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Perspective of Cataract and Oxidative Stress

Nsonwu M[*1], Ozims SJ[2] and Nnodim JK[3]

[1]*Department of Optometry, Imo State University, Owerri, Nigeria*
[2]*Department of Public Health, Imo State University, Owerri, Nigeria*
[3]*Department of Medical Laboratory Science, Imo State University, Owerri, Nigeria*

[*]**Correspondence:** Magnus Nsonwu, Department of Optometry, Imo State University, Owerri, Nigeria

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Abstract

One of the main causes of blindness is the multifactorial condition known as cataract. It is believed that oxidative stress plays a significant role in starting the cataractogenesis process. Today, it is a well-established fact that oxidative stress plays a role in both diabetes-induced cataract (diabetic) and age-related cataract (senile). The most likely cause of oxidative damage to the lens is a compromised antioxidant defense system brought on by age and diabetes-related increases in reactive oxygen species (ROS) production. The main factor contributing to cataract formation is systemic oxidative stress, which is produced externally to the lens. An imbalance between pro- and antioxidant-oxidants leads to oxidative stress. It is essential to eliminate hazardous free radicals because they are a byproduct of normal metabolism. Globally, cataracts are the primary cause of blindness. Oxidative stress is the direct cause of the lens's opacity. Although age is the main cause of cataracts, diabetes is also a common cause, as higher superoxide levels in the mitochondria arise from hyperglycemia. This review will look into ultraviolet (UV) light, diabetes, and diet (fat, alcohol, and vitamins) as risk factors for cataracts.

Keywords: perspective, cataract, oxidative stress

Abbreviations: ROS: reactive oxygen species; AMD: age-related macular degeneration; DR: diabetic retinopathy; RVO: retinal vein occlusion; RPE: retinal pigment epithelium; GSH-Px: glutathione peroxidase; CAT: catalase; AGEs: advanced glycation end-products; UV: ultraviolet; ATP: adenosine triphosphate; KEAP1: Kelch-like ECH-associated protein 1; BNIP3: adenovirus E1B interacting protein 3; NIX: Nip-like protein X

Introduction

A cataract is a clouding of the lens of the eye, which is ordinarily clear. Seeing through hazy lenses is similar to gazing through fogged-up or frosted glass for those who have cataracts. Cataract-related visual impairments can make it harder to read, drive (particularly at night), or read a friend's expression. Retinal illnesses such as cataract, age-related

macular degeneration (AMD), glaucoma, diabetic retinopathy (DR), and retinal vein occlusion (RVO) are all significantly accelerated by oxidative stress. Overproduction of reactive oxygen species (ROS) can cause abnormalities in the morphology and function of endothelial cells, retinal ganglion cells (RGCs), and retinal pigment epithelium (RPE). Here, we show that in animal models of AMD, glaucoma, DR, and RVO, the free radical scavenger edaravone reduced apoptotic cell death, oxidative damage to DNA and lipids, and angiogenesis by blocking the JNK and p38 MAPK pathways [1].

The World Health Organization (WHO) states that 51% of blindness worldwide is caused by cataracts. It is estimated that there are currently around 15.7 million cataract sufferers in Nigeria. Prevent Blindness research projections indicate that the number will rise to 25.6 million by 2050 and 28.5 million by 2032. In an effort to raise public awareness of cataract risk factors, symptoms, and treatment choices, Prevent Blindness has designated June as Cataract Awareness Month. A cataract is a clouding of the lens of the eye that prevents or modifies light from entering the eye. Usually, but not always, both eyes develop cataracts at different rates. They may proceed to a certain degree and then stop getting worse, or they may develop swiftly or slowly [2].

Cataracts can develop due to a variety of causes in addition to age. Cataracts can be brought on by eye infections, certain medications (like steroids), trauma, extreme heat, or radiation exposure. Cataract formation may also be aided by a number of illnesses, including diabetes and metabolic problems, as well as excessive exposure to ultraviolet (UV) light, which is the non-visible version of sunlight.

The majority of cataracts progress gradually and don't cause vision problems right away. However, cataracts will progressively impair your vision over time.

Initially, wearing glasses and better illumination will help you manage cataracts. But you may require cataract surgery if your normal activities are hindered by your reduced eyesight. Thankfully, cataract surgery is typically a safe and successful treatment [3].

A cataract is a thick, hazy patch that develops in the eye's lens. Clumps of proteins in the eye block the lens's ability to properly transfer images to the retina, which is how cataracts start. The retina functions by translating light entering the lens into messages. The optic nerve receives the signals from the retina and forwards them to the brain.

It progresses gradually till it obstructs your eyesight. Although cataracts can develop in both eyes, they typically do not occur simultaneously. Cataracts are prevalent among the elderly. The National Eye Institute states that by the time they are 80 years old, more than half of Americans either have cataracts or have had cataract surgery [4].

The following are common signs of cataracts: double vision in the affected eye, difficulty seeing at night, faded colors, increased sensitivity to glare, and the need for regular prescription lens changes.

Causes of cataract development

Cataracts have a number of underlying causes. Among them are:

- An excess of oxidants, which are oxygen molecules that have undergone chemical modification as a result of day-to-day living
- Taking a puff
- Rays of UV light
- The continuous use of prescription drugs and steroids
- Some illnesses, such as diabetes
- Injuries
- Radiation treatment

Types of Cataract

Cataracts can be of several types. They are categorized according to where and how they grow within your eye.

- Nuclear cataracts, which develop in the center of the lens, result in a yellowing or browning of the nucleus.
- Cortical cataracts develop along the borders of the nucleus and have a wedge-shaped appearance.
- Affected on the rear of the lens, posterior capsular cataracts develop more quickly than the other two varieties.
- Age-related cataracts are more common than congenital cataracts, which occur during a baby's first year of life or are present at birth.
- Drugs or illnesses can result in secondary cataracts. Diabetes and glaucoma are two conditions that are associated with the development of cataracts. Cataracts can occasionally result from the use of other drugs, including the steroid prednisone.
- It may take several years for traumatic cataracts to form following an eye injury.
- After receiving radiation therapy for cancer, a person may get radiation cataracts [5].

Cataract risk factors

The following are risk factors for cataracts:

- Advanced years
- Excessive alcohol consumption
- Taking a puff
- Weight problem
- Elevated blood pressure
- Past ocular trauma
- A history of cataracts in the family
- Excessive sun exposure
- Diabetes
- Radiation exposure from cancer treatments and X-rays [6].

Finding the cataracts

In order to evaluate your eyesight and check for cataracts, your doctor will do a thorough eye exam. This will involve tonometry to gauge your eye pressure and an eye chart exam to assess your vision at various distances.

A painless puff of air is used to flatten your cornea and measure your eye pressure in the most popular tonometry test. Additionally, to enlarge your pupils, your doctor may apply drops to your eyes. This facilitates the process of examining your eye's retina and optic nerve for damage.

A test may also be run to determine how sensitive you are to glare and how you perceive color [7].

Cataract therapy

Your doctor can help you manage your symptoms if you are unable or unwilling to have surgery. They might recommend thicker lenses, magnifying glasses, or anti-glare sunglasses.

Surgery

When cataracts make it difficult for you to do daily tasks like driving or reading, surgery is advised. It's also done when treating other eye conditions is hampered by cataracts.

Phacoemulsification is one surgical technique that uses ultrasonic waves to split the lens into pieces and remove them.

During extracapsular surgery, a lengthy corneal incision is made in order to remove the clouded portion of the lens. An artificial intraocular lens is implanted in the native lens's place following surgery.

Cataract removal surgery has a high success rate and is usually quite safe. Infection, hemorrhage, and retinal detachment are among the hazards associated with cataract surgery; nevertheless, the chances of all those consequences are less than 1%. The majority of patients are discharged from the hospital on the same day [8].

Prospects for a cataract

If neglected, cataracts can cause blindness and cause problems with daily tasks. Even though some of them cease growing, they don't naturally get smaller. According to the National Eye Institute, surgically removing cataracts is a relatively common operation that is extremely effective approximately 90% of the time [9].

Prevention of Cataracts

To lower the chance of cataract development, the following should be adhered:

- Wear sunglasses outside to shield your eyes from UVB radiation.
- Get regular eye exams
- Give up smoking
- Consume fruits and veggies high in antioxidants
- Retain a balanced weight
- Manage diabetes and additional health issues

Oxidative Stress

This is a disorder that could arise from the body having an excessive amount of unstable molecules known as free radicals and not having enough antioxidants to eliminate them. Damage to cells and tissues may result from this. Oxidative stress can be caused by a wide range of things, such as obesity, eating poorly, smoking, drinking alcohol, taking certain medications, and being exposed to radiation, chemicals, air pollution, sunshine, and pesticides. Chronic oxidative stress may contribute to chronic inflammation, cancer, and other disorders, as well as the aging process.

An imbalance between pro- and antioxidant-oxidants leads to oxidative stress. It is essential to eliminate hazardous free radicals since they are a byproduct of regular metabolism [10].

All living creatures, except for anaerobic microbes, need molecular oxygen as an electron acceptor in order to efficiently produce the energy needed for survival. Because oxygen is a potent oxidant, secondary oxidations that are a part of regular metabolism cannot be avoided. The idea of "oxidative stress," which refers to what happens when secondary oxidations brought on by oxygen and its derivatives are not successfully neutralized, originated from this theoretical foundation. This may result in illness, aberrant metabolism, loss of physiological function, and ultimately death.

ROS and reactive nitrogen species (RNS) build up in vivo or in cells, causing oxidative damage. Oxidative stress is defined as an imbalance between the generation and removal of oxygen-free radicals in the body or cells. Numerous studies have demonstrated the link between oxidative stress and the onset and progression of several diseases.

Two types of antioxidant systems exist. The first is an enzyme system, which consists of enzymes such as glutathione peroxidase (GSH-Px), catalase (CAT), and superoxide dismutase (SOD). The other is the non-enzymatic antioxidant system, which consists of trace elements, including copper, zinc, selenium, melatonin, α-lipoic acid, ergothioneine, vitamin C, vitamin E, glutathione, and so on [11].

An imbalance between the rate of oxidant synthesis and the rate of oxidant breakdown is correlated with oxidative stress. Water is the final result of the entire four-electron reduction of oxygen that takes place inside the mitochondria.

Superoxide and a number of reactive oxidative intermediates, including hydrogen peroxide, hydroxyl radicals, and singlet oxygen radicals, are produced during a partial reduction. Other sources include diet, air pollutants, tobacco smoke, exercise, ionizing radiation, infrared radiation, and, of course, the sun, in addition to these endogenous oxidants. The organism adjusts by repairing damaged molecules and tissues and blocking unwanted reactions with its endogenous and partially redundant antioxidant defense (glutathione reductase, glutathione superoxide dismutase, CAT, and GSH-Px). However, the few molecules and undesirable reactions that are not stopped or repaired will eventually build up and cause harm. Each of these circumstances will cause an abundance of oxidants to form as well as oxidative stress [12].

Antioxidants, defined as compounds that, at low concentrations relative to the substrate, limit the damage to the body's structural and functional molecules, namely proteins, lipids, carbohydrates, and DNA, counteract oxidative stress.

Antioxidants may work through a number of different methods.

Tocopherol functioning in the lipid phase; scavenging of free radicals implicated in chain reactions [13].

Regeneration of more antioxidants: ascorbate donates an H atom to decrease the tocopheryloxy radical to tocopherol, reacting (catalase with hydrogen peroxide) with oxidants or radical initiators.

Chelating or sequestering pro-oxidants such as albumin or polyphenols with cupric ions, which are catalysts made of transition metals.

Enzyme inhibition or activation: nitric oxide synthase is activated by ascorbate, while tyrosine kinase is inhibited by tocopherol and polyphenols.

A complex sensitive structure called the retina lines the inside surface of the rear of the eye's globe. The macula, which is responsible for "high-definition vision," is a well-defined area of the retina that is roughly 0.6 mm in size. It is separated into two zones: the fovea, which is located in the center, and the parafovea, which is located on the periphery. The parafovea is rich in rod photoreceptor cells, which are used for night vision, while the fovea has a high percentage of cone photoreceptor cells, which are used for photopic vision or seeing in well-lit environments. The interaction of the cells in the macula ensures central vision sharpness, which is necessary for the majority of everyday tasks [14].

The RPE, which makes up the external layer of the retina, is made up of highly specialized, polarized epithelial cells whose basal side is in contact with Bruch's membrane, the choroid's internal layer, and whose apical side is in contact with the photoreceptor outer segments. The health of photoreceptor cells depends on RPE. To ensure that photoreceptor outer segments operate at their best, RPE cells do in fact phagocytose them on a regular basis. Additionally, RPE cells move metabolic waste to the choroid for elimination by passing it across Bruch's membrane [15].

Large areas of the macula lose RPE cells and photoreceptors, which results in AMD, the leading cause of blindness in Western nations [16]. The extracellular deposits, or drusen, that build up between Bruch's membrane and the RPE are what define AMD. Drusen extracted from AMD samples contained advanced glycation end-products (AGEs) and carboxyethylpyrrole adducts, which are created by the oxidative alteration of fatty acids in photoreceptor tips. The idea that oxidative stress plays a significant role in AMD etiology and progression is supported by the presence of these compounds, which are linked to oxidative damage [17]. The receptor for advanced glycation endproducts (RAGE) is a transmembrane receptor that recognizes AGEs and acts as a pro-inflammatory mediator through nuclear factor-κB (NF-κB) signaling [18]. This suggests that inflammation is one of the pathogenic reasons for AMD.

This review discusses the impacts of pharmacologically produced antioxidant defenses and how oxidative stress contributes to macular degeneration based on these principles.

Induced oxidative stress by light

Light is electromagnetic radiation, and through intricate interactions between the brain and the eye, it can be converted into visual information. The electromagnetic spectrum spans wavelengths from UV (100–400 nm) to infrared (beyond 760 nm), only a small percentage of which interacts with the human eye [19].

Noell and colleagues first proposed light damage theories in 1966, including the possibility of light-induced oxidative processes. Specifically, it is thought that UV and blue light cause retinal damage linked to AMD [19]. Blue light-induced phototoxicity is expected to contribute more to human retinal illnesses as a result of increased video display exposure and the usage of light-emitting diodes (LEDs) as light sources [20]. When light interacts with an endogenous chromophore in the ocular tissue, such as proteins, flavoproteins, and the naturally existing pigment granules of lipofuscin and melanin in the RPE, photo-oxidative damage takes place [21]. Chromophores absorb light, which excites them to a triplet state. This highly reactive state then interacts quickly with other molecules, including molecular oxygen, to produce ROS [22]. As a result, OS has been recognized as a key participant in light-induced cellular stress.

UV light exposure causes RPE mitochondria to degenerate, which is known to increase ROS formation and decrease adenosine triphosphate (ATP) generation. A decrease in ATP synthesis may be the cause of a decrease in RPE phagocytic activity, which leads to RPE hyperpigmentation, an AMD risk factor since one of the primary functions of RPE is the phagocytosis of photoreceptor outer segments following photoactivation [23]. Furthermore, by activating NF-κB, UV light causes the overexpression of pro-inflammatory chemicals, which could hasten the production of drusen [8].

Stress from oxidation and aging

The accumulation of degenerative changes that reduce an organism's fitness and capacity to maintain homeostasis is known as the aging process [16]. According to Harman's 1956 "free radical theory" of aging, the buildup of free radicals over the course of a lifetime causes oxidative damage to a variety of macromolecule classes, which ultimately results in a decrease in the organism's physiological fitness. Subsequent to this, the "oxidative stress theory" of aging states that an imbalance between pro-oxidant species and antioxidant defenses drives the aging process. It is crucial to remember, though, that ROS are not just dangerous chemicals that cause OS; they also play a crucial part in cellular signaling, specifically redox signaling, which guarantees proper cellular activities. The scientific world has lately been aware of the concept of reductive stress, which is described as a condition of prolonged rise in cellular reducing equivalents linked to excessive Nrf2 activation [4]. Because of these factors, the "redox stress hypothesis" of aging has recently been put out, which contends that a progressive disruption of the redox-regulated signaling systems is the primary cause of functional deficits associated with aging [20].

The aging process is linked to an increase in macromolecule oxidative alterations and a corresponding decline in antioxidant defenses. Age-related increases in ROS formation may be explained by an increase in electron leakage from the electron transport chain [8]. Furthermore, it has been noted that aging is associated with a decreased capacity for antioxidants as well as a compromised adaptive induction of antioxidants [7].

Because of its high metabolic activity, RPE has more mitochondria than other cell types, which allows it to produce enough ATP for all of its physiological needs [9], AMD may result from age-related mitochondrial dysfunction increasing OS in the RPE [14].

Aging is also linked to a persistent low-grade inflammation described as "inflammageing," which is characterized by raised levels of inflammatory markers and a high risk of morbidity, including AMD [7].

Additionally, it has been suggested that cellular senescence of the RPE plays a part in the etiology of AMD. Age-related disorders and aging have been linked to cell senescence, or the permanent cessation of cell division. Senescent cells have been linked to glaucoma and cataracts, among other eye conditions [12]. According to [5], exposure to pro-

oxidants triggers the senescence process in proliferating human RPE in vitro, and mitochondrial ROS have a causal role in cellular senescence.

The circadian rhythm of the retina is impacted by aging, and the eye has a circadian system [24]. For instance, melatonin controls the regularity of photoreceptor phagocytosis through melatonin receptors, and mice lacking melatonin receptors exhibited an accumulation of lipofuscin in the RPE [25]. These findings imply that changes in the circadian rhythm may have a role in AMD pathogenesis, although further investigation is necessary. The circadian rhythm can be viewed as a target for AMD therapy since it controls the expression of half of the mammalian proteins, which are either drug targets or involved in drug transport and metabolism [26].

Defenses against antioxidants

The transcription factor Nrf2 must be activated in order for the RPE to maintain redox balance. Under normal circumstances, Nrf2 activity is kept low by binding to its inhibitor, Kelch-like ECH-associated protein 1 (KEAP1), an E3 ligase based on CUL3 that polyubiquitinates Nrf2 and causes the proteasome to constitutively degrade it. The preservation of redox equilibrium is made possible by the low baseline Nrf2 activity. Under OS circumstances, KEAP1's ubiquitin ligase activity is inhibited due to the oxidation of two redox-sensitive cysteine residues. Because of this, freshly produced Nrf2 is not broken down and instead moves to the nucleus, where it attaches to the electrophilic responsive element (ARE/EpRE) and antioxidant sequences on target genes' regulatory regions, thereby inducing the antioxidant response. In addition to KEAP1, two other ubiquitin ligase complexes, namely F-box/WD repeat-containing protein 1A (βTrCP) and synoviolin (Hrd1), can control Nrf2 activation. These complexes may have a role in AMD that warrants further research. Furthermore, it should be noted that the molecular clock protein BMAL1 has the ability to regulate Nrf2 expression [27].

The RPE has evolved to survive in OS circumstances as a result of the retina's strong production of ROS [28]. By absorbing excess light energy, the retina's many chromophores can guard against damage caused by light. An accumulation of melanolipofuscin granules, which contain both lipofuscin and melanin, has been seen in the aging RPE; this phenomenon is correlated with the development of AMD [29]. Furthermore, as was previously mentioned, the primary generator of ROS in the RPE is the mitochondria, and as people age, their leaking increases. Mitophagy is a kind of autophagy that is exclusive to mitochondria and is used by the RPE to eliminate damaged or defective mitochondria in order to preserve proper cell activities. According to certain theories, AMD pathogenesis may be influenced by impairment of mitophagy [30]. Increased ROS generation leads to mitochondrial depolarization, autophagy, and mitophagy. This process is triggered by the outer mitochondrial membrane proteins B-cell leukemia/lymphoma 2 (BCL-2)/adenovirus E1B interacting protein 3 (BNIP3) and Nip-like protein X (NIX) [31]. It is still unclear how BNIP3 and NIX function under AMD, though.

The buildup of oxidatively damaged molecules in AMD indicates that the body's defenses against ROS are insufficient to keep up with the growing quantity of ROS. There is growing evidence that aging reduces Nrf2 signaling, which in turn reduces antioxidant capability [32]. Nrf2 activation has been associated with the structural and functional integrity of the mitochondria, where it plays a crucial role during stressful situations. Moreover, a decrease in Nrf2 signaling may worsen NF-κB activation, which in turn may increase inflammation due to the established cross-talk between Nrf2 and NF-κB [33].

Conclusion

Although the idea of getting cataracts in the eyes can be frightening, you can avoid them by maintaining good eye health. Although older folks are more likely to get cataracts, you don't have to wait to begin preventing them. Taking good care of the eyes is all that is necessary to prevent the danger of acquiring cataracts.

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