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Full-Length Research Article

Maternal Environmental Temperature During Gestation Affects Renal Function Indices and Oxidative Stress in the Kidney of Offspring of Wistar Rats

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Summary: Maternal exposure to increased temperature reduces birth weight. Low birth weight is related to an adult-onset of non-communicable diseases. In this study, the effects of maternal exposure to various environmental temperatures during gestation on renal function and oxidative stress indices in offspring of Wistar rats were assessed. Fifteen pregnant Wistar rats were divided into three groups (n=5). The animals were housed in specialized thermoregulatory cages at 25^0C, 32^0C and 39^0C respectively. The animals were allowed to deliver spontaneously. At 12 weeks of age, the offspring were euthanized. Urea concentrations in serum, urine and creatinine clearance were assessed as renal function indices. Renal superoxide dismutase (SOD), catalase and malondialdehyde (MDA) activities were estimated as indices of oxidative stress. Histopathology and histomorphometry of the kidney were also assessed. Concentrations of urine creatinine and creatinine clearance of the temperature group 39°C were significantly higher than those of the 25°C and 32°C groups in both male and female offspring. Catalase and SOD activities in the kidneys of the male offspring were significantly decreased in temperature group 32°C when compared to the temperature groups 25°C and 39°C. Meanwhile, the MDA level was significantly higher in the 32^0C group. In the female offspring, exposure to 25°C significantly increased the concentration of serum creatinine, urea and renal MDA levels compared to other temperature groups. However, SOD activities were lowered in the 25^0C group. In conclusion, maternal environmental temperature during gestation affects renal function and oxidative stress indices in offspring of Wistar rats. These effects may be influenced by the sex of the offspring.

Keywords: *Environmental Temperature, kidneys, offspring, serum creatinine, serum urea, urine creatinine*

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INTRODUCTION

Maternal exposure to various environmental factors, such as temperature and stress, increases the susceptibility of offspring to various diseases that manifest either in childhood or adulthood (Brown, 2011). Alterations in body homeostasis have been discovered to alter metabolic changes in many nutrients in pregnant women, which can affect neonatal development (Sharma *et al*., 2013). According to Basu and Samet (2002), extreme temperatures have a detrimental impact on human health because they overburden the body's ability to self-regulate. The thermoregulatory and sympathetic nervous systems of fetuses and infants are not well developed, resulting in their extreme sensitivity to hot temperatures (Knobel & Holditch-Davis, 2007). Previous studies have demonstrated that the health of the fetus in its post-uterine life is negatively impacted by intense heat throughout pregnancy and the early postpartum period (Hanson & Gluckman, 2014).

The theory of fetal origins posits that the length of gestation has a major influence on an individual's developmental health and well-being from birth to maturity (Almond and Currie, 2011). According to O'Donnell and Meaney (2016), the two main aspects of fetal origin are genetic programming and latency, which refers to the possibility that conditions resulting from fetal effects won't become evident until much later in life for a particular individual.

Chronic kidney disease (CKD) in adults can be programmed by an adverse in-utero environment (Tain & Hsu, 2017). Furthermore, low birth weight (LBW) is linked to an elevated risk of adult-onset disorders, such as renal function dysfunction, and has been utilized as a clinical surrogate for a poor intrauterine environment (Calkins & Devaskar, 2011). Luyckx *et al*., (2011) in their study noted that decreased number of nephrons due to impaired nephrogenesis is an hypothesized mechanism that associates LBW with eventual hypertension and CKD risk. Additionally, there is a positive link between kidney weight and the number of glomeruli. The clinical symptoms include reduced glomerular filtration rate, azotemia, proteinuria, and glomerulosclerosis up to adulthood (Wang *et al*., 2015). In the same study, Wang *et al*., postulated that a decrease in

the number of nephrons induces glomerular hyperfiltration and compensatory hypertrophy, potentially at the cost of increasing intraglomerular pressures and eventual glomerulosclerosis, which leads to CKD via a separate, as-yet unknown mechanism. Sweating and inadequate water intake can cause electrolyte imbalance, and dehydration. According to Rampatzis *et al*. (2013), renal function may be hampered by compensatory physiological mechanisms such as circulatory adaptation and thermoregulation. Several factors including maternal and fetal starvation, exposure to glucocorticoids from the mother, and renin-angiotensin contributes to the loss of nephrons during fetal development (Wang *et al*. 2015).

In this study, we seek to investigate the effect of maternal exposure to various environmental temperatures during gestation on the serum analyte and renal function indices of the F1 offspring.

MATERIALS AND METHODS

Experimental Animal: Fifteen female Wistar rats were obtained from the Department of Physiology, Federal University of Technology, Akure. The animals were housed in standard, well-ventilated wooden cages in the departmental animal holding facility. They had free access to food (vital feed) and water. After two weeks of acclimatization, animals in proestrus were exposed to mature male overnight and the presence of sperm in their vaginal smear was taken as the first day of gestation.
After confirmation of gestation, the animals were randomly divided into three different temperature groups of five animals in each group. Group 1 were exposed to temperature of 25^0C while animals in Groups 2 and 3 were exposed to 32^0C and 39^0C temperature respectively. The animals were allowed to deliver spontaneously, immediately after the delivery the dams with their pups were moved into well ventilated cages under standard laboratory temperature. The study was conducted by the International Ethical Norms on Animal Care and Use as contained in NIH publication/80-23, revised in 2010. This study was carried out at the Department of Physiology, School of Basic Medical Sciences, Federal University of Technology, Akure, Nigeria.

Collection of Urine from Offspring: The offspring were allowed to grow to adulthood (12 weeks of age). A 24-hour urine sample was thereafter collected from the offspring to measure urine creatinine concentration, urinary urea concentration and creatinine clearance at PND 12 weeks. A specialized metabolic cage was used to collect urine. The female offspring were placed in the metabolic cage during their proestrous stage. The urine samples were centrifuged at 4000g for 10 minutes. The supernatant was aspirated and kept in a freezer for further assays.

Collection of Blood: Blood samples were collected from the animals via retro-orbital sinus into plain sample bottles. The blood samples were centrifuged immediately at 4000g for 10 minutes. The serum was aspirated and kept in a freezer for further assays.

Sacrifice of animals: At the end of the study (PND 12 weeks), the animals were euthanized via cervical dislocation under sodium thiopental anaesthesia (50 mg/kg, i.p.). The kidney of each animal was harvested and weighed with the dry weight recorded before being immersed in phosphate buffer solutions. The left kidney was put in phosphate buffer while the right kidney went into the formal-saline. The left kidney put in the phosphate buffer was homogenized using a homogenizer, after which the sample was centrifuged at 10,000g for 10 minutes in cold centrifuge. The supernatant was removed and stored in a refrigerator for analysis of oxidative stress indices. The biochemical analysis was done within 72hours of sample collection.

Biochemical analysis

Determination of Creatinine Concentration in Serum and Urine: Creatinine levels were determined using Jaffe method with creatinine kit from Fortress Diagnostics Limited, United Kingdom. Creatinine reacts with picric acid in an alkaline medium to form a deep yellow complex. The amount of complex formed is directly proportional to the level of creatinine in the sample.

Determination of Creatinine Clearance: This is measured using both the serum creatinine and urine creatinine as described in manufacturer manual (Fortress Diagnostic Limited, United Kingdom).

Determination of serum and urine urea: Urea levels were determined using Urea Kinetic assay (Fortress Diagnostics Limited, United Kingdom). Urea is hydrolyzed in presence of urease to produce ammonia and CO2. The ammonia produced combines with 2-oxoglutarate and NADH in presence of GLDH to yield glutamate and NAD.
Urea +H2O+2H+ Urease 2 NH+4 + CO2
NH4+ + 2-oxoglutarate + NADH GLDH H2O + NAD++ Glutamate
The relationship between the urea concentration and the decrease in absorbance resulting from a decrease in NADH content over time is proportional. This approach determines ammonia generated by various breakdown processes.

Determination of Protein Concentration: The protein contents of the different samples were ascertained using the Biuret method, which was slightly modified by adding potassium iodide to the reagent to stop the precipitation of Cu2+ ions as cuprous oxide, as reported by Gornal *et al*. in 1949.

Determination of Oxidative Stress (LPO Assessment): By quantifying the thiobarbituric acid reactive compounds (TBARS) generated during lipid peroxidation, lipid peroxidation was ascertained. This was done using the procedure outlined by Beuge and Aust in 1978.

Determination of Catalase Activity: Catalase activity was measured using Claiborne's (1985) technique. The technique is based on the absorbance loss that occurs when catalase breaks hydrogen peroxide, which is seen at 240 nm. Although hydrogen peroxide doesn't have a maximum absorbance at this wavelength, its absorbance and concentration can be correlated sufficiently for use in a quantitative experiment. The employed extinction coefficient was 0.0436 mM-1cm-1.

Determination of Superoxide Dismutase (SOD) Activity: Using Misra and Fridovich's approach (Misra and Fridovich, 1972), the amount of SOD activity was measured. This reaction serves as the foundation for a straightforward assay for this dismutase because SOD can prevent the autoxidation of epinephrine at pH 10.2. The oxidation of epinephrine to adrenochrome was triggered by the superoxide radical produced by the xanthine oxidase process. The yield of adrenochrome produced per superoxide injected rose as the pH and epinephrine concentration increased.

Histopathology of the kidney: Normal paraffin wax embedding procedures were performed on tissues preserved in 10% neutral buffered formalin. Hematoxylin and Eosin (H&E) staining was performed routinely to obtain sections that were 5 µm thick and assessed for histological alterations. A digital bright field microscope was used to examine the sections, and a photomicrograph was taken.

Histomorphometry: Photomicrographs were obtained at x100 magnification and imported unto Image J software. Glomeruli present per field were identified and counted using the Image J cell counter tool as previously described (Ebokaiwe *et al*. 2018).

Statistical Analysis: Standard Error of Mean (SEM) ± mean was used to express the data. For statistical analysis, GraphPad Prism version 8.02® (LA Jolla, CA, USA) was utilized. Two-way ANOVA was used to examine the values, which were shown as the mean ± SEM. At a significance threshold of $p<0.05$, the Tukey's multiple comparisons test was employed to identify significant differences between the means.

RESULTS

Effect of maternal exposure to various environmental temperature during gestation on creatinine concentration in serum and urine in offspring of Wistar rats: The statistical analysis of serum creatinine concentrations in offspring following maternal exposure to varying environmental temperatures revealed significant effects based on sex [$F(1, 24) = 1500$, $P < 0.0001$], interaction [$F(2, 24) = 123.7$, $P < 0.0001$], and treatment [$F(2, 24) = 106.8$, $P < 0.0001$] (Fig. 1).

Post hoc analysis indicated that the serum creatinine concentration in male offspring exposed to 39°C was significantly higher ($P < 0.05$) compared to those at 25°C and 32°C. In contrast, female offspring exhibited significantly reduced serum creatinine concentrations at 25°C, 32°C, and 39°C when compared to their male counterparts at the same temperatures.

Additionally, the statistical analysis of urine creatinine concentrations in offspring following maternal exposure to different environmental temperatures demonstrated significant effects related to sex [$F(1, 24) = 84.3$, $P < 0.0001$], interaction [$F(2, 24) = 14.17$, $P < 0.0001$], and treatment [$F(2, 24) = 205.5$, $P < 0.0001$] (Fig. 2).

The post hoc analysis revealed a significant increase ($P < 0.05$) in urine creatinine concentration in male offspring at 32℃ and 39℃ compared to those at 25℃. Conversely, urine creatinine concentration was significantly lower ($P < 0.05$) in the kidneys of female offspring at 25℃ and 32℃ when compared to 25℃ male offspring.

Additionally, there was a significant increase ($P < 0.05$) in urine creatinine concentration in female offspring at 32℃ and 39℃ relative to those at 25℃. Notably, the urine creatinine concentration was significantly higher ($P < 0.05$) in 39℃ female offspring compared to their 32℃ counterparts

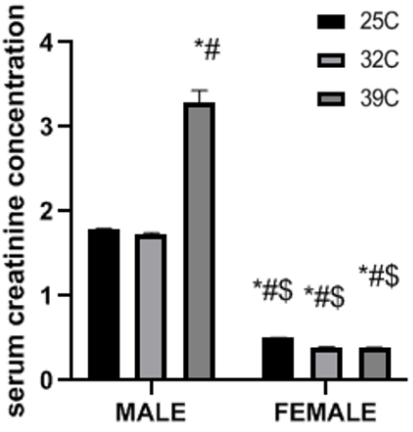

Figure 1:
Effect of maternal exposure to various environmental temperature during gestation on serum creatinine concentration of male and female offspring of Wistar rats. Values are mean ± SEM for 5 offspring per temperature group. $P < 0.05$. *P<0.05 compared to 25^0C male group; #P<0.05 compared to 32^0C male group; $P<0.05 compared to 39^0C male group;

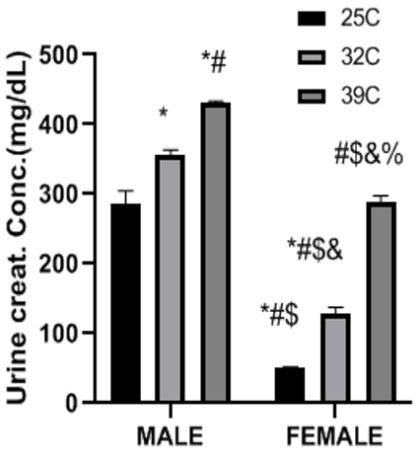

Figure 2:
Effect of maternal exposure to various environmental temperature during gestation on urine creatinine concentration in male and female offspring of Wistar rats. Values are mean ± SEM for 5 offspring per temperature group. $P < 0.05$. *P<0.05 compared to 25^0C male group; #P<0.05 compared to 32^0C male group; $P<0.05 compared to 39^0C male group; &P<0.05 compared to 25^0C female group; %P<0.05 compared to 32^0C female group

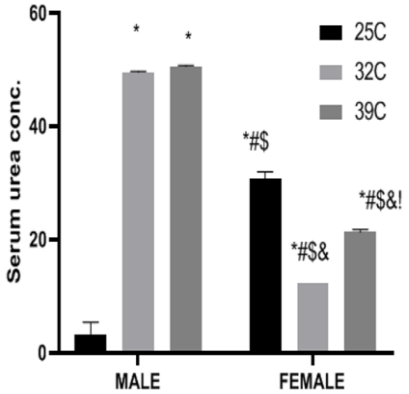

Figure 3:
Effect of maternal exposure to various environmental temperature during gestation on serum urea concentration in male and female offspring of Wistar rats. Values are mean ± SEM for 5 offspring per temperature group. $P < 0.05$..*P<0.05 compared to 25^0C male group; #P<0.05 compared to 32^0C male group; $P<0.05 compared to 39^0C male group; &P<0.05 compared to 25^0C Female group; !P<0.05 compared to 32^0C Female group

Effect of maternal exposure to various environmental temperature during gestation on Urea concentration in serum and urine in offspring of Wistar rats; The statistical analysis of serum urea concentration in Wistar offspring following maternal exposure to various environmental temperatures revealed significant effects based on sex [$F(1, 24) = 206.0$, $P < 0.0001$], interaction [$F(2, 24) = 509.7$, $P < 0.0001$], and treatments [$F(2, 24) = 160.2$, $P < 0.0001$] (see Fig. 3).

Post hoc analysis indicated a significant increase ($P < 0.05$) in serum urea concentration for male offspring at 32°C and 39°C compared to those at 25°C. Additionally, the serum urea concentration of male offspring at 32°C was significantly reduced ($P < 0.05$) when compared to that of male offspring at 39°C and female offspring at 25°C.

For female offspring, serum urea concentrations at both 39°C and 32°C were significantly lower ($P < 0.05$) compared to the male offspring at 32°C, 39°C, and the female offspring at 25°C. However, there was a significant increase ($P < 0.05$) in the serum urea concentration of female offspring at 39°C compared to those at 32°C.

Furthermore, the statistical analysis of urine urea concentration in the offspring, following maternal exposure to different environmental temperatures, showed no significant effects due to interaction [$F(2, 24) = 3.133$, $P = 0.0602$] and treatment [$F(2, 24) = 3.166$, $P = 0.0602$]. In contrast, the effects of sex on urine urea concentration were significant [$F(1, 24) = 10550$, $P < 0.0001$] (see Fig. 4).

The post hoc analysis demonstrated that urine urea concentration was significantly higher ($P < 0.05$) in male offspring at 39°C compared to those at 25°C. Conversely, the urine urea concentration in female offspring at 25°C was significantly higher ($P < 0.05$) than that in male offspring at 25°C, 32°C, and 39°C. Additionally, there was a significant increase ($P < 0.05$) in urine urea concentration for female offspring at 32°C when compared to the male offspring at 25°C, 32°C, and 39°C. Similarly, female offspring at 39°C exhibited a significant increase ($P < 0.05$) in urine urea concentration compared to male offspring at 25°C, 32°C, and 39°C.

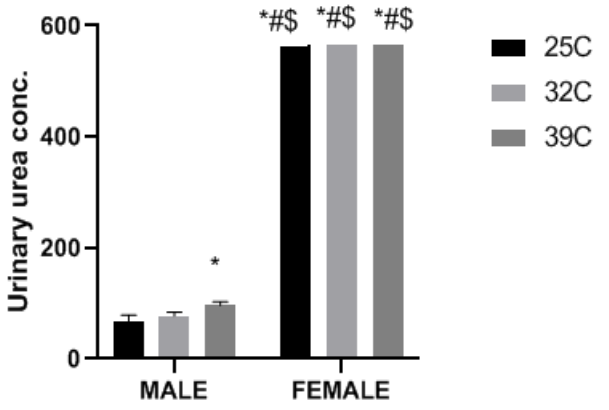

Fig. 4:
Effect of maternal exposure to various environmental temperature during gestation on urinary urea concentration of male and female offspring of Wistar rats. Values are mean ± SEM for 5 offspring per temperature group. $P < 0.05$. *P<0.05 compared to 25^0C male group; #P<0.05 compared to 32^0C male group; $P<0.05 compared to 39^0C male group

Effect of maternal exposure to various environmental temperature during gestation on creatinine clearance in offspring of Wistar rats

The statistical analysis of creatinine clearance in offspring following maternal exposure to various environmental temperatures revealed significant effects related to sex [$F(1, 24) = 39.85$, $P < 0.0001$], interaction [$F(2, 24) = 49.52$, $P < 0.0001$], and treatment [$F(2, 24) = 308.2$, $P < 0.0001$] (Fig. 5).

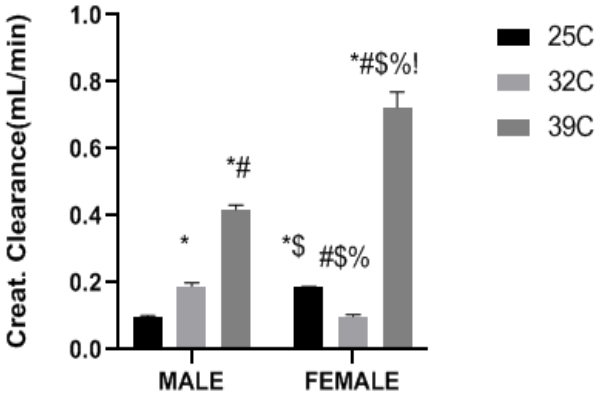

Figure. 5:
Effect of maternal exposure to various environmental temperature during gestation on creatinine clearance in male and female offspring of Wistar rats. Values are mean ± SEM for 5 animals per temperature group. $P < 0.05$. *P<0.05 compared to 25^0C male group; #P<0.05 compared to 32^0C male group; $P<0.05 compared to 39^0C male group; %P<0.05 compared to 25^0C Female group; !P<0.05 compared to 32^0C Female group.

Post hoc analysis indicated that creatinine clearance was significantly higher ($P < 0.05$) in male offspring at 32°C and 39°C compared to male offspring at 25°C, with a notable increase ($P < 0.05$) in creatinine clearance in 39°C male offspring relative to those at 32°C. Furthermore, the analysis revealed a significant increase ($P < 0.05$) in the creatinine clearance of female offspring at 25°C when compared to male offspring at 25°C, alongside a significant decrease ($P < 0.05$) relative to 39°C male offspring.

Additionally, the post hoc analysis showed that creatinine clearance in female offspring at 32°C was significantly lower ($P < 0.05$) compared to 32°C and 39°C male offspring as well as 25°C female offspring. In contrast, there was a significant increase ($P < 0.05$) in creatinine clearance levels for female offspring at 39°C when compared to 25°C, 32°C, and 39°C male offspring, as well as 25°C and 32°C female offspring.

Effect of maternal exposure to various environmental temperature during gestation on Malondialdehyde levels in the kidney of offspring of Wistar rats: The statistical analysis of renal malondialdehyde levels in offspring of Wistar rats, following maternal exposure to varying environmental temperatures, indicated a significant impact of sex [$F(1, 24) = 6927$, $P < 0.0001$], interaction [$F(2, 24) = 156.9$, $P < 0.0001$], and treatment [$F(2, 24) = 7.912$, $P = 0.0023$] (Fig. 6).

Post hoc analysis revealed that malondialdehyde levels (MDA) were significantly elevated ($P < 0.05$) in the kidneys of male offspring at 32°C and 39°C compared to those at 25°C, with a notable decrease ($P < 0.05$) when comparing

39°C male offspring to 32°C male offspring. Additionally, a significant decrease ($P < 0.05$) was observed in 32°C female offspring compared to those at 25°C. Furthermore, there was a significant increase ($P < 0.05$) when comparing female offspring at 25°C, 32°C, and 39°C to their male counterparts at the same temperatures.

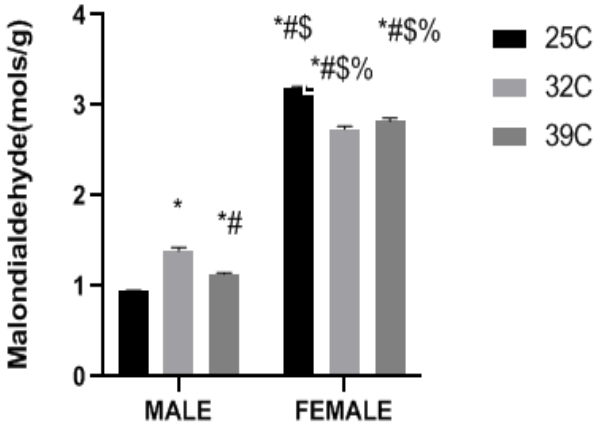

Figure 6:
Effect of maternal exposure to various environmental temperature during gestation on Malondialdehyde levels in male and female offspring of Wistar rats. Values are mean ± SEM for 5 animals per temperature group. $P < 0.05$. *P<0.05 compared to 25^0C male group; #P<0.05 compared to 32^0C male group; $P<0.05 compared to 39^0C male group; %P<0.05 compared to 25^0C female group.

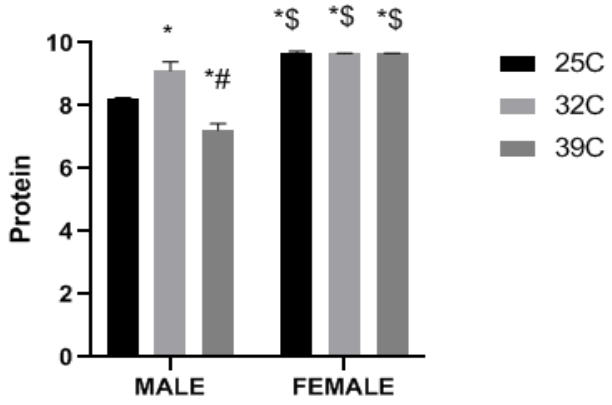

Figure 7:
Effect of maternal exposure to various environmental temperature during gestation on protein levels in male and female offspring of Wistar rats. Values are mean ± SEM for 5 animals per temperature group. $P < 0.05$. *P<0.05 compared to 25^0C male group; #P<0.05 compared to 32^0C male group $P<0.05 compared to 39^0C male group.

Effect of maternal exposure to various environmental temperature during gestation on protein levels in the kidney of offspring of Wistar rats: The statistical analysis of protein levels in Wistar rat offspring following maternal exposure to various temperatures revealed significant effects related to sex [$F(1, 24) = 157.4$, $P < 0.0001$], interaction [$F(2, 24) = 21.54$, $P < 0.0001$], and treatment [$F(2, 24) = 21.34$, $P < 0.0001$] (Fig. 7).

Post hoc analysis indicated that the protein levels in male offspring from the 32°C temperature group were significantly increased ($P < 0.05$) compared to those from the 25°C group. Conversely, the protein levels in the male offspring from the 39°C group were significantly decreased ($P < 0.05$) when compared to both the 25°C and 32°C male offspring. Furthermore, the post hoc analysis of protein levels in female offspring from the 25°C, 32°C, and 39°C groups showed a significant increase ($P < 0.05$) when compared to the male offspring from the 25°C and 39°C groups.

Effect of maternal exposure to various environmental temperatures during gestation on Superoxide Dismutase (SOD) activities in the kidney of offspring of Wistar rats
The statistical analysis of superoxide dismutase (SOD) activities in the offspring of Wistar rats, following maternal exposure to various environmental temperatures, revealed significant effects related to sex [$F(1, 24) = 430.4$, $P < 0.0001$], interactions [$F(2, 24) = 17.35$, $P < 0.0001$], and treatment conditions [$F(2, 24) = 12.11$, $P = 0.0002$] (see Figure 8).

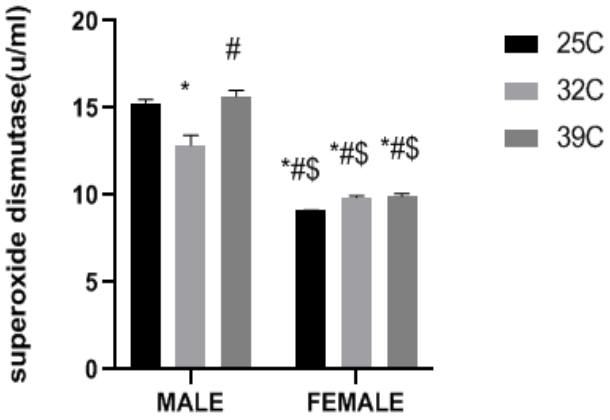

Figure 8:
Effect of maternal exposure to various environmental temperature during gestation on Superoxide Dismutase (SOD) levels in male and female offspring of Wistar rats. Values are mean ± SEM for 5 animals per temperature group. $P < 0.05$. #P<0.05 compared to 32^0C male group; *P<0.05 compared to 25^0C male group; $P<0.05 compared to 39^0C male group.

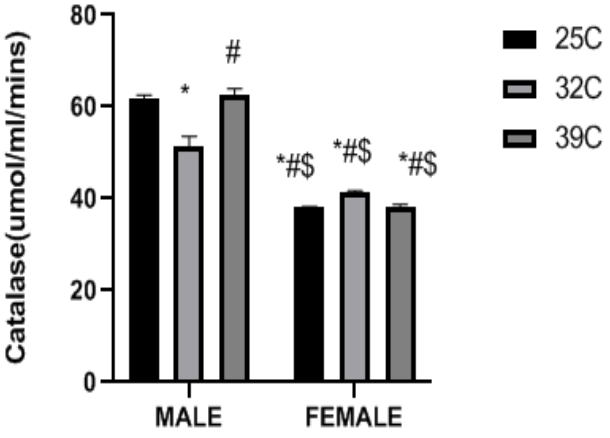

Fig. 9:
Effect of maternal exposure to various environmental temperature during gestation on catalase activity in male and female offspring of Wistar rats. Values are mean ± SEM for 5 animals per temperature group. $P < 0.05$. *P<0.05 compared to 25^0C male group; #P<0.05 compared to 32^0C male group; $P<0.05 compared to 39^0C male group.

Post hoc analysis indicated that SOD activities were significantly higher ($p < 0.05$) in male offspring from the 25°C and 39°C temperature groups compared to those from the 32°C group. In contrast, female offspring from the 25°C, 32°C, and 39°C groups exhibited a significant decrease ($p < 0.05$) in SOD levels when compared to all male offspring from the respective temperature groups.

Effect of maternal exposure to various environmental temperatures during gestation on catalase activities in the kidney of offspring of Wistar rats

The statistical analysis of catalase activities in offspring following maternal exposure to different environmental temperatures revealed a significant effect based on sex [$F(1, 24) = 409.8$, $P < 0.0001$], interaction [$F(2, 24) = 24.34$, $P < 0.0001$], and treatment (temperature) [$F(2, 24) = 7.436$, $P = 0.0031$] (Fig. 9).

Post hoc analysis indicated that catalase activity in male offspring at 32°C was significantly decreased ($p < 0.05$) compared to those at 25°C. In contrast, there was a significant increase ($p < 0.05$) in the catalase activity of male offspring at 39°C when compared to those at 32°C. However, no significant difference in catalase activity was observed between male offspring at 25°C and 39°C.

In female offspring, catalase activity was significantly reduced ($p < 0.05$) in all temperature groups (25°C, 32°C, and 39°C) when compared to their male counterparts at the respective temperatures.

Effect of Environmental Temperature during Gestation on the Histopathology and Histomorphometry of Kidney (Glomeruli Cells) in the Offspring of Wistar Rats: Histological examination of the kidney appears largely normal across all groups. In the renal cortex, renal corpuscles are distinctly outlined, with glomeruli displaying a normal appearance and surrounded by well-defined Bowman's space. The parenchyma of the renal cortex is populated by proximal and distal convoluted tubules, both of which exhibit normal morphology with intact cuboidal epithelial lining (Fig. 10).

Statistical analysis of the histomorphometry of the kidney in offspring subjected to maternal exposure to varying environmental temperatures revealed no significant effects based on sex [$F(1, 24) = 5.317$, $P = 0.301$] or treatment [$F(2, 24) = 0.6725$, $P = 0.5198$]. However, a significant interaction effect was observed [$F(2, 24) = 9.157$, $P = 0.0011$] (Fig. 11).

Post hoc analysis indicated a significant decrease ($P < 0.05$) in the glomeruli cell count of male offspring at 39°C when compared to their counterparts at 32°C. Additionally, female offspring at both 25°C and 39°C exhibited a significant increase in glomeruli cell count compared to the male offspring at 39°C.

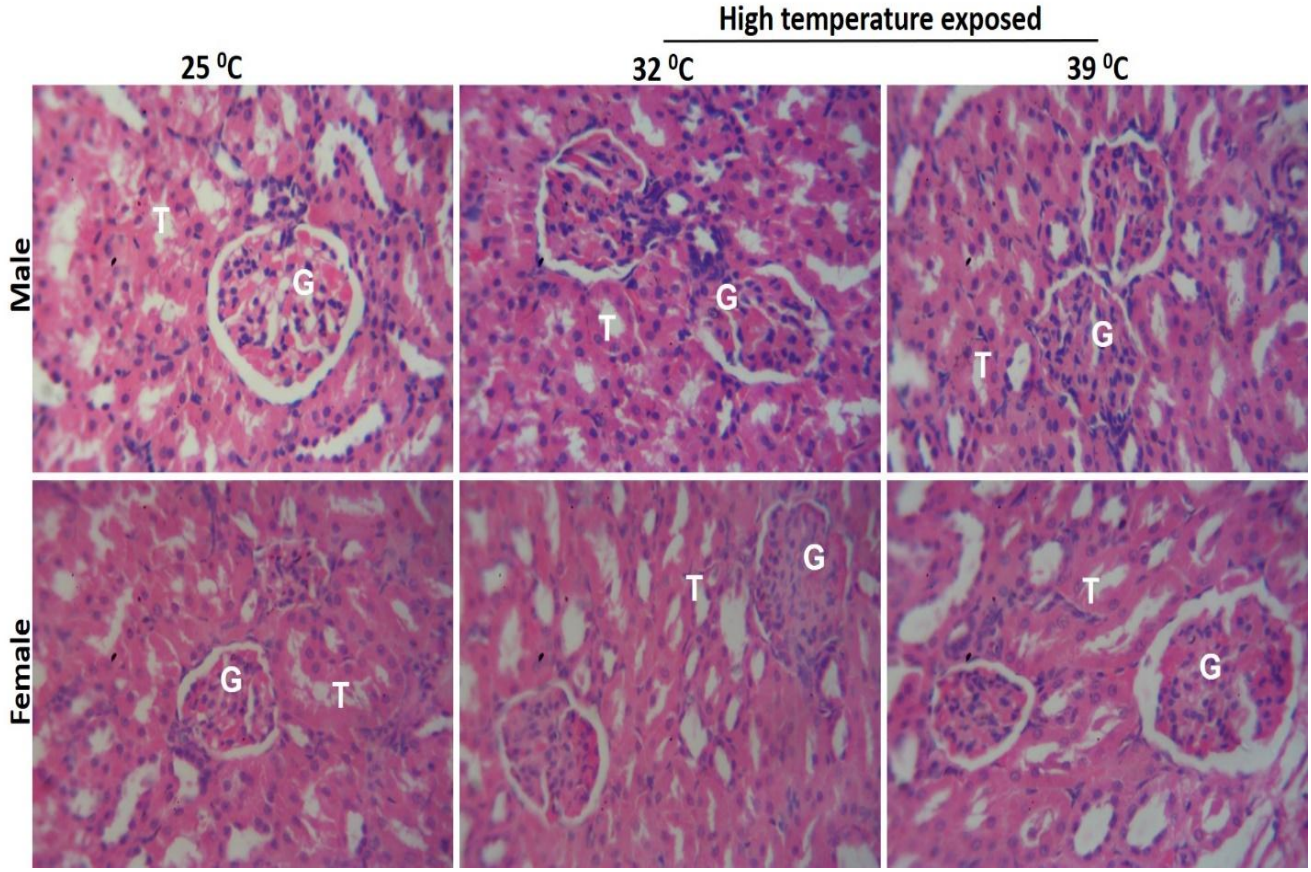

Plate. 10:
Histology of renal cortex of control and high temperature-exposed rats. H&E x 400. G – glomerulus; T – tubules.

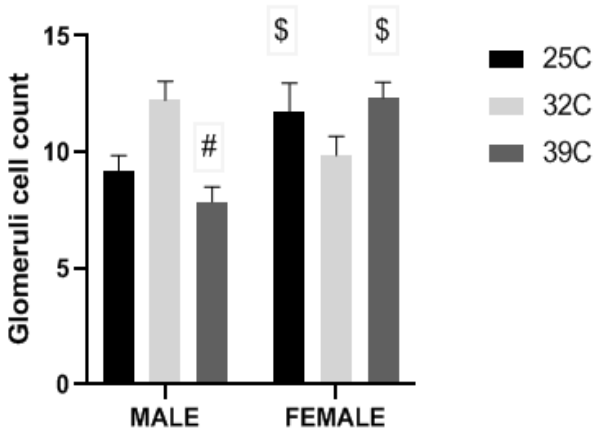

Fig. 11:
Effect of environmental temperature during gestation on histomorphometry of the kidney of offspring of Wistar rats. Values are mean ± SEM for 5 offspring per temperature group. P < 0.05. *P<0.05 compared to 25°C male group; #P<0.05 compared to 32°C male group; $P<0.05 compared to 39°C male group

Effect of maternal exposure to various environmental temperature during gestation on birth body weight of the offspring of Wistar rats.

The statistical analysis of birth weight suggest a significant reduction in birth in the male offspring exposed to 32°C and 39°C when compared with the 25°C male offspring. However, there no significant change in the birth weight of the female offspring exposed to various environmental temperatures.

However, in adulthood the significant reduction in body weight was only observed in male offspring exposed to 39°C during prenatal life.

Table 1:
The bdy weight of offspring following prenatal exposure to various environmental temperature

	Male Offspring			Female offspring		
Weight/ group	25ºC	32ºC	39ºC	25ºC	32ºC	39ºC
Birth weight (g)	4.3± 0.1	3.7±0 .02	3.3±0. 02*	2.2± 0.2	2.22± 0.1	1.9±0 .21
Weight at 12 weeks PND (g)	187± 2.4	179± 3.1	167±2. 46*	178± 2.2	181± 2.4	176± 3.4

*P<0.05 compared to 25°C group

DISCUSSION

This study provides insights into how prenatal elevated temperatures affect biochemical markers in both male and female offspring. The findings for male offspring raise important questions about the mechanisms behind increased serum creatinine and urea levels. Elevated serum creatinine, urea, and creatinine clearance levels suggest a potential metabolic response to higher temperatures, which may involve increased production rates despite the kidneys' ability to effectively clear these substances (Gounden et ak., 2024). References to heightened urea production or impaired clearance, as noted by Higgins 2016 and Gouden 2024, indicate a complex interplay between metabolism and kidney function that appears to vary with environmental stressors. This raises intriguing implications regarding how males might be physiologically adapting—or struggling to adapt—to higher prenatal-thermal conditions.

In contrast, the response observed in female offspring, where increased urine creatinine levels and clearance positively correlate with rising temperatures, suggests that their kidneys function more efficiently when exposed to this condition in utero. Increased urine creatinine levels and clearance in female offspring, positively correlating with rising temperatures, suggest a heightened efficiency of renal function n due to prenatal exposure to high environmental temperature. This contrasts with the generally more limited adaptive responses observed in male offspring. This might indicate sex-specific responses to prenatal environmental stress, potentially linked to hormonal differences or inherent physiological characteristics. Further exploration of these findings could involve examining the underlying mechanisms for these differing responses and how these metabolic changes might affect long-term health outcomes for both sexes.

In addition, increased MDA Level with a corresponding reduction in SOD and catalase activities in the male offspring of 32°C and 39°C suggest an increased exposure to oxidative stress in this tissue. However, in the female offspring, there was a reduction in MDA, SOD and catalase activities, this suggests a significant decrease in oxidative stress in this group. The study by Daenen *et al*. (2019) highlights the intricate relationship between oxidative stress and renal health. The results reinforce the idea that oxidative stress significantly influences the progression of renal disease, particularly due to the kidneys' high metabolic activity and vulnerability to oxidative damage.

Moreover, male offspring displayed significant variations in glomerular cell counts when compared with female offspring exposed to high environmental temperature during prenatal life Furthermore, the lack of significant changes in glomerular cell numbers in females points to possible sex-specific protective mechanisms against the adverse effects of thermal stress during gestation. The pattern of distribution of glomerular cell count suggests a possible association between the occurrence of oxidative stress and glomerular cell count. The reduced cell counts may be secondary to an increase in cell death associated with oxidative stress.

The study also highlights the physiological adaptations that occur during heat exposure. The hyperplastic response observed in male offspring at 32°C may reflect an evolutionary adaptation aimed at maintaining homeostasis. This mechanism might have been programmed during intra-uterine life in this offspring. However, the significant decrease in glomerular cell counts in the 39°C group raises concerns about the potential long-term implications for renal function, particularly under extreme temperature conditions. Exposure to a high environmental temperature as been previously reported to cause an increase in the occurrence of kidney diseases (Hansen *et al*. 2008; de Lorenzo and Liaño, 2017). The connection between heat exposure and conditions such as Acute Kidney Injury (AKI), Chronic Kidney Disease (CKD), and kidney stones underscores the urgency of understanding the effects of prenatal heat stress on kidney health.

In summary, the findings illustrate the complex interplay between gestational environmental factors, oxidative stress, and sexual dimorphism in renal responses. Understanding these relationships is crucial for developing preventative measures and therapeutic strategies to mitigate renal diseases linked to temperature fluctuations and oxidative stress exposure, especially in a changing climate where heat exposure is becoming more prevalent.

In conclusion, maternal exposure to increase environmental temperature during gestation might result in altered serum and urine analyte,glomeruli cell count and increased oxidative stress in the kidney of the offspring in a Wistar rats model.

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