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Microanatomical and Biochemical Influences of Lycopene on The Renal Status in Streptozotocin-Induced Diabetic Wistar Rats

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ABSTRACT

Introduction: Chronic hyperglycemia is pathognomonic of diabetes mellitus, however, this is not responsible for many of the morbidities. Drugs fairly readily regulate blood glucose, while this does not prevent long-term complications. Even with euglycemic control, damage persists in virtually every organ system. In this study, the histoarchitectural and biochemical layout of the kidneys of diabetic Wistar rats were observed to see if lycopene had any positive effects. **Objective:** To assess the histoarchitecture and biochemical parameters of the kidney of diabetic Wistar rats after intervention with lycopene, as well as to determine whether lycopene is more productive as a curative than a prophylactic agent. **Material and Method:** The rats were grouped into five sects (A, B, C, D, and E) of seven animals per group. Group A was the normal control that was given 2 ml/kg/day of citrate buffer per oral for 30 days. Group B was given 60 mg/kg of streptozotocin. Group C was treated with lycopene (20 mg/kg/day p.o.) for 30 days after diabetes induction. Group D was the group pretreated with lycopene (20 mg/kg/day) orally for 30 days. Group E was treated with insulin (5 IU/kg) for 30 days after diabetic induction. The rats were sacrificed under ketamine anesthesia at the end of the experiment. **Result:** The kidney's histological outline showed that the urinary space was much bigger in the diabetic group that received no treatment (B) and in the test groups (C and D) than it was in the healthy control group (A). It was observed that the blood glucose levels in the test groups significantly reduced ($p<0.05$) below the diabetic range. There was a significantly higher level ($p<0.05$) of antioxidants in the curative group than in the prophylactic group. **Conclusion:** This study showed that lycopene conferred a better ameliorative effect when used prophylactically than curatively.

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Highlights

1. The kidney's histoarchitecture revealed significant derangements in its parenchyma, such as widening of the urinary space and loss or effacement of podocytes and mesangial cells, which were restored to near-normal shapes in the treated groups.
2. In this study, biochemical parameters like blood glucose, insulin, and antioxidant levels were found to be different in the diabetic groups. However, these biochemical parameters returned to normal after the intervening agent was given.
3. The intervening agent was found to be a better prophylactic than curative therapy.

BACKGROUND

Diabetes mellitus (DM) comprises many disorders characterized by hyperglycemia; hence, it is described as a disorder of metabolism, manifested by chronic hyperglycemia accompanying variable dysfunction in carbohydrates, proteins, and lipid metabolism. It is possibly one of the earliest diseases known to man (World Health Organization, 2023). It was first reported in Egyptian literature approximately 3000 years ago (Ahmed, 2002).

The aetiopathomechanism of diabetes mellitus (DM) can vary significantly, but it always involves defects in either insulin secretion, insulin action, or both in the pathogenesis of the disease. Generally, patients with DM are classified into either type 1 or type 2, with the latter being the most common type, marked by hyperglycemia, insulin resistance, and relative insulin deficiency (American Diabetes Association, 2010). Type 2 diabetes results from the interplay between genetic, environmental, and behavioral predispositions. It can also be traced to the hormonal milieu of pregnancy, genetic defects, infections, and certain medications (World Health Organization, 2023).

The global incidence of DM has increased dramatically. As of 2011, approximately 366,000,000 individuals had diabetes, with type 2 accounting for about 90% of the cases (Chen, et al., 2012). The incidence of type 2 diabetes is increasing in all nations worldwide, with 8 out of 10 people with DM living in low- and middle-income countries (Olokoba, et al., 2012). Research revealed limited data on the occurrence of type 2 DM in Africa as a whole. Evaluation of statistics within the African context indicated a sharp increase in occurrence in both rural and urban areas, affecting both sexes proportionally (Manjeet Institute of Critical Care DMICC, 2014).

Despite the fact that type 2 diabetes is generally diagnosed in adults, its frequency has clearly risen among the pediatric age group in the last twenty years. T2DM now accounts for between 0.8 and 0.45 of every 10 new cases of diabetes reported in pediatric populations, depending on the group studied (American Diabetes Association, 2010). The occurrence of Type 2 diabetes in the pediatric age group is commoner among females than males, just as women has higher chance of having it than men (Rodriguez, et al., 2023).

The onset age range for type 2 diabetes is between 12 and 16 years. This coincides with the age of puberty, when a physiological stage of insulin resistance is reached. Type 2 diabetes develops when insufficient beta-cell function occurs, often in the presence of other comorbidities (e.g., obesity) (Rodriquez & O'Sullivan, 2023). Among the incidence rates of different populations, the lowest is in China (0.1 per 105 per year) and the highest is in Finland (37 per 105 per year), although there are significant variations (Maitra, et al., 2018). Globally, both females and males are similarly affected. Generally, the incidence increases with age, with puberty being the peak period. The incidence rate significantly decreases in young women after puberty but remains relatively high in young adult males up to the age of 29–35 (Soltesz, et al., 2007). Recently, as many as 5 out of 10 people with DM have remained undiagnosed (International Diabetes Federation, 2022). Diabetes must be detected early in its course, as therapeutic intervention can reduce complications associated with the disease. The risk of developing type 2 diabetes increases with age, obesity, and physical inactivity. The incidence of type 2 diabetes is rapidly rising, and by 2030, this figure is estimated to reach around 552 million (World Health Organization, 2024). Diabetes mellitus is ubiquitous, but it is more common (particularly type 2) in well-developed nations, where the majority of the affected population is between 45 and 64 years of age (American Diabetes Association, 2010). Diabetes may present with typical symptoms such as polydipsia, polyuria, blurred vision, and weight loss. The most severe clinical signs and symptoms

include ketoacidosis or a non-ketotic hyperosmolar state, which can lead to dehydration, coma, and, if untreated, death (World Health Organization, 2023).

Given the recent dramatic rise in the incidence of diabetes worldwide, which has contributed to an increase in kidney diseases, lycopene has been documented to possess antioxidant and anti-inflammatory properties, among its other therapeutic effects. Therefore, it is essential to contribute to the existing body of knowledge regarding the potential use of lycopene as an alternative therapy for managing diabetes and its complications (Leh & Lee, 2022).

OBJECTIVE

To assess the histoarchitecture and biochemical parameters of the kidneys of diabetic Wistar rats after intervention with lycopene, and to determine whether lycopene is more efficacious as a curative rather than a prophylactic agent.

MATERIAL AND METHOD

Thirty-five adult Wistar rats, weighing between 160-180 g, were used in this study. The rats were procured and housed in plastic cages in the animal holding area of the Anatomy and Cell Biology Department, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria. The animals were fed a high-fat diet and provided with feed and clean water ad libitum. They were acclimatized for two weeks, after which diabetes was induced.

Animal care

The rats were given tender care according to the guide of the Health Research Ethics Committee (HREC), Institute of Public Health (IPH), Obafemi Awolowo University (OAU), Ile-Ife, Nigeria. The study was assigned the ethical clearance number IPH OAU/12/1219 on 21-04-2021.

Design of the experiment

Animals were divided into five groups (A, B, C, D, and E), with seven rats in each group. Group A served as the normal control group, receiving a daily oral dose of 2 ml/kg of citrate buffer for thirty days. Group B was induced with 60 mg/kg of streptozotocin in citrate buffer via the intraperitoneal route once and observed for one week. Group C was treated with 20 mg/kg/day of lycopene orally for thirty days after diabetes induction with 60 mg/kg of streptozotocin in citrate buffer, and observed for one week. Group D was pretreated with 20 mg/kg/day of lycopene orally for thirty days before diabetes induction with 60 mg/kg of streptozotocin in citrate buffer, and observed for one week. Group E was treated with insulin (5 IU/kg) for thirty days after diabetes induction with 60 mg/kg of streptozotocin in citrate buffer, and observed for one week. At the end of the study, the rats were sacrificed under ketamine anesthesia

Table 1. Experimental design for the research.

Sn	Groups N=7	Agents	Doses	Routes	Duration
1	A	Citrate buffer	2ml/kg/day	Oral	30 days
2	B	Streptozotocin	60mg/kg/day	Intraperitoneal	1 week
3	C	Streptozocin + lycopene	60mg/kg/day + 20mg/kg/day	Intraperitoneal, Oral	1 week 30 days
4	D	Lycopene + streptozocin	20mg/kg/day + 60mg/kg/day	Oral, Intraperitoneal	30 days 1 week
5	E	Streptozocin + insulin	60mg/kg/day + 5 IU/kg	Intraperitoneal, subcutaneous	1 week 30 days

The rats were weighed weekly, and the average weight was recorded. The relative organ weight was then determined by measuring the weight of the organ at the time of sacrifice and dividing it by the average body weight, as shown in Equation 1 (Mossa, et al., 2015).

$$Relative\ weigh\ of\ organ\ t\ (\%) = \frac{organ's\ weight\ (g)\ x\ 100\%}{Animals'\ mean\ weight\ (g)} \qquad Eqn.\ 1$$

Biochemical studies

An intracardiac method was used to collect blood samples in plain and fluoride oxalate tubes. The clotted blood in the plain tube was centrifuged using the CENLBR-3L-1 benchtop centrifuge at 3000 rpm for ten minutes. The serum was then separated and immediately stored for serological analysis (Amegashie, et al., 2015).

The levels of glucose and insulin in the blood, along with antioxidants, were measured biochemically using the double antibody enzyme immunoassay method, which was explained in Bio-source Belgium kits. A urine sample from the previous 24 hours was also taken for analysis (Owolabi, et al., 2017).

Histological studies

The kidney tissues were prepared for histopathological examination using a method by Arumugam et al., (2003). The tissues were excised and processed for hematoxylin and eosin staining. First, the samples were placed in 10% neutral buffered formalin for fixation. Next, the tissues were embedded in paraffin, and 3 µm sections were cut and stained to create permanent slides. Hematoxylin and eosin staining was used to demonstrate the general histoarchitecture.

Photomicrography

The photomicrographs of the slides were observed and photographed using a LEICA DM 750 microscope at 1000x magnification. The microscope was attached to a digital camera (LEICA ICC50) and a desktop computer (Owolabi, et al., 2017).

Data Analysis

The data generated in this study were analyzed by one way ANOVA, then Student Newman-Keuls (SNK) test for multiple comparisons. Graph Pad Prism 5 (version 5.03, GraphPad Inc.) statistical package was used for data analysis. The significant value was set at $p<0.05$. Symbols α, β and δ were significant differences compared to groups A, B and between C D and E respectively

RESULT

Figure 1 shows the results of this study. It showed that after diabetes was caused and before the interventional agent was given, the random blood glucose level was significantly higher in all groups, including both treated and untreated diabetic rats. This is called hyperglycemia in the diabetic range. In contrast, the normal control group's blood glucose level was within the normal (euglycemic) range. There was no significant statistical difference ($p>0.05$) in the value across the test groups and the positive control, whereas there was a significant statistical difference ($p<0.05$) between the test groups (C, D, and E) and the negative control group (B).

After the administration of the intervening agent in the test groups C, D, and E, the blood glucose levels significantly decreased, falling below the diabetic range (Figure 2). Among these groups, the animals treated with insulin had the lowest glucose levels, approaching the normal random blood sugar (RBS) range. Group C, which was treated curatively, had a lower RBS compared to group D, which was treated prophylactically. In contrast, the untreated diabetic group (B) remained consistently high within the diabetic range.

Figure 3 demonstrates the insulin levels in the different experimental groups. The insulin levels in group A, as well as in the prophylactic and curative diabetic groups C and D, were all within normal

ranges. There were no statistically significant differences between the normal control and the test groups ($p < 0.05$). However, the untreated diabetic group (B) had significantly lower insulin levels than group A and the treated diabetic groups. Additionally, there was a statistically significant difference ($p < 0.05$) between the normal control and all other groups.

Figure 4 illustrates the antioxidant concentrations. It reveals that the treated groups had higher levels of antioxidant concentrations, specifically superoxide dismutase (SOD), compared to the untreated diabetic group (A). However, the curative group (C) had higher levels of SOD than the prophylactic group (D), and group E had higher levels of SOD than any other test groups from B to D.

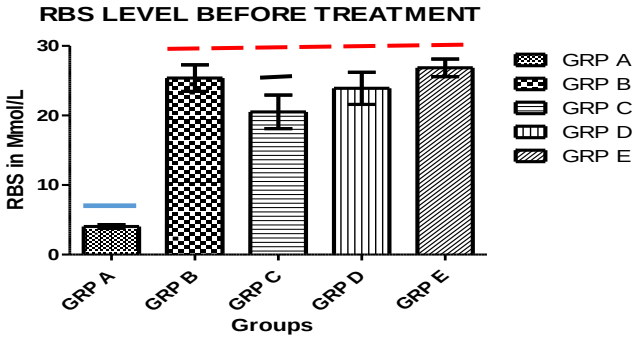

Figure 1. The mean random blood sugar levels of the rats across groups. Values were presented as mean ± SEM, n = 7 ($p < 0.05$).
Legends: α Significantly different from normal control at $p<0.05$ (-------)
β Significantly different from toxic control at $p<0.05$ (---------)
δ Significantly different from C, D and E at $p<0.05$ (---------)

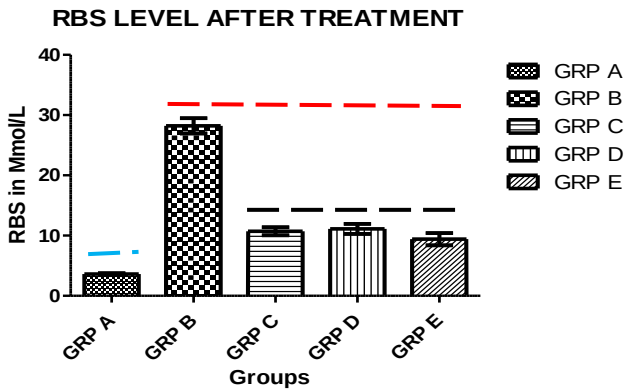

Figure 2. Mean random blood sugar levels of the Wistar rats across groups. Values were presented as Mean ± SEM, n=7 ($p<0.05$).
Legends: α Significantly different from normal control at $p<0.05$ (---------)
β Significantly different from toxic control at $p<0.05$ (--------)
δ Significantly different from C, D and E at $p<0.05$ (--------)

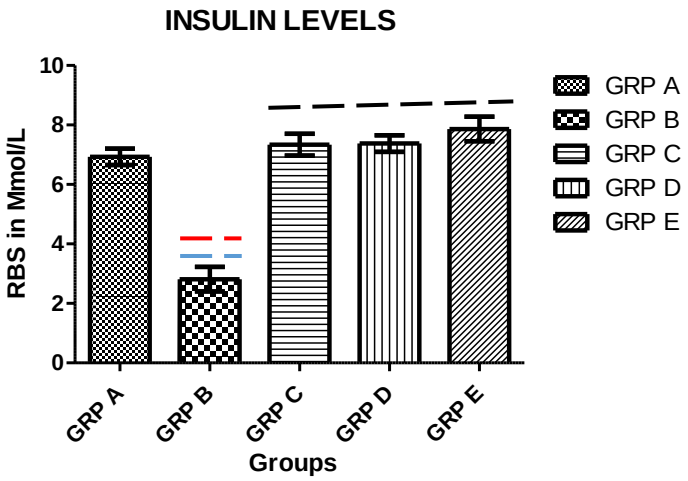

Figure 3. Mean insulin levels of the Wistar rats across groups.
Values were presented as Mean ± SEM, n=7 ($p<0.05$).
Legends: α Significantly different from normal control at $p<0.05$ (--------)
β Significantly different from toxic control at $p<0.05$ (--------)
δ Significantly different from C, D, E and F at $p<0.05$ (----------)

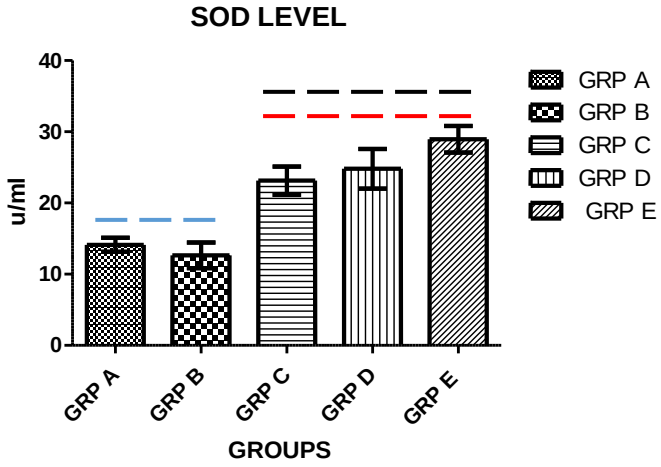

Figure 4. Mean superoxide dismutase levels in the Wistar rats across groups.
Values were presented as Mean ± SEM, n=7 ($p<0.05$).
Legends:α Significantly different from normal control at $p<0.05$ (-----)
β Significantly different from toxic control at $p<0.05$ (-----)
δ Significantly different from C, D, E and F at $p<0.05$ (------)

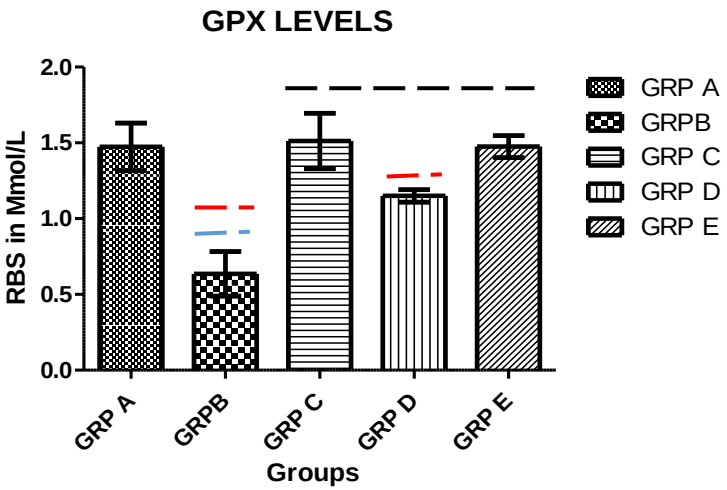

Figure 5. Mean glutathione reductase levels of the rats across the group.
Values were presented as mean ± SEM, n=7 ($p<0.05$).
Legends: α Significantly different from normal control at $p<0.05$ (-----)
β Significantly different from toxic control at $p<0.05$ (-----)
δ Significantly different from C, D, and E at $p<0.05$ (------)

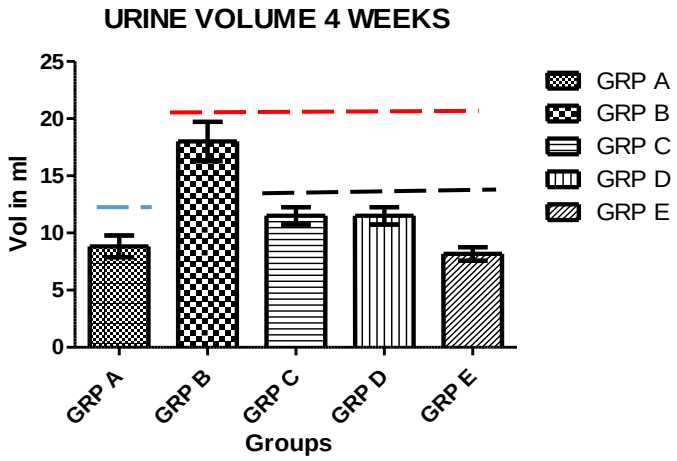

Figure 6. Mean urine volume of the rats across groups.
Values were presented as mean ± SEM, n= 7 $p<0.05$.
Legends: α Significantly different from normal control at $p<0.05$ (-----)
β Significantly different from toxic control at $p<0.05$ (-----)
δ Significantly different from C, D and E at $p<0.05$ (-----)

Figure 5 shows that the glutathione reductase concentration is higher in group D than in group E. Additionally, the group administered with insulin (group E) has the highest level of GPX compared to the other test groups. The negative control (group B) was observed to have the lowest level of glutathione reductase among all the groups.

Figure 6 Shows the urine output of the experimental rats over 24 hours. The total urine output was higher in the diabetic groups (B, C, and D) compared to group A and group E. Group B had the highest urine output, which was statistically significantly different ($p< 0.05$) from all other groups. Among the treated diabetic groups, the group administered with insulin had a lower urine output within the normal range, compared to the prophylactic and curative groups (C and D, respectively). Excessive urination continued unabated in the untreated diabetic group.

Figure 7 Shows the kidney's histological outline, revealing that the urinary space was wider in the untreated diabetic group (B) and the test groups (C and D) compared to the healthy control group (A).

The urinary space was also wider in the prophylactic group (C) and the curative group (D) compared to the insulin-treated group (E). In Figure 7(A) the renal corpuscles in the test (diabetic) groups had lost or worn away podocytes and mesangial cells, whereas these cells were still present in the normal control (non-diabetic) group, as indicated by the green and black arrows.

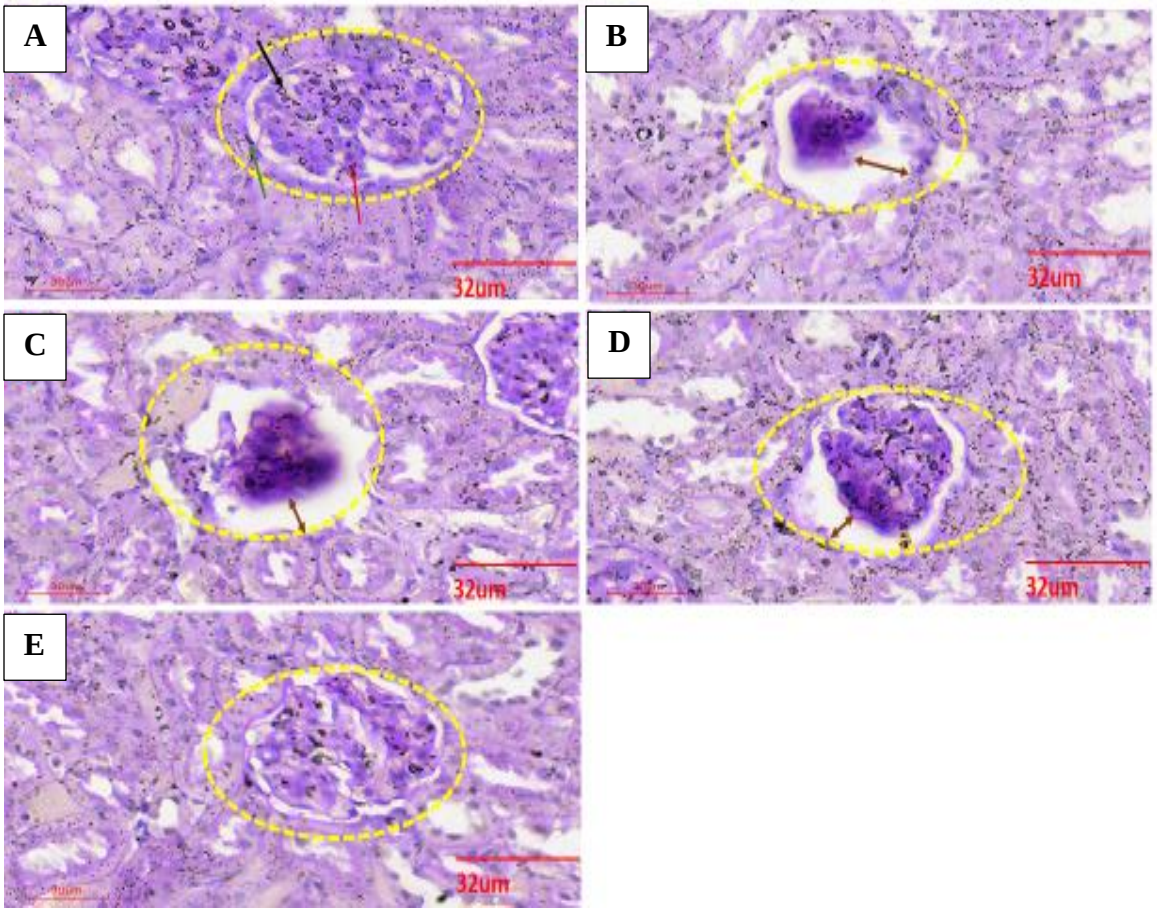

Figure 7. Representative photomicrographs of the histology of the kidneys of streptozotocin-induced diabetic Wistar rats.

Legends: The brown arrows show the gaps in the urinary space across the group, green and black arrows point to the podocyte and mesangial cells respectively, while the yellow circles indicate the renal corpuscles with varying degrees of affectation. H and E stain X 1000.

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DISCUSSION

Based on a review of the literature, there is a lack of reports detailing the microanatomy of diabetic kidneys. Therefore, it is crucial to investigate the biochemical and histological effects of diabetes on the kidney, as well as the role of intervening agents in reversing the initial damage caused by the disease.

Observable features in diabetic animals include poor grooming, reduced locomotor activity, wet fur, and alopecia, which may result from polyuria. Excessive urination has been a characteristic feature consistently associated with diabetes mellitus (Abdelmoaty, et al., 2010). Random blood glucose levels in both treated and untreated diabetic rats were markedly increased, resulting in polyuria, which occurs when glucose is present in the urine. This osmotic diuresis is responsible for the polyuria observed. These findings are consistent with the work of Xiao, et al., (2013), who suggested that altered bladder function in diabetic animals contributes to the wetness of fur, primarily caused by polyuria. Administration of the intervening agent in the test groups led to a drastic reduction in blood glucose levels, bringing them below the diabetic range. This provides evidence that streptozotocin-induced diabetes was reversed by the intervening agent (lycopene), which normalized the abnormal glucose levels in the treated diabetic groups. This finding is consistent with the work of Yin, et al., (2019), who reported that lycopene can regulate glucose and lipid metabolism in streptozotocin-induced diabetic rats. This study focused on insulin levels. The preventative and curative experimental groups were found to have levels within normal limits after the administration of the intervening agents. However, the insulin level in the untreated diabetic group was much lower than in both the normal control and treated diabetic groups. These findings align with the work of Pierine, et al., (2014), who suggested that the degree of basal hyperglycemia in diabetes mellitus likely serves as a bioassay for the impact of reduced insulin secretory capacity and insulin resistance. They also noted that a deficiency of beta cells can elevate basal plasma glucose, reflecting the hyperbolic nature of the normal insulin secretory response to varying glucose concentrations.

The study's antioxidant levels showed that the treated groups had higher levels of SOD than the untreated diabetic group. The levels were also higher in the curative group than in the prophylactic group, with the highest levels observed in the insulin-treated group compared to the other test groups. This can be attributed to lycopene, one of the most powerful antioxidants, which has twice the antioxidant power of β-carotene and ten times that of α-tocopherol. As Kanwugu, et al., (2022) stated, lycopene reduces the complications associated with diabetes. Furthermore, glutathione reductase concentration was higher in the prophylactic group than in the curative group, and the insulin-treated group had a higher level of GPX than the other test groups. Overall, the untreated group (B) had the lowest concentration of antioxidants. This is consistent with the research of Noreen, et al., (2023), who reported an inverse relationship between the hyperglycemic state of diabetes and antioxidant levels. It seems likely that lycopene's antioxidant properties help prevent and treat T2DM by lowering biomarkers of oxidative stress while activating antioxidant defense systems.

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The histological structure of the kidneys was examined under a microscope in both treated and untreated diabetic groups. The untreated diabetic group, as well as the experimental groups, had wider urinary spaces compared to the normal control group. Among the experimental groups, the prophylactic and curative groups also exhibited much wider urinary spaces than the insulin treatment group. Additionally, podocytes and mesangial cells were absent or degenerated in the renal corpuscles of the diabetic groups, whereas these cells were still present in the normal control group. These results support the findings of Pourghasem, et al., (2015) who reported that all renal cells including mesangial cells, podocytes, and tubulointerstitial cells are likely to be altered in diabetic kidney disease.

Strength and limitations

The strengths of this study lie in its broad exploration of the literature, which involved multiple databases, although it was restricted to the English language. The study highlighted that lycopene has

better prophylactic potential than curative potential. However, despite conducting an additional literature search in PubMed (MEDLINE), the study was limited by time and funding.

CONCLUSION

In this research, Lycopene reversed the morphological and biochemical alterations in the kidneys, and when used prophylactically, it conferred a better restorative effect than when used curatively. Further research in this area could potentially lead to improved management options compared to the current range of diabetic therapies.

Acknowledgment
All authors have contributed to this work in various ways.

Conflict of Interest
None.

Ethic Consideration
Ethical approval was obtained from the Health Research Ethics Committee (HREC), Institute of Public Health (IPH), Obafemi Awolowo University (OAU), Ile-Ife, Nigeria (IPH OAU/12/1219) on 21-04-2021.

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None.

Author Contribution
ABE contributed to conception and design, drafting of the article, critical revision of the article for important intellectual content, final approval of the article and obtaining of funding. SBA contributed to analysis and interpretation of the data, provision of study materials or patients, statistical expertise administrative, technical, or logistic support and collection and assembly of data.

REFERENCES

Abdelmoaty, M. A., Ibrahim, M. A. Ahmed, N. S., et al. 2010. Confirmatory studies on the antioxidant and antidiabetic effect of quercetin in rats. Indian Journal of Clinical Biochemistry: IJCB, 25(2): 188–92. doi: 10.1007/s12291-010-0034-x.

Ahmed, A. M. 2002. History of diabetes mellitus. Saudi medical journal, 23(4): 373–378. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11953758

Amegashie, E., Amidu, N., Owiredu, W. 2015. A comparison of fluoride-oxalate and plain (serum gel) tube on glucose measurement. Journal of Medical and Biomedical Sciences, 4(1): 34–40. doi: 10.4314/jmbs.v4i1.5.

American Diabetes Association. 2010. Diagnosis and classification of diabetes mellitus. Diabetes care, 33 Suppl 1(Suppl 1): S62-9. doi: 10.2337/dc10-S062.

Arumugam, T. V., Shiels, I. A., Strachan, A. J., et al. 2003. A small molecule C5a receptor antagonist protects kidneys from ischemia/reperfusion injury in rats. Kidney International, 63(1): 134–142. doi: 10.1046/j.1523-1755.2003.00737.x.

Chen, L., Magliano, D. J., Zimmet, P. Z. 2012. The worldwide epidemiology of type 2 diabetes mellitus present and future perspectives. Nature Reviews Endocrinology, 8(4): 228–236. doi: 10.1038/nrendo.2011.183.

International Diabetes Federation. 2022. IDF diabetes atlas 2021, IDF. Available at: https://diabetesatlas.org/atlas/tenth-edition/

Kanwugu, O. N., Glukhareva, T. V., Danilova, I. G., et al. 2022. Natural antioxidants in diabetes treatment and management: Prospects of astaxanthin. Critical Reviews in Food Science and Nutrition, 62(18): 5005–5028. doi: 10.1080/10408398.2021.1881434.

Leh, H. E., Lee, L. K. 2022. Lycopene: A potent antioxidant for the amelioration of type II diabetes

mellitus. Molecules (Basel, Switzerland), 27(7). doi: 10.3390/molecules27072335.
Maitra, A.,Sharma, A., Brand, R. E., et al. 2018. A prospective study to establish a new-onset diabetes cohort. Pancreas, 47(10): 1244–1248. doi: 10.1097/MPA.0000000000001169.
Manjeet Institute of Critical Care DMICC. 2014. Genetic basis of type 1 diabetes, type 2 diabetes, obesity, and their complications. Available at: https://www.niddk.nih.gov/-/media/Files/Strategic-Plans/Advances-in-Diabetes/DSP2011_03_GeneticBasis_508.pdf
Mossa, A. T. H, Swelam, E. S., Mohafrash, S. M. M. 2015. Sub-chronic exposure to fipronil induced oxidative stress, biochemical and histopathological changes in the liver and kidney of male albino rats 93(2): 775-784. doi:10.1016/j.toxrep.2015.02.009.
Noreen, S., Tufail, T., Bader Ul Ain, H., et al. 2023. Antioxidant activity and phytochemical analysis of fennel seeds and flaxseed. Food Science & Nutrition, 11(3): 1309–1317. doi: 10.1002/fsn3.3165.
Olokoba, A. B., Obateru, O. A., Olokoba, L. B. 2012. Type 2 diabetes mellitus: A review of current trends. Oman Medical Journal, 27(4): 269–73. doi: 10.5001/omj.2012.68.
Owolabi, O. O., Wong, K. L. M., Dennis, M. L., et al. 2017. Comparing the use and content of antenatal care in adolescent and older first-time mothers in 13 countries of west Africa: A cross-sectional analysis of Demographic and Health Surveys. The Lancet Child & Adolescent Health, 1(3): 203–212. doi: 10.1016/S2352-4642(17)30025-1.
Pierine, D. T., Navarro, M. E. L., Minatel, I. O., et al. 2014. Lycopene supplementation reduces TNF-α via RAGE in the kidney of obese rats. Nutrition & Diabetes, 4(11): e142–e142. doi: 10.1038/nutd.2014.39.
Pourghasem, M., Shafi, H., Babazadeh, Z. 2015. Histological changes of kidney in diabetic nephropathy. Caspian Journal of Internal Medicine, 6(3): 120–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26644877
Rodriguez, B. C., Astudillo, M., Tosur, M., et al. 2023. Characteristics of type 2 diabetes in female and male youth. Clinical Diabetes : A Publication of The American Diabetes Association, 41(2): 239–243. doi: 10.2337/cd22-0057.
Rodriquez, I. M., O'Sullivan, K. L. 2023. Youth-onset type 2 diabetes: Burden of complications and socioeconomic cost. Current Diabetes Reports, 23(5): 59–67. doi: 10.1007/s11892-023-01501-7.
Soltesz, G., Patterson, C., Dahlquist, G. 2007. Worldwide childhood type 1 diabetes incidence ? what can we learn from epidemiology?. Pediatric Diabetes, 8(s6): 6–14. doi: 10.1111/j.1399-5448.2007.00280.x.
World Health Organization. 2023. Breaking the silence on World Diabetes Day, hearing from people living with diabetes, WHO. Available at: https://www.who.int/news-room/feature-stories/detail/breaking-the-silence--stories-from-people-living-with-diabetes
World Health Organization. 2024. Diabetes, WHO. Available at: https://www.who.int/news-room/fact-sheets/detail/diabetes
Xiao, N., Wang, Z., Huang, Y., et al. 2013. Roles of polyuria and hyperglycemia in bladder dysfunction in diabetes. Journal of Urology, 189(3): 1130–1136. doi: 10.1016/j.juro.2012.08.222.
Yin, Y., Zheng, Z., Jiang, Z. 2019. Effects of lycopene on metabolism of glycolipid in type 2 diabetic rats. Biomedicine & Pharmacotherapy, 109: 2070–2077. doi: 10.1016/j.biopha.2018.07.100.