

Effect of Pre and Post Infection Administration of Zinc and Selenium on some Biochemical indices in Wistar Rats infected with *Trypanosoma brucei*

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Authors' contributions

This work was carried out in collaboration among all authors. Author TT designed the study, carried out the experiments and wrote the first draft of the manuscript. Author KMA designed and supervised the study. Author AOJ reviewed and edited the manuscript. Authors MAK and RA manage the analysis of the study and contributed to drafting of the manuscript. Authors TA and JLI managed the literature search. Author WDGC performed the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The effect of pre and post-infection administration of zinc and selenium on *Trypanosoma brucei brucei* infection in wistar rats on some biochemical parameters were investigated.

Study Design: The study was designed to evaluate the effect of pre and post infection administration of zinc and selenium on *Trypanosoma brucei brucei* infection in wistar rats.

Place and Duration of Study: The study was conducted at the Nigerian Institute for

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Trypanosomiasis Research (NITR), Kaduna and Department of Biochemistry, Ahmadu Bello University (ABU), Zaria, between January 2014 to March 2014.

Methodology: Fifty four (54) wistar rats were divided into nine groups of six (6) rats each. Groups III-IX were infected intraperitoneally with 1×10^3 parasite load. Animals in group III were infected but untreated while the infected/treated groups received prophylactic (IV, V and VI) and therapeutic (VII, VIII and IX) treatment with zinc and selenium 50mg/kg and 10mg/kg body weight respectively.

Results: Results obtained showed that serum alkaline phosphatase (ALP), alanine amino transferase (ALT) and aspartate amino transferase (AST) activities in the infected-untreated control group were significantly different ($P < 0.05$) and higher as compared to infected treated and normal control. Similarly, the two minerals significantly decreased ($P < 0.05$) the levels of Urea and Creatinine in the infected treated when compared to the infected untreated rats, with the exception of creatinine value of the post-infected treated with selenium where there was no significant ($P > 0.05$) decrease. On the other hand, a significant ($P < 0.05$) increase in serum levels of total Protein, albumin and total bilirubin and no significant ($P > 0.05$) difference in direct bilirubin was recorded in infected treated group compared to infected untreated and normal control.

Conclusion: It was concluded that administration of zinc and selenium ameliorate the infection-induced biochemical changes in tissues and organs associated with *Trypanosoma brucei brucei* infection in Wistar rats.

Keywords: Prophylactic; therapeutic; *Trypanosoma brucei brucei*; biochemical parameters.

1. INTRODUCTION

African trypanosomiasis is a parasitic disease that affects both humans, domestic and wild animals, posing a significant health challenge, especially in sub-Saharan Africa [1]. It is caused by flagellate protozoan parasite of the genus *Trypanosoma* which is transmitted by tsetse fly, a blood sucking fly of the genus *Glossina*. The disease is called sleeping sickness in humans and Nagana or "Sammore" in cattle and Surra in Camels [2]. Among the important species that cause the disease in livestock are *Trypanosoma vivax*, *Trypanosoma congolense* and *Trypanosoma brucei brucei* in cattle, sheep and goats, while *Trypanosoma evansi* in camels and *Trypanosoma simiae* in pigs [3,4]. *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense* cause the disease in humans. Trypanosome infections cause symptoms manifested by intermittent fever, anemia, and pyrexia, lymphatic enlargement with hepatomegaly.

Trypanosomiasis still remains a major constraint to human and animal health, and livestock production in most countries of Tropical Africa as well as constituting a major threat to food security in several parts of sub-Saharan Africa [5,6,7,1]. Nagana prohibits cattle rearing in a large area of Africa causing further malnutrition. Trypanosomiasis is fatal if left untreated and control is principally achieved by reducing tsetse

population, chemotherapy and chemoprophylaxis [8]. Most of these drugs for the control of both animal and human trypanosomiasis are chemically related [9] and have been in use for decades [10,11]. Also drug regimens are cumbersome in addition to being expensive as well as increasing incidence of resistance among the trypanosomes to the existing drugs. Formulations or natural products which boost the host immune system and possibly reduce parasitaemia or completely remove parasites from the host system could contribute extensively to the control or management of the disease [12,13].

Zinc, one of the most abundant trace elements in the body has been recognized as a micronutrient of diverse biological, clinical and global public health importance [14,15,16]. It is contained in hundreds of enzymes and involved in numerous aspect of cellular metabolism. It is also required for growth, optimum performance and modulation of immune system, partly due to its role as a co-factor of more than three hundred enzymes [17]. Zinc plays an important role in the structure and function of biological membranes [18]. In addition, selenium (Se) is an essential component of antioxidant enzymes such as glutathione peroxidase (GPx), thioredoxin reductase (TrxR) and iodothyronine deiodinases (IDD); it is also a natural antioxidant [19] and immunostimulant [20,21]. Based on these considerations, the aim of this study was to

evaluate the effect of zinc and selenium treatment on serum biochemical parameters of pre and post infection treated rats infected with *Trypanosoma brucei brucei*.

2. MATERIALS AND METHODS

2.1 Experimental Animals and Design

Fifty four (54) wistar rats of both sexes, weighing between 150-250 g, were used for the experiment. The rats were purchased from the animal house of Animal African Trypanosomiasis Research Department (AATRD), Nigerian Institute for Trypanosomiasis Research (NITR), Kaduna, Nigeria. They were fed, with standard feed (Vital Feeds, Jos, Nigeria) and water was provided *ad libitum*. The rats were randomized into nine (9) groups, with six (6) rats per group. Groups I and II served as controls, while group III served as infected untreated. Groups IV, V and VI represented the pre-treated infected rats that were administered intraperitoneally with daily dose of 50 mg per kilogram body weight of zinc gluconate [22], 10mg per kilogram body weight of selenium (Rayman, 2012) and combination of zinc gluconate and selenium respectively for seven (7) days. Rats in groups VII, VIII and IX represented the post-infected treated groups that were administered intraperitoneally with daily dose of 50mg per kilogram body weight of zinc gluconate [22], 10mg per kilogram body weight of selenium [23] and combination of zinc gluconate and selenium immediately parasite was sighted in the blood for seven (7) days. This study was scrutinized and approved by the Nigerian Institute for Trypanosomiasis Research Committee on Medical and Scientific Research Ethics. General care of the rats was provided in accordance with the Institutional Animal Care and Use Committee, as outlined in the Guide for the Care and Use of Agricultural Animals in Research and Teaching (https://www.aaalac.org/about/Ag_Guide_3rd_ed.pdf).

2.2 Trypanosome Strain/Infection

Trypanosoma brucei brucei (Federe strain) was obtained from the stabilates that was cryopreserved in Vector and Parasitology Research Department, Nigerian Institute for Trypanosomiasis Research (NITR), Kaduna, Nigeria. The parasite was maintained by serial passage in a donor rat. The infected blood from the donor rat (at peak parasitaemia) was collected and diluted with phosphate buffered

saline (PBS). The number of parasites in the diluted blood was determined as described by [24] and 0.1mL of blood containing approximately 1×10^3 trypanosomes was inoculated intraperitoneally into each rat in the infected groups.

2.3 Sample Collection and Biochemical Analyses

After the experimental period, the rats in different groups were decapitated under chloroform anaesthesia and bled via cardiac puncture. Blood samples were collected in tubes without anticoagulant to separate serum for the estimation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were assayed by the colorimetric method of Reitman and Frankel [25] using Randox assay kits. Serum level of alkaline phosphatase (ALP) was quantified by optimized standard method described by Haussament [26] using Randox assay kits. Total protein was determined colorimetrically according to the method described by Fine [27] using Randox assay kits. Serum albumin was determined by the method of Doumas et al. [28] using randox assay kit.

2.4 Statistical Analysis

Results were expressed as mean \pm standard deviation (SD). The data obtained was analyzed using one-way analysis of variance (ANOVA). The difference between the experimental groups were compared using the Duncan Multiple Range Test. P values less than 0.05 ($P < 0.05$) were taken as significant.

3. RESULTS AND DISCUSSION

3.1 Effects on Liver Marker Enzymes

Biochemical effects of pre and post infection administration of zinc and selenium on liver marker enzymes such as aspartate amino transferase (AST), alanine amino transferase (ALT) and alkaline phosphatase (ALP) in normal and *T. b. brucei* infected rats is presented in Table 1. The result shows that there was no significant ($P > 0.05$) difference in these marker enzymes in the animals that received combined Zn + Se without infection compared to the normal control. The result revealed that there was significantly ($P < 0.05$) higher values in the serum activities of AST, ALT and ALP in *Trypanosoma brucei brucei* infected untreated control when

compared to the normal and Zn + Se control groups. The result also shows significantly ($P<0.05$) higher values in the serum activities of AST, ALT and ALP in the pre-treated infected groups with the exception of the pre-treated infected group that received Zn which was not significantly ($P>0.05$) higher in AST and ALT compared to the normal and combined Zn + Se control groups. The pre-treated infected administered with Zn, Se, showed a significantly ($P<0.05$) higher values in the serum activities of AST, ALT and ALP with the exception of the group that received Zn + Se combined which was not significantly ($P>0.05$) higher in AST value compared to the normal and combined Zn + Se control groups.

The pre and post infected treated groups showed significantly ($P<0.05$) lower values in serum activities of AST, ALT and ALP compared to the infected untreated control group (Table 1).

3.2 Effects on Liver Function Parameters

Table 2 presents the results of effect of pre and post- infection administration of zinc and selenium on serum zinc level; liver function parameters of Total Protein (TP), Albumin (ALB) concentrations and the Bilirubin's: Total Bilirubin (TB), Direct Bilirubin (DB) and Indirect Bilirubin (IB).The rats that where infected untreated showed a significantly ($P<0.05$) lower values of TP, ALB and higher values in the levels of TB and IB compared to the normal and combined Zn +Se control groups. There was significantly ($P<0.05$) lower value in TP by Zn +Se combined in the pre-treated infected group compared to the normal and combined Zn +Se control groups. There was also a significantly ($P<0.05$) lower value in ALB by Zn, Se and combined Zn +Se

compared with the normal and combined Zn +Se control groups. The result also shows significantly ($P<0.05$) higher level of serum Zn in the pre-treated infected group administered with zinc, no significant ($P>0.05$) difference in Zn level by Se administered group and not significantly ($P<0.05$) higher in serum Zn level by the combined Zn +Se treated group compared to the normal and combined Zn +Se control groups. On the other hand, rats that where infected with *T. brucei brucei* post administration of Zn, Se and combined Zn +Se shows no significant ($P>0.05$) difference in TP and significantly ($P<0.05$) lower in ALB when compared to the normal and combined Zn +Se control groups. Also the post-infected treated rats was not significantly ($P<0.05$) higher in TB, serum Zn level and no significant ($P>0.05$) difference in DB, IB, when compared to the normal and combined Zn +Se control groups. All pre and post-infected treated groups shows increase ($P<0.05$) in TP and significantly ($P<0.05$) higher in ALB compared to the infected untreated group. There was significantly ($P<0.05$) lower values of TB, IB and no significant ($P>0.05$) difference in DB when compared to the infected untreated group. When the infected pre and post-infected treated groups were compared to the trypanosomiasis infected untreated control group, there was significantly ($P<0.05$) higher level of serum Zn in the pre-treated infected Zn administered group, no significant ($P<0.05$) difference in Zn level in the pre-treated infected Se administered group, and not significantly ($P<0.05$) higher in Zn level in the pre-treated infected Zn +Se administered group, post-infected treated with Zn, post-infected treated with Se and post-infected treated with combined Zn +Se compared to the infected untreated group (Table 2).

Table 1. Biochemical effect of pre and post infection administration of zinc and selenium on liver marker enzymes in wistar rats Infected *Trypanosoma brucei brucei*

Group	AST (U/l)	ALT (U/l)	ALP (U/l)
NC	33.50±4.85 ^a	33.30±1.75 ^a	120.17±3.67 ^a
N+ Zn +Se	35.00±3.58 ^a	34.67±2.16 ^a	123.83±4.14 ^a
Test Control	51.33±3.01 ^d	52.83±4.11 ^d	258.67±12.43 ^e
PRE TI +Zn	35.5±0.83 ^{ab}	36.17±0.79 ^{ab}	204.83±1.91 ^c
PRE TI + Se	44.50±4.22 ^c	35.12±2.89 ^{ab}	217.33±6.19 ^{cd}
PRE TI + Zn + Se	38.00±3.85 ^b	31.50±1.83 ^a	168.50±4.42 ^b
POST TI + Zn	41.20±5.58 ^{bc}	45.33±2.47 ^c	213.00±2.29 ^{cd}
POST TI + Se	42.16±6.01 ^{bc}	46.33±3.03 ^c	231.17±3.56 ^d
POST TI + Zn + Se	36.83±2.53 ^{ab}	40.83±1.76 ^b	200.50±2.32 ^c

Values are means ± SD of six replicate determinations. Values with different superscript down the column are significantly different ($P<0.05$). NC: Normal Control rats, N + Zn +Se: Normal rats + Zinc + Selenium, TC: Trypanosomiasis Control, PRE TI + Zn: Pre-Treated Infected + Zinc, PRE TI + Se: Pre-Treated Infected + Selenium, PRE TI + Zn + Se: Pre-Treated Infected + Zinc + Selenium, POST TI + Zn: Post-Treated Infected + Zinc, POST TI + Se: Post-Treated Infected + Selenium, POST TI + Zn + Se: Post-Treated Infected +Zinc + Selenium. AST: Aspartate amino transferase, ALT: Alanine amino transferase, ALP: Alkaline phosphatase

Table 2. Effects of pre and post infection administration of zinc and selenium on liver function parameters and serum zinc in *Trypanosoma brucei brucei* infected wistar rats

Group	TP (g/dl)	ALB (g/dl)	TB (mg/dl)	DB (mg/dl)	Zinc ($\mu\text{mol/l}$)
NC	44.17 \pm 1.47 ^b	42.67 \pm 1.75 ^e	10.88 \pm 1.12 ^a	6.52 \pm 0.48 ^a	0.49 \pm 0.30 ^a
N+ Zn +Se	42.33 \pm 1.50 ^b	40.00 \pm 2.28 ^e	10.13 \pm 1.39 ^a	7.10 \pm 0.42 ^a	1.00 \pm 0.37 ^{ab}
TC	37.83 \pm 3.54 ^a	31.83 \pm 2.48 ^a	14.15 \pm 1.29 ^c	7.08 \pm 0.60 ^a	0.32 \pm 0.69 ^a
PRE TI +Zn	40.17 \pm 0.52 ^{ab}	37.50 \pm 1.64 ^{cd}	11.62 \pm 1.28 ^{ab}	6.90 \pm 0.85 ^a	1.32 \pm 0.65 ^b
PRE TI + Se	39.67 \pm 2.92 ^{ab}	36.50 \pm 2.26 ^b	11.85 \pm 1.02 ^{ab}	7.00 \pm 0.84 ^a	0.42 \pm 0.29 ^a
PRE TI + Zn + Se	44.47 \pm 2.56 ^b	39.83 \pm 0.47 ^d	11.01 \pm 0.65 ^a	6.83 \pm 0.45 ^a	0.95 \pm 0.22 ^{ab}
POST TI + Zn	42.67 \pm 1.75 ^b	34.67 \pm 2.26 ^b	12.88 \pm 1.07 ^b	7.63 \pm 0.38 ^a	0.91 \pm 0.50 ^{ab}
POST TI + Se	38.83 \pm 4.00 ^{ab}	32.00 \pm 1.67 ^{ab}	12.20 \pm 1.84 ^{ab}	7.02 \pm 0.58 ^a	0.48 \pm 0.30 ^a
POST TI +Zn +Se	43.03 \pm 3.67 ^b	36.83 \pm 2.32 ^c	11.78 \pm 0.98 ^{ab}	6.00 \pm 0.31 ^a	0.85 \pm 0.30 ^{ab}

Values are means \pm SD of six replicate determinations. Values with different superscript down the column are significantly different ($P < 0.05$). NC: Normal Control rats, N + Zn +Se: Normal rats + Zinc + Selenium, TC: Trypanosomiasis Control, PRE TI + Zn: Pre-Treated Infected + Zinc, PRE TI + Se: Pre-Treated Infected + Selenium, PRE TI + Zn + Se: Pre-Treated Infected + Zinc + Selenium, POST TI + Zn: Post-Treated Infected + Zinc, POST TI + Se: Post-Treated Infected + Selenium, POST TI + Zn + Se: Post-Treated Infected + Zinc + Selenium. TP: Total protein, ALB: Albumin, TB: Total bilirubin, DB: Direct bilirubin

3.3 Effect on Kidney Function Parameters

Fig. 1 shows the mean Creatinine and Urea concentrations in the serum of pre and post-infection administration of zinc and selenium in normal and trypanosomiasis infected rats. The result indicates that, there was significantly ($P < 0.05$) higher level in concentrations of creatinine and urea in *T. b. brucei* infected untreated compared to the normal and combined Zn +Se control groups. In the pre-treated

infected groups, there was significantly ($P < 0.05$) higher level of creatinine and urea concentrations compared to the normal and combined Zn +Se control groups. There was also significantly ($P < 0.05$) higher level of creatinine and urea concentrations in the post-infected treated groups, with the exception of the group that was administered with combined Zn +Se where there was no significant ($P < 0.05$) difference in creatinine level compared to the normal and combined Zn +Se control groups.

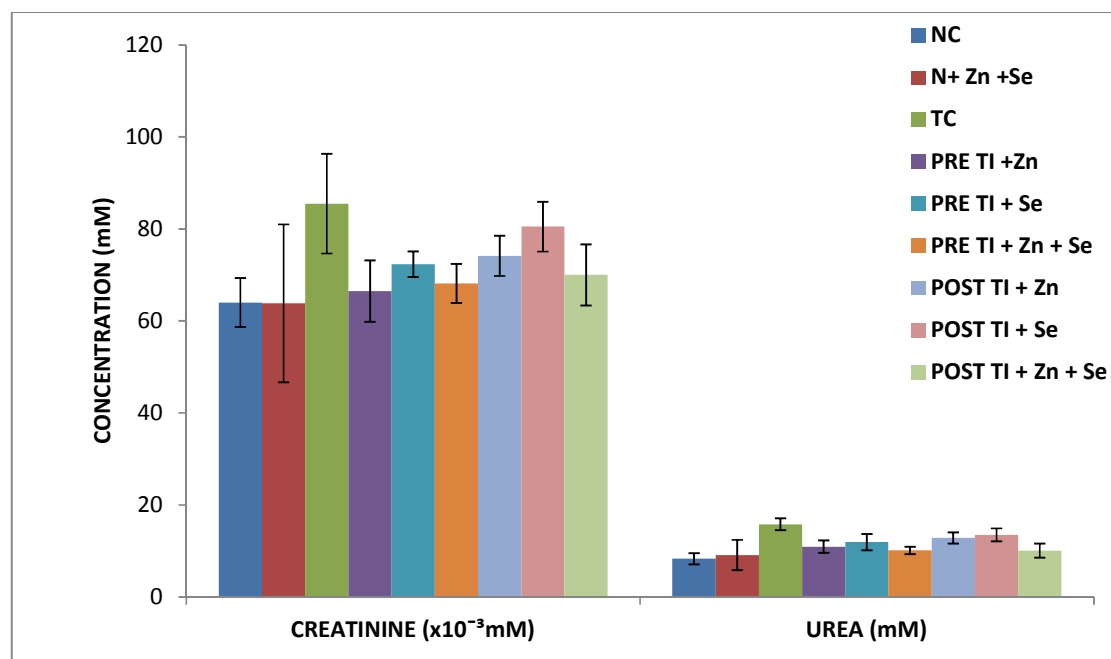


Fig. 1. Biochemical Effect of pre and post infection administration of zinc and selenium on serum creatinine and urea in wistar rats infected with *Trypanosoma brucei brucei*
Significant from normal control, * $P < 0.05$

3.4 Discussion

Trypanosoma brucei brucei infection, like other trypanosome infections may precipitate increased biochemical changes in the host in response to invading parasites and these changes in part could be responsible for infection-induced tissue damage. There are many enzymes, found in the serum that did not originally originate from the serum. During tissue damage, some of these enzymes from the liver cytosol find their way into the blood stream probably by leakage or changes in the permeability of liver membranes [29]. Generally, hepatic injury is often associated with alterations in the serum and liver levels of some enzymes notably Aspartate amino transferase (AST), Alanine amino transferase (ALT) and Alkaline phosphatase (ALP) [30]. The increase in serum alkaline phosphatase activity may indicate hepatic damage probably by the altered cell membrane permeability leading to the leakage of the enzymes from the tissues to the serum [31]. Alanine and aspartate amino transferase are considered to be sensitive indicators of hepatocellular damage and within limit can provide a quantitative evaluation of the degree of damage to the liver [32]. Infection with *T. brucei brucei* damaged the hepatic cells leading to a significant increase in serum levels of AST, ALT, and ALP. Higher levels of serum AST, ALT, and ALP activities were observed in infected untreated rats. These results are in agreement with previous studies where ALT was elevated in *Trypanosoma evansi* infected [33] and *T. brucei brucei* infected [34] animals. Several other studies have also reported elevated serum AST, ALT, and ALP (Abd El-Baky and Salem, 2011) [35] (Oluwatosin et al., 2013). Since these enzymes are the major liver marker enzymes; the elevation of these enzymes is usually an indication of liver damage, haemolytic conditions or partly to cellular damage caused by lysis or destruction of the trypanosomes [34]. Apparently it appears that the membrane damage seems to be the prime culprit for the marked increase in the serum marker enzymes, AST, ALT, and ALP. Serum levels of total protein (TP), total bilirubin (TB) and direct bilirubin (DB) are indices used to assess liver function as well as disease progression [36]. Serum levels of total protein and albumin were reduced significantly in the infected untreated. However administration of zinc and selenium led to elevation of total protein and albumin levels. The increased synthesis of protein occurs at the expense of muscle protein catabolism and loss in body weight. The gradual

decrease in serum total proteins, observed in this study, agrees with finding of [37], but contradicts observations made in sheep infected with *T. brucei* by Taiwo et al. [38], who observed no change in levels of total plasma proteins but in the later stage the levels increased significantly above pre-infection levels. Albumin is synthesized in the liver; therefore decrease in albumin concentration may be attributed to the damage in the liver where there could be less synthesis of albumin. This result obtained here agrees with that of Ogunsanmi et al., [39] who studied the serum biochemical changes in West African dwarf sheep experimentally infected with *T. brucei*. They found that the serum albumin values were markedly decreased. The findings suggest that there might be a hepatic and/or renal malfunction. Similar observations were noticed by Arora and Pathak [40] and Yusuf et al. [32]. The cause of the decrease in albumin is difficult to elucidate. Albumin is a negative acute phase protein during trypanosomiasis [41]. Its decrease could result from reduced synthesis in the liver as part of the acute phase response, loss through the kidney and intestine or increased utilization by the trypanosomes as a nutrient, since they require it for optimal survival [42]. Bilirubin is the main bile pigment that is formed from the breakdown of heme in the red blood cells. In addition, it is transported to the liver where it is secreted by the liver into the bile. As such interference with the normal liver functions affects its rate of conjugation or excretion. Thus a high level of bilirubin is used as indices for liver function and bile excretion status [43]. The present results showed a significant ($p < 0.05$) higher level of total Bilirubin in *T. brucei brucei* infected untreated control. The high level of total bilirubin in infected untreated rats in this experiment supports earlier observations in several trypanosome-infected animals [44,45]. Conjugation of bilirubin is a prerequisite for its excretion into the bile. The bilirubin formed from breakdown of red blood cells in the reticulo endothelial cells are transported in plasma bound to albumin [46], so the increase in bilirubin is suggestive of haemolytic anemia which may be due to the activity of proliferating parasites. It could also be associated to the inability of the liver to conjugate bilirubin [47]. The liver detoxifies harmful substances secretes bile into the intestine synthesizes and stores up important material, hence, it is common in clinical practice to screen for liver disease, monitor the progression of a known disease and monitor the effect of potentially hepatotoxic drugs [48]. Creatinine and urea are some of the indices for

assessment of kidney function. The kidney helps in maintaining homeostasis of the body by reabsorbing important material and excreting waste products. Creatinine is a waste product formed in muscle by creatinine metabolism. Creatinine is synthesized in the liver, passes into the circulation and is taken up almost entirely by skeletal muscle. Its retention in the blood is evidence of kidney impairment. Urea is the main end product of protein catabolism. Amino acid deamination takes place in the liver, which is also the site of urea cycle, where ammonia is converted into urea and excreted through urine. It represents 90% of the total urinary nitrogen excretion. Urea varies directly with protein intake and inversely with the rate of excretion. Renal diseases which diminish the glomerular filtration lead to urea retention. Infection with *T. brucei brucei* caused nephrotoxicity as indicated by significantly ($P < 0.05$) higher levels in serum urea and creatinine concentration. These results were in agreement with earlier findings [49,35,45].

4. CONCLUSION

Administration of zinc and selenium significantly ($P < 0.05$) lowered urea and creatinine levels in the pre and post-infected treated rats. The significant decrease in urea and creatinine level especially in the pre-treated infected groups indicated the ability of the micronutrients to provide some degree of protection to the kidneys during the course of the disease. We therefore suggest that the use of zinc and selenium may have significant application in the management of African trypanosomiasis.

CONSENT

All authors declare that 'written informed consent was obtained for publication of this report.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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