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Impact of Diabetes Mellitus on Female Reproductive Physiology: Role of Oxidative Stress and Metabolic Dysregulation

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Abstract

Diabetes mellitus is a chronic metabolic disorder marked by persistent hyperglycaemia and associated with significant reproductive dysfunctions, particularly affecting ovarian morphology and function. Hyperglycaemia-induced oxidative stress and hormonal imbalances impair folliculogenesis and steroidogenesis, leading to fertility issues and adverse pregnancy outcomes. Among antidiabetic therapies, insulin and metformin are widely used for glycaemic control, while canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, is gaining attention for its systemic antioxidant and anti-inflammatory effects. This study aimed to evaluate and compare the histological effects of insulin, metformin, and canagliflozin on the ovaries of streptozotocin (STZ)-induced type 2 diabetic pregnant Wistar rats. Thirty-five adult female Wistar rats were randomly assigned into five groups: Group A (non-diabetic control), Group B (diabetic untreated), Group C (diabetic + insulin), Group D (diabetic + metformin), and Group E (diabetic + canagliflozin). Diabetes was induced using intraperitoneal STZ injections (45 mg/kg and 35 mg/kg), and treatments were administered accordingly. After 28 days, the animals were sacrificed, and ovarian tissues were harvested for histological examination. Results indicated significant reductions in blood glucose levels in insulin, metformin, and canagliflozin-treated groups compared to the diabetic untreated group ($p<0.05$), with canagliflozin showing the greatest glycaemic improvement. Histologically, ovaries in the diabetic untreated group exhibited mild stromal alterations. Insulin-treated ovaries revealed stromal fatty degeneration, while metformin-treated ovaries maintained near-normal histoarchitecture. Canagliflozin-treated ovaries displayed the most preserved ovarian structure, comparable to control, with well-formed follicles and normal stroma. In conclusion, while all antidiabetic agents offered varying degrees of ovarian protection, canagliflozin showed superior efficacy in restoring ovarian morphology and improving metabolic status, suggesting its potential advantage in preserving fertility during diabetic pregnancy.

Keywords: *Diabetes mellitus; Ovary; Canagliflozin; Antidiabetic agents; Reproductive toxicity.*

Introduction

Diabetes mellitus, a chronic metabolic disorder characterized by persistent hyperglycaemia, continues to pose a significant threat to maternal health, foetal development, and overall reproductive outcomes (Nakshine and Jogdand, 2023). This endocrine condition is associated with a wide range of systemic complications that affect nearly every organ system, including the female reproductive system (Ornoy *et al*., 2021). Among the various organs impacted, the ovary is especially susceptible to the detrimental effects of chronic hyperglycaemia. Diabetes disrupts normal ovarian physiology by impairing folliculogenesis—the process through which ovarian follicles mature—altering steroidogenesis, and leading to hormonal imbalances that adversely affect the menstrual cycle and ovulatory function (Tiselko *et al*.,

2024). As a result, women with diabetes often face increased rates of infertility, irregular menstrual cycles, spontaneous abortion, and other gestational complications (Andlib *et al*., 2024; Khanna and Kumaresan, 2024). These reproductive challenges are further exacerbated during pregnancy, where the physiological demands of gestation create a state of heightened metabolic sensitivity. In diabetic pregnancies, the synergistic interaction between insulin resistance, hyperglycaemia, and disrupted hormonal signaling can lead to serious complications for both the mother and the fetus (Omoy *et al*., 2021; Leoni *et al*., 2022).

The ovary, as a primary organ of female reproduction, plays a pivotal role in gametogenesis and the regulation of sex hormones (Ma *et al*., 2023; Das *et al*., 2023). Its function is intricately tied to metabolic health, and any disruption in glucose homeostasis has the potential to compromise ovarian architecture and function. Chronic exposure to elevated glucose levels in diabetic states leads to the accumulation of reactive oxygen species (ROS) and increased oxidative stress within ovarian tissue (Akhigbe and Ajayi, 2021; Mukai *et al*., 2022). This biochemical imbalance results in cellular damage, mitochondrial dysfunction, and apoptosis, contributing to structural histopathological changes such as follicular atresia (degeneration of ovarian follicles), stromal fibrosis (accumulation of fibrous connective tissue), and vascular congestion, which impairs blood flow and nutrient delivery to the ovarian tissue (Mukai *et al*., 2022). These changes not only reduce the ovary's functional capacity but also negatively impact reproductive potential and pregnancy maintenance (Akhigbe and Ajayi, 2021).

To mitigate the deleterious effects of diabetes on reproductive organs, various pharmacological interventions have been developed and employed. Among these, insulin, metformin, and sodium-glucose co-transporter 2 (SGLT2) inhibitors such as canagliflozin have emerged as cornerstone agents in the management of hyperglycemia. Insulin therapy, which compensates for the body's inability to produce or effectively use endogenous insulin, is essential for achieving glycemic control, particularly in cases of type 1 diabetes and insulin-dependent type 2 diabetes (Bolli *et al*., 2021; Perkins *et al*., 2021). Beyond its role in glucose metabolism, insulin has been shown to exert direct trophic effects on the ovary, influencing granulosa cell proliferation, follicular development, and luteal function (Afradiasbagharani *et al*., 2022).

Metformin, a first-line oral antidiabetic agent belonging to the biguanide class, functions primarily by improving peripheral insulin sensitivity and inhibiting hepatic gluconeogenesis. It has also gained attention in the treatment of reproductive disorders such as polycystic ovary syndrome (PCOS), where it restores ovulatory cycles, reduces hyperandrogenism, and enhances fertility. In diabetic pregnancy, metformin's ability to improve metabolic parameters may also offer secondary benefits to ovarian tissue integrity by reducing oxidative stress and inflammation (Tarry-Adkins *et al*., 2022; Sirtori *et al*., 2024).

Canagliflozin, a member of the newer class of SGLT2 inhibitors, lowers blood glucose levels by promoting the excretion of glucose through the urine, independent of insulin. This mechanism not only assists in achieving better glycemic control but also reduces systemic oxidative stress and body weight—factors that are increasingly recognized for their role in reproductive health (Kondo *et al*., 2021). Although canagliflozin has not been widely studied in the context of pregnancy due to limited safety data, emerging preclinical evidence suggests that it may indirectly preserve ovarian morphology and function by ameliorating metabolic toxicity and reducing inflammatory responses in peripheral tissues, including the reproductive organs (Zaheer, 2023; Topsakal *et al*., 2024).

Despite their widespread use, the histological impact of these therapeutic agents on the ovary during diabetic pregnancy remains underexplored. Hence this study aimed to compare the safety profile of commonly used hypoglycemic agents; Insulin and Metformin with a new hypoglycemic agent (Canagliflozin), a sodium glucose co-transporter 2 on the Ovaries

of a Streptozotocin (STZ) induced type 2 diabetic pregnant Wistar rat.

Materials and Methods

Experimental Animals: A total of thirty-five female and five male Wistar rats, each weighing between 120 and 160 grams, were obtained from the Animal Laboratory Centre at the College of Medicine, University of Lagos. Upon arrival, the animals were housed in wire-mesh cages located within the Anatomy Department's animal facility at the University of Lagos. The housing units were organized into six equal compartments: five compartments housed seven female rats each, while the sixth compartment contained the five male rats. Following a three-week period of acclimatization under standard laboratory conditions, the female rats were weighed and then randomly assigned into five experimental groups for further study.

Oestrous Cycle Determination: The estrous cycle phases—proestrus, estrus, metestrus, and diestrus—were identified via daily vaginal smear analysis, following the method of Byers *et al.* (2012). Smears were collected once daily between 7:00 and 10:00 a.m. by gently restraining each rat and inserting approximately 0.2 ml of sterile saline 2–3 mm into the vagina using a borosilicate glass dropper. The fluid was immediately withdrawn and placed on a glass slide for microscopic examination. Observations were recorded over three weeks. Ten rats with regular estrous cycles and twenty-five with irregular cycles were selected. Individual rats were marked with distinct colors on their body for identification. All procedures complied with standard laboratory animal care guidelines.

Experimental Design: The animals used in the experiment weighed between 120 and 160 grams and were randomly divided into five groups. Group A served as the non-diabetic control group and received 0.5ml of distilled water. Group B consisted of diabetic rats that also received 0.5ml of distilled water. Group C included diabetic rats treated with 1 IU insulin, while Group D received 200 mg/kg body weight metformin. Group E comprised diabetic rats treated with 30 mg/kg body weight canagliflozin.

Diabetes Induction: Diabetes mellitus was experimentally induced in rats that had been fasted overnight by administering two intraperitoneal doses of Streptozotocin (STZ) at 45 mg/kg and 35 mg/kg body weight, dissolved in 0.1 M sodium citrate buffer (pH 4.5), as outlined by Akbarzadeh *et al.* (2007). Following STZ administration, food and water consumption were carefully observed on a daily basis to monitor changes in metabolic behavior. To confirm the onset of diabetes, fasting blood glucose levels were measured 48 hours post-injection using blood samples collected from the tail vein after a 12-hour fast. A portable glucometer (Accu-Chek, Roche Diagnostics, Germany) was used for the measurements. Rats presenting with fasting blood glucose levels of 120 mg/dL or higher, along with classical diabetic symptoms such as excessive eating (polyphagia), increased thirst (polydipsia), and frequent urination (polyuria), were classified as diabetic and subsequently included in the study.

Blood Sugar Determination: Blood glucose levels were measured using a glucometer, which detects glucose concentration in a small blood sample (Hunter and Garvey, 1998). A test strip was inserted into the designated slot of the glucometer with the absorbent pad facing upward. Once the meter displayed a flashing blood drop symbol, a small incision was made on the rat's tail using a sterile scalpel blade to obtain a drop of blood. The blood sample was then applied to the test strip, and after a brief delay of a few seconds, the glucose reading appeared on the device's screen (Osinubi *et al.,* 2007).

Histology and Photomicrography: The harvested kidney tissues were processed and routinely stained using hematoxylin and eosin, according to the method previously reported by Drury and Wallington (1980). Photomicrographs of the tissue sections of the liver, pancreas, and ovary were obtained using Binocular microscope lens WF-10, Xli camera in the Department of Pathology, University of Lagos.

Statistical Analysis: All data are expressed as Mean±SD (standard deviation of mean). Significant differences were tested using ANOVA. Values of $p < 0.05$ were considered statistically significant.

Results

Table 1: Blood glucose level and weights before and after treatment across the experimental groups.

	GROUP	BEFORE EXPERIMENT		AFTER EXPERIMENT	
		Blood Glucose Level	Body Weight	Blood Glucose Level	Body Weight
A	(Non-diabetic control)	93.84±1.59	136.00±11.26	91.92±3.47*	152.12±14.30
B	(Diabetic + Distilled water)	202.60±55.40*	136.04±6.89	183.50±67.12*	132.78±7.33
C	(Diabetic + Insulin)	237.20±18.63 *	120.20±6.19	158.70±9.00*	124.55±6.05
D	(Diabetic + Metformin)	280.60±51.08 *	116.62±10.0	166.30±15.82*	121.52±14.57
E	(Diabetic + Canagliflozin)	236.20±27.01*	117.20±3.51	134.65±14.40*	135.31±18.09

Values are given as Mean ±SD. * $p < 0.05$.

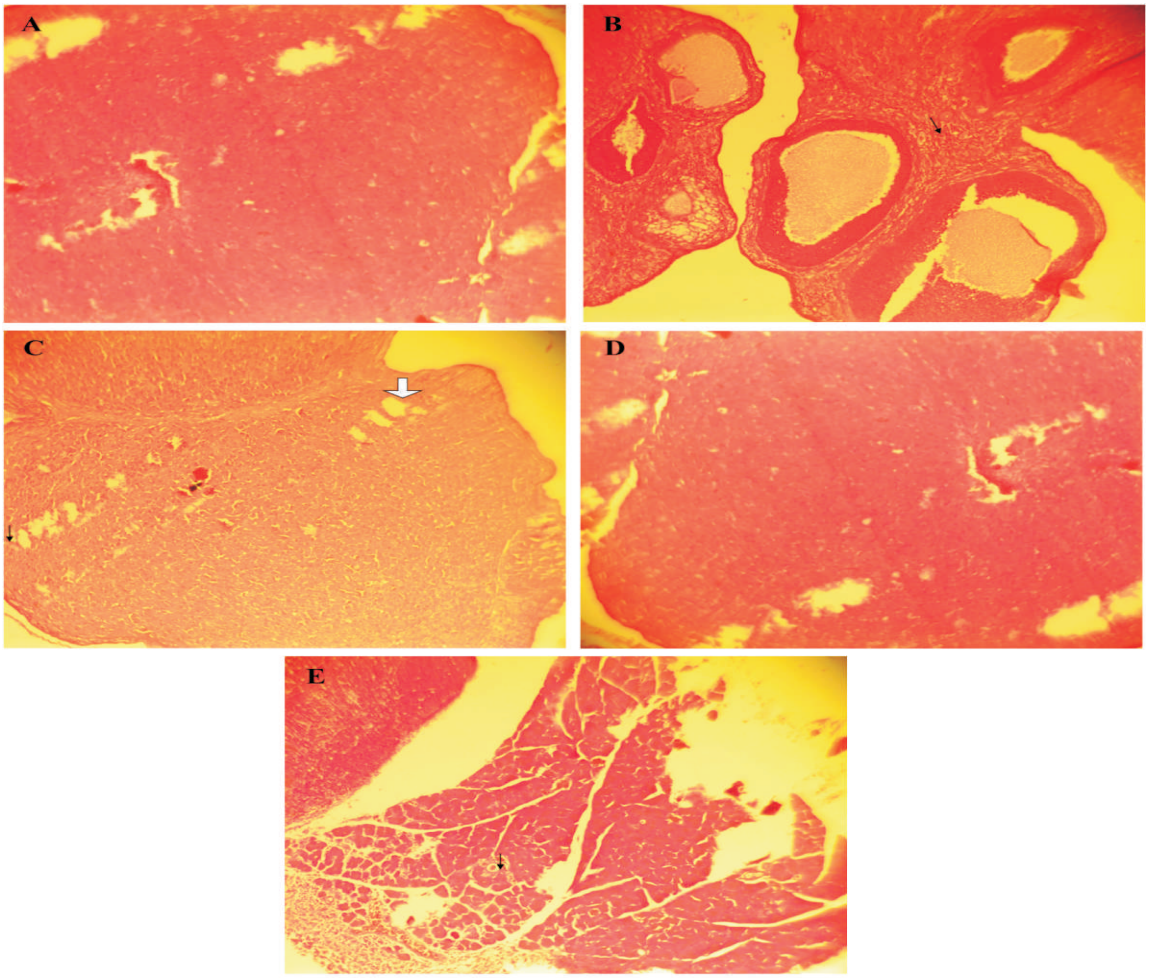

Figure 1: Photomicrograph of Ovary in (A) Control showing: normal ovarian stroma; (B) Diabetic showing: normal ovarian stroma with follicles (small arrow); (C) Diabetic with insulin showing: fatty ovarian stroma (big arrow) and follicles (small arrow); (D) Diabetic with metformin; Showing a normal ovarian stroma; (E) Diabetic with canagliflozin showing a normal ovarian stroma with ovarian follicles (small arrow).

Discussion

The ovary is a critical endocrine and reproductive organ, intricately regulated by hormonal and metabolic cues to maintain follicular development, steroidogenesis, and overall fertility (Ma *et al*., 2023; Babaniyi *et al*., 2024). In diabetic states, chronic hyperglycaemia and oxidative stress compromise ovarian structure and function, leading to disrupted ovulatory cycles, follicular degeneration, and impaired reproductive capacity (Ramalho-Santos *et al*., 2008; Andib *et al*., 2024). This study investigated the histological and metabolic responses of the ovary to diabetes mellitus and the therapeutic potential of insulin, metformin, and canagliflozin in mitigating these pathologies.

Body weight and glycaemic status are essential physiological indicators that reflect both the metabolic burden of diabetes and the effectiveness of pharmacological interventions (Ramalho-Santos *et al*., 2008). In the diabetic control group, persistent hyperglycaemia was observed throughout the study period, with only a marginal decline in glucose levels post-treatment. This was accompanied by a decrease in body weight, consistent with the catabolic effects of insulin deficiency and increased proteolysis, a hallmark of uncontrolled diabetes (Kelkar *et al*., 2019). In contrast, the non-diabetic control group exhibited stable glucose levels and an expected increase in body weight, underscoring the physiological balance in euglycemic animals.

Among the treatment groups, all three antidiabetic agents—insulin, metformin, and canagliflozin—significantly reduced fasting blood glucose levels when compared to the diabetic control group. Canagliflozin demonstrated the greatest reduction in glucose levels, followed by metformin and insulin. This result aligns with emerging evidence that SGLT2 inhibitors not only improve glycemic control via renal glucose excretion but also reduce systemic oxidative stress and improve mitochondrial efficiency in peripheral tissues, including the ovary (Llorens-Cebrià *et al.,* 2022; Rakic *et al*., 2023).

Weight gain in diabetic animals treated with insulin and metformin remained modest, which may be attributed to their respective mechanisms of action. Insulin promotes anabolic processes and glucose uptake in insulin-responsive tissues, but its influence on adipogenesis and weight gain is well documented (da Silva Rosa *et al*., 2020; Li *et al*., 2022). Metformin, while improving insulin sensitivity, exerts weight-neutral or even weight-reducing effects through appetite suppression and inhibition of hepatic gluconeogenesis (Antel and Hebebrand, 2012; Pernicova and Korbonits, 2014). Interestingly, the canagliflozin-treated group showed a more pronounced increase in body weight compared to other diabetic groups, which could reflect improved glycemic balance and reduced muscle proteolysis following effective glucose clearance and reduced glucotoxicity.

Histological examination of ovarian tissues further revealed the detrimental effects of hyperglycaemia on reproductive structures. In the untreated diabetic group, marked histological alterations such as degenerating follicles, distorted stroma, and increased stromal lipid infiltration were observed, suggesting oxidative stress-induced apoptosis and impaired folliculogenesis (Garris and Garris, 2003; Abdel-Gaber *et al.,* 2020). These features are consistent with previous findings that associate chronic hyperglycaemia with mitochondrial dysfunction and abnormal follicular development in diabetic conditions (Abdel-Gaber *et al*., 2020).

Insulin treatment led to partial improvement in ovarian architecture, with some preservation of follicles, although fatty infiltration of the stroma remained prominent. This may reflect the dual role of insulin in promoting both glucose uptake and lipogenesis, the latter contributing to lipid accumulation when energy homeostasis is not tightly regulated (Saltiel, 2016; Qaid and Abdelrahman, 2016). Conversely, the metformin-treated group exhibited substantial histological restoration with preservation of follicular units and reduced stromal distortion. Metformin's ability to enhance insulin sensitivity and reduce oxidative stress may underlie its cytoprotective effects on the ovary, as previously documented in PCOS and diabetic models (Furat Rencber *et al*., 2018; Taheri *et al*., 2021).

The most remarkable ovarian recovery was seen in the canagliflozin-treated group, which displayed near-normal ovarian stroma and well-preserved follicles. This suggests that beyond glycemic control, canagliflozin may exert direct or indirect protective effects on ovarian tissue. The reduction in systemic inflammation, improvement in mitochondrial function, and attenuation of ROS generation by SGLT2 inhibitors have been implicated in restoring ovarian physiology in hyperglycemic states (Chen *et al.,* 2022). Furthermore, the antifibrotic and anti-apoptotic effects observed in other organs under SGLT2 inhibition may similarly extend to ovarian tissue, promoting functional and structural recovery.

Conclusion and Recommendations

Collectively, these findings demonstrate the deleterious impact of diabetes on ovarian function and highlight the differential efficacy of antidiabetic agents in restoring ovarian morphology and metabolic homeostasis. While insulin and metformin provided moderate protective effects, canagliflozin showed the greatest therapeutic potential in preserving ovarian structure and improving glycemic outcomes. These results underscore the importance of considering organ-specific benefits when selecting antidiabetic therapies, especially in reproductive-age females where fertility preservation is a concern. Further studies exploring the molecular pathways through which canagliflozin confers ovarian protection are warranted.

Conflict of Interest: The authors declare that there is no conflict of interest

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