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Research Article

Dose-Dependent and Sex-Specific Hematological Perturbations Induced by Illicit Methamphetamine ("Mkpurummiri") in Wistar Rats

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Abstract

Methamphetamine usage continues to be a serious global public health problem due to its link with neurotoxicity, oxidative stress, inflammatory activation and systemic organ dysfunction. There is rising toxicological and forensic worry over the increasing consumption of locally synthesised illegal methamphetamine ("mkpurummiri") in Nigeria, although data on its haematological effects are sparse. This study assessed the dose- and sex-dependency of haematological dysregulation induced by illegal methamphetamine ("mkpurummiri") in Wistar rats utilising selected haematological indices as biomarkers of systemic toxicological response. Male and female Wistar rats were grouped into normal control and methamphetamine-treated groups of 1 mg/kg, 2 mg/kg, and 5 mg/kg methamphetamine. Blood samples were collected into whole blood tubes containing ethylenediaminetetraacetic acid (EDTA) and analysed using an automated haematology analyser (SYSMEX KX-21, Switzerland). The parameters assessed were red blood cell count (RBC), haematocrit (HCT), haemoglobin concentration (Hb), white blood cell count (WBC), platelet count (PLT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC). Data were analysed by one way analysis of variance (ANOVA) followed by Tukey's post hoc test at $p<0.05$. Methamphetamine exposure generated significant haematological changes in female and male Wistar rats in a dose- and sex-dependent manner. RBC, HCT, Hb, WBC and PLT values increased progressively with increasing doses of methamphetamine. MCV and MCH values were reduced in both sexes. The RBC levels were increased from $6.30 \pm 0.19 \times 10^6/mm^3$ in controls to $7.33 \pm 0.26 \times 10^6/mm^3$ after exposure to 5 mg/kg in females and from $6.96 \pm 0.09 \times 10^6/mm^3$ to $7.80 \pm 0.07 \times 10^6/mm^3$ in males. The maximum female WBC count was seen at 2 mg/kg exposure and was $15.53 \pm 2.50 \times 10^3/mm^3$, but the male WBC values rose dose-dependently. Both sexes exhibited similar increases in platelet counts following methamphetamine treatment. Illicit methamphetamine ("mkpurummiri") consumption produces profound haematological dysregulation characterised by erythrocytic modulation, leukocytic modifications, increase in platelets and erythrocyte indices in a dose- and sex-dependent way. Our data imply that oxidative stress, inflammatory activation, vascular dysfunction and impaired haematopoietic control may be important contributing factors to methamphetamine-associated hematotoxicity.

Keywords: *Illicit methamphetamine; Mkpurummiri; Haematological dysregulation; Hematotoxicity; Oxidative stress; Wistar rats; Psychostimulant toxicity; Nigeria.*

Introduction

Methamphetamine is a strong synthetic psychostimulant of the amphetamine-type stimulant (ATS) category and is still one of the most overused illicit drugs in the world. The rising manufacture, smuggling and use of methamphetamine has raised serious medical, toxicological, forensic and social issues globally. According to the United Nations Office on Drugs and Crime World Drug Report, amphetamine-type stimulants are one of the fastest growing classes of abused psychoactive substances, and methamphetamine accounts for a large proportion of stimulant-related morbidity and mortality worldwide [1] Methamphetamine addiction is associated with severe neuropsychiatric problems, cardiovascular dysfunction, liver injury, nephrotoxicity, immunological dysregulation, and multi-organ toxicity, leading to a serious worldwide public health concern [2]

The pharmacological effects of methamphetamine are mainly mediated through overstimulation of dopaminergic, serotonergic and noradrenergic neurotransmission. It also increases the amount of monoamines in the synapse by increasing transmitter release and at the same time blocks the reuptake of monoamines by the presynaptic neurone. Thus, chronic exposure results in oxidative stress, mitochondrial dysfunction, neuroinflammation, endothelial damage, apoptosis and metabolic dysregulation in numerous tissues and organ systems [3] Moreover, experimental and clinical studies have shown that chronic methamphetamine exposure results in alterations in cellular redox homeostasis due to the excessive production of reactive oxygen species (ROS), weakened antioxidant defence systems, lipid peroxidation and activation of inflammatory pathways [4].

Methamphetamine usage has increased dramatically in recent years in various African nations including Nigeria where the locally manufactured crystal methamphetamine colloquially known as “mkpurummiri” has become a growing public health and forensic problem. The increased occurrence of “mkpurummiri” in the southeastern part of Nigeria has been blamed for escalating levels of addiction, psychological problems, violence, criminality and social instability. The increasing detection of clandestine methamphetamine laboratories and illicit ATS trafficking networks in the country has been reported by the National Drug Law Enforcement Agency, raising serious toxicological and epidemiological concerns regarding the biological effects of locally available methamphetamine preparations [5]. Illicit methamphetamine preparations may contain toxic synthesis byproducts, precursor residues, heavy metals, organic solvents and adulterants which can exacerbate systemic toxicity and alter biological responses following exposure [6].

The toxicity of methamphetamine is not limited to the central nervous system. It is now well recognised as a systemic toxicological illness encompassing cardiovascular, hepatic, renal, endocrine, haematologic, and immunologic dysfunctions (Ramli et al., 2025). Chronic methamphetamine exposure has been associated with vascular damage, endothelial dysfunction, hyperthermia, inflammatory activation, rhabdomyolysis and metabolic changes which may compromise physiological homeostasis [7]. Clinical studies have also linked methamphetamine intoxication to increased inflammatory markers, changes in leukocyte counts, coagulation disorders and cardiovascular events [8]. These findings show that haematological changes may be key markers of systemic methamphetamine-induced toxicological stress. Haematological measures are commonly employed as sensitive biomarkers to assess physiological adaptability, inflammatory reactions, immunological competence and toxicant-induced systemic harm. Changes in erythrocyte indices such as the red blood cell (RBC) count, haemoglobin concentration (Hb), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC) may imply disruption of erythropoiesis, capacity of oxygen transportation, membrane integrity, cellular hydration status, and oxidative balance [9]. Similarly, white blood cell (WBC) and platelet (PLT) characteristics provide crucial information on inflammatory activation, immunological regulation, vascular integrity, thrombogenic potential and haematopoietic adaptation during pathological or toxicological stress situations [10].

Several investigations have shown that overuse of stimulants may have a major effect on haematological and immunological homeostasis . Amphetamine abusers have been documented to have severe haematological abnormalities and leukocyte changes, emphasising the link between psychostimulant intake, immunological dysregulation and inflammatory activation. The experimental data further suggest that the methamphetamine-mediated oxidative stress may affect the haematopoietic signalling pathways by increased ROS formation, activation of inflammatory cytokines, mitochondrial damage, and lipid peroxidation[11]. In toxicological stress situations, oxidative damage to erythrocyte membranes has also been related with altered blood rheology, decreased membrane stability, and aberrant erythrocytic indices [12].

Haematological alterations by methamphetamine-associated catecholaminergic hyperactivity may also involve stress-mediated glucocorticoid release, vasoconstriction, dehydration, endothelial dysfunction and inflammatory signalling. Hemoconcentration and adaptive changes of erythrocytic and platelet parameters may be due to hyperthermia and dehydration of methamphetamine intoxication [13]. Platelet activation and endothelial damage have been implicated in methamphetamine-associated cardiovascular problems, thrombosis, and vascular dysfunction (Kevil et al., 2021; Darke et al., 2023). Moreover, inflammatory activation generated by methamphetamine exposure has been linked to leukocyte modulation, altered cytokine production, and decreased host defence responses that can influence systemic immunological homeostasis [14]

Sex-dependent differences are another essential but less investigated feature of methamphetamine toxicity. Biological sex has a major impact on pharmacokinetic and toxicodynamic reactions, because of differences in hormonal regulation, body composition, vulnerability to oxidative stress, inflammatory signalling, and neurotransmitter metabolism [15]. Previous studies have demonstrated that male and female patients may differ in their susceptibility to methamphetamine-induced neurotoxicity, oxidative stress, cardiovascular damage, and inflammatory responses [16]. Sex differences in methamphetamine-induced haematological responses may need to be assessed. Although the worldwide concern for methamphetamine toxicity is developing, only a limited number of research have extensively assessed the haematological dysregulation associated with illegal methamphetamine consumption, particularly with preparations derived from African contexts. The studies available have primarily investigated neurobehavioral endpoints, oxidative stress indicators, or organ specific toxicities, while dose-dependent haematological responses and sex-associated variations have been relatively less studied. Furthermore, experimental toxicological data on illicit Nigerian methamphetamine ("mkpurummiri") remains rare, despite increasing reports of its abuse and forensic importance across the area. The present investigation was therefore undertaken to examine the dose- and sex-dependent haematological dysregulation generated by illegal methamphetamine ("mkpurummiri") in Wistar rats utilising chosen erythrocytic, leukocytic and platelet indices as biomarkers of systemic toxicological response. The study was designed to offer experimental evidence of the hematophysiological implications of exposure to locally circulating illicit methamphetamine and to contribute to the growing body of toxicological data on methamphetamine misuse in Nigeria and sub-Saharan Africa.

Materials and Methods

Chemicals and Reagents

Illicit methamphetamine ("mkpurummiri") used in this study was obtained from street-level sources within Owerri, Imo State, Nigeria. Preliminary identification and characterization of the substance were previously confirmed using forensic analytical techniques including gas chromatography mass spectrometry (GC–MS) and Fourier transform infrared spectroscopy (FTIR). All reagents and chemicals used during the study were of analytical grade.

Experimental Animals

Healthy adult Wistar rats of both sexes weighing between 150 and 220 g were used for the study. The animals were obtained from a certified animal breeding facility and housed in clean polypropylene cages under standard laboratory conditions of temperature (22 ± 2°C), relative humidity (50–60%), and a 12 h light/dark cycle. The animals were allowed free access to standard laboratory feed and clean drinking water ad libitum throughout the experimental period.

The animals were acclimatized for two weeks prior to commencement of the experiment. Experimental procedures involving animals were conducted in accordance with internationally accepted principles for laboratory animal care and use as outlined in the National Research Council Guide for the Care and Use of Laboratory Animals.

Experimental Design

The animals were randomly divided into four experimental groups for each sex (n = 3 per group):

Female Groups

- Group I: Normal control
- Group II: 1 mg/kg methamphetamine-induced group
- Group III: 2 mg/kg methamphetamine-induced group
- Group IV: 5 mg/kg methamphetamine-induced group

Male Groups

- Group V: Normal control
- Group VI: 1 mg/kg methamphetamine-induced group
- Group VII: 2 mg/kg methamphetamine-induced group
- Group VIII: 5 mg/kg methamphetamine-induced group

Methamphetamine was administered orally once daily at doses of 1 mg/kg, 2 mg/kg, and 5 mg/kg body weight respectively for the experimental duration, while the normal control groups received distilled water.

The selected doses were chosen to evaluate dose-dependent hematological responses associated with increasing methamphetamine exposure.

Blood Sample Collection

At the end of the experimental period, the animals were fasted overnight and anesthetized using mild chloroform inhalation. Blood samples were collected via cardiac puncture into ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes for hematological analysis.

Hematological Analysis

Hematological parameters were determined using whole blood samples collected into ethylenediaminetetraacetic acid (EDTA)-containing tubes immediately after collection. Hematological analysis was performed using an automated hematology analyzer (SYSMEX KX-21, Switzerland) in accordance with the manufacturer's operational guidelines and standard laboratory procedures.

The evaluated hematological indices included:

- Hemoglobin concentration (Hb)
- Hematocrit (HCT)
- Red blood cell count (RBC)
- White blood cell count (WBC)
- Platelet count (PLT)
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)

These hematological parameters were selected as biomarkers for evaluating erythrocytic integrity, hematopoietic function, inflammatory response, immune modulation, platelet dynamics, and systemic hematophysiological alterations associated with illicit methamphetamine ("mkpurummiri") exposure in Wistar rats.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison test to determine significant differences among experimental groups within each sex.

Differences were considered statistically significant at $p < 0.05$. Statistical analyses and graphical presentations were performed using appropriate statistical software.

Results

Table 1: Hematology parameters for normal control female and male groups with their respective 1mg/kg 2mg/kg and 5mg/kg meth induced control groups

	RBC (x106/mm3)		PCV (%)		Hb (g/dl)		WBC(x103/mm3)		PLT (x103/mm3)		MCV (fl)		MCH (pg)		MCHC (g/dl)	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Normal Control	6.30 ± 0.19^{a}	6.96 ± 0.09^{a}	42.00 ± 1.73^{a}	44.67 ± 0.58^{a}	14.43 ± 0.21^{a}	15.00 ± 0.20^{a}	8.53 ± 0.23^{a}	8.71 ± 0.12^{a}	321.33 ± 3.21^{a}	337.67 ± 9.29^{a}	66.69 ± 0.79^{a}	64.21 ± 0.55^{a}	22.93 ± 0.39^{a}	21.56 ± 0.32^{a}	34.39 ± 0.97^{a}	33.58 ± 0.23^{a}
1mg/kg meth	6.33 ± 0.14^{b}	6.82 ± 0.35^{b}	42.33 ± 1.15^{b}	43.00 ± 2.65^{b}	13.73 ± 0.31^{b}	14.90 ± 0.56^{b}	11.47 ± 1.16^{b}	13.23 ± 1.46^{b}	333.33 ± 7.37^{b}	352.00 ± 7.00^{b}	66.87 ± 0.48^{b}	63.00 ± 0.80^{b}	21.70 ± 0.06^{b}	21.85 ± 0.31^{b}	32.44 ± 0.31^{b}	34.69 ± 0.92^{b}
2mg/kg meth	6.96 ± 0.66^{c}	7.44 ± 0.78^{b}	45.67 ± 2.89^{b}	46.00 ± 5.29^{b}	14.97 ± 0.91^{c}	15.90 ± 1.28^{b}	15.53 ± 2.50^{c}	15.47 ± 1.81^{c}	365.00 ± 3.00^{c}	367.00 ± 10.44^{b}	65.70 ± 1.95^{b}	61.81 ± 0.65^{b}	21.54 ± 0.72^{b}	21.42 ± 0.63^{b}	32.78 ± 0.36^{b}	34.67 ± 1.38^{b}
5mg/kg meth	7.33 ± 0.26^{c}	7.80 ± 0.07^{b}	46.00 ± 1.00^{b}	47.33 ± 0.58^{b}	15.03 ± 0.25^{c}	16.17 ± 0.29^{b}	9.32 ± 0.56^{d}	14.67 ± 0.65^{c}	364.00 ± 9.54^{c}	366.67 ± 12.50^{b}	62.81 ± 1.06^{b}	60.71 ± 0.47^{b}	20.53 ± 0.46^{b}	20.73 ± 0.25^{b}	32.68 ± 0.18^{b}	34.15 ± 0.19^{b}

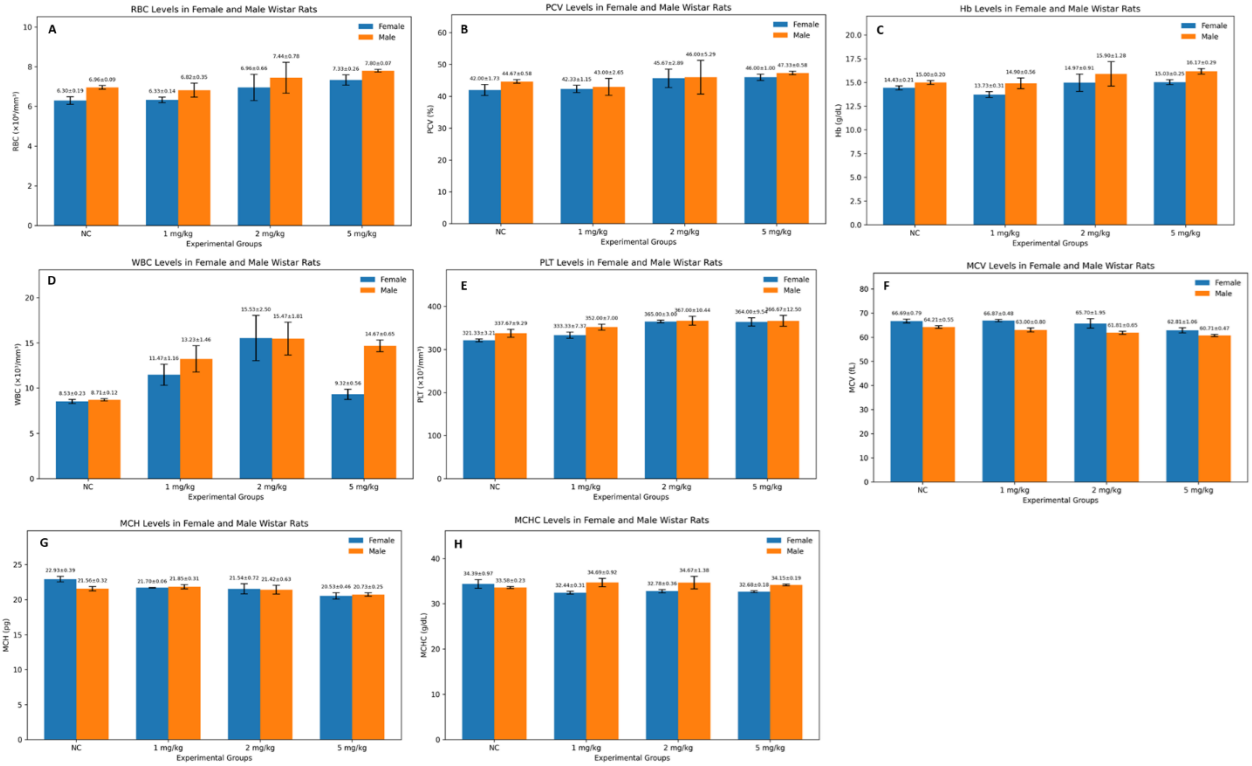
Data are presented as mean ± standard deviation (SD) for n = 3 animals per group per sex. Female and male values are presented side-by-side for each parameter. RBC = Red Blood Cell count (×10⁶/mm³) PCV = Packed Cell Volume (%) Hb = Hemoglobin concentration (g/dL) WBC = White Blood Cell count (×10³/mm³) PLT = Platelet count (×10³/mm³) MCV = Mean Corpuscular Volume (fL) MCH = Mean Corpuscular Hemoglobin (pg) MCHC = Mean Corpuscular Hemoglobin Concentration (g/dL) NC = Normal control (no methamphetamine exposure) 1 mg/kg, 2 mg/kg, 5 mg/kg meth = Methamphetamine-induced control groups representing increasing levels of exposure.

Superscripts (a–d) indicate statistical groupings within each column:

- Values sharing at least one superscript letter are not significantly different from each other at $p < 0.05$.
- Values with no shared superscripts are significantly different at $p < 0.05$.

Superscripts reflect dose-dependent variation, with progression from normal control to increasing methamphetamine exposure levels.

Within each sex, statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison test for each hematological parameter.



Hematological Parameters in Methamphetamine-Induced Female and Male Wistar Rats

The effects of illicit methamphetamine ("mkpurummiri") exposure on hematological parameters in female and male Wistar rats are presented in Table 1. Methamphetamine administration produced dose- and sex-dependent alterations across several hematological indices, including erythrocytic, leukocytic, and platelet parameters.

In female rats, red blood cell (RBC) count demonstrated a progressive increase with increasing methamphetamine dose. The normal control group recorded an RBC value of 6.30 ± 0.19 $\times 10^6/mm^3$, while the 1 mg/kg, 2 mg/kg, and 5 mg/kg methamphetamine groups showed values of 6.33 ± 0.14, 6.96 ± 0.66, and 7.33 ± 0.26 $\times 10^6/mm^3$, respectively. A similar trend was observed for packed cell volume (PCV) and hemoglobin concentration (Hb), with higher methamphetamine doses associated with elevated values relative to the normal control group. Female PCV increased from 42.00 ± 1.73% in the control group to 46.00 ± 1.00% at 5 mg/kg methamphetamine exposure, while Hb increased from 14.43 ± 0.21 g/dL to 15.03 ± 0.25 g/dL across the same groups.

Male rats similarly exhibited increases in erythrocytic parameters following methamphetamine exposure. RBC values increased from 6.96 ± 0.09 $\times 10^6/mm^3$ in the normal control group to 7.80 ± 0.07 $\times 10^6/mm^3$ in the 5 mg/kg methamphetamine group. PCV values increased from 44.67 ± 0.58% in controls to 47.33 ± 0.58% following 5 mg/kg methamphetamine administration, while Hb values increased from 15.00 ± 0.20 g/dL to 16.17 ± 0.29 g/dL. These findings indicate progressive erythrocytic modulation associated with increasing methamphetamine exposure in both sexes.

White blood cell (WBC) counts demonstrated variable responses between sexes and across dose levels. In female rats, WBC count increased from 8.53 ± 0.23 $\times 10^3/mm^3$ in the normal control group to 15.53 ± 2.50 $\times 10^3/mm^3$ at 2 mg/kg methamphetamine exposure before declining to 9.32 ± 0.56 $\times 10^3/mm^3$ at 5 mg/kg. In contrast, male rats exhibited a more progressive elevation in WBC count with increasing methamphetamine exposure, rising from 8.71 ± 0.12 $\times 10^3/mm^3$ in the control group to 14.67 ± 0.65 $\times 10^3/mm^3$ at 5 mg/kg methamphetamine administration.

Platelet (PLT) count also increased following methamphetamine exposure in both sexes. Female platelet values increased from 321.33 ± 3.21 $\times 10^3/mm^3$ in the control group to 365.00 ± 3.00 $\times 10^3/mm^3$ at 2 mg/kg methamphetamine exposure, with a slightly lower value observed at 5 mg/kg (364.00 ± 9.54 $\times 10^3/mm^3$). Male platelet counts similarly increased from 337.67 ± 9.29 $\times 10^3/mm^3$ in controls to 366.67 ± 12.50 $\times 10^3/mm^3$ at the highest methamphetamine dose.

Methamphetamine exposure additionally influenced erythrocyte indices including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Female MCV values decreased progressively from 66.69 ± 0.79 fL in controls to 62.81 ± 1.06 fL at 5 mg/kg methamphetamine exposure, while male MCV decreased from 64.21 ± 0.55 fL to 60.71 ± 0.47 fL across the same groups. Female MCH values

similarly decreased from 22.93 ± 0.39 pg in controls to 20.53 ± 0.46 pg following 5 mg/kg methamphetamine administration, whereas male MCH decreased from 21.56 ± 0.32 pg to 20.73 ± 0.25 pg. Alterations in MCHC were comparatively less pronounced, although fluctuations were observed across treatment groups in both sexes.

Overall, illicit methamphetamine exposure produced significant dose-dependent hematological alterations characterized by modulation of erythrocytic parameters, leukocyte responses, platelet dynamics, and erythrocyte indices in both female and male Wistar rats. The observed variations further suggest the presence of sex-dependent hematophysiological responses associated with increasing methamphetamine exposure.

Discussion

The present study assessed the dose and sex-related haematological dysregulation generated by illegal methamphetamine ("mkpurummiri") in Wistar rats utilising selected erythrocytic, leukocytic and platelet indices as biomarkers of systemic toxicological response. The results indicated that methamphetamine treatment induced significant changes in the haematological parameters in both sexes, but the size and pattern of response differed between the dose levels and between male and female animals. The major findings were increases in red blood cell (RBC) count, packed cell volume (PCV/HCT), haemoglobin concentration (Hb), platelet count (PLT) and white blood cell (WBC) count with concomitant decreases in erythrocyte indices, such as mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH). Together these results show complicated hematophysiological adaptability and systemic toxicological dysregulation related to illegal methamphetamine consumption.

One of the most interesting findings of the present investigation was the progressive increase in erythrocytic parameters including RBC count, PCV and Hb concentration with increasing exposure to methamphetamine. Female RBC values indicated increases from 6.30 ± 0.19 ×106/mm3 in normal control to 7.33 ± 0.26 ×106/mm3 in 5 mg/kg methamphetamine exposed group. Male rats also showed increases from 6.96 ± 0.09 ×106/mm3 to 7.80 ± 0.07 ×106/mm3 . Corresponding increases occurred in PCV and in Hb levels. These findings may be explained by compensatory erythropoietic responses to methamphetamine caused physiological stress, tissue hypoxia, dehydration, hyperthermia and altered vascular dynamics.

Methamphetamine induces severe sympathomimetic stimulation evidenced by vasoconstriction, hypermetabolism, hyperthermia, and elevated catecholaminergic activity, which can all contribute to hemoconcentration and disturbed erythrocytic homeostasis [17]. Hyperthermia may lead to fluid loss and dehydration, which can decrease plasma volume, leading to a relative increase in erythrocyte concentration and to increased PCV and Hb levels. Similar increases in erythrocytic parameters have been documented in stimulant-associated physiological stress circumstances after exposure to cocaine, amphetamine, and methamphetamine [18]. Increased RBC characteristics may also be an adaptive response to maintain oxygen supply in the context of increased metabolic demand and tissue hypoxia due to vasoconstriction. Furthermore, oxidative stress may potentially be an important factor in the haematological abnormalities seen in this study. Methamphetamine metabolism is closely related with overproduction of reactive oxygen species (ROS), mitochondrial dysfunction, lipid peroxidation and reduced antioxidant defence mechanisms [19]. Erythrocyte membrane damage caused by oxidative stress could affect erythrocyte turnover, deformability and haematopoietic signalling pathways. Previous studies have shown that oxidative stress generated by psychostimulants might affect erythropoiesis by activating inflammatory cytokines, stimulating haematopoiesis through glucocorticoids and disrupting redox-sensitive cellular pathways [20]

Although RBC, Hb and PCV increased after methamphetamine consumption, erythrocyte indicators such as MCV and MCH showed gradual decreases in both sexes. Female MCV fell from 66.69 ± 0.79 fL in controls to 62.81 ± 1.06 fL at 5 mg/kg methamphetamine exposure while male MCV decreased from 64.21 ± 0.55fL to 60.71 ± 0.47fL. Similarly, MCH values decreased progressively with increase in dose levels. A reduction in MCV and MCH can be indicative of changes in the maturation and stability of red blood cells or the response of the haematopoietic tissues of the body to prolonged toxicological stress.

In the earlier studies, microcytic modifications of the erythrocyte indices were connected with oxidative membrane damage, altered iron metabolism, compromised haemoglobin synthesis and inflammatory stress conditions [21]. Methamphetamine-induced oxidative stress may damage the integrity of erythrocyte membrane by lipid peroxidation and protein oxidation which may impair cell shape and erythrocytic parameters . In addition, inflammatory mediators produced after methamphetamine exposure could affect erythropoietic control and iron homeostasis, hence causing minor reductions in erythrocyte size and haemoglobin content despite the overall increases in erythrocyte quantity. In the present investigation, significant changes were found in leukocytes after exposure to methamphetamine. In female rats, WBC counts increased from 8.53 ± 0.23 ×103/mm3 in controls to 15.53 ± 2.50 ×103/mm3 at 2 mg/kg exposure, but decreased at 5 mg/kg. In male rats, the WBC count showed a more gradual increase with the dose. The increase in leukocytes in methamphetamine-exposed rats may be a consequence of inflammatory activation, stress leukocytosis, immunological stimulation, and neuroimmune dysregulation associated with psychostimulant exposure. It has been

shown that methamphetamine induces inflammatory signalling through activation of microglial cells, macrophages, endothelial cells and peripheral immunological pathways [22]. Also, the production of excess catecholamines and glucocorticoids during stimulant intoxication may mobilise leukocytes into systemic circulation, adding to high WBC counts. Similar leukocytic responses have been described in laboratory models of amphetamine toxicity and chronic stimulant addiction [23] The decrease in female WBC at the highest dose level may suggest immunological exhaustion, altered leukocyte redistribution or adaptive suppression due to prolonged toxicological stress. Exposure to methamphetamine also raised platelet numbers in both sexes. The elevated platelet levels in the present investigation may be indicative of endothelial dysfunction, inflammatory activation, vascular stress and thrombogenic adaptation associated with methamphetamine toxicity. Prior studies have implicated platelet activation, coagulation problems, and increased cardiovascular risk with methamphetamine-induced vasoconstriction and endothelial damage [24]. Therefore, the increase in platelet synthesis could be a compensatory haematopoietic response to vascular injury and inflammatory stress associated with psychostimulant consumption.

The observed sex-dependent differences in haematological responses further emphasise the role of biological sex in determining methamphetamine toxicodynamics. Male rats generally showed more progressive dose-dependent increases in WBC and erythrocytic parameters than females, but females showed greater variability in leukocyte responses at higher exposure levels. Sex hormones may be important in these differences by modulating inflammatory signalling, susceptibility to oxidative stress, vascular function, and regulation of haematopoiesis [25]. Some antioxidant and anti-inflammatory properties of oestrogen have been documented and may influence toxicological consequences . On the other hand, testosterone can increase oxidative and inflammatory responses in some pathological circumstances. A key feature of the present study is the use of locally circulating illicit methamphetamine (“mkpurummiri”), which may have different toxicological characteristics compared to pharmaceutical-grade methamphetamine due to variation in clandestine synthesis pathways, impurities, precursor residues, and chemical adulterants. Illicit methamphetamine preparations may contain hazardous chemicals that may potentiate oxidative stress, vascular damage, inflammatory activation and systemic haematological dysregulation [26]. Thus, the haematological changes seen in the present investigation may be attributable to the combined toxicological effects of methamphetamine and the synthesis-related pollutants present in locally circulating preparations[27].

Thus, the present findings provide crucial experimental evidence on the systemic haematological implications of illicit methamphetamine consumption in a Nigerian setting. The observed haematological disturbances may have substantial public health consequences in view of the increasing incidence of “mkpurummiri” abuse among youths in the southeastern Nigeria and other parts of sub-Saharan Africa. Chronic methamphetamine addiction related continued disruption of blood cell regulation may be a contributing factor to inflammatory diseases, vascular dysfunction, decreased immunological competence, altered oxygen transport dynamics and more widespread systemic toxicological consequences.

Some limitations should be recognised in the present investigation providing useful information regarding methamphetamine-associated haematological dysregulation. The relatively small sample size may restrict extrapolation of the findings to a larger population[28]. Evaluation of additional biomarkers such as inflammatory cytokines, oxidative stress indices, coagulation markers, and bone marrow histopathology would offer a deeper mechanistic understanding of methamphetamine-induced hematotoxicity. However, the study was able to reveal significant dose- and sex-dependent haematological changes related with illicit methamphetamine intake and provides baseline toxicological data on “mkpurummiri” in the Nigerian setting[29].

Conclusion

The present investigation revealed that administration of illegal methamphetamine (“mkpurummiri”) caused considerable dose- and sex-dependent haematological dysregulation in Wistar rats. Administration of methamphetamine led to significant changes in erythrocytic, leukocytic, platelet, and erythrocyte index parameters, which is indicative of a considerable disturbance of hematophysiological homeostasis after exposure. There was a dose-dependent increase in red blood cell count, packed cell volume, haemoglobin concentration, white blood cell count, and platelet count with increasing doses of methamphetamine. Mean corpuscular volume and mean corpuscular haemoglobin decreases suggested changes in erythrocyte morphology and haematopoietic physiology. Collectively, these data suggest that methamphetamine exposure may elicit complex adaptive and pathological haematological responses, including oxidative stress, inflammatory activation, vascular dysfunction, immunological modulation, and dysregulation of erythropoietic control.

The discovered sex-dependent differences further underscore the role of biological sex as a predictor of methamphetamine toxicodynamics and haematological response patterns. Males often displayed more progressive haematologic changes, while females exhibited somewhat varied leukocyte responses at the higher levels of exposure. These findings emphasise the importance of sex-specific assessment in experimental and clinical methamphetamine toxicity investigations. Importantly, the work provides crucial baseline toxicological data on regionally circulating illicit Nigerian methamphetamine (“mkpurummiri”), a drug for which experimental haematological data remain scarce, despite

increasing regional misuse. The findings thus add to the growing body of research regarding the systemic toxicological repercussions of illegal methamphetamine exposure and highlight the possible public health issues associated with continued misuse of locally synthesised methamphetamine formulations. In conclusion, the present investigation demonstrates that illegal methamphetamine consumption is linked with severe haematological alterations that can impact erythrocytic integrity, immunological function, vascular homeostasis and systemic physiological balance in a dose- and sex-dependent way.

References

1. Akinyemi, A. J., Adeniyi, P. A., & Oluwafemi, O. S. (2021). Oxidative stress and erythrocyte membrane alterations in toxicological disorders. *Toxicology Reports, 8*, 1345–1354.
2. Loftis, J. M., Choi, D., Hoffman, W., & Huckans, M. S. (2021). Methamphetamine causes persistent immune dysregulation: A cross-species review. *Neuroscience and Biobehavioral Reviews, 123*, 34–46.
3. Matsumoto, T., Kamijo, A., Miyakawa, T., Endo, K., Kishimoto, H., & Okudaira, K. (2022). Contaminants and toxicological implications of illicit methamphetamine production. *Forensic Toxicology, 40*(1), 1–14.
4. Bain, B. J., Bates, I., Laffan, M. A., & Lewis, S. M. (2023). *Dacie and Lewis practical haematology* (13th ed.). Elsevier.
5. Coffin, P. O., & Santos, G. M. (2023). Methamphetamine-related morbidity and mortality in the United States. *New England Journal of Medicine, 388*(2), 97–98.
6. Dluzen, D. E., & Liu, B. (2020). Gender differences in methamphetamine use and responses: A review. *Gender and the Genome, 4*(2), 24–31.
7. Fernandes, N. C., Sriram, U., & Goforth, H. W. (2023). Methamphetamine-associated oxidative stress and inflammatory signaling pathways. *Frontiers in Pharmacology, 14*, 1178634.
8. Loftis, J. M., & Janowsky, A. (2022). Neuroimmune basis of methamphetamine toxicity. *International Review of Neurobiology, 162*, 211–240.
9. McCutcheon, R. A., Bloomfield, M. A. P., & Marques, T. R. (2025). Methamphetamine-associated inflammation and systemic toxicity. *Brain, Behavior, and Immunity, 123*, 120–132.
10. Courtney, K. E., & Ray, L. A. (2022). Methamphetamine: An update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug and Alcohol Dependence, 232*, 109311.
11. Darke, S., Kaye, S., & Duflou, J. (2023). Cardiovascular disease risk among methamphetamine users. *Addiction, 118*(3), 445–456
12. Halpin, L. E., Collins, S. A., & Yamamoto, B. K. (2022). Neurotoxicity of methamphetamine and related psychostimulants. *Neuropharmacology, 209*, 108982.
13. Volkow, N. D., & Morales, M. (2021). The brain on drugs: From reward to addiction. *Cell, 184*(6), 1486–1501.
14. Gillies, G. E., Pienaar, I. S., Vohra, S., & Qamhawi, Z. (2021). Sex differences in Parkinson's disease. *Frontiers in Neuroendocrinology, 63*, 100937.
15. Costa, G., Frau, L., & Pinna, A. (2022). Oxidative stress and methamphetamine toxicity: Biological implications and therapeutic perspectives. *Antioxidants, 11*(6), 1135.
16. Yamamoto, B. K., Moszczynska, A., & Gudelsky, G. A. (2020). Amphetamine toxicities: Classical and emerging mechanisms. *Annals of the New York Academy of Sciences, 1187*(1), 101–121.
17. Harms, R., Morsey, B., Boyer, C. W., Fox, H. S., & Sarvetnick, N. (2020). Methamphetamine administration targets multiple immune subsets and induces phenotypic alterations suggestive of immunosuppression. *PLoSONE, 15*(3), e0229973.
18. Kokane, S. S., & Perrotti, L. I. (2021). Sex differences and the role of estradiol in mesolimbic reward circuits and vulnerability to cocaine and opiate addiction. *Frontiers in Behavioral Neuroscience, 14*, 74.
19. McDonnell-Dowling, K., & Kelly, J. P. (2017). The role of oxidative stress in methamphetamine-induced toxicity and sources of variation in the design of animal studies. *Current Neuropharmacology, 15*(2), 300–314.
20. Ramli, F. F., Mohd Yusof, N. S., & Abdul Hamid, Z. (2025). A mechanistic review on toxicity effects of methamphetamine. *International Journal of Medical Sciences, 22*(2), 482–501.
21. Saito, T., Takahashi, Y., & Hasegawa, M. (2022). Methamphetamine-associated immune activation and leukocyte dysregulation. *Journal of Neuroimmune Pharmacology, 17*(3), 514–526.
22. McKenzie, S. B., Williams, J. L., & Landis-Piwowar, K. R. (2022). *Clinical laboratory hematology* (4th ed.). Pearson.

23. Bowyer, J. F., & Hanig, J. P. (2021). Amphetamine- and methamphetamine-induced hyperthermia: Implications of oxidative stress and neurotoxicity. *NeuroToxicology, 86*, 97–107.
24. Cadet, J. L., & Krasnova, I. N. (2021). Molecular bases of methamphetamine-induced neurodegeneration. *International Review of Neurobiology, 158*, 101–132.
25. Mohammed, M. A., Abd El-Aziz, T. A., & El-Hadidy, M. A. (2024). Hematological and inflammatory alterations among amphetamine abusers. *Scientific Reports, 14*, 61182.
26. Jones, C. M., Compton, W. M., & Mustaquim, D. (2020). Patterns and characteristics of methamphetamine use among adults—United States, 2015–2018. *Morbidity and Mortality Weekly Report, 69*(12), 317–323.
27. Kiyatkin, E. A., & Sharma, H. S. (2021). Acute methamphetamine intoxication: Brain hyperthermia, blood-brain barrier, brain edema, and morphological cell abnormalities. *International Review of Neurobiology, 158*, 65–100.
28. Becker, J. B., & Chartoff, E. (2019). Sex differences in neural mechanisms mediating reward and addiction. *Neuropsychopharmacology, 44*(1), 166–183.
29. Moratalla, R., Khairnar, A., Simola, N., Granado, N., García-Montes, J. R., Porceddu, P. F., Tizabi, Y., Costa, G., & Morelli, M. (2021). Amphetamine-related drugs neurotoxicity in humans and in experimental animals: Main mechanisms. *Progress in Neurobiology, 155*, 149–170.
30. Sharma, H. S., & Kiyatkin, E. A. (2020). Rapid morphological brain abnormalities during acute methamphetamine intoxication in the rat: An experimental study using light and electron microscopy. *Journal of Chemical Neuroanatomy, 108*, 101807.

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