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Assessment of Chronic Drug Abuse on some Biochemical and Hematological Parameters in Human: A Multivariate Analysis

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Abstract

Ongoing substance abuse poses substantial public health concerns, primarily due to its wide-ranging impact on physiological processes. This study investigates the biochemical and hematological alterations associated with long-term drug abuse and seeks to elucidate the broader physiological consequences for both clinical assessment and public health planning. In the present case-control study, 100 male participants were divided into 60 drug abusers and 40 non-abusers. Thyroid hormones, liver enzymes, kidney function tests, and hematological tests like CBC (complete blood count) were analyzed in blood samples. There were notable differences between the groups; drug abusers showed higher serum levels of T4, urea, ALP, alanine transaminase (ALT), white blood cells (WBC) and lymphocyte counts, and lower levels of hematocrit (HCT) and red blood cells (RBC). No significant difference was found between drug use duration or frequency and the aforementioned parameters. The findings emphasize the importance of regular monitoring of these measures in people with history of drug abuse. Also, the study highlighs the need for more research to determine the mechanisms underlying these changes and potential interventions.

Keywords: Biochemical parameters, Correlation, Drug abuse, Hematological indices

تقييم شامل للتعرض المستمر للأدوية المخدرة على المعلمات الكيميائية الحيوية والدموية البشرية: تحليل متعدد المتغيرات

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الخلاصـــة

يمثل تعاطي المخدرات المستمر تحديات كبيرة على الصحة العامة ويرجع ذلك في المقام الأول إلى التأثير المتعدد الجوانب على الوظائف الفسيولوجية. تستكشف هذه الدراسة التغيرات البيوكيميائية والدموية المرتبطة بتعاطي المخدرات على المدى الطويل، وتهدف إلى تحديد العواقب الفسيولوجية الأوسع لكل من التقييم السريري

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وتخطيط الصحة العامة. تم في هذه الدراسة استخدام تصميم الحالات ومجموعة السيطرة، وشمل البحث 100 مشارك من الذكور، تم تصنيفهم إلى مجموعتين: 60 من متعاطي المخدرات و40 غير متعاطين. تم تحليل عينات الدم لمعرفة هرمونات الغدة الدرقية وإنزيمات الكبد واختبارات وظائف الكلى ومؤشرات الدم بما في ذلك تعداد الدم الكامل (CBC). وقد لوحظت فروق ذات دلالة إحصائية بين المجموعتين، أظهرت نتائج تحاليل المتعاطين قراءات عالية في مستويات هرمون الغدة الدرقية (T4)، واليوريا، والفوسفاتيز القلوي (ALP)، وناقلة أمين الألانين (ALT)، وخلايا الدم البيضاء (WBC)، وتعداد الخلايا الليمفاوية، ومستويات أقل بالنسبة للهيماتوكريت (HCT)، وخلايا الدم الحمراء (RBC). لم يتم العثور على ارتباطات هامة بين مدة أو تكرار تعاطي المخدرات والمعلمات المذكورة أعلاه. تؤكد النتائج على أهمية المراقبة الروتينية لهذه المعايير لدى الأفراد الذين لديهم تاريخ من تعاطي المخدرات. بالإضافة إلى ذلك، تؤكد الدراسة ضرورة إجراء المزيد من الأبحاث لفهم الآليات الأساسية التي تؤدي إلى هذه التغييرات، واستكشاف التدخلات المحتملة.

1. Introduction

According to the United Nations Office on Drugs and Crime (UNODC), an estimated 275 million people (about 5.5% of the world population) abused drugs in 2020, and this number is expected to increase by 11% worldwide by 2030 [1]. It is reported that around 36 million people in the world are suffering from drug abuse disorders. Drug abuse kills more than 583,000 people annually, with methamphetamine-related deaths contributing to approximately 31,000 of those deaths. While drug abuse contributes to the increase of infectious diseases also, including HIV and hepatitis. Addressing drug abuse requires a multi-sided approach including prevention, treatment, effects reduction, and international cooperation [2].

Continued exposure to drugs of abuse leads to a number of biological and physiological diseases, which can have a significant impact on human health, as well as contribute to the introduction of addiction abuse Chronic drug abuse can damage neurotransmitter systems, causing release of dopamine, serotonin, and other neurotransmitters depression is imbalanced health problems It also contributes to mood disorders [3]. Moreover, it can cause liver and kidney damage, respiratory problems, cardiovascular complications, and immune suppression [4]. Understanding the effects of long-term drug exposure on vital biochemical and hematologic parameters is important for the development of effective interventions and treatment programs that account for the consequences of drug addiction misuse occurs in many aspects of the overall health and well-being [5].

Biochemical markers, such as thyroid hormone (T3, T4), thyroid-stimulating hormone (TSH) [6], liver enzymes such as (ALT, AST, Alkaline phosphatase) [7], kidney function tests (Urea and Creatinine) [8], and hematological parameters (RBC, Hematocrit, Hemoglobin, WBC, Platelets, Mean Corpuscular Hemoglobin Concentration, Mean Corpuscular Volume Mean Corpuscular Hemoglobin) [9], provide valuable insight into the systemic effects of drug abuse. These concepts refer to the health status of major organ systems, including endocrine, liver, kidney, and hematopoietic systems, that can be compromised by drug abuse.

Prolonged exposure to medications prescribed by psychiatric may significantly affect many biochemical and hematological parameters in humans. Regular monitoring through blood tests is pivotal to detect any adverse effects and ensure patient's safety. Certain psychiatric medications, like valproate (Depakene®, Depakote®) can cause liver injury and necessitating regular monitoring of the liver enzymes, like aspartate aminotransferase (AST), bilirubin levels and alanine aminotransferase (ALT). Clozapine (Clozaril®) an atypical antipsychotic medication requires monitoring of the liver function tests due to the risk of hepatotoxicity [10]. Prolong use of Lithium, a mood stabilizer, is associated with reduced renal function. Therefore, it is essential to measure glomerular filtration rate (GFR) and serum creatinine [11].

Second-generation antipsychotics, such as quetiapine (Seroquel®) and olanzapine (Zyprexa®), may cause metabolic dysfunction and changes in the glucose metabolism, thus necessitating regular monitoring of the lipid panels and hemoglobin A1C levels [12]. Specifically,

antipsychotics, such as risperidone (Risperdal®), can increase prolactin levels, leading to potential side effects, including galactorrhea, amenorrhea, and sexual dysfunction [13]. Clozapine (Clozaril®) can cause potentially life-threatening agranulocytosis, which requires monitoring of the complete blood count [14]. For the medications like lithium and clozapine therapeutic drug monitoring through blood tests is essential to ensure that drug levels are within the appropriate range of therapy, and to reduce the risk of toxicity [15].

It is pivotal for psychiatrists to collaborate with primary care providers, or order necessary blood tests themselves to regularly monitor these parameters. Establishing baseline values before the start of treatment and periodic monitoring can facilitate the early detection of the adverse effects and adequate treatment adjustments or interventions [16]. Close monitoring and proper interventions can increase patient safety and treatment results in patients exposed to continuous psychiatric drugs [17].

The aim of this study was to determine the effects of chronic drug abuse on biochemical and hematological parameters in humans using a multivariate analysis. This study also aims to investigate the physiological effects of continuous drug intake, by assessing both the physiological changes in these parameters. These findings will enhance our understanding of how chronic drug use impacts various organ systems and inform clinical assessment and management, as well as public health policies designed to mitigate the effects of drug abuse.

2. Materials and Methods

2.1 Design of Study

This observational study was conducted at the Ibn-Rushed Psychiatric Teaching Hospital, a specialized institution in Baghdad that specializes in mental health and substance use disorders. The study received ethical approval from the Ministry of Health, Baghdad Al-Rusafa Health Department, Training and Human Development Center (No. 20919) on the 4th March 2024. The study lasted 4 months from January 2024 to April 2024. Our study used a case-control design that involved two groups: drug abusers and non-drug abusers serving as the control group. The method allowed comparison of biochemical and hematological changes associated with drug abuse where the study included 100 male participants, divided into two groups. Sixty subjects with a documented history of substance abuse between 3 months and 5 years were allocated as the experimental group, these subjects were selected on the basis of a documented history of substance abuse and met the study inclusion criteria. The control group consisted of 40 non-abusive men matched for age and socioeconomic status, for comparison purposes. Methamphetamine (crystal meth) was abused predominantly in the experimental study group, and many participants also used Cannabis (Marijuana®) and Pregabalin (Lyrica®). Methamphetamine was the most commonly used substance by the participants.

Participants in the experimental group were diagnosed with drug addiction by two-way clinical and laboratory testing to ensure accurate diagnosis and proper classification. Experienced clinicians have clinical conducted a comprehensive conceptual study with a particular focus on psychoanalysis and behavioral assessment. Furthermore, laboratory tests played an important role in this study. These tests included detailed blood analysis that aimed to detect the presence of various drug metabolites, thereby confirming recent and future drug use.

This specific diagnostic criteria would undoubtedly ensure that the classification of participants into the experimental or control group was based on clinical and practical evidence. The test group inclusion criteria included males aged 18-47 with documented drug-abusing history ranging from 3 months to 5 years. They must have positive clinical evaluations and laboratory tests for the drug metabolites. For the control group inclusion criteria males aged

between 18-47 without a history of substance abuse matched by socio-demographic characteristics to test group were adopted.
Individuals with chronic disease affecting metabolic or hematological functions, those on long-term medication that could alter test results, and anyone under the therapeutic regime for mental health disorders other than substance abuse as excluded from both groups.

The present study was conducted with the explicit approval of the Ethics Committee of Ibn-Rushed Psychiatric Teaching Hospital, in accordance with the ethical approval granted by the Ministry of Health, Baghdad Al-Rusafa Health Department, Training and Human Development Center (No. 20919) on March 4, 2024. Strict adherence to ethical standards was maintained all over the research process. Confidentiality and namelessness for all participants were strictly protected to secure their privacy and personal information. In according with established ethical guidelines all participants gave their verbal consent before their inclusion in the study. This informed consent process was completely documented and monitored to ensure that study individuals were informed of the nature of the study, potential impacts, and procedures before agreeing to participate.

2.2 Collection of data

Data collection for this study was conducted using a structured questionnaire specifically designed to gather detailed demographic and drug usage information from each participant. The questionnaire captured current age, body weight in kilograms, and height in centimeters under demographic information. Drug usage details included the type of drug used, dose per intake in grams, duration of use in months or years, and frequency of intake per day. Additionally, the questionnaire assessed the consumption of alcohol, specifying the frequency and quantity, as well as the use of painkillers, noting the type and frequency of intake. Participants completed the questionnaire under supervision to ensure accuracy and completeness facilitating thorough the analysis of the impact of drug use on various biochemical and hematological parameters.

2.3 Blood Sample Collection

Blood samples were collected using venipuncture for hematological and biochemical investigations including tests for thyroid hormones, liver enzymes, kidney function tests (Urea, Creatinine), and various hematological indices. Each participant provided approximately 10 mL of blood, which was immediately labeled and transported to the laboratory under controlled conditions to prevent hemolysis and contamination. After clotting at room temperature for 30 minutes, centrifugation of samples was done in 3000 rpm for a time of 10 minutes to separate serum. The resulting clear serum was then transferred to new sterile tubes and stored at -20° C until biochemical analysis. We conducted hematological tests by using fresh samples to ensure accuracy. The careful process was essential to preserve the integrity and reliability of samples in subsequent analysis.

2.4 Hematological and Biochemical Investigations

An automated hematology analyzer was used to perform hematological tests and complete blood count (CBC).
This system accurately quantified a range of hematological indices, including, platelets, red blood cells (RBC), hematocrit (HCT), white blood cells (WBC), hemoglobin (Hb), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV).

The biochemical investigations were conducted by Cobas e 411 analyzer, Germany to ensure the precise measurements of various biochemical markers involving thyroid hormones

TSH, T3, and T4 were measured by using an immunoassay analyzer. Liver enzymes that include alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were assessed with the automated biochemistry analyzer Respons®920 Germany.

2.5 Statistical Analysis

The statistical analysis employed mean and standard deviation calculations, F-statistics, (Welch's ANOVA) to compare means, Games-Howell postdoc test for pairwise comparisons, an independent t-test for group comparisons, and Mann-Whitney test that was adopted for non-normally distributed variables. The correlations test between drug use duration/frequency and parameter changes were assessed using Spearman's correlation. A significance threshold of <0.05 was used for the p-value.

3. Results

3.1 Characteristics of Participants

The distribution of study individuals by group is summarized in Table 1. The majority of participants fall within the 26-45 years age range, comprising 68.33% of the total. The 15-25 years age group represents 30% of the participants indicating a significant presence of the younger individuals. Those over 45 years are minimally represented accounting for only 1.67% of the sample.

The same Table delineates the distribution of substance use among the participants in the study, illustrating the prevalence of specific drug types. Methamphetamine, referred to as "Crystal meth" was the most commonly used substance, accounting for approximately 56.67% of usage among participants. Cannabis labeled as "Marijuana®" was used in 21.67% of participants, while "Lyrica®" was utilized in 20% of the sample. Additionally, combined use of Marijuana® and Crystal meth in the cohort, followed by significant usage rates of Marijuana® and Lyrica®.

An examination of the dosages of the drugs administered to the participants revealed distinct consumption patterns. A total of 30.00% of participants reported with less than 1 gram of the drug while 21.67% used 1 gram. Additionally, 28.33% consumed 2 grams and 20.00% used 3 grams. These results indicate the diverse range of drug dosages among the subjects.
Regarding the duration of drug use, 15.00% of participants reported using drugs for less than 6 months. Those who used drugs for 6 months to 1 year constituted 21.67% of the study population, while 23.34% had been using drugs for 1 to 2 years. The percentages for 2 to 3 years and more than 3 years were 15.00%, and 25.00%, respectively, highlighting a significant number of long-term users.

The intake frequency showed that 26.7% of participants took the drug once per day, 31.7% twice per day, and 28.3% three times per day, illustrating varying patterns of drug consumption. Alcohol intake was also recorded, with 68.33% of the participants consuming alcohol and 31.67% abstaining, indicating a high percentage of accompanying alcohol use.
Regarding the use of painkillers, 21.67% of the participants used Paracetamol, and a significant 78.34% used Diazepam (Valium®), pointing to a prevalent use of these medications among the drug-using population.

Table 1: Distribution of Study Participants based on multiple characteristics

Characteristic	Frequency (No.)	Frequency (%)
Age Group		
● 15-25 years	18	30.00%
● 26-45 years	41	68.33%
● > 45 years	1	1.67%
Type of Drug		
● Methamphetamine	34	56.67%
● Cannabis	13	21.67%
● Pregabalin	12	20.00%
● Cannabis and Methamphetamine	1	1.67%
Dose of Drug (gm)		
● < 1 gram	18	30.00%
● 1-<2 gram	13	21.67%
● 2 <3grams	17	28.33%
● >3 grams	12	20.00%
Duration of Drug Using		
● < 1 year	9	15.00%
● 1-2 years	13	21.67%
● 2-3 years	14	23.34%
● 3-4 years	9	15.00%
● 4 years	15	25%
Intake Frequency (Per day)		
● Once	16	26.7%
● Twice	19	31.7%
● 3 times	17	28.3%
Alcohol Intake		
● Yes	41	68.33%
● No	19	31.67%
Pain Killer Used		
● Paracetamol	13	21.67%
● Diazepam (Valium®)	47	78.34%

3.2 Results of Thyroid Function Tests in Study Individuals

Table 2 shows that T4 (Thyroxine) levels were significantly lower in the drug-abuser group in comparison to the control group ($p<0.05$). No significant differences were observed in T3 (Triiodothyronine) or TSH (Thyroid Stimulating Hormone) levels.

Table 2: Thyroid Hormone Levels (Mean ± SD) in Study Individuals

Hormone	Test Group (Drug Abuser) Mean ± SD	Control Group (Drug Non-abuser) Mean ± SD	F-Statistics	P value
T3 ng/mL	1.63 ± 0.39	1.54 ± 0.26	F=2.456	p=0.1193
T4 nmol/L	80.11 ±21.92	91.14±22.15	F=9.872	p=0.0022
TSH mIU/L	1.87 ±1.07	1.77 ±0.94	F=0.325	p=0.5699

F-tests showed unequal variances for T3 and TSH, but equal variances for T4 between the test and control groups. Welch's ANOVA was used to account for unequal variances, revealing a significant difference in means for T4 (F=9.872, p=0.0022), but not T3 (F=2.456, p=0.1193) or TSH (F=0.325, p=0.5699). The Games-Howell post-hoc test confirmed a statistically significant mean difference of -11.0285 for T4 between the drug abuser and non-abuser groups (p=0.0022,95% Cl: -18.1193). In summary, T4 levels differed significantly between groups after controlling for unequal variances, while T3 and TSH did not show significant differences.

3.3 Results of Urea and Creatinine Levels in Drug Abusers and Non-Abusers

A comparative analysis of urea and creatinine levels were compared between a test group of drug abusers and a control group of non-abusers using Games-Howell post hoc and Welch's ANOVA tests as shown in Table 2.

For urea levels, Welch's ANOVA detects significant differences among the groups (F (95.54), p = 0.0008). The Games-Howell test confirmed this difference, with the drug-abuser group having a significantly higher mean urea level of 18.15 mg/dL compared to 15.275 mg/dL in the non-abuser group (mean difference = 2.875, 95% Cl = 1.247 to 4.503).

However, for creatinine levels, Welch's ANOVA there was no statistically significant difference between the groups (F (96.99), p = 0.69). The mean of creatinine was 0.815 mg/dL in the drug-abuser group and 0.8235 mg/dL in the non-abuser group.

Overall, drug abusers exhibited significantly elevated urea levels compared to non-abusers, potentially indicating impaired kidney function. The analysis showed that creatinine levels did not differ significantly between the two groups.

Table 3: Urea and Creatinine Levels (Mean ± SD) in Drug Abusers and Non-Abusers

Kidney Function Tests	Test Group (Drug Abuser) Mean ± SD	Control Group (Drug Non-abuser) Mean ± SD	F-Statistics	P value
Urea mg/dL	18.15 ± 5.03	15.275±3.51	95.54	0.0008
Creatinine mg/dL	0.815 ± 0.145	0.8235±0.123	96.99	0.69

3.4 Results of Liver Enzyme Levels in Drug Abusers and Non-Abusers

Liver enzyme levels such as ALT, AST and ALP in this study were compared between a test group of drug abusers and a control group of non-abusers using Games-Howell post-hoc and Welch's ANOVA tests as shown in Table 4.

For ALT levels, Welch's ANOVA detected a significant difference between the study groups (F (1,77.54) = 8.41, p = 0.005). The results of the Games-Howell test corroborated this finding, with the drug-abuser group having a significantly higher mean ALT level of 26.75 U/L compared to 19.55 U/L in the non-abuser group (mean difference = 7.20, 95% CI = 2.11 to 12.29).

However, for AST levels, Welch's ANOVA did not find a statistically significant difference between the groups (F (1, 89.95) = 0.27, p = 0.60). The mean AST was 17.12 U/L in the drug-abuser group and 16.00 U/L in the non-abuser group.

Regarding ALP levels, Welch's ANOVA showed a significant difference between the groups (F (1,89.95) = 33.89, p < 0.0001). The Games-Howell postdoc test confirmed this difference, with the drug-abuser group having a significantly higher mean ALP level of 116.48 U/L compared to 84.50 U/L in the non-abuser group (mean difference = 31.98, 95% CI = 22.74 to 41.22).

Table 4: ALT, AST, and ALP Levels (Mean ± SD) in Drug Abusers and Non-Abusers

Liver Function Tests	Test Group (Drug Abuser) Mean ± SD	Control Group (Drug Non-abuser) Mean ± SD	F-Statistics	P value
ALT	26.75 U/L±17.24	19.55 U/L±6.51	8.41	0.005
AST	17.12 U/L±11.36	16.00 U/L±5.89	0.27	0.60
ALP	116.48 U/L±31.71	84.50 U/L±17.02	33.89	< 0.0001

3.5 Results of Complete Blood Count in Drug Abusers and Non-Abusers

To investigate potential differences in complete blood count parameters between drug abusers and non-abusers, we performed statistical comparisons on values of hematocrit (HCT), platelet count (PLT), red blood cell count (RBC), white blood cell count (WBC), hemoglobin (HGB), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH),), mean corpuscular volume (MCV), neutrophil count (NEUT#), mixed cells percentage (MXD%), neutrophil percentage (NEUT%), mean platelet volume (MPV), lymphocyte percentage (LYM%), lymphocyte count (LYM#), red cell distribution width - standard deviation (RDW-SD), mixed cell count (MXD#), and red cell distribution width - coefficient of variation (RDW-CV), as shown in Table 5. First, F-tests revealed unequal variances between the two groups for WBC, RBC, and HCT, violating the assumption of homogeneity of variances. Consequently, Welch's ANOVA was employed, which is robust to this violation. The results showed highly significant differences in group means for WBC (Welch's $F = 28.91$, $p < 0.0001$), RBC (Welch's $F = 24.32$, $p < 0.0001$), and HCT (Welch's $F = 53.44$, $p < 0.0001$). For HGB, where variances were equal, the classic one-way ANOVA indicated a significant mean difference ($F = 4.51$ $p = 0.038$).

To determine which specific group means differed, the Games-Howell post-hoc test was conducted, as it does not assume equal variances. The test revealed significantly higher WBC (mean difference = 2.73, 95% CI [1.92, 3.54], $p < 0.0001$), RBC (mean difference = 0.38, 95% CI [0.28, 0.48], $p < 0.0001$), and HCT (mean difference = 3.81, 95% CI [2.76, 4.86], $p < 0.0001$) in the drug abuser group compared to non-abusers. However, no significant difference was found for HGB (mean difference = 0.44, 95% CI [-0.03, 0.91], $p = 0.07$) between the two groups.

Overall, the analysis demonstrated that drug abusers exhibited significantly elevated levels of WBC, RBC, and HCT compared to non-abusers, potentially indicating hematological abnormalities associated with substance abuse. These findings highlight the importance of monitoring complete blood count parameters in persons with a drug-abusing history.

The F-test revealed equal variances between the two groups for MCV, while unequal variances were observed for MCH, MCHC, and PLT. Consequently, Welch's ANOVA was employed for MCH, MCHC, and PLT, whereas the classic one-way ANOVA was used for MCV. The results showed no significant differences in group means for MCV ($F = 0.37$, $p = 0.545$), MCH (Welch's $F = 1.71$, $p = 0.197$), MCHC (Welch's $F = 2.16$, $p = 0.148$), and PLT (Welch's $F = 0.13$, $p = 0.722$).

For lymphocyte percentage (LYM%), the F-test indicated unequal variances between the groups. Welch's ANOVA revealed a significant difference in LYM% means (Welch's $F = 10.89$, $p = 0.002$). The Games-Howell post-hoc test further confirmed a significantly lower LYM% in the drug abuser group compared to non-abusers (mean difference = -6.74, 95% CI [-11.05, -2.43], $p = 0.002$).

The F-test revealed equal variances between the two groups for MXD% and NEUT#, while unequal variances were observed for NEUT%, LYM#, and MXD#. Consequently, Welch's

ANOVA was employed for NEUT%, LYM#, and MXD#, whereas the classic one-way ANOVA was used for MXD% and NEUT#.

The results showed no significant differences in group means for MXD% ($F = 0.16$, $p = 0.693$), NEUT% (Welch's $F = 0.11$, $p = 0.744$), and NEUT# ($F = 0.24$, $p = 0.629$). However, significant differences were observed for LYM# (Welch's $F = 6.91$, $p = 0.011$) and MXD# (Welch's $F = 35.89$, $p < 0.001$).

The Games-Howell post-hoc test further confirmed a significantly lower LYM# in the drug-abuser group compared to non-abusers (mean difference = -0.55, 95% CI [-0.98, -0.12], $p = 0.011$). Additionally, the test revealed a significantly higher MXD# in the drug abuser group (mean difference = 0.64, 95% CI [0.44, 0.84], $p < 0.001$).
The analysis revealed no significant differences were observed in MXD%, NEUT%, and NEUT%, between the two groups. However, a statistical significantly reduced lymphocyte count and elevated mixed cell count in individuals with a history of drug abuse compared to non-abusers.

It was found significant differences in Mean Platelet Volume (MPV) and Red Cell Distribution Width - Standard Deviation (RDW-SD), but not in Red Cell Distribution Width - Coefficient of Variation (RDW-CV). RDW-SD was significantly lower in drug abusers (35.94 ± 8.00 fL) compared to non-abusers (42.68 ± 3.52 fL), while MPV was higher in non-abusers (12.44 ± 1.27 fL) than abusers (11.79 ± 1.22 fL). RDW-CV showed no significant difference between groups.

Table 5: Complete Blood Count (Mean ± SD) in Drug Abusers and Non-Abusers

Complete Blood Count	Test Group (Drug Abuser) Mean ± SD	Control Group (Drug Non-abuser) Mean ± SD	F-Statistics	P value
WBC	10.19 $x10^9$/L±3.45 $x10^9$	7.46 $x10^9$/L±1.39 $x10^9$	28.91	0.0001
RBC	4.83 $x10^{12}$/L±0.44 $x10^{12}$	4.45 $x10^{12}$/L± 0.23 $x10^{12}$	24.32	0.0001
HGB g/dL	13.77 ± 0.99	13.33 g/dL± 0.98 g/dL	4.51	0.038
HCT	44.10 %± 2.93 %	40.29%± 1.96%	53.44	0.0001
MCV	84.96 fL± 4.33	84.43 fL± 3.38 fL	0.37	0.545
MCH	27.07 pg± 2.32	27.61 pg± 1.17 pg	1.71	0.197
MCHC	32.08 g/dL±1.27	32.45 g/dL± 0.84 g/dL	2.16	0.148
PLT	276.28 $x10^9$/L± 95.91 $x10^9$	269.85 $x10^9$/L± 63.11 $x10^9$/L	0.13	0.722
LYM%	23.97%± 12.18%	30.71% ± 4.51%	10.89	0.002
MXD%	9.20%±6.01%	9.75% ± 4.72%	0.16	0.693
NEUT%	58.50%± 13.92%	59.55% ± 5.46%	0.11	0.744
LYM#	2.12 $x10^9$/L± 0.96 $x10^9$	2.67 $x10^9$/L ± 0.69 $x10^9$	6.91	0.011
MXD#	1.12 $x10^9$/L /L± 0.62 $x10^9$	0.48 $x10^9$/L ± 0.22$x10^9$/L	35.89	0.001
NEUT#	6.85 $x10^9$/L± 5.77 $x10^9$/L	5.94 $x10^9$/L ± 7.15$x10^9$/L	0.24	0.629
RDW-SD	35.94 fL ± 8.00 fL	42.68 fL ± 3.52 fL	18.727	0.001
RDW-CV	12.80% ± 4.01%	12.91% ± 4.95%	0.008	0.928
MPV	11.79 fL±1.22fL	12.44 fL±1.27fL	3.923	0.050

3.6 Correlation Analysis of Drug Abuse Duration, Frequency, and Biochemical Parameters

The correlation between drug abuse duration, drug use frequency, and various biochemical parameters was investigated using Spearman's rank correlation analysis. The results are presented in Table 6.

For participants with a drug abuse duration of 2 years or more, no significant correlation was found between duration and any of the biochemical parameters measured, including T4 (ρ=-0.138, p=0.329), T3 (ρ=-0.131, p=0.351), TSH (ρ=-0.015, p=0.903), urea (ρ=-0.094, p=0.537), creatinine (ρ=0.019, p=0.878), ALT (ρ=-0.002, p=0.988), AST (ρ=0.065, p=0.638), and ALP (ρ=-0.016, p=0.892). The p-values were over than 0.05 indicating no significant correlation.

Similarly, participants with a drug use frequency of 3 times per day, no significant correlations were observed between use frequency and the biochemical parameters including T4 (ρ=-0.073, p=0.643), T3 (ρ=0.162, p=0.321), TSH (ρ=0.031, p=0.837), urea (ρ=-0.073, p=0.642), creatinine (ρ=-0.112, p=0.472), ALT (ρ=0.079, p=0.614), AST (ρ=0.068, p=0.677), and ALP (ρ=-0.086, p=0.573). All p-values were over than 0.05 indicating no significant correlation.

The data shows that neither a drug abuse duration of 2 years or more, nor a high drug use frequency of 3 times per day, had any significant correlation with levels of thyroid hormones (T4, T3, TSH), kidney function markers (urea, creatinine), or liver enzymes (ALT, AST, ALP) in this study population.

Table 6: Spearman's Correlation Coefficients Analysis of Drug Abuse Duration, Frequency, and Biochemical Parameters

Parameter	Drug Abuse Duration (2 Years)		Drug Use Frequency (3 times per day)	
	Spearman's ρ	p-value	Spearman's ρ	p-value
T4	-0.138	0.329	-0.073	0.643
T3	-0.131	0.351	0.162	0.321
TSH	-0.015	0.903	0.031	0.837
Urea	-0.094	0.537	-0.073	0.642
Creatinine	0.019	0.878	-0.112	0.472
ALT	-0.002	0.988	0.079	0.614
AST	0.065	0.638	0.068	0.677
ALP	-0.016	0.892	-0.086	0.573

3.7 Correlation Analysis of Drug Abuse Duration, Frequency and Hematological Parameters

Table 7 presents the correlations between drug abuse duration (2 years) and drug use frequency (3 times per day) with various hematological parameters. Spearman's correlation was chosen due to the non-normal distribution of the data, ensuring the validity of the test for this analysis.

For drug abuse duration of 2 years, there were no statistically significant correlations found for any of the hematological parameters. The spearman's correlation coefficients varied from -0.053 to 0.037, with a p-value exceeding 0.05 for all correlations tested. This suggests that there is no linear relationship between duration of abuse and these blood profiles. Notably, a moderate negative correlation was observed between duration of abuse and platelet count (MPV) (ρ = -0.053, p = 0.638).

Similarly, no statistically significant association was found with the frequency of drug use 3 times per day. Spearman correlation coefficients ranged from -0.083 to 0.088, with p-values greater than 0.05 for all correlations. This suggests that there is no linear relationship between frequency of drug use and these blood profiles.

Table 7: Spearman's Correlation Coefficients Analysis of Drug Abuse Duration, Frequency, and Hematological Parameters

Parameter	Drug Abuse Duration (2 Years)		Drug Use Frequency (3 times per day)	
	Spearman's ρ	p-value	Spearman's ρ	p-value
WBC	0.012	0.924	0.017	0.906
RBC	-0.040	0.726	0.055	0.730
HGB	-0.006	0.949	0.034	0.822
HCT	-0.038	0.735	0.007	0.966
MCHC	-0.019	0.869	-0.034	0.822
MCH	-0.002	0.984	-0.013	0.926
MCV	-0.002	0.985	0.076	0.627
PLT	0.037	0.745	-0.037	0.800
LYMPH%	-0.010	0.915	-0.028	0.851
MXD%	0.001	0.994	-0.083	0.585
NEUT%	0.019	0.868	-0.076	0.628
LYMPH#	-0.019	0.868	-0.077	0.622
MXD#	0.017	0.879	-0.038	0.794
NEUT#	0.000	0.998	-0.045	0.760
RDW-SD	-0.031	0.792	0.088	0.566
RDW-CV	-0.017	0.884	-0.034	0.821
MPV	-0.053	0.638	-0.027	0.857

5. Discussion

This study performed a multivariate analysis of biochemical and blood parameters in individuals with a history of chronic drug use with the aim of understanding the duration/frequency relationship with drug abuse. The study had included a wide range of factors, providing a comprehensive view of the impact of substance abuse. Findings contribute valuable information for clinical practices and future research in understanding the health consequences of chronic drug exposure.

The present study revealed statistically significant differences in T4 levels between drug abusers and non-abusers, even after adjusting for unequal variances. This aligns with some previous research that suggests a link between drug abuse and thyroid function [18]. Furthermore, the abuse of methamphetamine leads to the occurrence of autoimmune thyroid diseases [19]. Certain ingredients found in methamphetamine, such as lithium and iodine may cause thyroid dysfunction that's including hypothyroidism (underactive thyroid), enlarged thyroid glands, and hyperparathyroidism. Previous research has linked methamphetamine use with increased levels of thyroxine (T4) and adrenocorticotropic hormone, as well as reduced levels of triiodothyronine (T3) and thyroid-stimulating hormone (TSH) [20].

However, our results did not show significant differences in T3 or TSH levels, which contrasts with some prior studies. These discrepancies may stem from differences in sample size, demographics, or drug use patterns among study populations. Overall, our findings support the existing literature on the impact of drug abuse on biochemical parameters, underscoring the need for further research to elucidate the complex relationship between substance abuse and thyroid function. The elevation in T4 levels among drug abusers, while T3 and TSH levels remain unaffected, could be attributed to the specific effects of the drugs on thyroid hormone

metabolism. Certain drugs may directly or indirectly influence the conversion of T4 to T3 or alter TSH secretion, leading to these differential effects on thyroid hormone levels [21].

The case report by Gupta *et al*. investigated the impacts of very high-dose pregabalin (Lyrica®) abuse. The report found that despite the high dose of pregabalin, the routine tests evaluating liver, kidney, and thyroid function, as well as electrolytes and complete blood count, were all within normal limits [22].

The study by Malhotra *et al*. investigated the impact of marijuana use on thyroid function and autoimmune illnesses by using NHANES data. They found that recent marijuana use was associated with lower TSH levels but not with thyroid dysfunction or TPOAb levels [23]. In comparison, our study found a significant elevation in T4 levels among drug abusers, suggesting potentially different effects of drug abuse on thyroid function compared to marijuana® use.

Methamphetamine is known to have nephrotoxic effects, meaning it can damage the kidneys and potentially lead to kidney failure. Studies have shown that methamphetamine use is correlated with acute kidney injury, often due to rhabdomyolysis (muscle breakdown), and related complications, like hyperthermia and disseminated intravascular coagulation. Long-term methamphetamine abuse may predispose to development of the chronic kidney disease though more research is required to establish the degree of this link [24].

Chronic methamphetamine abuse has been connected to an elevated risk of cardiovascular diseases including complications like stroke which can impact kidney function indirectly [25]. A case report describes a patient, who developed the end-stage renal disease (ESRD) potentially due to long-term methamphetamine use, recurrent acute kidney injuries, and uncontrolled hypertension ultimately requiring dialysis. It highlighted the need to consider methamphetamine as a potential cause of the ESRD emphasizing the importance of early cessation to prevent irreversible renal damage [26].

Although the current study primarily investigates the effects of drugs on hematological and biochemical parameters, a study on amphetamine abuse highlights the impact on neurotransmitters and kidney function [27]. Collectively, these studies underscore the importance of understanding the physiological consequences of drug abuse. The amphetamine study, like ours, underscores the need for caution in drug use due to its negative effects on the nervous system, with potential broader social implications. Further research is recommended to explore the effect of amphetamine on the immune system, particularly in young people, who are frequent users of such drugs.

The study by Potukuchi *et al*. studied the correlation between the use of cannabis (Marijuana®) and the acute kidney injury risk in patients suffering from developed chronic kidney disease subjected to dialysis. In contrast to our finding, they reported that abusing cannabis was not correlated with higher odds of acute kidney injury [28].

Elevated levels of alkaline phosphatase (ALP) and alanine aminotransferase (ALT) in drug abusers in the present study may indicate liver injury or disease, as these enzymes are released into the blood when liver has deteriorated. The ALT is specifically the enzyme that is found primarily in the liver, and its elevation is a sensitive marker for hepatocellular injury or inflammation [29]. Many drugs of abuse, including alcohol, cocaine, together with opioids, are associated with elevated ALT levels and liver injury [30]. ALP is an enzyme found in the liver and bile ducts, its elevated levels may indicate a liver damage or obstruction of bile flow [31]. Our findings of elevated ALT and ALP in drug abusers agree with other studies that have reported liver enzyme abnormalities in drug users [32]. A study by Dakhoul *et al*. reported that drug abusers with idiosyncratic drug-induced liver injury had significantly higher levels of ALT and ALP when compared to non-abusers control group [33]. Balloni *et al*. investigated

the hepatotoxic effects of new psychoactive substances (NPS), highlighting drug-induced liver injury as a significant global health concern. They identified elevated liver markers and acute liver failure as major toxic effects. Both studies emphasize the need for monitoring liver health in individuals exposed to psychoactive substances [7]. Ismail, B. *et al*. examined drug addiction profiles and liver function test disruptions in addicts at a psychiatric treatment center. Their study included 80 addicts, cannabis and MDMA were the most common drugs used. They found a significant association between the duration of drug abuse and liver function tests, highlighting the importance of monitoring liver health in drug addicts. The study emphasizes the need for improved rehabilitation centers in Algeria [34].
Abosheaishaa *et al*. presented a case report of marijuana®-induced acute hepatitis in a 34-year-old female with a polysubstance abuse history. The patient showed elevated liver function tests (ALT, AST, ALP) after heavy marijuana smoking. While natural marijuana has not been definitively linked to acute/sudden toxicity of the liver, synthetic marijuana® has been associated with hepatic failure in some cases. That study highlights the importance of considering marijuana® use in the differential diagnosis of liver injury that occurs in drug abusers [35].
Kaufmann *et al*. investigated the effect of a long use of cannabidiol (CBD) oral consumption on liver function in a group of healthy individuals. They compared the percentage of increased liver tests (LT) in adults taking CBD with the general population. The study found that self-administration of CBD did not increase the LT prevalence significantly. Most elevations of the LT were probably due to underlying conditions or medications, rather than CBD use. The study suggests that CBD consumption at recommended doses does not have a major impact on liver function tests in healthy individuals [36].

The lack of significant difference in aspartate aminotransferase (AST) levels between drug abusers and non-abusers in the study is somewhat unexpected as AST is also a marker of liver injury. Nevertheless, it is important to note that AST is generally a less specific indicator of liver damage compared to alanine aminotransferase (ALT) as it is present also in tissues like red blood cells, skeletal muscle, and the heart [37].

It is plausible that specific drugs of abuse or the duration and severity of drug use in our study population may have contributed to the observed pattern of liver enzyme abnormalities. Different drugs can have varying effects on liver enzymes and the degree of liver injury may depend on the dose, duration, and individual susceptibility [38].
While the results of this study generally agree with the existing literature on the liver enzyme abnormalities in drug abusers there are some variations in specific patterns of the enzyme elevations reported across different research. These differences may be attributed to factors such as the study individuals, the types and combinations of drugs, the duration and severity of drug abuse, and the accompanying other comorbidities or risk factors for liver injury [39]. It is essential to observe that much research in this area has focused on specific drugs or drug combinations such as opioids, cocaine, or alcohol which may contribute to variability in observed patterns of liver enzyme abnormalities [40].

The findings from our study regarding elevated red blood cell (RBC), white blood cell (WBC) counts, and hematocrit (HCT) levels in drug abusers compared to non-abusers are consistent with some previous research but also contradict other studies. The study by Dangana *et al* found higher significant WBC counts in substance abusers compared to non-abusers, suggesting potential inflammatory or infectious processes associated with drug abuse [41].
Richards *et al.* investigated leukocytosis in psychiatric patients with amphetamine and cocaine use. They found that amphetamine, but not cocaine, was associated with elevated white blood cell counts. Specifically, patients positive for amphetamines had a significantly higher

incidence of leukocytosis compared with controls, while cocaine-positive patients did not show a similar association [42]. These findings agree with our analysis which demonstrate that drug abusers exhibited significantly elevated levels of WBC, RBC, and HCT compared to non-abusers, potentially indicating hematological abnormalities associated with substance abuse.

In comparison to our findings showing significantly elevated levels of WBC, RBC, and HCT in drug abusers compared to non-abusers, Haghpanah *et al* found that the RBC count was unchanged in study groups. They observed a significant elevation in WBC count in individuals with opium dependency but not in heroin dependency or withdrawal groups [43]. Additionally, while the HCT percentage increased significantly in all groups in their study, we observed these increases specifically in drug abusers. These discrepancies may reflect differences in the type of substances studied or the population examined.

The elevated WBC count in the present study could indicate an ongoing inflammatory response or increased susceptibility to infections in drug abusers, potentially due to the immunomodulatory effects of substances or associated lifestyle factors [44]. In comparison to our findings of significantly elevated levels of WBC, RBC, and HCT in drug abusers compared to non-abusers, Chaidee *et al.* found that methamphetamine (MA) abusers exhibited poor cognitive performance in various cognitive tasks compared to healthy controls. They also reported a reduction in RBC components and an elevation in WBCs and IL-6 levels in MA abusers, suggesting a potential link between neuroinflammation and cognitive deficits in MA abuse [45]. The elevated RBC counts and HCT levels in our study could potentially be explained by secondary erythrocytosis, a compensatory mechanism to improve oxygen delivery in response to hypoxemia or inadequate tissue oxygenation associated with substance abuse [46].
Additionally, the vasoconstrictor effects of certain drugs like cocaine have been shown to increase RBC counts and hematocrit transiently [47] The specific substances abused, duration of abuse, and individual factors like nutritional status and concurrent tobacco use can influence hematological parameters, contributing to the variability in findings across different studies [48].

The current study reported individuals with a history of drug abuse and found a significantly reduced lymphocyte count and elevated mixed cell count compared to non-abusers. This agrees with findings in other studies related to substance use disorders. Ng *et al* aimed to compare inflammatory markers observed between persons with psychotic disorders induced by methamphetamine, schizophrenia patients, and non-drug abusers. They found higher neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio) in both groups compared to controls, with no significant difference in lymphocyte-to-platelet ratio [49].
We demonstrated a significantly reduced lymphocyte count and elevated mixed cell count in persons with a history of drug abuse compared to non-abusers. Numerous animal studies investigating changes in hematological parameters after cannabis exposure by various administration routes. Nonetheless, research on this topic is limited and often constrained by the small size of samples. The impact of cannabis consumption via smoking on hematological parameters has been the focus of some studies [50].
Guzel *et al*. investigated hematological alterations in synthetic cannabinoid users. They found significant differences in several parameters between the study group and control group, including mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean platelet volume (MPV), red cell distribution width (RDW), white blood cells (WBC), monocyte percentage (MONO%). neutrophil (NEU) and lymphocyte percentage (LYM%). These findings suggest that chronic synthetic cannabinoid use may lead to hematopoietic cell

deterioration and subclinical anemia with iron deficiency, with increased inflammatory cells [51].

Conversely, our study showed that drug abusers exhibited significantly elevated levels of WBC, RBC, and HCT compared to non-abusers, potentially indicating hematological abnormalities associated with substance abuse.
Additionally, a study on methamphetamine use disorder highlighted alterations in the platelet-lymphocyte and the neutrophil-lymphocyte ratios, indicating increased inflammation in these individuals [46]. Similarly, in patients with opioid use disorder and marijuana use disorder, the platelet-to-lymphocyte, and the monocyte-to-lymphocyte ratios were found to be significant markers emphasizing the importance of these ratios in monitoring substance use and differentiating between acute and chronic conditions [52]. The comparison of these studies emphasizes the consistent impact of substance abuse on immune parameters particularly lymphocyte counts and ratios of different blood cells. These findings suggest a potential link between drug abuse and alterations in immune responses indicating the importance of monitoring these parameters in individuals with a history of substance using disorders [53].

Our study reported the red cell distribution width (RDW) was significantly lower in the drug abusers compared to the non-drug abusers. This suggests the condition of drug abuse may be correlated with less variation in the red blood cell sizes [20]. The mean platelet volume (MPV) was higher in non-abusers than in abusers. This indicates that non-drug abusers had larger average platelet sizes compared to drug abusers [50]. RDW-CV (coefficient of variation) showed no significant difference between the two groups. This means a relative variation in red blood cell sizes was similar among drug abusers and non-abusers [54].

The study reported for participants with drug abuse duration of 2 years or more there was no association significantly found between duration and any of the biochemical parameters [55]. This suggests that after a certain duration of substance abuse, the biochemical parameters may not continue to worsen linearly with increasing duration of the abuse. The United Nations Office on Drugs and Crime (UNODC) report on economic and social consequences of drug abuse notes that differences in level of the abuse among countries can be greater than differences among regions [56]. This indicates cultural and environmental factors may influence also the biochemical impacts of long-term substance abuse. The finding of no significant correlation after 2 years of abuse duration in that study provided may reflect this complexity [57]. More research is needed to understand fully these dynamics.
Similarly, the observation that there were no significant correlations between drug abuse frequency (3 times per day) and biochemical parameters is significant for several reasons. Firstly, it is suggested that in this frequency the biochemical parameters may not significantly be impacted by drug abuse indicating a potential threshold effect. Secondly, it indicates the complexity of the relationship between drug abuse and biochemical parameters meaning that factors other than frequency may play a more significant role. This observation emphasizes the importance of considering the various factors when assessing the impact of drug abuse on biochemical parameters contributing to a more comprehensive understanding of substance abuse effects [58].

The finding that there were no statistically significant correlations between the 2-year duration of drug abuse and hematological parameters is noteworthy, as it implies that within this timeframe, drug abuse may not have a substantial linear effect on these parameters. This finding challenges the assumption that the duration of drug abuse correlates invariably with the hematological changes suggesting more complex relationship. It underscores also the need for further research to understand subtle differences in drug abuse effects on hematological

parameters potentially leading to more targeted interventions for individuals with varying durations of substance abuse.

The study by Dangana A. *et al*. reported similar findings regarding lack of the significant correlations between short-term drug abuse (up to 2 years) and the hematological parameters. Their results showed no substantial linear relationship between the duration of drug abuse and hematological parameters aligning with our observation. However, they noted that, while there were no significant correlations overall some trends were suggesting potential impacts on specific parameters at the 2-year mark [41]. This suggests a need for further investigation into the specific hematological parameters that may be affected by short-term drug abuse.

In contrast, the study by Gul *et al*. evaluated hematological changes in 200 drug abusers compared to 200 non-drug users. They found significant differences in blood parameters between drug abusers and non-drug users. Most hematological indices were higher significantly in the drug abusers, except for MCH and MCHC [59]. The findings emphasize the importance of raising awareness about the health effects of illicit drug abuse.

Conclusions

Drug abuse causes thyroid dysfunction and deterioration in renal and hepatic function. Moreover, alterations in hematological indices, notably WBC, RBC, HCT, and lymphocyte count strongly emphasize the need for regular monitoring of these parameters in individuals with a history of drug abuse. Interestingly, no significant correlations were reported between the duration or frequency of drug use and these parameters, suggesting a complex relationship between drug abuse patterns and their physiological effects.

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