INTRODUCTION

When the lens of eye (which are normally clear) become opaque, this is called ‘cataract’ and leads to a decline in the amount of light entering the eye. The result of cataract is a significant reduction in vision. Normally, the lens is consists of natural crystalline materials that are combined in specific quantities with proteins and water to form a transparent structure that allows light to pass. Therefore, the occurrence of cataract will lead to a vision that is similar to looking through a paper or a waterfall.³

It was estimated that in the year 2010 alone that cataract was responsible for the morbidity of 10.8 million people (of overall 32.4 million blind people around the world), and 35.1 million people (of overall 191 million vision impaired people around the world). In regions with high income, these rates were lower. On the other hand, they increased in Southeast Asia and Oceania. Cataract is considered to be the most common cause of visual impairment in Saudi Arabia. Other less common causes in include diabetic neuropathy and refractive error.³
When talking on a public health levels, cataract-caused blindness is considered a difficult challenge for physicians and ophthalmologists. Being solved only by surgery, it causes significant economic burden on the society. Therefore, there have been approaches to reduce the burden of this issue by identifying and, possibly, modifying factors which will lead to the prevention or at least delay of the disease (up to 10 years). This was found to cause a dramatic decrease in the rate of surgeries needed by 45% or even more. Therefore, efforts have been made to focus on preventive medicine when it comes to cataract. Moreover, this better understanding of the disease and its risk factors will surely positively affect management and thus prognosis of patients.

METHODS

Data sources and search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE, from January 1970 to March 2017. The following search terms were used: cataracts, pathogenesis of cataracts, pathophysiology in cataracts, ageing lens, aging and vision loss, lens degeneration.

Data extraction

Two reviewers have independently reviewed the studies, abstracted data and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

This study was done after approval of Review Board of King Abdulaziz University.

DISCUSSION

Lens anatomy and physiology

Composition

Lens consists of cells derived from an ectodermal origin at different stages of differentiation. These ectodermal cells are surrounded then by the basal lamina and finally the lens capsule. When looking from the anterior aspect, they form a monolayer of epithelial cells. On the other hand, when looking from the interior, they represent shells of fibers which form the main bulk of the lens. These fibers are either superficial and metabolically active, or deep, organelle-free, adult fibers. Glucose is the main source of energy used by these fibers to grow and become transparent. Aerobic reactions are responsible for only 30% of ATP production in the lens, and over 70% ATP come from anaerobic glycolysis.4 Ion channels (including the Ca²⁺/ATPase and the Na⁺/K⁺ATPase) work to maintain homeostatic environment in the lens.5

Free radicals

Free radicals (like hypochlorous acid (HClO), hydroxyl radical (‘OH), free superoxide (O₂⁻), and H₂O₂) are constantly present in any living cell and are the cause of oxidative stress to these cells. To relieve this stress, several homeostatic mechanisms in the lens are usually involved. These include repair systems and scavenger molecules in the membranes the cytosol, and the mitochondria. Examples are reduced glutathione (GSH), cysteine, ascorbic acid, vitamin E, methionine, glutathione peroxidase, thioredate transferase (TTase), thioredoxin (TRx), and glutathione reductase (GR). The combined work of these molecule will lead to a stable environment that is free of oxidative stress.6 Other homeostatic and repair systems in the lens work to remove damaged proteins and nucleic acids.7

The most important molecule that works in the lens as an antioxidant is GSH. It is synthesized and secreted by the epithelium, and directly protects proteins from oxidation. On the other hand, ascorbate also has an important role in antioxidation, but its product dehydroascorbic acid (DHA), was experimentally found to cause cataracts in the absence of GSH.8 Therefore, GSH has an important role of reducing DHA either directly or through the TTase system (which we will describe below). GSH also works to protect the epithelium from other oxidative mechanisms, and its absence was found to cause DNA strand breaks on exposure to oxidative stress in mice.9

As age passes, syntheses and secretion of GSH decreases, causing a progressive increase in GSSG levels. High GSSG levels are directly caused by the significantly decreased activity of GR. This will eventually result in a nucleus that is vulnerable to oxidative stress [8]. This reduction in GSH levels has been established to be present in lens with cataract. Moreover, the presence of methionine sulphoxide reductase A can potentially revers the dysfunction of α-crystallin chaperone.10

The presence of higher levels of oxidative stress will cause proteins to be thiolated by γ-glutamyl cysteine, GSSG, and cysteine, to synthesize PSSG, PSSγGC, PSSC, and mixed disulphides.6 It is possible to restore protein disulphides and mixed disulphides to their original state by using to main repair mechanisms. The first mechanism is the GSH-dependent enzyme system, which is also known as glutaredoxin, and is present in the cytosole and metachondria. It works to catalyze PSSG, and later turn it into GSH.11

The other mechanism is the TRx enzyme that is also present in the cytosol and mitochondria, and is NAPDH-dependent. Its role is to reduce inter- and intra- molecular PSSP. Both TRx and TTase work together to maintain and restore the structure, function, and conformation of proteins. Therefore, TRx, and TTase levels are both upregulated in cases of significant oxidative stress. When a living cell is exposed to H₂O₂, they can both work to...
activate G3PD. However, their activity also significantly decreases with age.\textsuperscript{12}

**Lens transparency**

Avascularity of fibers, the thin inter-fiber spaces, and the regular organization of proteins and cells, are the main factors on which the transparency of lens depend. Within the fibers themselves, crystallins are present in short ranges, which are shorter than light wavelength (similar to glass). The small size of molecules (being less than 10 nm) plays an important role in achieving this.\textsuperscript{13}

Within the lens cortex high spatial order of fibers and thin spaces play a significant role in enhancing transparency. When it comes to the lens nucleus, the spatial order of crystalline is not of that important role due to the absence of major differences between the refractive index of cytoplasm and fibers.\textsuperscript{14}

**Age related changes causing cataract**

**Changes in physical behavior with age**

Increased scattering of light is a result of a continuous series of reactions, and biochemical changes that start from the prenatal period. These reactions may also lead to the stiffness and even coloration of the lens. These previously mentioned consequences affect the nucleus more significantly that the cortex, and they are the main reasons that cause the loss of lens accommodation.

**Increasing light-scatter**

As age progresses, and in the absence of cataract, the overall scattering of light increases steadily, and this starts to be important after the age of 40 years. Previous large studies have proved this increase with age, which was found to be more prominent in the deep cortex than superficial cortex. Another study conducted by Smith et al, concluded that the risk is highest in the deep cortex, then followed by the nucleus and the superficial cortex. Intraocular scattering of light also increases with age, as a previous study of 2044 normal eyes has revealed. This study found that scattering remained normal until the age of 40, then doubled by 65 and tripled by 77 years.\textsuperscript{15}

**Decreasing elasticity**

During accommodation, there is a significant increase in the lens refractive power. This increase occurs as a result of thickness changes of the lens along with changes in the curves of the lens, and is achieved by the contraction of ciliary muscles. Using magnetic resonance imaging techniques, and Scheimpflug photography, it was found that about 90% of the increase in the thickness of lens was caused by thickening of the nucleus of the lens. On the other hand, this stable increase in rigidity of the lens, which starts from birth, can affect the cortex less significantly that it affects the nucleus. Therefore, this is considered an essential factor in the determination of the onset and progression of cases of presbyopia. The nucleus of the lens can stay deformable, and with low rigidity, until the age of 40 years.\textsuperscript{16}

Rigidity and stiffness of the lens continues to increase with age, and as we previously mentioned, this increase is present in nucleus more prominently than the cortex. On the other hand, young adults are found to have an elastic deformable lens.\textsuperscript{17} Elasticity and stiffness will become equal in both nucleus and cortex around the age of 40 years. Then, the nucleus will gradually become more rigid and stiff than the cortex. At age 50 years, ciliary muscles become unable to modify the lens shape with their contractions. This previously discussed mechanism of accommodation failure is the main cause of presbyopia. All these changes in stiffness and elasticity are caused by age progression what leads to changes in proteins concentrations. Other contributing factors include the size of the lens and its capsule.\textsuperscript{18}

**Changes in the lens proteins with age**

(i) **Post-translational changes to the lens crystalline**

Crystallin are considered to be stable proteins that are restored in their original state but undergo major modifications starting from early life. These modifications are non-enzymatic, effect both the function and the structure, and include deamidation, thiolation, carbamylation, glycation, phosphorylation, acetylation, proteolysis, and cys-methylation. Proteolysis, specifically, will lead to the truncation and release of fragments of crystalline.\textsuperscript{19}

This process of deamidation starts as soon as the prenatal period, and continue with age (especially in cases predisposed to cataract). These changes include the modification of the structure of the proteins into an insoluble structure of α- and β-crystallins. These modifications of crystallins (that are considered to be post-translational) are achieved by derivatives from sugars, and significantly correlate with the loss of transparency and the later development of cataracts. Glycation is considered a non-enzymatic reaction, and the most important glycators are fructose, glucose, some pentoses, glyoxal, threose, ascorbate, along with some products of degradation. All these together constitutes Schiff-base compounds that are later rearranged into more stable molecules like fructoselysine.\textsuperscript{20}

Generally, proteins that are unfolded and/or denatured become more vulnerable to oxidation. This is also the case when talking about the proteins of the lens. Other predisposing factors to this vulnerability to oxidation is the significant decline in the ability of the lens to perform antioxidant reactions with age, due to the decrease in GSH enzymes levels. This will further lead to the accumulation of disulphide cross-linked crystallins, mixed disulphides, and GSH-regenerating enzymes.\textsuperscript{19}
Cleavage occurs to both α- and β-crystallins, leading to unstable protein products with large amounts. Crystalline fragments concentrations also increase in the lens fibers through age, and in the nucleus more than the cortex. Another important pathway in the lens is the ubiquitin–proteasome pathway that plays an essential role in the removal of proteins that are a result of oxidative process. However, the conjugation activity of Ubiquitin also decreases significantly with age causing oxidized crystallins accumulation, mainly in the nucleus.21

(ii) Conformational changes

Oxidative stress causes significant harms to crystallins that will eventually result in the formation of insoluble, high-molecular-weight, cross-linked proteins. These proteins will lead to significant disruption of the short-range ordering of the crystallins, causing higher scattering of the light along with loss of transparency of the lens. This also causes increased rigidity and stiffness of the lens, especially the nucleus.22

Maillard products are considered to be an extremely important contributor to the accumulation of chromophores. These products, along with AGEs are a result of the ascorbilation and/or glycation. Other chromophores are formed as the result of tryptophan (‘UV filter’ compounds) including 3-hydroxy kynurenine and GSH-3-OHKG. These lead to the formation of crystalline derivatives that are cross-linked. N-formylkynurenine also plays a role in crystallins modifications and are present in the lens. These molecules are thought to cause significant functional and structural effects.23

(iii) Loss of chaperone function

The activity of α-crystallin chaperone significantly decreases with age, and this is the reason of the increased aggregation, and insolubility of proteins along with the increased scattering of light and loss of transparency of lens. All these mentioned mechanisms are a result of normal aging.8

Within the normal young lens, the interactions of α-crystallin will cause the formation of soluble aggregates that contains all types of crystallins. These are known to conserve their functions fully. However, starting from age of 40, new protein synthesis decreases significantly, and the already present α-crystallin levels decrease significantly and become depleted. When individuals become older than 50 years, the lens nucleus will start to contain larger proportions of cross-linked crystallins. Moreover, chaperone function and subunit exchange also decrease significantly.19

(iv) Loss of antioxidant and free-radical scavenging capacity

The continuous decline in the function of chaperone starting from middle age occurs along with the decrease in the capacity of the lens to scavenge free-radicals. Therefore, all these proteins become more vulnerable to oxidative stress. Reduced GSH levels negatively correlate with age. A significant decline in cysteine in the lens nucleus is also observed. However, this decline is not observed in the cortex. In patients with cataract, GSH levels are usually unmeasurable.24

Sweeney and Truscott et al, have conducted a study to explain this significant vulnerability and lack of protection against oxidative stress, and were successful in demonstrating the appearance of a barrier to the diffusion of GSH that starts after the age of 30. This can potentially explain the vulnerability of the nucleus to oxidative stress starting from the age of 40. When crystallins themselves increase the cross-linking between them, this will further lead to the obstruction and would provide a plausible explanation for the increase in chromophores in the lens nucleus. All these mechanisms will lead eventually to a nucleus with ‘frozen’ structural proteins.25

The impact of age-related cataract on vision and its prevalence

The prevalence of cataract in individuals aged between 70 and 79 years old, can be as high as 40% in regions with high temperature, and can even reach 45% in tropical regions. These numbers were estimated based on studies that were conducted in Singapore, Iceland, and Japan.26 When studying rural USA, the prevalence of cataract was found to reach 42% of individuals older than 72 years. Reports from Australia have demonstrated similar results, with a prevalence of about 40%.27

On the other hand, moderate or severe cataract can be found in up to 15% of individuals in the same age groups. This prevalence can reach 60% of individuals in subtropical and tropical regions and in 80 per cent in a rural population in the USA.26 Prevalence in the Netherlands was also found to be similar; up to 20% of individuals aged between 31-45 years, and 30% of individuals aged 76-90 years were found to have small mild cataracts. Larger more severe cataracts were found only in 10% of individuals aged 31-45 years but in 45% of individuals aged 76-90 years. Although cataract has this relatively high prevalence, the management of is quite simple and straightforward: surgery is the most effective way to treat cataract.28

CONCLUSION

Cataracts heavily impacts the vision, thereby, the lives of individuals suffering from it. Due to its large prevalence, the impact on economy is large too. Although surgery as a management is very promising, newer approach is focusing on its pathophysiology to emphasize on preventive options. Several changes, including oxidative stress, reduction in reductive enzymes, lens elasticity, and specific age related degeneration play major roles in its
pathophysiology. More studies must be done upon devising methods on preventing cataracts from occurring.

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