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The relationship between serum uric acid levels and severity of addiction in individuals with substance use disorders

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ABSTRACT

Objectives: This study aimed to compare serum uric acid levels in patients with methamphetamine and synthetic cannabinoid use disorders pre- and post-detoxification treatment with healthy controls. Secondly, to determine the relationship between the serum uric acid levels of the cases and the severity of the addiction.

Methods: Fifty methamphetamine, 50 synthetic cannabinoids, and 40 healthy controls were evaluated on the specified dates. Venous blood samples were taken from the participants to measure serum uric acid and creatinine levels. The arrangement was made by taking the Uric acid/creatinine ratio to neutralize the confounding effect of kidney functions. The Addiction Profile Index was applied to determine the severity of substance abuse in the case group.

Results: A statistically significant difference was found between the uric acid values of all three groups when the One-way ANOVA test was performed ($p < 0.001$). UA values were significantly lower in the case groups than in the healthy control group. When the substance use characteristics of the case groups were compared, a statistically significant difference was found in the duration of substance use ($p < 0.010$) and motivation ($p = 0.031$) subtests. Duration of substance use and craving were higher in the synthetic substance group, and motivation was higher in the methamphetamine group. According to the Pearson analysis, the severity of addiction was deduced not to be correlated with serum uric acid and uric acid/creatinine levels in both case groups.

Conclusions: Serum uric acid and uric acid/creatinine levels were found to be statistically significantly lower in individuals with methamphetamine and synthetic cannabinoid exposure compared to healthy controls. In this study, it was thought that the lower uric acid levels in the case group compared to the control group may be due to the use of uric acid as an antioxidant or a decrease in purinergic transformation. Future studies may focus on making this distinction.

Keywords: Methamphetamine, synthetic cannabinoid, uric acid, severity of addiction

Uric acid (UA), the end product of the purinergic system, is converted from two nucleotides, adenosine monophosphate, and guanosine monophosphate, as a result of the oxidation of purines [1, 2]. The purinergic system includes adenosine and adenosine triphosphate (ATP) receptors and is commonly found in the central nervous system [3]. UA is involved in the transmission of adenosine [3]. Adenosine A1 and

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A2 sub-receptors exert their inhibitory effects on the central nervous system and heart by secreting neurotransmitters. High UA decreases this inhibitory effect by slowing down adenosinergic transmission [4].

Extracellular UA can have both antioxidative and prooxidative functions. UA constitutes an important part of the antioxidants in the plasma and acts as an antioxidant at normal serum levels. However, high serum UA levels show prooxidative and proinflammatory effects [5, 6]. It provides antioxidant activity in neurological diseases by scavenging free radicals [5, 7, 8]. UA has a pro-oxidative effect inside the cell [9]. UA has been reported to maybe cause low-grade systemic inflammation by producing proinflammatory cytokines [10]. High production of UA leads to increased oxidative stress and systemic inflammation [11].

Some studies have been carried out to examine the uric acid level in psychiatric disorders. UA blood serum levels were found to be high in manic and depressive periods of bipolar disorder [12-14]. UA elevation has been found to be associated with impulsivity, disinhibition, aggression, and sensation seeking behavior [15]. Impulsivity, hostility, aggression, irritability, and sensation-seeking behavior are known to be common in patients with substance use disorder [16, 17]. There are not enough studies in the literature evaluating the serum UA level in these patients.

The aim of this study was to evaluate whether serum UA levels were different from healthy controls the pre- and post-detoxification treatment in patients with methamphetamine and synthetic cannabinoid use disorders. Secondly, to determine the relationship between serum UA levels and the severity of addiction.

METHODS

Study Population

This study was carried out in the Alcohol and Substance Addiction Treatment Clinic of a Training and Research Hospital. The patient group was formed from male participants diagnosed with substance use disorder according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) diagnostic criteria, between the ages of 18-65, and have been using substances for at least 1 year. Same-sex participants were included in the study to control for the confounding effect of gender. Those with a comorbid psychiatric disease, multiple substance use, those using antidepressant and antipsychotic drugs, and those with gout, hypertension, inflammatory diseases, chronic renal failure, hypertriglyceridemia, hyperglycemia, or other medical conditions, causing hyperuricemia were excluded from the study.

The study sample consisted of 140 participants in equal numbers from 3 groups: methamphetamine use disorder, synthetic cannabinoid use disorder, and control groups. The case group consisted of hospitalized patients. The control group consisted of hospital personnel and their relatives whose demographic characteristics were similar to the study group. All of the participants in both groups were smokers.

All participants reviewed the informed consent form and their written consent was obtained. Illegal substance use of the patients was confirmed by measuring urine samples with Siemens Advia 1800 chemistry analyzer using the Enzyme Multiplied Immunoassay Technique (EMIT).

This study was designed in accordance with the 2013 version of the Declaration of Helsinki and was approved by the local ethics committee (dated 17.11.2021 and decision number 2011-KAEK-25 2021/11-23). Good clinical practice principles were followed throughout the study.

Biochemical Parameters

One tube of venous blood sample was obtained from all participants at the time of enrollment to measure serum uric acid and creatinine levels. Venous blood samples were taken again to measure the same values 1 month after the detoxification treatment from the patient group. After the blood samples were centrifuged at 300 rpm for 15 minutes, plasma and serum samples were separated. Serum samples were stored at -80 °C. Uric acid was analyzed using the Abbott Architect c800 device. The normal range of UA was determined as 3.5-7.2 mg/dl. The arrengement was made by taking the Uric acid/creatinine (UA/Cr) ratio to neutralize the confounding effect of kidney functions. Peripherally measured blood plasma levels of UA are highly correlated with cerebrospinal fluid levels in the central nervous system (CNS) [18]. In this study, serum uric acid levels in peripheral blood were analyzed to determine oxidative stress in the CNS.

Assessment Tools

Sociodemographic Data Form

This form, prepared by the researchers, consists of questions about the participants' sociodemographic characteristics, substance use patterns, and past illnesses.

Addiction Profile Index (API)

The scale developed by Ögel *et al*. [19] to determine the severity of the addiction is a self-report questionnaire consisting of 37 items and 5 subscales. The subscales measure the characteristics of substance use, the diagnosis of addiction, the effect of substance use on one's life, craving, and motivation to quit the substance. Below 12 points are considered as low addiction severity. Ögel *et al*. [19] conducted a validity and reliability study in Turkish.

Statistical Analysis

Demographic and clinical characteristics of the cases evaluated in the study were clarified with descriptive statistical methods such as number, percentage, mean, and standard deviation. Independent samples t-test and chi-square test were used to compare substance use characteristics between the two groups. Non-parametric Mann-Whitney U test was used to compare continuous variables. One-way ANOVA and LSD post hoc tests were performed to evaluate the difference between groups. Pearson analysis was used to identify the relationship between variables. The conformity of the data to the normal distribution was evaluated according to the kurtosis and skewness coefficients (±1.5). IBM SPSS 22.0 program was benefitted for the analysis.

RESULTS

In this study, the absence of divorce in marital status in the healthy control group created a significant difference. There is no statistically significant difference in terms of other sociodemographic data (Table 1).

Considering the normality test results, other variables except motivation values were evaluated with parametric tests. When the substance use characteristics of the two groups of substance users were compared, a statistically significant difference was found in the duration of substance use ($p < 0.010$), and motivation (Mann Whitney U, $p < 0.031$) subtests. Duration of substance use and craving were higher in the synthetic substance group, and motivation was higher in the methamphetamine group (Table 2).

When the One-way ANOVA test was performed between the pre-detoxification uric acid values of all

Table 1. Sociodemographic data of sample groups

	MA Group (n = 44)	SC Group (n = 46)	HC Group (n = 40)	*p* value
Age (years) (mean ± SD)	32.59 ± 5.89	5.89 ± 8.29	32.67 ± 7.56	0.943
Educational background, n (%)				0.664
Primary school graduate	8 (18.2)	8 (17.4)	6 (15.0)	
High school graduate	29 (65.9)	34 (73.9)	26 (65.0)	
University graduate	7 (15.9)	4 (8.7)	8 (20.0)	
Marital status, n (%)				**< 0.050**
Married	19(43.2%)	17(37.0%)	24(60.0%)	
Single	18(40.9%)	21(45.7%)	16(40.0%)	
Widow/Divorced	7(15.9%)	8(17.3%)	0(0%)	
Working status, n (%)				0.526
Has a regular job	19 (43.2)	19 (41.3)	20 (50.0)	
No regular job	25 (56.8)	27 (58.7)	20 (50.0)	

SD = Standard deviation, MA = Methamphetamine, SC = Synthetic cannabinoid, HC = Healthy Control *$p < 0.05$,

Table 2. Comparison of substance use characteristics between two groups (with t-test and chi-square)

	MA Group (n = 44)	SC Group (n = 46)	*p* value
Age at onset of substance use	27.38 ± 7.85	25.46 ± 8.38	0.263
Duration of substance use	4.88 ± 2.81	6.78 ± 3.93	**0.010**
Substance use dose per a day, n (%)			0.538
Between 0.5-1 gr	17 (38.6)	15 (32.6)	
Over 1 gr	27 (61.4)	31 (67.4)	
Suicide attempt, n (%)	9 (20.5)	15 (30.4)	0.278
Substance use characteristics	2.26 ± 1.32	2.03 ± 1.39	0.431
Diagnosis	14.25 ± 4.99	13.71 ± 4.74	0.597
Effect of substance use on one's life	28.91 ± 9.70	28.70 ± 7.83	0.909
Craving	9.14 ± 3.96	9.70 ± 3.67	0.489
Motivation	10.82 ± 1.93	10.09 ± 2.12	**0.031**
API total score (Severity of addiction)	12.29 ± 3.04	11.96 ± 2.52	0.577

Data are shown as mean ± standard deviation or n (%). MA = Methamphetamine, SC = Synthetic cannabinoid

three groups, a statistically significant difference was found at the level of $p < 0.001$. It is seen that the group that made a significant difference in LSD posthoc tests was the healthy control group. The uric acid values of the healthy control group were statistically significantly higher than both drug user groups. There is no statistically significant difference between the pre-detoxification uric acid values of methamphetamine and synthetic substance users ($p = 0.431$), but there is a statistically significant difference between the methamphetamine group and the healthy control group ($p < 0.001$). There is a significant difference between uric acid values of synthetic substance users and healthy controls ($p < 0.001$). There was no statistically significant difference between pre-and post-detoxification the uric acid, creatinine values, and uric

Table 3. Uric acid, creatinine values, uric acid/creatinine ratios the pre-and post-detoxification

	MA Group (n = 44)	SC Group (n = 46)	HC Group (n = 40)	*p* value
Pre-detoxification uric acid	5.48 ± 0.97	5.14 ± 1.15	6.21 ± 1.10	**< 0.001**
Post-detoxification acid	5.36 ± 1.00	5.11 ± 1.47	-	0.371
***p* value**	0.467	0.870		
Pre-detoxification Creatinine	0.87 ± 0.12	0.83 ± 0.13	0.80 ± 0.10	0.064
Post-detoxification Creatinine	0.83 ± 0.13	0.81 ± 0.14		
***p* value**	**0.022**	0.447		
Pre-detoxification UA/Crea ratio	6.39 ± 1.15	6.29 ± 1.59	7.82 ± 1.58	**< 0.001**
Post-detoxification UA/Crea ratio	6.54 ± 1.34	6.24 ± 1.83		
***p* value**	0.361	0.830		

Data are shown as mean ± standard deviation or n (%). MA = Methamphetamine, SC = Synthetic cannabinoid, HC = Healthy Control, UA/Crea = Uric acid/creatinine

Table 4. Comparison of pre-and post-detoxification values of uric acid, creatinine, and API subtest scores in the methamphetamine group according to Pearson Correlation Analysis

	UA-1	UA-2	Crea-1	Crea-2	Characteristics of SU	Diagnosis	Effect of SU on one's life	Craving	Motivation	API Total
UA-1	1	r = 0.49 ***p* < 0.001**	r = 0.42 ***p* = 0.040**	r = 0.08 *p* = 0.622	r = 0.05 *p* = 0.712	r = 0.13 *p* = 0.388	r = 0.05 *p* = 0.713	03 *p* = 0.828	r = -0.06 *p* = 0.678	r = 0.09 *p* = 0.554
UA-2	r = 0.49 ***p* = 0.001**	1	r = 0.12 *p* = 0 .449	r = 0.34* ***p* = 0.034**	r = 0.27 *p* = 0.081	r = 0.26 *p* = 0.096	r = 0.22 *p* = 0.159	r = 0.05 *p* = 0.717	r = 0.19 *p* = 0.238	r = 0.26 *p* = 0.096
Crea-1	r = 0.42 ***p* = 0.040**	r = 0.12 *p* = 0.449	1	r = 0.62** ***p* < 0.001**	r = 0.15 *p* = 0.332	r = 0.32 ***p* = 0.030**	r = 0.12 *p* = 0.402	r = 0.19 p=0.198	r = 0.23 p=0.134	r = 0.27 p=0.070
Crea-2	r = 0.08 *p* = 0.622	r = 0.34 ***p* = 0.034**	r = 0.62** ***p* < 0.001**	1	r = 0.27 *p* = 0.092	r = 0.25 *p* = 0.122	r = 0.04 *p* = 0.793	r = 0.05 *p* = 0.729	r = 0.17 *p* = 0.285	r = 0.20 *p* = 0.215

UA = Uric acid, UA-1 = Pre-detoxification uric acid, UA-2 = Post-detoxification uric acid, Crea-1 = Pre-detoxification creatinine, Crea-2 =Post-detoxification creatinine SU = Substance use, API = Addiction Profile Index

acid/creatinine ratios in methamphetamine and synthetic substance users. The pre-detoxification creatinine values were statistically different between the methamphetamine and healthy groups ($p = 0.021$).

The pre-detoxification uric acid/creatinine ratio was statistically different between the three groups. While the healthy group created a statistically significant difference from the substance user groups, there was no significant difference between the methamphetamine and synthetic substance user groups (Table 3).

In the methamphetamine group, pre-detoxification uric acid, post-detoxification uric acid (r = 0.49, $p < 0.001$), and pre-detoxification creatinine (r = 0.42, $p = 0.040$) values were positively correlated. The post-detoxification uric acid value correlated with the post-detoxification creatinine value (r = 0.34, $p = 0.034$). There was also a positive correlation between the pre- and post-detoxification creatinine values (r = 0.62, $p < 0.001$). The pre-detoxification creatinine value was correlated with the API diagnostic criteria subscale (r = 0.32, $p = 0.030$) (Table 4).

In the synthetic substance group, the pre-detoxification uric acid was positively correlated with post-detoxification uric acid values (r = 0.67, $p < 0.001$). There was also a positive correlation between the pre- and post-detoxification values of creatinine (r < 0.69, $p < 0.001$). (Table 5).

DISCUSSION

In this study, serum UA values in pre-detoxification were found to be statistically significantly lower in MAG and SCG compared to CG. This low level suggests that purinergic transformation due to substance use may decrease in case groups. Future studies may focus on the evaluation of the purinergic system components in individuals with substance use disorders (SUD).

In the literature, the use of MA and SC has been reported to increase oxidative stress and inflammation in the CNS. Increased oxidative stress and proinflammatory cytokines in MA abusers cause inflammation in the CNS [20]. The most effective of the compounds in SC is tetrahydrocannabinol [21]. Cannabis use has been clarified to increase oxidative stress and inflammation [22].

Table 5. **Comparison of pre-and post-detoxification uric acid and creatinine values in the synthetic substance group with API sub-test scores according to Pearson Correlation Analysis**

	UA-1	UA-2	Crea-1	Crea-2	Characteristics of SU	Diagnosis	Effect of SU on one's life	Craving	Motivation	API Total
UA-1	1	r = 0.67 **$p < 0.001$**	r = 0.28 $p = 0.054$	r = 0.09 $p = 0.540$	r = -0.13 $p = 0.361$	r = 0.11 $p = 0.453$	r = -0.01 $p = 0.900$	r = 0.05 $p = 0.743$	r = - 0.09 $p = 0.515$	r = 0.03 $p = 0.805$
UA-2	r = 0.67 **$p < 0.001$**	1	r = 0.21 $p = 0.168$	r = 0.23 $p = 0.139$	r = -0.21 $p = 0.165$	r = -0.05 $p = 0.744$	r = -0.27 $p = 0.076$	r = -0.09 $p = 0.553$	r = 0.00 $p = 0.979$	r = 0.19 $p = 0.220$
Crea-1	r = 0.28 $p = 0.054$	r = 0.21 $p = 0.168$	1	r = 0.69 **$p < 0.001$**	r = 0.04 $p = 0.752$	r = 0.19 $p = 0.186$	r = 0.08 $p = 0.583$	r = 0.25 $p = 0.086$	r = 0.08 $p = 0.583$	r = 0.21 $p = 0.144$
Crea-2	r = 0.21 $p = 0.16$	r = 0.23 $p = 0.139$	r = 0.69 **$p < 0.001$**	1	r = 0.19 $p = 0.232$	r = 0.13 $p = 0.395$	r = -0.03 $p = 0.819$	r = 0.21 $p = 0.174$	r = -0.00 $p = 0.986$	r = 0.16 $p = 0.310$

UA = Uric acid, UA-1 = Pre-detoxification uric acid, UA-2 = Post-detoxification uric acid, Crea-1 = Pre-detoxification creatinine, Crea-2 = Post-detoxification creatinine SU = Substance use, API = Addiction Profile Index

Oxidation products formed as a result of substance use are cleared by uric acid, a powerful antioxidant of plasma [14]. In this study, the low serum uric acid levels in case groups compared to CG were thought to maybe related to their consumption as an antioxidant. In this study, the fact that serum uric acid levels did not show a statistically significant difference in both case groups compared to the control group during the withdrawal period was thought to be related to the decrease in UA consumption in plasma as a result of the decrease in oxidative stress and plasma oxidation products after treatment.

In our study, pre- and post-detoxification uric acid and creatinine levels were positively correlated in the case groups. Both uric acid and creatinine are antioxidant substances in plasma [14, 23]. It is thought that there may be a positive correlation due to the decrease in consumption of uric acid and creatinine levels in the tissues during the period of substance withdrawal.

It has been stated that uric acid can prevent neuronal death by being a strong antioxidant of plasma, reducing systemic inflammation and decreasing permeability in the blood-brain barrier [24]. In SUD, a low uric acid level can lead to an increase in oxidation products, especially free radicals, and neuron damage in the plasma. Our findings suggest that antioxidant defense may be decreased due to uric acid reduction in SUD. As a result, the low uric acid level may contribute to oxidative damage.

In our study, the serum uric acid levels of the case group before detoxification were figured out not to be related to the severity of the addiction. Studies on the relationship between low serum uric acid levels and oxidative stress and inflammation status are limited in the literature. New studies are needed to support our findings in the study.

In the comparison of the case groups in our study, motivation in MAG, craving, and duration of substance use in SCG were high. Although high motivation is a positive factor for treatment, it is accepted that it increases the severity of the addiction. Craving increases the API scores and the severity of addiction [19].

It was thought that the higher craving in the SCG group compared to MG might be related to multiple substance use. As anticholinergic, synthetic opioid, etc. substances are added to strengthen the effect of synthetic cannabinoids, SC can be considered as a

multi-substance in practice. When using synthetic cannabinoids, substance users are also exposed to multi-substance intoxication due to the many chemicals sprayed into them [25]. Individuals with multiple substance use experience more severe withdrawal symptoms and have higher relapse rates [26]. In the CNS substance exposure has been reported to cause craving and impairment in cognitive functions [27]. Therefore, treatment of this inflammation can reduce craving [28, 29].

Systemic inflammation has been mentioned to maybe persist for years in individuals using substances during the withdrawal period [30].

In our clinical practice, we observe that craving and impairment in cognitive functions during the withdrawal period of SUD patients complicate the treatment of patients. Our findings suggest that antioxidant defense may be decreased due to reduced uric acid in methamphetamine use disorders. Evaluation of serum uric acid levels may be useful in the treatment of patients with SUD.

Low uric acid levels are can be corrected with diet and pharmacological intervention. In order to support the findings of our study, new studies evaluating serum uric acid levels in patients with SUD are required.

Limitations

This study has some limitations. First, the relatively small number of male subjects did not evaluate uric acid levels in the long term after withdrawal. The female gender was excluded from the study. A large sample study involving both genders can be done in the future. Although a certain diet was recommended for hospitalized patients, a light diet was recommended for healthy controls 1 day before blood collection. However, the dietary compliance of the groups may be different. In this study, the levels of purine metabolites other than uric acid were not evaluated and their relationship with each other could not be understood. Finally, not evaluating the oxidative stress products and oxidant/antioxidant balance in the participants is among the limitations of our study.

CONCLUSION

SUA levels were found to be statistically significantly different in individuals with MA and SC exposure compared to healthy controls. These results did not change when we consider the glomerular filtration rate. In this study, it could not be evaluated whether the lower uric acid levels in the case group compared to the control group were due to the use of uric acid as an antioxidant or to a decrease in purinergic transformation. Future studies may focus on making this distinction.

Authors' Contribution

Study Conception: ÇT; Study Design: ÇT, SÜ; Supervision: ÇT, SÜ; Funding: ÇT; Materials: ÇT, SÜ; Data Collection and/or Processing: ÇT; Statistical Analysis and/or Data Interpretation: ÇT, SÜ; Literature Review: ÇT, SÜ; Manuscript Preparation: ÇT, SÜ and Critical Review: SÜ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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