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Effects of *Trypanosoma brucei* on thyroid hormones in albino rats

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Abstract

Infections with trypanosomes bring about various modifications in the body. Thyroid hormone affects almost all body organs. Thyroids are secreted by the thyroid gland in three forms namely; triiodothyronine (T3), tetraiodothyronine (T4) and thyroid stimulating hormone (TSH). The aim of this research is to investigate the effects of *Trypanosoma brucei* on thyroid hormone and the functioning of liver and kidney in albino rats. The effect of *T. brucei* on these hormones was investigated by setting up two groups A and B (treatment and control) each comprising of ten albino rats. The control group were not infected by *T. brucei* while the treated group were infected. The concentrations of the thyroid hormones in serum were measured using Enzyme-Linked Immunosorbent Assay (ELISA) at seven-day interval for a period of twenty-eight days. Data were analyzed using the graph pad prism. There were no significant changes (p>0.05) observed in the level of TSH in week 1 of the treated group (3.09 ± 0.14) compared to the control (2.77 ± 0.19). At week 2 there was also no-significant decrease (p>0.05) in TSH level (3.04 ± 0.20) compared to control (3.35 ± 0.13). At week 3, there is significant decrease in the treated group when compared to the control (2.74 ± 0.11 vs. 3.40 ± 0.13). In the first week of treatment T3 level was non-significant when compared to the control group (0.20 ± 0.02 vs. 0.23 ± 0.02); T3 level was significantly lower (p< 0.05) in the second week compared to the control (0.12 ± 0.01 vs. 0.23 ± 0.03). At week three T3 level was significantly lower (p<0.05) compared to the control group (0.15 ±0.01 vs. 0.19 ± 001). There was a non-significant decrease (p>0.05) in the level of T4 in the treated group when compared to the control group at week 1 (5.42 ± 0.23 vs. 5.60 ± 0.21). At week 2 T4 level was non-significantly lower (p>0.05) in treated group compared to group B (5.31 ± 0.25 vs. 5.87± 0.15). At week 3 group A significantly reduced (p<0.05) in the treated group compared to the control (4.81 ± 0.24 vs. 5.65 ± 0.10). In conclusion, *Trypanosoma brucei* infection depresses thyroid gland functions which causes reduced production of the thyroid hormones which in turn causes hepatic and renal toxicities in albino rats.

Key words: *Thyroid hormones, Trypanosoma brucei, Infection, Albino rats*

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1. Introduction

African trypanosomiasis popularly known as sleeping sickness is the name of various diseases in vertebrates caused by a microscopic flagellated protozoan of the genus *Trypanosoma* (Center for Disease Control CDC, 2020; World Health Organizations WHO, 2021). It is an ailment that is transferred into the body through a bite by the tsetse fly and is endemic in thirty-six countries in sub-Saharan Africa where there are tsetseflies. The disease is deadly without treatment (WHO, 2021). It is a disease of humans and animals that have similar cause or origin, distribution, pattern and disease conditions (Dietmar, 2008). The pathogen live and multiply extracellularly in blood and tissue fluids of their hosts (Molyneux *et al*., 1996). Populations most affected are those living in remote areas where access to adequate health services is limited. In addition, poverty, war and displacement of population are key factors that aid the spread of the disease. African trypanosomiasis in humans takes two faces, with subject to the subspecies of the parasite in question: *Trypanosoma brucei gambiense* is the most frequently reported with 95% cases (WHO, 2021). It also affects economic development in Africa; about five hundred million farmers in the villages of Africa have been made to live in lack and under food scarcity (Deveze, 2010; Liana *et al*., 2020).

Averagely, 70,000 cases are reported yearly in the sub-Saharan Africa and above a million cattle die each year due to trypanosomiasis and economic loss of between $2 and $4.5 bn annually (Moore *et al*., 2011). The pathogen is rated 9th out of the twenty-five human transmittable diseases in Africa because of its socioeconomic effect (Geiger *et al*., 2011).

Animal trypanosomiasis remains a key restraint to livestock production in sub-Saharan Africa regardless of numerous policies in place to curb, treat and eradicate the disease. The disease is caused by several species of trypanosomes, and the species and strain of parasite can have great influence on the severity and course of infection, and also the epidemiology of host-parasite-vector relationships (Auty *et al*., 2015). The major pathogenic trypanosome species responsible for causing disease in animals are *Trypanosoma congolense, T. vivax, T. brucei brucei and T. simiae* (Adamu *et al*., 2009). Although humans and animals are infested by *Trypanosoma brucei*, livestocks are frequently infected due to tsetsefly feeding predilection. Male and female tsetse flies can both transmit *Trypanosoma,* not like other diseases like malaria that are vector borne and the female mosquito is the only one that can suck the blood and transmit the disease (Rock *et al*., 2015). The severity and prevalence of the illness depends on the strain of the parasite and the infected host species (Takeet and Fagbemi, 2009). Some of these infections may stay undetected until they get to the second fatal stage (Wastling *et al*., 2011).

The aim of this work is to determine the effect of *T. brucei* on Triiodothyronine (T3), Tetraiodothyronine (T4) and thyroid stimulating hormone (TSH); investigate the effects of *T. brucei* on the functioning of the liver andinvestigate the effects of *Trypanosoma brucei* on functioning of the kidney.

2. Materials and methods

2.1. Ethical approval

Animals were handled and used in accordance with the guidelines of the National Institute of Health guide for the care and use of laboratory animals (Washington DC): National Academic Press (US) (National Research Council, 1996; Gaiuson *et al*., 2020). Ethical approval was given by the Adamawa State University, Mubi.

2.2. Laboratory animal

Twenty (20) healthy male and female albino rats were obtained from National Veterinary Research Institute (NITR) Vom, Plateau State Nigeria. The animals were controlled and monitored in a clean metal cage containing sawdust as bedding material with routine cleaning and disinfection throughout the period of study. They were allowed to acclimatize to the laboratory andfed between 123.9 g – 187 g body weight (Kabiru *et al*., 2015; Gaiuson *et al*., 2020).

2.3. The source of Trypanosoma brucei

The Trypanosoma parasite strain used for this research was originally obtained from the Nigeria Institute for Trypanosomiasis Research, Vom Plateau State, Nigeria. Four donor rats were used to multiply the parasites in the Department of Zoology, Adamawa State University Mubi.

3. Experimental procedure

Two groups (A and B) were setup for this research. The groups were housed separately with feed and water given separately; each consisting of ten albino rats. Group A were infected by *Trypanosoma brucei*, while group B were not infected as in Takeet and Fagbemi (2009). Blood was obtained from the donor rats by tail bleeding into normal saline and the parasitaemia adjusted to 2 x 10^6 trypanosomes per milliliter (mL) by the method of Herbert and Lumsden (1976). Each rat in group A were given 1 mL of saline containing *T. brucei*. Group B was the control with no parasite. The infection was by intraperitoneal injection. The site was swabbed aseptically with methylated spirit. For the period of ten days, 0.1 ml of blood was collected daily from all the infected rats between 9.0 am and 10.0 am for the detection of parasite and estimation. When the parasites are established, 5 mL of blood samples intended for the research was collected in commercially prepared sample tubes containing lithium heparin for liver function test and kidney/renal function test and subsequently at seven-day interval until the completion of the research (Takeet and Fagbemi, 2009).

4. Data analytical techniques

Data collected was analyzed using graph pad prism (Miceli *et al.*, 2012). The Statistical analyses tool used was the independent sample *t*-test at a significant value of $p < 0.05$ (Anyogu *et al.*, 2020). The results were presented in bar charts.

5. Results

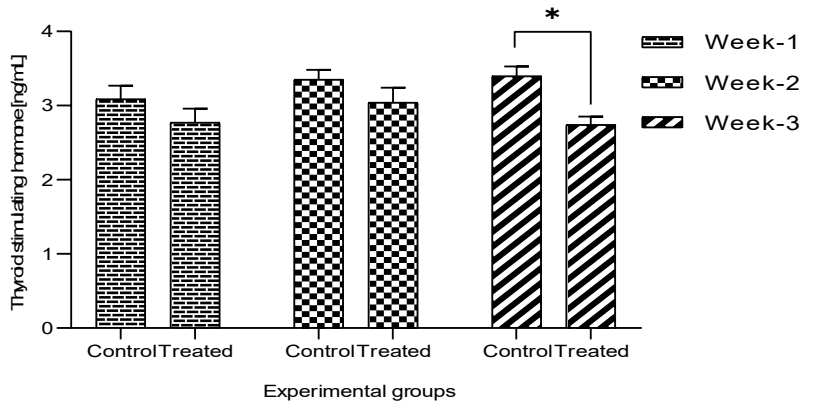

Figure 1: Serum thyroid stimulating hormone in adult albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

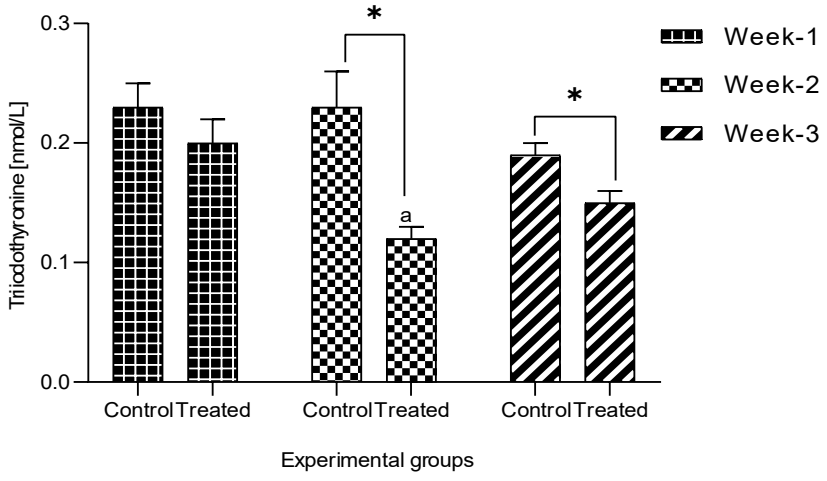

Figure 2: Serum Triiodothyronine hormone in adult albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

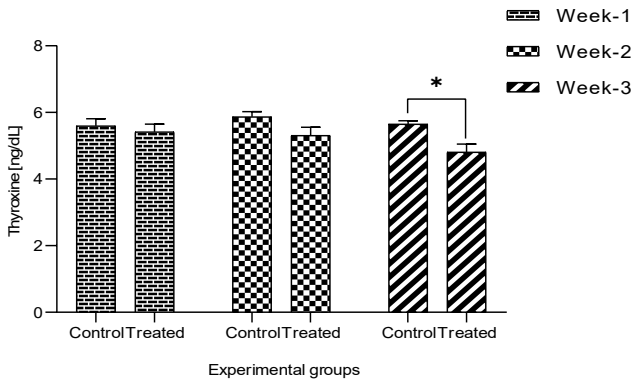

Figure 3: Serum Triiodothyronine hormone in adult albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

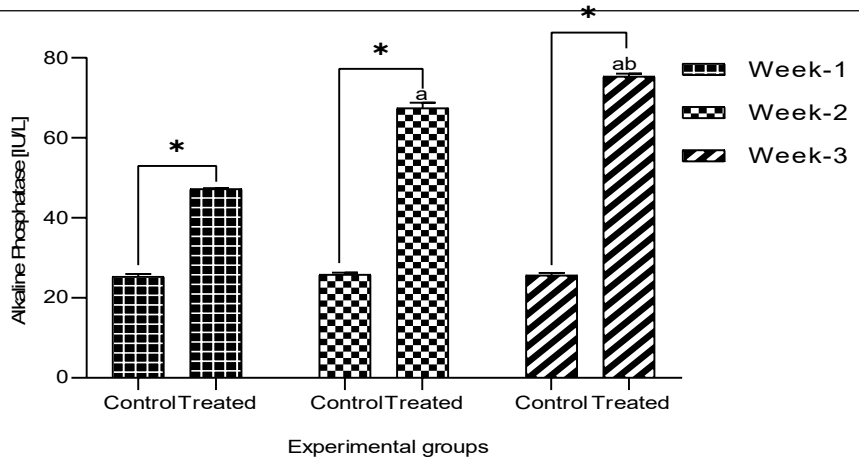

Figure 4: Serum alkaline phosphatase albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

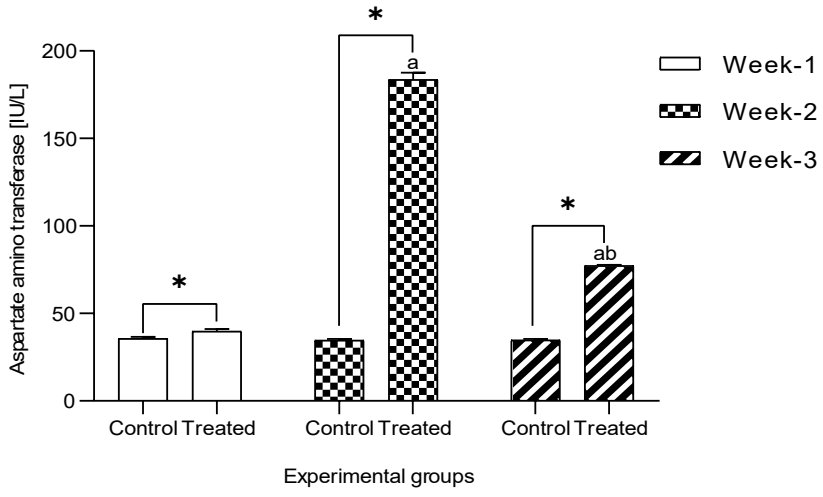

Figure 5: Serum aspartate amino transferase in albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

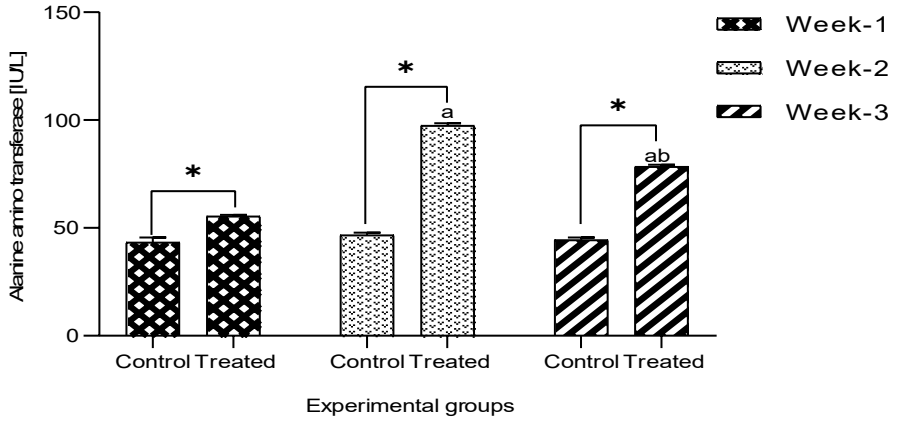

Figure 6: Serum Alanine Transaminase in albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

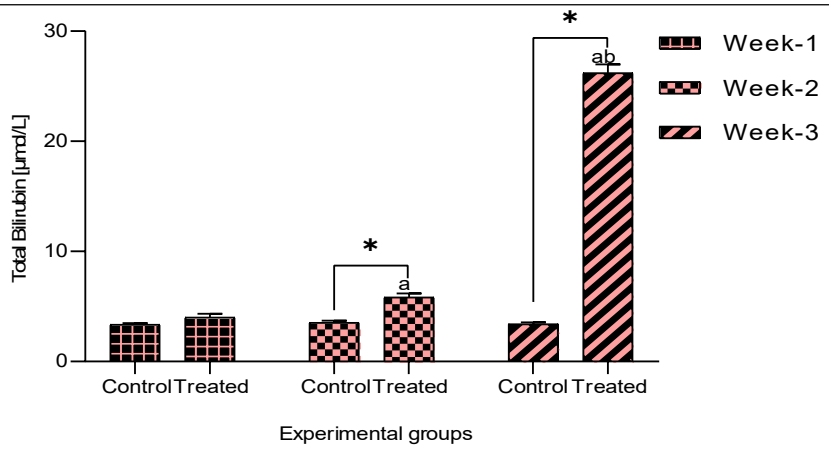

Figure 7: Total Bilirubin in albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

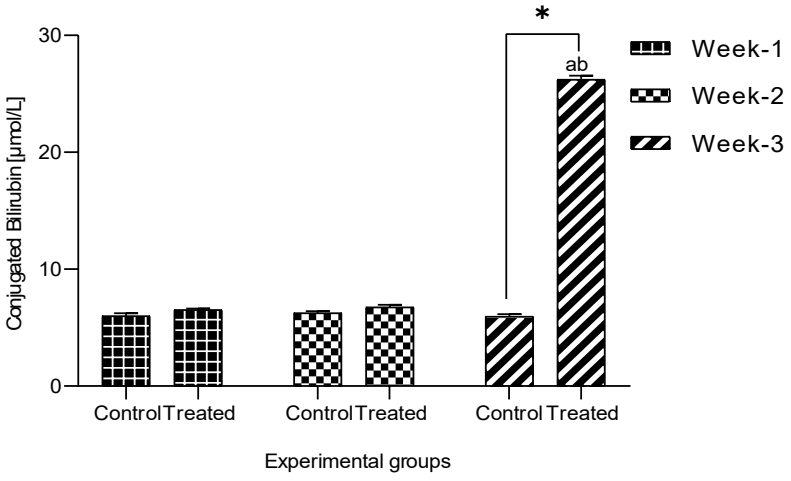

Figure 8: Conjugated Bilirubin in albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

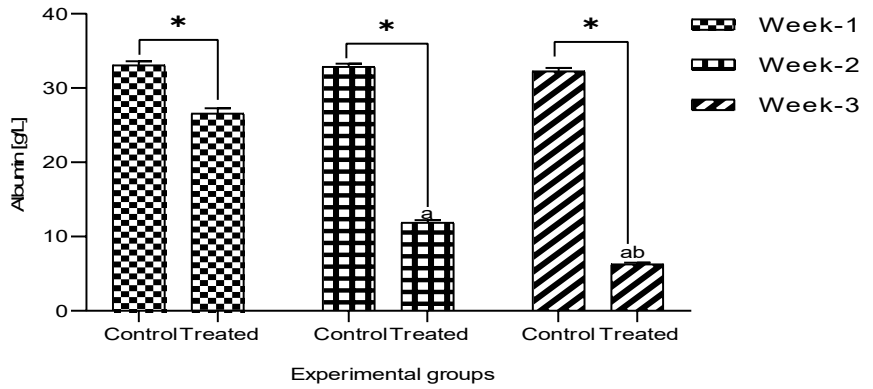

Figure 9: Conjugated Bilirubin in albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

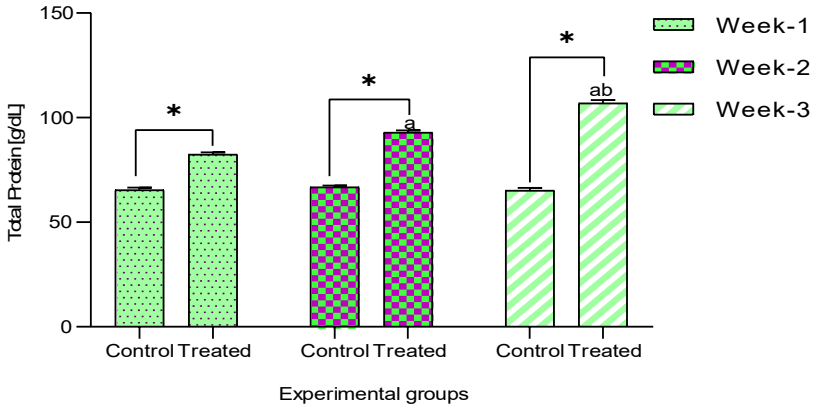

Figure 10: Serum Total protein in albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

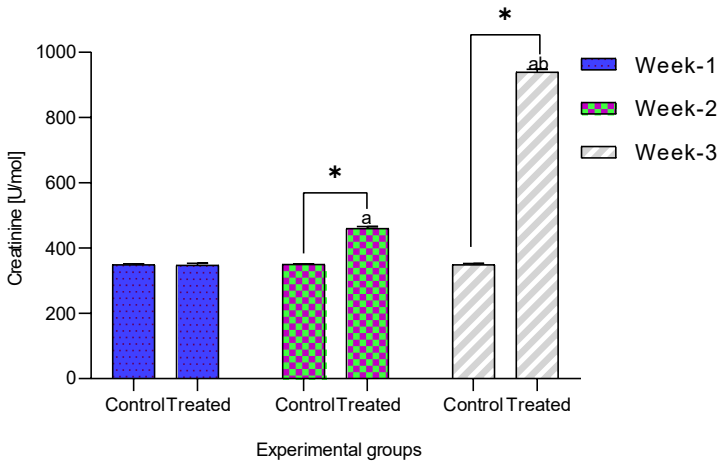

Figure 11: Serum total creatinine in albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

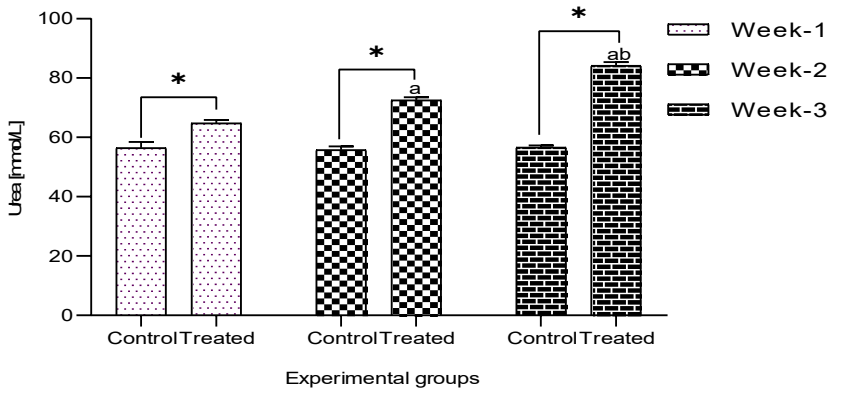

Figure 12: Serum total urea in albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

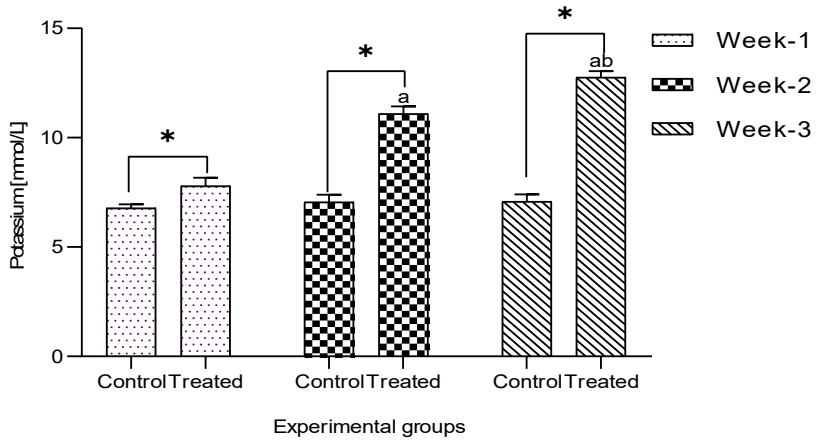

Figure 13: Serum potassium in albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

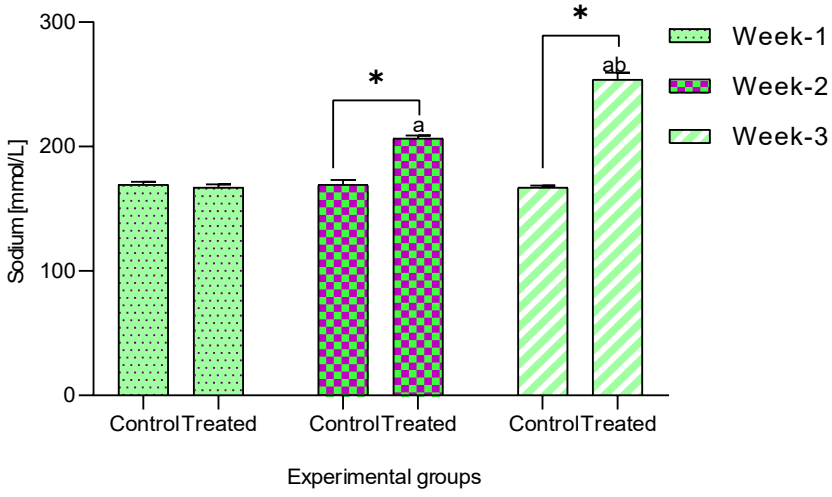

Figure 14: Serum sodium in albino rats

Note: Asterisk (*) indicates statistically significant difference (p<0.05) between control and treated groups of the same week.

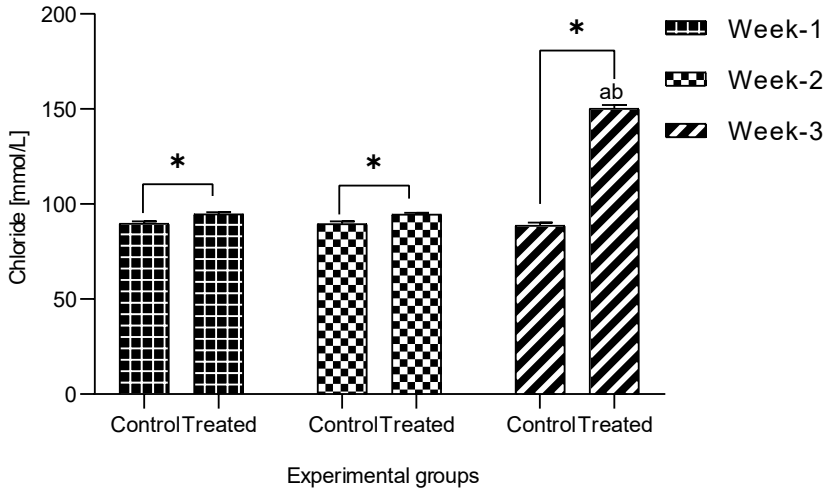

Figure 15: Serum chloride in albino rats

Note: Asterisk (*) indicates statistically significant difference ($p < 0.05$) between control and treated groups of the same week.

6. Discussion

The thyroid function is primarily regulated by the thyroid stimulating hormone and its receptors (TSHR) (Szkudlinski *et al*., 2002). Thyrotropin-releasing hormone stimulates the anterior pituitary-based synthesis of thyroid-stimulating hormone (TSH) (Rawindraraj *et al*., 2022). *Trypanosoma brucei* treatment resulted in a significant decrease in serum TSH, which in this study suggests that the hypothalamus may be inhibited. This would lead to a decrease in thyrotropin-releasing hormone and, in turn, a decrease in TSH in the adenohypophysis.

The slight increase in TSH shown in the treated group in the second week post-infection compared to the first week in this study could be interpreted as the body mounting a possible defense against the abrupt reduction in TSH release. Increased TSH synthesis and release may have helped achieve this. The third week's considerable drop in the serum level of TSH in the animals treated with *T. brucei* suggests that this potential compensatory response may have been repressed due to parasite growth. Additionally, *T. brucei* can invade the parenchyma of the central nervous system with infection progression, resulting in severe chronic neuroinflammation (Laperchai *et al*., 2018), all of which adds to the reduction of normal hypothalamic functions (Kennedy, 2013; Buscher *et al*., 2017).

The findings of TSH in this study can be used to explain the decrease in triiodothyronine and thyroxine hormones seen in *T. brucei* infected animals. Thyroid follicular cell development is accelerated and thyroid hormones are released as a result of TSH. Therefore, in this study, lower TSH would have resulted in less stimulation of the thyroid follicular cells, which in turn would have resulted in lower release of both T_3 and T_4. Although TSH was greater in the treatment group compared to the control group at week 2 of this study, the significant decline in serum T_3 at that time points to and suggests a potential feedback mechanism where the hormone levels have an inversely proportional connection with TSH. Consequently, decreased TSH release is caused by lower thyroid hormone levels and vice versa (Eghtedari and Correa, 2022). Even at week 3 after infection, this feedback mechanism was still not more fully evident in any of the infected group. This might have resulted from the parasites' harmful activities on the thyroid gland.

Thyroid hormone results in this study support the presence of infection in the infected animals. Additionally, a potential decline in receptor sensitivity of both T_3 and T_4 receptors located at the adenohypophysis may have contributed to the results of the thyroid hormones seen in this study. According to a research by Moreno *et al*. (2019), *T. brucei* has phospholipase C (PLC) enzyme on the surface of its membranes, which could be harmful to membrane receptors, which are proteins in and of themselves. However, there is continuous discussion over how parasites enter and spread throughout the central nervous system (CNS).

Grab *et al*. (2004) reported that trypanosomes can pass the layer of human brain microvascular endothelial cells that makes up the blood-brain barrier (BBB), but that this only results in a temporary loss of barrier

integrity. Additional assertions made by the research of Nikolskaia *et al*. (2006) and Grab *et al*. (2009) suggest that the capacity of trypanosomes to cross the BBB and enter the CNS may depend on both parasite and host enzymes as well as the activation of calcium signaling pathways at the endothelial cell layer.

The liver is the largest internal organ in the body, weighing roughly 1.5 kg. The liver, which also plays a number of other crucial tasks in sustaining life, is the major site for the production of all circulating proteins other than globulins (Amitava, 2015). Hepatocellular injury is determined when AST and ALT values are abnormally high when compared to alkaline phosphatase levels (Kwo *et al*., 2017). Due to disruption to the cell and organelle membranes, intracellular enzymes after hepatocellular injury leak into the blood. Alkaline phosphatase (ALP), aspartate transaminase (AST), and alanine transaminase (ALT) are a few examples of these enzymes (Amitava, 2015).

The significant increase observed in the result of serum ALP in the *T. brucei* treated animals suggests the presence of liver, bone and other diseases. The enzyme alkaline phosphatase is an important serum analyte. Additionally, the result of ALP in this study could also be associated with bile duct obstruction as reported by Sharma *et al*. (2014). The results of AST and ALT in this study are also similar to that of ALP with significant increase in all these serum liver enzymes in the *T. brucei* infected animals. These changes could be explained by increased inflammation of the liver among other vital organs from the infection. These results are consistent with those of Maclean *et al.* (2001), who found that *T. brucei* infection was associated with a rise in cytokines and other inflammatory biomarkers. Therefore, the leakage and buildup of these liver enzymes in the serum of the infected animals in this investigation could be explained by a possible compromise of membrane permeability brought on by the infection or inflammation. Additionally, *T. brucei*'s influence on the liver enzymes measured in this study may have resulted from the protozoan's lytic action on the host's defense mechanism (Kennedy, 2004).

In this study, except for serum ALP, serum AST and ALT were significantly higher at week 2 relative to their levels at week 1, however with a significant decrease observed at week 3 relative to week 2. These seemingly disproportionate changes are as a result of the different phases of trypanosome infection which have been reported to abate at week three characterized by decrease of some of the biochemical perturbations observed in the acute and chronic phase (Akinseye *et al*., 2020).

The significant increase in serum total and conjugated bilirubin seen in the *T. brucei* treated group in this study is attributable to the hepatocytes being destroyed as a result of the inflammatory reactions brought on by the infection. The hepatocyte internalizes free bilirubin, which is then conjugated to glucuronic acid (Kalakonda *et al*., 2022). As shown by this study's findings, the death of the aforementioned hepatocytes would cause bilirubin to build up in the blood. Haematological alterations associated with African trypanosomiasis have a significant impact on the development of the illness (Stijlemans *et al*., 2018).

The pathogenesis of anemia in an infection is influenced by the biologically active molecules trypanosomes produce as well as cellular interactions between the host and trypanosomes (Boada-Sucre *et al*., 2016; Akinseye*et al*., 2020). Therefore, the higher serum levels of conjugated and total bilirubin in this study's *T. brucei*-infected group would suggest that red blood cells may have been destroyed, which would have led to an increase in the breakdown of heme. The results of this study are consistent with those of Abimbola *et al*. (2013), who also noted elevated levels of serum bilirubin in association with *T. brucei* infection, and that of Gow *et al*. (2007), who also noted elevated levels of bilirubin in association with trypanosoma infection. According to Takeet and Fagbemi (2009), this may be a sign of obstructive jaundice or hemolytic anemia. Therefore, this might have played a role in the variations of total and conjugated (direct) bilirubin seen in this study. Albumin is attached to circulating bilirubin in order to shield various organs from the compound's potentially harmful effects. However, with progressive infections more bilirubin can overwhelm the binding sites (Stijlemans *et al*., 2018). This may perhaps explain the substantial increase in circulating bilirubin observed in this study.

Albumin is a crucial protein that transports and binds drugs for a variety of compounds in plasma and regulates the blood's osmotic pressure (Rabbani *et al*., 2018). Low serum albumin levels can result from impaired liver function during acute inflammatory processes or from an increase in renal excretion (Levitt and Levitt, 2016; Rabbani and Ahn, 2021). As a result, the significant drop in serum albumin level found in this study is consistent with the aforementioned findings and supports the existence of inflammatory processes associated with *T. brucei* infection. The steady decline in serum albumin throughout the course of this investigation also raises the possibility of chronic or slow-remitting liver inflammation or renal damage, which would increase albumin excretion.

These results coincide with those of Akinseye *et al*. (2020), who noted a decline in albumin levels in association with *T. brucei* infection. Furthermore, the lower serum albumin level seen in this study may have also been caused by the actions of inflammatory mediators, which have been known to reduce albumin synthesis in favor of other acute phase reactants. Additionally, these mediators raise vascular permeability, allowing albumin to escape and cause the low albumin levels as seen in this study (Soeters *et al*., 2019). These recent findings correspond with those of Sulaiman and Adeyemi (2010), who revealed that *T. brucei* infection is associated with a drop in serum albumin level.

The total protein concentration is the total amount of two types of proteins in a blood fluid component; albumin and globulin (Landri and Bazari, 2016). This significantly higher serum total protein level in this current study may have been caused by enhanced globulin synthesis in the *Trypanosoma brucei*-infected group. During trypanosome infection, total proteins, albumin, and the albumin/globulin ratio are frequently measured (Akinseye *et al*., 2020). Due to the tissue destruction caused by *T. brucei* infection, falling albumin and rising globulin levels have been observed in individuals with the infection (Wassell, 2000).

The increased total protein in this study is in contrast to those of Sadique *et al*. (2001), who found that *T. brucei* infection was associated with a decrease in total protein. The results of this investigation are in agreement with those of Taiwo *et al*. (2003), who found that globulin formation throughout the chronic phase of the infection led to a considerable rise in the amount of total protein. Due to the important roles that globulins play in enhancing body immunity, this is an immunological reaction (Lushaikyaa *et al*., 2011).

Blood and other bodily fluids contain ions called electrolytes that carry electric charges and can conduct electricity (Osadoloh and Emokpae, 2010). The main functions of the electrolytes include the regulation of extracellular fluid, neuronal excitation, systemic blood pressure, and electron transfer reactions. They also act as co-factors in metabolic processes (Tanko *et al*., 2013).

The body has a mechanism that help keep potassium in equilibrium; for instance, it pushes out cellular potassium to prevent a dip that would be expected when potassium is lost through the renal system. The liver and kidney damage inflicted on the animals by *T. brucei* may be the cause of the study's considerable rise in serum potassium levels. This is due to the fact that the liver is a component of the extra-renal systems that regulate potassium homeostasis (Arroyo *et al*., 2011). This result is in line with what was discovered in the study about sodium and chloride. The aldosterone hormone, which is essential for maintaining the balance of electrolytes, and other mineralocorticoids could have been affected by an adrenal gland malfunction, which would have caused these outcomes. The increase observed in this current study could also be from a possible malfunction of the sodium-potassium pumps. However, these parameters were not assayed in this current study. The findings of this study contradict that of Abdullahi *et al*. (2019) who reported decrease in serum electrolytes with *T. brucei* infection.

The breakdown product of creatinine phosphate in the muscle is creatinine typically created by the body muscle at a consistent pace (Allen, 2012). As a result, the *T. brucei*-infected rats in this study had significantly higher serum creatinine levels, which is suggestive of renal dysfunction. This is because the kidney's glomerular filtration process removes the majority of the creatinine (Allen, 2012). Therefore, renal disease would be the cause of a higher serum creatinine level. These results support those of Nassef *et al*. (2018) who found that *T. brucei* infection was associated with an increase in creatinine. Although serum creatinine in the *T. brucei*-treated group was considerably higher at week 2 compared to the control group in this investigation, it was significantly lower at weeks one and three. Increased creatinine tubular secretion as well as other non-renal variables including muscle mass, liver function, and a potential gastrointestinal elimination, as reported by Doi *et al*. (2009) may have had an impact on this difference. The drop in serum creatinine seen at week 2 may also have been brought about by a change in the group's ability to produce creatinine.

The main organic component of human urine is urea, which is a waste product of numerous living things. The final result or series of events that breaks down the amino acids that make up proteins is Klein *et al*. (2011). Periods of parasitemia and fever, which happened in acute infection, cause high urea levels. The urinary tract blockage, increased protein catabolism, and kidney illness such as glomerulonephritis are the main contributors to this rise (Anosa, 1988). Thus, the results of the current study on serum urea are consistent with *T. brucei* infection. Throughout the course of this test, the increase in serum urea was also progressive. As a result, protein catabolism increased during the course of the current investigation.

7. Conclusion

In conclusion, *Trypanosoma brucei* infection depresses thyroid gland functions which causes fluctuations in the production of the thyroid hormones which in turn causes hepatic and renal toxicities in albino rats.

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