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Methamphetamine's effects on oxidative stress markers may continue after detoxification: a case–control study

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ABSTRACT

OBJECTIVE: Substance use disorder (SUD) is a critical public health problem. The use of methamphetamine is increasing daily worldwide. The aetiology of SUD is related to numerous factors that have not been fully elucidated. It is known that there are some changes in oxidative stress in substance use disorder. However, to the best of our knowledge, there is no study showing changes in thiol/disulphide homeostasis (TDH) in methamphetamine use disorder (MUD).

METHODS: Forty-four male patients with MUD and forty-five healthy male controls were included in the study. Only patients who had used methamphetamine in the last three months were included. Blood samples were taken from the patients one day after hospitalization and after detoxification for measurement of the thiol/disulphide level.

RESULTS: The levels of native thiol, total thiol, and disulphide in the MUD group were significantly higher than in the control group. At the end of the detoxification period, the levels of native thiol and total thiol did not change significantly, but an increase in the disulphide level was observed.

CONCLUSION: The results of our study show that there was a shift in the disulphide direction in the TDH, which is an indicator of oxidative stress in the patient group, and this shift continued after the detoxification period of between 5 and 21 days. There is no other study in the literature evaluating TDH in patients with MUD. Therefore, our study is important for clarifying the aetiopathogenesis of SUD.

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Introduction

The abuse of addictive substances dates back to the periods of the first early human communities [1]. The low cost of purchase and the cheap production of these substances also increased their addiction frequency. In recent years, synthetic drugs and the incidence of methamphetamine use disorder (MUD) have been increasing rapidly. Methamphetamine has become one of the most addictive drugs in the world [2–4]. Addiction is an important brain disease that is repetitive and causes loss of function and physiological changes in many parts of the brain [5]. Therefore, dependency is a major public health problem that needs to be better understood [2]. However, the aetiopathogenesis of addiction has not been fully elucidated [6]. Substance addiction is now defined as substance use disorder (SUD) in the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 [7].

It has been shown in animal studies that psychostimulant drugs and similar substances have neurotoxic effects [8,9]. Addictive substances and methamphetamine are known to cause oxidative stress [2,10–12].

Oxidative stress is generally defined as the deterioration of the balance between oxidant and antioxidant mechanisms. Oxidative stress products damage many biological molecules, including proteins, nucleic acids, and lipids [13]. Thiols are a class of organic compounds that are important for biological systems. Thiol, an important antioxidant, plays an important role in the elimination of reactive oxygen molecules [14,15]. Thiols enter reactions with oxidant molecules and form a disulphide bond. There is a mutual exchange between the reduced state of thiols and the disulphide groups to form an oxidized state. The disulphide bonds can be reduced back to thiol groups to maintain homeostasis [16,17]. Dynamic thiol-disulphide homeostasis (TDH) is necessary for detoxification, the regulation of signalling pathways, and the regulation of apoptosis and enzymatic reactions [17,18]. Oxidative stress can lead to disulphide formation, disrupting TDH, and consequently impairing protein functions.

The brain is sensitive to changes in oxidative mechanisms. Oxidative damage may be involved in the aetiology of neuropsychiatric diseases [19,20]. Studies

have shown impaired TDH in psychiatric disorders such as heroin addiction [10], depression [21,22], bipolar affective disorder [23], and schizophrenia [24,25].

There is no study showing how TDH is affected in the increasingly widespread MUD. In this study, we aimed to investigate TDH in patients with MUD compared to healthy controls. We also compared the baseline at hospitalization with the prior-to-discharge thiol and disulphide levels and evaluated the effect of the detoxification process on homeostasis.

Methods

Volunteer group

This study was conducted between May 2018 and December 2018. After the evaluation of previous study results, a power analysis was performed. The alpha and beta errors were stated, respectively, as 0.05 and 0.20. The minimum number of patients needed to obtain 80% power was calculated as 18 for each group. The study included 45 healthy male controls and 44 male patients with MUD, who were admitted to the Alcohol and Drug Addiction Research and Treatment Centre, followed-up, and treated. The patient flow chart is shown in Figure 1. The patient group consisted of male patients between 18 and 65 years of age who applied to the clinic consecutively according to DSM-5 diagnostic criteria [7], who met the SUD diagnostic criteria, and who used only methamphetamine for at least three months. The patients were examined by two different psychiatrists and their anamnesis and medical records were documented. Patients with comorbid psychiatric disease (schizophrenia and other psychotic disorders, mood disorders, obsessive compulsive disorder, anxiety disorders, attention deficit hyperactivity disorder etc.), chronic physical disease (hypertension, diabetes mellitus, rheumatic diseases, oncological diseases, heart diseases, neurological diseases etc.), or endocrine disorders, and those who were hospitalized for less than five days were excluded from the study. Patients with multiple substance use disorder, i.e. patients who used substances other than methamphetamine and nicotine in the past three months, were excluded from the study. Since all of the patients in the study sample used nicotine, those who used nicotine in addition to methamphetamine were necessarily included in the study. Only one female patient was admitted during the study period. Sufficient female patients were not included in the study to compare the sexes. The control group consisted of healthy hospital staff and their relatives.

Sampling

A total of 5 mL of blood was collected from the participants from the antecubital vein at 8.00 am one day after

being admitted to the clinic. The blood samples were centrifuged at 1500 rpm for 10 min and their serums were separated and stored at -80°C until analysis. Another 5 mL blood sample was collected at 08.00 am on the day of discharge, at the end of a period when patients stay for at least five days. Blood samples from the control group consisting of hospital personnel and their relatives were taken at 08.00 am, and similar procedures were performed.

Biochemical analysis and calculation

The plasma native thiol and total thiol levels were measured using a biochemical method developed by Erel and Neselioglu [26]. In this method, free functional thiol groups are obtained by reducing reducible disulphide bonds and all thiol groups containing native and reduced thiol groups were measured. The percentage of coefficients of variations (CV) values were 13%, 5%, and 4% for the concentrations 7.15, 16.0, and 29.1 $\mu\text{mol/L}$, respectively. Half of the difference between the amount of total thiol and native thiol gives the disulphide amount. In addition, the ratios of native thiol, total thiol, and disulphide were calculated ($\text{index1} = [\text{disulphide/native thiol}] \times 100$; $\text{index2} = [\text{disulphide/total thiol}] \times 100$; and $\text{index3} = [\text{native thiol/total thiol}] \times 100$).

Sociodemographic data form

The sociodemographic data form, which was prepared by the researchers and included age, height, weight, smoking, and clinical and demographic characteristics of the disease, was filled out.

Statistical analysis

Statistical analyses were performed using SPSS 22.0 (Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA). The categorical variables were expressed as a percentage and number. The continuous variables were presented using means and standard deviations. The suitability of the variables to a normal distribution was examined by visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test). In the patient and control groups, an independent group t-test was used to compare the native thiol, total thiol, and disulphide, and index 1, index 2, and index 3 values. Chi-square tests were used to compare categorical variables. In the patient group, t-tests were performed in dependent groups for the comparison of native thiol, total thiol, and disulphide, and index 1, index 2, and index 3 values, measured immediately after hospitalization and before discharge. A two-tailed statistical comparison was performed. Statistical significance was accepted as $p < 0.05$.

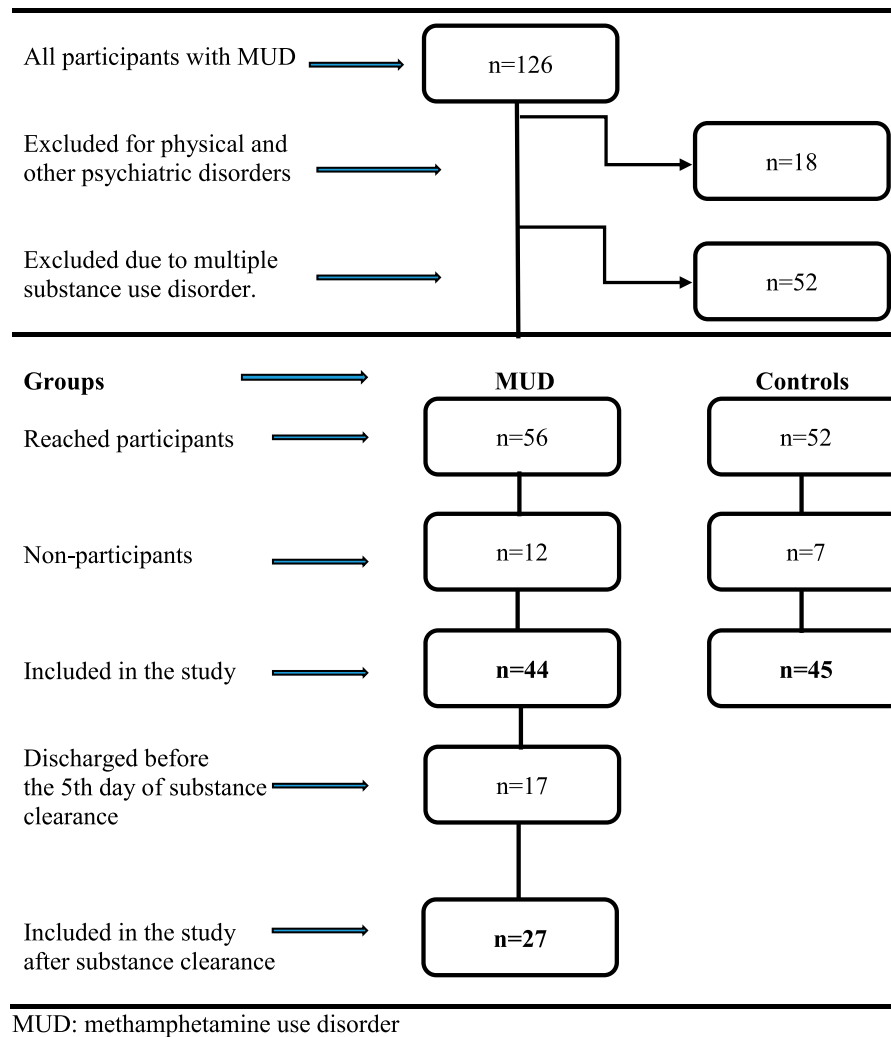


Figure 1. Flow chart of participants. MUD: methamphetamine use disorder.

Ethical approval

The individuals who agreed to participate in the study were informed about the study and written informed consent was obtained from all participants before they began their participation. The study was approved by the local Ethics Committee of Yozgat Bozok University with protocol number of 2017-KAEK-189_2018.05.30_02 and performed under the ethical principles of the Declaration of Helsinki for medical research involving human subjects.

Results

The study included 44 male patients (mean age \pm SD: 26.48 ± 5.97 years) with MUD and 45 healthy men (mean age \pm SD: 28.04 ± 5.77 years) (Figure 1). The patient and control groups were similar in age ($p = 0.212$) and educational characteristics ($p = 0.480$). All the patients smoked, and the rate of smoking was significantly higher than in the control group ($\chi^2: 42.061$; $p < 0.001$) (Table 1). The values of native thiol, total thiol, disulphide, index 1, and index 2 were significantly higher in the patient group than in the control

group ($p < 0.001$), whereas index 3 was significantly lower in the patient group ($p < 0.001$) (Table 2). The native and total thiol levels were not affected by the initial or repeat hospitalization status (Table 3). The values of measured disulfide and indexes 1 and 2 before discharge were significantly higher than those measured at initial admission. The index 3 values were significantly lower before discharge than initial admission ($p < 0.001$) (Table 3). When a post-hoc power analysis was applied with alpha 0.05, the power of the study was found to be 0.9999.

Discussion

The main findings of this study were that the levels of native thiol, total thiol, and disulphide were higher in men with MUD than in men in the control group. In addition, the ratio of disulphide to total thiol and disulphide to native thiol in the patient group was higher than that in the control group, and the ratio of native thiol to total thiol was lower in the patient group than the control group. At the end of the detoxification period, the levels of native thiol and total thiol did not change significantly, whereas the level of disulphide

Table 1. Sociodemographic data of the patient and control group.

	MUD (<i>n</i> = 44, male) Mean \pm SD Median (IR)	Control (<i>n</i> = 45, male) Mean \pm SD Median (IR)	<i>t</i>	<i>p</i> ^a
Age (years)	26.48 \pm 5.97 24 (8)	28.04 \pm 5.77 25.5 (9)	-1.258	0.212
Education (years)	7.55 \pm 2.39 8 (3)	7.91 \pm 2.46 8 (2)	-0.709	0.480
BMI	23.10 \pm 2.29 23.21 (3.15)	23.92 \pm 1.72 24.22 (1.99)	-1.910	0.059
Number of cigarette per day	22.75 \pm 10.72 20 (5)	17.19 \pm 6.57 17.50 (10)	1.940	0.057
Percentage smoking	%100 (<i>n</i> = 44)	%36.5 (<i>n</i> = 16)	χ^2 :42.061	<0.001 ^{b**}
MUD duration (months)	60.98 \pm 36.63 60 (36)	–		
Number of hospitalizations for treatment [min–max]	2 (1) [1–6]	–		
Hospitalization duration of last treatment (days) [min–max]	13 (13.5) [5–26]	–		

^aStudent-*t* test; ^bChi-square test; ***p* < 0.001; MUD: methamphetamine use disorder; BMI: body mass index; SD: standard deviation; IR: interquartile range.

was higher than initial admission. In addition, at the end of the detoxification period, the ratio of disulphide to total thiol and disulphide to the native thiol was higher than upon initial admission, and the ratio of native thiol to total thiol was lower than that upon the first admission. The increase in index 1 and index 2 indicated that the increase in disulphide was higher than that of thiol. The results of our study showed that there was a shift in the disulphide direction in the TDH in the patient group and this shift continued in the 5–21 days of the detoxification period.

Normally, reactive oxygen radicals and antioxidant defence mechanisms are in balance in healthy individuals. Oxidative stress in the body is caused by the imbalance between antioxidants and reactive oxygen radicals. In chronic drug addiction, the antioxidant defence system is defeated. An increase in oxidative stress and an insufficient antioxidant defence mechanism disrupts the physiological balance and induces a number of pathologies [27]. Methamphetamine and similar substances affect the neurotransmitter systems and neuronal structures in the brain and produce neurotoxic effects [4,28]. There are studies showing that TDH is impaired in those with SUD. In a study of heroin-dependent males, it was reported that the native thiol and total thiol levels were lower and the disulphide levels were higher than in the controls. In the same study, the ratio of disulphide to total thiol and

disulphide to native thiol was found to be higher, and the ratio of native thiol to total thiol was found to be lower than that of healthy controls [10]. These results indicate that TDH in heroin-dependent males is impaired in the direction of disulphide bond formation. In our study, a shift towards disulphide bond formation was observed in MUD. However, in our study, the thiol levels were also higher in the patient group. The high levels of both thiol and disulphide in patients may be the result of the oxidative and antioxidant properties during oxidative stress and the mechanism of maintaining the balance between them. Therefore, as the level of disulphide increases, the thiol level may be increased as a stabilizer. This difference may also be related to the different pharmacological properties of methamphetamine from heroin [29,30].

There was no significant change in the native and total thiol levels after the detoxification period and the levels of disulphide increased. Whereas the oxidative stress parameters affected by oxidative stress are expected to normalize over time, this was not the case in our study. There may be several reasons for this. First, although the patients did not use methamphetamine in the clinic, the half-life of methamphetamine and its metabolites and the effects of activated mechanisms on the oxidative system may be prolonged. Second, the factors affecting the

Table 2. Comparison of thiol and disulphide levels of patients between in the control group after the first day of hospitalization.

	MUD (<i>n</i> = 44, male) Mean \pm SD	Control (<i>n</i> = 45, male) Mean \pm SD	<i>t</i>	Effect size (Cohen's <i>d</i>)	<i>p</i> ^a
Native thiol	596.48 \pm 74.91	381.67 \pm 46.61	16.199	3.4517	<0.001**
Total thiol	680.87 \pm 93.90	415.44 \pm 46.44	16.843	3.5957	<0.001**
Disulfide	42.19 \pm 12.06	16.88 \pm 5.28	12.676	2.7277	<0.001**
Index 1	7.00 \pm 1.53	4.50 \pm 1.59	7.556	1.6012	<0.001**
Index 2	6.11 \pm 1.16	4.09 \pm 1.30	7.728	1.6363	<0.001**
Index 3	87.77 \pm 2.33	91.81 \pm 2.60	-7.698	1.6300	<0.001**

^aStudent-*t* test; ***p* < 0.001; MUD: methamphetamine use disorder; SD: standard deviation; Index 1 = (disulphide / native thiol) \times 100; Index 2 = (disulphide / total thiol) \times 100; Index 3 = (native thiol / total thiol) \times 100.

Table 3. Comparison of thiol and disulphide levels of patient groups in repetated measurements.

	MUD At the beginning of hospitalization (n = 27) Mean ± SD	MUD Before discharge (n = 27) Mean ± SD	t	Effect size (Cohen's d)	p ^a
Native thiol	598.09 ± 64.49	583.57 ± 78.09	0.839		0.409
Total thiol	676.41 ± 81.75	681.21 ± 82.95	−0.261		0.796
Disulphide	39.15 ± 10.10	48.81 ± 9.62	−5.424	1.0438	<0.001**
Index 1	6.48 ± 1.22	8.49 ± 1.91	−5.448	1.0485	<0.001**
Index 2	5.71 ± 0.96	7.21 ± 1.39	−5.472	1.0530	<0.001**
Index 3	88.57 ± 1.92	85.57 ± 2.78	5.498	1.0580	<0.001**

^aPaired Samples-t Test; **p < 0.001; MUD: methamphetamine use disorder; SD: standard deviation; Index 1 = (disulphide / native thiol) × 100; Index 2 = (disulphide / total thiol) × 100; Index 3 = (native thiol / total thiol) × 100.

oxidative system may have been eliminated, however, the change in parameters and can last 2–4 weeks [31]. Therefore, the time period of 5–21 days in which the patients stayed in the hospital may not be sufficient for the expected change to occur. In addition, it has been reported that smoking increases oxidative stress and shifts TDH in the direction of disulphide [32]. In our study, one of the reasons for the continued increase in disulphide during the detoxification period may be the continued use of cigarettes. Patients may even have increased the consumption of cigarettes to reduce the withdrawal symptoms of methamphetamine during hospitalization. However, this explanation is only speculative, since the daily cigarette consumption of the patients was not recorded during the hospitalization period.

There are few studies evaluating TDH homeostasis in addiction. Therefore, it is necessary to evaluate the results of studies performed with other parameters that are indicative of the oxidative system. Malondialdehyde (MDA) is the most important biomarker for the evaluation of oxidative stress and the determination of lipid peroxidation. It has been reported that MDA levels were increased in opioid and methamphetamine users (abusers) compared to the control group, although there was no significant difference between opioid and methamphetamine users [11]. The MDA level has been shown to be higher in the alcohol withdrawal period and in remission after abstinence than in healthy controls [33]. In the same study, the protein carbonyl levels were found to be higher during the remission period of patients than in the control group, however, there was no difference during the withdrawal period. Therefore, the level increased over time. Protein carbonyl exhibits oxidative properties similar to that of a disulphide. Both findings indicate that oxidative stress continued for some time after the withdrawal period.

There are studies showing that thiol levels are affected by nutrition and smoking. Although methamphetamine may cause a decrease in appetite due to its stimulant properties, the body mass index (BMI) of the patient and control groups was similar in our study. All patients included in the study were smokers. Due to the mechanism of addiction, patients with

methamphetamine addiction are also predisposed to other dependencies. This might explain why in our study, the smoking rate was higher in patients than the healthy controls.

There are some limitations to this study. The oxidative stress system is a very sensitive mechanism affected by many factors. Although the patient and control groups were selected from the volunteers who exhibited homogenous characteristics, it was not possible to control for a large number of factors that might affect these systems. Since the patients used different medications during the treatment period in hospital, a group analysis could not be performed according to the treatment regimen. The drugs used in the detoxification of patients may also have an effect on the oxidative system. In this study, according to the ethical rules, we did not intervene in the treatment of the patients. The severity of addiction can affect some oxidative parameters. Therefore, another limitation is that the severity of the addiction was not evaluated in the study and, consequently, a correlation analysis between the severity of addiction and thiol-disulphide levels was not performed. Another limitation was that only male patients were included in the study. Most of the patients included in the study were discharged from the clinic upon their own request after a short stay in the hospital. Therefore, blood samples could not be taken from a number of patients. Another limitation is that measurements were not performed at the end of a long period of detoxification. Life style, exercise, and obesity have also been reported to affect TDH homeostasis [34]. In our study, although the BMI of the patient and control groups were similar, their life style and duration of exercise were not questioned. Finally, the parameters studied in the serum may be far from reflecting the oxidative state in the central nervous system. Therefore, it is difficult to interpret changes in the central nervous system from parameters measured in serum.

The study, however, does have its strengths. A large number of patients with substance use disorder use multiple substances at the same time. In our study, only patients that had used only methamphetamine in the past three months were selected. Therefore, other factors that may affect the oxidative system were largely excluded.

As a result, TDH, which is an indicator of the oxidative system, was shown to be impaired in patients with MUD. The disulphide levels continued to increase at the end of the detoxification period. There is no other study in the literature evaluating TDH in patients with MUD. Therefore, our study is important for clarifying the aetiopathogenesis of SUD. Illumination of the aetiology of MUD, which is an increasing health problem, may contribute to the follow-up and treatment of this disease.

Disclosure statement

No potential conflict of interest was reported by the authors.

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