Acta Biomedica Scientia
e - ISSN - 2348 - 2168
Print ISSN - 2348 - 215X
www.mcmed.us/journal/abs
Research Article

PATHOGENESIS OF DIABETIC CATARACT

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ABSTRACT

India is considered to diabetes capital of the world. Diabetes mellitus produce number of chronic complication which affects every organ in the body and eye is not an exception to this. Age related cataract remain the common cause of blindness worldwide. In India, as per national survey on blindness, it contributes to about 62.6 % of the blindness. For this though surgery is the effective treatment, prevention may be one of the effective ways of controlling incidence of cataract. This review is mainly focused on various pathogenic mechanism of diabetic cataract and various clinical studies on association between diabetes and cataract.

Keywords :-Diabetes, cataract, blindness.

Access this article online	
Home page: http://www.mcmed.us/journal/abs DOI: http://dx.doi.org/10.21276/abs.2017.4.1.7	Quick Response code

Received:25.01.17	**Revised:**12.02.17	**Accepted:**15.03.17

INTRODUCTION

According world Health Organisation, worldwide 171 million had been affected with diabetes mellitus in year 2000 and by the year 2030, 366 million people would be affected with diabetes. India is considered to diabetes capital of the world. As per WHO data about 31.7 millions people are affected with diabetes mellitus and by the year 2030, this figure will rise to around 79.4 millions [1]. Diabetes mellitus produce number of chronic complication which affects every organ in the body and eye is not an exception to this. Frequent complication seen in eye is diabetic retinopathy for which frequent follow up and strict glucose level control is needed [2]. Age related cataract remain the common cause of blindness worldwide. In India, as per national survey on blindness, it contributes to about 62.6 % of the blindness [3]. For this, lens extraction is the very effective treatment, however growing need of these surgeries imposes heavy personnel and socioeconomic burden on the sufferer, further risk of complication after cataract surgery is higher in diabetic person. So the prevention by modifying risk factor may be one of the effective ways of controlling incidence of cataract. In recent years, various risk factors including age, diabetes, smoking, lack of consumption of antioxidants and exposure to UV-B light have been reported to play critical roles in cataract development [4]. Dramatic increase in the incidence as well as prevalence of diabetes is seen in last 50 years. Thus diabetes may be one of the important risk factor which should be kept in mind for cataract. In this review, we had discussed various pathogenic mechanism of diabetic cataract and various clinical studies on association between diabetes and cataract.

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Pathogenesis of diabetic cataract

Various major mechanism explained in diabetic cataract are non-enzymatic glycation of eye lens proteins, oxidative stress, and activated polyol pathway in glucose disposition.

The enzyme aldose reductase [AR] catalyzes the reduction of glucose to sorbitol through the polyol pathway, a process linked to the development of diabetic cataract. Sorbitol is synthesized from aldose reductase utilising the NADPH and does not cross the cell membranes; it can accumulate in the cells and can cause cell damage by disturbing osmotic homeostasis. Sorbitol leads to osmotic swelling, changes in the membrane permeability, leakage of glutathione, myoinositol, the generation of free radicals and hydrogen peroxide which may cause cataract. [5] Alan YWL et al had done one study in transgenic mice that overexpress aldose reductase [AR] in their lenses.[6] They found that the flux of glucose through the polyol pathway is themajor cause of hyperglycemic oxidative stress. Further he found that glucose autoxidation and nonenzymaticglycation do not contribute significantly to oxidative stress in diabetic lenses. Aldose reductase reduction of glucose to sorbitol probably contributes to oxidative stress by depleting its cofactor NADPH, which is also required for the regeneration of GSH. Sorbitol dehydrogenase, other enzyme in Polyolpathway that converts sorbitol to fructose, also contributes to oxidative stress, most likely because depletion of its cofactor NAD [6]. Chronic oxidative stress generated by the polyol pathway is likely to be an important contributing factor in the slow-developing diabetic cataract. It may also act through stimulating apoptosis and glial cell activation [7].

Furthermore, increased glucose levels in the aqueous humor may induce glycation of lens proteins, which leads to generation free radicals and advanced glycation end product. These products interact with receptor in the lens and may induce cataract. Laboratory studies have shown that prolonged exposure of lens proteins to elevated glucose concentrations results in extensive glycation, the consequences of which may include oxidation, cross-linking, aggregation, and precipitation of the modified lens proteins [8]. This glycosylation imparts an increased susceptibility of the lens to sulfhydryl oxidation. Disulfide crosslinks result in the formation of high molecular weight aggregates and opalescence in the crystallin solutions. The addition of reducing agents prevents as well as reverses this process. Cortical region of the lens is more prone to this [9]. In addition, higher glycemic load was observed to be linked with higher plasma concentrations of the inflammatory marker C-reaction protein, which may play an important rolein the pathogenesis of age related cataract [10-12]. Reduction in concentration of glutathione, antioxidant enzymes such as catalase, superoxide dismutase [SOD], glutathione Reductase, glutathione peroxidase play role in caractogenesis [13] The loss of antioxidantsis exacerbated by glycation and inactivation oflens antioxidant enzymes like superoxide dismutases [14]. Copper-zink superoxide dismutase 1 [SOD1] is the most dominant superoxide dismutase isoenzyme in the lens which is important for the degradation of superoxide radicals into hydrogen peroxide [H2O2] and oxygen [15-17]. Thus they may oxidise DNA, proteins and lipids to cause cytotoxic effect. Cytotoxic effects seen are lipid peroxidation, protein nitration and nitrosylation, DNA breakage and base modification, impairment of cell signaling, depolarization of mitochondrial membrane, PARP [poly ADP ribose polymerase protein] and metalloproteinase activation, lipoxygenase activation and, in extreme cases, necrosis and premature apoptosis. Diabetic patient are more prone to free radical induced damage. Parameters of their antioxidative defense are lower and those of oxidative stress are higher in serums and in the lenses and humour aqueous. [18]

Lin HJ et al found that Single-nucleotide polymorphisms in chromosome 3p14.1- 3p14.2 is associated with susceptibility of type 2 diabetes with cataract. The major functions of the genes are voltage-dependent anion-selective channel proteins, long myosin light chain kinase, adenylyl cyclase-associated proteins and retinoic acid receptors and are all closely related with the pathogenesis of T2D and cataractogenesis [19]. The voltage-gated channel may influence intracellular iron concentration and cause cataract formation. Thyroid hormone which acts through retinoic acid receptor has protective effect oxidative damage. Retinoic acid inhibits calcium elevation and calpains activation. Myosin light chain kinase act through Rho kinase. Adenylyl cyclase-associated protein was identified as a most efficient substrate of matrix metalloproteinases. Metalloproteinases act on metaloprotein substrate in the lens. Sorbitol may cause osmotic stress in the lens. A study was done in transgenic mice overexpressing aldose reductase and phospholipase D [PLD] genes [20]. It was found that aldose reductase gene play main role development of osmotic stress. Study was done in young patient where rapid cataract formation was seen due to the extensive swelling of cortical lens fibers [21]. Levels of AR in red blood cells were positively correlated with the prevalence of posterior subcapsular cataracts [22]. Osmotic stress is caused by the accumulation of sorbitol induces stress in the endoplasmic reticulum [ER], the principal site of protein synthesis, ultimately leading to thegenerationof free radicals.

ER stress may also result from fluctuations of glucose levels initiating an unfolded protein response [UPR] that generates reactive oxygen species [ROS] and causes oxidative stress damage to lens fibers [23].

Thus to summarise, various ways by which diabetes induce caractogenesis are sorbitol pathway activity, non-enzymatic glycation and glycoxidation, enhanced oxidative-nitrosative stress, proteinkinase C, poly[ADP-ribose] polymerase and lipoxygenase activation. Thus with the knowledge of pathogenesis, various attempts have been done to prevent it.

Most important ways by which it could be prevented is control of glucose level because glucose level is main initiating event for all pathogenic mechanism.

Drel VR et al [7] found that aldose reductase inhibitor fidarestat counteracts diabetes-associated cataract formation, retinal oxidative nitrosative stress, glial activation, and apoptosis. Signs of lens damage like degeneration, swelling, or disruption of lens fibers were also not seen with use of Renirestat [24]. Beneficial effect of other adose reductase inhibitor is also shown [25,26]. Nonsteroidal anti-inflammatory drugs, such as sulindac, [27] aspirin or naproxen [28-30] have been reported to delay cataract in diabetic rats through a weak AR inhibitory activity.

Blakytny R, Harding JJ had assessed the effect of aspirin, paracetamol [acetaminophen] and ibuprofen in prevention of cataract [31]. They found that blood glucose levels were a little lower in diabetic rats treated with aspirin and ibuprofen than in untreated diabetic rats. Similarly, the increased glycation [non-enzymic glycosylation] of lens proteins caused by diabetes was less in the diabetic rats treated with aspirin and ibuprofen. The fall in glutathione induced by diabetes was also alleviated by aspirin and ibuprofen. Paracetamol appeared to afford similar protection against the biochemical changes but its effect was not statistically significant. As already discussed the decrease in glutathione and increase in glycation were related to the progression of lens opacification, these had given protection through this mechanism. Nonsteroidal anti-inflammatory drugs have been found to have a weak AR inhibitory activity. Nonsteroidal anti-inflammatory drugs [NSAIDs] act through the cyclooxygenase enzymes thus they decrease prostaglandin formation. NSAIDs may also reduce the incidence, duration and severity of cystoid macular edema by inhibiting the release and breakdown of the blood-retina barrier [32,33] Nepafenac, a topical NSAID and prednisolone had been used for prevention and treatment of pain and inflammation after cataract surgery. They have been found to decrease cystic macular edema [34,35]. Suryanarayana P et al had evaluated the role of curcumin and turmeric in streptozotocin-induced diabetic cataract in rats. He found that, both curcumin and turmeric did not prevent streptozotocin induced hyperglycemia, but they delayed the progression and maturation of cataract [36]. Curcumin and turmeric treatment appear to have countered the hyperglycemia-induced oxidative stress, minimized osmotic stress by acting on polyol pathway enzymes. Also aggregation and insolubilization of lens proteins due to hyperglycemia was prevented by turmeric and curcumin. Turmeric was more effective than curcumin. Role of many medicinal plants had been described in literature. Some act through aldose reductase while some has antioxidant activity [37].

Similarly antioxidant use had delayed the development of and progression cataract. Lipid soluble vitamin, Vitamin E [38] and endogenous antioxidant, Pyruate has been considered useful for this [39]. Various studies had been done where increased chances of caractogenesis was seen in diabeteics. In this section, we will take short overview of these studies.

Mcguinness R found that diabetes is not the important cause of lens opacity. However progression of cataract in diabetic is fast and they require earlier extraction as compared to that of non-diabetic. [40] Similarly Klein BEK, found three to four fold increased prevalence of cataract in diabetic below 65 years of age and two fold increase prevalence in diabetic above 65 years.[41] Risk increased with the duration of diabetes and poor metabolic control. Snow flake cataract was seen in type 1 diabetes mellitus [41]. Saxena S et al had done a population-based, cohort study of 2335 persons with baseline ages 49 years or older resident in the Blue Mountains region, west of Sydney, Australia. His aim was to investigate longitudinal associations between diabetes and the 5-year incidence of cataract and cataract surgery. His finding suggested that impaired fasting glucose, a pre-diabetic condition, may be a risk factor for the development of cortical cataract.[42] SimilarlyRowe NG et al had done Blue Mountain eye study. He found that diabetes has a harmful effect on the lens [43].

Janghorbani M & Amini M et al estimated the incidence of and risk factors for the development of cataract in type 2 [insulin-treated and non-insulin-treated] diabetes in Iran. They found incidence of 33.1 per 1000 person-years of observation after mean 3.6 years' follow-up, thus diabetic cataract clearly poses a formidable health threat to Iranian diabetic patients [44]. Olafsdottir E et al evaluated the prevalence and risk factors of lens opacities in a geographically defined population [Laxa region] of 275 subjects with type 2 diabetes mellitus compared with a 256 control population. Their study showed that cortical cataract

is associated with diabetes mellitus, not necessarily defined by glucose control, whereas posterior subcapsular cataract is associated with glucose levels [9]. Nuclear cataract is not associated with diabetes mellitus, but is more frequent in women. Mukesh BN et al showed that diabetes mellitus was an independent risk factor for posterior subcapsular cataract when present for more than 5 years [45].

Similarly, Klein BEK et al [41,46,47] had done Wisconsin epidemiological study and Beaver Dam eye studies while Leske MC et al [48] had done Barbodos eye study. Incidence and progression of cortical and subcortical cataract was associated with diabetes. They were more prone to develop cortical cataract. Risk increased with duration and level of glycated haemoglobin. Incidence of cataract surgery was higher in persons with type 2 diabetes. Predictors of cataract surgery included age, severity of diabeticretinopathy and proteinuria in type 1 diabetics whereas age and use of insulin were associated with increased risk in type 2 diabetics

Seong Il Kim and Sung Jin Kim evaluated the prevalence and risk factors of cataracts in Eight hundred fifty patients Korean patients with type 2 diabetes mellitus. He found cataract in 50 % of the patients. He concluded that the duration of diabetes was the most significant risk factor for cataracts in patients with diabetes. The accumulated effect of hyperglycemia was considered to be related to lens transparencyin patients with diabetes [49].

Janghorbani MB et al found that age at diagnosis, duration of diabetes mellitus, diabetic retinopathy and poor metabolic control was a significant independent predictor of cataract for the diabetes mellitus [50]

Li L et al had done meta-analysis to know the risk of cataract in type 2diabetes. He had included total of 8 studies involving 20837 subjects. He found increased incidence of cataract in patient of type 2 diabetes mellitus. He concluded that special attention should be paid on the ophthalmic extermination, especially for cataract in T2D patients [51]

Sabanayagam Cetal studied the relationship between metabolic syndrome components and age-related cataract. Metabolic syndrome and its two key components, high BP and diabetes were associated with age-related cataract [52].

Machan CM et al found that statin use was substantially higher in patients with type 2 diabetes and was associated with age related cataracts. In non-statin user, it appeared late [53].

Then we had come across some study where association was seen between glycaemic load and cataract were studied

Turati F had done case control study in Italy. He found the positive association between dietary glycaemic load and the risk of cataract extraction, independently from diabetes, and a lack of association for glycemic index [54]. Tan J et al investigated the associations between dietary glycemic index, glycemic load, total carbohydrate intake, and 10-y incident nuclear, cortical, and posterior subcapsular cataract in an Australian cohort [10]. He found that poorer dietary carbohydrate quality, reflected by high glycaemic index, was associated with high incident cortical cataract. Similar result was also found by some of the autors. [11,12]

Wu H et al had done metanalysis of seven studies which indicated that higher dietary carbohydrate quantity and GI may be associated with the risk of cortical and nuclear cataract, respectively [55].

Thus common risk factor for development of cataract is age at diagnosis, duration of diabetes mellitus, diabetic retinopathy, poor metabolic control, carbohydrate quality, dietary glycemic index, glycemic load and associated use of drug like statin group.

Thus diabetic cataract poses a challenge for the community, a significant research has been done in this field everywhere however we had not come across any study which is done in Indian population. So we recommend that studies in Indian population should be encouraged. Secondly, for diabetic cataract our main focus should be on early diagnosis and treatment. Because control of glucose level will be the mainstay of treatment and risk of complication especially after cataract surgery will be less in those patient.

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Cite this article:
Hulke SM, Dhone PG, Vaidya PV, Gupta SB. Pathogenesis Of Diabetic Cataract. *Acta Biomedica Scientia*, 2017;4(1):28-34. DOI: **http://dx.doi.org/10.21276/abs.2017.4.1.7**