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Evaluating Oxidative DNA Damage in Methamphetamine Addicts: The Predictive Role of 8-hydroxy-2'-deoxyguanosine

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Abstract

Methamphetamine addiction presents a substantial public health challenge in Iraq, detrimentally affecting individuals' physical and psychological health, as well as the broader social fabric. This study investigates the role of oxidative stress in methamphetamine addiction by measuring various biomarkers in addicts. Sixty methamphetamine users, categorized into untreated and under-treatment groups, along with thirty healthy controls, were evaluated. The biomarkers measured include total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), malondialdehyde (MDA), and 8-hydroxy-2'-deoxyguanosine (8-OHdG). The results revealed that methamphetamine addiction significantly elevates TOS, OSI, and MDA levels, while reducing TAS, indicating increased oxidative stress in addicts. Both untreated and under-treatment groups showed higher levels of 8-OHdG compared to controls, establishing it as a reliable biomarker for predicting methamphetamine addiction. The Receiver Operating Characteristic (ROC) curve analysis confirmed the high sensitivity and specificity of 8-OHdG in diagnosing methamphetamine addiction. The study concludes that oxidative stress induced by methamphetamine leads to significant oxidative DNA damage, as evidenced by elevated 8-OHdG levels. These findings highlight the importance of early detection and intervention strategies to mitigate the oxidative damage associated with methamphetamine addiction.

Keywords: Addiction, Methamphetamine, Oxidative stress, 8-hydroxy-2'-deoxyguanosine, Malondialdehyde.

تقييم الضرر التأكسدي للحمض النووي لدى مدمني الميثامفيتامين: الدور التنبؤي لمؤشر 8-هيدروكسي-2'-ديوكسي كوانوسين

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الخلاصة

إدمان الميثامفيتامين يمثل تحديًا كبيرًا للصحة العامة في العراق، حيث يؤثر سلبًا في الصحة البدنية والنفسية للأفراد، إضافةً إلى تأثيره على النسيج الاجتماعي بشكل عام. تهدف هذه الدراسة إلى استقصاء دور الإجهاد التأكسدي في إدمان الميثامفيتامين من خلال قياس مجموعة من المؤشرات الحيوية لدى المدمنين. شملت العينة ستين مستخدمًا للميثامفيتامين، قُسِّموا إلى مجموعتين (غير خاضعين للعلاج وتحت العلاج)، إضافةً إلى ثلاثين فردًا من الأصحاء كمجموعة ضابطة. تضمنت المؤشرات الحيوية المقاسة: الحالة التأكسدية الكلية (TOS)، الحالة المضادة للتأكسد الكلية (TAS) ، ومؤشر الإجهاد التأكسدي(OSI) ، والمالوندايالدهيد(MDA) ، و8-هيدروكسي-2'-ديوكسي كوانوسين (8-OHdG) .أظهرت النتائج أن إدمان الميثامفيتامين يرفع بشكل ملحوظ مستويات TOS و OSIوMDA، مع انخفاضTAS ، مما يشير إلى زيادة الإجهاد التأكسدي لدى المدمنين. كما أظهرت كل من المجموعتين (غير الخاضعين للعلاج وتحت العلاج) مستويات أعلى من 8-OHdG مقارنةً بالمجموعة الضابطة، مما يثبت كونه مؤشراً حيوياً موثوقاً للتنبؤ بإدمان الميثامفيتامين. وأكّد تحليل منحنى (ROC) الحساسية والنوعية العاليتين لـ 8-OHdG في تشخيص إدمان الميثامفيتامين. وتخلص الدراسة إلى أن الإجهاد التأكسدي الناجم عن الميثامفيتامين يؤدي إلى تلف تأكسدي ملحوظ في الحمض النووي، يتجلى بارتفاع مستويات 8-OHdG .وتبرز هذه النتائج أهمية الكشف المبكر واستراتيجيات التدخل للتقليل من الأضرار التأكسدية المرتبطة بإدمان الميثامفيتامين.

1. Introduction

Addiction is a chronic, and relapsing, brain disorder characterized by complex interactions between biological and environmental elements [1]. Drug addiction, especially to methamphetamine, has increased in Iraq, posing a serious concern due to its numerous negative and destructive impacts on human health, economy, and social well-being. Methamphetamine, known for its stimulating and euphoric effects, is among the most commonly abused illicit substances worldwide, ranking second only to cannabis [2, 3].

Methamphetamine abuse disorder is a global concern, impacting users' organ systems, particularly the neurological and cardiovascular systems. Psychosis and decreased cognitive performance are harmful mental consequences of methamphetamine addiction, in addition to the harmful effects on the body's organs and systems, such as the brain, heart, lungs, muscles, and kidneys, as a result of methamphetamine toxicity [4]. One of the mechanisms explaining the emergence of these multiple harmful effects of methamphetamine addiction is oxidative stress [4].

Oxidative stress, resulting from an imbalance between oxidative and antioxidative processes in cells, plays a crucial role in the development of various chronic-degenerative diseases. This redox imbalance triggers chains of reactions that compromise cells and perturb core macromolecules—lipids, proteins, and DNA [5].

In oxygen-dependent tissues, reactive radicals initiate peroxidation by attacking membrane polyunsaturated fatty acids (PUFAs). Arachidonic acid is notably susceptible, generating cyclic peroxides and hydroperoxides that can progress to malondialdehyde (MDA). MDA, in turn, can adduct to DNA bases, creating potentially mutagenic lesions and highlighting the downstream chemical complexity of oxidative events within cells [6]. For this reason, MDA quantification is commonly employed to gauge reactive oxygen species (ROS)–mediated injury in biological systems [7].

Radicals also target the genome directly: they modify purine and pyrimidine bases and the deoxyribose backbone, yielding base lesions, single- and double-strand breaks, and DNA–protein crosslinks. Oxidation of guanine and thymine produces 8-hydroxy-2′-deoxyguanosine (8-OHdG) and thymine glycol, respectively—characteristic products of oxidative DNA damage [6]. 8-OHdG is therefore recognized as a marker of oxidative DNA injury and an indicator of oxidative stress, with levels often higher in mitochondrial than in nuclear DNA [8, 9].

Free radicals induced by methamphetamine are generated as a result of the oxidation of dopamine accumulated inside the dopaminergic cell and the synapse due to the interaction of methamphetamine with dopamine transporter and vesicular monoamine transporter-2. In addition to the production of hydrogen peroxide as a result of the interaction of methamphetamine with both monoamine oxidase and catecholamine-o-methyl transferase, which react with a transition metal ion to produce the hydroxide radical, leading to generate more free radicals that damage cells [10].

This study aimed to assess health status outcomes in un-treated and under-treated methamphetamine addicts by comparing them with healthy individuals by evaluating body mass index and values of biomarkers of oxidative stress, especially 8-OHdG.

2. Materials and Methods

2.1 Subjects

The study received approval from Mustansiriyah University (document number, 4078/11-8-2022) and the Baghdad/Al-Rusafa Health Department (document number, 97623/ 22-8-2022), with informed consent obtained from all participants. The Poison Counseling Center and Al-Ataa Hospital for Addiction Treatment and Psychological Rehabilitation were chosen for this purpose.

Sixty male methamphetamine addicts were enrolled, all meeting the diagnostic criteria for methamphetamine use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).The results of their urine toxicology test results were positive and they were divided into two groups: a group of non-treated methamphetamine addicts (G1) (N= 30 with age range (16-37) years) and a group of under-treated methamphetamine addicts (G2) (N=30 with age range (16-37) years).The used treatments were (Risperidone, Quetiapine, Carbamazepine, Escitalopram, Olanzapine, Chlordiazepoxide and Amitriptyline) that do not contain antioxidants, as these medications are prescribed and dosed according to the specific needs and circumstances of each patient. Thirty healthy individuals (C) without clinical evidence of drug addiction and whose ages were similar to those of addicts were also selected. Those who suffered from systemic diseases such as liver, kidney, respiratory, blood, immune, and diabetes diseases were excluded, as well as those who suffered from psychological diseases such as schizophrenia and psychosis and those who used other addictive substances.

2.2 Chemicals

Xylenol orange, O-dianisidine, Thiobarbituric acid (TBA), Potassium chloride and Sodium chloride were obtained from BDH (England). Ferrous ammonium sulfate, Hydrogen peroxide, Trichloroacetic acid (TCA), Sulfuric acid and Tris-HCl were procured from Sigma-Aldrich (USA). Other chemicals obtained from other origins such as Vitamin C (reagent world, USA), HCl (Scharlau, Spain), and Sodium sulfate (Fluka, Switzerland).

2.3 Blood and Urine collection

Blood samples were collected from each participant. Ten milliliters of blood were placed into gel containers and incubated at room temperature for thirty minutes. After that, sera were separated by centrifuging the sample at 3000 × g for 10 minutes. The serum that was generated was divided among three Eppendorf tubes and stored at -20ºC in a deep freezer until it was required for biochemical parameter measurement.

Samples of urine were taken at any time of day and stored in dry, clean containers. Before being analyzed, these urine samples could be kept for up to 48 hours at 2–8°C, while they were frozen at -20ºC for longer storage. The purpose of urine collection was to assess methamphetamine addiction.

2.4 Estimation of urinary methamphetamine level

Urine specimens were screened for methamphetamine use with a multidrug test-panel kit (all test, China). Following kit instructions, results were read at ~5 minutes and recorded dichotomously as positive or negative.

2.5 Determination of TOS, TAC, and OSI

Total oxidant status (TOS) and total antioxidant capacity (TAC) were quantified using the Erel assays [11, 12]. The oxidative stress index (OSI) was then derived as:
$OSI = TOS\ (\mu mol\ H_2O_2\ Eq/L) / TAC\ (\mu mol\ Vit.\ C\ Eq/L).$
as described previously [13].

2.6 Determination of malondialdehyde (MDA)

Lipid peroxidation was assessed by measuring MDA via thiobarbituric acid (TBA) reactivity. In this reaction, MDA—the peroxidation byproduct—forms a chromogenic adduct with TBA. MDA concentrations were determined using the modified Satoh procedure [14].

2.7 Determination of 8-hydroxy-2′-deoxyguanosine (8-OHdG)

Serum 8-OHdG was measured with a commercial ELISA kit (SunLong, China) employing a one-step double-antibody sandwich format on 96-well plates pre-coated with anti-8-OHdG antibody, following the manufacturer's protocol.

2.8 Statistical analysis

Analyses were performed in SPSS (version 26). Descriptive statistics (means and variability) and significance testing were conducted with one-way ANOVA and paired-samples *t*-tests, with $p < 0.05$ indicating statistical significance. Pearson correlation coefficients were computed to evaluate associations among biochemical variables.

To evaluate the diagnostic accuracy of serum 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels in distinguishing between methamphetamine user groups (G1 and G2), a Receiver Operating Characteristic (ROC) curve analysis was performed. The ROC curve determines the optimal cutoff value for identifying the true condition of participants by incorporating both sensitivity and specificity. The area under the curve (AUC) was used to assess diagnostic performance, interpreted as follows: 0.50–0.60 = poor test, 0.60–0.70 = fair, 0.70–0.80 = good, 0.80–0.90 = very good, 0.90–1.00 = excellent

3. Results and Discussions

Table 1 presents the study results, showing the mean ± SD for each measured parameter among participants.

Table 1: Clinical parameters of the study participants

Parameter	*Group (N=30) in each group*	*Mean ± SD*	*P-value*
Age (Years)	G1	25.27 ± 5.40	ns
	G2	23.80 ± 5.26	
	Control	24.57± 5.69	
BMI (Kg/m²)	G1	18.97 ± 0.86[a]	*
	G2	19.06 ± 0.99[b]	
	Control	19.80 ± 1.38	
TOS µmol /L	G1	138.03 ± 42.64[a]	*
	G2	134.83 ± 46.51[b]	
	Control	110.20 ± 37.89	
TAS µmol/L	G1	3.80 ± 0.75[a]	*
	G2	3.82 ± 0.79[b]	
	Control	4.25 ± 0.77	
OSI	G1	37.76 ± 13.06[a]	**
	G2	36.74 ± 14.16[b]	
	Control	26.52 ± 10.51	
MDA nmol/ml	G1	14.567 ± 6.1614[ac]	**
	G2	10.267 ± 4.7499	
	Control	8.945 ± 3.1576	
8-OHdG pg/mL	G1	1108.43 ± 241.36[a]	**
	G2	1071.88 ± 210.10[b]	
	Control	708.06 ± 344.29	

*Where (a) represent the significance of G1 with control (b) represent the significance of G2 with control (c) represent the significance of G1 with G2, ns: non-significance, *: p< 0.05, **: p<0.01*

Initiating drug use early, particularly during adolescence, is linked to a greater risk of advancing from use to abuse and dependence, higher frequency of misuse across a lifetime, and a faster shift to dependence. Because their brain areas in charge of risk assessment, decision-making, and consequential evaluation are not fully mature until their mid-20s, teenagers and young adults are especially susceptible to drug use disorders. Early users of addictive drugs are more prone to use these drugs more regularly and develop greater rates of substance use disorders [15-17].

The results showed a statistically significant difference ($p < 0.05$) in BMI among the groups, with both untreated and treated methamphetamine addicts having lower BMI than controls. Although this reduction was statistically significant, it was modest and may not be clinically meaningful. These findings coincide with Alharbi RS et al. study. Similarly, groups II and III saw a significant decrease in average BMI values both at the beginning and after the detoxification phase, compared to the control group ($P < 0.05$) [18]. It is well recognized that amphetamine-type stimulants (ATS) suppress appetite and have historically been used to treat obesity[19].The significant difference in BMI among the studied groups is due to methamphetamine's effects on appetite and metabolism. Methamphetamine reduces appetite, leading to decreased food intake and lower body weight. Additionally, it increases energy expenditure by stimulating the central nervous system [20].

In our study, TOS and OSI were significantly elevated and TAS was reduced in both the untreated and under-treatment methamphetamine groups versus controls, indicating a shift toward a pro-oxidant state. Methamphetamine use promotes generation of ROS, and the sustained excess of ROS plausibly overwhelms endogenous antioxidant defenses, which is reflected by the higher OSI values—i.e., a ratio signaling that oxidative processes outpace antioxidant capacity and thereby favor cellular injury.

The rise in TOS specifically denotes a higher aggregate burden of oxidants. By design, the TOS assay integrates multiple oxidizing constituents in biological samples—particularly ROS and free-radical species—yielding a practical estimate of total oxidant load and overall oxidative stress status [21]. Taken together, our results are consistent with an imbalance between oxidant production and antioxidant protection in methamphetamine users.

Clinically, elevated TOS is linked to adverse outcomes, including cellular damage and increased risk across neurological and cardiovascular conditions [22]. Consistent with this framework, methamphetamine misuse has been associated with higher TOS values than those observed in non-users, supporting the view that drug-induced oxidative stress contributes to the increased oxidant milieu in affected individuals [23].

According to a study by Viola et al., those with drug use disorder (SUD), including methamphetamine, show reduced antioxidant indicators and more oxidant markers than healthy controls [24]. SUD was linked especially to increased levels of lipid peroxidation, thiobarbituric acid reactive chemicals, and oxidant indicators malondialdehyde. On the other hand, in the SUD group the overall antioxidant capacity/status and the antioxidant superoxide dismutase dropped. The network of defensive systems offers the total antioxidant capacity (TAC) of the system to guard the cellular targets from oxidative harm. Water and lipid soluble antioxidants constitute the molecular defence; this network can be split into the enzymatic defence containing superoxide dismutase, catalase and glutathione peroxidase (SOD, CAT, and GSH-Px). These defence systems stop DNA, proteins, and lipids from oxidizing [25].

Plasma TAC was discovered in blood samples of Methamphetamine dependent patients to be lower than in those of healthy controls in a previous work [26]. These findings are in line with those of the present research showing that methamphetamine users had much reduced plasma TAC levels. Plasma TAC induction happens to scavenge generated free radicals. In comparison with healthy persons, malnutrition in chronic methamphetamine users causes a loss of plasma TAC [27].

The study demonstrated that the serum MDA level in the un-treated methamphetamine addicted group was significantly elevated ($P \leq 0.01$) compared to the control group. In the under-treated methamphetamine addicted group, the serum level of MDA was also significantly higher ($p<0.05$) compared to the control group.

Methamphetamine increases ROS in the central nervous system (CNS) in both *in vivo* and *in vitro*, causing oxidative stress in the nervous system. The elevated accumulation of MDA in the brain is linked to this increased lipid oxidation and is observed in those who use methamphetamine. In both animal and human models, elevated levels of MDA are associated with different diseases [28].

These findings are consistent with prior studies. As an example, when evaluating left ventricular function in rats, Kevin et al. discovered that the blood ROS levels were more than doubled when administered methamphetamine compared to usual values [29]. Bryan et al. also showed that rats given methamphetamine had changes in oxidative stress markers such MDA, which caused oxidative brain damage [30]. In addition, Najafi et al. found that methamphetamine addicts had far higher serum MDA concentrations than control subjects, indicating a statistically significant difference in serum MDA levels between the two groups [27]. The case group did not show a statistically significant increase in serum MDA levels when compared to the control group, according to Shadnia et al. MDA serum levels are considerably

elevated in methamphetamine-dependent patients, as demonstrated by a prior study [31]. In another study, the MDA level was significantly elevated in postmortem brain samples from chronic methamphetamine abusers [32].

Deoxyribonucleic acid (DNA) damage, protein modification, and lipid peroxidation are the results of excessive ROS reacting with cellular macromolecules, thereby impairing a variety of physiological functions. The DNA adduct 8-hydroxy-2′-deoxyguanosine is excreted in body fluids as a result of the highly active hydroxyl radical reacting at the C-8 position of guanine through hydroxylation, resulting in DNA strand breaks and DNA base modifications. Current scientific evidence indicates that 8-OHdG can be detected in both urine and blood; however, in this study, we measured it only in serum, as its extracellular concentrations are only slightly affected by cell death or diet [33, 34].

Systemic oxidative stress is present in various physical and neuropsychiatric conditions, such as diabetes mellitus, Parkinson's disease, and alcohol dependency, has been extensively assessed using blood levels of 8-OHdG. Winhusen et al. discovered that methamphetamine-dependent patients exhibited more significant executive dysfunction when their oxidative DNA damage was quantified using single-cell gel electrophoresis (also known as the Comet assay) [35]. A systemic response to an enhanced oxidative stress may be suggested by elevated levels of 8-OHdG in methamphetamine consumers. Previous human studies have documented an increase in oxidative stress after methamphetamine administration. For instance, lipid peroxidation, a sign of increased oxidative stress, is significantly enhanced in methamphetamine and amphetamine users. The direct impact of methamphetamine on DNA degradation has been investigated in animal studies. The authors of that study demonstrated that DNA damage was caused by recurrent methamphetamine exposure, while a single dose did not produce significant damage [33, 34].

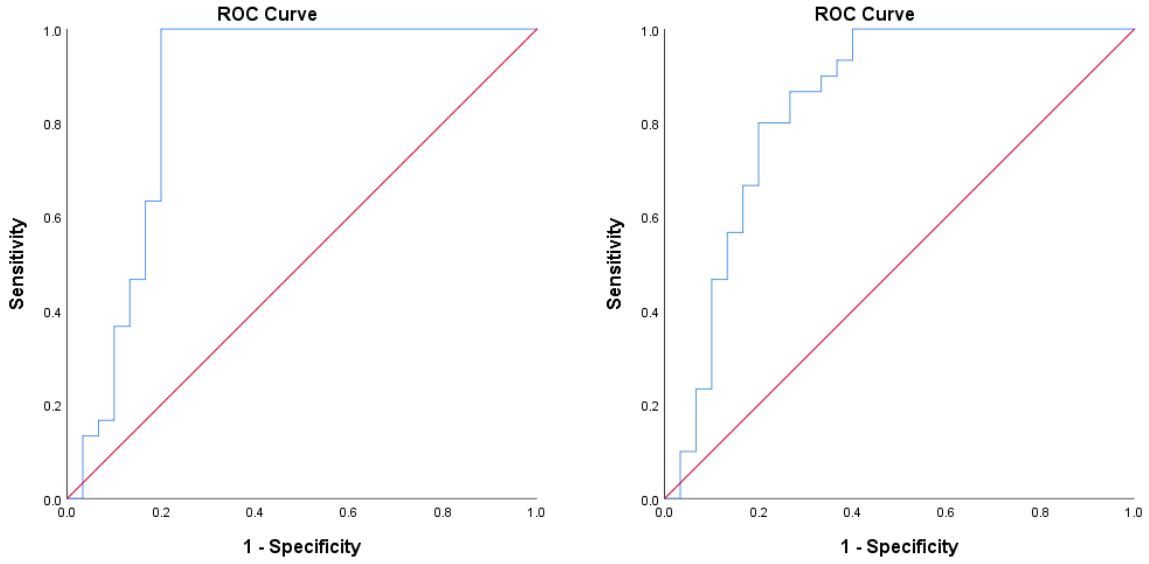
The biological mechanisms underlying these findings involve the excessive production of free radicals and oxidative species, particularly following methamphetamine exposure, as detailed below: Superoxide, hydroxyl radicals, hydrogen peroxide, and quinones are among the free radicals that are produced when dopamine undergoes fast auto-oxidation. Hydrogen peroxide is a consequence of monoamine oxidase's enzymatic conversion of excess dopamine to dihydroxyphenylacetic acid. Further interactions between hydrogen peroxide and metal ions might result in the production of extremely reactive hydroxyl radicals, which can worsen oxidative damage to neurons. The fact that methamphetamine exposure raises both synaptic and circulating levels of catecholamines may help to explain the systemic increase in oxidative stress that may be linked to it [35, 36].

In un-treated METH addicted patients, the 8-OHdG level in serum is a reliable biomarker for the prediction of methamphetamine addiction. The optimal cut-off point value is > 886.2 pg/mL, with an AUC of 0.859 and a sensitivity of 100% and a specificity of 80%. Table 2 and Figure 1 indicate that this biomarker is a useful predictive tool for methamphetamine addiction, as the result showed a significant difference $P<0.01$.

The optimal cut-off point value is > 888.25 pg/mL, with an AUC of 0.840 and a sensitivity of 80% and a specificity of 80%. This outcome demonstrated a statistically significant difference ($P<0.0001$), as illustrated in Figure 2 and Table 2.

Table 2: The ROC curve of 8-OHdG in un-treated and under treated methamphetamine addicted patients.

Parameter	*AUC*	*p-value*	*Sensitivity%*	*Specificity%*	*Best cut-off*
8-OHdG Group1	0.859	0.0001	100	80	>886.2
8-OHdG Group2	0.840	0.0001	80	80	>888.25



(a) **(b)**

Figure 1: (a) ROC curve analysis for 8-OHdG in patients with untreated methamphetamine addiction. (b) ROC curve analysis of 8-OHdG in patients with methamphetamine addiction receiving therapy.

With 100% sensitivity, this biomarker is a crucial tool for the early detection and intervention of methamphetamine addiction. The 80% specificity rate indicates that it correctly identifies a substantial proportion of persons who do not have an addiction. Oxidative stress and DNA damage are indicated by 8-OHdG. Oxidative stress in the body can result from methamphetamine abuse, which has the potential to damage DNA. Elevated 8-OHdG levels are probably a sign of severe oxidative DNA damage, which may be particularly noticeable in methamphetamine addicts.

Findings suggest that blood 8-OHdG levels are useful indicators for METH addiction diagnosis. Identification of METH addicts is significantly aided by 8-OHdG, an indicator of oxidative stress; the threshold values for untreated and treatment-underprivileged individuals are comparable. The biomarkers' dependability in clinical settings is highlighted by the results' statistical significance ($P < 0.0001$), which provides helpful tools for early METH addiction detection and treatment.

4. Conclusion

This study demonstrates that methamphetamine addiction significantly increases oxidative stress markers, especially 8-hydroxy-2'-deoxyguanosine (8-OHdG), indicating considerable oxidative DNA damage. Both untreated and under-treatment methamphetamine addicts display increased levels of TOS, OSI, and MDA, and lower TAS compared to controls. Notably, serum 8-OHdG levels can serve as a reliable biomarker for predicting methamphetamine addiction,

even in patients currently receiving treatment, thereby underscoring its value in early diagnosis and intervention.

Moreover, the absence of a significant difference in TOS, TAS, and OSI between the untreated and under-treatment groups suggests that current treatment protocols may not effectively reduce oxidative stress or restore antioxidant defences in the short term. This observation implies that oxidative damage may be too extensive to permit rapid improvement, or that a longer duration and alternative therapeutic interventions may be required to restore the antioxidant system in methamphetamine addicts. Future research should investigate the potential therapeutic benefits of antioxidant supplementation in mitigating oxidative damage among methamphetamine addicts.

5. Disclosure and conflict of interest

Conflict of Interest: The authors declare that they have no conflicts of interest.

6. Acknowledgement

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