. Climatic Droplet Keratopathy (CDK)

CDK is associated with chronic UV-A and UV-B exposure [21]. A high prevalence has been reported in geographical areas with high levels of UV exposure [73]. CDK is very highly correlated with chronic UVR exposure. One study found a direct link between the severity of the CDK and UV exposure [74]. CDK is a spheroidal degeneration of the superficial corneal stroma. Translucent material accumulates in the superficial corneal stroma within the interpalpebral strip, beginning peripherally and spreading centrally [75]. In young subjects, the deposits appear in narrow bands close to the limbus nasally and temporally symmetrically in both eyes; with time and continued exposure, they accumulate over the visual axis and form a complete band. In the most advanced stages, raised nodules develop that are yellow-brown in color [73]. Sector iridectomy, corneal epithelial debridement, lamellar keratoplasty, and penetrating keratoplasty are all methods to treat visually incapacitating CDK [75].

2.7. Age-Related Macular Degeneration (AMD)

AMD is a disease in which extracellular deposits, called drusen, accumulate slowly in the retina, causing visual acuity impairment. AMD is the most common cause of blindness in older individuals in developed countries [76]. The exact pathogenesis is unknown, but one of the main components is thought to be oxidative stress. The retina receives high oxygen concentration and intense light exposure, thus is susceptible to oxidative damage [76].

Animal and human studies have suggested that exposure to intense bright sunlight or UVR may cause changes similar to AMD [77]. However, epidemiological evidence with several case–control studies showed no relationship to sunlight exposure and AMD [78–82]. There is some evidence that the disease is more common in patients with light iris color [83], although not all studies confirm this association [78]. Wang *et al.* indicated that the condition might be more common in those with very fair skin, although the elevated risk is modest [84]. Miguel *et al.* studied albino rats after exposure to UV-C and UV-B radiation and showed significant changes in the nuclei and cytoplasmic organelles representative of apoptotic processes in the exposed *versus* the unexposed retinae [85].

The lack of a clear association between UVR exposure and AMD is not surprising because the lens absorbs almost all UV-B radiation, so only very small amounts of this waveband can reach the retina.

2.8. Uveal Melanoma

Uveal melanoma is the most common primary malignant intraocular tumor of adults, with a high incidence of metastasis. Approximately 50 percent of affected patients die of uveal melanoma within 10–15 years after treatment [86].

It has been reported that exposure to UV light is a risk factor for uveal melanoma [87]. Tucker *et al.* found that exposure to natural or artificial UVR may contribute to melanoma, and they determined that there is an elevated risk of ocular melanoma in people who born in the southern US that were exposed to higher levels of UVR in childhood in comparison with those born in the North [88]. A national case–control study demonstrated an increase in risk of the cancer with increasing sun exposure prior to age of forty [89]. Additionally, other studies have determined that occupational exposure to artificial UV light has been associated with uveal melanoma [90–93]. Data from case-control studies have indicated that subjects with blue or grey eyes and light hair and skin color have an elevated risk of developing ocular melanoma [90,94,95].

However, the role of acute and chronic sunlight exposure alone in intraocular melanomas still remain inconclusive [88]. In contrast, two studies showed a gradient of risk for developing uveal melanoma with cumulative intense sun exposure; they found a two-fold increased risk in the highest exposure group [88,90]. From our literature review, we have noted that there is a strong association with lifetime UV light exposure and the development of intraocular melanomas, however the role of acute or chronic sunlight exposure should be examined further.

2.9. Photokeratitis

Photokeratitis, also known as "snow blindness" or "welder's arc" is a painful superficial punctate keratopathy caused by acute exposure to UV-B and UV-C radiation. Photokeratitis represents the acute corneal response to UVR exposure. It appears up to 6 hours after exposure to UVR and resolves within 8–12 h [21]. The primary response occurs in the epithelium, but the keratocytes and endothelium can also be damaged [21]. There appears to be no direct effect on Bowman's layer, basement membranes, or the stromal fibrils. Corneal epithelial damage causes a gritty feeling in the eye coupled with photophobia and tearing [21]. This may also cause corneal edema, which results in a haze or clouding of vision. Photokeratitis occurs in conditions where the UVR reflectivity of the environment is extremely high such as during skiing, during mountain climbing, or excessive time at the beach. Occupational exposure is also a significant artificial source of UVR causing photokeratitis, including the "welder's flash" during arc welding.

3. Occupational Exposure

Welding arcs are the most predominant occupational exposure to UV radiation. Ocular effects from UVR exposure in welding include photokeratitis, erythema, pterygium and some types of cataracts [96].

Welding was found to be a significant risk factor for development of uveal melanoma [93] and possibly predispose the patient to the development of bilateral uveal melanoma [97]. Other studies have determined that exposure to welding arcs results in a higher risk of phototoxic maculopathy [98]. A study conducted among 405 Nigerian welders showed that pingueculum, pterygium, corneal opacity, and pigmentary macular deposits were the most common eye disorders [99].

Each type of welding process emits a different spectrum and intensity of optical radiation. For most processes, ultraviolet and visible radiation are the main components of the emission [100]. A range of control measures is available, but nevertheless, many workers (particularly those exposed to solar UVR) do not make full use of these [96].

4. Protection Against UVR

There are several types of photoprotective agents which minimize effect of UVR on eye. We can categorize them as below.

4.1. Environmental Photoprotection

UVR that passes through the stratosphere (10–50 km above sea level) is scattered by molecules such as oxygen and nitrogen. It then passes through the troposphere (0–10 km above sea level), where it is absorbed and scattered by pollutants such as soot and attenuated by clouds. Clouds reduce the intensity of UVR but not to the same extent that infrared intensity is reduced; therefore, the sensation of heat is diminished, which results in the potential for overexposure [5].

Pollutants and fog can decrease the intensity of UVR reaching the earth's surface by scattering; shorter wavelengths are scattered more than longer ones. On the other hand, snow, ice, sand, glass, and metal can reflect up to 85% of UVB [101].

Ozone (triatomic oxygen) is the major photoprotective agent formed in the stratosphere [102]. Almost all of UVC and large amounts of UVB is screened out by the stratospheric ozone. However, small amounts of UVA and visible light are absorbed. Ozone depletion has had a significant effect on the amount of UVB that reaches the earth. Concentration of ozone increases toward polar regions; however, there has been a decrease at the South Pole in the last 15 years [101].

Latitude, altitude, season, time of the day, clouds, and the ozone layer are the main factors which determine the amount of solar UVB and UVA reaching the surface of the earth. The highest irradiance is at the equator and higher elevations. The ratio of UVA to UVB is 20:1. The strongest UV radiation is between 10 AM to 4 pm [103]. Human exposure to UVR is increasing because ozone depletion and global climate changes are influencing surface radiation levels [104,105].

The most effective method is avoiding sunlight. Cloud-cover does not necessarily block UVR, and people should be counseled to avoid sun exposure even in overcast weather conditions [104].

4.2. Ocular Photoprotection

Eyes have many defense mechanisms against the photochemical reactions and damage induced by UV radiation. These include antioxidants, lens chromophores, melanin, glutathione (GSH) peroxidase, superoxide dismutase, and heme oxygenase [106]. Radical scavengers such as vitamin E, vitamin C, [107,108] beta carotene, and ubiquinone [107] are other defense mechanisms.

These antioxidants were shown to prevent changes in enzymatic activity after UVB radiation [109]; however, they might not be fully protective under strong oxidative stress. Aging causes decreased antioxidant levels [110]. UV radiation and short-wavelength visible light can cause acute and chronic changes in ocular structure; such changes may comprise irreversible damage. Unfortunately, major ocular tissues such as the lens and retina do not possess the capacity of cellular regeneration [110,111]. It is for this reason that physical photoprotection against UV radiation should be of consideration.

4.3. Physical Photoprotection

Photoprotection is very important in the ultraviolet waveband, under 400 nm. At the same time, it is important that we do not block too much of the visible waveband 400 nm–700 nm in order to maintain our visual capacity. This presents a problem unique to ocular science [112,113].

Wearing sunglasses can provide adequate protection against UVR. Ideally sunglasses should block all UVR and some blue light as well [114]. The American Academy of Ophthalmology suggests that sunglasses should block 99% of all UVR [115]. Other major US visual health organizations recommend that sunglasses absorb 97% to 100% of UVR [10,115,116]. Unfortunately, the public currently has little concern about eye protection [117,118]. Surveys found that public knowledge about the effects of sunlight on the eyes was low. Most of the people who responded to the survey had sunglasses, but only used them occasionally [117].

The first article that outlined US standards for sunglasses was published in 1972 [119]. American National Standards Institute [ANSI] (Z80.32008) was issued to categorize the different types of sunglasses based on the degree of shading and UV absorption profile (see Table 1). However, the manufacturer is not obligated to build or label products according to the standards because compliance in the United States with ANSI standards is voluntary [120].

Unfortunately, the money that people spend for brands and polarizing sunglasses does not guarantee optimal UVA protection [121,122]. Sunglasses may provide shade without adequate UV protection. This diminishes the amount of visible light transmitted, which can disable the squinting mechanism and dilate the pupil causing cataract and maculopathy, respectively. In addition, the efficacy of sunglasses against UVR depends on their size and shape.

The size and shape of sunglasses is another important factor in protection against UVR. Most ocular damage from UVR results from scattered and reflected light from the periphery. Both cortical cataracts and pterygium involve predominately the nasal aspect of the eye [123,124], which supports that most of UV damage is induced by oblique peripheral rays [125]. Therefore, an ideal pair of sunglasses is wrapped very closely to the eye [120]. Sunglasses should be worn in the times when the most ocular damage occurs: morning and late afternoon. At these times, the incident UV rays are parallel to the pupil axis. Additionally, sunglasses should be worn when light intensity is weak because during off-peak hours, the incident angle of UV rays is low and can bypass the brow ridge and eyelid and the light intensity does not stimulate pupillary constriction, which increases exposure to UVR [120]. It is recommended that people wear sunglasses outdoors when working, driving, participating in sports, taking a walk, or running errands [126].

Clear glasses absorb the vast majority of radiation below 320 nm, however additional protection against UVA is recommended; plastic film containing zinc, chrome, nickel, or other metals that block UVR over a wide range should be used with these for protection against UVA [127]. Lastly, wearing a hat with a brim can greatly reduce the UVR exposure to the eyes and surrounding skin.

More recently, contact lens manufacturers have begun incorporating UV-blocking polymers into the chemical mixture of their lens material formulas. The ANSI requires a minimum absorption of 95% UVB and 70% UVA for a contact lens to be considered UV blocking [113]. A contact lens that adequately blocks UVR provides good protection because it provides coverage from obliquely incident UV rays and rays potentially reflecting from the posterior surface of sunglasses. In general, soft contact

lenses offer more protection than a rigid gas permeable lens because the former provides complete corneal and partial conjunctival coverage while the latter only covers a portion of the cornea [128].

Table 1. Transmittance properties for nonprescription sunglasses according to ANS Z80.3 2008.

		Mean UV Transmittance			
		UVB		UVA	
Lens	Luminous transmittance (tv)	Normal use	Prolonged exposure	Normal use	Prolonged exposure
Cosmetic lens (light)	>40%	≤12.5% tv	≤1% UVB	Tv	≤50% tv
General purpose lens(medium to dark)	8%–40%	≤12.5% tv	≤1% UVB tv	Tv	≤50% tv
Special purpose lens(very dark)	3%–8%	≤1% UVB	≤1% UVB	_50% tv	≤50% tv
Special purpose lens(strongly colored)	>8%	≤1% UVB	≤1% UVB		≤50% tv

Luminous transmittance (tv) is the ratio of the total transmitted light to the total incident light.

Transmission of UVR through car windows depends on many characteristics of the glass including types, color, and thickness. Some companies manufacture plastic films containing zinc, chrome, nickel, or other metals that block UVR over a relatively wide spectrum, which are incorporated into windshields of cars. Windshields can block UVA up to 380 nm in length, but longer waves are transmitted through [129]. In contrast, side and back windows block only 21% UVA radiation [130]. Both side window glass and windshields can block all UVB radiation, but it is important to keep in mind that windshields provide better UV protection than side window glass [117]. Drivers and passengers in a vehicle should consider utilizing UV protection for this reason.

The UV index was developed in 1994 by the National Weather Service in consultation with the US Environmental Protection Agency and the Centers for Disease Control and Prevention. The UV index predicts the intensity of UV light for the following day on the basis of the sun's position, cloud movements, altitude, ozone data, and other factors [131]. The World Health Organization and World Meteorological Organization have developed the Global Solar UV index (UVI), which provides the public with an estimate of UVR on any given day [1]. (see Table 2).

Table 2. UV index.

UV Light Intensity	**Minimal**	**Low**	**Moderate**	**High**	**Very High**
International color codes	Green	Yellow	Orange	Red	Purple
Index	0–2	3–5	6–7	8–10*	≥11

* avoid outdoor exposures from 10 am to 4 pm if the UV index is 8 or higher.

Higher UV index indicates more intense UVR exposure. The index is available online for thousands of cities at www.weather.com, and the UV index can be found in the weather section of many daily newspapers, in weather reports on local radio, and on television. The UV index can be helpful to plan outdoor activities. Sun-protection strategies should be applied at even minimal levels of the UV index, and it should be taken more seriously when the UV index increases [131]. If the UV index is 8 or higher, indoor activities are suggested [128].

5. The role of Therapeutic UVR in the Eye

5.1. Increased Corneal Graft Survival

There has been extensive literature on the immunosuppressive effects of UV radiation suggesting that it may modify the functional behavior of immunocompetent cells without killing them [11,13,14,29,132–134]. The mechanism by which UV radiation modifies immunogenicity is not completely understood. Destruction of allograft endothelium is the most important prognostic factor for graft rejection, and treatment with UVB can induce structural alterations in the endothelium. Several studies have indicated an increase in graft survival in corneal transplants after UVB irradiation of the corneal epithelium of donor rabbit and mouse before grafting [132,133,135]. It is suggested that increased graft survival is related to depletion of antigen presentation based on cytokine pattern induced by the UVR [133]. However, the clinically useful range of UVB energy which favorably alters immunogenicity without causing cellular damage is likely narrow [133].

5.2. Antimicrobial Effect

In the 1960s, it was established that riboflavin (B2), when subjected to either visible or UV light, could inactivate the RNA of tobacco mosaic virus [136]. UVA and B2 in combination have since been used as an antimicrobial agent for contamination in blood products [137]. *In vitro* experiments have supported the view that there is a bactericidal effect of activated riboflavin by using 365-nm UV light [138,139]. When activated by UV light 365–370 nm, riboflavin acts as a photosensitizer in tissues and becomes a generator of reactive oxygen species, creating free radicals to induce new chemical bonds [140–146]. The aim of treatment with UVA and riboflavin is to create additional chemical bonds inside the cornea in the anterior stroma while minimizing exposure to the surrounding structures of the eye; free radicals generated by this process can cause oxidative damage to DNA and RNA molecules in the surrounding structures [146,147].

5.3. Collagen Crosslinking in the Cornea

Infectious Keratitis

Recently, scientists have examined treatment with riboflavin and ultraviolet A light (UVA) in cases of severe infectious keratitis [140,148–151]. The mechanism by which this process is thought to work is via collagen crosslinking. Oxidation of corneal collagen induces cross-linking and strengthens the collagen matrix [146]. This enhances its rigidity, and prevents bacteria and fungi from enzymatically digesting the tissue, preventing corneal melting [136].

A study by Makdoumi *et al.* conducted the first clinical series of bacterial keratitis treated by riboflavin UV photosensitization without antibiotics [152]. This pilot study included 16 patients diagnosed with bacterial keratitis. All of the eyes responded to the photochemical treatment with improvement of symptoms and reduced signs of inflammation; epithelial healing was achieved in all cases and only two required antibiotic administration, one requiring an amniotic membrane transplant [152]. The adjunctive use of UVA and B2 therapy seems to be a possible alternative for medication-resistant *Acanthamoeba keratitis* (AK) [151]. Treatment of AK is noticeably challenging and is faced with difficulties such as long and intensive regimens, resistance to medication, adverse effects from the medications, and reinfection after surgical management. Contact lens wear remains the most important risk factor for AK development. As the number of contact lens wearers continues to increase, the number of cases of AK increases [153,154].

Corneal Ectasia

Keratoconus is a bilateral, progressive, non-inflammatory and often asymmetrical corneal stromal thinning and subsequent ectasia. Mild cases can be treated with contact lenses; RGP lenses are required as the disease progresses, and surgery is necessary in 15%–20% of patients. The adjunctive riboflavin (B2)/ultraviolet light A (UVA) exposure to the cornea for corneal collagen crosslinking [146] has been used by ophthalmologists to treat and slow the progression of keratoconus, post-LASIK keratectasia, and bullous keratopathy [155–157] with great results. Schnitzler *et al.* reported four cases of noninfectious corneal ulcers that were successfully treated with this process, corneal crosslinking (CXL) [158].

Because the UV light causes an effect only where it is absorbed, it is desirable that the treatments be designed so that as much as possible of the irradiation is absorbed only in the corneal tissue.

5.4. UVR in Prevention of Progression of Myopia

Some longitudinal studies have found an association between more time spent in outdoors/sports activity and a reduction in the risk and onset of juvenile myopia. A systemic meta-analysis of the association between time spent outdoors and myopia in children indicated a 2% reduced odds of myopia occurred per additional hour per week of time spent outdoors. Additionally, light levels have been shown to influence refractive development in several animal models. However, further studies are necessary to determine a causal relationship [159,160].

6. Conclusions

The role of UVR and its role in pathology and diseases in the ocular system is a very important public health issue. The use of physical photoprotection can significantly reduce the lifetime exposure of UVR and can reduce risks of developing CDK, cataracts, pterygium, OSSN, basal and squamous cell carcinoma, and uveal melanoma, however prevalence of the use of these barriers to UV exposure is low in the general public. It is important for further inquiry into reasons why prevalence of sunglass use is low, especially in regions with high UV radiation in order to make more significant public health campaigns promoting safer practice. More education on this subject is necessary, especially near the equator, where increased use of physical photoprotection can significantly reduce the disease burden. It

is important additionally to recognize also that the UVR-induced immunosuppressive qualities that facilitate the formation of neoplasia can be used therapeutically in the management of both systemic and ocular disease. The molecular interplay in the mechanism of action is complex and interesting, and further exploration into this may be clinically significant, especially regarding UVA/B2 as a treatment ofinfectious keratitis and keratoconus.

Conflict of Interest

The authors declare no conflict of interest.

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