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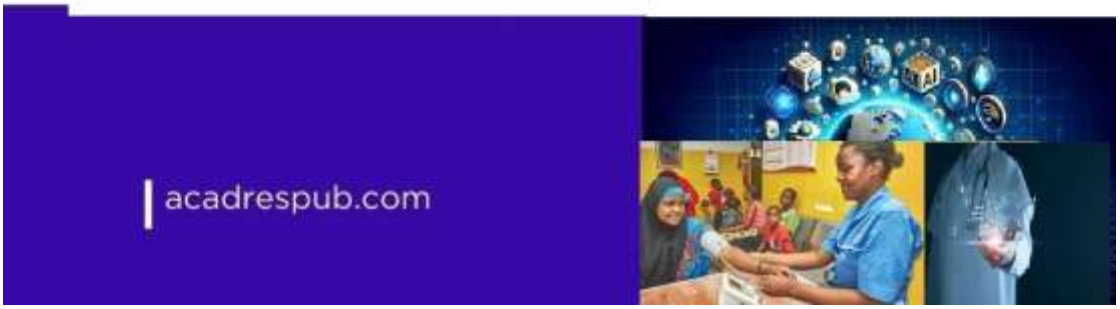

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HISTOPATHOLOGICAL CHARACTERIZATION OF ALLOXAN-INDUCED DIABETES ON THE PROSTATE GLAND: A COMPARATIVE STUDY OF STRUCTURAL DEGENERATION AND PHARMACOLOGICAL INTERVENTION IN SPRAGUE-DAWLEY RATS

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ABSTRACT

Background: Diabetes mellitus (DM) remains a global health priority, with increasing evidence suggesting its role in systemic organ dysfunction, including the male reproductive system. While the relationship between DM and prostate neoplasia remains debated, the immediate structural impact of hyperglycemia on prostate tissue requires further elucidation. Methods: This study utilized thirty Sprague-Dawley rats divided into three cohorts: Negative Control (distilled water), Diabetic Untreated (alloxan-induced, 150 mg/kg), and Diabetic Treated (glibenclamide, 5 mg/kg/day). Histopathological assessments were conducted via Haematoxylin and Eosin (H&E) staining following a 14-day experimental period.

Results: Untreated diabetic rats exhibited significantly elevated fasting blood glucose levels ($p < 0.001$) compared to control and treated groups. Histological analysis revealed marked regressive changes in the untreated group, including the absence of luminal eosinophilic secretions and a significant reduction in papillary epithelial infoldings. In contrast, glibenclamide treatment partially preserved acinar architecture and secretion profiles.

Conclusion: Short-term alloxan-induced hyperglycemia induces rapid structural adaptation and physiological impairment in the prostate, underscoring the need for early glycemic management to mitigate reproductive organ damage.

Keywords: Alloxan-induced diabetes, Prostate histopathology, Acinar architecture, Oxidative stress, Male reproductive dysfunction,

Introduction

Diabetes mellitus (DM) represents a burgeoning global health crisis, with its prevalence accelerating most notably within developing and newly industrialized nations (Lin et al., 2020). As a chronic metabolic disorder, DM is characterized by persistent hyperglycemia arising from impaired insulin secretion, diminished insulin sensitivity, or both. This state precipitates systemic metabolic disruptions in the processing of carbohydrates, proteins, and lipids, ultimately leading to multi-organ dysfunction (Aga et al., 2020). The clinical trajectory of the disease is marked by severe, often irreversible complications, including nephropathy, retinopathy, vasculopathy, and neuropathy. Furthermore, its pathological reach extends to cardiovascular disease and a broad spectrum of hepatic morbidities, ranging from non-alcoholic fatty liver disease (NAFLD) and abnormal glycogen accumulation to advanced cirrhosis and hepatocellular carcinoma (Cusi et al., 2025; Mantovani et al., 2020).

Beyond these classical complications, DM significantly compromises the male reproductive system. Proper glucose metabolism is a fundamental requirement for spermatogenesis, providing the energetic basis for cellular function and the maintenance of sperm motility and fertilizing capacity (Zu-bin et al., 2021). Both type 1 and type 2 diabetes whether clinical or experimentally induced adversely impact male fertility by degrading sperm DNA integrity and altering seminal plasma composition. These disruptions extend to the epigenetic level, where DM interferes with critical processes such as DNA methylation, histone modification, nucleosome remodeling, and the regulatory roles of noncoding RNAs (Lismer & Kimmins, 2023; Rotondo et al., 2021). The prostate gland, a critical accessory organ, is particularly susceptible to the metabolic shifts associated with DM. Research by Zhao et al. (2023) and Daryabor et al. (2020) demonstrated significant alterations in cellular proliferation within the prostate following alloxan-induced diabetes, indicating that hyperglycemia triggers immediate and lasting shifts in cell maturation and apoptosis. Histological investigations by Erdoğan et al. (2022) further reveal that diabetes disrupts the differentiation and development of the prostatic ventral lobe. Microscopic evidence suggests glandular atrophy, characterized by the transformation of acinar cells into a diminished cuboidal morphology and a reduction in secretory granules, which facilitates an expansion of the interstitial space (Joseph et al., 2021; Kang et al., 2021).

These regressive alterations are corroborated by histomorphometric analyses showing significant reductions in tubular diameter, volume, and the surface density of the acinar epithelium and lumen (Sanches et al., 2020). Furthermore, streptozotocin (STZ)-induced hyperglycemia has been shown to impair the biochemical profile of the ventral prostate, leading to a down-regulation of androgen and estrogen receptors and a decline in glucose oxidation (Bakhshwin et al., 2022). These metabolic deficiencies are often accompanied by a significant reduction in the activities of essential enzymes, including alkaline and acid phosphatases (Eid & Abdel-Naim, 2020).

Materials and Methods

Experimental animals

A total of 30 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, Faculty of Basic Medical Medical science, Igbinedion University, before the commencement of research.

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 the various treatment combinations.

Experimental design

The animals were divided into 3 groups of 10 rats each and study was done for 14 days as follows:

Group I: Negative control rats on distilled water.
Group II: Alloxan-induced Diabetic Untreated rats extract
Group III: Alloxan-induced Diabetic Treated rats given 5mg/kg/day of glibenclamide
The body weight gain/loss and fasting blood glucose values of all the rats were documented at regular intervals during the experimental period. 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 (15) day of the research, the animals were sacrificed by the chloroform inhalation method. The prostate was removed and fixed in 10% neutral buffered formalin for histological analysis.

Histopathological tissue processing

The fixed tissues were dehydrated through changes of graded alcohols. This was done to remove water inherent in tissues as follows; two changes of 70% and 95% alcohol for a period of two hours each, three changes of absolute alcohol for a period of two hours (2hrs). Dehydrated tissues were cleared using xylene (2 changes). Tissues were impregnated with two changes of paraffin wax all the procedures done in Slee MTP Automatic Carousel Spin tissue processor (Nieder-Olm, Germany) set at the temperature of 60^{o}C at two hours (2 hours) each to enable embedding. After infiltration tissues cassette were transferred from the final wax bath. The tissues were taken out of the cassette placed in proper anatomical orientation inside the mould filled with molten wax, and covered with the corresponding cassette. The embedded tissue blocks were allowed to solidify. The paraffin tissue blocks were trimmed, and the trimmed surfaced were placed on ice bar for cooling to enhance the plasticity and tissue-paraffin homogeneity for proper sectioning. The tissues were sectioned at five micronmetres (5µm), and ribbons were gently picked with Carmel brush and dropped in a Floating water bath at 60^{o}C to enable ribbons float, expand and flatten out. Slides were rubbed with thymol containing egg albumen, and gently dipped into the bath to pick up the flattened-out tissue ribbons (Bancroft, 2019).

Staining technique

Staining technique employed in the course of the research was Haematoxylin and Eosin stain

Heamatoxylin and eosin staining technique

The tissue sections were taken to water by deparaffinising in two changes of xylene. They were hydrated by passing through descending graded series of ethanol and rinsed in water before staining in Haematoxylin for ten minutes (10 mins). The sections were rinsed and differentiate in 1% acid alcohol and blued in running water until they appear sky blue. The blued sections were counterstained in 1% eosin solution, for three minutes (3 mins). The tissues were rinsed properly in water and dehydrated in ascending graded ethanol, cleared in xylene, mounted in DPX with coverslips and viewed under a light microscope (Bancroft *et al.,* 2019).

Photomicrography

The light microscope (Leica DM750) Leica Microsystems, Wetzlar, Germany was used for microscopy.
Statistical analysis

The mean and standard deviation of the data were calculated. One-way ANOVA was used, followed by tukey for post-hoc analysis for mean difference analysis between groups. The software IBM SPSS ver.25.0 (SPSS Inc., Chicago, Illinois, USA) was used. p-value of less than or equal to 0.05 was termed statistically significant difference.

Result

Fasting Blood Glucose Measurements

The average blood glucose level to determine and confirm the diabetic status of the rats across the groups were shown in group table 1. The result showed that glucose level of the untreated

group was statistically significantly higher ($p<0.001$) than both negative and treated groups from 5-hour measurement to the 14th day of the experiment. There was no statistically significant different in the glucose level of the treated and the untreated group on the first measurement (before drug)

Table 1: showing the average blood glucose measure across the groups

Durations	Groups	No	Mean±SD mmol/L	F-value	p-value
Before drug	Negative Control	5	6.6 ± 0.28^{a}	45.94	<0.001
	Diabetic Untreated	3	19.31 ± 2.07^{b}		
	Diabetic treated	4	19.79 ± 2.59^{b}		
Day 5	Negative Control	5	5.88 ± 0.49^{a}	702.24	<0.001
	Diabetic Untreated	3	17.82 ± 0.23^{c}		
	Diabetic treated	4	11.63 ± 0.41^{b}		
Day 7	Negative Control	5	6.31 ± 0.61^{a}	125.47	<0.001
	Diabetic Untreated	3	18.63 ± 0.81^{c}		
	Diabetic treated	4	9.07 ± 0.86^{b}		
Day 14	Negative Control	4	5.92 ± 0.17^{a}	807.72	<0.001
	Diabetic Untreated	3	16.93 ± 0.39^{b}		
	Diabetic treated	5	6.22 ± 0.51^{a}		

Value with same superscript (a, b and c,) were not statistically significantly different

Histopathological Changes in the Prostate Tissue across the Groups by Haematoxylin and Eosin Stained Slides

The histological changes in the prostate of the rats as demonstrated by Haematoxylin and eosin technique were shown in Plate 1-3. The prostate section of the negative control group (plate 1) showed normal prostate tissue histology with feature of normal acini with its eosinophilic secretions and abundant epithelia infoldings. The prostate of the untreated diabetic group (plate 2) showed acini with few to absence of short epithelial infoldings and no eosinophilic secretions seen in the acini. The prostate section of diabetic treated group (Plate 3) showed acini with eosinophilic secretion and abundant epithelial infoldings. The prostate section of the untreated diabetic and treated diabetic group showed wide interglandular space with thin fibre of fibromuscular stroma.

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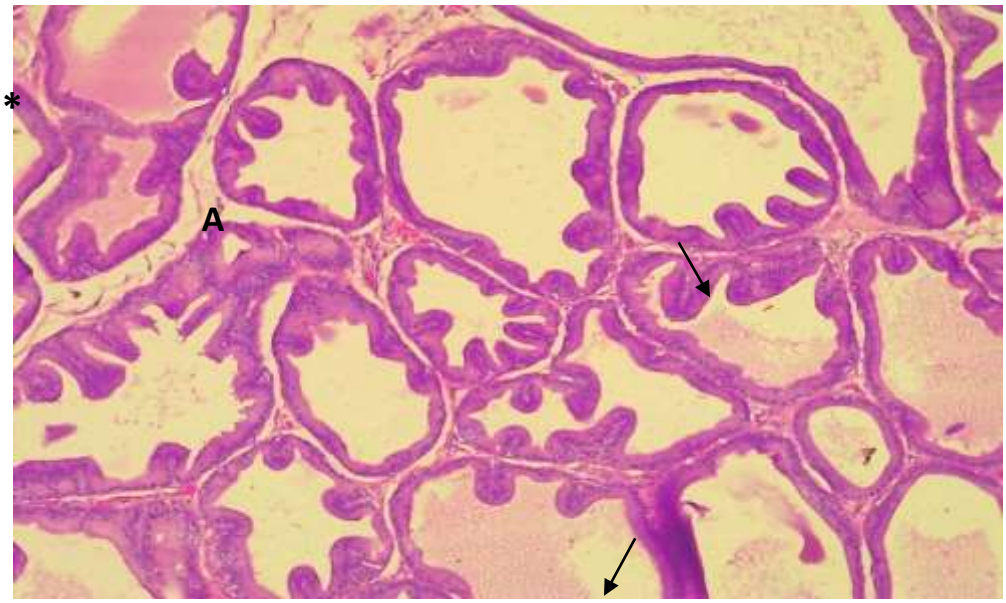

Plate 1: Photomicrograph of the Prostate of Negative Control goup (Group I): It showed acini (A) lined with cuboidal epithelial, with abundant papillary epithelial infoldings (arrow). Some acini showed luminal eosinophilic secretions (asterisk). No lesion seen. H&E stain, x100 magnification.

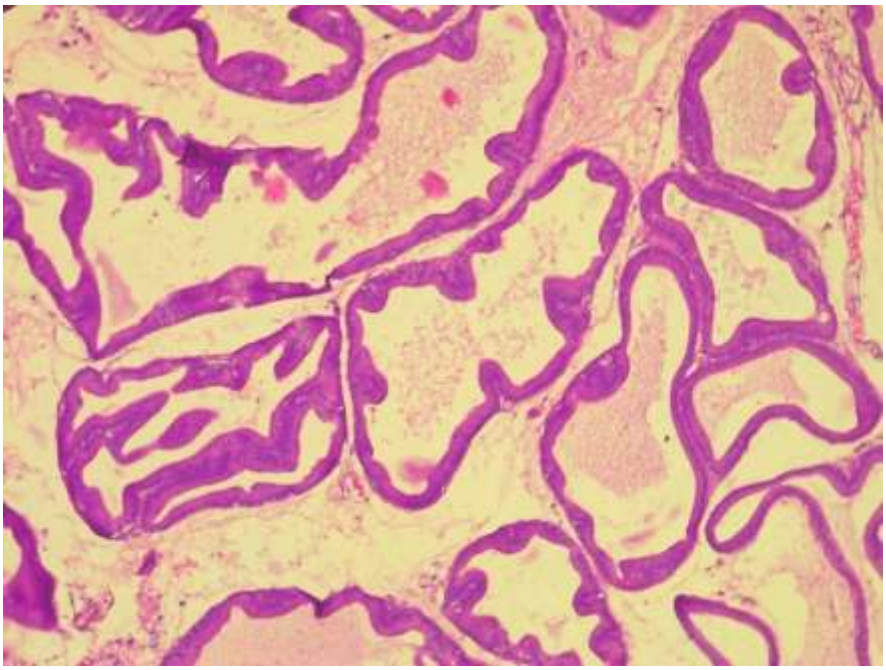

Plate 2: Photomicrograph of the Prostate of Test group (Group II) : It showed acini (A) lined with cuboidal epithelial, with occasional short papillary epithelial infoldings (arrow). Absence of luminal secretion. The interglandular space were widened with thin fibre of fibromuscular stroma compare to control. H&E stain, x100 magnification.

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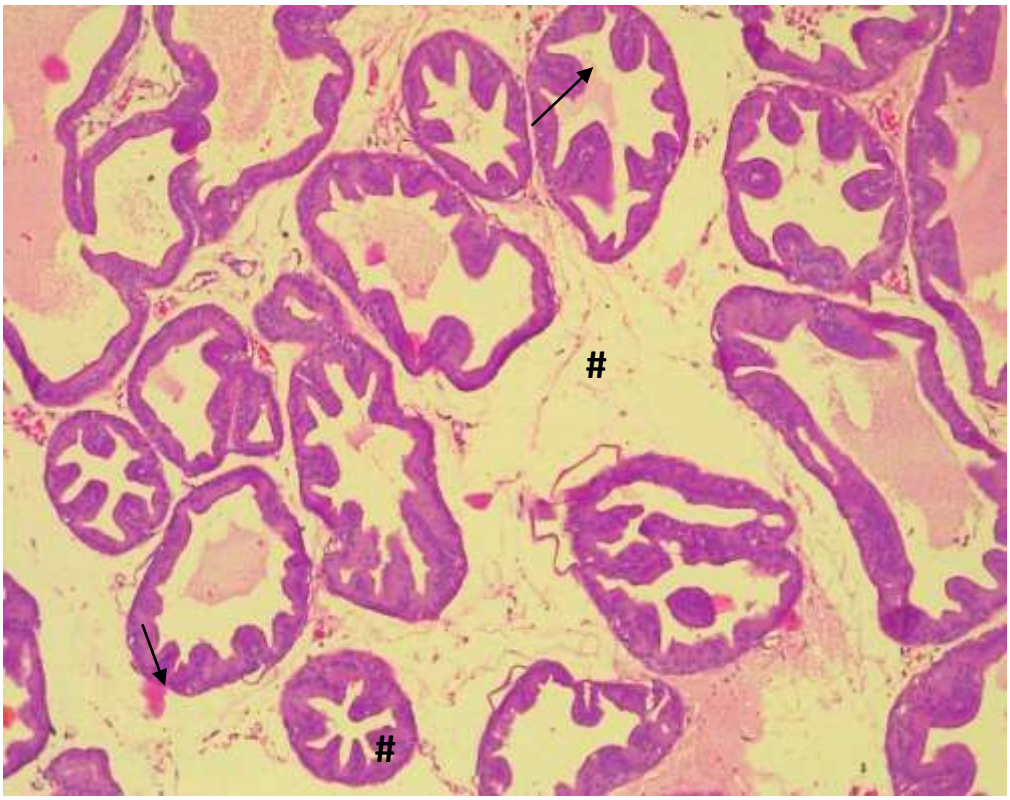

Plate 3: Photomicrograph of the Prostate of Positive control group (Group III): It showed acini (A) lined with cuboidal epithelial, with short papillary epithelial infoldings (arrow). some acini showed luminal eosinophilic secretions (asterisk). The spaces between glands were widened with thin fibre of fibromuscular stroma (#). H&E stain, x100 magnification.

Discussion

The present investigation elucidates the acute impact of alloxan-induced diabetes on the prostatic architecture of Sprague-Dawley rats. Within a 14-day experimental window, the most significant observation was that hyperglycemia while not inducing immediate inflammatory or neoplastic transformations instigated profound regressive structural adaptations. These findings suggest that the diabetic state independently drives the morphological deterioration of the prostate gland. This atrophic progression is likely linked to the hypoinsulinemic state and the subsequent decline in systemic testosterone levels, both of which are fundamental to sustaining epithelial cell proliferation and maintaining normal glandular secretory activity (Guo et al., 2022).

A hallmark observation in this study was the widening of interglandular spaces alongside a marked reduction in the fibromuscular stroma in both the untreated and treated diabetic cohorts (Ebrahim et al., 2021). Such stromal thinning indicates that the prostate's supportive architectural framework is acutely sensitive to metabolic fluctuations. This reduction in the fibromuscular component may stem from accelerated protein catabolism or impaired collagen synthesis—pathological hallmarks of uncontrolled diabetes. These alterations demonstrate that DM inherently predisposes the prostate to structural instability, even in the absence of chronic inflammatory markers (Defeudis et al., 2021; Vidal et al., 2021).

The total absence of luminal eosinophilic secretions in untreated diabetic rats underscores a critical physiological impairment (Feng et al., 2022). Given that the primary function of the prostate is the synthesis of these secretions—essential for the viability and motility of spermatozoa—their cessation suggests that diabetes-induced hyperglycemia severely disrupts the secretory machinery of the acinar cells. Notably, the partial restoration of these

secretions following glibenclamide treatment identifies glycemic control as a primary determinant of prostatic functional integrity (Huang et al., 2024; Zhong et al., 2021).

The significant reduction in the frequency and length of papillary epithelial infoldings in the untreated diabetic group further highlights the regressive trajectory of the disease (Erdoğan et al., 2022). As these infoldings normally maximize the surface area for secretory output, their loss reflects a state of advanced glandular atrophy (Fukui et al., 2023). This structural adaptation suggests a "down-regulation" of the prostate's metabolic activity in response to systemic insulin deficiency and glucose toxicity. Elucidating the cellular mechanisms behind this reduction, such as disrupted androgen receptor signaling or localized apoptotic pathways, may provide deeper insights into the prostate's adaptive response to metabolic stress (Ahmad et al., 2021; Cannarella et al., 2021).

Despite the clear degenerative changes observed, no evidence of neoplastic progression was detected. This aligns with recent epidemiological data suggesting a decreased risk of prostate cancer among certain diabetic populations (Guo et al., 2022; Al-Mrabeh et al., 2020). The findings of glandular atrophy and depleted secretory granules support the hypothesis that the diabetic milieu may be inherently inhibitory to prostatic cellular proliferation (Bernal-Soriano et al., 2020; Lin et al., 2020; Pagano et al., 2024). The transition from high-columnar secretory cells to a less active, diminished morphology may, paradoxically, serve as a barrier against oncogenic transformation, albeit at the significant cost of reproductive function (Brennen et al., 2021; Crowley et al., 2020).

Conclusion

In conclusion, the 14-day induction of alloxan-induced diabetes resulted in rapid and measurable structural decay of the prostate gland. The depletion of stromal density, the reduction in epithelial infoldings, and the cessation of luminal secretions collectively characterize the "diabetic prostate." These findings underscore the clinical necessity for early therapeutic intervention to mitigate permanent accessory gland dysfunction in diabetic subjects.

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