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Original Article

Serum Levels of Lead and Selected Acute Phase Proteins in Patients with Substance Use Disorders

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Abstract: Background: Chronic inflammation, immune system dysfunction and elevation in the levels of toxic metals such as lead (Pb) are common observations in patients with substance use disorders (SUD). However, there is little information on the acute phase profile of SUD patients with different serum levels of Pb. Therefore, serum levels of selected acute phase proteins in SUD patients with different serum levels of Pb were determined in this study. Methods: A total of 84 adults consisting of 45 patients with SUDs and 39 controls were enrolled into this case-control study. Serum levels of Pb, albumin and C-reactive protein (CRP) were determined using Atomic Absorption Spectrophotometer, bromocresol green (BCG) colorimetric method, and ELISA, respectively. Thereafter, CRP-albumin ratio (CAR) was calculated as appropriate. Results: Serum levels of Pb and albumin were significantly higher in patients with SUDs compared with the controls. Considering variation in acute phase proteins based on Pb level, the serum level of albumin was significantly lower, while the serum CRP level and CAR were slightly higher in patients with SUDs whose Pb level was higher than 5 µg/dL compared with patients whose Pb level was ≤5 µg/dL. No significant differences were observed in the levels of Pb, albumin, CRP, CAR in patients with SUDs who abuse single substance compared with those who abuse multiple substances. Conclusion: SUD is associated with increased serum levels of Pb and albumin, and alteration in the serum levels of acute phase proteins appears to be influenced by the serum Pb level. Therefore, there is the need for routine measurement of Pb level in patients with SUDs as they could benefit from therapeutic interventions involving chelation of Pb which could prevent disordered acute phase responses in the patients and facilitate optimal response to antipsychotics.

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INTRODUCTION

Substance use disorders (SUDs) constitute a significant portion of public health concerns on a global scale (Wang *et al.*, 2007). Substances that are abused are usually used for recreation, celebration, and coping with difficult life situations and health problems. These substances include alcohol, marijuana, hallucinogens, depressants (tranquilizers and sedatives), cocaine, prescription stimulants, inhalant, methamphetamine, and heroin among others (Raftery *et al*., 2020).

In 2021, the World Drug Report showed that 36 million individuals were diagnosed with SUDs, globally. In 2019, substance abuse problems were associated with the loss of almost 18 million years of healthy life. Also, roughly 180,000 deaths were directly related to SUDs, and an additional 500,000 deaths were linked to the use of illegal drugs (Heikkilä *et al.*, 2021; UNODC, 2021; Onaolapo *et al.*, 2022). Unfortunately, substance abuse, particularly among teenagers and young people, is alarmingly rising throughout Africa (Acuda *et al.*, 2011). In most of the African countries, the World Health Organization and the United Nations Office on Drugs and Crime have reported an exponential rise in the per capita consumption of alcohol and cannabis, with suggestions that this could have negative socioeconomic and public health effects. As at 2013, the 22 countries with the biggest growth in the use of alcohol and other psychoactive substances, such as cannabis, tobacco, cocaine, and heroin, included ten African nations (United Nations Office on Drugs and Crime, 2013; Onaolapo *et al.*, 2022). In Nigeria, substance abuse is also a major public health issue with alcohol being the most abused. Other substances that are frequently abused include tobacco, sedatives, stimulants, cannabis and cocaine (Gureje *et al.*, 2007; Jatau *et al.*, 2021).

Lead (Pb) is a highly poisonous metal affecting almost every organ in the body. Young children and infants are vulnerable to even low concentrations of Pb, which can result in behavioural issues, and learning disabilities (Wani *et al.*, 2015). Also, fatal exposure to high levels of lead has been connected to severe brain and renal damage in both adults and children. Reports abound showing that elevated level of Pb is a common observation in patients with SUDs (Ghaemi *et al.*, 2017; Ahmadinejad *et al.*, 2019; Ghaderi *et al.*, 2023). The reports of Adeniyi and Anetor (1999) and Ghaemi *et al.* (2017) showed that there is a significant association between blood Pb levels and excessive use of alcohol, tobacco and opium.

Over the years, consequences of substance abuse on immunity have become significant clinical concern (Friedman *et al.*, 2003). The effects of the substances on the immune system could be direct via the direct action of the substances on cells of the immune system or indirect via the activation of the hypothalamic-pituitary-adrenal axis (HPA) with resultant production of glucocorticoids which have profound effects on the activities of immune cells (Friedman *et al.*, 2003). The report of Olatunbosun *et al.* (2020) showed that there is hyperinflammation as exhibited by elevated level of interleukin (IL-6) in patients with SUDs. These reports clearly show that substance abuse has profound effects on both the innate and adaptive immune response.

CRP is a positive acute phase protein with important roles in innate immunity. It is a reliable early indicator of inflammation during infection or injury (Zimmerman *et al.*, 2003). Costello *et al.* (2013) reported that long-term alcohol use increases peripheral and brain's production of pro-inflammatory cytokines. Similarly, Grodin *et al.* (2023) reported that chronic alcohol exposure is associated with elevation in central and peripheral

markers of inflammation including CRP. Furthermore, CRP levels have been reported to be higher in individuals with tobacco, alcohol, or cannabis use, and with nicotine dependence (O'Loughlin *et al.*, 2008; Arnson *et al.*, 2010; Costello *et al.*, 2013). These reports clearly demonstrated that there is significant association between inflammation and substance abuse (Niemelä *et al.*, 2019).

Albumin, primarily synthesized in the liver, is a negative acute phase protein. It is involved in several processes, such as binding and transportation of hormones and drugs, as well as preservation of oncotic pressure. The ligand-binding capabilities of albumin, particularly to metal ions like copper and iron, are also responsible for its antioxidant properties (Chen *et al.*, 2021). Presently, there is limited report on the effect of substance abuse on serum albumin level. Nazrul Islam *et al*. (2002) reported that longer periods of substance abuse resulted in a significant reduction in serum albumin level.

Although there are avalanche of reports on serum levels of Pb, CRP and albumin in patients with SUDs, it is presently unknown if the serum Pb level has significant effect on the alteration of acute phase proteins levels in SUD patients. Also, majority of the available reports were on single substance abuse and not on multiple substance abuse, which is a common practice in Nigeria. It is therefore, unknown if there are differential effects of single substance abuse or multiple substances abuse on acute phase proteins alteration in SUD patients. These thus, serve as the basis for this study.

MATERIALS AND METHOD

Study Participants

A total of 84 adults consisting of 45 treatment-experienced patients (aged 19 years - 55 years) with SUD and 39 apparently healthy individuals (aged 26.0 – 68.0) who served as controls were enrolled into this case-control study using a convenient sampling method. All the patients with SUDs were enrolled from the New World Psychiatry Hospital, Ibadan, Nigeria and the Department of Psychiatry, University College Hospital, Ibadan, Nigeria. The study participants were enrolled between June 2023 and February, 2024.

Diagnosis of Substance Use Disorder

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria was used for the diagnosis of SUD (APA, 2013).

Exclusion criteria

Patients with history of schizophrenia, mood disorders and anxiety disorder were excluded from the study. Also, patients with occupational exposure to Pb and those with active infection or chronic liver disease were excluded from the study.

Ethical Consideration

The study was approved by the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Committee (UI/EC/23/0360). Also, written informed consent or assent was obtained from each study participant or their relatives/guardians as appropriate, before enrolment into the study.

Blood sample collection

Venous blood sample (5 mL) was obtained from each study participant and dispensed into plain sample bottles to obtain serum as appropriate. The serum obtained was stored at -20^{0}C until analysed.

Laboratory Analysis

Serum level of CRP was determined using the immunoturbidimetric method following the manufacturer's instruction (Fortress Diagnostics, UK). Also, the serum level of albumin was determined using the bromocresol green (BCG) colorimetric method following the manufacturer's instruction (DIALAB, Austria). However, the serum level of Pb was determined using AAS (AAS 320, MRC Scientific Instruments, Israel).

Calculation of CRP-Albumin Ratio

CRP-albumin ratio (CAR) was calculated as a ratio of the serum level of CRP to the serum level of albumin (Seringec Akkececi, 2019).

Data Analysis

Data analysis was done using SPSS, version 23.0. The distribution of the data was assessed using histogram with normal distribution curve. Thereafter, differences in means of variables with Gaussian distribution were determined using the Student's t-test, while the differences in the median of variables with non-Gaussian distribution were determined using the Mann Whitney *U* test. *P*-values less than 0.05 were considered as statistically significant. Results are presented as mean ± standard deviation or median (interquartile range) as appropriate.

RESULTS

The characteristics and types of substances abused by the patients have been earlier reported (Rahamon *et al.*, 2024). Briefly, 68.9%, 24.4%, 51.1%, 6.7%, 2.2%, 6.7% and 15.6% of the SUD patients abuse marijuana, nicotine, alcohol, tramadol, heroin, cocaine and Colorado, respectively. Marijuana was the most abused substance among the patients with SUDs.

As shown in Table 1, serum levels of PB and albumin were significantly higher in patients with SUDs compared with the controls. However, the median serum levels of CRP and CAR were insignificantly different between the two groups.

Table 1: Serum levels of Albumin, C-reactive protein, C-reactive protein-Albumin Ratio (CAR) and Lead in patients with Substance Use Disorders and controls

Parameters	SUDs (n = 45)	Controls (n = 39)	P-value
Albumin (g/dL)	6.39 ± 1.02	5.67 ± 1.31	0.006*
CRP (mg/L)	6.48 (4.15 - 15.17)	9.07 (4.28 - 48.74)	0.227
CAR	0.88 (0.62 - 2.33)	1.74 (0.73 - 8.05)	0.075
Lead (µg/mL)	2.12 (0.55 - 3.90)	0.05 (0.00 - 0.44)	0.000*

*Significant at P<0.05, SUDs = Substance use disorder, CRP = C-reactive protein, CAR = CRP-Albumin Ratio

As shown in Table 2, SUD patients were stratified into 2 groups based on the World Health Organisation (WHO) Pb cut-off value (5 µg/dL; 0.05 µg/ml) (World Health Organisation, 2021). The mean serum level of albumin was significantly lower in patients with SUDs whose Pb level was higher than the cut-off (>0.05 µg/ml) compared with patients whose Pb level was within the tolerable limit (≤0.05 µg/ml). In contrast, the median serum level of CRP and CAR were slightly higher in patients with SUDs whose Pb level was higher than the cut-off (>0.05 µg/ml) compared with patients whose Pb level was within the tolerable limit (≤0.05 µg/ml) (Table 2).

Table 2: Serum levels of albumin, C-reactive protein and CRP-albumin ratio in in SUD patients with different levels of Pb

Parameters	≤0.05 (µg/ml of lead) (n = 5)	>0.05 (µg/ml of lead) (n = 40)	P-value
Albumin (g/dl)	7.33 ± 1.59	6.27 ± 0.89	0.027 *
CRP (mg/L)	5.70 (4.93 - 9.59)	6.74 (3.63 - 21.26)	0.920
CAR	0.85 (0.66 - 1.34)	1.06 (0.55 - 3.46)	0.841

*Significant at P <0.05, SUD = Substance use disorder, CRP = C-reactive protein, CAR = CRP-Albumin Ratio

Comparing patients with SUDs who abuse single or multiple substances, no significant differences were observed in the levels of albumin, CRP, CAR and Pb between the two groups (Table 3).

Table 3: Serum levels of albumin, C-reactive protein, C-reactive protein-albumin ratio and lead in patients with substance use disorders abusing single or multiple substances

Parameters	Single substance (n = 19)	Multiple substance (n = 26)	P-value
Albumin (g/dl)	6.20 ± 0.67	6.52 ± 1.21	0.310
CRP (mg/L)	5.70 (2.85 - 27.74)	7.26 (4.15 - 11.93)	0.542
CAR	0.85 (0.43 - 4.21)	0.91 (0.62 - 1.76)	0.940
Lead (µg/mL)	2.24 (0.27 - 3.93)	2.01 (0.75 - 3.89)	1.000

SUDs = Substance use disorder, CRP = C-reactive protein, CAR = CRP-Albumin Ratio

DISCUSSION

Lead is one of the most dangerous and cumulative environmental contaminants that can enter the body through the

food, water, or air and impact all the biological systems of the body (Patra *et al.*, 2011). Due to the inability of the body to eliminate Pb properly, it results in both acute and long-term adverse health effects (Charkiewicz and Backstrand, 2020). In this study, the observed elevated serum level of Pb in SUD patients corroborates the reports of Norton *et al.* (1996) and Mostafazadeh *et al.* (2017) which showed that serum Pb level was elevated in users of substances such as opioids, methamphetamine, and alcohol. Our observation as well as that of previous studies suggest that substances that are abused are contaminated with Pb, which could have occurred during the process of preparation of the substances thereby, resulting in raised serum level. Chandler *et al*. (1990) reported Pb poisoning in 12 patients who had been injecting methamphetamine. They also reported that 60% of the weight of the methamphetamine tested was composed of Pb. Similarly, Busse *et al*. (2008) and Mostafazadeh *et al*. (2017) reported that Pb toxicity in substances such as opioids, marijuana and methamphetamine are mainly due to the addition of Pb to the illegal substances during the preparation process.

Chronic inflammation and immune system dysfunction have been linked to the pathophysiology of substance use and related mental health disorders. The brain becomes more prone to inflammation with chronic exposure to addictive substances in substance use disorders (Agarwal *et al*., 2022). Previous studies have reported elevated serum level of CRP in patients with SUD abusing different substances. Costello *et al.* (2013) reported elevated level of serum CRP in adolescents using marijuana. Also, cannabis use, misuse, or dependency were associated with increased CRP levels. This suggests that increased CRP levels are linked to long-term cannabis usage, which may indicate a proinflammatory state (Costello *et al.*, 2013). It was also reported that the long-term opioid use increases peripheral TNFα, CRP, IL-6, and IL-1β levels. The chronic use of opioids produces dependence, tolerance, and addiction that are mediated by immune dysregulation (Morcuende *et al*., 2021). Similarly, Alho *et al.* (2004) and Stewart *et al.* (2024) reported elevated CRP level in patients with alcohol abuse. However, in this study, similar level of serum CRP was observed in patients with SUD and controls. This observed inconsistency may be attributable to differences in the selection of study participants. Participants in this study were not drug naïve and reports have shown that antipsychotics such as aripiprazole enhances anti-inflammatory signalling thereby, limiting potentially damaging inflammatory processes. This anti-inflammatory property has been shown to lower the chance of metabolic abnormalities and helps to ameliorate psychopathological symptoms (Sobiś *et al.*, 2015; Hefner *et al.*, 2016; Juncal-Ruiz *et al.*, 2018).

Albumin is a multipurpose plasma protein. It is the most prevalent circulating protein and it is responsible for 60% of the colloidal osmotic pressure since it makes up 60% of the intravascular protein pool (Wong, 2007). Albumin is a negative acute phase protein which reduces in level during inflammation (Ceciliani *et al.*, 2002). In this study, the serum level of albumin was significantly higher in patients with SUD compared with the controls. This observation could suggest increased synthesis of albumin in patients with SUD. Immunologically, this was not expected as the levels of negative acute phase proteins are expected to reduce during inflammation-associated conditions. However, our observation is consistent with the reports of Tyulina *et al.* (2006) and Alatalo *et al.* (2008) which showed elevated albumin level in heavy drinkers of alcohol. Similarly, studies in cell cultures have shown elevated hepatic protein synthesis rates following chronic ethanol administration (Potter *et al.*, 1985; Ohtake *et al.*, 1986; Rothschild *et al.*, 1988; Karinch *et al.*, 2008). Presently, the mechanisms underlying the observed elevated albumin level in SUD patients remain unclear. Therefore, further studies are suggested to unravel the interplay between serum albumin level and substance use disorders.

CAR has been reported to be a reliable marker of inflammation (Seringec Akkececi *et al.*, 2019). In this study, CAR was insignificantly lower in patients with SUDs compared with healthy controls. This observation could be due to the observed elevated serum albumin level in patients with SUDs.

We observed that the serum level of albumin was significantly lower in SUD patients with serum Pb level higher than the WHO Pb cut-off value of 5 µg/dL compared with patients with SUDs having acceptable limit of serum Pb level. This indicates that there is decreased synthesis of albumin in SUD patients with increasing serum Pb level. Expectedly, CRP level and CAR were slightly higher in SUD patients with elevated serum Pb level compared with SUD patients with acceptable limit of serum Pb level. These observations are not surprising as Pb is a known inducer of oxidative stress which is significantly associated with dysflammation. Exposure to Pb has been shown to induce cellular oxidative stress by generating reactive oxygen species (ROS) which trigger inflammatory signalling pathway (Machoń-Grecka *et al.*, 2018). Similarly, Harshitha *et al.* (2024) reported that Pb significantly contributes to the onset and development of inflammation by influencing gene expression and synthesis of proinflammatory proteins. Mechanistically, entry of Pb into the cell is followed by the mobilization of calcium ions, which cleave phosphatidylinositol bisphosphate (PIP2) into diacylglycerol (DAG) and inositol trisphosphate (IP3). Subsequently, protein kinase C (PKC) is activated and relocates to the cytoplasmic membrane. This leads to elevation of inflammatory gene expression and formation of the c-jun and c-fos proteins, which further play a role in the formation of nuclear transcription factor activator protein 1 (AP-1) by dimerization and post phosphorylation of the 2 proteins. At least, one AP-1 binding site exists in the promoter region of the IL-6 gene, resulting in enhanced expression of the IL-6, a cytokine that induces the liver to produce CRP (Ngwa *et al*., 2022; Harshitha *et al.*, 2024). This report probably explains our observed reduction in albumin, a negative acute phase protein, and concurrent slight elevation in CRP, a positive acute phase protein, and CAR, a marker of inflammation in SUD patients with elevated serum Pb level.

The observed insignificant differences in the serum levels of albumin, CRP, Pb and CAR in patients abusing single substance compared with patients abusing multiple substances might indicate that alterations in these parameters are not influenced by the multiplicity of the substances abused.

Small sample size and inability to enrol drug-naïve patients were limitations in this study. Therefore, large population studies are suggested to explore the possible differences in acute phase proteins in patients with SUDs on single or multiple substance abuse and in those with different toxic metals levels.

It could be concluded from this study that SUD is associated with increased serum levels of lead and albumin and alteration in the serum levels of acute phase proteins appears to be influenced by the serum Pb level. Also, multiple substance abuse does not have cumulative effect on serum levels of lead, albumin, C-reactive protein and CRP-albumin ratio. Therefore, there is the need for routine measurement of Pb level in patients with SUDs as they could benefit from therapeutic interventions involving chelation of Pb which could prevent disordered acute phase responses in patients and facilitate optimal response to antipsychotics. Also, there is the need for effective implementation of policies that will facilitate reduction and prevention of drug abuse in Nigeria with a view to reducing SUD-associated disorders including possible Pb toxicity.

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Statement of Ethics

This study protocol was reviewed and approved by the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Committee, approval number (UI/EC/23/0360). Also, written informed consent or assent was obtained from each study participant or their relatives/guardians as appropriate, before enrolment into the study.

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Data Availability Statement
All data generated during this study are included in this published article.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Author Contributions
SKR conceived and designed the study; SKR, MAO, JGO, OO and VOL collected the samples; MAO, SAY and SKR did the laboratory analysis, SKR wrote the initial draft, SKR, MAO, SAY, JGO, OO and VOL reviewed the final draft, SKR and SAY supervised the entire research.

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