ASSESSMENT OF OXIDATIVE STRESS MARKERS IN DIABETIC AND SENILE CATARACT PATIENTS

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Abstract:
The present study was aimed to compare the role of oxidative stress markers in diabetic and senile cataract patients. A total of 135 patients were included in this study, of which, 50 patients had diabetic cataract while, remaining 85 were having senile cataract. Blood glucose concentration and serum oxidative stress markers like, xanthine oxidase (XOD), superoxide dismutase (SOD) and malondialdehyde (MDA) levels were estimated by using commercial available kits. HbA1c levels (%) estimated by using HPLC technique present in central diagnostic laboratory of SMI hospital. Fasting and post-prandial plasma glucose levels in diabetic cataract patients were significantly higher ($p<0.001$) as compared to the senile cataract patients. The activity of superoxide dismutase (SOD) was significantly decreased while Xanthine oxidase (XOD) activity and serum MDA levels were significantly increased in diabetic patients with cataracts in comparison to patients with senile cataracts ($p<0.001$). Serum XOD, SOD and MDA level was positively correlated with the HbA1c levels. We concluded that the hyperglycemic condition may associated with the increased production of reactive oxygen species (ROS) that trigger non-enzymatic glycation, increased production of lipid peroxidation products and advanced oxidative protein product which may contribute to the development of diabetic cataract. Therefore, the antioxidant therapy can delay the onset and progression of diabetic cataract.

Keywords: Oxidative stress, Antioxidant, Cataract, SOD, MDA, XOD, Hyperglycemia.

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INTRODUCTION:

Cataract is one of the most common causes of visual impairment across the world. It includes opacity of the lens or lens capsule which is a multi-factorial disease and a major cause of the loss of lens transparency particularly in the aging population [1]. Cataract is responsible for about 50-90% of blindness particularly in developing countries [2]. As per nearly 50% of blindness cases across the globally [3].

Several factors like metabolic disorders, genetic factors, aging, ultraviolet irradiation, drugs, trauma, toxins and oxidative stressleads to the formation of cataract [4, 5]. Surgery is considered to be the most common and successful method to remove cataract. However, surgery is either unaffordable or inaccessible in the developing countries and therefore, researchers are now emphasizing on the importance of alternative methods [6].

Several studies have suggested that cataract is one of the leading causes of vision loss among diabetic patients [7, 8]. Diabetes mellitus has become a major health concern worldwide in recent scenario [9]. It is a severe chronic metabolic disorder of carbohydrate, lipid and protein metabolism [10]. It is characterized by hyperglycemia due to impairment in secretion or action of endogenous insulin [11].

Common symptoms of diabetes mellitus include polyuria (frequent urination), polydipsia (increased thirst), polyphagy (increased hunger), tiredness, weight loss and blurred vision [12]. Diabetes mellitus includes macrovascular complications like (peripheral vascular disease, coronary heart disease, and stroke), microvascular comlications like (neuropathy, retinopathy and nephropathy) and both micro- and macrovascular complication that is (diabetic foot) [13].

In senile cataract, lens proteins undergo extensive oxidative modifications which contribute to the etiology and pathogenesis of cataractogenesis. Cataract formation in diabetes mellitus include several mechanism such as excessive concentration of tissue sorbitol, abnormal glycosylation of lens proteins, alterations in phosphoinositides metabolism, imbalance of antioxidant enzymes, impaired glutathione metabolism, formation of lipid peroxides and elevated production of free radicals in the intraocular space [14,15]. Which often result in an increasing clouding of the lens until it loses its normal transparency and becomes white and opaque [16, 17].

Oxidative stress refers to imbalance between pro-oxidants and antioxidants [18]. It results in the increased production of free radicals or reduced activity of cellular antioxidant defence system or both. Reactive oxygen species (ROS) may initiate toxic biochemical reactions in eye cells.

These reaction results in damage of DNA, lipid peroxidation, aggregation of intracellular protein and precipitation[19, 20] Free radicals, including numerous ROS such as H_2O_2, superoxide anion radical ($\cdot O_2^-$), and hydroxyl free radical ($\cdot OH$), cause damage to the crystalline lens and involved in the formation of cataract. Thus, the ROS level should be regulated properly in order to prevent the celular damage [21].

Antioxidant capacity of plasma is considered to be a marker to evaluate the status of oxidative stress in the body. Plasma contains several compounds which act against the oxidative stress and thus, protect the cell and cellular biomolecules from oxidative damaged. The antioxidant defense mechanisms take place via enzymatic as well as non-enzymatic processes.

Vitamins like A, C, and E, α-lipoic acid, carotenoids, glutathione, co-enzyme Q10 (CoQ10), flavinoids, minerals like zinc, selenium, manganese and copper, cofactors like folic acid, compounds like uric acid, albumin, and water soluble vitamins like B1, B2, B6, and B12 are included in non enzymatic antioxidants. Catalase, glutathione peroxidase, superoxide dismutase, and glutathione reductase are considered to be as enzymatic antioxidants [22].

The aim of present study was to assessment the oxidative stress markers, antioxidants levels in serum sample and to compare the oxidative stress markers between the two groups i. e. diabetic and senile cataract patients. Thus studying the role of stress in causing diabetic and senile cataract and explore the possibility of the rapeutic role of antioxidants in prevention of cataract.

MATERIALS AND METHOD:

Ethical clearance for this study was obtained from the Ethical committee Faculty of Medicine, S. G. R. R. University, Dehradun. A total of 135 patients (50 diabetic cataract and 85 senile cataract patients attending the Ophthalogy OPD of SMIH hospital, Dehradun were included in the present study. Diabetic cataract patients (n=50) were aged

40 years or above and diagnosed as having diabetic cataract. Senile cataract (n=85) patients were aged 50 years or above and diagnosed as non diabetic senile cataract. The fasting and post prandial venous blood sample was collected in sodium fluoride-potassium oxalate anticoagulant vacutainers for blood glucose analysis. Serum separator tube (SST) was used to collect blood samples for oxidative stress markers analysis.

Further blood collection was also done in EDTA vial for the estimation of HbA1c from diabetic cataract patients. Plasma and serum was separated by centrifugation at 3500 rpm for 15–20 min. The analysis of sample was done at department of biochemistry of Shri Guru Ram Rai University, Dehradun.

Serum and plasma with lipemia and hemolysis was excluded in this study. Serum samples were stored at -80°C until further analysis. A complete ophthalmological examination including slit lamp examination of the patients was done by a single experienced ophthalmologist.

Exclusion criteria was history of cardiovascular diseases, hepatic functions disorders, gastrointestinal disorders, renal dysfunction, anemia, arthritis, osteoporosis, hypothyroidism, hyperthyroidism with traumatic cataract and toxic cataract. Patients consuming alcohol and those who had used oral or tropical anti-oxidant preparation were also excluded from this study.
The following parameters were analyzed to assess the oxidative stress markers and assess the circulating plasma levels of antioxidant enzymes and compounds in diabetic cataract and senile cataract.

Malondialdehyde (MDA): The concentration of human malondialdehyde in serum was measured by sandwich ELISA method by employing Malondialdehyde ELISA Kit (Chongqing Biospes Co., Ltd., Chongqing, China). MDA levels were determined by reading the color intensity at wavelength of 450 nm and compared to the standard curve in micro plate ELISA reader [23].

Superoxide Dismutase (SOD): The activity of serum SOD was measured by sandwich ELISA method by using SOD ELISA Kit (Chongqing Biospes Co., Ltd., Chongqing, China). The colour production was read at wavelength at 450 nm and by reading the color compared to the standard curve in micro plate ELISA reader [24].

Xanthine Oxidase (XOD): The activity of serum XOD was also measured by sandwich ELISA method by employed using Human XOD ELISA Kit (Chongqing Biospes Co., Ltd., Chongqing, China). The colour change was determined at wavelength 450 nm and compared to standard curve obtained by micro plate ELISA reader [25].

Blood Glucose: The blood glucose level includes (fasting blood sugar and post-prandial blood sugar) was estimated by (GOD-POD) Trinder's method using the blood glucose assay kit (Transasia Biomedical Ltd., ERBA Diagnostics Mannheim, Germany). Blood glucose level was assessed by reading the absorbance of standard and test tubes against reagent blank at 505 nm on biochemistry analyzer [26].

Glycosylated Hemoglobin: The glycosylated hemoglobin (HbA1c) in whole blood was measured by HPLC method using Bio- Rad D-10 Hemoglobin Testing System [27, 28].

Statistical Analysis: The results were expressed in the form as mean± standard deviation (SD). Data were analyzed by using SPSS software (SPSS® for Windows ® 10.0). Statistical analysis between the senile cataract patients and diabetic cataract patients was evaluated by post hoc student's t test. $p<0.001$was accepted as statistically significant.

RESULTS:
The characteristics of the patients like age, gender, hypertension, smoking or non smoking, duration of the diabetes, concentration of blood glucose in diabetic patients and senile cataract patients (controls) and HbA1c % are presented in **Table 1**. The mean age of the diabetic and senile cataract patients were 58.64±6.19 and 59.01±8.21 years respectively, fasting blood glucose in diabetic cataract was significantly higher (144±2.53 mg/dl) ($p<0.001$) whereas the senile cataract patients had a normal fasting plasma glucose concentration (84±2.15 mg/dl). The post prandial plasma glucose in diabetic cataract was significantly higher (214±3.51 mg/dl) ($p<0.001$) as compared to that of senile cataract patients (115±3.19 mg/dl). The HbA1c percentage in diabetic cataract patients is 7.96±0.76.

The activity of antioxidant enzyme, superoxide dismutase (SOD) was found significantly ($p<0.001$) decreased in diabetic cataract patients (20.65±1.26 ng/ml), as compared to senile cataract patient (27.98±2.02 ng/ml). Xanthine oxidase (XOD) activity was found significantly ($p<0.001$)

increased in diabetic cataract patients (511.48±3.71 pg/ml) as compared to senile cataract patients (386.81±4.36 pg/ml). Serum MDA level isfound significantly (p<0.001) higher in diabetic cataract patients (33.22±0.92 mmol/l) than senile cataract patients (19.97±0.73 mmol/l) are presented in **Table 2**. The correlation between HbA1c (%) and XOD (Rho=0.139), SOD (Rho=0.173) and MDA (Rho= 0.111) was done and the results are presented in **Fig 1, 2 & 3**.

Table 1 Demographic and biochemical characteristics of cataract patients

	Diabetic cataract (n = 50)	Senile cataract(n= 85)	p- value
Age (Years)	58.64±6.19	59.01±8.21	
Gender (male/female)	23/27	37/48	
Hypertension (yes/no)	22/28	27/58	
Current Smoker (yes/no)	10/40	8/77	
Duration of diabetes (years)	5.98±1.97	NA	
Fasting plasma glucose (mg/dl)	144±2.53	84±2.15	<0.001
Post-prandial plasma glucose (mg/dl)	214±3.51	115±3.19	<0.001
HbA1c (%)	7.96±0.76	NA	

Table 2 The impact of oxidative stress markers on diabetic cataract and senile cataract

Stress markers	Diabetic cataract (n = 50)	Senile cataract (n= 85)	p- value
Superoxide dismutase (ng/ml)	20.65±1.26	27.98±2.02	<0.001
Xanthine oxidase (pg/ml)	511.48±3.71	386.81±4.36	<0.001
Malondialdehyde (mmol/l)	33.22±0.92	19.97±0.73	<0.001

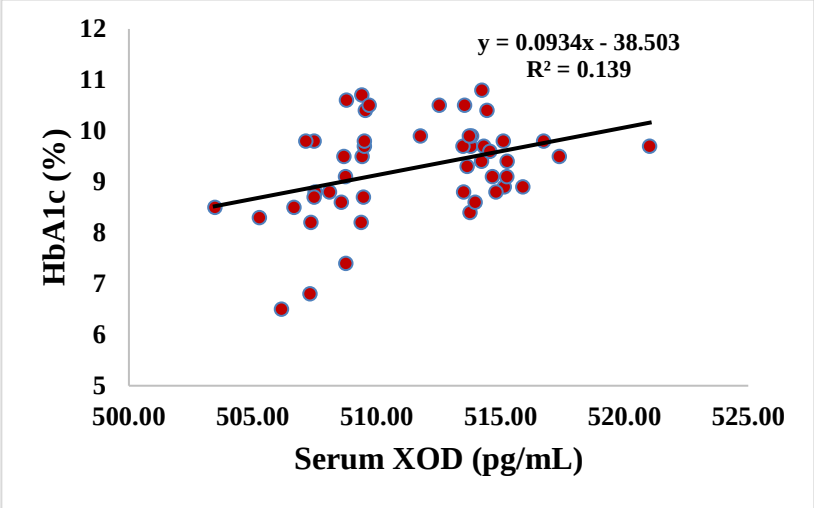

Fig. 1: Correlation between blood HbA1c and serum XOD activity

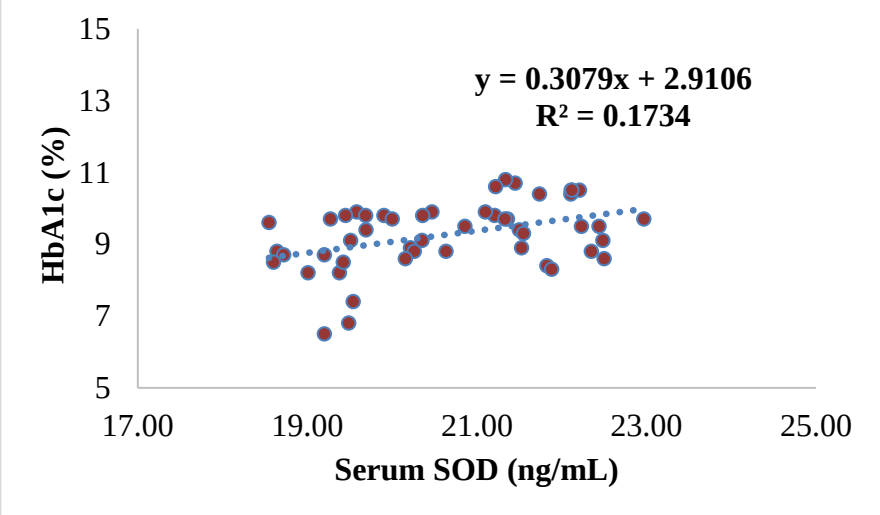

Fig. 2: Correlation between blood HbA1c and serum SOD activity

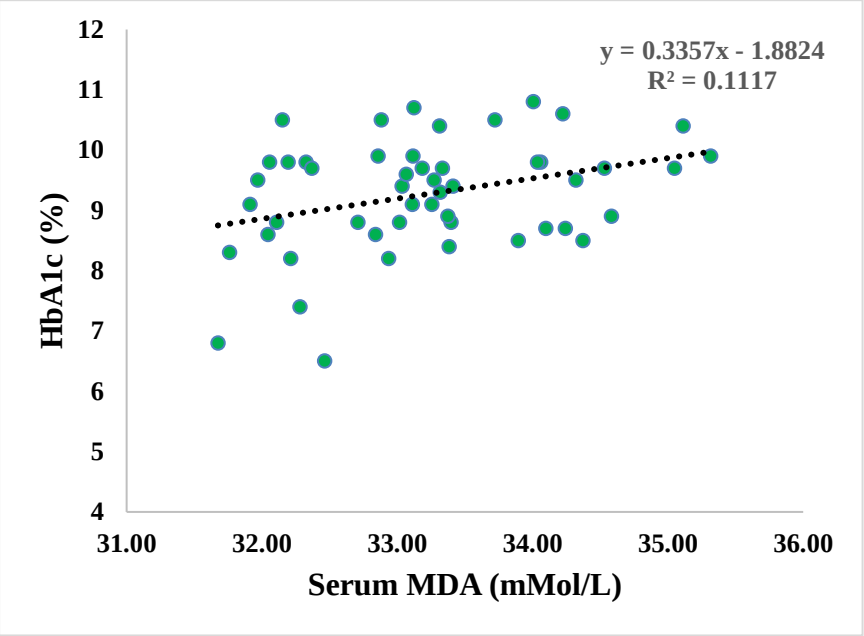

Fig. 3: Correlation between blood HbA1c and serum MDA level

DISCUSSION:

Oxidative stress due to free radicals is responsible for several chronic disorders, like diabetes, cancer, inflammation and neurological disorders. The oxidative stress is refers to a condition in which imbalance occurs between free radicals and an antioxidant system of the body. This is caused by a relative overburden of ROS, which includes singlet oxygen, superoxide, hydrogen peroxide, hydroxyl radicals, that contributes to pathophysiology of many diseases including cataract [29, 30]. Antioxidant defence systems acts as free radical scavengers by means of certain enzymes such as, XOD, SOD, glutathione peroxidase, glutathione reductase, compounds like uric acid and flavonoides.

It has been observed that oxidative mechanisms play a vital role in the aetiology of cataract. In diabetic patients, cataractogenesis progresses much faster towards maturity as compared to non-diabetics [31, 32]. One of the significant mechanisms that lead to cataract formation in diabetic subjects is non-enzymatic glycation [33]. Several studies revealed that glycation results in severe damage of lens proteins affecting their normal function [34].

The aim of the present study was to analyse the activity of antioxidant enzymes, like xanthine oxidase (XOD), superoxide dismutase (SOD), lipid peroxidation product malondialdehyde (MDA) in both diabetic cataract as well as senile cataract patients. SOD is considered as enzymatic antioxidant that provides first line of defense against the free radicals due to its ability to quench O_2^- and convert it into H_2O_2 [35]. In our study SOD levels were decreased in diabetic cataract. This may be due to ROS like $O2^-$ are produced in diabetic cataract. In such condition SOD is being used during the conversion of O_2^- to H_2O_2 which causes inhibition of SOD activity [36]. However, few researchers revealed no significant changes [37] or increased activity of serum SOD activity in diabetic cataract patients [38, 39]. The decreased antioxidant status in the diabetic cataractous lens tissues suggested a role of antioxidant enzymes in the formation of cataract in diabetic patients [40]. The loss or decrease of the enzymatic activities of antioxidant enzymes allows H_2O_2 and free radicals to induce irreversible harmful effects on lens proteins including decrease in Na- K ATPase activity [41].

Obara et al., 1995 reported the increased levels of lipid peroxides in lens and levels of oxidized lipoprotein and decreased activities of Cu, Zn-SOD due to the excessive production of ROS, especially hydroxyl radicals (HO_) inside the cataractous lenses. Further the higher concentration of lens glucose, advanced glycated protein and lipid peroxides was observed in diabetic cataract patients as compared to patients with senile cataract [42]. In some recent studies have been found that osmotic stress also involves in diabetic cataract formation [43, 44]. This finding is consistent with a previous study done by [45].

Xanthine oxidase (XOD) is an enzyme responsible for the breakdown of the purine derived from nucleic acids and serves as a source of oxidizing agents [46]. Increased XOD activity in cataractous lenses was previously reported [47]. Some researchers suggested that the relationship between formation of cataract and chronic ingestion of allopurinol which is an inhibitor of XOD [48, 49]. In the present study, significantly increased XOD activity in diabetic patients was observed. The increased (<0.001) XOD activity in diabetic patients may generate higher amount of oxygen radicals. It has been reported that conversion of xanthine dehydrogenase into xanthine oxidase responsible for ischemia-reperfusion injury of the retina [50]. Hyperglycemic condition may contribute to the lens oxidative damage by increased ocular as well as systemic XOD activity [51]. The low level of XOD is expressed in several ocular tissues, including lens and corneal epithelium and endothelium [52] and human retinal endothelium and photo-receptors [53]. Therefore, oxidants produced through XOD during purine catabolism can participate in chronic ocular oxidative stress, and possibly in formation of cataract. XOD system can induce peroxidation of lipid and disrupt the sodium-potassium-ATPase activity [54]. Such early event can be observed in cataract formation which affects osmo-regulation mechanisms. Hyperglycemia and hypoxia show increased XOD activity, regulated at pre-translational and post-translational levels [55, 56].

In our study, was significantly elevated serum MDA level was observed in patients with diabetic cataract compared to non diabetic patients with senile cataract that suggested the increased oxidative stress in diabetic cataract patients. Result of this present study is closely resembled tothe study reported by [57]. Further, the study done by Donma et al (2002) revealed that patients with diabetic cataract have shown increased levels of lipid peroxidation products in plasma [58]. The findings of this present investigation are similar to the study by [59, 60]. Increased lipid peroxidation products also observed in lens of cataract patients by [61].

The increased levels of MDA level in diabetes is mainly due to the production of reactive oxygen species (ROS) caused by hyperglycemia and hyper lipidemia which are commonly associated with diabetes [62]. Lipid peroxidation products may causes micro vascular damage in diabetic patients and alteration in blood–ocular barrier. Several researchers reported the increased levels of lipid peroxides products in diabetic patients [63], while in few reports no significant there was increase in lipid peroxidation in diabetic patients [64]. In a similar study it was formed that serum XOD, SOD and MDA level was positively correlated with HbA1c levels [65, 66].

CONCLUSION:

In present study we studied, the oxidative stress markers, i. e. serum XOD and SOD activity and levels of MDA in diabetic cataract patients compared with senile cataract patients. Results of this study clearly showed increase in activity of XOD, decrease SOD activity and increase levels of MDA in diabetic cataract patients. Oxidative stress is in the foreground of the cataract formation. The entry of glucose into the diabetic lens and its oxidation occurs through the polyol pathway, leads to the accumulation of sorbitol into the lens, which causes an osmotic stress that may be considerable factor that contributes to development and progression of diabetic cataract. The oxidative stress produces direct influence on the solubility of lens proteins, which increase the opacity of the lens. In addition the increased concentration of glucose might be involved in the deficiency of activity of enzymatic antioxidant as well as the production of lipid peroxidation. Hence supplementation of an adequate dose of antioxidant to diabetic patients at initial stage of disease might be beneficial in delaying the development of especially cataract as well as other complications.

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REFERENCES:

1. Asbell PA, Dualan I, Mindel J, Brocks D, Ahmad M, Epstein S. Age-related cataract. The Lancet. 2005; 365(9459):599-609.
2. Kyselova Z, Stefek M, Bauer V. Pharmacological prevention of diabetic cataract. Journal of Diabetes and its Complications. 2004; 18(2):129-40.
3. Resnikoff S, Pascolini D, Etya'Ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. Bulletin of the world health organization. 2004; 82(11):844-51.
4. Davidson MG, Nelms SR. Diseases of the lens and cataract formation. Veterinary ophthalmology. 1999; 2:1199-233.

5. Spector A. Oxidative stress and disease. Journal of Ocular Pharmacology and Therapeutics. 2000; 16(2):193-201.
6. Hashim Z, Zarina S. Osmotic stress induced oxidative damage: possible mechanism of cataract formation in diabetes. Journal of diabetes and its complications. 2012; 26(4):275-9.
7. Harding JJ, Egerton M, Van Heyningen R, Harding RS. Diabetes, glaucoma, sex, and cataract: analysis of combined data from two case control studies. British Journal of Ophthalmology. 1993; 77(1):2-6.
8. Drinkwater JJ, Davis WA, Davis TM. A systematic review of risk factors for cataract in type 2 diabetes. Diabetes/metabolism research and reviews. 2019; 35(1):e3073.
9. Dawud FA, Eze ED, Ardja AA, Isa AS, Jimoh A, Bashiru M, et al. Ameliorative effects of vitamin C and zinc in alloxan-induced diabetes and oxidative stress in Wistar rats. Current Research Journal of Biological Sciences. 2012; 4(2):123-9.
10. Eiselein L, Schwartz HJ, Rutledge JC. The challenge of type 1 diabetes mellitus. ILAR journal. 2004; 45(3):231-6.
11. Rosin D, Sapna LS. Supplementation effects of vitamin C and vitamin E on oxidative stress in post menopausal diabetes women. J Appl Res. 2012; 12:108.
12. Kolluru GK, Bir SC, Kevil CG. Endothelial dysfunction and diabetes: effects on angiogenesis, vascular remodeling, and wound healing. International journal of vascular medicine. 2012; 2012.
13. Asmat U, Abad K, Ismail K. Diabetes mellitus and oxidative stress—A concise review. Saudi pharmaceutical journal. 2016; 24(5):547-53.
14. Doelman CJ. Lens lipid peroxides in diabetic cataract. Annals of Clinical Biochemistry. 1997; 34(6):700-700.
15. Ferlita S, Yegiazaryan A, Noori N, Lal G, Nguyen T, et al. Type 2 diabetes mellitus and altered immune system leading to susceptibility to pathogens, especially Mycobacterium tuberculosis. Journal of clinical medicine. 2019; 8(12):2219.
16. Freeman EE, Munoz B, Schein OD, West SK. Hormone replacement therapy and lens opacities: the Salisbury Eye Evaluation project. Archives of ophthalmology. 2001; 119(11):1687-92.
17. Anathanaryanan PH. A comparative study of lens protein glycation in various forms of cataract. Indian Journal of Clinical Biochemistry. 2004; 19(1):110-2.
18. Venkatesh P, Satpal G, Verma L, Kumar TH, Garg S. Antioxidants: Basis concepts in relation to the eye. Indian Journal of Clinical Biochemistry. 2001; 16(1):9-14.
19. Datiles MB, Kinoshita JH. Modification by oxidative damage. Duans Ophthalmogy. 1998; 73:11394e11660.
20. Boscia F, Grattagliano I, Vendemiale G, Micelli-Ferrari T, Altomare E. Protein oxidation and lens opacity in humans. Investigative ophthalmology & visual science. 2000; 41(9):2461-5.
21. Ho MC, Peng YJ, Chen SJ, Chiou SH. Senile cataracts and oxidative stress. Journal of clinical gerontology and geriatrics. 2010; 1(1):17-21.
22. Maritim AC, Sanders A, Watkins Iii JB. Diabetes, oxidative stress, and antioxidants: a review. Journal of biochemical and molecular toxicology. 2003; 17(1):24-38.
23. Bakirezer SD, Yaltirik CK, Kaya AH, Yilmaz SG, Ozdogan S, Billur D, et al. The evaluation of glutathione reductase and malondialdehyde levels in patients with lumbar disc degeneration disease. in vivo. 2019; 33(3):811-4.
24. Wang Q, Xu X, Zeng Z, Hylkema MN, Cai Z, Huo X. PAH exposure is associated with enhanced risk for pediatric dyslipidemia through serum SOD reduction. Environment international. 2020; 145:106132.
25. Kohsari M, Ansari MH, Rasmi Y. Serum Level of Xanthine Oxidase, Uric Acid, and NADPH Oxidase 1 in Stage I of Multiple Myeloma. Asian Pacific Journal of Cancer Prevention: APJCP. 2020; 21(8):2237.
26. Trinder P. Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Annals of clinical Biochemistry. 1969; 6(1):24-7.
27. Marzullo, C., &Minery, M. (2008, January). Evaluation of D10 hemoglobin testing system for hemoglobin $A1_C$ assay. In Annales de Biologie Clinique (Vol. 66, No. 1, pp. 95-99).
28. Yis OM, Pehlivan MB, Bugdayci G, Yuce N. Evaluation of Bio-Rad D-10Ž and arkray adams HA-8160Ž HPLC analyzers in HbA1c measurement.
29. Özmen B, Özmen D, Erkin E, Güner İ, Habif S, Bayındır O. Lens superoxide dismutase and catalase activities in diabetic cataract. Clinical Biochemistry. 2002; 35(1):69-72.
30. Vinson JA. Oxidative stress in cataracts. Pathophysiology. 2006; 13(3):151-62.
31. Javadi MA, Zarei-Ghanavati S. Cataracts in diabetic patients: a review article. Journal of ophthalmic & vision research. 2008; 3(1):52.

32. Kiziltoprak H, Tekin K, Inanc M, Goker YS. Cataract in diabetes mellitus. World journal of diabetes. 2019; 10(3):140.
33. Rolo AP, Palmeira CM. Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress. Toxicology and applied pharmacology. 2006; 212(2):167-78.
34. Thampi P, Zarina S, Abraham EC. A-Crystallin chaperone function in diabetic rat and human lenses. Molecular and cellular biochemistry. 2002; 229(1):113-8.
35. Irshad M, Chaudhuri PS. Oxidant-antioxidant system: role and significance in human body.
36. Garg R, Verma M, Mathur SP, Murthy PS. Blood lipid peroxidation products and antioxidants in senile cataract. Indian Journal of Clinical Biochemistry. 1996; 11(2):182-6.
37. Jacques PF, Chylack LT, McGandy RB, Hartz SC. Antioxidant status in persons with and without senile cataract. Archives of Ophthalmology. 1988; 106(3):337-40.
38. Uçakhan ÖÖ, Karel F, Kanpolat A, Devrim E, Durak İ. Superoxide dismutase activity in the lens capsule of patients with pseudoexfoliation syndrome and cataract. Journal of Cataract & Refractive Surgery. 2006; 32(4):618-22.
39. Yildirim Z, Yildirim F, Ucgun N, Kilic N. The evaluation of the oxidative stress parameters in nondiabetic and diabetic senile cataract patients. Biological trace element research. 2009; 128(2):135-43.
40. Özmen B, Özmen D, Erkin E, Güner İ, Habif S, Bayındır O. Lens superoxide dismutase and catalase activities in diabetic cataract. Clinical Biochemistry. 2002; 35(1):69-72.
41. Green K. Free radicals and aging of anterior segment tissues of the eye: a hypothesis. Ophthalmic research. 1995; 27(Suppl. 1):143-9.
42. Obara Y. The oxidative stress in the cataract formation. Nippon Ganka Gakkai Zasshi. 1995; 99(12):1303-41.
43. Ross WM, Creighton MO, Trevithick JR, Stewart-DeHaan PJ, Sanwal M. Modelling cortical cataractogenesis: VI. Induction by glucose in vitro or in diabetic rats: prevention and reversal by glutathione. Experimental eye research. 1983; 37(6):559-73.
44. Pereira PC, Fernandes R, Ramalho JS, Mota MC, Oliveira CR. A technical approach to the evaluation of glucose oxidation: Implications for diabetic cataract. Ophthalmic research. 1996; 28(5):275-83.
45. Balcı M, Akyol Ö, Zengin N, Kural G. Antioxidant enzyme status in alloxan diabetic rat lenses. Türk J. Med. Res. 1994; 12(1):1-4.
46. Tubaro E, Lotti B, Santiangeli C, Cavallo G. Xanthine oxidase: an enzyme playing a role in the killing mechanism of polymorphonuclear leucocytes. Biochemical Pharmacology. 1980; 29(21):3018-20.
47. Zengin N, Akyol Ö, Balcı M, Durak I. Xanthine oxidase in human lens. Its possible role in cataractogenesis. Turk J Med Sci. 1994; 20:91-3.
48. Lerman S, Megaw JM, Gardner K. Allopurinol therapy and cataractogenesis in humans. American journal of ophthalmology. 1982; 94(2):141-6.
49. Guerrero RO, Guzmán AL. Inhibition of xanthine oxidase by Puerto Rican plant extracts. Puerto Rico Health Sciences Journal. 2016; 17(4).
50. Szabo ME, Droy-Lefaix MT, Doly M, Carre C, Braquet P. Ischemia and reperfusion-induced histologic changes in the rat retina. Demonstration of a free radical-mediated mechanism. Investigative ophthalmology & visual science. 1991; 32(5):1471-8.
51. Miric DJ, Kisic BB, Zoric LD, Mitic RV, Miric BM, Dragojevic IM. Xanthine oxidase and lens oxidative stress markers in diabetic and senile cataract patients. Journal of Diabetes and its Complications. 2013; 27(2):171-6.
52. Čejková J, Ardan T, Čejka Č, Luyckx J. Favorable effects of trehalose on the development of UVB-mediated antioxidant/pro-oxidant imbalance in the corneal epithelium, proinflammatory cytokine and matrix metalloproteinase induction, and heat shock protein 70 expression. Graefe's Archive for Clinical and Experimental Ophthalmology. 2011; 249(8):1185-94.
53. Fox NE, Van Kuijk FJ. Immunohistochemical localization of xanthine oxidase in human retina. Free Radical Biology and Medicine. 1998; 24(6):900-5.
54. Varma SD, Hegde K, Henein M. Oxidative damage to mouse lens in culture. Protective effect of pyruvate. Biochimica et Biophysica Acta (BBA)-General Subjects. 2003; 1621(3):246-52.
55. Pacher PA, Nivorozhkin A, Szabó C. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. Pharmacological reviews. 2006; 58(1):87-114.
56. Portugal-Cohen M, Kohen R. Exposure of human keratinocytes to ischemia, hyperglycemia and their combination induces oxidative stress via the enzymes inducible nitric oxide synthase and xanthine oxidase.

Journal of Dermatological Science. 2009; 55(2):82-90.
57. Bhatia G, Abhang S, Sontakke A. Significance of aldose reductase in diabetic cataract. Int J Cur Res Rev. 2017; 9:48.
58. Donma O, Yorulmaz EÖ, Pekel H, Suyugül N. Blood and lens lipid peroxidation and antioxidant status in normal individuals, senile and diabetic cataractous patients. Current eye research. 2002; 25(1):9-16.
59. Ali SL, Siddiqui JA, Khanam A, Memon S. Oxidative stress and antioxidant vitamins in cataract patients.
60. Jalees SS, Rosaline M. Study of malondialdehyde and estimation of blood glucose levels in patients with diabetes mellitus with cataract. International Journal of Clinical Biochemistry and Research. 2017; 4(3):319-23.
61. Babizhayev MA. Accumulation of lipid peroxidation products in human cataracts. Acta Ophthalmologica. 1989; 67(3):281-7.
62. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. Endocrine reviews. 2002; 23(5):599-622.
63. Altomare E, Grattagliano I, Vendemaile G, Micelli-Ferrari T, Signorile A, Cardia L. Oxidative protein damage in human diabetic eye: evidence of a retinal participation. European Journal of Clinical Investigation. 1997; 27(2):141-7.
64. Sklodowska M, Gromadzinska J, Wasowicz W. Lipid Peroxide Concentration, Selenium Level, and Glutathione Peroxidase Activity in Blood of Type II (Non-Insulin-Dependent) Diabetic Elderly People. Journal of Clinical Biochemistry and Nutrition. 1989; 7(1):35-41.
65. Haddad NI, Nori E, Ali SH. The Effect of Type Two Diabetes Mellitus on Superoxide Dismutase (SOD) Activity and its Correlation with HbA1c in Iraqi Patients. International Journal of Engineering Research & Science. 2016; (2):7-15.
66. Bokhary K, Aljaser F, Abudawood M, Tabassum H, Bakhsh A, Alhammad S, et al. Role of Oxidative Stress and Severity of Diabetic Retinopathy in Type 1 and Type 2 Diabetes. Ophthalmic Research. 2021; 64(4):613-21.