A review: Cataract, a common ocular complication in Diabetes

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Abstract

With increasing prevalence of diabetes and its associated complications is a priority of health service globally. Diabetic ocular complications are most common in both type-1 and type-2 diabetes, considering the fifth most common cause of legal blindness. According to WHO, cataract is 33% of all type of visual impairment. Simply diabetic cataracts are characterized by cortical or posterior subcapsular opacities. Aldose reductase and polyol are responsible for diabetes ocular complications. Intracellular accumulation of sorbitol leads to osmotic stress resulting in the formation of lens opacities. Several clinical studies investigated the role of phacoemulsification surgery and its post surgery complications. Researchers are trying to develop aldose reductase inhibitors and antioxidants, may be effective treatment to prevent or cure diabetes cataract.

Keywords: Diabetes mellitus, Cataract, Aldose Reductase, Polyol Pathway, Sorbitol.

1. Introduction

Addressing the increasing prevalence, and associated disease burden, of diabetes is a priority of health services internationally. The global diabetes epidemic is a major public health challenge worldwide, and one of the greatest contributors to the global burden of disease, with an estimated 65% increase in diabetics by 2025, to 380 millions [1, 2].

Diabetes is a well-recognized cause of premature death and disability, increasing the risk of cardiovascular disease, kidney failure, blindness and lower-limb amputation [3]. Hyperglycemia, blood lipids and blood pressure has been three major factors to be considered for diabetes complication and disease progression [4, 5]. A frequent complication of both type 1 and type 2 diabetics is diabetic ocular complications, which is considered the fifth most common cause of legal blindness. In 95% of type 1 diabetic and 60% of type 2 diabetics with disease duration longer than 20 years, signs of diabetic retinopathy occur [6-8].

Cataract is considered a major cause of visual impairment in diabetic patients as the incidence and progression of cataract is elevated in patients with diabetes mellitus [4, 5]. The association between diabetes and cataract formation has been shown in clinical epidemiological and basic research studies. Globally, Cataracts occur remain the leading cause of blindness, affecting approximately 18 million people. Cataracts occur at an earlier age and 2-5 times more frequently in patients with diabetes, thus the visual loss has a significant impact on the working population [9-11].

According to World Health Organization, cataract is 33% of all type of visual impairment. Overall, up to 20% of all cataract procedures are estimated to be performed for diabetic patients [12]. Rate of cataract and cataract surgery is high as cataract is most common cause of visual impairment.

Cataract surgery most common ophthalmic procedure worldwide, but main aim to delay or prevent the development of cataract in diabetes patients remains a challenge. Particularly in developing countries, both diabetes and cataract become health and economic burden, where diabetes treatment is insufficient and cataract surgery often inaccessible [13].

In this review, understanding of the pathophysiological significance of aldose reductase are presented that would be relevant to diabetic cataract. An extensive review on the pathogenesis of diabetes complications is outside the scope of this review.

2. Ocular complication in Diabetes

Diabetes is metabolic disorder affecting many organs including eye. Diabetes cataracts are characterized by cortical or posterior subcapsular opacities, and in adults the opacities are known to be an acceleration of age related cataracts [14]. Intensive control of blood glucose and systemic hypertension reduces the risk of new onset diabetic retinopathy and slow the progression of existing diabetic retinopathy. Studies related to cataract formation in diabetic
patients have shown that hyperglycemia is associated with loss of lens transparency in a cumulative manner. Hyperglycemia may induce temporary lens opacification and swelling as well as transient hyperopia. It has been suggested that rapid glycemic control can irreversibly increase lens opacities [15, 16].

3. Risk factors for cataract in diabetes

Cataract can be considered as an earliest complication of diabetes mellitus. Diabetic patients are 2-5 times more prone to develop cataract than non diabetics and risk may reach 15-25 times in diabetics less than 40 years of age [10, 16].

4. Pathogenesis of diabetic cataract

If large amounts of glucose are present in blood (as in diabetes mellitus), hexokinase becomes saturated and the excess glucose enters the polyol pathway when aldose reductase (AR) reduces it to sorbitol illustrated in Fig. 1.

![Fig: 1 Polyol Pathway](image)

Aldose reductase is a cytosolic enzyme present in most of the mammalian cells, although the distribution of the enzyme is not uniform among tissues. Around 60 years ago the polyol pathway was first identified in the seminal vesicle by Hers [17], who demonstrated the conversion of blood glucose in to fructose, an energy source of sperm cells. The presence of diabetic rat lens demonstrated by Van Heyningen [18]. Later researcher has opening a new way concerning the pathological role of aldose reductase and the polyol pathway in the development of diabetes complications on eye, kidney and nerve. Since those days, inhibition of aldose reductase has been expected to become a potential therapy for diabetes and its complications. However, it is necessary to understand the pathological and physiological role of the polyol pathway in contrast of possible side effect of long term inhibition of aldose reductase in diabetic patients.

Intracellular accumulation of sorbitol leads to osmotic changes resulting in hydropic lens fibers that degenerate, ultimately results in the formation of lens opacities (form sugar cataracts). The speed of conversion sorbitol is faster than it is converting to fructose by the enzyme sorbitol dehydrogenase. These findings have led to the “Osmotic Hypothesis” of sugar cataract formation, emphasizing that the intracellular increase of fluid in response to AR-mediated accumulation of polyols results in lens swelling associated with complex biochemical changes ultimately leading to cataract formation [19-21].

According to the “osmotic stress” hypothesis, diabetic cataracts are the consequence of swelling of lens epithelial cells caused by accumulation of osmotically significant amounts of polyol. Swelling of epithelial cells then initiates a cascade of metabolic imbalances culminating in rupture of epithelial cells and formation of cataracts. The osmotic hypothesis is based primarily on two lines of evidence:

1. The accumulation of millimolar concentrations of sorbitol in the lens of diabetic
2. Elevation of the osmolarity of incubation media prevents a variety of metabolic abnormalities in lenses incubated at elevated glucose levels in vitro.

While the osmotic hypothesis is consistent with a considerable body of experimental data on the lens, its role in the pathogenesis of diabetic cataracts is questioned, and it is generally considered to be untenable as an explanation for the pathogenesis of diabetic complications in most other tissues in which sorbitol concentrations never exceed the micromolar range and in which no evidence of cellular swelling is evident by electron microscopy [22].

Studies showed that transgenic hyperglycemic mice over expressing AR and phospholipase D (PLD) genes
became susceptible to develop diabetic cataract in contrast to diabetic mice over expressing PLD alone, an enzyme with key functions in the osmotic regulation of the lens [23].

These findings show that impairments in the osmotic regulation may render the lens susceptible to even small increases of AR mediated osmotic stress, potentially leading to progressive cataract formation.

Type 1 diabetic patient more susceptible to rapid cataract formation due to the extensive swelling of cortical lens fibers [24]. Person under 60 years of age having short duration of diabetes were positively correlated with the prevalence of posterior subcapsular cataracts [25].

It has been proven that the polyl pathway is the primary mediator of diabetes induced oxidative stress in the lens. Researcher has focus on first step of polyl pathway as initiating factor in diabetic cataract formation.

The fact behind this, accumulation of sorbitol induced stress as osmotic stress in the endoplasmic reticulum (ER), main site of protein synthesis, leads to generation of free radicals. ER stress may be due to glucose level disturbance initiating an unfolded protein response that generates reactive oxygen species that cause oxidative stress damage to lens fibers [26, 27].

There are number of publications are describing oxidative stress damage to the lens fibers, but not any particular evidence that these free radicals initiating or increasing lens opacity. Studies showed that increase level of free radical like hydroxyl (OH-) or nitric oxide (NO-) free radical, may lead to an increased peroxynitrite formation, which leads to cell damage due to its oxidizing properties [28, 29]. Moreover, increase level of glucose in the aqueous humor may leads to glycation of lens protein, resulting generation of superoxide radicals (O2-) [30].

One side increase level of free radicals and another side loss of antioxidants by glycation and inactivation of antioxidants enzymes like superoxide dismutase, which is important for degradation of free radicals (O2-) into hydrogen peroxide (H2O2) and oxygen, finally minimize the protective effect of superoxide dismutase in the presence of diabetes mellitus has been shown in various in vitro and in vivo animal studies [31-33].

In conclusion, initiating mechanism in diabetic cataract formation is the polyl pathway and increased osmotic stress in the lens fibers resulting its swelling and rupture.

5. Surgery as Solutions for cataract

While there is no way to prevent cataracts, there are only things to slow their formation. Modifiable factors that increase the risk of cataract include smoking, high blood pressure, obesity, excessive alcohol intake, and last but not least blood glucose level.

In the beginning stages of cataracts, vision may be slightly improved using forms of visual correction. However, in the later stages, surgery is required. Fortunately, surgery has proven to be extremely successful in the removal of cataracts.

There are two main type of surgical procedure using throughout the world. One is phacoemulsification (Phaco) and second involves two different types of extracapsular cataract extraction (ECCE). In most surgery intraocular lens is incerted. ECCE utilises a larger incision (10-13mm) and therefore usually requires stitching, and this in part led to the modification of ECCE known as manual small incision cataract surgery (MSICS). Cataract extraction using intracapsular cataract extraction (ICCE) has been superseded by phaco & ECCE, and is rarely performed [34, 35].

Phacoemulsification is the most commonly performed cataract procedure in the developed world. However, the high cost of a phacoemulsification machine and of the associated disposable equipment means that ECCE and MSICS remain the most commonly performed procedure in developing countries.

5.1 Phacoemulsification

Phacoemulsification is most popular and preferred technique in most types of cataract, developed by kelman in1967 and was not widely accepted until 1996 [36]. Later it can be taught safely and effectively to residents with no cataract surgery experience as a primary surgeon [35].

Patients with diabetes may have poorer vision outcomes than those without diabetes. Surgery may cause rapid acceleration of retinopathy, induce rubiosis or lead to macular changes [37, 38]. Even uncomplicated cataract surgery may induce postsurgical inflammation and vitreous instability that may subsequently cause postoperative macular edema in normal individuals.

Several clinical studies investigated the role of phacoemulsification cataract surgery on the progression of macular edema and diabetic retinopathy. Macular edema is a well-known complication after cataract surgery. When the post cataract macular edema is associated with a decrease in visual acuity, it can be categorized as clinical pseudophakic cystoid macular edema.

Diabetic retinopathy has long been implicated as a risk factor for more prominent postoperative macular edema and poorer visual outcomes. In eyes with diabetic retinopathy, the blood-retina barrier is often impaired to a variable degree, which may cause the eyes to be more prone to develop postoperative macular edema. The incidence of post...
phacoemulsification macular edema in diabetic retinopathy has been reported to range from 31% to 81%, which is much higher than the incidence of post phacoemulsification in non-diabetic patients [39].

Studies showed that phacoemulsification surgery severely affects the blood aqueous barrier in diabetic patients with proliferative diabetic retinopathy than non diabetic patients [40].

A study on diabetic beneficiaries (n=139759) from 1997 to 2001 showed that the rate of cystoid macular edema formation after cataract surgery in diabetic patients is significantly higher than non diabetic patients [41].

Diabetic eyes have a high incidence 22% of increased center point thickness on optical coherence tomography as macular edema after cataract surgery. Treatment to prevent this might improve outcomes in similar individuals after surgery [42].

Wielders et al to evaluate the optimum medical strategy to prevent cystoid macular edema (CME) after cataract surgery showed topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids, in non-diabetic and mixed populations. A combination of topical NSAIDs and corticosteroids reduced the odds of developing CME in non-diabetic and diabetic patients, as compared to topical corticosteroids [43].

6. Cataract treatment

Cataract is a visual impairment caused due to opacification or optical dysfunction of crystallin lens affecting more than 17 million people around the world. Even though the incidences of cataract are increasing day by day among the elderly persons but, still except surgery no other ways of treatment have been successfully developed so far [44].

6.1 Aldose reductase inhibitors.

Researcher has continuing to try from natural and synthetic way to prevent or cure diabetic cataract. Studies on natural products with known aldose reductase activity e.g. Flavanoid extract of Vernonia Cinerea [45], Caesalpinia pulcherrima [46], Nobiletin, one of the most abundant polymethoxyflavones in citrus peel [47], glycoside and lignin extract of Cornus Officinalis [48], ethanolic extract of Chromolaena Odorata [49], Foeniculum vulgare Mill [50], Pterocarpus marsupium bark [51], Ocimum sanctum, Withania somnifera, Curcuma longa, and Azadirachta indica [52, 53].

Nonsteroidal anti inflammatory drugs, such as sulindac, aspirin or narproxin have been reported to delay cataract in diabetic rats through a aldose reductase activity [43, 54-58].

Several experimental studies has been reported the role of aldose reductase inhibitor in prevent or delaying diabetic cataract formation in animal models. Renirestat, Fidararestat, Kenostat, Alrestatin, Imrestat, Ponalrestat, Epalrestat, Zenarestat, and Minalrestat have been support to prevent diabetic cataract animal model. These studies provide a rationale for a potential future use of ARI in the prevention or treatment of diabetic cataracts [59].

6.2 Antioxidant treatment of diabetic cataract

It has been discussed earlier that the polyol pathway is the primary mediator of oxidative stress in the lens, resulting cataract formation.

The antioxidant alpha lipoic acid has been shown to be effective in prevent and delaying diabetic cataract in adult SD rats [60, 61].

Yoshida et al. demonstrated that the treatment with vitamin E protect from cataract in animal studies [62], but the study on 1193 human subject, Vitamin E given for 4 years at a dose of 500 IU daily did not reduce the incidence of or progression of nuclear, cortical, or posterior subcapsular cataracts. These findings do not support the use of vitamin E to prevent the development or to slow the progression of age-related cataracts [63].

Post translational modifications in lens crystallins due to glycation and oxidation have been suggested to play a significant role in the development of cataracts associated with aging and diabetes. Pyruvate, alpha keto acids can protect the lens against fructose mediated damage to lens alpha crystalline due to oxidative damage [64].

Conflicts of interest: ‘Conflicts of interest: none’

References


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