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INVESTIGATING GAMMA-H2AX LOCALISATION IN DNA DOUBLE-STRAND BREAKS IN THE CORNEA AND RETINA OF A RAT MODEL IN ALLOXAN-INDUCED DIABETES

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ABSTRACT

Diabetes is associated with increased oxidative stress, which can lead to cellular damage in various tissues, including the eyes. This study investigates the impact of alloxan-induced diabetes on DNA double-strand breaks (DSBs) in the cornea and retina of albino rats. Fifteen rats were divided into three groups: a control group, a diabetic group, and a diabetic group treated with glibenclamide. Over a 14-day period, blood glucose levels were monitored, followed by euthanization and tissue analysis. Histopathological examinations revealed significant structural alterations in the corneal and retinal layers, including epithelial degeneration and vacuolation in the retina. Despite these changes and the elevated levels of malondialdehyde (MDA) observed, immunohistochemical staining for γ H2AX, a marker of DNA DSBs, showed negative reactivity in the corneal and retinal tissues. These findings suggest that while oxidative stress contributes to histopathological changes in diabetic ocular tissues, DNA double-strand breaks may not be significantly induced in the early stages of diabetes. This study highlights the complexity of oxidative damage in diabetes, where DSBs may not be a primary mechanism in the initial phases of disease progression in the eye.

Keywords: Immunohistochemistry; Double Stranded Breaks; Malondiadehyde; Oxidative stress, Epithelial degeneration; vacuolation

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Introduction

High blood sugar levels can harm nearly every cell in the body, with the eyes being especially vulnerable. The cornea and retina are particularly affected by hyperglycemia. In diabetics, the cornea is exposed to glucose levels four times higher than those in non-diabetics, leading to corneal problems known as diabetic keratopathy, which affect 70% of diabetic patients. The retina is where most vision loss in diabetics occurs, with diabetic retinopathy being the leading cause of blindness in individuals over 50. (Lutty 2013). When blood sugar levels are high, several biological processes are activated, such as glucose auto-oxidation, the polyol pathway, prostanoid synthesis, and protein glycation. These processes increase the production of free radicals, causing oxidative stress, which is a key factor in the development of diabetes and its complications. (Ayad *et al.*, 2019).

Research has shown that diabetics experience significant oxidative stress and damage (Yıldız Dinçer *et al.*, 2002). Reactive oxygen species (ROS) easily oxidize polyunsaturated fatty acids, creating fatty acid radicals that, in turn, produce new free radicals by interacting with nearby lipid molecules. This lipid peroxidation results in reactive aldehydes, such as MDA, which can react with proteins and DNA, forming harmful adducts with these molecules (Niki *et al.*, 2005). Additionally, high blood sugar levels produce ROS, leading to oxidative stress in various tissues. This stress results in modifications to proteins, lipids, and DNA, potentially causing birth defects or cancer (Bodvarsdottir, 2005; Jee, 2005). Consequently, there is growing concern about the impact of DNA damage in chronic diseases.

DNA damage evaluation using γ -H2AX, a phosphorylated form of the histone variant H2AX, is a widely used method for assessing DNA double-strand breaks (DSBs) induced by various factors. γ -H2AX serves as an early marker of DSBs and can be triggered by both exogenous conditions, such as ionizing radiation (IR), smoking, heat, and drugs, as well as endogenous conditions, including physiological stress (Valente *et al.*, 2022; Watanya Trakarnphornsombat & Kimura, 2023)

Prior research has highlighted various ocular changes in diabetic patients, such as diminished corneal sensitivity and innervation, shifts in endothelial morphology and function, modifications to the corneal epithelial basement membrane, and an augmented corneal thickness (Shih *et al.*, 2017). Changes in the epithelial basement membrane, inadequate tear production, and neuropathy-related nerve loss have all been associated with abnormalities in the ocular surface (Cousen *et al.*, 2007; Azar *et al.*, 1992). These structural changes are likely to negatively impact the corneal epithelium.

Furthermore, despite its rapid turnover, prolonged hyperglycemia can directly affect the epithelium by generating reactive oxidative species and impairing cellular function (Yin *et al.*, 2011)

Some studies reported an increase in total retinal layer thickness, likely due to retinal edema, a recognized morphological feature of diabetic retinopathy (Deguchi *et al.*, 2017; Lu *et al.*, 2012; Yu *et al.*, 2007), thinning of the Inner Plexiform layer (IPL) and Outer Nuclear Layer (ONL) (Aizu *et al.*, 2002; Zhang *et al.*, 2008), while several studies also documented a reduction in cells within the GCL (Kern *et al.*, 2010; Zeng *et al.*, 2000; Sadikan *et al.*, 2020). These findings suggest significant cellular and structural alterations in the retina due to STZ-induced diabetic conditions. According to Igodaro *et al.* (2002), 30% of diabetes research employs Alloxan as an inducing agent. However, its diabetogenic effect on DNA damage, specifically DNA double-strand breaks (DSBs), has not been adequately studied. This research aims to elucidate the impact of Alloxan-induced diabetes on DSBs.

Material and Methods

A total of 15 albino rats with weights ranging between 150-180g were used for the induction of experimental diabetes. The animals were gotten and kept under standard environmental conditions and had unrestricted contact to animal feed and water *ad libitum*. Cages were kept clean throughout the duration of the experiment. Animals were adapted for 14 days in the Animal House of the Department of Medical Laboratory Science, School of Basic Medical Sciences, Igbinedion University Okada, before the commencement of research. The animals were handled as approved by the Animal Ethics Committee, Igbinedion University Teaching Hospital Okada with number IUTH/R.23/VOL 1/13. Histological and immunological stainings were carried out at the department of Medical Laboratory Science, School of Basic Medical Science, College of Health Sciences, Igbinedion University Okada.

Experimental induction of diabetes

The animals were fasted overnight with free access to water and inducement of diabetes was done by a single intraperitoneal injection of freshly prepared alloxan solution (150 mg/kg) in 0.9% saline solution. Seventy-two (72) hours after the injection of alloxan, the blood glucose values of the alloxan-induced rats were assessed for the development of diabetes. The rats with hyperglycaemia having moderate diabetes of blood glucose level (above 200mg/dl) were considered as diabetic and were included in the study for different observations.

Experimental design

The animals were divided into 3 groups of 5 rats each and study was done for 14 days as follows:

Group I: Negative control rats on distilled water.

Group II: Alloxan-induced Diabetic positive rats extract

Group III: Alloxan-induced Diabetic positive rats given 5mg/kg/day of the blood glucose levels were measured and documented before induction, 72 hours after induction and at the end of 0, 1, 3, 5, 7, 24 and 7, 14 days of administration. The blood glucose level was measured in the experimental rats using the tail tipping method and a Finetest glucometer.

Termination of experiment

On the fifteenth (15th) day of the research, the animals were euthanized using ketamine. The eye samples obtained were randomly selected in pairs for biochemical assay evaluation and histological techniques. The samples for histological analysis were fixed in modified Davidson's fixative and 10% neutral buffered formalin for 6 hours and 32 hours, respectively

Histopathological Technique

The fixed tissues were dehydrated through changes of ascending grades of ethanol (two changes of 70% and 95% and three changes of absolute ethanol for a period of two hours each), cleared using two changes of xylene. The tissues were then infiltrated with two changes of molten paraffin wax. All the procedures were done using SLEE MTP Tissue Processor (Am (Nieder-Olm, Germany). The tissues were sectioned at five micrometres (5µm) placed on adhesive slides (Bancroft, Layton & Suvarna, 2019). The sectioned were stained with Haematoxylin and eosin for general histopathology evaluation and γ-H2AX polyclonal antibody for the localization of DNA double strands break.

Haematoxylin and eosin staining technique

The tissue sections were deparaffinised in xylene, hydrated in ethanol, and stained with Haematoxylin for 10 mins. Subsequently, the sections were differentiated in 1% acid alcohol, blued in water, and counterstained with 1% eosin for 3 mins. Following staining procedures, the tissues were rinsed, dehydrated in ethanol, cleared in xylene, mounted in DPX, and examined under a light microscope. (Bancroft *et al.*, 2019).

Immunohistochemical Detection Histone H2AX Phosphorylation

To detect DNA damage, tissue samples from each group was examined using γH2AX primary antibody (γH2AX; Elabscience, Wuhan, China).

The protocol involved deparaffinization of sections by incubating in two changes of xylene for 10 minutes, followed by hydration in graded alcohols (100%, 95%, 70%) for 5 minutes each. Antigen retrieval was achieved by incubating sections in 10 mM citrate buffer (pH 6.0) at 100°C for 60 minutes. Endogenous peroxidase activity was neutralized with a 3% H₂O₂-methanol solution, while non-specific reactions were blocked with 10% normal goat serum. Primary polyclonal antibody (γH2AX) was applied for 60 minutes, followed by incubation with Goat Anti-rabbit HRP conjugated secondary antibody (# ; Elabscience, Wuhan, China) for 30 minutes. Detection of the antigen-antibody reaction was performed using diaminobenzidine (DAB; Elabscience, Wuhan, China), followed by counterstaining with Harry's haematoxylin for 1 minute. Sections were rinsed in PBS and distilled water, dehydrated in ascending graded alcohol, cleared in xylene, and mounted with DPX.

Evaluation Lipid Peroxidation

Measurement of lipid peroxidation typically relies on Malondialdehyde (MDA) levels, with the methodology introduced by Buege and Aust in 1978 being a common approach. In this method, 0.1ml of the supernatant is combined with 2ml of TCA-TBA-HCl (tricarboxylic acid-thiobarbituric acid-hydrochloric acid) in a 1:1:1 ratio. The resulting mixture is then boiled at 100°C for 15 minutes and subsequently cooled prior to centrifugation at 3000rpm for 10 minutes. Following centrifugation, the resulting supernatant is extracted, and its absorbance is measured at 532nm against a blank. The activity level of MDA is determined using a molar extinction coefficient for the MDATBA-complex of $1.56 \times 10^5 \text{M}^{-1} \text{CM}^{-1}$.

Reduced Glutathione Determination

The tissue's reduced glutathione (GSH) content, representing non-protein sulfhydryls, was determined using the method outlined by Sedlak and Lindsay in 1968. Initially, 0.1ml of the homogenate was mixed with 10% trichloroacetic acid (TCA) and subjected to centrifugation. Subsequently, 1.0ml of the resulting supernatant was combined with 0.5ml of Ellman's reagent (containing 19.8mg of 5,5' dithiobisnitrobenzoic acid (DTNB) in 100ml of 0.1% sodium nitrate) and 3.0ml of phosphate buffer (0.2M, pH 8.0). The absorbance of the mixture was then measured at 412nm.

Table 1: The average Malondialdehyde and Glutathione level in the eye of Sprague dawley rat after experimentation

Variables	Groups	N	Mean±SD	F-value	P-value
MDA(μmol/mL/mg)	I	3	2.99±0.89	0.49	0.63
	II	3	3.57±1.40		
	III	3	3.78±0.57		
GSH (μmol/mL/mg)	I	3	31.69±1.02	1.24	0.35
	II	3	29.52±2.49		
	III	3	31.28±1.53		

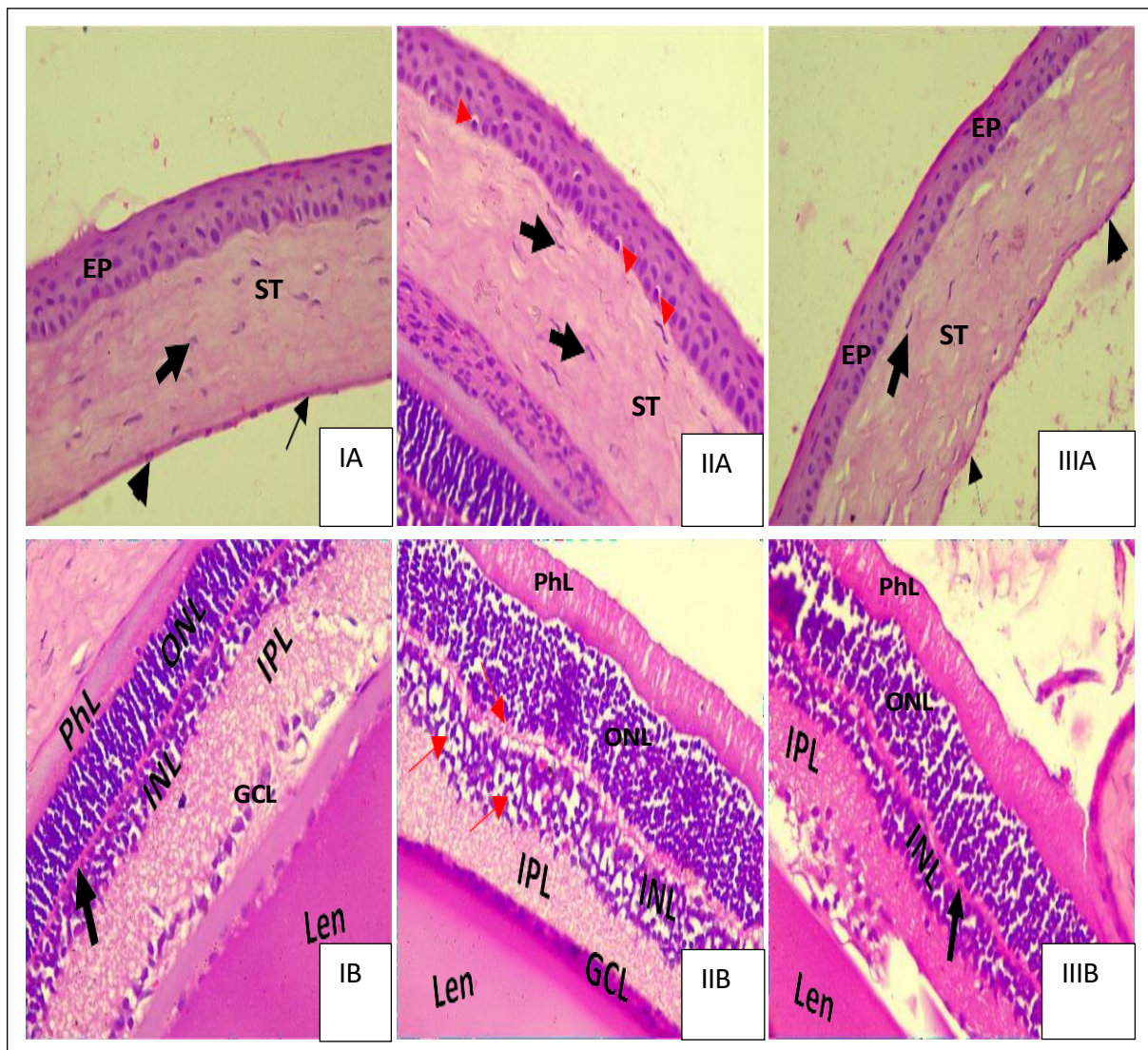


Figure 1: Photomicrograph of the Cornea (IA-III A) and retina (IB-III B) sections.

(IA-III A): Corneal sections displayed the epithelium (EP), stroma (ST), keratocytes (thick black arrow), endothelium (arrowhead), and Descemet’s membrane (thin arrow). Group I (IA) shows normal epithelium and stromal structure. Group II (II A) shows a perinuclear halo (thin red arrow) and contracted keratocyte nuclei (thick black arrow). Group III (III A) shows normal epithelial

structure. (IB-III B): Retinal sections showed the photoreceptor layer (PhL), outer nuclear layer (ONL), outer plexiform layer (OPL) (arrow), inner nuclear layer (INL), inner plexiform layer (IPL), and ganglion cell layer (GCL). Group I (IB) showed normal retinal structure. Group II (IIB) exhibits degeneration and vacuolation (red arrows) in the INL and OPL. Group III (III B) shows normal retinal architecture.

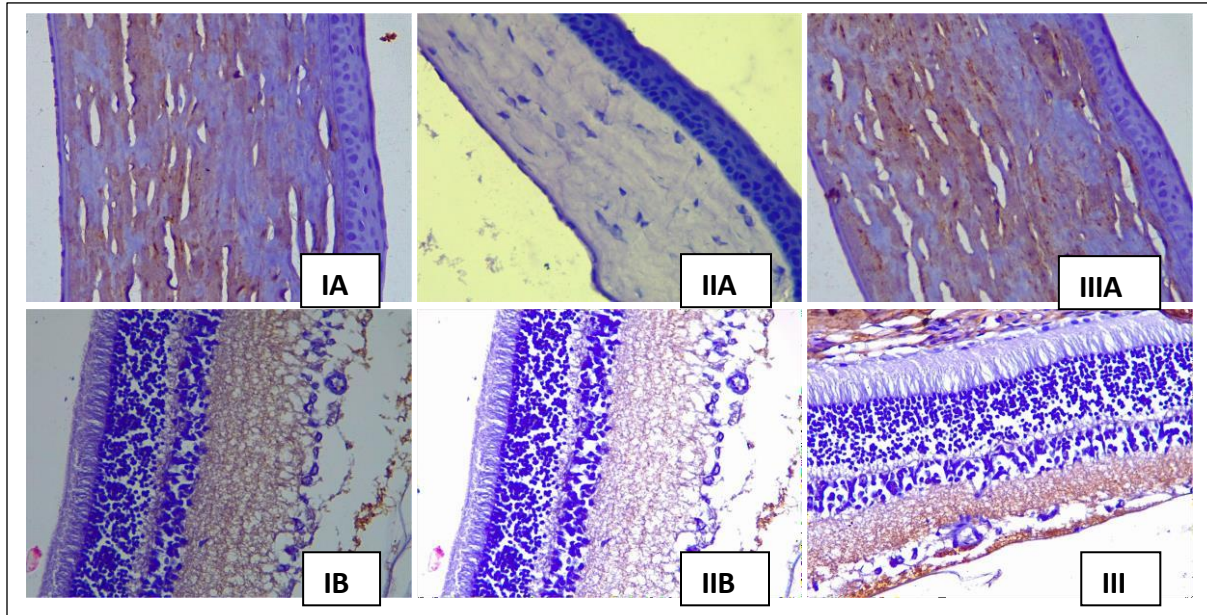


Figure 2: Photomicrographs of Corneal (IA-III A) and Retinal (IB-III B) Sections with γH2AX Staining for DNA Double-Strand Break Localization.

(IA-III A): The epithelial and stromal layers of the cornea exhibit negative reactivity for DNA double-strand breaks as indicated by γH2AX staining.

(IB-III B): The retinal epithelium in alloxan-induced rats also shows negative reactivity for DNA double-strand breaks with γH2AX staining.

Results

Malondialdehyde and Antioxidants in the eye tissue

Histopathological changes and Immunohistochemical reactivity in the corneal and retina

In the anterior epithelium of the cornea in alloxan-induced rats (Group II), a perinuclear halo was observed, contrasting with the intact epithelium seen in the control group (Group I). The keratocyte nuclei in Group I were primarily vesicular, whereas in the alloxan-induced

The analysis of lipid peroxidation and glutathione levels among the groups revealed no statistically significant differences ($p > 0.05$) in their mean difference. However, a closer examination of the data indicated that the diabetic-induced group (3.57 ± 1.40) and the diabetic-induced group treated with glibenclamide (3.78 ± 0.57) exhibited elevated levels of lipid peroxidation compared to the control group (2.99 ± 0.89). Additionally, the levels of glutathione in both the diabetic-induced only group (29.52 ± 2.49) and the diabetic-induced group treated with glibenclamide group (31.28 ± 1.53) were lower compared to the control group (31.69 ± 1.02).

groups (II & III), the nuclei were predominantly contracted and pyknotic. The structural and cellular architecture of the retinal layers in the control group appeared normal. In contrast, the alloxan-induced group exhibited epithelial disorientation and degeneration in the inner nuclear layer and outer plexiform layer (Figure 1e). The localization of DNA double-strand breaks, assessed using γH2AX primary antibody (Elabscience, Wuhan,

China), showed negative reactivity across the layers of both the cornea and retina.

Discussion

Our study aimed to elucidate the impact of Aloxan-induced diabetics on retinal and corneal histopathology, focusing on changes in epithelial cells, endothelial cells, and overall tissue architecture in diabetic-induced rats and those treated with glibenclamide.

Analysis of lipid peroxidation revealed elevated levels of MDA in both the diabetic-induced group and the glibenclamide-treated group compared to the control group, although the differences were not statistically significant. This suggests an increased oxidative burden in diabetic conditions, which may induce epithelial degeneration in the eye tissue. Moreover, the decrease in glutathione levels in diabetic-induced rats, was further lowered in the glibenclamide-treated group, indicates compromised antioxidant defense mechanisms, potentially exacerbating oxidative damage.

Histopathological changes

In this study microscopic examination of corneal histology in diabetic-induced rats revealed decreased endothelial cells and a focal perinuclear space of the epithelium, the outcome that agrees with a study conducted by Siribunkum et al., 2001 and Kim et al., 2010. There was no difference in the thickness of the cornea of the control group and the induced group. This result was in congruent with study conducted by Yin et al., 2011 where they reported that there were no notable alterations observed in the corneal thickness, but our report differs on the histopathology of the epithelium, where we observed a degenerated epithelium with evidence of cytoplasmic vacuolation.

Similarly, retinal histopathology demonstrated alterations in retinal layers, depicting epithelial degeneration of the inner nuclear layer and outer plexiform layer. These changes highlight the structural damage inflicted by oxidative stress on both corneal and retinal tissues in diabetic conditions.

DNA Damage Assessment:

Despite the observed structural alterations in corneal and retinal layers, assessment of DNA double-strand breaks using γ H2AX staining showed negative reactivity, suggesting the absence of extensive DNA damage in our experimental conditions. This indicates that while oxidative stress contributes to tissue injury in diabetics, DNA double strands break may not be a primary mechanism involved in the early stages assessed in our study. A study conducted by *shi et al.*, 2019 report the presence of numerous nuclear γ H2AX foci within insulin-positive cells of islets from 16-week-old mice, but not in

those from 10-week-old mice, indicates an increased occurrence of double-strand breaks (DSBs) specifically within β -cells of mice with a more chronic diabetic condition. This could explain the reason for the negative demonstration of DNA double strand break by γ H2AX antibody. The outcome of this study was also in discordant with study conducted by Kim et al., 2010, where there was a notable evident of oxidative induced DNA strands breaks by using 8-OHdG (8-hydroxy-2'-deoxyguanosine) primary antibody for localization of single strand break (SSBs). While diabetics-induced oxidative stress can lead to both single-strand breaks (SSBs) and double-strand breaks (DSBs) in DNA, the majority of DNA damage induced by ROS is in the form of SSBs. This is because SSBs are more common (2000 to 1 ratio) and are generated through the direct action of ROS on DNA molecules. In contrast, DSBs are less frequent and often require more severe or prolonged oxidative stress conditions to occur (Sharma et al., 2016)

Conclusion and Recommendation

The negative expression of γ H2AX confirms that there are no significant DNA breaks at this stage. Its negative result means that early diabetic eye damage is mainly due to stress and cellular problems not severe DNA damage. These results suggest that DNA breaks might happen later in a diabetic individual. So it is crucial to act to limit oxidative damage, in diabetes. The findings also highlight the need to focus on preventing stress in the early stages of diabetic ocular injury. Early intervention can help prevent long-term damage and Future studies should employ longer experimental periods beyond 14 days to capture late-stage diabetic effects, as DNA double-strand breaks (DSBs) and γ H2AX expression may occur only under prolonged or chronic oxidative stress conditions.

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