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Review on Lenticular Metabolism and Cataract

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Abstract

Cataract, characterized by the opacification of the eye lens, remains the leading cause of blindness globally. Among various etiological factors, disruptions in lenticular metabolism have been recognized as a critical contributor to cataractogenesis. The avascular nature of the lens necessitates a highly regulated metabolic environment to maintain its transparency and function. This review explores the intricate metabolic pathways within the lens, particularly focusing on glucose metabolism through glycolysis, the pentose phosphate pathway, and the sorbitol (polyol) pathway. Under physiological conditions, these pathways support cellular homeostasis, maintain redox balance, and provide essential metabolic substrates. However, metabolic imbalances-particularly those associated with diabetes mellitus-can lead to excessive accumulation of sorbitol and oxidative stress, thereby inducing osmotic imbalance, protein aggregation, and ultimately, lens opacification. Furthermore, the review highlights the role of antioxidant defenses, including glutathione and enzymatic systems like superoxide dismutase and catalase, which are vital in protecting the lens from oxidative damage. Age-related decline in these defenses, along with cumulative metabolic insults, contributes significantly to cataract formation. Genetic factors influencing enzyme activities and transporter functions are also examined for their role in individual susceptibility to metabolic cataracts. Understanding the biochemical and molecular mechanisms of lenticular metabolism offers insights into potential therapeutic targets for delaying or preventing cataract development. This review underscores the importance of maintaining metabolic integrity and oxidative balance within the lens as a strategy for cataract prevention and management.

Keywords: Cataract, Lenticular Metabolism, Cataractogenesis, Lens Opacification, Osmotic Imbalance

Introduction

Globally, there are about 285 million visually impaired individuals, 39 million of whom have total blindness, while the remaining 246 million have low vision [1]. The number of those with total blindness is expected to rise to 75 million by 2020 [2, 3]. The main cause of severe and moderate visual impairment is uncorrected refractive errors, as indicated by World Health Organization. Approximately 80% of the visually impaired are found in Africa and Asia, especially in the rural area of low resource nations of these regions, where there are insufficient and under-utilized ophthalmological facilities [4, 5]. About 28, 000 new cases of visual impairment are reported daily, around the world, with cataract accounting for approximately 50% [6] making it the leading cause of blindness worldwide [7, 8]. In Nigeria, various studies have reported the prevalence of blindness ranging from 0.78% to 5.6% [9,10] implicating cataract as the cause of about 42.9% of them [10, 6].

Blindness directly interferes with various activities of daily living and imposes developmental challenges in children. In adults, it compromises gainful employment, leisure and ability for independent living with resultant loss of status and self-esteem [1]. Currently, surgical removal (cataract surgery) of the clouded or opaque lens of the eye and subsequent replacement with a new clear artificial lens (intraocular lens implant or IOL), encapsulated in the normal lens capsule, is the only method used in management of cataracts [3]. Cataract surgery has an extremely high rate of success: although there is often the risk of posterior capsular opacification, in which case a second surgery is required. Posterior capsular opacification is the product of ectopic growth of remaining epithelial cells in the posterior lens capsule, leading to obstruction of the visual axis, wrinkling of the capsule and its eventual scattering of light [8].

Low in-come, lack of employment, lack of trust on the experts, poor awareness, cost of surgery, social/religious beliefs, distance from eye care services, lack of transport, and fear of the bad outcome have been identified as the major barrier to accessing cataract surgical care in Nigeria [11, 12, 13, 1]. Apart from cataract surgery cost and its complications, an intraocular lens (artificial lens) cannot give the optical qualities of a typical ocular lens.

Cataract remains a major public health problem, and to effectively deal with it, its mechanism of formation must be well understood, in order to ascertain the key steps which may be used as targets for therapeutic regimes [14]. According to World Health Organization over 80% of the world's population rely on the use of herbal medicine as a remedy [15, 16].

The Lens

The crystalline lens is a unique transparent, biconvex structure of a fully developed eye [17], that together with the cornea, refracts light, causing it to be focused precisely on the retina. Lens is avascular that is, it has no blood vessels, connective tissue or nerves [18] that would interfere with light; and depends on its avascularity for ocular lens transparency [19]. The lens gets majority of its oxygen and nutrients it requires from vitreous and aqueous humour, secreted by the cilliary body. Waste products are also removed through these fluids [17].

The lens changes shape such that it could change the focal length of the eye so as to focus on objects at varying distance, thus permitting a genuine picture of the object of interest to be focused on the retina. This process is called accommodation [20]. With age, ocular lens grows and hardens gradually, diminishing the ability to accommodate [20] in response to cilliary muscle contraction resulting in the need for reading aid. Visual problems occur when the ocular lens loses its transparency [14].

The lens grows all through a lifetime, developing layers of fibre cells around a central core. It contains structurally organised proteins, called crystallin that makes it transparent and allows passage of light [21]. Some of the proteins present at the centre of the ocular lens may be there throughout life time. Any alteration in these proteins could lead to cataract or other age related diseases. Lens contains antioxidant vitamins and enzymes, and other antioxidant molecules that protect it from oxidative stress [22].

The lens is made up of three compartments namely: epithelium, capsule and lens fibres. The lens epithelium is situated in the anterior portion (front part) of the lens capsule and fibres. All the metabolic processes like synthesis, detoxification and transport, occur in lens epithelium [19]. The lens fibres are thin, long, transparent cells, which make up most of the material for the lens. The lens capsule forms a smooth and transparent membrane around the lens. During accommodation, external forces are translated to the internal mass of the lens tissue through the lens capsule. During aging, the loss of accommodation is partly as a result of the lens capsule not being able to apply molding pressure to the lens because of lack of elasticity [23].

Lens Composition

Protein

A lens protein constitutes up to 33 per cent of lens total mass and represents its high refractive index [19]. The major constituent of lens protein is primarily known as crystallins, which make up 80% to 90% of total water soluble protein [17] and 60% of the lens fibre mass, which is the highest protein concentration in the mammalian body [24, 25]. Lens transparency depends primarily on the high stability and solubility of lens crystallins' structure. The crystallins are comprises of three main types namely: α-, β- and γ-crystallins. α- and β-crystallins exist as oligomers, whereas the γ-crystallin exists as a monomer [17].

The most abundant lens protein is α-crystallin, which constitutes about 40 per cent of the total lens protein [24, 26]. It is one of the small heat shock proteins [25], a family of proteins that protect and maintain viability of cell under stressful conditions such as those occurring during thermal and oxidative challenges simply by refolding and stabilizing denatured proteins [27] and help maintain lens transparency [28]. It exists as a heterogenous multimeric complex of molecular weight 800,000, consisting of two subunits, αA and αB-crystallin in the ratio 3:1 [29, 26, 8, 30]. αA-Crystallin is present only in crystalline lens fibres, while αB-crystallin is present in other organs like the lungs, heart, brain, skeletal muscle and kidney [31, 32, 33]. Elevated expression of αB-crystallin is found in several neurological disorders, cancer and diabetic conditions [34, 17, 32]. αA-Crystallin and the chaperone-like αB-crystallin, bind specifically the unfolded or denatured protein to prevent unspecific aggregation. This function is fundamental to the maintenance of ocular lens transparency and cataract prevention [31, 17, 8]. The lenticular proteins are extremely long-lived and undergo very little or no protein turnover. In differentiated lens fibres, proteins, including α-crystallins undergo age related post translational modification such as proteolysis, glycation, deamination, truncation and phosphorylation [26, 17, 19]. These modifications may lead to lens opacification and cataractogenesis by inducing protein aggregation and insolubility, in aged and cataractous lens [17]. The mechanism by which this occurs is not completely understood. Other proteins found in the lens include cytoskeletal (about 2-4% of lens protein) consisting microtubules, vimentin and microfilaments [35, 17] and membrane proteins, such as actin, filensin, spectrin, myosin, tropomyosin, transporters, channel and junctional proteins [35].

Water

Water enters the lens through the outer coat (anterior) of lens epithelium and flows out through the posterior of the lens fibre cell [36]. The lens has very low water content, a property, which in conjunction with high protein content is important for maintainining lens transparency [37, 18]. The low lenticular water content mostly mirrors the novel protein composition of fibre cell cytoplasm. According to Delamere, the matured human lens capsule contains about 80% water, with its cortex and nucleus having 68.6% and 63.4% water, respectively [22]. There is no significant alteration in age.When the interaction between the refractile crystallin and low water content is altered, cataract can occur [37].

Electrolytes

Normal ocular lens contains high potassium and low sodium content [22]. Lenticular K^+ content is 125 mmol/kg of lens water, while that of Na^+ is about 14-26 mmol/kg [38, 22]. Lens chloride is seen as simply, the counter-ion to lens sodium, and its level in the lens is around 26 mmol/kg of lens water [38]. It forms the major cation-anion pair in the extra cellular space. The lenticular low sodium and high potassium cation levels often balances one another, and is maintained by the activity of the Na^+-K^+ ATPase pump, which in turn maintains the permeability of the lens membrane. Alteration in the levels of either of these ions may lead to lenticular cationic imbalance which may lead to cataract formation [38, 22]. In the normal human lens, calcium ion is often found to be at a very low level, and changes in calcium concentration could be an important risk factor for cataract development.The free calcium concentration present in lens cytoplasm is just about 100 nM. Normally, calcium is essential for maintenance of lens cell membrane permeability. Most of the processes that contribute to the modification of the structures of lens biomolecules involve abnormally high concentrations of intracellular calcium [39]. Lens is very rich in magnesium so much that it is not sensitive to the level in aqueous humour.

Ascorbic Acid

Ascorbic acid is more concentrated in the lens and aqueous humour than in the blood [22]. Ascorbate (its reduced form), functions as a free radicals' scavenger in the lens and aqueous humour, thereby, preventing damages to lens nucleic acids, proteins and lipids [22, 40]. It also averts UV radiation-induced cation pumps' damage, and decreases photo-induced oxidative damage in the membranes [41]. As a reducing agent ascorbic acid may likewise act as pro-oxidant, since in the presence of metallic ions, and in conjunction with light, ascorbic acid can create H_2O_2 [42, 41]. Ascorbic acid works with glutathione in protecting the lenticular protein against oxidation [42].

Lipid

Most of the lipids in ocular lens are connected with proteins (protein lipid complex), thus decreasing their movement [43]. Cholesterol is the most abundant lipid found in ocular lens, constitute up to half (50%) of the total lens lipid [44]. The most abundant phospholipid in the human lens is the myelin-like lipid known as dihydrosphingolipid, which is less abundant in other tissue. This myelin-like lipid was reported to be the main lipid remaining in frozen mammoth 40,000 years, in a stable state after its death. Sphingolipid content is found in large amount in lens but not as large as cholesterol [45] and is essential for lens transparency because of the smoothness of the surface of lens lipid membrane [46]. Elevated cholesterol content together with high content of sphingolipid in human lens are the major reason the lens cell membranes are unusually rigid [44]. During aging, lens lipid composition is altered such that: cholesterol level doubles, sphingomyelin remarkably increases, phosphatidylethanolamine and phosphatidylcholine levels decrease. These changes may serve as markers of oxidative stress, since they alter cell membrane structure, influencing lens cell membrane function and cause changes in ion permeability [47].

Glutathione

Lenticular glutathione mostly occur at high concentrations in epithelium mainly at a reduced state, where they work as important antioxidant for the maintenance of lens transparency, normal tissue hydration, protecting the lens against oxidative damage and protein synthesis [48]. Glutathione has been reported to be at the concentration of 2-4mM in the lens epithelium. It is synthesized by the lens epithelium and cortical layers where it is available in a reduced form with the highest levels being at the centre of the lens epithelium and cortical fibres and lowest in lens core [41]. Any oxidized glutathione (GSSG) is reduced rapidly to GSH by enzyme, glutathione reductase that uses the coenzyme, NADPH. Regenerating reduced glutathione from oxidized glutathione is important because it is the chemically reduced form of glutathione that neutralizes reactive molecules directly, protecting exposed protein thiols from oxidation [19]. In addition, glutathione metabolism helps in removal of xenobiotics from the lens [49]. Glutathione levels reduce significantly in aging and cataract formation [48, 50]. The lens depends on a balanced redox system to maintain its transparency. In cataractous lens, an increase in GSSG leads to an imbalance in GSH/GSSG ratio and protein modification such as insolubility, cross-linking, with loss of glutathione [48].

Taurine

Taurine, one of the most abundant amino acid found in the ocular tissues (cornea, iris, cillary body, lens, retina and vitreous humour), is not metabolized or incorporated into proteins; and is highly concentrated in the lens [51]. It is effectively transported into the lens, although it can be produced within, from methionine and cysteine in the presence of vitamin B_6 [22, 52]. Taurine may help to counteract damage to cells by acting as an antioxidant, osmoregulator and modulator of ion transport in lens epithelial cells [22]. Studies have shown that taurine protects human corneal epithelial cells exposed to conditions of hyperosmotic stress by acting as osmoregulator. It protects the lens, corneal cells and retina against oxidative stress, and the lens from hyperglycaemia-induced cataract [51].

Lenticular Metabolism

Protein Metabolism

Protein synthesis occurs mainly (and slowly), in the lens epithelium and superficial cortex [24]. The pattern of protein synthesis in the lens epithelium differs from that in lens cortex [22]. Crystallins are synthesized at different times during lens development, that is when the epithelial cells differentiate, elongating to become lens fibres [19]. α-Crystallin are synthesized in the differentiated lens fibres [31] and are reported to be the first crystallin synthesised in the lens during embryogenesis in a normal lens cell development [31]. The two subunits of α-crystallin are synthesis continuously as new lens fibres develops. Proteins in the matured lens fibre cell remain in the crystalline lens throughout life [53]. Studies have shown that, during the aging, lens proteins may undergo some covalent modification including deamidation, oxidation, glycation and truncation. Damaged proteins (aging) are broken down by peptidases and proteases in the lens. Proteins can also be degraded by a proteasome. There is a little continual turnover of proteins in the epithelium, and it depends on lens fibre maturation and the need for degradation of proteins that are damaged during aging [22].

Glutathione Metabolism

The tripeptide, glutathione(γ-glutamyl-cysteinyl-glycine) is synthesized and degraded in the lens epithelium and cortex, via ATP dependent processes [19]. In human lens, glutathione is synthesized denovo from cysteine, glutamate and glycine, in a two stage process [41]. First, gamma-glutamyl cysteinyl synthetase catalyzes the combination of glutamate and cysteine. Next, GSH-synthetase catalyzes the reaction of gamma-glutamylcysteine with glycine to form GSH. As GSH levels rise, they self-limit further GSH synthesis; otherwise, cysteine availability is usually rate limiting.

High level of glutathione in a reduced form, functions to protects lens protein sulfhydryl groups (-SH) against oxidation [54, 42]. This is because with low level of glutathione, due to high level of oxidative damage, crystallins become thiolated by GSSG, cysteine and to a lesser degree γ-glutamylcysteine, forming the disulphides bond(mixed disulphide), known as protein oxidised glutathione(PSSG), protein oxidized cysteine(PSSC) and protein oxidized γ-glutamylcysteine (PSSγGC), whose further oxidation leads to the formation of protein-protein disulphides (PSSPs) [19], leading to protein cross linking, insoluble lens protein and light scattering (Truscott, 2000). At the point when the system works accurately, glutathione (GSH) becomes oxidized: two molecules of glutathione become linked by a disulphide bridge to form disulphide or oxidized glutathione (GSSG) [22].The recycling of oxidized glutathione back to the reduced form is achieved by glutathione reductase which uses reducing equivalents from NADPH to reconvert GSSG to 2GSH [19, 41]. In an ocular lens, glutathione deficiency is a risk factor for cataract formation [48]. According to Ballatori *et al*., the synthesis and recycling of glutathione falls with age. During aging, inability of ocular lens to synthesis glutathione may be caused by a loss of L-cysteine and gamma-glutamylcysteinyl synthetase required for its biosynthesis [48] (Fig 1).

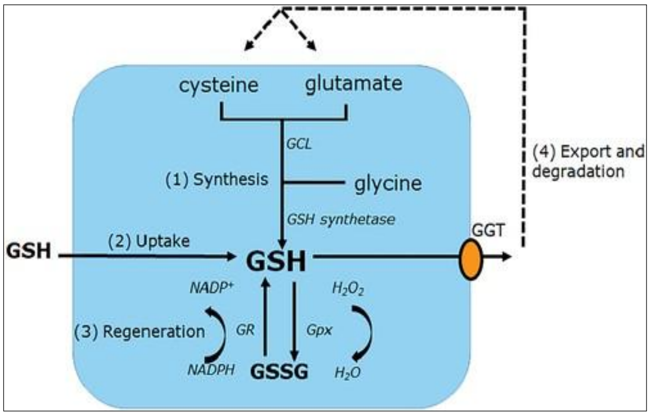

Fig 1: glutathione metabolism [55]

Ascorbic Acid Metabolism

To maintain high concentration of vitamin C in ocular structure, ascorbic acid must be moved into the lens fluid (aqueous humour) in an oxidized form as dehydroascorbic acid(DHA), which enters the lens through a glucose transporter. It is then converted to the reduced form by the activity of the glutathione-dependent enzyme known as dehydroascorbate reductase [42] or through non-enzymatic processes, using low molecular weight antioxidants like GSH or cysteine [41]. However, if ascorbic acid-DHA recycling are absent, DHA, will undergo an irreversible degradation to form diketogulonic acid which also participates in modifying and crosslinking lens protein [41]. In senile cataract formation, ascorbic acid level is decreased while DHA level is increased.

Electrolyte Homeostasis

Active cation-transport occurs in the ocular lens between the lens epithelium and aqueous humour. The epithelium contains abundance of Ca/K-ATPase and Na/K-ATPase for the active transport of electrolytes. The activity of Na/K-ATPase is higher in the epithelium than any other part of the lens [56]. Lenticular epithelial cells have the capacity of synthesizing new Na-K-ATPases to support the activity of the sodium pump in response to cell damage [22].

The lenticular levels of Na^+ and K^+ are built up by the activity of Na/K-ATPase, which removes sodium forcefully and accumulates potassium inward to balance ion leakage in the opposite direction, is important for maintaining accurate concentrations of sodium and potassium in the lens [22, 56]. Once the activity of Na/K-ATPase is inhibited, lens loses potassium and gains sodium; as in the case of senile corticol cataract, where lens Na^+ is higher than 100mmol/kg lens water, and $K^+$is abnormally low (usually 80mmol/kg lens water) [57]. Once this occurs, osmotic equilibrium is disturbed. Osmotic disturbance brought about by ionic changes, causes water to accumulate in lens cells, which in turn leads to cell lysis and the appearance of liquid droplets that scatter light and hinder transparency [22, 57].

Lens cells use two primary mechanisms to extrude Ca^{2+}, the Na-Ca exchanger (NCX) and the plasma membrane Ca-ATPase (PMCA) [58]. The plasma membrane Ca-ATPase is responsible for the outward transport of calcium from the cytoplasm, and assumes a fundamental part in extruding calcium from the lens. Na-Ca exchanger uses the inwardly directed Na^+ electrochemical gradient to drive Ca^{2+} efflux [58]. Calcium is also extruded from the cytoplasm through another type of Ca-ATPase, found on the surface of endoplasmic reticulum [58]. Ca-ATPase pumps are seen only in the epithelium and its activity is 50% lower in cataractous lens. Excessive calcium level can harm the lens cells by increasing calcium levels in human lens. Increase in calcium level, in cortical cataract (senile cataract), play a significant role in the opacification process [58]. Lenticular chloride channels have been recognised to be essential for the regulation of chloride concentrations in the lens.

Glucose Metabolism

The lens, like other cellular tissues, generates a continuous supply of ATP, which provides energy for the maintenance of lens transparency, synthesis of protein and lipid and maintenance of lens dehydration [21]. Energy is needed most in the lens within the lens epithelium, and about half of the energy requirements in epithelium are supplied aerobically.

Energy production in lens depends entirely on glucose metabolism, which is achieved via three main routes: glycolysis, pentose phosphate shunt and the polyol pathway [21]. Glucose enters the lens by simple diffusion through glucose transporter proteins (GLUT-1 and GLUT-3). It takes a considerable amount of time to diffuse from the surface cells to the nucleus. In the human lens, it takes about 4 to 8 days. Nonetheless, it is believed that inward flow of fluid, occurs along the intercellular clefts at the anterior and posterior poles of the lens, and this accelerates the penetration of glucose into the lens cell mass.

There is no significant difference between the glycolytic pathway of the lens and that of other tissues. The lens depends on anaerobic glycolysis to produces almost all the ATP needed for its energy requirement. Enzymes required for glycolysis are found within the lens. Hexokinase, the main regulatory enzyme in glycolytic sequence, which catalyzes the phosphorylation of glucose to glucose-6-phosphate, is available at very low concentrations and appears to be the rate-limiting factor for lenticular glucose metabolism [59], as it prevents the generation of glucose-6-phosphate for both glycolysis and the pentose phosphate shunt. Aging decreases the concentration of hexokinase. It could alter the lens' ability to cope with stress and consequently, increases the tendency for opacification [53].

About 70 per cent of glucose that enters the lens is converted to lactate by means of anaerobic glycolysis. Lactate generated is dissipated in two ways. It is converted to pyruvate, and subsequently to acetylcoA which channelled through Krebs cycle. Alternative, it diffuses into the aqueous humour, from through which it removed from the eye. This further explains why the aqueous humour leaving the eye often has a much larger amount of lactate than newly formed aqueous humour. The aerobic utilization of glucose (which includes glycolysis and Krebs cycle) is more efficient than anaerobic glycolysis, because for every mole of glucose, 38 moles of ATPs is generated, whereas anaerobic glycolysis generates only 2 ATPs. In the lens, however, ATP production via Krebs cycle is mostly limited to lens epithelium and perhaps some of the newly formed fibre cells at the lens equator [22]. Hexose monophosphate shunt generates low amount of ATP in lens. It is an important source for the production of reduced form of NADP (NADPH), required by other metabolic pathways such as glutathione reductase and sorbitol pathways [21]. About 14% of lens glucose is metabolized by the hexose monophosphate shunt, in rabbits. Glucose-6-phosphate, which is the starting(initial) substrate in the hexose monophosphate pathway is used to generate pentoses (used in the synthesis of nucleic acids), and NADPH(an important cofactor in numerous biochemical reactions) [22]. A portion of the pentoses generated are recycled to re-enter the glycolytic sequence; while carbon dioxide(CO_2) produced by the pathway, diffuses into the aqueous humour [22]. Sorbitol pathway accounts for about 5% of glucose metabolism by the lens. When sorbitol builds up within lens cells, it creates a hyperosmotic gradient that leads to an infusion of fluid and lens swelling, resulting to loss of lens transparency [60].

Cataract

Cataract is an opacification of the natural crystalline lens of the eye, leading to deterioration in lens transparency [17, 8]. It is also defined as the clouding of the ocular lens which leads to decrease in vision. Decrease in vision occurs as a result of the opacification, which causes visible light to scatter as it passes through the lens of the eye [8]. Although its mechanism of formation is unclear, it has been suggested to occur as a result of protein aggregation and cross linking, loss of redox cycle, imbalance in electrolytes, and loss of ATP content [61]. Cataract progression can be graded as mild, moderate, or severe. It may be early or advanced. It can also be graded as mature, immature and hyper-matured.

Prevalence of Cataract

Globally, visually impaired is estimated at 285 million; of these, 39 million are blind and 37 million have cataract [7]. In sub-Saharan Africa, more than 50% of their population have cataract [1]. The population of people aged over 60 years is projected to increase from the current estimate of 400 million to about 800 million in the year 2020 due to the exponential increase in the world's population and life expectancy [1]. This will result to high number of people having cataract-related visual impairment that will need cataract surgical services. In Nigeria, prevalence of blindness is estimated as 0.78% overall, and 43.0% among those aged 50 years or older, have cataract [6, 1].

Classification of cataract

Childhood Cataract

Childhood cataracts are cataract that occurs at birth or in childhood, due often, to abnormal lens development during pregnancy. They are the commonest cause of blindness, and accounts for about 10-30% of all childhood blindness. Childhood cataract is called, congenital cataracts, when it is present at birth or juvenile when it appears shortly thereafter and is usually related to a specific cause [62].

Congenital and Juvenile Cataracts

Congenital or infantile cataracts usually manifests in the first year of life, while juvenile cataracts occur in the first decade [62]. They both range from mild and benign, to advanced and sight-threatening. They are among the main reasons for blindness in children. Approximately 33% of these cataracts are inherited (inborn). Lens opacity present at childbirth shows pathological changes during embryonic development of the crystalline lens [17]. Congenital cataract may be isolated, or can be associated with other developmental disorders. Attempts have been made by researchers to map out the genes responsible for this eye disease [63]. These have led to the identification of genetic mutations that cause autosomal dominant congenital cataract, and identification of fifteen genes that are involved in cataract formation. The following is a morphologic classification of congenital cataracts.

Total (or Mature or Complete)

These cataracts are fully opaque or blurred at birth. Most of them are associated with systemic abnormalities or disorders.Examples are galactosemia, Lowe's syndrome and rubella. They are inherited as autosomal dominant or autosomal recessive [64].

Partial (Incomplete)

A. Polar cataracts: These cataracts involve the lens capsule in the anterior or posterior pole of the lens (or both, in which case they are referred to as bipolar). Anterior polar cataracts are located in the front part of the eyes lens, while posterior polar cataracts appear at the back part of the eyes lens. The familial type is bilateral and inherited as an autosomal-dominant trait [64].

B. Zonular cataracts: In this type of cataract, only a region or zone of the lens is clouded [64]. They may be stationary, or in some cases advance. The following are their various subtypes:

1. **Lamellar**: These are the commonest types of congenital cataracts, and are characterised by being bilateral and symmetric, with varying density of opacification [64]. They may be inherited as an autosomal-dominant trait,

but in some cases may be due to the transient intrauterine toxic material, affecting only the layer of cells developing at the time of foetal exposure [64].

2. **Stellate**: (or Sutural) cataracts, affect the sutural regions of the foetal nucleus, at which the ends of the lenticular fibre cells converge [65]. Their shapes depend on the stage of development at which they were formed[64]. Anterior sutural cataracts are Y-shaped while posterior sutural cataracts are shaped like an inverted Y [65].
3. **Nuclear**: These appear at the central part of the lens, and are usually bilateral and involve the embryonal or foetal nucleus [64]. They may be inherited as an autosomal-dominant, autosomal-recessive or X-linked trait.
4. **Coronary**: These cataracts are bilateral demonstrating club-shaped and focal dots opacities, distributed radially in the periphery of the cortex near the lens equator. They do not impair vision, because they are located on the periphery of the cortex [64]. They are dominantly inherited and have been described in cases of Down's syndrome and myotonic dystrophy.
5. **Cerulean***:* Cerulean (or "blue dot") cataracts, are composed of small bluish dot-like opacities in the lens cortex and nucleus [65]. They are usually found in both eyes of infants, are non- progressive, and do not cause any reduction of vision, and may be present together with other congenital cataracts [64].

C. Capsular*:* Capsular (or membranous) cataracts can occur from resorption of lens proteins after capsular rupture, from either an intact or a traumatized lens [65]. They result in the fusion of the anterior and posterior lens capsules, producing a dense white membrane [64].

Age Related Cataract/Senile Cataract

The normal lens mass increases as the lens continue to grow. As new lens cells are formed, the older ones are pushed towards the centre of the lens, losing their nuclei and organelles in the process. All the metabolic activities including the breakdown and synthesis of protein reduce in the older lens cells. The colour of the lens changes to yellow. The lens which focuses light onto the retina hardens, with a resultant decline in its ability to modify its shape in response to contractions by cillary muscles.

This causes presbyopia [14], due to lens exposure to cumulative effects of radiation, oxidation and post-translational modification. The oxidation of lens proteins, together with other ageing-induced gradual, molecular changes almost certainly reduces vision. However, in many cases, the aging process appears to be accelerated or metabolism is affected in a way that there is a significant decrease in transparency, resulting in visual impairment. It is at this point that the age related cataract exists.

Age related cataract, the commonest type of visual-impairment, is characterized by gradual or progressive thickening of the lens of the eyes [66]. Globally, it is the leading cause of blindness, and hence remains a general health problem [17]. In Nigeria, most cataracts are age related, affecting more than half of all Nigerians older than 50 years. It has been estimated that by delaying the onset of cataract by just ten years, would reduce the need for cataract surgery by nearly 50%. Such a delay would improve the quality of life for a great part of the world's diabetic and older population, and gradually remove the economic burden due to cataract related disability and surgery. There are no FDA approved drug treatment options for cataract. Factors such as age, gender, diet, smoking or chronic exposure to wood smoke, trace metal, hypertension, diabetes, family history, poor infantile development, exposure to UV light, steroid and alcohol intakes are involved in age related cataract [61]. Age is the most important risk factor for age related(senile)cataract due to the accumulation of oxidative damage over many years [67, 68, 61]. With the low oxygen tension in the lens, the physiological source of the ROS(reactive oxygen species) is not clear.

High levels of reduced glutathione protect lenticular proteins from oxidation; while ageing induced significant decreases in reduced glutathione in the lens nucleus are reported to contribute to cataract progression and development [67, 8]. The damaged caused by oxidative stress was demonstrated using sodium selenite, in suckling pup lens since the same biochemical changes that occur in human senile cataract occur in sodium selenite cataract [17, 8].

Another evidence of oxidative damage in cataract is the high level of lipid peroxidation. Lipid peroxidation increases significantly in age related cataract as it was demonstrated with selenite-induced cataract and the OXYS rat. Some of the changes that occur in senile(age related) cataract could be as a result of the obstruction of the movement of small molecules between the central lens nucleus and the metabolically more active lens epithelium [67]. In the case of lenticular crystallins, these changes include proteolysis, deamidation, racemization, phosphorylation, non-enzymatic glycosylation, and carbamylation, accumulation of fluorescent chromophores and phase separation [63, 19, 8]. In contrast some of the alterations observed in lens crystallin do not appear to cause opacity of the lens and may even help to protect lens crystallins from modifications that may be harmful [65]. Many age related cataract takes years to develop to the point where vision is seriously impaired while some occur, sequel to the normal aging process.

Molecular Changes that Result In the Formation of Age-Related Cataract

Cataract is a multifactorial disease with many mechanisms contributing to the progressive loss of lens transparency. Its formation is the result of imbalance in electrolyte transport, loss of reduced glutathione redox system, abnormality in membrane permeability, protein aggregation and loss of ATP content. During aging crystallins may undergo changes such as deamination, oxidation and cross linking, truncation, glycation, phosporylation, and carbamylation, and many of these are enhanced in the presence of osmotic, oxidative, or other stresses [63, 8].

As individual ages, the damaged β- and γ-crystallins slowly accumulates, thereby losing the ability to participate in normal intermolecular interactions, and even to remain in solution [65]. The resultant denaturing and precipitation, causes them to be bound by the chaperone-like α-crystallins, forming soluble complexes and reducing light scattering, without renaturing them and releasing them into the cytoplasm, as do true chaperones [65]. Over time, these complexes increase in size as additional damaged proteins are bound, until they begin to approach sizes large enough to scatter light [65]. As the available α-crystallin is overwhelmed by increasing amounts of modified βγ-crystallin, the complexes precipitate within the lens cells to form the insoluble protein fraction, whose concentration characteristically increases in cataractous lenses and with age.

Mendelian cataract models support both denaturation, as is seen in the association of some severe crystalline mutations with cataracts, and simple insolubility with maintained protein folds as is seen in other cataracts. Various mouse models of cataracts due to mutations in lens crystallin, have shown that the presence of large amounts of unstable or precipitated crystallins, or other lens proteins, damages the lens cell, and contributes eventually to cataracts, directly through the scattering of light by protein aggregates and/or indirectly through disruption of cellular metabolism and architecture. Similarly, mutations that disrupt lens cells' intracellular homeostasis can damage their constituents over time, thereby predisposing to age-related cataract [63].

Types of Age-Related Cataract

Age-related lens opacities originate in 1 of 3 regions of the lens: the nucleus, cortex or the posterior pole, just beneath the posterior capsule, consequent upon which they termed nuclear, cortical or posterior sub-capsular cataracts (PSCs), respectively, which are the 3 main types of age-related cataract [36]. The following are the various types of age-related cataract.

1. Nuclear cataract

Nuclear cataract also known as nuclear sclerotic is a type of age related cataract, due to the hardening and yellowing or clouding of the central portion of the lens, or opacity in the central fibre cells, resulting from the aggregation and insolubilization of lens proteins and their increased association with membranes [36]. It is one of the most common types of cataract in tropical areas, accounting for approximately 60% of age related cataracts [36].

With increasing age, many types of modifications such as protein truncation, oxidation, denaturation, cross-linking, amino acid racemization, glycation and deamidation, occur in the abundant crystallin proteins of the lens nucleus [36]. As these proteins accumulate post modifications, they form protein aggregates that scatter light. They also changes colour with age; in some nuclear cataracts, the colour can become dark brown or even black and this may lead to even difficulties in distinguishing colours. This is termed brunescent nuclear cataract. Biochemical changes that occur in nuclear cataract are, increase in concentration of protein, significant increase in potassium concentration, and decrease in hydration [19]. These changes can influence the true nucleus, and with time, spread to affect the deep cortex to produce a 'nuclear' cataract that surpasses the confines of the true nucleus. Such large nuclear cataracts may create surgical difficulties during extra-capsular extraction [19]. Nuclear cataract is usually associated with myopia (near-sightedness).

2. Cortical Cataract

Cortical cataract is one of the commonest types of senile (age-related) cataract. It refers to white opacities, or cloudy areas that occur in mature (anucleate) fibre cells in the outer half or cortex of the lens cells that were formed post-natally [36]. Morphological studies found evidence of physical damage early in cortical cataract formation, involving the scission and fragmentation of the cortical fibre cells [19]. As it develops in the lens cortex, it moves gradually to the centre in a manner that resembles spokes. It is believe that most cortical cataracts are osmotic in nature due to accumulation of water in or between the lenticular fibre cells, resulting from imbalance in cation levels responsible for maintaining the metabolic and ionic homeostasis of the whole lens. Such damages could disturb the normal membrane permeability characteristics, or damage or denature proteins involved in ion transport, forming opacity, and the lens having a pearly white appearance [69]. For example, in cortical cataracts, there is a decrease in potassium levels with an increase in sodium, chloride, and calcium, resulting in an imbalance that leads to water influx. The vacuoles or "lakes" that contains this water have a low refractive index relative to the protein-rich cytoplasm in the fibres, and the discontinuities create light scatter and cataract [69].

3. Posterior Sub-Capsular Cataracts (PSCs)

Posterior sub-capsular cataract is a type of cataract found at the backside of the lens immediately beneath the lens capsule. Because of its location, it has an effect on vision that is disproportionate to its density. It occurs in combination with nuclear or cortical cataract in the late stage. Posterior sub-capsular cataract occurs due to abnormal differentiation of lens fibres by the lens epithelium and is associated with failure in the growth of the crystalline lens [19]. Sub-capsular cataract can reach advanced stage within a matter of months. Examination of post-mortem lenses identified streams of swollen cells that appeared to be migrating from the equator to the posterior(back) pole. During the progression of PSCs, more of these swollen cells gather along the suture planes at the posterior of the lens, forming disordered clusters of cells which degrade visual acuity, by virtue of their location in the optic axis.

It is usually seen in individuals, who take corticosteroid medication/therapy, and those who have diabetes, extreme near-sightedness or retinitis pigmentosa, are exposed to radiation with x-rays on a long-term, and trauma. Early stage of this type of cataract comes with glare,disability and difficulty concentrating on objects, particularly close objects. This is due to the fact that when the pupil constricts during accommodation, light entering the eye becomes focused to the location of the posterior capsular cataract, leading to the scattering of the light, and inability of the eye to focus the image on the retina. This opacity lying near or at the nodal point of the eye interferes with focusing the image on the retina.

4. Cataract Associated with Systemic Diseases, or Pre-Senile Cataract

Cataracts are found in association with other ocular pathology such as microphthalmia, uveitis, glaucoma, tumours, and pigmententary degenerations of the retina. The lens relies on the health of the eye for its metabolism and so is affected when the eye is unable to supply nutrients and oxygen, or when lethal substances are produced. Diseases associated with cataract can be grouped under several heading such as metabolic disorder, blood disorder, disorder due to exogenous substances, systematic infections, diseases having primarily dermatologic manifestation, chromosomal disorders, syndromes including pigmentary degeneration of the retina, skeletal disorder, miscellaneous syndrome and ectopia lentis.

A. Metabolic Disorder

The underlying biochemical abnormality in errors of metabolism (whether inborn or acquired) is likely to be an enzyme or endocrine defect. They can either be the cause of, or are associated with cataract. They include diabetes, hypocalcaemia, hypothyroidism, hypoxia, hypoglycaemia of childhood, nutritional deficiency, dehydrational crises, aminoaciduria, hypercholesterolemic xanthomatosis, myotonic dystrophy, Fabry's disease. Others include Refsums syndrome, galatosaemia, Lowe's syndrome, Wilson disease, sialidosis type 1, mannosidosis and Hurler's disease.

B. Disorders due to Exogenous Substances

Drugs and other toxic substances may cause cataracts, regardless of how they are administered. They include mercury, allopurinol, chloroquine, isotretinoin, miotics of the anticholinesterase group, antimitotic agents, chloropromazine, sodium selenite [61], corticosteroids and phenothiazine derivatives. Sinha *et al*. reported an association between inhaled and oral corticosteroid use and 10-year incidence of cataract [70]. Current users had a greater risk of developing nuclear cataract and posterior sub-capsular (PSC) cataract but not cortical cataract. In subgroup analyses, only those who used both oral and inhaled steroids had a higher risk of PSC cataract. Various poisons that have produced cataracts when administered systemically in humans include naphthalene, dinitrophenol, paradichlorobenzene, and ergot. Incident cataract after a 5-year interval with respect to various medication use, have also been reported [70]. A lower incident of nuclear cataracts was observed among those who took thiazide diuretics and aspirin at the baseline examination. There were significantly increase of cortical cataracts observed among those who took oral steroids, amitriptyline, oral hypoglycaemic agents, and insulin and higher incidence of posterior sub-capsular cataracts were also observed among those taking potassium-sparing diuretics and oral hypoglycaemic agents.

Diseases having Primarily Dermatologic Manifestation (Dermatogenic or Syndromatic Cataracts)

The relationship between skin disorder and cataract is understandable because both the skin and the lens are derived from the surface epithelium of the embryo. Dermatogenic or syndromatic cataracts occur at young age, and are bilateral. The mechanism of this cataract is not clear, although, habitual tapping and rubbing of the face may play a part.There are several conditions in which the association is well established. They include Rothmund-Thomson syndrome, anhidrotic ectodermal dysplasia, Werner syndrome, Marshall's syndrome, atopic dermatitis (eczema, neurodermatitis). Cataract has also been reported in association with congenital ichthyosis, Siemen's syndrome (congenital atrophy of the skin), and incontinentia pigmenti. Sinha *et al.* reported on ocular complications in individuals treated for serious atopic dermatitis. According to them, cataract was seen in 20 cases (25.3%), and retinal detachment in 9 (11.4%) cases [70]. The cataract development or retinal detachment had no relationship with individual history of respiratory atopy, serum IgE levels, treatment with systemic corticosteroid or the length of time of topical corticosteroid use on the face.

C. Blood Diseases

Examples of such diseases include: thalassemia, congenital haemolytic jaundice, childhood leukaemia, hyperferritinemia-cataract syndrome [3]. A study of the incidence and severity of cataracts in 37 children with acute lymphoblastic leukaemia revealed that 32% of them had mild posterior sub-capsular opacities. All of the children received both corticosteroids and cranial irradiation, both of which are known to be cataractogenic. The irradiation perhaps caused an inhibition of mitosis in the equatorial germinative lens fibres [70].

D. Pigmentary Degeneration of the Retina

This involves a progressive destruction of the visual cells leading to blindness. It is associated with other illnesses, constituting a syndrome such as Bardet-Biedl syndrome, Hallgren`s syndrome, Usher`s syndrome, Cockayne's syndrome.

5. Other Conditions

It is also associated with reduction in female hormones (oestrogen). A study suggested the protective effects of oestrogen or estradiol treatment against cataractous eyes up to 25%, in ovariectomized rat. Women have a higher incidence of cataracts than men, and the increased risk may be because of absence of oestrogen in post-menopausal years, and gastro-intestinal (diarrhoea). In renal dysfunction, there is a 12-fold relative risk for cataract, probably due to the accumulation of urea resulting in carbamylation of lens proteins. Minassian *et al* reported that one scene of dehyrational crises from extreme cholera-like diarrhoeal disease is 4.1 times more likely to cause cataract. According to them, the risk rose to 21% with two or more scenes of cholera-like diarrhoeal disease, and was still higher in those with history of both heatstroke and severe diarrhoea. Harding stated that dehydration, diarrhoea, high level of urea in the body, acidosis, and associated osmotic imbalances, lead to accumulation of cyanate, thereby adversely affecting the glutathione level, leading to cataract.

Risk Factors for Cataractogenesis

Age is the major cause of age-related(senile) cataract. Several other factors have been identified to increase cataract risk, in addition to the pathological roles of oxidative stress in the formation of cataract.

1.) Age

There is a strong association of cataract development with age and oxidative damage. Since there is little or no turnover of lens epithelial cells, the accumulation of oxidative damage over a long time is an important component of cataract development [67, 68].

2.) Medication

An increased risk of cortical cataract prevalence was associated with the use of amiodarone, oral beta-blockers, and thyroid hormones (Age-Related Eye Disease Study Research Group. Also, an increase of risk for nuclear cataract was associated with the use of phenothiazines and a decreased risk (protective effect) with the use of nonsteroidal anti-inflammatory drugs (Age-Related Eye Disease Study Research Group. The risk factors for posterior sub capsular cataract were the use of thiazide diuretics, mepacrine, and long-term aspirin intake.

3.) Smoking and Alcohol Consumption

Studies have reported a 2-3 fold increased risk of cataract in smokers. People who smoke have a high risk of developing cataract, especially nuclear cataract. Aromatic compounds present in the inhaled smoke are believed to oxidatively modify lenticular components. A number of studies have shown that high alcohol intake is a risk factor for different types of cataract, especially posterior sub-capsular opacities.

4.) Gender

Studies have shown that there is a higher incidence of cataracts in women than men. This may be because women live longer than men and thus are more likely to have increased age-adjusted risk of cataract. In Africa, this may be due to low accessibility to and use of services, since women are less likely to express a need for sight due to fear of being seen as a burden, and the fact that some household heads usually support surgery for elderly men more than women.

5.) Diabetes

Clinical studies have confirmed the higher prevalence and early onset of cortical cataract and posterior sub-capsular opacities in diabetic patien. It has been suggested that about 4% of all cataract is attributed to diabetes. Since diabetes is characterized by elevation of blood sugar, glycation reactions occur more rapidly and frequently, which explains a great deal of the association between diabetes and opacity. Therefore, careful monitoring of blood sugar level helps to reduce the risk of developing cataract.

6.) Exposure to Radiation

Exposure to even low UV radiation(sunlight) increases the risk for nuclear cataract. This risk factor is usually found more, among people who are exposed to ionizing radiation, such as X-rays or ultraviolet (UV) for a long period. WHO estimates that 20% of world blindness from cataract may be due to UV radiation exposure. The use of brimmed hat and UV-B protecting sunglasses and also avoiding direct sunlight at the peak hours of UV-radiation have been suggested as powerful ways of preventing cortical cataract [70].

7.) Poor Nutrition

A lot of studies have shown possible association between cataract and diet. These studies suggested that eating food rich in a variety of minerals and vitamins, especially antioxidants vitamin E and C and zeaxanthin and lutein, may protect the crystalline lens from cataract development.

8.) Ethnicity and Race

Caucasians have a lower risk of developing cataract than African- and Hispanic-Americans. Among Hispanics, cataract is the major cause of visual impairment. This may be due to other medical illness (especially diabetes), and lack of medical care.

9.) Heavy Metal Toxicity

Exposures to heavy metals(e.g. lead, gold and copper) and their compounds (e.g., sodium selenite), have been hypothesized to increase the risk of cataract development. Metals tend to deposit as granules in the capsule and anterior cortex of the pupillary area of the lens.

Prevention/Treatment of Cataract

The occurrence of cataracts can be delayed, even though they are not completely preventable. Avoiding overexposure to sunlight and excess alcohol, quitting smoking and eating plenty of fresh fruits and vegetables are important protective measures, which may delay the formation of cataracts.

Treatment of Cataract with Surgery

Cataract surgery has always been the only cure recommended for treatment of cataract. It involves the removal of the cataract, and replacement of the abnormal lens with a permanent implant called intraocular lens (IOL). In some cases, however, a cataract may be removed without implanting an artificial lens. Some cataracts do not need surgery. Cataract surgery is usually done once cataract starts to interfere with the daily activity of individuals. Two methods are mostly used in cataract surgery. They are phacoemulsification and extra-capsular extraction.

Prevention using Phytochemical Compounds

Similarly as with most diseases, prevention or treatment of cataract at an early stage is more viable than attempting to reverse the disease process [7]. Studies have demonstrated that consumption of botanical compounds rich in antioxidants may prevent the breakdown of crystallins(proteins) in the eye, and help to reduce cataract development. For a long time curcumin, a phenolic compound, found in turmeric, has been reported to be important for eyesight because of its antioxidant property. The protective role of its oral administration in Wistar rats with streptozotocin-induced diabetic retinopathy have been reported [7]. Other studies recommend that curcumin was viable against the development of diabetic, naphthalene-induced, galactose-induced, and selenite-induced cataracts. Likewise dietary supplementation of curcumin prevented the loss of chaperone-like activity of eye lens α-crystallin in diabetes-induced cataractogenesis, thereby preventing the development of cataract in the rat lens. Gingseng has been seen as a promising plant for individuals with cataract because of its properties(anti-apoptotic and anti-oxidative properties). Gingseng showed a beneficial effect in diabetes: including blood glucose reduction, increased insulin production and weight gain control. Quercetin is one of the flavonoids found in very high amounts in the human diet. Quercetin is known to exhibit strong anti-cataract properties because it has the ability of neutralizing reactive oxygen species (ROS). During an *in vitro* study on antioxidant property of quercetin, it inhibited cataract caused by oxidative stress in rat eye lens cultured in a H_2O_2 environment. At a dose of 25-50mg/kg, it was found to show antioxidant behaviour against the oxidative stress caused by streptozotocin-induced diabetes mellitus in rats. Other botanical compounds that can be used in the treatment of cataract include resveratrol, rutin and melatoin.

Prevention of Cataract by Living a Good Lifestyle

Since free radical damage appears to be the primary factor in age related cataract, individuals ought to maintain a strategic distance from direct daylight, bright light, and wear protective eyewears (sunglasses) when outdoors [70]. Weight gain, alcohol and cigarette smoking should also be avoided.

Prevention of Cataract with Diet

Healthy intake of natural antioxidant foods/vitamins is the key to preventing cataract development. Natural antioxidants prevent generation of reactive oxygen species, lipid peroxidation, and oxidation of proteins, thus acting as upstream barrier to oxygen species. Intake of vitamin C through diet (fruits and vegetables), prevent cataract. But, supplements could provide additional benefits. Supplementing food with additional antioxidant nutrients like vitamins A, C and E, selenium, zinc, glutathione and N-acetyl-cysteine (NAC, a precursor to glutathione) could help to prevent cataract. Use of Vitamin C, greater than 1,000 mg in a day for a long time could increase the risk of developing cataract. Hence, it is best to reduce daily Vitamin C dosage to 500 mg or less. Lifetime use of antioxidant supplement might protect the lens and prevents surgery.

Conclusion

Disruptions in glucose metabolism, oxidative stress, and protein aggregation significantly contribute to cataract formation. Understanding these biochemical pathways provides valuable insights into cataractogenesis and potential therapeutic targets. Continued research is essential to develop effective preventive and treatment strategies, ultimately aiming to reduce the global burden of cataract-related visual impairment and improve ocular health outcomes.

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