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The Effect of Narcotic Substances on Serotonin, Melatonin, Neurofilament Light, and Certain Electrolytes in Addicts, Both Treated and Untreated

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ABSTRACT
Narcotic substance abuse is a global problem that causes many functional and psychological problems for addicts. This research study identifies, demonstrates and understands the effects of drugs on addicts, specifically their impact on neurophysiological variables, including serotonin, melatonin, and Neurofilament Light (NEFL), as well as on certain electrolytes in blood serum, such as potassium K^+ chloride Cl^- sodium Na^+ and magnesium Mg^{+2}. The study included groups of untreated addicts, treated addicts at the Medical Rehabilitation Center affiliated with the Anti-Narcotics Department in Kirkuk Governorate, and a control group. The results for serotonin (5-HT), melatonin (MT), and NEFL concentrations showed a significant decrease ($P \leq 0.05$) in the blood serum of both untreated and treated addicts compared to the healthy control group. Furthermore, a more pronounced and significant decrease ($P \leq 0.05$) was observed in the concentrations of these three parameters in treated addicts compared to untreated addicts, as measured by ELISA. The results of serum electrolyte analysis also showed that potassium (K^+) levels showed no significant difference ($P \leq 0.05$) between treated and untreated addicts compared to healthy controls. However, sodium (Na^+) and chloride (Cl^-) levels showed significant increases ($P \leq 0.05$) in untreated addicts compared to healthy controls and treated addicts. Meanwhile, serum magnesium (Mg^{+2}) levels showed a significant decrease ($P \leq 0.05$) in both treated and untreated addicts compared to healthy controls, but no significant differences ($P \leq 0.05$) were observed between treated and untreated addicts. Furthermore, the current study concluded that drug abuse is a societal scourge that causes numerous health problems, particularly methamphetamine (crystal meth), which causes harmful physiological changes, neurodegeneration, and functional impairment to human health.

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1. INTRODUCTION

Narcotic substances are among the biggest health and social problems facing societies in the modern era. Drugs are defined as chemical substances that affect the central nervous system and lead to changes in mood, behavior, and perception. Drugs vary between legitimate drugs used for medical purposes under medical supervision and illicit drugs that are traded illegally and cause serious harm to their users and to society.

Statistics on drug infection and addiction in the world are high and cause severe damage, including damage to vital organs such as the liver, kidneys, and heart, and can lead to failure of the functions of these organs. Continued use leads to serious respiratory problems, including respiratory arrest and cancerous respiratory diseases [1,2]. This is indicated by the 2023 research estimates issued by the United Nations Office on Drugs and Crime (UNODC). It is estimated that approximately 300 million people used narcotic substances that year. This is a serious global health problem resulting from physical, psychological, and social disorders and is a major factor in increasing the risk of suicide, making drug use a global issue [3,4]. Researchers have found increasing evidence that repeated drug use causes brain disorders, leading to severe behavioral disturbances in addicts. These gradual changes, which persist even years after cessation of drug use, make addiction a chronic and recurring disease [5]. Drugs, particularly methamphetamine, affect the central nervous system, altering a person's mood, thinking, and behavior. Psychoactive drugs can be categorized into groups including sedatives, stimulants, hallucinogens, and others [6]. The American Society of Addiction Medicine (ASAM) defines addiction as an inability to control or manage one's behavior and a perception of significant difficulties in one's behavior, interpersonal relationships, and various emotional responses [7]. Malnutrition, severe tooth decay, respiratory problems, kidney and liver damage, infection, violent behavior, paranoia, severe anxiety, weight loss, psychosis, and sadness are considered important side effects of long-term drug use in humans [8]. The consequences of drug use may begin as a form of extended personal risk, and illicit drugs represent the largest part of the criminal cases examined by forensic laboratories. Drug use becomes a societal problem when criminal activity is the only means of obtaining the money needed for addiction, which increases the effects of drug-related crimes or accidents and raises the costs of health insurance and medical care for everyone due to drug users [9].

2. MATERIALS AND METHODS

The study included collecting blood samples from people aged between 18 and 55 years. The total number of samples was 120 males, distributed into 40 samples from each group, which included untreated addicts treated addicts as well as a healthy control.

Collection of Samples: Blood was collected using 8 ml medical syringes at the drug user rehabilitation center and the drug addicts' detention center, both under the jurisdiction of the Kirkuk Anti-Narcotics Directorate. Donors were then inquired about their health status, specifically regarding hereditary and acquired diseases, and confirmed to be free of such diseases. Blood samples were collected and stored in sealed tubes for serum separation using a centrifuge.

Measurement of neurophysiological factors and Biochemictry (serotonin, melatonin, NEFL) and electrolytes. (K^+, Cl^-, Na^+, Mg^{+2}). The ELISA device was used to measure the concentration of serotonin, melatonin, and neurofilament light (NFL) using a ready-made kit from the Chinese company Elabscience. The same kit was also used to measure the concentration of magnesium (Mg^{+2}) in blood serum using the colorimetric method. This method relies on the reaction of magnesium with the reagent Calmagite in an alkaline medium, forming a colored complex whose light absorption intensity is directly proportional to the magnesium concentration in the sample. Additionally, an automatic electrolyte analyzer (Auto Analyzer) was used to measure the electrolyte ratio in blood serum, which includes Na^+, Cl^-, and K^+. This device utilizes ion-selective electrode technology.

Statistical analysis. The study results were statistically analyzed using software (SAS, 2001) and an ANOVA table. Significant differences between the study groups were determined using Duncan's multiple range test at a significance level of $P \leq 0.05$ [10].

3. RESULTS AND DISCUSSION

3.1 Determining the concentration of serotonin (5-HT) and melatonin (MT) in the Neurofilament Light (NEFL)

The results in Table (1) for the concentrations of serotonin (5-HT), melatonin (MT), and NEFL showed a significant decrease ($P \leq 0.05$) in untreated and treated addicts compared to the healthy control group. A more pronounced significant decrease ($P \leq 0.05$) in concentrations of the three parameters was also observed in treated addicts compared to untreated addicts.

Table (1): The percentage of physiological and neurological variables MT, NFL 5-HT

Groups	Serotonin (5-HT) ng/mL	Melatonin (MT) ng/ml	Neurofilament Light (NEFL) ng/ml
Control	236.25 ± 54.71 a	146.50 ± 11.94 a	99.90 ± 7.92 a
Untreated addicts	114.09 ± 8.01 b	60.31 ± 12.31 b	45.45 ± 9.03 b
Treated addicts	80.33 ± 11.77 c	54.28 ± 7.59 c	40.99 ± 6.33 c

The Different letters in the columnar table cells indicate statistically significant differences at a probability level of P≤0.05.
The numbers represent the mean and standard deviation values.

The significant decrease in serotonin 5-HT concentration is attributed to a greater increase in the release of neurotransmitters with a greater inhibition of their reabsorption as a result of the narcotic substance (crystal) [11,12]. This causes a loss of serotonin stores in nerve endings, and continuous exposure to drugs causes damage to serotonin cells. This may be due to a greater decrease in concentration levels as a result of withdrawal phases and long-term effects [13]. It may also be attributed to the fact that methamphetamine (crystal meth) is a strong stimulant for the release of neurotransmitters, including serotonin, and leads to neurotoxicity as a result of oxidative stress, as well as reducing the concentration of the enzyme eryptophan hydroxylase, which is responsible for serotonin synthesis. The reason for the decrease in concentrations in treated addicts may be due to a decrease in the level of serotonin storage, which may require a recovery period to repair and restore the release of neurotransmitters. This is observed during the withdrawal period after the large stimuli to which the nerve cells were exposed, which need to restore balance after the loss of the stimulating substance [14,15,16].

Melatonin levels also showed a "significant decrease" (P≤0.05) in both untreated and treated addicts with a healthy control group. A more pronounced decrease (P≤0.05) was observed in treated addicts compared to untreated addicts. This may be due to several factors, including the effects of methamphetamine (crystal meth) on the nervous system, particularly in different brain regions. Methamphetamine disrupts mitochondrial function, increases ROS reactions, stresses the endoplasmic reticulum, and increases neuronal excitability [17]. Increased accumulation of reactive oxygen species activates the signaling pathway that induces apoptosis, impairing mitochondrial integrity and function. This promotes the release of cytochrome c from mitochondria into the cytosol, a process that stimulates apoptosis by activating caspase-3, leading to cytoskeletal breakdown and DNA destruction [18,19]. The effects of crystalline substances are not limited to mitochondria; they also significantly impact the endoplasmic reticulum and auto-inflammatory processes. They increase the disruption of calcium regulation within the endoplasmic reticulum, which is crucial for protein folding and assembly in the cytosol, leading to protein accumulation and increased reactive oxygen species [20]. These disruptions are counteracted by melatonin's role as an antagonist to these physiological and inflammatory effects, resulting in imbalances and strains in melatonin concentration due to heightened resistance to reactive oxygen species and inflammatory conditions [21]. Furthermore, a decrease in melatonin concentration may be attributed to a decrease in serotonin, as serotonin is a precursor in melatonin synthesis. Therefore, they have a direct relationship at the sites of melatonin production within the pineal gland.

The significant decrease P≤0.05 among treated addicts is largely attributed to disturbances in melatonin production, degeneration of nerve cells, lack of serotonin stores in nerve vesicles, withdrawal period, lack of stimulating substance to provide raw materials for melatonin production, and stress resulting from biological clock disturbances [22].

The results of the NEFL in Table (1) also showed a "significant decrease" P≤0.05 in untreated and treated addicts compared to the healthy control. A more severe significant decrease was also observed in the concentrations of serotonin and melatonin in treated addicts, although these results were inconsistent with some studies that often show a significant increase in the concentrations of NEFL in addicts who use narcotic substances. This differed from Bavato *et al*., [23] who indicated a high NEFL index in cocaine users, which has an effect pathway close to that of amphetamine (crystal meth) because they are neurostimulants and cause changes in the axons of nerve cells. Similarly, in a study by Zimmermann et al [24]. on another type of drug called 3,4-methylenedioxymethamphetamine (MDMA,

commonly known as Ecstasy), no significant differences were found between the study groups in the NEFL index. However, the lower statistical significance observed in our study may be due to the chronic effects and the different types of crystal meth on the nervous system and nerve cells, particularly axons composed of protein structures. Chronic cellular stress resulted in lower levels of this biomarker compared to healthy controls. Furthermore, research sources confirm that this drug affects protein levels in the body, leading to structural failure. Methamphetamine also causes oxidative stress in endothelial cells, resulting in decreased levels of structural junction proteins and ultimately leading to chronic blood-brain barrier dysfunction due to severe oxidative stress, as well as disturbances in mitochondrial and endoplasmic reticulum functions [20,25,26].

Studies conducted on laboratory animals have also shown the effects of methamphetamine on brain-derived neurotrophic factor (BDNF), which is considered one of the important factors in the growth and repair of nerve cells and the regulation of neurotransmitters [27,28]. These functional disturbances indicate a defect in the structure of these structural proteins (NEFL), which may show a significant increase in the early stages of addiction in the neurotoxic stages before they progress to the neurodegenerative stage. Their development requires a healthy and complete metabolic environment, as the performance of their vital functions depends on their building and repair in organs and factors whose functions have been damaged as a result of the chronic effect of methamphetamine.

The significant decrease ($P \leq 0.05$) in neurofilament light NEFL was more pronounced in the treated group compared to the untreated group. This improved control is attributed to neuronal repair following the removal of the pathogens and toxins caused by methamphetamine (crystal meth). The research confirmed that aerobic exercise promotes the restoration of the blood-brain barrier and repairs neuronal damage in patients addicted to crystal meth. This damage causes permeability of the blood-brain barrier, leading to leakage of NEFL proteins, which is reflected in a significant decrease in its blood concentration [29]. The decrease in NEFL concentration is also due to recovery processes in the brain, nervous system, and organs involved, particularly the cellular organelles in the construction of these proteins. The conditions caused by methamphetamine, including oxidative stress, stimulation of inflammatory glial cells, and stimulation of inflammatory cytokines, are all sources that contribute to axonal damage to nerve cells and the release of NEFL. With the onset of treatment and abstinence, these processes decrease over time, and the release of NEFL into the blood decreases [30,31]. Studies have also indicated that increased oxidative stress in the body is one of the mechanisms that triggers microneuropathy, as studies show a direct relationship between increased markers of oxidative stress and neuropathy and impaired neurological function [32].

3.2 Electrolytes estimate

The Table (2) shows the results for serum electrolyte concentrations in the study groups, including potassium, chloride, sodium, and magnesium. Potassium levels showed no significant differences ($P \leq 0.05$), between the study groups (treated and untreated addicts) and the healthy control group. Chloride levels, however, showed a significant increase ($P \leq 0.05$) in untreated addicts compared to the healthy control group and a significant decrease ($P \leq 0.05$) between treated addicts, the healthy control group, and untreated addicts.

Sodium levels showed a significant increase ($P \leq 0.05$) in untreated addicts compared to the healthy control group and treated addicts. No significant differences ($P \leq 0.05$) were found between the healthy control group and treated addicts.

The results also showed no significant differences ($P \leq 0.05$) between the healthy control group and treated addicts. As for the magnesium results, they showed a significant decrease $P \leq 0.05$ for both groups, including untreated addicts and treated addicts, compared to the control group, while there was no significant. Differences $P \leq 0.05$ were recorded between treated and untreated addicts.

Table (2): The percentage Electrolyte concentration in the study groups

Groups	Potassium K^+	Chloride Cl^-	Sodium Na^+	Magnesium Mg^{+2}
Control	4.33 ± 0.58 a	99.9 ± 0.84 b	142.57 ± 2.67 b	1.84 ± 0.55 a
Untreated addicts	4.30 ± 0.49 a	101.65 ± 1.29 a	143.87 ± 5.51 a	1.60 ± 0.44 b
Treated addicts	4.22 ± 0.51 a	98.45 ± 1.06 c	141.8 ± 2.01 b	1.60 ± 0.44 b

The Different letters in the columnar table cells indicate statistically significant differences at a probability level of P≤0.05.
The numbers represent the mean and standard deviation values.

3.2.1 Interpreting Potassium Concentration Results

Potassium is an essential intracellular ion, with 98% located inside cells and 2% outside. The body has vital physiological functions, including sodium-potassium pumps, the hormone aldosterone, and kidney function, to maintain potassium concentration within a very precise range of 3.5-5 mmol/L. Any disturbance in this level can lead to cardiac arrest [33]. It is also worth noting that the result indicates the absence of acute complications resulting from the effects of crystals, such as acute kidney failure and muscle breakdown, which can increase blood potassium levels [34].

Recent studies have shown that crystal methamphetamine may cause an imbalance in potassium concentration through renal effects, dehydration, and oxidative stress. However, the severity of the change varies according to the duration of use and clinical condition. Meanwhile, the results of our study and the interpretation of research studies may be consistent with the answer to the study questionnaire question, in which no kidney disorders were reported by addicts, except for a small number who reported a disturbance in kidney function in response to the questionnaire question: Did you suffer from a disturbance in your body organs during the period of use?

3.2.2 Interpretation of chloride (Cl^-) and sodium (Na^+) ion concentration

The results showed a significant increase (P≤0.05) in chloride and sodium ion concentrations in untreated addicts compared to healthy controls and treated addicts. Sodium levels did not show a significant difference (P≤0.05) between treated addicts and healthy controls, while chloride (Cl^-) levels showed a significantly lower decrease (P≤0.05) in treated addicts compared to untreated addicts and healthy controls. These results were consistent with the study by Umoren et al., [35] which observed a significant increase in sodium (Na^+) and chloride (Cl^-) ions in methamphetamine (crystal) addicts. This increase may occur as a result of dehydration and acid-base imbalance in the body due to the toxic effects of methamphetamine use on metabolic functions, as well as its effect on the components of the excretory system. Increased nerve signals and nerve stimulation may also increase muscle activity, leading to changes in the balance of bicarbonate and chloride levels. Additionally, the increased fever caused by crystal use, due to its effect on the sympathetic nervous system, increases vasoconstriction, respiration, and sweating, which exacerbates dehydration and leads to an increase in chloride concentration [36]. Furthermore, methamphetamine stimulation of the sympathetic nervous system leads to vasoconstriction through the release of endothelin, which increases the narrowing of arterial blood vessels. This reduces renal blood flow and glomerular filtration rate, potentially triggering a drop in blood pressure. This, in turn, triggers the release of renin to activate the RAAS system [37]. Upon activation of this system, angiotensin II is produced. Angiotensin II is the primary regulator of the proximal convoluted tubule cells in the kidney and activates the sodium-hydrogen transporter type III located in the apical membrane of these cells. These changes enhance the kidney's ability to reabsorb sodium and chloride from the filtered fluid and return them to the bloodstream, thus preventing salt loss and maintaining blood pressure [38]. Chloride is also drawn into the bloodstream following the release of aldosterone, stimulated by angiotensin. Aldosterone acts on the terminal structures of the nephron, including the distal convoluted tubule and the sensitive distal nephron. Aldosterone promotes sodium reabsorption via sodium channels and a positively charged cotransporter, generating a negative electrical potential within the tubule. Maintaining electrical neutrality is therefore necessary, leading to chloride uptake for the purpose of maintaining homeostasis [39]. All these changes, along with alterations in sweating, vasoconstriction, and reduced glomerular filtration rate, contribute to increased blood chloride and sodium levels. These effects of methamphetamine (crystal meth) on various bodily

functions are also a factor in the increased chloride and sodium levels in the blood.

The significant decrease ($P \leq 0.05$) in chloride and sodium ion concentrations in treated addicts is attributed to the restoration of bodily functions, particularly acid-base balance and metabolic balance, after the removal of methamphetamine's toxic effects [40]. The more pronounced ($P \leq 0.05$) significant decrease in chloride ion concentration observed in treated addicts compared to controls is due to the instability of physiological and functional states. The body may return to a state of equilibrium after a period of time due to the significant effects of methamphetamine on bodily functions, or the side effects may persist as a result of neurodegeneration or functional impairment.

3.2.3 Interpretation of Magnesium Concentration (Mg^{+2})

The results showed a significant decrease ($P \leq 0.05$) in serum magnesium (Mg^{+2}) concentration in both untreated and treated addicts compared to the healthy control group. However, no significant difference ($P \leq 0.05$) was found between treated and untreated addicts in the study groups.

Magnesium (Mg^{+2}) is one of the most important and abundant cations within cells after potassium. Its crucial role is in mitochondria and electron transport and ATP production and cell signaling, antioxidant activity and transcription regulation, DNA and RNA synthesis, and enzyme and ion channel activation [40,42]. Magnesium deficiency has detrimental effects on nerve, brain, heart, bone, and muscle function. Symptoms include tremors, muscle spasms, and weakness. Severe magnesium deficiency can lead to seizures, heart problems, and even death. Low blood magnesium levels are a long-term risk factor [40,43,44].

The significant decrease ($P \leq 0.05$) in untreated addicts may be attributed to methamphetamine's effects on the nervous, renal, and metabolic systems. Methamphetamine increases neuronal excitability and neurotransmitter secretion, leading to increased metabolic and oxidative stress. This, in turn, causes cellular magnesium consumption due to the need to meet intracellular metabolic requirements. Magnesium is essential for antioxidant enzymes and is also a crucial component in ATP production. These processes require magnesium, increasing its mobilization from outside the cell to the inside to compensate for the intracellular depletion caused by methamphetamine stimulation, thus reducing serum magnesium concentration [45,46].

Studies have also indicated that oxidative stress and free radical formation resulting from methamphetamine affect kidney function, leading to magnesium loss through urination. Dehydration, malnutrition, and loss of appetite are also significant causes of magnesium depletion [47]. Furthermore, methamphetamine causes significant mitochondrial dysfunction due to free radical formation, dopamine oxidation, and cell membrane damage. This increases the energy demand for repair, particularly in nerve and muscle tissues, as magnesium is a key component in ATP metabolism. Therefore, magnesium is continuously depleted as the toxic effects of methamphetamine persist [48,49]. However, the continued significant decrease $P \leq 0.05$ in treated addicts is due to the depletion of magnesium stores, especially in bones, intracellular, and soft tissues, as a result of the large depletion that these stores were exposed to during the cellular and metabolic toxicity of addiction, which keeps its concentration low in the serum for long periods of treatment.

4. CONCLUSION

The current study concluded that drugs, particularly methamphetamine (crystal meth), have harmful neurophysiological and biochemical effects. These drugs caused significant changes in the human body, impacting neurophysiological states, with a marked decrease in serotonin and melatonin levels and neurofilament light. This methamphetamine also altered electrolyte levels, increasing chloride and sodium levels and decreasing magnesium levels, while showing no change in potassium levels.

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