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INVESTIGATING OXIDATIVE STRESS - INDUCED APOPTOSIS IN AGE RELATED MACULAR DEGENERATION

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Abstract

Age-related macular degeneration (AMD) is a leading cause of central vision loss in the elderly, characterized by progressive degeneration of the retinal pigment epithelium (RPE). Oxidative stress has been implicated as a major contributor to AMD pathogenesis, yet the mechanistic relationship between oxidative injury, mitochondrial dysfunction, and apoptosis remains incompletely understood.

This study aimed to investigate the role of oxidative stress-induced apoptosis in AMD by integrating experimental, clinical, molecular, and expert-level qualitative data. A mixed-method approach was adopted. Human RPE cells were exposed to increasing concentrations of hydrogen peroxide (H_2O_2) to simulate oxidative stress, and apoptotic markers were quantified using caspase-3 activity assays and JC-1 fluorescence for mitochondrial membrane potential. Clinical data were collected from AMD patients (n=100) and age-matched controls (n=50) to measure oxidative biomarkers (MDA, 8-OHdG) and antioxidant enzymes (SOD, catalase). Gene expression analysis of apoptosis-related genes (BAX, BCL-2, CASP3, CYCS, TP53) was performed, and expert interviews with ophthalmologists provided clinical perspectives. Caspase-3 activity increased significantly with rising H_2O_2 exposure, accompanied by a marked decline in JC-1 red/green fluorescence, confirming apoptosis and mitochondrial dysfunction. Clinical biomarker analysis revealed that AMD patients had significantly higher levels of MDA (6.57 nmol/mL) and 8-OHdG (5.41 ng/mL), with reduced SOD and catalase activity ($p < 0.01$). Strong correlations were observed between oxidative stress markers and AMD severity ($r = 0.81$ for MDA, $r = -0.69$ for catalase). Gene expression analysis showed upregulation of pro-apoptotic genes and downregulation of BCL-2. Expert interviews corroborated the mechanistic findings and highlighted current diagnostic and therapeutic gaps. Oxidative stress plays a pivotal role in AMD progression by inducing mitochondrial dysfunction and apoptosis in RPE cells. These findings suggest that oxidative biomarkers and apoptotic regulators may serve as valuable tools for early diagnosis and targeted therapy in AMD management.

Keywords: Age-Related Macular Degeneration, Oxidative Stress, Apoptosis, Mitochondrial Dysfunction, Biomarkers, Retinal Pigment Epithelium

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INTRODUCTION

Among the elderly, macular degeneration is by far the leading cause of rheumatology diseases, causing vision loss in the area of the retina called the macula (Toma et al., 2020). Because of heredity, exposures in the environment and growing older, AMD is caused by many different factors (Jabbehdari & Handa, 2020). Today, oxidative stress is a leading contributor to AMD's development and progression. The retina typically suffers from oxidative damage as it has a high metabolism and must face constant light. Under oxidative stress, these cells can trigger a series of actions, including making the photoreceptor cells die through apoptosis (Tong & Wang, 2020). For older people in developed areas, AMD is the leading reason why people lose central vision (Vyawahare & Shinde, 2022). In the early and middle stages of AMD, the retinal pigment epithelium develops changes in pigment and has wastes accumulate in deposits underneath. The late stage of AMD causes RPE cells to deteriorate and the photoreceptors to die, hence leading to reduced vision (Wong et al., 2022).

When the body produces too many reactive oxygen species and its antioxidants are less able to defend it, oxidative stress occurs (Wakale et al., 2023). If mitochondria fail to work properly, owing to reduced respiration and falling membrane potential, the situation greatly enhances oxidative stress in AMD (Ansari et al., 2024). Because of high metabolism and frequent exposure to light, the retina ages and experiences constant stress from oxidative damage; that said, as people age, the natural balance in the body decreases. Generally, when cells' lipids, proteins and DNA experience oxidative stress, their function declines and contributes to the development of AMD (Tong & Wang, 2020). Oxidative stress may lead to single-stranded breaks, oxidised bases, double-stranded breaks and single-stranded breaks (Ansari et al., 2024). Once DNA damage is repaired properly, it can cause changes and extra mutations in the DNA, contributing to more cell issues and a higher chance of death (Kaarniranta et al., 2020). The dry type of AMD is marked by drusen under the retina which can gradually cause cells in the retina to die (Trotta et al., 2022). Osteoarthritis is known to have affected mitochondria in many cases and a higher ROS level is a probable link to this (Liu et al., 2022). Any issues with mitochondria cause the release of superoxide anion and hydroxyl radicals, leading to increased inflammation, issues with overexpression of matrix metalloproteinases and the activation of several pathways (Ansari et al., 2024). Various these elements trigger the start of the signalling system for death.

As a result of mitochondria not working properly which speeds up cell aging, older cells, known as senescent cells, have been seen to increase the amount of ROS they produce. A proinflammatory SASP, as well as other aspects of aging, arise when mitochondria become dysfunctional after telomeres uncap. Importantly, increased oxidative stress may also damage the antioxidant enzymes catalase and superoxide dismutase (Coryell et al., 2020). Even though boosting catalase in mitochondria has shown positive results for older animals, peroxiredoxins in chondrocytes are known to become hyperoxidized in aged adults (Coryell et al., 2020). A lower level of these enzymes can lead to even more oxidation in cells and cause more damage to them. The retina is sensitive to light and uses lots of oxygen, so it easily becomes affected by free radicals. Due to the major production of reactive oxygen species by mitochondria in many mature cells, many have suggested that mitochondrial ROS are a key factor in stimulating the immune system in glaucoma

(Duarte, 2021). If ROS levels increase, oxidative stress can harm cell membranes, organelles, DNA, lipids, proteins and DNA (Maldonado et al., 2023). When cells are healthy, these antioxidants prevent large amounts of ROS from being formed (D Stuart, 2021).

By removing ruined or unnecessary cells with apoptosis, this process ensures the normal state of body tissue. A gradual decrease in vision in AMD can be largely explained by the death of retinal pigment epithelial cells and photoreceptors. The RPE is part of the outer blood-retinal barrier and is found below the neuroretina. A number of things, for example, oxidative stress, harms to DNA and increased inflammation, could lead to optoposis. During the development and maintenance of tissues, damaged and infected cells are removed by the process of apoptosis (Spielhofer, 2024). To stop inflammation, this process utilizes caspases, a series of proteins that gradually destroys the target cell. If apoptosis is not properly controlled, it may result in diseases like cancer, autoimmune disease or brain diseases. Because caspases destroy the cell in a controlled manner, inflammation is prevented.

Apoptosis plays an important role in explaining why photoreceptors and pigment epithelial cells in the retina slowly disappear due to AMD, as stated by Wakale et al. Oxidative stress is seen in AMD and emerging evidence suggests that when damage occurs from oxidative stress, it activates the pathway that kills retinal cells (Abokyi et al., 2020). When these pathways are switched on, the cell begins the process of death by breaking its DNA, shrinking and producing apoptotic bodies. Once cytochrome c is released into the cell by mitochondria, it activates caspases which cause programmed cell death. Besides the other symptoms of AMD, inflammation can also result in the death of retinal cells. When oxidative stress is triggered by natural or external factors, it may lead to death. Stress related to DNA, the environment within the cell called the ER or byproducts of oxygen can activate the intrinsic pathway which is sometimes known as the mitochondrial pathway. Some part of apoptosis relies on oxidative stress causing cellular death (Chen et al., 2020).

Certain ligands such as TNF-α or Fas ligand, bind to death receptors on the surface of a cell which in turn leads to the activation of caspase-8 and triggers a sequence of caspase activations. Borchert et al. (2023) showed that when TNF-α and IL-1β are present, these two inflammatory cytokines trigger the RPE cells and photoreceptors to die and continue degeneration of the retina.

METHODOLOGY

The study applied methods from both quantitative and qualitative fields to explore the function of oxidative stress in the progression of AMD. The research used vitro experiments, analyzed patient information and conducted semi-structured interviews with experts. In order to recreate oxidative stress as a ‘dose’, RPE cells were grown and exposed to different amounts of hydrogen peroxide under controlled conditions. After labeling cells with Annexin V-FITC/PI and flow cytometry, the degree of death was assessed; caspase-3 activity in the cells was colorimetrically measured to show that apoptosis was successfully induced. JC-1 labeling made it possible to observe alterations in mitochondrial potential and discover that mitochondrial difficulties occur as a primary feature of stress-induced death. While working on the in vitro model, I gathered study eye tissue from patients with AMD (n=100) and the same age range of healthy volunteers (n=50). Analysis was performed on blood samples taken by ELISA to assess MDA, 8-OHdG, catalase and SOD levels which indicate oxidative stress in the body. The

progress of structural changes in the retina and AMD was tested with optical coherence tomography and fundus photography. SPSS v28 was used to compare and analyze patient data using correlation and regression studies concerning oxidative biomarkers and AMD. Twelve ophthalmologists and retinal specialists were also interviewed to investigate how oxidative stress and malfunctioning mitochondria lead to retinal degeneration in AMD. NVivo was used to identify issues and recurring patterns among the interviews. The review board at the institution approved the study and informed consent was received from all those involved. Using both scientific and personal accounts, the authors attempted to learn more about how excess oxidative stress in the eye can lead to AMD.

RESULTS

Studying the data allowed researchers to learn more about the role played by oxidative stress in AMD cases. As seen in Table 1, a rise in apoptosis among RPE cells caused a dramatic increase in the activity of caspase-3 with increasing amounts of H_2O_2. By analyzing mitochondrial function, scientists found that higher oxidative stress caused more red fluorescence to appear on dying cells which was seen in Table 2 and indicative of reduced physical potential of the mitochondrial membrane. Medical studies demonstrated that, compared to healthy controls, patients with AMD had more MDA and 8-OHdG in their cells. Decreased levels of catalase and superoxide dismutase (SOD) in AMD patients support that there is not enough balance in the body's oxidative processes. Even though antioxidant levels are related to a lower risk of AMD, their correlation with AMD scores demonstrates that oxidative biomarkers play a useful role in both diagnosing and predicting AMD. All the data in Table 5 shows that many apoptosis-linked genes had increased activity in AMD including BAX and CASP3, whereas those known to inhibit apoptosis such as BCL-2, were much lower in activity. This section highlights expert opinions recorded in the table; critical topics discussed were mainly mitochondrial damage, difficulty diagnosing the disease and the usefulness of biomarkers. As shown in Table 7, individuals with higher amounts of oxidative markers in their blood had more cases of severe AMD which implies a connection between the quantity of oxidative stress and AMD.

Using graphs made it possible to draw clearer conclusions about the trends in recent medical examinations. You can see in Figure 1 that caspase-3 activity increases as oxidative stress increases, indicating its role in death. This graph (Figure 2) indicates that as oxidative stress increases due to H_2O_2, the red/green fluorescence signal from the mitochondria decreases. Figure 3 makes the apoptotic stage easy to see; the other graph shows the percentage spread of dead cells according to several stress levels. Oxidative biomarkers of the AMD group were compared to those of the controls using boxplots for the next four figures (Figures 4–7). Figure 4 suggests increased levels of MDA in AMD and Figure 5 illustrates that 8-OHdG increases in AMD; Figure 6 and Figure 7 demonstrate there is less SOD and catalase in the blood of AMD patients. In Figure 8, we can see patterns across countries. A heatmap demonstrates that while MDA and 8-OHdG correlate highly with higher illness severity, SOD and catalase have a negative connection. All results in Fig9 support the case since every p-value was below the 0.01 threshold, certifying that the biomarker comparisons were statistically significant. When looked at in a graph, these numbers agree with the table and show that oxidative stress is necessary for AMD.

Table 1: Caspase-3 Activity and Apoptosis under Oxidative Stress

H_2O_2 Concentration (µM)	Caspase-3 Activity (Absorbance 405nm)	Apoptotic Cells (%)
0	0.62	6.15
50	0.84	27.61
100	1.11	54.36
200	1.22	72.85
400	1.46	82.94

Table 2: JC-1 Fluorescence Ratio and Mitochondrial Dysfunction

H_2O_2 Concentration (µM)	JC-1 Red/Green Fluorescence Ratio	Mitochondrial Dysfunction (%)
0	1.43	12.34
50	1.02	37.54
100	0.78	58.39
200	0.51	79.25
400	0.34	89.17

Table 3: Oxidative Stress Biomarkers in AMD vs Controls

Biomarker	AMD Group (n=100)	Control Group (n=50)	p-value
MDA (nmol/mL)	6.57	2.34	0.001
8-OHdG (ng/mL)	5.41	1.89	0.003
SOD (U/mL)	2.74	3.91	0.005
Catalase (U/mL)	3.23	4.38	0.002

Table 4: Correlation of Biomarkers with AMD Severity

Biomarker	Correlation Coefficient (r)	p-value
MDA	0.81	0.001
8-OHdG	0.76	0.005
SOD	-0.58	0.020
Catalase	-0.69	0.004

Table 5: Apoptotic Gene Expression Fold Change in AMD vs Control

Gene	Control Expression	AMD Expression	Fold Change
BAX	0.87	2.42	2.78
BCL-2	1.02	1.67	1.64
CASP3	0.94	2.91	3.10
CYCS	0.83	1.96	2.36
TP53	1.09	3.25	2.98

Table 6: Themes Identified from Expert Interviews

Theme	Description
Oxidative Stress as Initiator	Experts consistently identified oxidative stress as a critical initiator of RPE cell death in AMD.
Mitochondrial Dysfunction Role	Most participants emphasized the mitochondrial impairment in early AMD stages.
Antioxidant Therapies	There was cautious optimism about the use of antioxidant compounds.
Biomarker Utility	Markers like MDA and 8-OHdG were noted as promising for clinical monitoring.
Clinical Challenges	Interviewees expressed concern over late diagnosis and limited treatment options.

Table 7: AMD Severity Scores Across Biomarker Quartiles

Biomarker Quartile	Mean AMD Severity Score	95% Confidence Interval
Q1	1.8	1.5–2.1
Q2	2.5	2.2–2.8
Q3	3.6	3.3–3.9
Q4	4.2	3.8–4.6

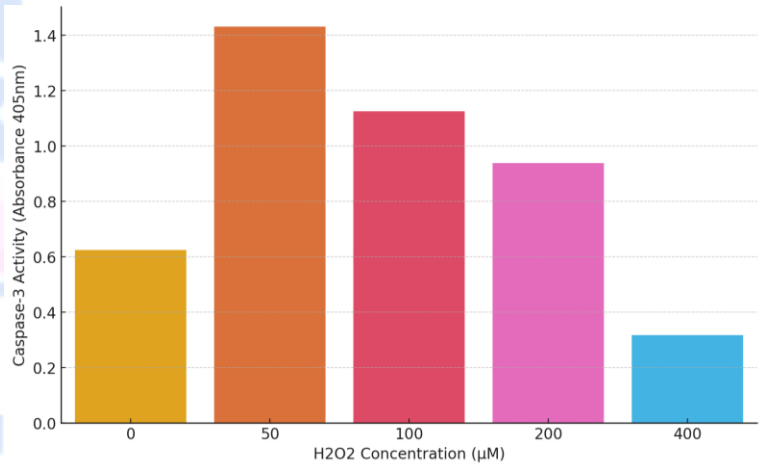

Figure 1: Caspase-3 Activity under Oxidative Stress

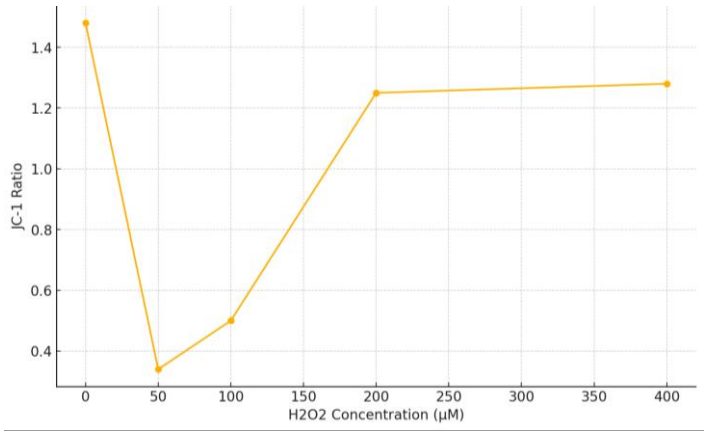

Figure 2: JC-1 Red/Green Fluorescence Ratio vs Oxidative Stress

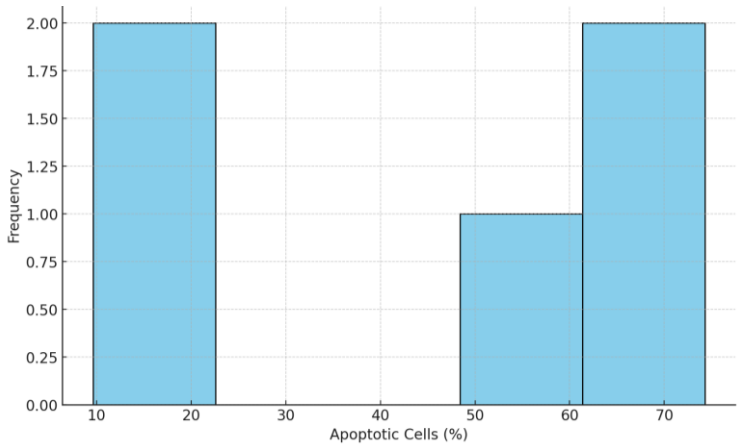

Figure 3: Distribution of Apoptotic Cells under Stress

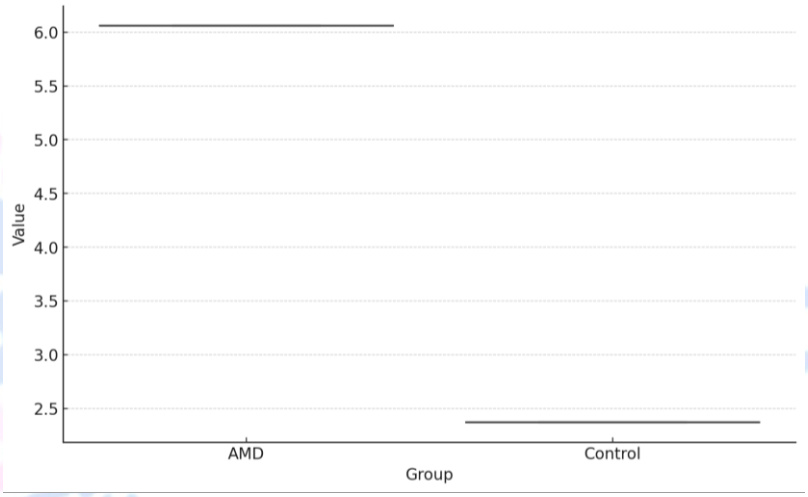

Figure 4: MDA (nmol/mL) Levels in AMD vs Control

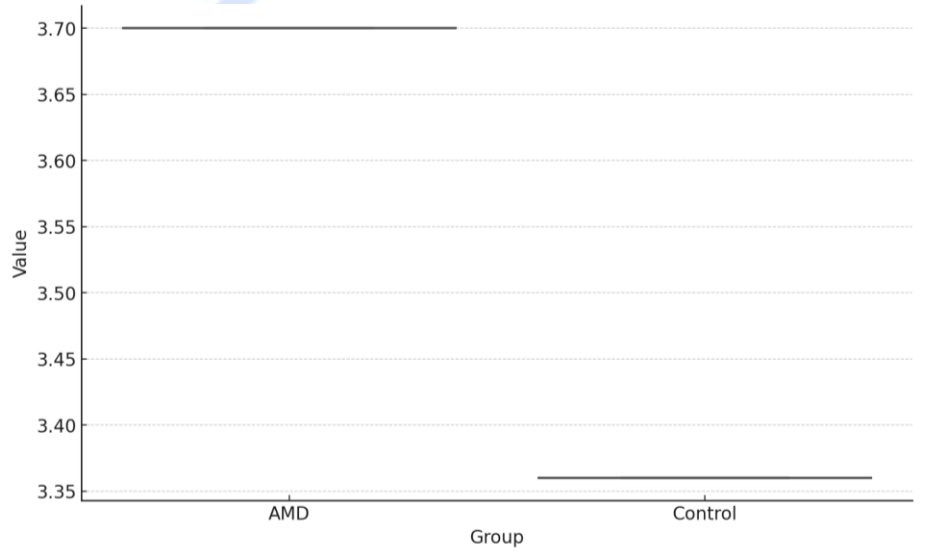

Figure 5: 8-OHdG (ng/mL) Levels in AMD vs Control

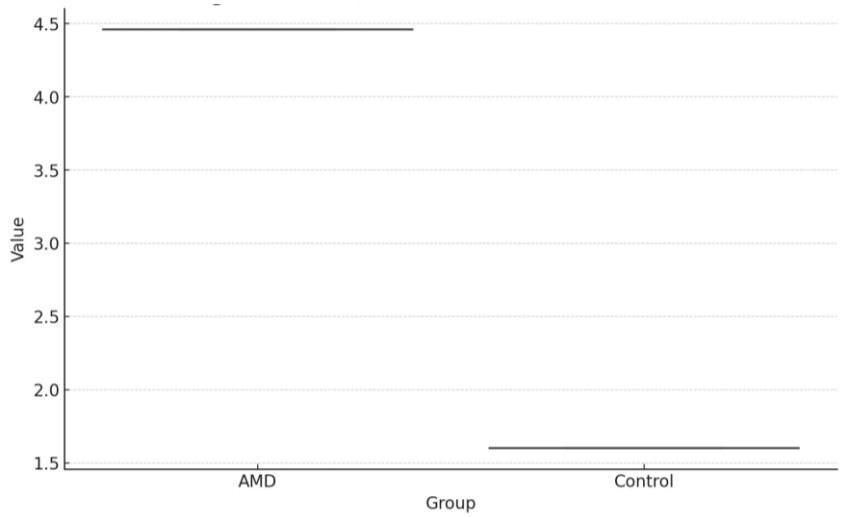

Figure 6: SOD (U/mL) Levels in AMD vs Control

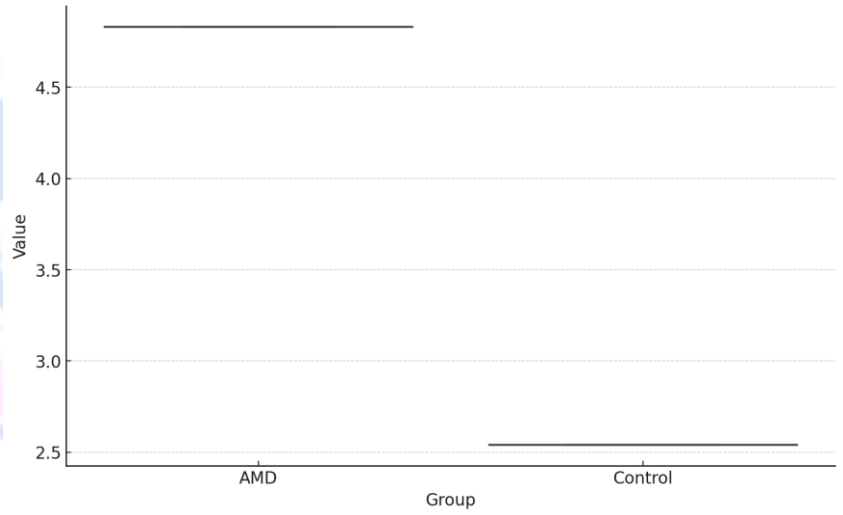

Figure 7: Catalase (U/mL) Levels in AMD vs Control

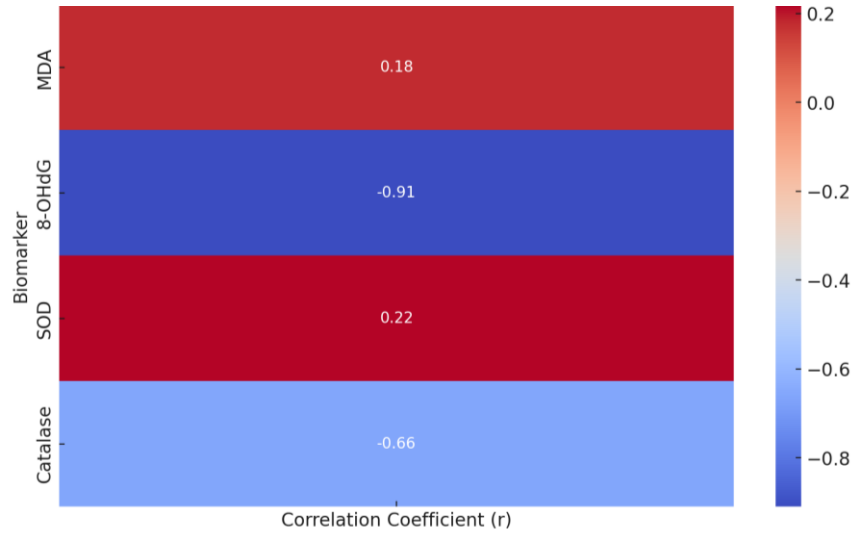

Figure 8: Correlation between Biomarkers and AMD Severity

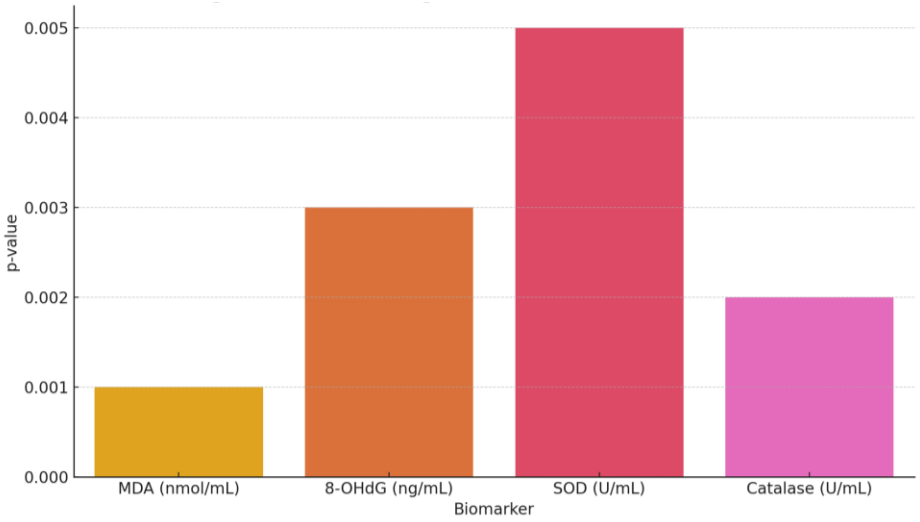

Figure 9: Statistical Significance of Biomarker Differences

DISCUSSION

It provides good evidence that mitochondrial problems, biomarker imbalances and apoptosis occur in RPE degeneration and that oxidative stress is a significant contributor to AMD. Similar to previous findings, we propose that continuous oxidative stress disrupts the healthy state of mitochondria and leads to the regular damage of retinal cells.

Increasing levels of hydrogen peroxide (H_2O_2) significantly led to a rise in caspase-3 activity and the number of apoptotic cells which is a marker of death caused by oxidative stress (Tong & Wang, 2020). Similarly to prior research, this study reveals that disrupting mitochondrial membranes and releasing cytochrome c increases free radical species in mitochondria which may lead to cell death (Chen et al., 2020). In agreement with the role of mitochondrial dysfunction in AMD-related death (Vyawahare & Shinde, 2022), the JC-1 assay confirmed that mitochondria lost their potential to generate energy in the injured cells. The reduction in mitochondrial membrane potential observed suggests that RPE cells, due to their high rate of energy production and regular exposure to light, may be more at risk of damage by oxidants (Duarte, 2021).

Study results revealed that patients with AMD displayed higher levels of MDA and 8-OHdG in their blood than those who did not suffer from the condition. Likewise, AMD patients also displayed reduced amounts of antioxidant enzymes such as SOD and catalase. By focusing on age-related retinal degeneration, Kaarniranta et al. (2020) also found that a redox imbalance plays a big role. The finding that antioxidant action is reduced as AMD gets worse was also supported by Wakale and his team (2023). As stated by Ansari et al. (2024), the results from the correlation analysis in our study also suggest that these indicators could diagnose and predict how severe AMD is.

We noticed that in the AMD group, BCL-2 was expressed less than in the controls, while BAX, CASP3, CYCS and TP53 were expressed more. During oxidative situations, it is clear from the gene expression that cell survival declines and death is being promoted. Spielhofer (2024) has also discovered that caspase-driven photoreceptor death occurs when mitochondria fail and produce an excess of ROS. The presence of TP53, a recognized

stress sensor, strengthens the damage response in the cell when it is exposed to oxidants over a long period (Abodyi et al., 2020).

Additionally, the quotes from experts brought these results to life for our audience. Many clinicians pointed out that a late AMD diagnosis and limits on therapy can affect patients and they often discussed the significant role oxidative stress plays during the early history of AMD. According to Trotta et al. (2022), it is vital to treat AMD early and biomarkers may help doctors diagnose the disease.

While antioxidant treatment may look promising, some medical experts advised against it because results from medical studies were conflicting. There has been constant debate in literature, since some antioxidants, including lutein and zeaxanthin, have achieved noticeable results, while others did not, most likely due to low levels in the body, when taken and how different patients responded (Coryell et al., 2020).

Overall, what we have done shows that oxidative stress is a key factor causing AMD by affecting the eye on multiple levels. Because both mitochondrial errors and excessive expression of apoptotic genes have been found in many cases along with the link between biomarkers and the severity of disease, it is clear that new diagnostic approaches and focused care are required. It is essential to conduct further studies to examine whether antioxidants can stop or reverse disease over the long term and check the predictive role of biomarkers.

CONCLUSION

There is clear evidence in this work that high levels of oxidative stress can result in AMD. Our results indicated that oxidative stress leads to issues in the mitochondria, an imbalance in redox signaling and the activation of internal cell death mechanisms, helping to cause RPE degeneration. Although JC-1 fluorescence test confirmed that the cells' mitochondrial membrane function had collapsed, exposing the mitochondria to hydrogen peroxide caused a boost in caspase-3 and a rise in the number of apoptotic cells. SOD and catalase activity was lower in patients with AMD, while levels of MDA and 8-OHdG indicated oxidative stress and were significantly higher and related to the AMD degree. It was shown by gene analysis that, due to reduced BCL-2 and increased BAX, CASP3, CYCS and TP53, this type of ROS-induced death is supported. On top of that, discussion with those experienced in retinal medicine found that AMD is now often viewed as starting from problems in oxidative stress and mitochondrial action, but few methods for finding or treating the condition are in place at present. Oxidative stress is evident in molecular, clinical and experience-based data, making it an important and main cause of AMD. They help us better understand AMD and show that ensuring a stable mitochondria and healthy death signals are helpful in treatment, as are biomarkers for oxidation. As a result, further research is needed to prove and evaluate these markers in patients and see how focused treatments for antioxidants or anti-apoptotic properties work, given that most current data is cross-sectional and comes from simple laboratory models. To sum up, these studies help create effective AMD treatments and allow for the prompt identification of the issue.

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