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***Research Article** (Open Access)*

COMPARATIVE STUDY TO CHECK THE SUCCESS RATE OF INDUCTION OF TYPE-1 DIABETES WITH STREPTOZOTOCIN IN ALBINO RATS

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ABSTRACT
The present study aimed to check the successful induction of Type-1 diabetes in both male and female albino rats with the dose of streptozotocin (STZ) 50mg/kg. 32 albino rats of both sexes were grouped and administered by intraperitoneal injection of STZ. All animals were successfully induced with type- 1 diabetes. A comparative study of body weight, glucose level, hematology, and histology of the experimental group diabetic male, female and control group animals was done. Reduced body weight, hyperglycemia, anemia, and morphological changes in the liver, kidney, and pancreas were observed. The adverse effects of STZ and complications of diabetes were seen more in diabetic females than in diabetic males. This two-week study concluded that a 50 mg/kg streptozotocin dose was effective for diabetes induction. This dose was found to be lethal in females, resulting in a higher mortality rate than in males. Kidney and pancreatic damage were worsened in diabetic females compared to diabetic males. That could be the reason for the high mortality.

Keywords: *Diabetes, Streptozotocin, intraperitoneal, hematology, pancreas*

INTRODUCTION
Diabetes mellitus is a metabolically associated chronic disease where hyperglycemia persists in the body. The glucose level in the blood becomes high in the body due to insufficient insulin production from the pancreas or receptors of the target cells do not respond smoothly to the signals (Lal, 2016). Diabetes mellitus in itself is enough to imperil the patient's life, but it also causes several other complications and makes the patient prone to other infections. Diabetes mellitus also exerts its harsh effects on the hematopoietic system, including changes in blood indices etc. Increased levels of reactive oxygen species in the body alter the structure of vascular endothelium and raise the chances of cardiovascular disease (Mansi & Lahham 2008); (Alamgeer *et al.,* 2012); (Helal *et al.,* 2005). Diabetes mellitus affects individuals worldwide mainly with Type 1 diabetes, also called insulin-dependent diabetes mellitus, in which insufficient insulin is produced by the pancreatic gland of the body, while in Type 2, receptors for insulin do not function or do not act in response to insulin (Lal 2016). Induction of diabetes experimentally in albino rats through streptozotocin (STZ) is the most prevalent method accepted by researchers because the diabetogenic action of streptozotocin directly damages the beta cells of the pancreas so that the production of insulin in the blood decreases and hyperglycemic conditions develop (Punithavathi *et al.,* 2008); (Fadillioglu *et al.,* 2008). Scientists used different doses of streptozotocin for the induction of diabetes in different strains of the same species for short-term or long-term pathological studies. A higher dose of STZ 65 mg/kg body weight of animals caused nephrotoxicity, hepatotoxicity, and gastric ulcerations. It is a crucial step to choose a dose of STZ for the induction of diabetes with minimal causalities in animals (Piyachaturawat *et al.,* 1988); (Piyachaturawat *et al.,* 1991). According to the previous study lower doses of STZ at levels of 30-40mg/kg showed spontaneous recovery in the animal after induction of diabetes through streptozotocin (Katsumata & Katsumata 1992). In the present study, streptozotocin was used for induction of diabetes in albino rats and comparative study was done.

MATERIALS AND METHODS

***Test chemicals*:** STZ used for the induction of diabetes was freshly prepared in 0.1M citrate buffer at pH 4.5 (Gajdosik *et al.*, 1999).

***Animals*: -** Three to four-month-old 32 albino wistar rats of both sexes were used for this study. The animals were acclimatized for one week in controlled laboratory conditions with a temperature of 22°-24°c and LD: 12:12 (Petlevski *et al.*, 2006).

***Induction of diabetes*: -** Animals were weighed, and the fasting glucose level of their blood was checked before the induction of diabetes. Suitable animals have fasted overnight before the administration of the STZ injection. Diabetes was induced intraperitoneally by the injection of a single dose of STZ 50mg/kg at pH of 4.5 of body weight in animals. To prevent hypoglycemia, animals were given a 1% sucrose solution after being induced with diabetes (Zafar *et al.*, 2010). Control animals were injected with buffer solution only. After 72 hours of induction, the animals whose glucose level was above 250mg/dl were considered diabetic and used for the study.

***Experimental design*: -** After successful induction of diabetes, all animals were grouped. Sixteen animals (8 male and 8 female) were grouped in the diabetic group and 16 animals of control group (8 male and 8 female). Rats were closely observed during the experiment after grouping. Bodyweight, food and water intake, glucose level and other activities were observed during the study. After two weeks of study, the animals were sacrificed.

***Blood and organ collection*:** Blood was collected from each rat into EDTA tubes for hematological studies such as hemoglobin level, total leukocyte count (TLC), neutrophil, lymphocyte, monocyte, eosinophil, basophil, RBC count, Packed cell volume, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution were all measured using automated hematology analyser. Organs such as the liver, kidney, and pancreas were removed and stored in 10% formalin for further histopathological investigation (Erukainure *et al.*, 2013).

Statistical analysis

The statistical analysis was performed using t-test. Values were expressed as the mean ± S.E.

RESULTS AND DISCUSSION

After the induction of diabetes, animals' bodyweight was drastically reduced; polyuria, loss of appetite, dehydration, and laziness were seen. The glucose level of the animals was continually high during the experiment. Mortality of some animals was also observed.

Success rate: - Diabetes was successfully induced in all animals. A dose of 50 mg/kg of STZ was adequate for the induction of diabetes in both sexes of albino rats.

Bodyweight: Measuring animals' bodyweight before, after, or during the experiment is the most crucial step for calculating doses or studying histopathological changes. During the experiment, the bodyweight of some diabetic animals was severely reduced even after availability of food (Table-1), and few animals in both male and female groups were able to manage their weight. Weight gained by both male and female was observed less than that of the control group animals.

Glucose level: During the experiment, the fasting glucose level of animals was checked every 5^{th} day with a glucometer. Before the induction of diabetes, the glucose levels of all animals were in the normal range. After administering an STZ injection, blood glucose levels rise in male and female animals. During the experiment, mortality was seen in some male and female rats due to the persistence of high glucose levels and increased glucose levels cause metabolic disturbances and enlargement of the intestines. Diabetic female rats recorded higher glucose levels than diabetic male rats during the experiment (Table-2).

Table 1: Bodyweight (g) of Control and Streptozotocin (STZ) treated albino rats

Animals (Bodyweight) / (g)				
	Male		Female	
Parameters	**Control group**	**Diabetic group**	**Control group**	**Diabetic group**
Pre-diabetic weight	79.38±2	86.12±4.74	90.25±2.6	81.75±3.45
Post-diabetic weight	87.38±2.55	85±6.05	91±2.52	80.62±2.43
Days	**During experiment**			
1	96.75±1.53	84.25±3.27	94.38±1.82	**74.25**±3.02
2	106.12±2.15	79.75±3.94	98±1.79	**77.00**±1.68
3	107.62±2.04	76.38±3.54	100.75+1.87	**67.88**±9.88
4	106±2.56	76.12±2.95	103.5+1.82	**50.25**±14.76
5	108.88±2.13	66.62±10.15	106.88+2.08	**31**±15.15
6	109.62±2.74	56.38±12.59	109.38+2.49	**30**±14.64
7	113.25±2.73	48.25±14.31	112.12+2.68	**31.5**±15.38
8	114.88±2.81	49.75±14.74	114.38+2.42	**31.12**±15.21
9	117.88±3.21	50.25±14.89	116.25±2.3	**32.75**±16.07
10	119.12±3.75	52.38±15.52	118.75+2.3	**31.62**±15.63
11	118.88±3.19	52.88±15.58	121.38+2.72	**32.38**±15.98
12	121.12±3.38	53.12±15.66	123.62+2.75	**32.5**±16.42
13	122.12±3.42	55.50±16.37	126.75+2.86	**33.25**±16.52
14	121.88±3.08	56.25±16.59	127.88+2.48	**35.88**±17.67

***All values are mean** ± S.E. Values are significantly ($p < 0.05$) different from controls*

Table 2: Glucose level of STZ treated male and female albino rats
All values are mean ± S.E. Values are significantly ($p < 0.05$) differ from control

Animals		**Glucose level (mg/dl)**		**Experimental Days**		
		Pre diabetic	Post diabetic	5^{th} day	10^{th} day	14^{th} day
Male group	**Control**	149.75±4.56 (injected with buffer only)	135.88± 5.69	131.75± 7.85	130.75± 7.2	120.88± 6.29
	Diabetic	128.5±7.07	537.75± 25.69	573.5± 26.5	379.2± 62.91	433.4± 33.08
female group	**Control**	133.38±7.59 (injected with buffer only)	140.88± 7.92	120.5± 7.47	126±5.68	126.75± 5.09
	Diabetic	136.38± 3.73	523.88± 18.4	596.67± 3.35	443.33± 64.76	438.67± 52.34

Hematological indices- This study showed that diabetic male rats had significantly higher leukocytes and neutrophil count than normal male rats. RBCs indices (RBC count, Hb, PCV, MCV, MCHC) were extensively reduced and no significant alteration was found in MCH as compared to normal male rats. But platelets count was significantly higher in diabetic male rats. Lymphocyte percentage was reduced in the diabetic male rats and no significant changes occurred in eosinophil, basophil, or monocyte percentage compared to control rats. Diabetic female rats also had significantly reduced RBCs count,

Hemoglobin, MCH, MCHC compared to control female rats. Lymphocytes reduced and platelets raised as was seen in diabetic male rats compare to control rats. Leukocytes and neutrophil count was significantly increased and no significant changes were noticed in PCV and MCV count in diabetic female rats compared to normal female rats (Table-4).

Table 4: Showing Hematological Analysis of Control and Diabetic Rats

Haematological parameters	Male rats		Female rats	
	Control	Diabetic	Control	Diabetic
Haemoglobin(Hb) (g/dl)	14.26±0.220	12.04±0.09	14.38±0.17	12.72±0.27
Total leukocyte count (TLC) (/mm^3)	6300±173.21	9000±71.71	7580±177.2	10060±92.74
Neutrophil (%)	20±0.71	25±1	20.4±0.93	25±1
Eosinophil (%)	1.2±0.2	1.2±0.2	1.2±0.2	1.2±0.2
Lymphocyte (%)	74.8±1.16	68.4±1.21	74.6±2.11	61.8±0.86
Monocyte (%)	1	1	1	1
Basophil (%)	0	0	0	0
RBC count ((millions /mm^3)	7.73±0.06	6.29±0.08	7.85±0.08	5.92±0.27
P.C.V. (%)	54.82±1.01	41.24±1.09	39.18±0.26	38.56±0.23*
MCV (FL.)	70.48±0.77	62.06±0.53	50.26±0.34	48.58±0.46*
MCH (picogram)	18.12±0.42	16.26±0.34*	21.54±0.29	15.3±0.19
MCHC (gm/dl)	31.98±1.33	22.56±0.84	36.16±0.22	30.4±0.36
Platelets count (lakh/mm^3)	3.11±0.27	7.3±0.35	4.9±0.31	8.22±0.32

All values are mean ± S.E. Values are significantly different $p < 0.05$. * Values are not significantly different (P>0.05).

HISTOLOGICAL STUDY

Pancreas

The pancreatic structure of both the control male and female groups was normal. Pancreatic islets, blood vessels, acini, and interlobular ducts were observed in both groups. When compared to diabetic males, diabetic females' pancreas was severely damaged. The Complete loss of islets of the pancreas was seen in diabetic females. The pancreas being so much affected could be the reason for high mortality in diabetic females compared to diabetic male rats Fig 1.

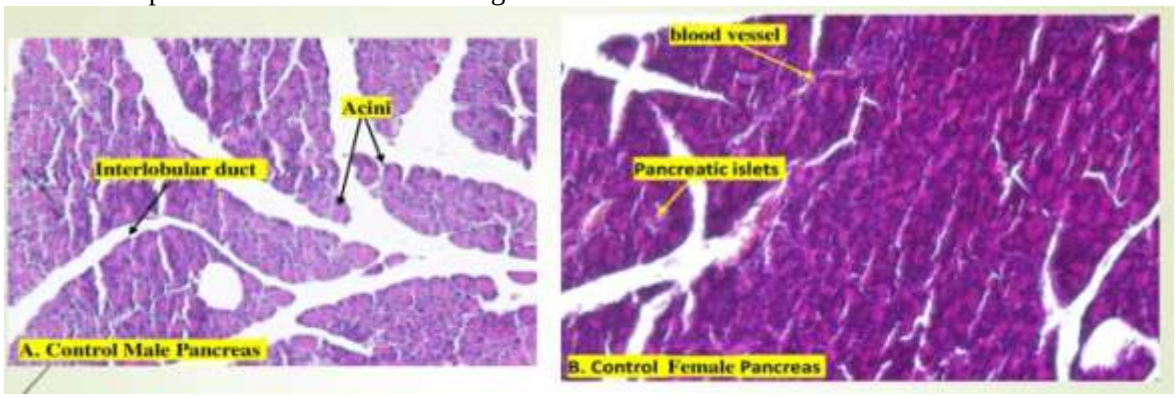

Figure 1: Histology of pancreas

1. Control Male Pancreas shows the compact structure of cells, acini, and interlobular duct is clearly seen.
2. Control The female pancreas demonstrates blood vessels in the pancreatic islets.

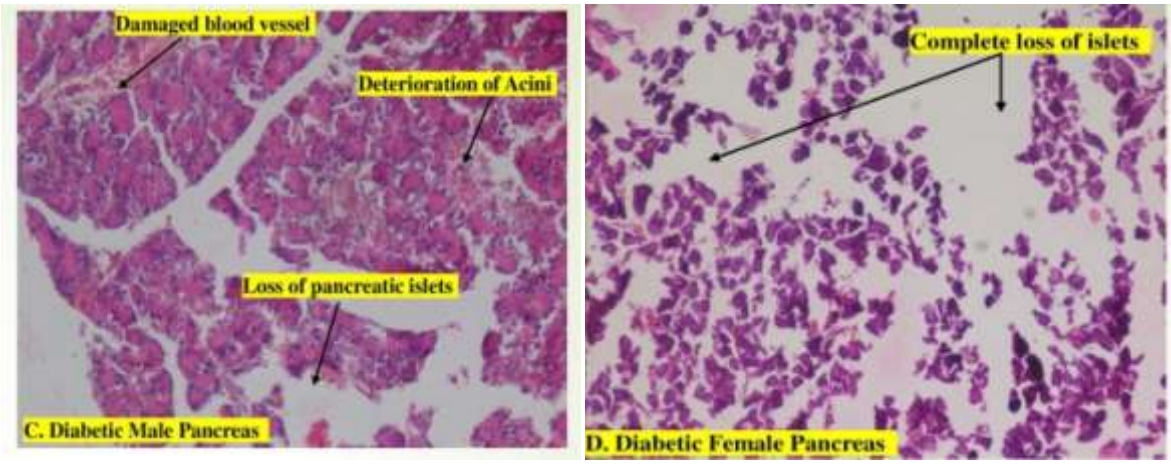

Figure 1: Histology of pancreas

3. Diabetic male pancreas exhibits damaged blood vessels, loss of pancreatic islets, and altered acini structure.
4. A Diabetic Female Pancreas shows affected cells, complete loss of islets, and other structures that are not clearly visible.

Liver

The liver cells of control rats were compact, and the structure of the central vein was clearly seen in both control groups. The liver of diabetic groups was affected. Distorted central vein and portal vein were observed in the male group, and apoptosis in hepatic cells was seen in the diabetic female group Fig 2.

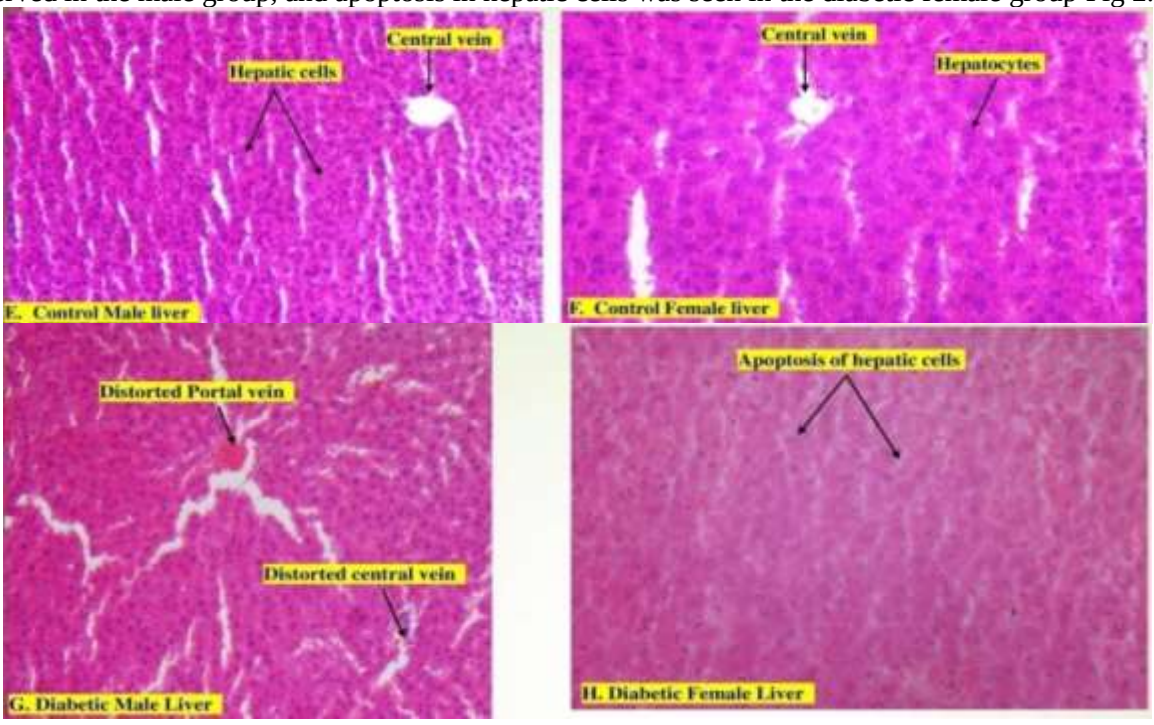

Figure 2: The Liver's Histology

1. Controlled male liver with hepatic cell plates and a central vein.
2. Hepatocytes and the central vein are visible in the control female liver.
3. A diabetic male liver shows distorted central and portal veins.
4. A female diabetic liver shows apoptosis in hepatic cells.

Kidney

A histological study of the kidney showed normal glomerulus and bowmen's capsule in control rats. Proximal convoluted tubes were also seen as normal in both control groups. Damaged glomerulus and PCT were observed in female diabetic rats. The same alterations were seen in diabetic male rats. Rat renal failure could be one of the reasons behind the mortality of rats Fig 3.

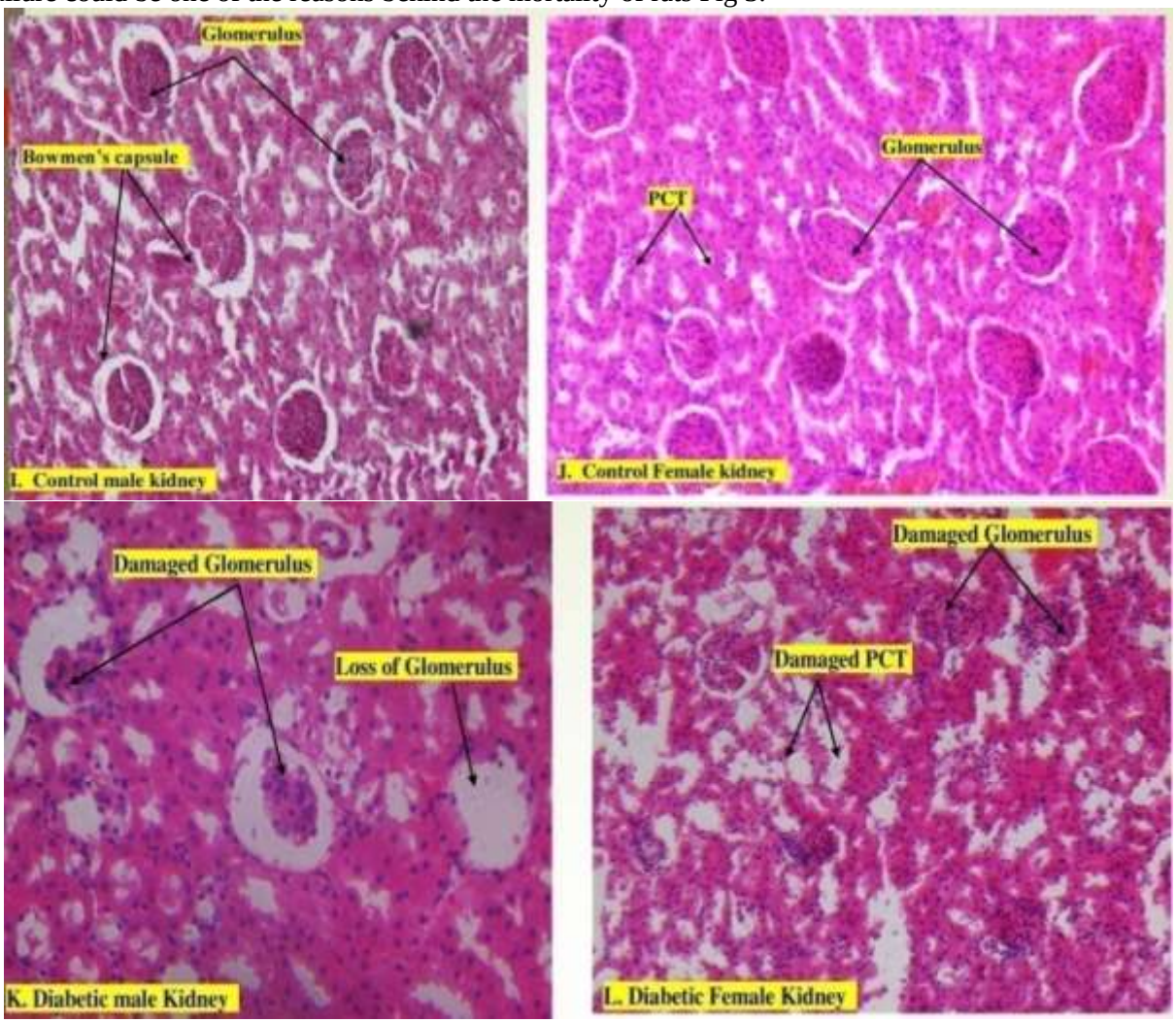

Figure 3: Histology of the kidney

1. Normal glomeruli and glomerulus capsule in a male kidney.
2. The control female kidney also shows normal PCT and glomerulus
3. Diabetic male kidney showing damaged glomerulus
4. Damaged PCT and glomerulus in a diabetic female kidney

Streptozotocin is widely used for the induction of diabetes in laboratory animals. The diabetogenic effect of Streptozotocin drugs efficiently affects the pancreatic islets and causes hyperglycemia in rats (Ragbetli & Ceylan 2010). An important issue is selecting an effective dose of streptozotocin for inducing stable diabetes with persistent hyperglycemia. The dose of 70mg/kg was lethal for animals and caused mortality in rats (Gajdosik *et al.*, 1999). In present study, the dose of STZ was 50 mg/kg was successfully induced diabetes in albino rats same observed by (Oscika *et al.*, 2000).The success rate of induction of diabetes in both groups male and female was 100%. The result and observation of the present experiment confirmed

that an appropriate dose of streptozotocin produces hyperglycemia in both sexes of animals which fully agree with (Habibuddin *et al.,* 2008); (Lee *et al.,* 2008); (Kim, 2006); (Heidari *et al.,* 2008).
The study of the haematological parameters of diabetic rats can be used to determine the adverse impact of diabetes on blood constituents (Muhammad *et al.,* 2004); (Ashafa *et al.,* 2009). In diabetes, reactive oxygen species (ROS) are generated, which alter the hematopoietic system of cells (Rao *et al.,* 2003). Diabetes mellitus induced oxidative stress result of immunological and hematological alterations in albino rats (Akpan & Ekaidem, 2015). According to several findings, a reduced level of RBCs indices in diabetic rats compared to normal rats suggests anemia (Alamgeer *et al.,* 2012), (Francis *et al.,* 2013). Reduction in MCH, MCHC, and MCV in diabetic rats indicates defective blood osmoregulation and abnormal synthesis of hemoglobin (Stookey *et al.,* 2007). In the present study, diminished levels of RBCs, MCH, MCHC and Hemoglobin in diabetic female rats showed anemia similar to (Erukainure *et al.,* 2013) findings. In diabetic male rats, hematlogical markers like RBCs, MCHC, Hemoglobin and PCV were significantly reduced according to prior hematological studies reporting anemia as a pathophysiological complication of diabetes mellitus (Akindele *et al.,* 2012).The concentration of MCH in diabetic male rats and PCV and MCV concentration in diabetic female rats were not significantly reduced compared to control rats ($p>0.05$). The rise in the number of total WBCs indicates inflammation in diabetic rats. The increase in platelet count symbolizes the activation of the megakaryocyte-platelet system in diabetic rats compared to control rats (Asgary *et al.,* 2005), (Akinsegun *et al.,* 2014). Diabetes mellitus changes the histology of the pancreas, liver, and kidney. Wide intracellular spaces and dilated blood vessels were observed in the diabetic group by (Faried *et al.,* 2019). Complete loss of islets, blood vessels, and other pancreas structures was observed in females. From these findings, females were more sensitive than male groups.
Oxidative stress caused degenerative changes in the liver and kidney; degradation in the glomerulus region decreased filtration and caused polyuria in diabetic rats. Diabetic females have more urine secretion than diabetic male rats because their proximal convoluted tubules and glomerulus are damaged. Renal hypertrophy could also be a cause of high mortality in females. Glomerular hypertrophy was seen in the absence of of mesangial cells in glomerular pathology in diabetic rats (Malatiali *et al.,* 2008). Histology of the liver reveals the impact of STZ on liver hepatocytes because hepatocytes express GLUT2 (Eleazu *et al.,* 2013). ROS production in diabetes causes structural changes in the liver also. In diabetic rats, hepatic changes were seen like apoptosis of hepatic cells and hydropic degeneration (Gowda *et al.,* 2009). In the present study, congestion and dilation of the central vein occurred in both diabetic groups.

CONCLUSIONS

The current study found that STZ successfully induced diabetes in all laboratory animals, regardless of gender. Reduced body weight, hyperglycemia, polyuria, inactivity, and mortality were observed in both groups, but females were more affected and showed high. Hematological indices and histological studies showed alterations in the liver, kidney, and pancreas morphological structure that caused anaemia in diabetic rats

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