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Effects of unilateral adrenalectomy on serum levels of liver and kidney function biomarkers and electrolytes in albino rats

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Abstract

Unilateral adrenalectomy allows patients indicated for the surgical removal of one of the adrenals (following adrenal neoplasms or other conditions that will lead to hyperaldrenalism) to lead a normal quality life. As part of a long term monitoring programme of the homeostatic status of such adrenalectomized individuals, knowledge of their pathophysiologic and biochemical profile is important. The present study evaluated the effects of unilateral adrenalectomy on the serum biochemical markers of liver and kidney function and serum levels of selected electrolytes in the albino rat model. Twelve female albino rats with a mean body weight of 215.37 ± 3.16 g were used for the study. The rats were randomly assigned to two groups of six rats each. Group 1 was unilaterally adrenalectomized following laparotomy, while laparotomy alone that left the adrenal glands intact was performed on Group 2 rats that were designated sham control group. Three weeks after the surgery, blood samples were collected from both groups and the serum were analyzed for levels of urea, creatinine, chloride, potassium, sodium, aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine transaminase (ALT), total protein (TP) and albumin. Unilaterally adrenalectomized rats had significantly ($p < 0.05$) higher serum levels of creatinine, urea and bilirubin when compared to sham control group (with intact adrenals). There were no significant differences between the two groups in all other parameters assayed. The finding in this study suggests that unilaterally adrenalectomized individuals may have a predisposition to kidney dysfunction and biliary disorders, and thus must be regularly monitored.

Keywords: Unilateral adrenalectomy; Albino rat model; Serum biochemical profile; Liver function; Kidney function; Electrolytes.

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Introduction

The first reported surgical removal of the adrenal glands was in 1914 following a case of adrenal gland neoplasm (Maccara and Mihai, 2016). Since then, adrenalectomy (the surgical removal of one or both adrenal glands) has been indicated and performed for various disease conditions. Indications for adrenalectomy include functional and non-functional adrenal gland tumours either with confirmed or suspicions of malignancy (Uludağ *et al.,* 2020) and any conditions causing hyperadrenalism, e.g. Cushing's syndrome (hypersecretion of glucocorticoids), Conn's syndrome (hypersecretion of aldosterone) and phaeochromocytomas which produce excess catecholamines (Uludağ *et al.,* 2020).

The adrenal glands, also known as supra renal glands, are small triangular-shaped endocrine glands located on top of each kidney and made up of two distinct parts; an outer adrenal cortex and an inner medulla, with each part producing a distinct variety of hormones (Burford *et al.*, 2017). The adrenal cortex produces three types of steroid hormones: mineralocorticoids, glucocorticoids and androgens. Mineralocorticoids (e.g. aldosterone) help in the regulation of blood pressure and electrolyte balance; the glucocorticoids (e.g. cortisol and cortisone) function in regulation of metabolism and immune system suppression; while the androgens are sex hormones produced and transported to the gonads and other target organs. The medulla of the adrenal gland produces the catecholamines (adrenaline and nor-adrenaline) responsible for triggering the body's so called 'fight or flight' response (Dutt *et al*., 2023).

Any indications for adrenalectomy must be properly evaluated to determine whether a complete or a unilateral adrenalectomy is required. In cases of complete adrenalectomy, the patients are placed on monitored lifelong hormone replacement therapy (Shen *et al*., 2006), but it has been reported that unilaterally adrenalectomized individuals can live a normal quality life without hormone therapy, following compensatory changes by the remaining adrenal gland (Citton *et al*., 2019).

Biochemical and pathophysiologic profiles have over the years been consistently used to evaluate and monitor health and disease states in man and animals (Moore *et al*., 2007). They have been very useful in the diagnosis of disease and monitoring of pathologies, efficacy of treatment protocols and prognoses.

The endocrinology of intact and completely adrenalectomized individuals have been extensively studied particularly in man, mostly as case studies. Some studies have investigated the response of adrenalectomized animals to varied treatment regimens and disease states vis-à-vis endocrinological changes, physiologic functions and some biochemistry. Again, most of these studies have been on completely adrenalectomized animals. However, there are no reports in literature available to the authors on the serum biochemical profile of unilaterally adrenalectomized animals. It is important that the pathophysiologic and biochemical status of unilaterally adrenalectomized individuals are profiled and documented as reference or guide. This is necessary for the purpose of further studies and as a guide in monitoring and managing the health and other disease conditions in these individuals. The present study evaluated the effects of unilateral adrenalectomy on the serum biochemical markers of liver and kidney function and serum levels of selected electrolytes in the albino rat model.

Materials and Methods

Twelve female albino rats with a mean body weight of 215.37 ± 3.16 g, were used for the study. They were acclimatized for 1 week, fed

standard rat feed (Chikun® Finisher, Crown Flour Mills, Lagos, Nigeria) and provided water *ad libitum* all through the duration of the experiment. Ethical approval was obtained from the University Ethics Committee (Approval Reference Number: MOUAU/CVM/REC/202401).

The rats were randomly assigned to two groups of 6 rats each. Group 1 rats underwent laparotomy and had left unilateral adrenalectomy, while Group 2 rats underwent laparotomy alone and their adrenal glands were not removed (Sham control group).

Before the surgery, the rats were pre-medicated with xylazine (5 mg/kg) and anaesthetized using ketamine at the dose of 35 mg/kg. Unilateral adrenalectomy was carried out using the paracostal approach as described by Fossum (2013), but with the glands removed intact without ligation of the blood vessels.

The rats were allowed three weeks to recover from the surgery under standard post-operative care after which they were euthanized using inhalation anaesthesia and blood was collected from the heart for serum biochemical analyses. The three weeks period was to allow for sufficient time for the rats to fully recover from the surgery and for monitoring sustained homeostasis and return to normal life after the remaining adrenal gland has assumed compensatory functionality. All procedures were in accordance with the prescribed guidelines of the Institutional Animal Research Ethics Committee (MOUAU/CVM/REC/202401).

Biochemical analyses were done following standard procedures. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity were determined based on the Reitman & Frankel colorimetric method (Reitman and Frankel, 1957). Serum total protein was assayed by the Biuret method (Tietz, 1995), while serum albumin levels was determined following the bromocresol green (BCG) dye-binding method (Doumas et al., 1971), and the globulin levels were calculated by subtracting the serum levels of albumin from the serum total protein levels. Serum urea levels were determined by the enzymatic colorimetric method (Tietz, 1983), while the serum creatinine levels were assayed by the Jaffe method (Henry, 1974). Serum bilirubin levels were determined by the Jendrassik colorimetric method (Garber, 1981). The conjugated and unconjugated bilirubin levels were also determined. These tests were done using Randox® test kits (Randox Laboratories Ltd., UK). Serum alkaline phosphatase (ALP) activity was determined based on the p-nitrophenyl phosphate substrate method (Kochmar and Moss, 1976); while the assay of serum sodium, potassium and chloride levels were done based on the colorimetric method (Henry, 1974; Young, 2001). The assays for ALP and the electrolytes were done using TECO test kits (TECO Diagnostics®, U.S.A).

Data obtained from the study were analyzed using IBM SPSS software® (Version 20). Student's t-test was used to compare the results of the two groups. Significance was accepted at $p < 0.05$. Summary results were presented as mean ± standard error of means (SEM) in tables and bar charts.

Results

Kidney function: The results of the serum urea and creatinine assay are shown in Table 1 and Figure 1. The Group 1 rats (that were unilaterally adrenalectomized) had a significantly higher ($p < 0.05$) serum level of urea and creatinine when compared to the Group 2 sham control group (Table 1). However, there was no significant difference ($p > 0.05$) between the groups when the urea: creatinine ratio for both groups were compared (Figure 1).

Table 1. Serum urea and creatinine levels of unilaterally adrenalectomized female albino rats, compared with a sham control group (intact adrenals).

Parameters (units in brackets)	Mean serum urea and creatinine levels ± standard error	
	Group 1 (Unilaterally adrenalectomized rats)	Group 2 (Sham control rat group with intact adrenals)
Creatinine (mg/dl)	1.44 ± 0.05 [a]	1.18 ± 0.15 [b]
Urea (mg/dl)	41.54 ± 2.11 [a]	31.26 ± 0.76 [b]

[a, b] Different alphabetical superscript in a row indicate significant difference between the means ($p < 0.05$)

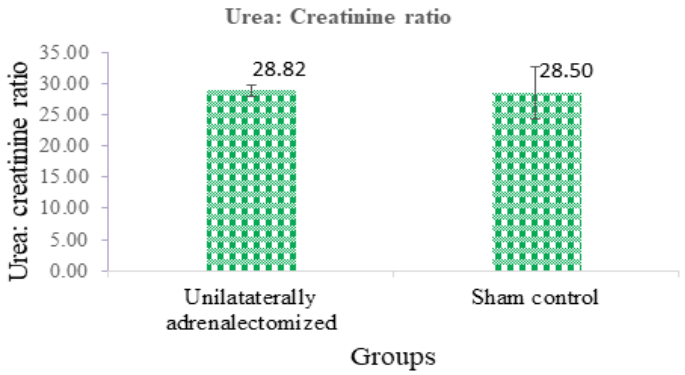

Figure 1. Ratio of serum urea: creatinine levels of unilaterally adrenalectomized female albino rats, compared with a sham control group (with intact adrenals).

Table 2. Serum chloride, potassium and sodium levels of unilaterally adrenalectomized female albino rats, compared with a sham control group (with intact adrenals).

Parameters (units in brackets)	Mean serum electrolyte levels ± standard error	
	Group 1 (Unilaterally adrenalectomized rats)	Group 2 (Sham control rat group with intact adrenals)
Chloride (mEq/L)	90.56 ± 8.51	90.42 ± 1.27
Potassium (mEq/L)	20.66 ± 1.22	22.53 ± 0.83
Sodium (mEq/L)	126.30 ± 3.37	116.84 ± 4.70

No significant difference between the means ($p > 0.05$)

Serum electrolytes: There was no significant difference ($p > 0.05$) in the serum concentrations of chloride, potassium and sodium ions of the unilaterally adrenalectomized group compared to the sham group (Table 2). There was also no significant difference ($p > 0.05$) in the chloride: sodium (Figure 2) and the sodium: potassium (Figure 3) ratios when the unilaterally adrenalectomized group was compared with the sham control group.

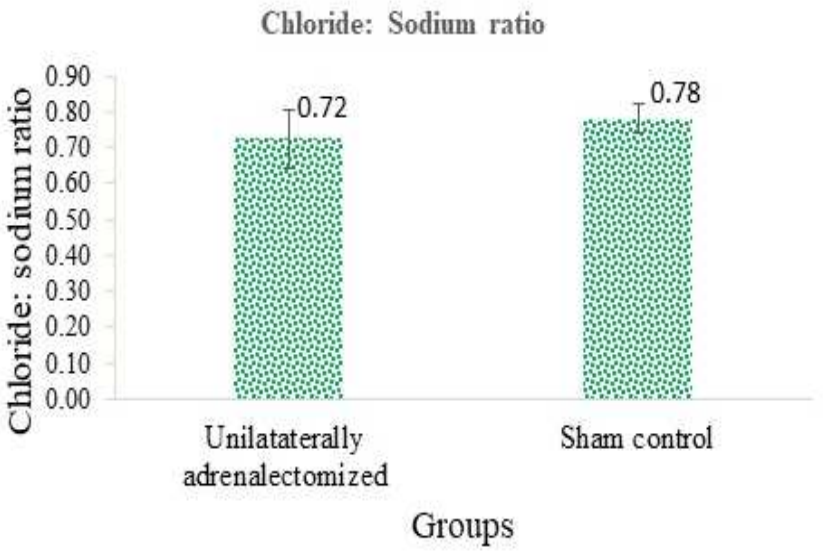

Figure 2. Serum levels of chloride: sodium ratio of unilaterally adrenalectomized female albino rats, compared with a sham control group (intact adrenals).

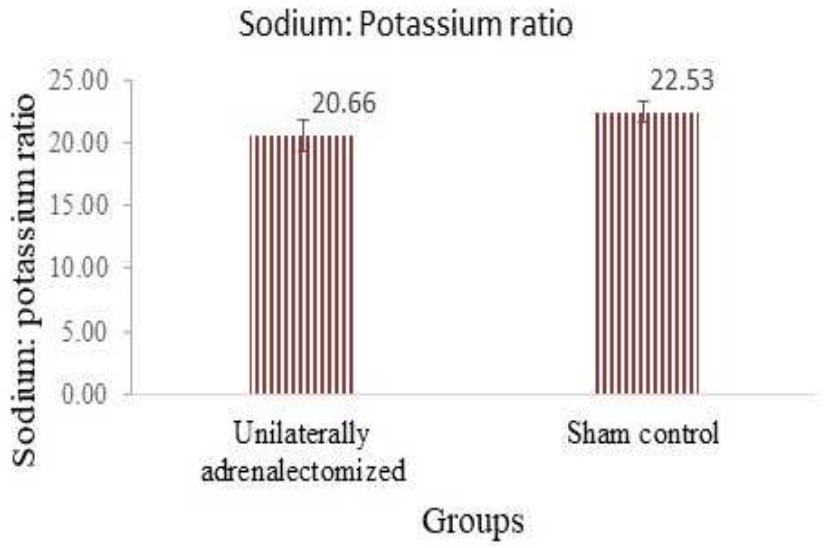

Figure 3. Serum levels of sodium: potassium ratio of unilaterally adrenalectomized female albino rats, compared with a sham control group (intact adrenals).

Liver function: There were no significant differences ($p > 0.05$) in the serum activity/levels of aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine transaminase (ALT), total protein (TP) and albumin between the unilaterally adrenalectomized group and the sham control group (Table 3). The serum total bilirubin levels of the adrenalectomized group was significantly ($p < 0.05$) higher than that of the sham control group (Table 3). The ratios of conjugated: unconjugated bilirubin, AST: ALT and Albumin: Globulin did not significantly ($p > 0.05$) differ between the two groups (Figures 4, 5 and 6).

Table 3. Serum levels of liver function test parameters of unilaterally adrenalectomized female albino rats, compared with a sham control group (intact adrenals).

Parameters (units in brackets)	Mean serum levels of parameters ± standard error	
	Group 1 (Unilaterally adrenalectomized rats)	Group 2 (Sham control rat group with intact adrenals)
Aspartate aminotransferase (IU/L)	27.76 ± 1.53	25.18 ± 2.26
Alanine aminotransferase (IU/L)	14.32 ± 1.39	13.04 ± 1.43
Alkaline phosphatase (IU/L)	102.36 ± 2.23	96.34 ± 2.09
Total Protein (g/dl)	5.84 ± 0.42	5.22 ± 0.31
Albumin (g/dl)	3.86 ± 0.19	3.78 ± 0.62
Globulins (g/dl)	1.98 ± 0.50	1.44 ± 0.37
Total bilirubin (mg/dl)	0.92 ± 0.06 [a]	0.62 ± 0.06 [b]

[a, b] Different alphabetical superscript in a row indicate significant difference between the means ($p < 0.05$)

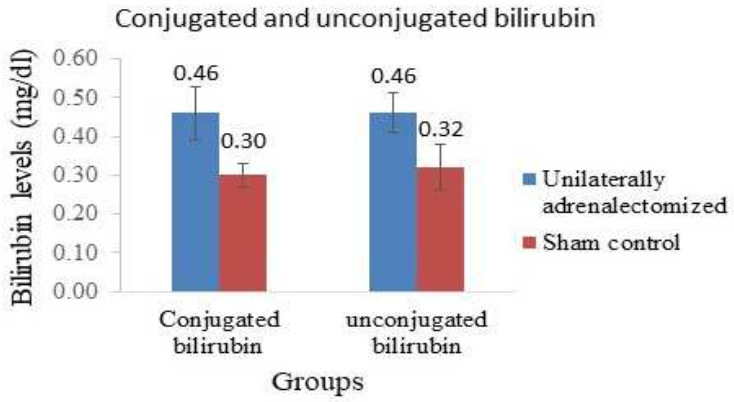

Figure 4. Serum levels of conjugated and unconjugated bilirubin of unilaterally adrenalectomized female albino rats, compared with a sham control group (intact adrenals).

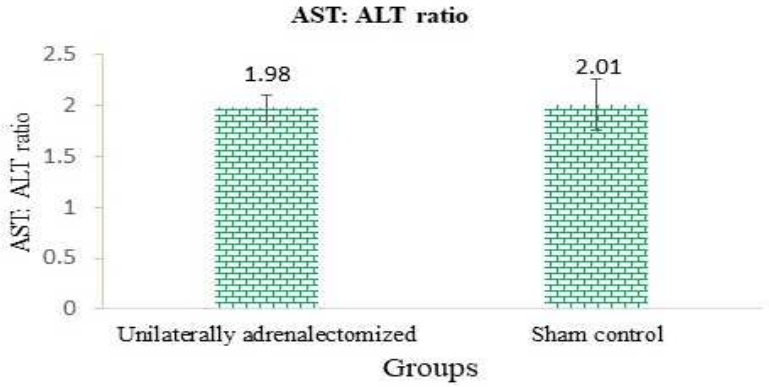

Figure 5. Serum activity of AST: ALT ratio of unilaterally adrenalectomized female albino rats, compared with a sham control group (intact adrenals).

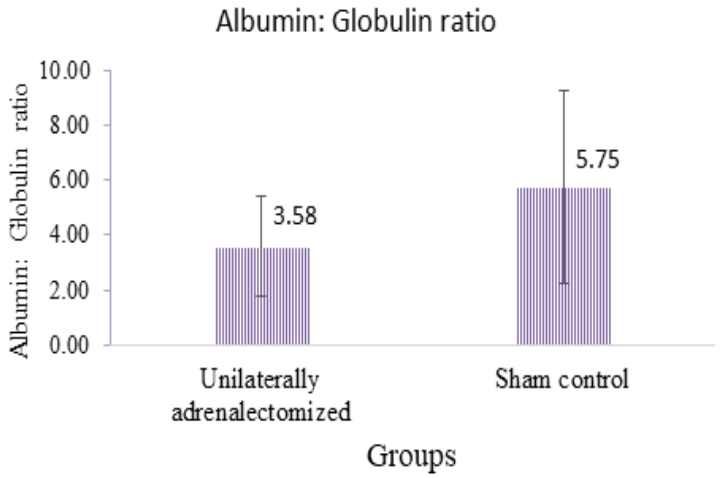

Figure 6. Serum albumin: globulin ratio of unilaterally adrenalectomized female albino rats, compared with a sham control group (intact adrenals).

Discussion and Conclusion

Serum concentration of urea and creatinine in animals and humans are routinely assayed to assist in the assessment of the functional status of the kidneys in health and disease. The urea to creatinine ratio (urea:creatinine) or UCR, together with the individual concentrations of both biochemical components give a more complete assessment of the functional status of the organs (Higgins, 2016). A consistent ratio as observed in this work indicated there was no disproportionate increase or decrease in the value of one component over the other. Serum urea and creatinine concentrations are affected by other factors other than kidney failure. These factors include; protein intake, endogenous protein catabolism, hydration status, hepatic urea synthesis, renal urea excretion (for urea), body muscle mass and assessment technique used (especially for creatinine) (Hosten, 1990). The findings in the present study that the individual serum concentrations of both urea and creatinine in the unilaterally adrenalectomized rats were significantly higher than that of the sham control group may be a subtle indicator of the vulnerability of the kidneys of the adrenalotomized rats to failure which may warrant further or regular monitoring in adrenalectomized individuals, perhaps using glomerular filtration rate (GFR) tests and other more direct confirmatory tests. This finding of significantly higher serum urea and creatinine is in agreement with earlier reports by Lee *et al*., (2019), which demonstrated that acute kidney injury occurred in individuals with primary aldosteronism after unilateral adrenalectomy.

The serum electrolyte panel is used to assess metabolic health, and thus reflects the electrolyte homeostatic status of individuals (Moore *et al*., 2007). The finding in the present study of no significant difference between the two rats groups in their serum levels of sodium, potassium and chloride is an indication that three weeks post-surgery, following recovery from the procedure, the unilaterally adrenalectomized rats, with their remaining adrenal gland were able to return to full homeostatic electrolyte balance, comparable with their intact counterparts.

The finding in the present study of no significant differences in the values of most of the liver function test parameters (except total bilirubin) is an indication that unilateral adrenalectomy did not lead to any significant hepatocellular damage or hepatic synthetic

dysfunction. The findings of significantly higher serum total bilirubin in the adrenalectomized rats points to possible biliary disorder associated with unilateral adrenalectomy.

Conclusion and Recommendations: Unilateral adrenalectomy in rats led to significantly higher serum levels of creatinine, urea and total bilirubin in adrenalectomized rats compared to sham control rats with intact adrenals. This finding suggests that there may be need to regularly monitor unilaterally adrenalectomized individuals against a possible predisposition to kidney failure and biliary disorders. The study further highlighted the need to profile the effect of unilateral adrenalectomy on the physiology and biochemistry of humans and other domesticated species for reference and monitoring purposes. Further studies are recommended to assess the effect of unilateral adrenalectomy on endocrine and reproductive health of subjects.

Conflict of Interest

The authors declare that there is no conflict of interest.

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