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Research Article

Dose-dependent changes in Haematological and Serum Biochemical Variables in Male Wistar Rats Exposed to Sodium Metavanadate'

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Summary: The interest in the role of vanadium compounds in living organisms has grown tremendously especially since the report of its glycemic normalization activity in the 1980s. There has been reports of both its toxic as well as positive effects, thus there is a paucity of information on the essentiality of this element in biological systems. In this study, the effect of different doses of sodium metavanadate on the haematological and biochemical variables of male Wistar rats was investigated. Twenty male Wistar rats were divided into four groups of five each and were given tap water containing various concentrations of sodium metavanadate (0ppm- group 1, 50ppm- group 2, 100ppm- group 3, or 200ppm- group 4) for 10weeks. Weekly body changes were noted and blood was collected at the end of 10 weeks by retro orbital puncture for haematological and serum biochemical variables. Histological sections were also performed on liver and kidney tissues. There was a significant increase in body weight in the 50ppm group compared with control. Sodium metavanadate at 200ppm caused a significant decrease in packed cell volume (PCV), red blood cell count (RBC), white blood cell count (WBC) and Lymphocytes with significant increases in neutrophils and neutrophil-lymphocyte ratio when compared with control values. There was also a significant decrease in ALP, ALT and a significant increase in urea concentration in the 200ppm group when compared with control values. All doses of sodium metavanadate significantly reduced blood glucose level. Sections of liver and kidney revealed severed damage at 200ppm compared with control. The results from this study showed that vanadium affects both haematological and biochemical parameters and could be toxic at higher concentrations, while at low concentration could be beneficial as seen with the enhanced body weight.

Keywords*: Vanadium, Haematology, Serum biochemicals, Body weight, Toxicity, Wistar rats*

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INTRODUCTION

Vanadium as a heavy metal has gained considerable attention over the past few years due to its increase in concentration in the environment yearly, leading to high concentrations in the atmosphere, soil and in water bodies as well as it is increased used as a dietary supplement for body building (Lin *et al*., 2004). The prevalence of vanadium exceeds that of such well-known metals as copper and lead, and equals that of zinc and tin. In a study conducted by Wogu and Okaka, (2011) in Warri River, Delta state Nigeria, vanadium content ranges from 0-0.26mg/L collected at different sites of the river, and was seen to be higher than the concentration of cadmium, chromium and lead in the same water. Vanadium compounds exist in over 50 different mineral ores at concentrations of between 10 and 4100ppm and in association with fossil fuels, particularly coal (at concentrations of between 19 and 126ppm in ash) and crude oil (at concentrations of between 3 and 257ppm) (Gummow, 2011). The average worldwide soil levels of vanadium have been reported to be approximately 100mg/kg (IPCS, 2001).

Vanadium like other heavy metals cannot be destroyed through biological degradation, thus it accumulates in the protoplasm of organism, both plants and animals (Marcano *et al*., 2006). It has long been known that vanadium is toxic to both man and animals. However, the pathogenesis of vanadium poisoning is still poorly understood. There are varying reports on the effects of vanadium to human health as some authors have reported its toxicity on body systems especially on the respiratory, nervous and on haematological parameters (Dabros *et al*., 2006; Worle-Knirsch *et al*., 2007; Ngwa *et al*., 2009; Olopade *et al*., 2011). However, there are also reports on its therapeutic effect in the management of certain diseases such as diabetes (Francik *et al*., 2011; Saima, 2013), osteoporosis in diabetes model (Barrio and Etcheverry, 2006; Sanchez-Gonzalez *et al*., 2017), cancer (Das *et al*., 2012) as well as in gastric ulcer (Kemeir, 2013; Omayone *et al*., 2016). It can therefore be seen that the essentiality as well as the toxic effect of vanadium to humans is still poorly understood. The effect of vanadium is dependent on mode of administration, concentration and duration of exposure. Most of the reports on vanadium toxicity are based on exposure via inhalation,

while reports on oral exposure have shown little or no toxicity. With its dual effect, the need to determine an effective as well as a toxic concentration of vanadium exposure orally therefore necessitates this study.

MATERIALS AND METHODS

Chemical: Vanadium in the form of sodium metavanadate ($NaVO_3$) was purchased from BDH Chemicals Ltd Poole England product.

Animals and treatment: Twenty male albino rats of Wistar strain weighing between 90-120g were used for the study. Animals were obtained from the Central Animal House, College of Medicine University of Ibadan, and were exposed to food and water *ad libitum*. Animals were randomly divided into four groups of five animals each and exposed to various concentration of vanadium (0ppm-control, 50, 100 and 200 ppm) in their drinking water for 10 weeks. Blood samples were collected by retro orbital puncture after 10 weeks of exposure as described by Hoff, (2000) into an Ethylene-diamine-tetra-acetic acid (EDTA) bottle. The blood was then analyzed for haematological and biochemical parameters. Liver and kidney were excised and fixed in 10% formalin for histological assessment.

Haematological Analysis: The haematolotical studies were perform on packed cell volume, Haemoglobin levels, white blood cell count (WBC), Red blood cell count (RBC), Platelets, Lymphocytes, Neutrophils, Monocytes, Eosinophils. This was done according to the method of Dacie and Lewis 1994.

Biochemical Analysis: Plasma levels of levels of Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP), Glucose, Creatinine, Urea and Cholesterol were measured by a colorimetric method using commercial kits (Randox laboratories limited, United Kingdom). Plasma protein was determined by the method of Gornal *et al*., (1949).

Statistical analysis: All values are presented as mean ± SEM and were analysed using One-way ANOVA. The statistical difference was taken to be significant at $p<0.05$.

RESULTS

Body weight gain: The administration of sodium metavanadate at 50 ppm for 10 weeks significantly increase body weight of animals beginning from the 6th week compared with the control group ($p < 0.05$). The body weight gain for other vanadium treated groups showed no significant difference compared with control group. The result is shown in Fig 1.

Haematological variables in blood after sodium metavanadate exposure: Sodium metavanadate showed a dose dependent decrease in PCV, HB, RBC count (Figures 2, 3 and 4 respectively) which was only significant at 200 ppm compared with control. White blood cell and Platelet counts (Figures 5 and 6 respectively) were also decreased in a dose dependent manner and was significant at 100 and 200 ppm compared with control.
Lymphocyte count (Figure 7) was significantly decreased in 200 ppm group, while a significant increase neutrophil count (Figure 8) as well as neutrophil-lymphocyte ratio (NLR) (Figure 9) was noticed in 200ppm group compared with control group at $p<0.05$. The 50ppm group showed no significant changes in all the parameters compared to the control group.

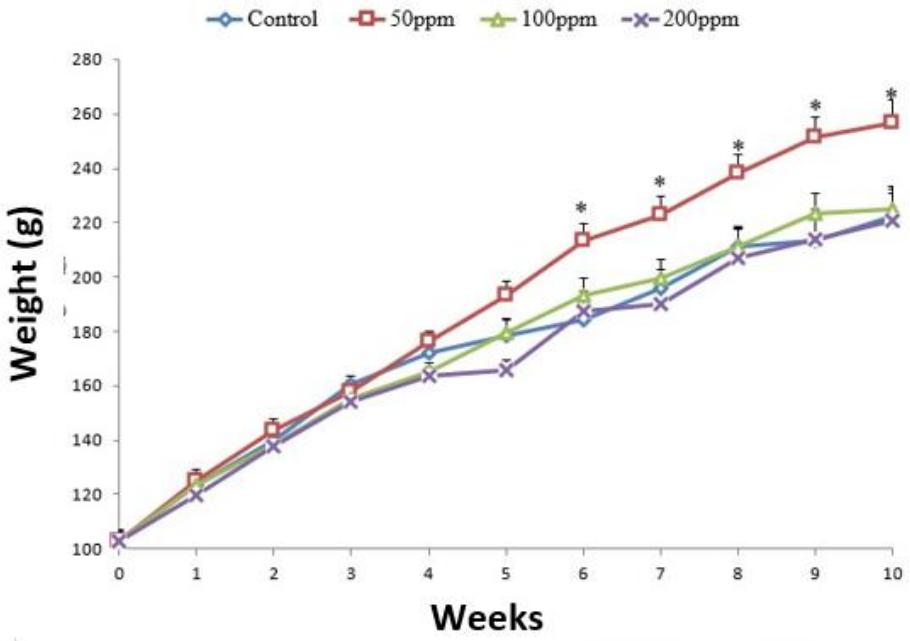

Figure 1:
Effect of Vanadium on body weight after 10 weeks exposure
Values are presented as Mean ± SEM, n=5
** Significant at p<0.05 when compared with control*.

Effect of vanadium on hematological and serum biochemical variables

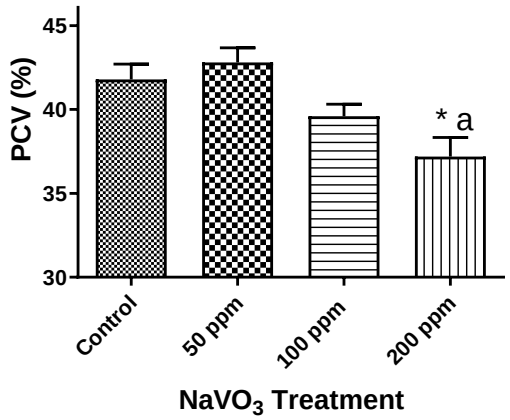

Figure 2:
Effect of Vanadium on PCV after 10 weeks exposure
Values are presented as Mean ± SEM, n=5
** Significant at p<0.05 when compared with control.*
a Significant at p<0.05 when compared with 50 ppm.

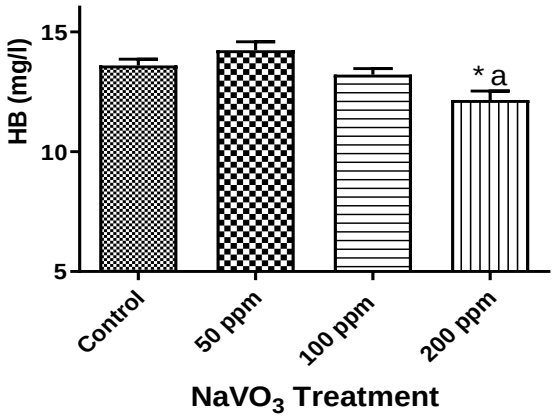

Figure 3:
Effect of Vanadium on HB after 10 weeks exposure
Values are presented as Mean ± SEM, n=5
** Significant at p<0.05 when compared with control*
a Significant at p<0.05 when compared with 50 ppm.

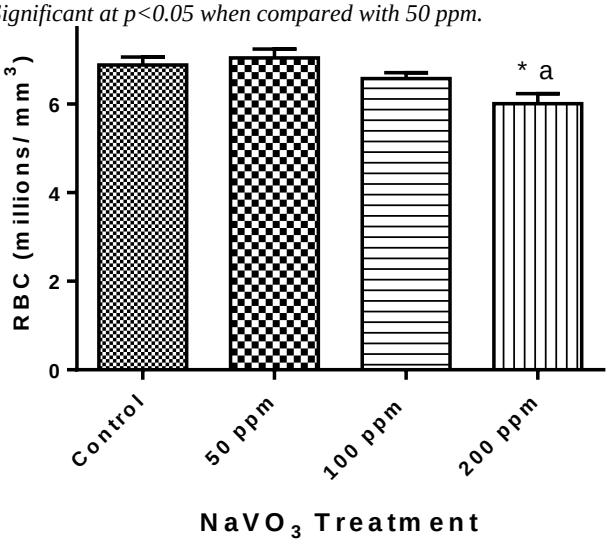

Figure 4:
Effect of Vanadium on RBC after 10 weeks exposure
Values are presented as Mean ± SEM, n=5
** Significant at p<0.05 when compared with control.*
a Significant at p<0.05 when compared with 50 ppm.

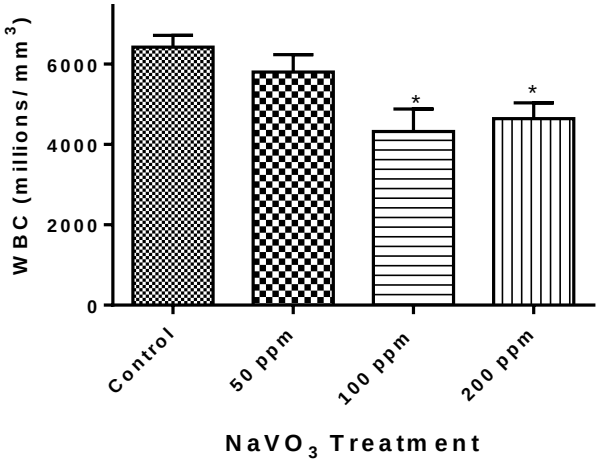

Figure 5:
Effect of Vanadium on WBC after 10 weeks exposure
Values are presented as Mean ± SEM, n=5
** Significant at p<0.05 when compared with control*

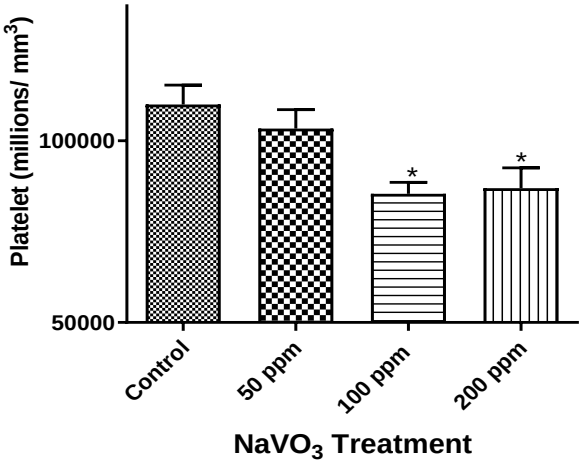

Figure 6:
Effect of Vanadium on Platelet after 10 weeks exposure
Values are presented as Mean ± SEM, n=5
** Significant at p<0.05 when compared with control*

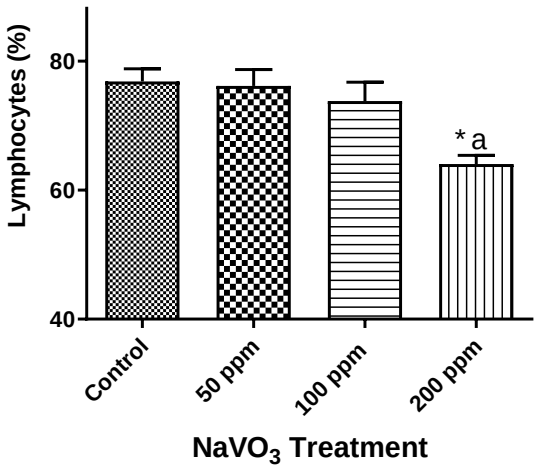

Figure 7:
Effect of Vanadium on lymphocyte after 10 weeks exposure
Values are presented as Mean ± SEM, n=5
** Significant at p<0.05 when compared with control*
a Significant at p<0.05 when compared with 50 ppm.

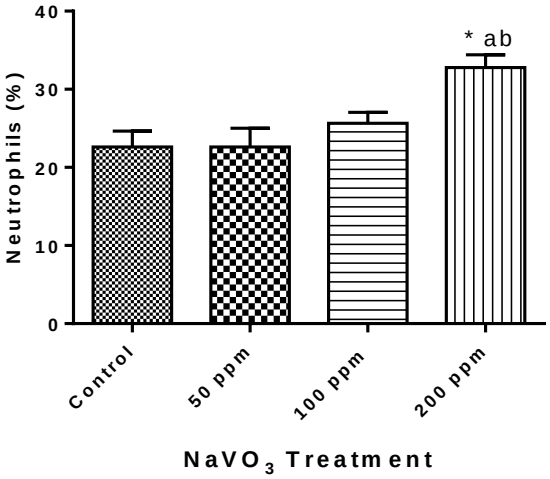

Figure 8:
Effect of Vanadium on neutrophils after 10 weeks exposure
Values are presented as Mean ± SEM, n=5
* Significant at p<0.05 when compared with control
a Significant at p<0.05 when compared with 50 ppm.
b Significant at p<0.05 when compared with 100 ppm.

Changes in plasma biochemical variables after sodium metavanadate exposure: Plasma proteins (globulin and albumin) changes were not significant in all vanadium treated groups compared with control group. Changes in AST were also not significantly different in vanadium treated groups compared with control. ALT and ALP were significantly decreased by 200 ppm sodium metavanadate, while 50 ppm and 100 ppm groups had no significant changes compared with control.

Urea and cholesterol were significantly higher in 100ppm and 200 ppm respectively compared with control group. All vanadium treated groups had significantly lowered plasma glucose level compared with control group, while no significant change was observed in creatinine concentration. The results are presented in Table 1.

Changes in liver and kidney histology after sodium metavanadate exposure: The architecture of liver and kidney were significantly distorted by vanadium at a concentration of 200ppm. Histological sections of the liver and kidney showed blood vessel congestion and severe infiltration of inflammatory cells respectively.

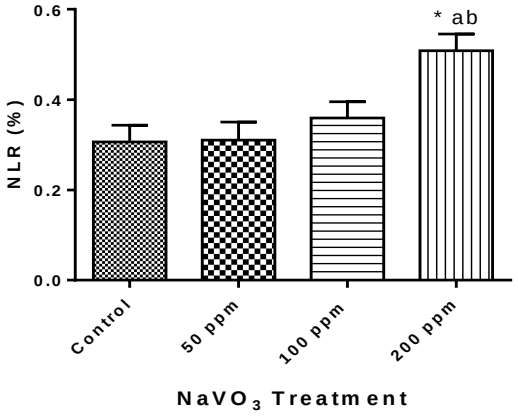

Figure 9:
Effect of Vanadium on neutrophil-lymphocyte ratio after 10 weeks
Values are presented as Mean ± SEM, n=5
** Significant at p<0.05 when compared with control*
a Significant at p<0.05 when compared with 50 ppm.
b Significant at p<0.05 when compared with 100 ppm.

Table 1:
Effect of Sodium metavanadate on some biochemical parameters after 10 weeks exposure.

		Control	50ppm	100ppm	200ppm
Parameters	Albumin	4.88±0.15	4.82±0.17	4.46±0.09	5.0±0.15
	Globulin	3.14±0.02	3.14±0.14	3.16±0.02	3.08±0.14
	Total Protein	8.02±0.15	7.96±0.22	7.62±0.09	8.08±0.19
	AST	42.2±1.07	43.4±0.68	42.4±0.87	40.2±0.58
	ALT	30.4±0.68	30.6±0.24	31.6±0.51	27.6±0.87*
	ALP	119.2±4.64	112.4±5.35	109.2±4.35	104±2.82*
	Creatinine	0.9±0.13	0.96±0.12	0.96±0.17	0.94±0.11
	Glucose	129±1.70	115.8±0.80*	118.4±1.21*	116.2±0.37*
	Urea	13.8±0.73	13.0±0.71	14.4±0.51	16.0±0.45*
	Cholesterol	52.8±4.28	55.8±5.81	67.2±4.87*	60.2±2.91

*Significant at * p<0.05 compared to control.*

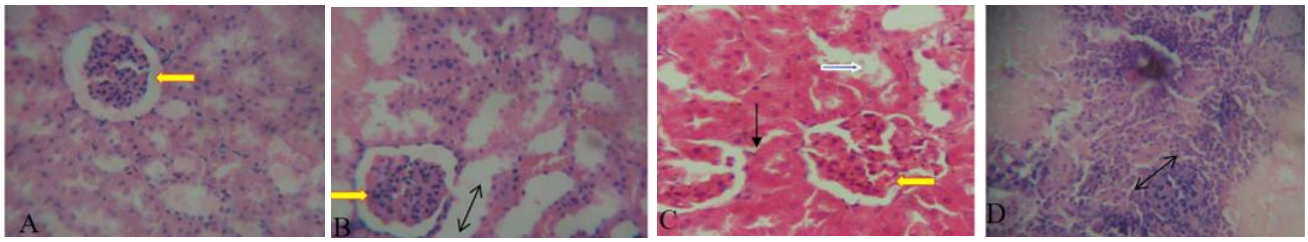

Plate 1:
The figures above show H&E staining of the kidney (X 100 magnification). **A**. Control group having normal nephron with normal glomerulus (yellow arrow). **B**. 50 ppm group showing normal glomerulus (yellow arrow) and mild sloughing off of nephron tubules (black arrow). **C.** 100 ppm group showing normal glomerulus (yellow arrow); some of the renal tubules are collapsed with diminishing lumen (black arrow) and sloughing off of nephron tubules. **D** 200 ppm group having nephritis due to severe infiltration of inflammatory (spanning arrow).

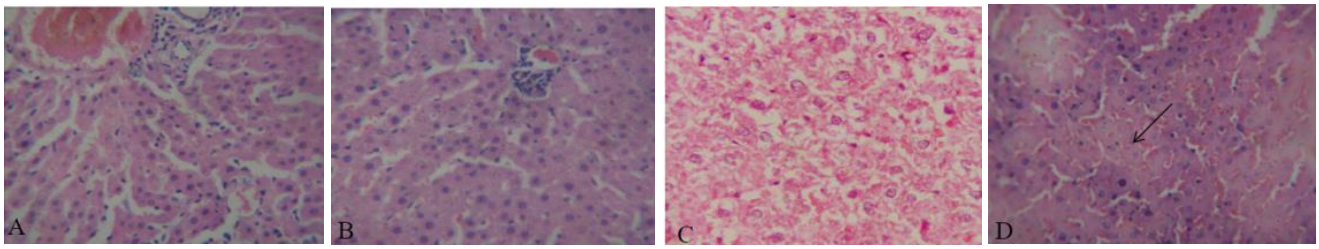

Plate 2:
The figures above show H&E staining of the Liver (X100 magnification). **A.** Control group having normal hepatic cells. **B.** 50ppm V group also having normal hepatic cells. **C.** 100ppm V group having normal appearance of sinusoids and **D.** 200ppm V group showing moderate congestion of blood vessels (black arrow).

DISCUSSION

There are conflicting reports on the effects of vanadium on body weight. Some experimental works have reported significant decrease in body weight of animals exposed to vanadium in comparison to control (Adachi *et al*., 2000; Olopade *et al*., 2011), while some others reported no significant difference in body weight (Dai *et al*., 1995; Scibior, 2005). Most reports on body weight loss noticed are either due to administration of high concentration of vanadium orally for a short duration or via inhalation and injection. However, in our experiment we observed that vanadium exposed group at 50ppm had significant increase in body weight beginning from the 6^{th} week to the 10^{th} week. The increase in body weight correspond with the work of Schroeder and Mitchener, 1975 where male mice given vanadium at 5mg/L as vanadyl sulfate in drinking water for life span had significantly higher body weights than control. Likewise, Krosniak *et al*., (2019) reported a significant increase in body weight in diabetes model of mice exposed to vanadium.

Vanadium in this research showed toxic effects in most of the haematological variables. As observed, vanadium toxicity was dose dependent with some significant toxic effect seen at 100 ppm and the most toxic effect recorded at 200ppm. Noteworthy decrease was detected in RBC count, Hb concentration, PCV, WBC count, and Lymphocyte, while a significant increase in Neutrophils was seen. The result corresponds to the work of Scibior *et al*., (2006) who reported that vanadium significantly decreases RBC count and Hb concentration at a vanadium concentration of 0.125mg V/mL administered in drinking water for 6 weeks. Also, Obianime *et al*., (2009) reported that ammonium metavanadate significantly decrease Hb, PCV, WBC and lymphocytes over a 28 days treatment. Their observation also implies that the effect of vanadium was dose and time dependent. However, the no significant difference observed in these variables at 50ppm and 100ppm correspond to the report of Dai *et al*., (1995) that administered 0 or 9.7mg vanadium/kg body weight for 12 weeks and no difference in haematological parameters was observed between the groups. Increase in neutrophil-lymphocyte ratio has been reported in various disease condition as a marker for inflammation (Salami *et al*., 2015) and this variable was markedly increased in the 200ppm compared to control. This is indicative that vanadium at high concentration is capable of causing systemic inflammation and eventually oxidative stress. The activation of neutrophil has been reported as one of the mechanisms by which vanadium mediate the formation of hydroxyl radical (OH^-). Thus, from our study as well as other reports, it shows that with increasing concentration, vanadium seems to affects haematological parameters.

Vanadium at 200ppm significantly reduces plasma levels of ALP and ALT and also shows a reduction in the level of AST which is a confirmation of the work of Adachi *et al.* 2000 who reported that vanadium showed a significant decrease in these parameters in rats fed with diet containing 100ppm of sodium metavanadate. It has also been reported that vanadium is a potent inhibitor of the enzyme alkaline phospatase (ALP) (Lopez *et al*., 1976), as well as other enzymes including phospho-transferase (Lindquist *et al*., 1973), Na^+ and K^+ ATPases (Cantley *et al*, 1978), Ca-Atpase (O'Neil *et al*., 1979). However, vanadium at 50ppm and 100ppm had no substantial effect in ALT and AST.

A decrease in glucose level was observed in all vanadium treated groups. This buttresses the anti-diabetic property of vanadium as vanadium has been reported to normalize glucose level in insulin-dependent diabetic rats and humans as well as inhibit glucose-6-phosphatase which is a key enzyme involved in the final step in gluconeogenesis and glycogenolysis (Cam *et al*., 2000; Kiersztan *et al*., 2004; Saima 2013). Urea concentration was seen to be increased in vanadium group treated with 100ppm and 200ppm sodium metavanadate and was significant at 200ppm. Also, comparing the cholesterol level, vanadium showed an increase in all vanadium treated group and was significant in group 3 (100ppmV). These corroborate the work of Mona *et al.*, (2007) where it was reported that cat fish fed with diet containing 15mg/kg vanadium causes a significant increase in urea and cholesterol levels.

The significant changes observed in serum biochemical variables is an indication of the toxic action on vanadium on the kidney and liver. Histological observations on the kidney revealed severe inflammation of the nephron and in the liver, there was blood congestion. The liver and kidney are major organs for vanadium toxic effect and have been reported to be major sites for vanadium bioaccumulation after absorption (Sabbioni *et al.*, 1978; Ramanadham *et al.*, 1991; Sanchez*et al*., 1998). Thus, these organs are severely affected irrespective of the mode of vanadium exposure however, since the liver is an accessory organ to the gastrointestinal tract, substances consumed first pass through the liver before entering the general circulation. This could be a probable reason why the toxic effect of vanadium in our study was more on the liver than the kidney and it is consistent with the report of Kemeir *et al*., (2011).

In conclusion, vanadium proved to be beneficial by enhancing body weight at low concentration, while evoking systemic inflammation at high concentrations. Vanadium also is indeed a potential agent for diabetes treatment as all concentrations of vanadium in this study caused a decrease in glucose level.

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