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Role of Enzymatic and Biochemical Properties in Senile And Diabetic Cataract: A Systematic Review

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ABSTRACT

Cataract is a major cause of curable blindness worldwide. With the increasing burden of diabetes, progression to cataract development hastens. Oxidative stress in diabetic has been the major cause for increasing incidence for cataract in diabetics. Release of various enzymes and proteins is also implicated in some studies. A systematic review for this was undertaken by literature search. The search gave a total 12 relevant articles from 2003 to 2023 which are included in the present study. A total of 7 biochemical parameters and 20 enzymatic parameters were compared. Most of the parameters were found to raised or altered in diabetics hastening the cataract development.

INTRODUCTION

Cataract remains the major cause of visual impairment in the general population^[1,2], as well as in the diabetic population^[3-5]. Diabetics have accelerated development of cataract as compared to normal senile cataract^[6]. Diabetes mellitus (DM) is one of the major risk factors for cataract occurring two to five times more frequently in patients with DM than in those without DM^[7,8]. Various researches have shown relationship between DM and cataract development^[7]. As independent diseases DM and cataracts, impose immense morbidity as well as economic burden on developing countries where treatment options are restricted^[9]. Aging is a known risk factor for development of both DM and cataract enhancing burden on health care services^[10]. Risk factor identification for these preventable blindness becomes crucial. Oxidative stress is the most common among most of the diabetic complications including diabetic cataract^[11]. Oxidative stress leading to expression of various enzymes is also implicated for development of cataractous changes in lens in old age^[12].

Comparison of expression of both enzymatic and biochemical parameters in diabetic cataract and senile cataract remains the unexplored area by the researchers. Hence, in this systematic review we compared various enzymatic and biochemical parameters expressed in cataractous lens of both diabetic and age related cataract.

MATERIALS AND METHODS

Research Method: The report of this review study was based on a systematic review and meta-analysis (PRISMA)^[28,29]. Review of literature of various studies was done by searching databases (Google Scholar, PubMed). Studies whose full text was available in English from the year 2003 to 2023 were included and the following concepts were built to answer the review question on enzymatic and biochemical properties of lens in age related cataract and diabetic cataract^[27].

Concept 1 Cataract: MeSH terms identified for this concept were "Cataract" [MeSH], "Cataract/enzymology" [MeSH] and "lens, crystalline" [MeSH].

Concept 2 Age Related or Senile Cataract: MeSH terms used were "Cataract, Age Related Nuclear," "Cataract, Age Related Cortical." Key words identified were "age-related cataract" and "senile cataract."

Concept 3 Diabetic cataract: MeSH term "Diabetes Mellitus"[MeSH] and key word "Diabetic cataract" were identified. The combination of the MeSH terms (Boolean operators) and keywords was

used to search in Google Scholar. The following combinations were used: [("Cataract"[MeSH] OR "Cataract/enzymology"[MeSH]) AND ("Age related cataract" OR "senile cataract")) AND ("diabetic cataract")].

Inclusion and Exclusion Criteria: The data included into the study complied with the following criteria:

- The articles consisted of original research, case report and review articles from year 2003-2023
- Only human studies were selected
- There were no restrictions related to the demographic characteristics of the sample study (race, sex and age)
- Non English articles were disqualified

Study Selection and Data Extraction: The initial database search with MeSH words yielded 10,500 articles. After applying our inclusion and exclusion criteria 785 articles remained for screening. Duplicate and non-relevant articles were excluded giving 347 articles. After reviewing titles and abstracts only 12 articles were found eligible for the study.

RESULTS AND DISCUSSIONS

Results are derived by reviewing all the articles found relevant during the literature search. The results are as under.

Enzymatic parameters : The mean serum levels of SOD and catalase were lower as age increased. These enzymes were significantly lower in diabetic cataracts (9.13 and 16.42 units/ml, respectively) compared to senile cataracts (25.30 and 57.27 units/ml, respectively)^[12]. Senile cataract was associated with significantly low levels of erythrocyte catalase, GPX and SOD, when compared to diabetic cataract^[13].

After adjusting for age, plasma MDA levels were significantly higher in diabetic cataracts ($P < 0.001$) and nondiabetic cataract subjects ($p < 0.05$), compared to nondiabetic subjects with clear lens. Plasma advanced glycation end products index was significantly higher ($p < 0.05$) only in diabetic cataracts. Aldose reductase activity and sorbitol levels were significantly higher ($p < 0.001$) in both diabetic and nondiabetic subjects with cataract compared to nondiabetic subjects with clear lens^[14]. The serum MDA were significantly raised in diabetic cataract patients ($p < 0.0001$) and levels of vitamin C was significantly decreased in diabetic cataract patients ($p < 0.0001$) as compared to healthy individuals^[15]. Significantly decreased levels of serum magnesium, GH and glutathione peroxidase-3 (GPX-3) and increased level of MDA were found in diabetic cataract patients compared to senile cataract patients. Significant negative correlation of serum magnesium

with MDA and positive correlation with GPX-3 were observed^[16]. In a study by Li *et al.*^[17] on down regulation of activated protein kinase AMPK-dependent FOXO3 and TFEB involves in the inhibition of autophagy in diabetic cataract. As compared to age related cataract patients, the expression of autophagy related genes ATG5, FYCO1, ATG8, ATG12, Beclin1 and ULK1 in the anterior capsule lens epithelial cells (LECs) of diabetic cataract patients was significantly down regulated.

Biochemical Parameters: In diabetic cataract, the lens weight increased significantly ($p < 0.001$) with maturation of cataract. Diabetic lens also showed a reduction in total proteins in comparison to normal lenses, which was statistically significant ($p < 0.05$). The mean lens weight increased significantly ($p < 0.001$) with maturation of cataract. Total proteins in senile cataract lenses also decreased gradually from immature to hyper mature cataract. The concentration of lens taurine decreased significantly ($p < 0.01$) in comparison to normal lens in senile and diabetic cataracts^[18]. Zhu *et al.*^[19] studied and compared the racemization in cataractous lens from diabetic and aging individuals. Compared to nondiabetic cataractous lenses, diabetic cataractous lenses showed a significantly increased cortex/nucleus ratio of d-Asp 58, which originated primarily from an increased percentage of d Asp 58 in the lens cortex of diabetic cataracts. Decreased protein solubility was seen in diabetic cataractous lenses. The role of transient receptor potential vanilloid 2 (TRPV2) in the development of diabetic cataracts was given by Chen *et al.*^[20] in China and they stated that TRPV2 expression levels were significantly increased in the lens epithelial cells of patients with diabetic cataracts compared to those with senile cataract.

A recent study by khare *et al.*^[21] showed that mean aldose reductase (AR) levels in lens of the diabetic patients was 2.07mU/mg of protein while non diabetic group was 0.22Mu/mg with p-value less than 0.001. Mean glutathione activity (GSH) in the diabetic group was 3.38 $\mu\text{Mol/g}$ of lens and the non diabetic group was 7.47 $\mu\text{Mol/g}$ of lens ($p < 0.001$). In a ongoing cohort study (CALS) - China Aging Longitudinal Study role of elevated levels of GPNMB were seen in patients with diabetic cataract which abate the expression of connexin 43 and stimulate the upregulation of integrin beta-1 to promote cataract formation was seen.^[22]

Comparison of Enzymatic and Biochemical Parameters: GSH, superoxide dismutase (SOD), catalase and serum magnesium were found to be raised in senile cataract, while the other remaining factors were raised in diabetic cataract. A comparative list of the enzymatic and biochemical parameters in

both cataracts has been presented in Table 2. In this narrative review, after evaluating results from the 12 articles, seven biochemical parameters and 20 enzymatic parameters with various factors was discussed and the results of all the studies were found to be comparable.

Enzymatic Parameters: GSH levels were found to be lower in age-related cataractous lens^[16]. Maurya *et al.*^[12] observed a similar finding of low serum levels of SOD and catalase in diabetic cataract compared to senile cataract. Also, decreased levels of both the enzymes were observed with increase in age. Plasma oxidative stress markers such as the lipid per oxidation end product MDA, protein oxidation products, protein carbonyls and DNA oxidative damage marker 8 hydroxy 2 deoxyguanosine were found to be higher in diabetic cataract compared to the nondiabetic cataract and in patients with clear lens^[14,15]. Indicators of oxidative stress such as serum magnesium were found to be reduced in diabetic cataract and antioxidants such as GSH and GPX-3 were decreased in diabetic cataract compared to senile cataract. Increased level of serum MDA was observed in diabetic cataract. Hypomagnesemia may be a significant causative factor for increased oxidative stress and it triggers earlier cataractogenesis in patients with type 2 DM^[16].

The levels of erythrocyte catalase, GPX and SOD were significantly low in senile cataract compared to diabetic cataract^[23]. Significant downregulation of expression of autophagy-related genes was observed in diabetic cataract than senile cataract. This may be the underlying mechanism of diabetic cataract formation^[17]. Few researchers had shown association of aqueous humor (AH) parameters and cataract formation in diabetics and senile cataract. The chromium (Cr) level in the serum and AH was found to be lower in senile cataract than in diabetic cataract by

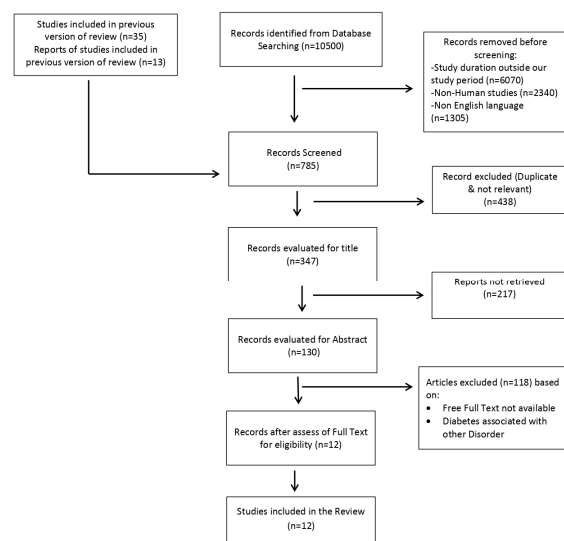


Fig. 1: PRISMA diagram of included articles into process

Table 1: Review of literature of enzymatic and biochemical parameters of lens in ARC and diabetic cataract

Authors	Year	Parameter	Methodology	Result
Anthrayose <i>et al.</i> ^[18]	2004	Biochemical	Estimation of protein and taurine	The lens weight was found to be significantly increased (P<0.001) with development and maturation of cataract. The concentrations of total lens protein (P<0.05) and taurine (P<0.01) were found to be significantly decreased in cataractous lens compared to normal lens.
Raitelaitiene <i>et al.</i> ^[13]	2005	Ultrasonic and biochemical study		Mean lens thickness was more in cataractous lens compared to the normal lens (statistically insignificant). Mean attenuation coefficient (dB/cm MHz) and ultrasound attenuation coefficient were also more in cases of senile and diabetic cataract lens.
Maurya <i>et al.</i> ^[12]	2006	Enzymatic	SOD and catalase	Amount of soluble protein was lesser in diabetic cataract when compared to senile cataractous lens. The mean serum levels of SOD and catalase were lower as age increased. These enzymes were significantly lower in diabetic cataracts (9.13 and 16.42 units/ml, respectively) compared to senile cataracts (25.30 and 57.27 units/ml, respectively).
Chandrasena <i>et al.</i> ^[24]	2006	Enzymatic	Erythrocyte catalase, GPX and SOD activities were assayed	Senile cataract was associated with significantly low levels of erythrocyte catalase, GPX, and SOD, when compared to diabetic cataract.
Chitra <i>et al.</i> ^[14]	2020	Enzymatic	Plasma oxidative stress markers such as the oxidative products, protein carbonyls and DNA lipid peroxidation end product MDA, protein oxidation damage marker 8-hydroxy-2-deoxyguanosine were evaluated. Plasma advanced glycation end products index, erythrocyte aldose reductase activity and sorbitol levels were evaluated.	After adjusting for age, plasma MDA levels were significantly higher in diabetic cataracts (P<0.001) and non-diabetic cataract subjects (P<0.05), compared to non-diabetic subjects with clear lens. Plasma advanced glycation end products index was significantly higher (p<0.05) only in diabetic cataracts. Aldose reductase activity and sorbitol levels were significantly higher (P<0.001) in both diabetic and nondiabetic subjects with cataract compared to nondiabetic subjects with clear lens.
Zhu <i>et al.</i> ^[19]	2021	Biochemical	Comparison of racemization of Asp 58 residue, a hotspot position in α A-crystallin, from the cortex and nucleus of diabetic and age-matched senile cataractous lenses, by identifying L-Asp/I-IsoAsp/d-Asp/ d-IsoAsp by mass spectrometry.	Diabetic cataractous lenses showed a significantly increased cortex/nucleus ratio of d-Asp 58 and decreased protein solubility.
Kaliaperumal <i>et al.</i> ^[16]	2021	Biochemical and enzymatic	Serum magnesium Serum MDA, an indicator of oxidative stress bio-marker. Antioxidant status such as serum GSH and GPX-3.	Significantly decreased levels of magnesium, GSH, GPX-3 and increased level of MDA in diabetic cataractous lens compared to senile cataractous lens.
Li <i>et al.</i> ^[17]	2021	Enzymatic	Anterior capsule specimens from diabetic cataract (DC) and age-related cataract (ARC) patients were obtained to compare the expression difference of autophagy-related genes. The phosphorylation levels of AMPK-AMP activated protein kinase mTOR- mammalian target of rapamycin (AMPK, AKT and mTOR) and the expression of FOXO3 and TFEB were measured.	The expression of autophagy-related genes ATG5, FYCO1, ATG8, ATG12, Beclin1 and ULK1 in the anterior capsule LECs of diabetic cataracts lens was significantly down regulated when compared to senile cataracts lens. AMPK and AMPK-dependent transcription factors, FOXO3 and TFEB, were also inhibited in cataractous lens.
Kim sharma and yogita soni ^[15]	2021	Biochemical	Serum MDA and vitamin C levels as a marker for oxidative stress in diabetic patients with cataract were compared with healthy individuals.	The serum MDA were significantly raised in diabetic cataract patients (p<0.0001) and levels of vitamin C was significantly decreased in diabetic cataract patients (p<0.0001) as compared to healthy individuals.
Chen <i>et al.</i> ^[20]	2022	Biochemical	Determining the role for TRPV2 in the development of diabetic cataracts using immunohisto-chemistry and western blotting analysis.	TRPV2 expression levels were significantly increased (which, in turn, enhanced the reactive oxygen species-induced lens epithelial cell apoptosis) in the lens epithelial cells of patients with diabetic cataracts compared to those with senile cataract.
Da Huo <i>et al.</i> ^[21]	2023	Biochemical	Serum glycoprotein non-metastatic melanoma protein B (GPNMB) level as a biomarker for diabetes related cataract.	Elevated levels of GPNMB were seen in patients with diabetic cataract which abate the expression of connexin 43 and stimulate the upregulation of integrin beta-1 to promote cataract formation.
Khare <i>et al.</i> ^[22]	2023	Biochemical and enzymatic	GSH and Aldose reductase levels as markers for oxidative stress in lens from diabetic and non diabetic cataractous lenses.	Mean aldose reductase (AR) levels in lens of the diabetic patients was 2.07mU/mg of protein while non diabetic group was 0.22mU/mg with p<0.001. Mean glutathione activity (GSH) in the diabetic group was 3.38 μ Mol/g of lens and the non diabetic group was 7.47 μ Mol/g of lens (p<0.001).

ARC = Age-related cataract, GPX-3 = Glutathione peroxidase-3, GSH = Reduced glutathione, MDA = Malondialdehyde, TBARS = Thiobarbituric acid-reactive substances, TRPV2 = Transient receptor potential vanilloid 2, GPNMB= Serum glycoprotein non metastatic melanoma protein B

a few researchers^[24]. Mitrovic *et al.*^[25] demonstrated disturbed AH micro environment in diabetic cataract, with significant changes in vascular endothelial growth factor (VEGF), interleukin (IL-10) and Fas ligand (FasL). In a study by khare *et al.*^[21] increased levels of aldose reductase enzyme triggers sorbitol formation leading to oxidative stress to endoplasmic reticulum causing abnormal phosphorylation of AKT via binding to CD44 which downregulates connexin 43 and upregulates integrin beta-1 to promote cataract formation as per recent (CALS) study^[22].

Biochemical Parameters: In both diabetic and senile cataracts, weight increases with maturation of cataract. Protein content in cataractous lens decreases both in diabetic cataract and senile cataract when compared to the normal lens. Also, the taurine content decreases in both diabetic and senile cataracts^[18]. Proteins and taurine content in lenses were altered with maturity of cat aract and were not related to age or sex. Similar finding of decreased protein solubility in diabetic cataractous lenses was reported by Zhu *et al.*^[19]. Also, the amount of soluble protein was less in diabetic lens compared to the senile cataractous lens. Compared to the normal lens, ultrasound attenuation coefficient was higher in senile and

diabetic cataracts^[13]. Qianqian *et al.*^[26] compared the lens proteomic profiles between diabetic cataract (type-1) and age-related cataract and concluded that the α b and β B1-crystallin may accelerate the development of diabetic cataracts, particularly in type 1 diabetes. Zhu *et al.*^[19] compared racemization of Asp 58 residue, a hotspot position in α A crystallin, from the cortex and nucleus of diabetic and age-matched senile cataractous lenses, where they reported diabetic cataractous lenses had increased cortex/ nucleus ratio of D Asp 58, compared to non diabetic cataract. Chen *et al.*^[20] studied the role of TRPV2 in the development of diabetic cataracts immunohistochemically and by western blotting analyses and showed that TRPV2 expression levels were increased in the lens epithelial cells of patients with diabetic cataracts compared to those with senile cataract. The mechanism suggested was enhanced reactive oxygen species-induced lens epithelial cell apoptosis by upregulating TRPV2 expression and TRPV2 mediated Ca^{2+} overload in a high glucose environment.

Limitations of the Study: Only articles with free access were included for the review.

Table 2: Comparison between enzymatic and biochemical parameters

Characteristics	Non diabetic (senile) cataract	Diabetic cataract
Enzymatic property		
Lens lipid peroxide		Raised
Reduced glutathione	More	
Cytochrome c oxidase		More
Superoxide dismutase	More	
Catalase	More	
Erythrocyte catalase		More
Plasma advanced glycation end products index		More
Aldose reductase		More
Sorbitol		More
Plasma malondialdehyde		More
Serum magnesium	More	
Serum GSH	More	
GPX-3	More	
Tryptophan		More
Autophagy-related genes		Down regulated
Serum chromium		More
Total antioxidant status and uric acid levels	More	
Serum GPNMB		More
Aldol reductase in lens		Increased
Lens GSH levels		Decreased
Biochemical parameters		
Weight	Raised	Raised
Protein content	Decreased	Decreased
Taurine	Decreased	Decreased
Mean lens thickness	Increased	Increased
Soluble protein		Decreased
Cortex-to-nucleus ratio of D-Asp 58		Increased
TRPV2		Increased

GPX-3=glutathione peroxidase-3, GSH=reduced glutathione, TRPV2=transient receptor potential vanilloid 2, GPNMB- Serum glycoprotein non metastatic melanoma protein B

CONCLUSION

This review gives an insight into various biochemical and enzymatic parameters expressed in age-related cataract and diabetic cataract which will help in understanding pathogenesis of age - related cataract and diabetic cataract. This will enable ophthalmologists to take appropriate decisions and help them in management of these conditions especially diabetic cataract which is curable visual impairment. Nonetheless, further research is needed in this regard.

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