Role of Lipid Peroxidation in Diabetic and Senile Cataract - A Review

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ABSTRACT

The association of lipids in cataract has been discussed for about two centuries and lipid peroxidation is identified as the inceptive stage, causing lipid-lipid and lipid-protein interactions which lead to lens opacity causing cataract. Reactive oxygen species play a significant role in lipid oxidation and forms byproducts by reacting with lipids. Worldwide blindness due to cataract is increasing steadily and diabetes patients are more prone when compared to non-diabetic patients. With the advancement in surgical procedures, there exist postoperative and intraoperative complications with higher risk in ocular co-morbid conditions, thus identifying the exact pathomechanism can pave the way for alternative treatment. This review focuses on lipid peroxidation products that play an essential part in opacification of the lens. The present study gives an insight of lipids in the cataract of diabetic and non-diabetic patients concerning the presence of their byproducts in plasma, lens tissue and aqueous humor.

Keywords: Senile cataract, diabetes mellitus, lipid peroxidation

INTRODUCTION

Clouding of lens or lens opacity which leads to a poor visual outcome is termed as cataract. Of the 37 million blind people in the world, cataract stands as a leading cause.⁴ According to the results of leading national surveys, cataract in India is expected to reach about 8.25 million in 2020. The possibility of WHO initiative “Vision 2020: The right to sight” may not be attained, due to the increased current prevalence with the person’s age above 60, projected incidence rate and poor visual outcome after surgery.⁴ Cataract affects the visual power of an eye, and so working and living of a person with cataract condition is hampered. Cataract is the primary cause of blindness worldwide and, accounting for 50% of blindness overall.⁴

Surgical extraction of the cataractous lens remains the only treatment despite some post-surgical complications. The surgical rate in developed countries has been increased above the WHO estimated range from 3000 per million people per year to 7000 – 11000 per million people.⁴⁻⁶ Researchers are thus aiming for an alternative treatment which might be prevented or delay the onset and progression of cataract by ten years, which can reduce the surgery rate to more than 45%, henceforth reducing the worldwide
economic burden. Various risk factors are included for the occurrence of cataract namely aging, diabetes mellitus, malnutrition, hypertension, renal disease, smoking, and others. Though there are many risk factors for cataract, Diabetes mellitus and oxidative stress plays a key role in cataractogenesis. It has been already suggested that oxidation of lipids, proteins and DNA is a major contributing factor in lens transparency.

In later year if once life, senile cataract is manifested and as per estimate estimated if the frequency of cataract is delayed for another couple of years, then the costs of operation are reduced by half.

In this review, we aimed to focus on pronouncement due to influence of lipids in cataract and diabetic cataract by their oxidation products, increasing insight into the etiopathogenesis of lens transparency, development of mature cataract through oxidative stress and defense of the lens against lipid peroxidation.

**Role of lipids in ocular diseases and cataract**

The role of lipids in cataract has been identified, two centuries ago with elevated level of cholesterol in human cataractous lenses. Lipids are molecules which have long hydrocarbon chains and the human lens lipids contain phospholipids, glycolipids and cholesterol. Most of the lipids are bound to protein, thereby limiting its movement and also guarantees its role in lens opacity. In human cataract, the composition of lens lipid changes markedly. Studies show that long-chain polyunsaturated fatty acids in the human lens are involved in the pathogenesis of most ocular diseases. There is considerable degradation of phospholipids in cataract in contrast with increase in age, which may be due to lipid oxidation. A study suggested that lens lipid composition with increase in age may contribute to mortality since it may act as markers for oxidative stress.

**Risk factors for diabetic cataract**

Aging is the primary factor for cataract as well as for diabetes. The risk of visual loss is increased in diabetes patients when compared to non-diabetes and cataract remains an essential cause of blindness in younger onset and older-onset diabetes persons. Lipid accumulation has been implicated in the formation of cataract in diabetes. Simonelli, concluded that along with retinal damage there is a higher risk for onset of cataract in diabetes and the mechanism was proposed to be that, in diabetes, the MDA, one of the breakdown products of lipid peroxidation binds to the amino group of lens proteins which disrupt them causing more vulnerable to stress.

There is an increased level of glutathione, a known antioxidant, which defense against lipid peroxidation in diabetic cataract than in non diabetes cataract. There are numerous studies in animal models induced with cataract and diabetes. In an aim to identify the mechanism involved in the cataract of normal and diabetic animal model it is difficult to compare the results of the animal lens with human lens since they vary with different species. Hence a detailed study on human lens lipids in cataract as well as in diabetic cataract may find a new insight into the etiology of cataract.

**Function of Lipid peroxidation in cataractogenesis**

Lipid peroxidation is a free radical chain reaction formed by removal of a hydrogen atom from a molecule and leaves an unpaired electron due to the attack of reactive oxygen species, namely superoxide radical, hydroxyl radical, nitric oxide radical etc. Dysfunctioning of cell permeability, cell proliferation, metabolism of lipid and proteins are caused by lipid peroxidation and thus found to be one of the primary pathogenic factors of senile cataract and cataract in diabetic patients.

Lipid peroxidation is one of the likely mechanisms during cataractogenesis. During lipid peroxidation there is an extreme fabrication of reactive oxygen species (ROS) in aqueous environments and that causes a reduced defense of the lens...
supported by antioxidant. In another way, one can say that development of cataract is progressing at its early stage, mostly influenced by the intense process of lipid peroxidation. Lipid peroxidation is otherwise initiator of cataractogenesis process which regulates production of ROS, therefore, affect the lens by its propagation.

Akkus and coauthors reported that there is a relationship between immune reactions and ROS, which leads to lipid peroxidation. Admittedly, we can find that in diabetes, lipid peroxidation is produced by ROS were due to the increase in aging and involvement of the immune system. It has also been reported an increased level of lipid peroxidation and increased antioxidant activity in diabetes patients. Supplementation of superoxide dismutase to diabetes patients reduces the diabetic complications which show the role of lipids peroxidation diabetes. Previously it was stated that lipid peroxidation is of two types non-enzymatic which is due to free radicals and enzymatic due to enzymes. In both conditions, there is an addition of the O2 molecule. In recent studies, this lipid peroxidation was divided into three forms, namely free radical-mediated oxidation, free radical independent, non-enzymatic oxidation and enzymatic oxidation which was proposed by Yasukasu et al., Initiation, propagation and termination are the three forms of process under a non-enzymatic lipid peroxidation. Lipid peroxidation products play an important role in modifying proteins and DNA bases and produces toxic effects. And one can control their effects by identifying the time, the site and the amount of their formation. Supported by antioxidant. In another way, one can say that development of cataract is progressing at its early stage, mostly influenced by the intense process of lipid peroxidation. Lipid peroxidation is otherwise initiator of cataractogenesis process which regulates production of ROS, therefore, affect the lens by its propagation.

Role of the lipid peroxidation underlying cataractogenesis mechanisms

In general all the cell membranes have lipoprotein structure, and in normal controlled conditions the lipid peroxidation usual process affects the cell membrane permeability. The increased or decreased cell permeability causes change the cell cytoplasm content and, therefore, structural changes in cell membrane lead to re-configuration of the lens. The most adverse effects during this process occur under conditions of impaired balance of prooxidative and antioxidative factors in the cell. That is why lipid peroxidation (LPO) is considered a pathogenic factor of cataractogenesis.

There are various reasons which cause the excess level of lipid peroxidation with cortical nuclear (CN) and nuclear subcapsular (NP) in cataract lens. During the lifetime of a human, some type of barrier or abstraction are formed in lens nuclear and cortical parts, which restrict the diffusion of molecules to the other side of the nucleus. Due to barrier central part of the lens become more sensitive to oxidative damage and possibly the unsteady lipid peroxidation product molecules. So as the process further enhanced nuclear plasma of membrane gets damaged due to oxidation which had earlier minimal extracellular space and arranged the lens fiber very compactly in nuclear part. Apart from these changes, the accumulated oxygen in lipid layer also plays role in the phospholipid molecules modification, leading to changes in the structure of lipid-lipid and protein-lipid bilayer of the lens fibers.

Products of lipid peroxidation and their role in cataract

Hydroxyoctadecadienoic acid (HODE)

It is the free radical-mediated oxidation product of linoleates which are present in most of the polyunsaturated fatty acids (PUFA) in vivo. It exists as an unstable lipid peroxides (LOOH) 9-hydroperoxy-10,12-octadecadienoic acids (9-HPODEs) and 13-hydroperoxy-9,11-octadecadienoic acid (13-HPODEs) and under biological conditions, it gets readily reduced to stable 9-hydroxy-10,12-octadecadienoic acids (9-HODEs) and 13-hydroxy-9,11-octadecadienoic acids (13-HODEs) respectively. Li et al., measured concentration of (Z, E) HODE in plasma of cataract patients and the results were significantly higher in early cataract patients when compared with control indicating that...
oxidative stress and lipid peroxidation plays a role in lens opaqueness. 10-(Z, E) HODE and 12- (Z, HODE has been identified as a suitable marker to find the diabetes in the early stages; however it has not been found in diabetic cataract patients. This 10 and 12 – (Z, E) HODE are specific, non-enzymatic singlet oxygen-mediated products. Interactions between biological lipid peroxyl radicals might be one of the reasons for the production of singlet oxygen in-vivo. [45-51]

**Isoprostanes F2a**

Isoprostanes are produced by non-enzymatic free radical oxidation of PUFA. When a free radical strikes the cell membrane phospholipids of lipoproteins and arachidonic acid, it gets converted to isoprostanes by cleavage, rearrangement and gets into the surrounding fluids. [52] It also acts as a mitogen for smooth muscle cell and fibroblast thus causing a tissue injury. [53-55] Bin Wang et al., [56] reported that there is a significant increase in 8 Isoprostane F2 level in the plasma of age-related cataract patients when compared with controls, assuming higher oxidative stress in ocular tissues could be a risk factor for cataractogenesis. At the same time, Li L and his team [43] found no significant results between control and early cataract patients. 8 Isoprostane F2 alpha acts as a valid and a novel biomarker for assessing the oxidative stress in-vivo. [57-61]

**Conjugated diene and fluorescent products**

The formation of the conjugated diene is associated with the early peroxidation process of lipids. [26] Chajes et al., [62] suggested this diene conjugation is the initial unstable intermediary product of lipid peroxidation. Few studies reported the presence of conjugated diene in the early stages of cataract. [27, 63, 64] Whereas fluorescent compounds were present at the end products of lipid peroxidation due to free radicals. [14,32] It is formed by reaction with toxic aldehydes to form Schiff's bases with residues of proteins to increase the carbonyl group. [27] These above authors proved higher concentration of the conjugated diene and fluorescent products in cataract when compared to control group.

**4-Hydroxynonenal (HNE)**

It is formed by the attack of free radicals at PUFA to form primary lipid peroxides and further decompose to lipid aldehyde. [65] H2O2 which causes peroxidation of lipids, produces HNE, which is found to be increased in cataract patients. [65,66] It also produces s protein-HNE adducts in the epithelial cells. [66,67] This protein-HNE adducts disturb the cell membranes, changes the membrane fluidity which leads to calcium influx thereby facilitating caspases to induce apoptosis in cataract. [68,69]

**Malondialdehyde (MDA)**

Malondialdehyde is the secondary degradation product of poly-saturated fatty acids. It has a longer half-life and diffusing property, thereby causing biotransformation and adducts formation in DNA, proteins. This malondialdehyde is the common biomarker used to find the extent of lipid peroxidation level in-vivo and there are several studies to represent it. So we have reviewed with respect to cataract and diabetes. The level of malondialdehyde has also been studied in the aqueous humor, lens and the plasma of cataract, diabetes and in diabetic cataract patients which is tabulated below.

Various studies have been performed stating the role of lipid peroxidation products and their antioxidant enzyme activity, which causes blocks in corticonuclear lens during the life time. However, changes in the lens due to these products and lipid peroxidation molecules are induced by several other risk factors present, affect the pace of commencement or the progress of cataract. The progress of cataract can probably be reduced by slowing down the formation of products by process lipid peroxidation. [27]

**Defense against lipid peroxidation in the lens**

Low molecular mass compounds such as GSH, ascorbic acid, α- tocopherol provide first contour defense against lipid peroxidation in the lens. These molecules...
act mainly against peroxyl radicals involved in radical propagation. The main function of these compounds is to terminate the free radical propagation and mediated reactions which then interrupt lipid peroxidation functioning in the autocatalytic chain reaction.

**Defense molecule and their function against**

The chief compounds which form the defense against lipid peroxidation in the lens are reduced glutathione (GSH), GSH-dependent enzymes, such as glutathione peroxidase (GPx) and glutathione S-transferase (GST). The main function of these molecules in the lens is to defend the lens structures from the function of the products of lipid peroxidation. \[^{[70-73]}\]

Glutathione reductase (GR) is one of important among all others, plays a key role in safeguarding thiol (-SH) groups in the lens its transparency. Possibly due to lower activity of GR might cause a blur vision in defective eyes in comparison to normal activities and also its predominantly allocated in the cortical of lens fiber cells normally. A low level of H2O2 causes the glutathione redox cycle to be responsible for protecting the lens from H2O2-induced damage and it maintains high levels of GSH. \[^{[27]}\] In a lens with cataract the concentration of GSH is reduced, therefore possibly consumption of GSH during would certainly help in oxidative stress with its conversion into oxidized form, which then conjugate with protein thiol groups to defend against the lipid peroxidation effect.

Another important defense molecule is glutathione peroxidase (GPx), which was shown to at low activity in defective or cataract lens compared with normal lenses. The function and activity of GPx decrease with the progress of cataract. \[^{[24]}\] In case there is reduced activity of GPx it may cause the increase accumulation of lipid hydroperoxides in the lens with cataract.

Superoxide dismutase (SOD) is yet another defense molecule against lipid peroxides which function to catalyze the dismutations of superoxide anion radicals (O2•-) to hydrogen peroxide and molecular oxygen in the presence of hydrogen donor. The study showed that the cells with increased activity of SOD are resistant to oxidative damage, caused by radicals. So it is obvious that it might be helping to prevent the beginning of the cataract in lens cells. \[^{[74]}\]

**DISCUSSION**

From the above reviews, we can find that there could be a strong relationship between cataract/ diabetic cataract with peroxidation of lipids. Cataract is the opacification of the lens which leads to blindness and its accounts for about 50% of visual loss worldwide. Ageing is the main risk factor for cataract though the changes are due to the disturbance in physical behavior and lens proteins. \[^{[75]}\] Alteration in the lipid composition is a well-known element for cataract over a century, but the correlation between them about composition, function, structure, morphology of the membrane lipids and lens clarity is still an illusion. \[^{[76]}\] Senile cataract connects with the overall well being of the people and it is related systemically to other ailments such as heart disease, cancer, diabetes and other age-related diseases. \[^{[77]}\] Mortality risk is doubled when it is linked with lens opacity \[^{[78-80]}\] and cataract surgery. \[^{[81-85]}\] Diabetic patients are prone to cataract formation compared to age relates or senile one. \[^{[86]}\] \[^{[22]}\] Arorre R, et al. 2013 \[^{[35]}\] established a link between lipid peroxidation and diabetes stated that lipid peroxidation is caused by reactive oxygen species which involves immune reaction. This immune system may be responsible for diabetes either directly or indirectly. And also, ageing is associated with diabetes and lipid peroxidation by ROS. Diabetes is caused by both enzymatic and non-enzymatic methods of lipid peroxidation. \[^{[35]}\] Earlier studies have some discrepancies in understanding the mechanism of polyol pathway causing cataract in diabetes. There are also studies reporting that oxidative damage causes diabetic cataract. Lipid
peroxidation has a role in the pathophysiology of diabetic cataract. [25]

Though MDA and HNE, secondary aldehydes produced during lipid peroxidation were widely measured, they lack specificity and sensitivity. The products of lipid peroxidation are lipid hydroperoxide (LOOH), Isoprostanes, Malondialdehyde (MDA), conjugated diene, lipid DNA adduct, lipofuscin pigments, lipid-protein adduct, exhaled gases and these rely on the type and location of lipids. [67] One of the byproducts of lipid peroxidation by arachidines, 8 isoprostane F2 alpha have been proved to be present in plasma of diabetes [44,87] and cataract [88,43] patients, there makes a possibility of its role in diabetic cataract patients. At the same time, HODE byproduct of linoleic acid has also been present in plasma of diabetes [47] and cataract patients. [39] Two earlier studies are showing the presence of the initiation and final products of lipid peroxidation process, namely conjugated diene and lipofuscin like the end products in lens homogenate [27] and aqueous humor [63] of cataract patients. So, it is hypothesized that it may be present in the cataract of diabetic patients.

The above four byproducts may serve as some good biomarkers to find the mechanism occurring in peroxidation of lipids in cataract as well as in diabetic cataract patients. Ultimately the pathomechanism of both might be understood in-vivo. Typical parameters which are measured for oxidative damage till now are malondialdehyde, total antioxidant capacity, liperoxides, entire sulfhydryl groups. In Indian scenario, only these parameters were observed in plasma and lens of few cataract patients. Though India has a number of cataracts as well diabetes patients, the research on this path will provide a better understanding of the disease.

Declaration of interest:
The authors report no conflicts of interest.

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