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The Relationship of Serum Uric Acid, Serum Uric Acid Creatinine Ratios With Disease Severity and Metabolic Syndrome in Schizophrenia Patients

Şizofreni Hastalarında Serum Ürik Asit, Serum Ürik Asit Kreatinin Oranlarının Hastalık Şiddeti Ve Metabolik Sendrom İle İlişkisi

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ABSTRACT

Aim: The objective of this research was to examine the association between serum uric acid (SUA) and serum uric acid/creatinine ratio (SUA/Cre), disease severity and metabolic syndrome in schizophrenia with a multifaceted etiopathogenesis.
Methods: The study comprised 240 participants in total, 120 of whom were healthy controls and 120 of whom were schizophrenia patients. Sociodemographic, clinical and laboratory data was collected and metabolic syndrome was assessed according to the established criteria. SUA and creatinine levels were measured and the SUA/Cre ratio was calculated. The severity of the disease was evaluated utilizing the Positive and Negative Syndrome Scale (PANSS). Statistical analyses were conducted to ascertain correlations and associations.
Results: SUA levels and SUA/Cre ratio higher in schizophrenia patients than controls (p=0.14, p=0.010, respectively). SUA/Cre ratio was positively correlated with PANSS negative score (r=0.266, p=0.03). SUA levels were elevated in individuals diagnosed with schizophrenia who also had metabolic syndrome, in comparison to those who did not have metabolic syndrome (p=0.009). Linear regression analyses showed that the association between SUA levels and SUA/Cre ratio and schizophrenia persisted when the effects of gender, age, metabolic syndrome, BMI and smoking were fixed.
Conclusions: This study highlights the association of SUA and SUA/Cre ratio with disease severity and metabolic syndrome among individuals diagnosed with schizophrenia.

Keywords: Schizophrenia, Uric acid, Uric acid creatinine ratio, Metabolic syndrome, Disease severity

ÖZ

Amaç: Bu araştırmanın amacı çok yönlü etiyopatogeneze sahip şizofrenide serum ürik asit (SUA) ve serum ürik asit/kreatinin oranı (SUA/Cre) ile hastalık şiddeti ve metabolik sendrom arasındaki ilişkiyi incelemektir.
Yöntem: Çalışmaya 120'si sağlıklı kontrol ve 120'si şizofreni hastası olmak üzere toplam 240 katılımcı dahil edilmiştir. Sosyodemografik, klinik ve laboratuvar verileri toplandı, kriterlere göre metabolik sendrom durumu değerlendirildi. SUA ve kreatinin düzeyleri ölçülmüş ve SUA/Cre oranı hesaplanmıştır. Hastalığın şiddeti Pozitif ve Negatif Sendrom Ölçeği (PANSS) kullanılarak değerlendirilmiştir. Korelasyon ve ilişkileri tespit etmek için istatistiksel analizler yapılmıştır.
Bulgular: SUA düzeyleri ve SUA/Cre oranı şizofreni hastalarında kontrol grubuna göre daha yüksekti (sırasıyla p=0.14, p=0.010). SUA/Cre oranı PANSS negatif skoru ile pozitif korelasyon gösterdi (r=0.266,p=0.03). SUA düzeyleri, metabolik sendromu da olan şizofreni tanılı bireylerde, metabolik sendromu olmayanlara kıyasla daha yüksekti (p=0.009). Doğrusal regresyon analizleri, SUA düzeyleri ve SUA/Cre oranı ile şizofreni arasındaki ilişkinin cinsiyet, yaş, metabolik sendrom, BMI ve sigara içmenin etkileri sabitlendiğinde de devam ettiğini göstermiştir.
Sonuç: Bu çalışma, şizofreni tanısı almış bireylerde SUA ve SUA/Cre oranının hastalık şiddeti ve metabolik sendrom ile ilişkisini vurgulamaktadır.

Anahtar Kelimeler: Şizofreni, Ürik asit, Ürik asit kreatinin oranı, Metabolik sendrom, Hastalık şiddeti

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Introduction

Schizophrenia is a psychiatric picture of chronic deterioration with a rate of approximately 1% in the population. In this psychiatric context, there are many psychiatric findings including hallucinations, delusions, disorganised speech and behavior. Although etiopathogenesis is still unclear, it has been reported that a number of factors may be responsible [1]. Although the role of dopaminergic, serotonergic and glutamatergic pathways in the etiology is emphasized, the immune system, inflammation, oxidative stress and related pathways are considered to play a role. It is thought that these pathways may be important in the evaluation of parameters not only in the etiology, but also the clinical course and response to treatment [2].

Uric acid is formed in the body from a compound called purine. Purines are involved in the purinergic cycle, a cycle that cells use to produce energy. In this cycle, they react with oxygen and are converted into uric acid, which in turn acts as an antioxidant in the body and fights free radicals. Free radicals are molecules that damage cells and lead to a condition called oxidative stress [3]. The formation and evolution of mental diseases are both significantly influenced by oxidative stress, which is a fundamental component. Thus, serum uric acid levels (SUA) have been associated with psychiatric disorders. In schizophrenia and some psychiatric disorders, SUA levels are lower than normal [4, 5]. This may indicate disruption of the purinergic cycle or decreased antioxidant activity [5]. However, some studies have also reported that SUA levels are higher than normal in patients with schizophrenia [6, 7]. This may suggest that the body produces uric acid as a defence mechanism against oxidative stress or when uric acid excretion is reduced [6]. The fact that the level of SUA gives different results in various neurological and psychiatric diseases suggests that its effect on diseases cannot be explained only by its antioxidant properties.

The presence of abdominal obesity, insulin resistance, dyslipidemia and hypertension are the defining characteristics of the metabolic syndrome, which is the principal condition. Individuals who receive a diagnosis of metabolic syndrome and satisfy the specified criteria are exposed to various risks including coronary diseases, type 2 diabetes and premature death [8]. The association between schizophrenia and metabolic syndrome predates the introduction of antipsychotic drugs in the 1950s [9]. Individuals diagnosed with schizophrenia or schizoaffective disorder, who have not previously received antipsychotic medication, have demonstrated hepatic insulin resistance in comparison to a control group. This implies that there may exist a direct relationship between schizophrenia and insulin resistance, regardless of the administration of antipsychotic medication [10].

The serum uric acid creatinine (SUA/Cre) ratio is a parameter that can be used to assess SUA levels independently of renal function. Since uric acid is metabolised in the kidney and excreted in the urine, serum uric acid concentration may vary according to age and gender. Therefore, both SUA levels and SUA/Cre ratios were compared in the studies. The SUA/Cre ratio was developed and used to reduce the interference on SUA caused by gender and renal function [11].

To the best of our knowledge, the relationship between SUA/Cre ratios and schizophrenia has not been investigated in the literature. The objective of our research was to examine the association between SUA, SUA/Cre ratios with disease severity and metabolic syndrome in schizophrenia patients.

Material methods

Study setting

The investigation was conducted at the psychiatry outpatient clinic and ward of Kütahya Evliya Çelebi Training and Research Hospital, involving patients diagnosed with schizophrenia according to DSM-V (Diagnostic Statistical Manual-V) criteria. The study employed a semi-structured interview method. The research received approval from the Ethics Committee of Kütahya Health Science University (2023/01-24). Each participant provided written informed permission to participate in this research.

Participant selection

A total of 240 participants were recruited,

comprising 120 individuals with schizophrenia (study group) and 120 healthy individuals (control group). Patients voluntarily agreed to participate and informed consent was obtained from either the participants themselves or their legal guardians. The control group included healthy people who were matched with the patient group based on age, gender and BMI. Participants in the control group sought medical attention for reasons unrelated to psychiatric disorders and willingly participated in the study.

Exclusion criteria

Participants with comorbid neurological diseases, chronic renal failure, gout, vegetarianism, chronic kidney disease, anemia, heart disease, obstructive pulmonary disease, chronic liver disease, chronic inflammatory bowel disease, thyroid dysfunction, tumors, cancer, active infections, excessive exercise habits, a history of steroid, colchicine, allopurinol, ascorbic acid, L-Dopa, alpha-methyldopa, isoniazid, isotretinoin, furosemide, indapamide, thiazide diuretics, antifungals, chemotherapeutics, excessive alcohol consumption or substance use, were all excluded.

Data collection

All participants completed a sociodemographic data form designed by the researcher, which included inquiries about age, gender and smoking habits. In the patient group, additional information was gathered, including age at onset of the disease, age at first treatment, age at first hospitalization, duration of illness (in years), time until treatment, number of hospitalizations, family history, suicide attempts and regular drug use. PANSS was employed to evaluate the intensity of pathological symptoms in the group diagnosed with schizophrenia. The publication was authored by Stanley Kay, Lewis Opler, and Abraham Fiszbein in the year 1987 [12]. Kostakoğlu et al. developed the Turkish version of the scale in 1999 [13].

Physical measurements

After completing the sociodemographic data form, height, weight, waist circumference and blood pressure were measured and recorded for each participant.

Metabolic Syndrome assessment

Each participant underwent evaluation for metabolic syndrome (MetS) using the criteria established by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III). MetS diagnosis required the presence of three or more of the following factors: abdominal obesity (waist circumference: M>102 cm, F>88 cm), hypertriglyceridemia (>150 mg/dL), low HDL (M<40 mg/dL, F<50 mg/dL), hypertension (BP>130/85 mmHg), and hyperglycemia (fasting blood glucose>110 mg/dL) [14].

Biochemical analysis

Biochemical blood parameters, including fasting blood glucose, triglyceride, HDL, uric acid, and creatinine levels, were determined from venous blood samples obtained after an 8-hour fasting period.

Statistical analysis

The Statistical Package for the Social Sciences (Version 22, SPSS Inc., Chicago, IL, USA) was used to analyse the data. The Kolmogorov-Smirnov test, the Shapiro-Wilk test and some histograms were used to evaluate the normality of distributions. Normally distributed data was expressed as mean + SD, non-normally distributed data was expressed as median (min-max) and categorical data was expressed as n (%). An independent sample test was used for normally distributed parameters and the Mann Whitney U test was used for non-normally distributed parameters. The Chi-square and Fisher Exact tests were used to compare categorical data. The Pearson correlation test was used for correlation analyses. Linear regression analysis was used to evaluate the parameters that may affect serum uric acid and SUA/Cre ratios. p significance value was considered significant as two-way and <0.05.

Results

Table 1 compares the demographic, clinical and laboratory characteristics of schizophrenia patients and healthy control group. It shows clinical characteristics of schizophrenia patients such as age at onset of illness, age at first treatment, age at first hospitalization, duration of illness, time to treatment, number of hospitalizations,

family history, suicide attempt, regular medication use, regular follow-up visits and PANNS scores. Schizophrenia patients and controls are similar in terms of age, body mass index (BMI), gender, systolic and diastolic blood pressure, fasting blood glucose, creatinine and metabolic syndrome. However, patients with schizophrenia had significantly higher smoking rates, triglycerides, waist circumference, SUA, and SUA/Cre ratio compared to the control group (p=0.001, p=0.38, p=0.001, p=0.14, p=0.010, respectively). In addition, HDL levels of patients with schizophrenia were significantly lower compared to the control group (p=0.001).

Table 1. Demographic, clinical and laboratory characteristics of the patient and control groups

Parameters		Patient (n=120)	Control (n=120)	p value
Age		45.3 ± 10.4	46.2 ± 10.3	0.516*
BMI (kg/m2)		28.3 ± 5.9	29.2 ± 4.6	0.199*
Gender	Female	53(44.2%)	65(54.2%)	0.121**
	Male	67(55.8%)	55(45.8%)	
Smoking		70(58.3%)	41(34.2%)	0.001**
Systolic blood pressure (mmHg)		124.3 ± 10.5	126.2 ± 8.4	0.120*
Diastolic blood pressure (mmHg)		78.8 ± 7.9	80.4 ± 6.9	0.084*
Fasting blood glucose (mg/dL)		113.3 ± 33.5	118.7 ± 23.3	0.145*
Triglyceride (mg/dL)		192.4 ± 139.0	163.3 ± 62.8	0.038*
HDL (mg/dL)		41.1 ± 9.9	45.7 ± 10.5	0.001*
Waist circumference(cm)		92.5 ± 13.1	86.7 ± 9.1	0.001*
Metabolic syndrome		57(47.5%)	55(45.8%)	0.796**
SUA levels (mg/dL)		5.7 ± 1.3	5.2 ± 1.6	0.014*
Creatinine (mg/dL)		1.0 ± 0.1	1.0 ± 0.2	0.713*
SUA/Cre ratio		6.0 ± 1.5	5.5 ± 1.6	0.010*
Age at disease onset		21.8 ± 5.3		
Age at first treatment		24.3 ± 6.3		
Age at first hospitalisation		25.3 ± 6.2		
Disease duration(years)		23.5 ± 9.7		
Time until treatment		2 (0 - 16)		
Number of hospitalizations		3 (0 - 20)		
Family history		39 (32.5%)		
Suicide attempt		30 (25.0%)		
Regular use of medication		27 (22.5%)		
Regular check-ups		103 (85.8%)		
PANNS Negative		25.2 ± 10.0		
PANNS Positive		18.1 ± 7.8		
PANNS General		44.5 ± 15.8		
PANNS Total		87.9 ± 30.3		

Data were given as mean± SD. * independent t test, ** Chi Square test(n%) , BMI: Body Mass Index, HDL: High Density Lipoprotein, SUA: Serum Uric Acid, SUA/Cre: Serum Uric Acid/ Creatinine, PANSS: Positive and Negative Syndrome Scale, p <0.05 was considered significant.

Table 2 compares the demographic, clinical and laboratory characteristics of schizophrenia patients according to the presence of metabolic syndrome. Patients with schizophrenia who were positive for metabolic syndrome had significantly higher BMI, systolic and diastolic blood pressure, fasting blood glucose, triglycerides, waist circumference and uric acid levels than patients with negative metabolic syndrome (p=0.001, p=0.001, p=0.001, p=0.001, p=0.001, p=0.001, p=0.001, p=0.009, respectively). In addition, HDL levels of schizophrenia patients with positive metabolic syndrome were significantly lower than those with negative metabolic syndrome (p=0.001). In addition, the PANNS general scores and the number of hospitalizations of schizophrenia patients with positive metabolic syndrome were significantly higher than those with negative metabolic syndrome (p=0.039, p=0.005, respectively).

The PANNS Negative Score has a weak positive correlation with the SUA/Cre ratios (r = 0.266, p = 0.03) and is not significantly correlated with SUA levels(p> 0.05) (Figure 1).

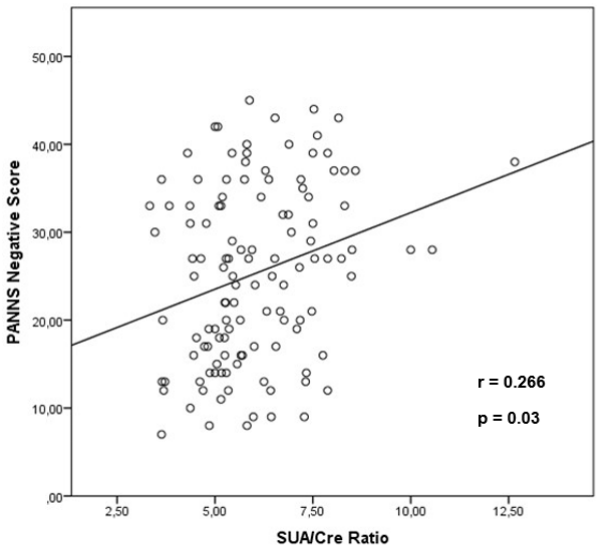

Figure 1. The Correlation between PANSS Negative Score and SUA/Cre Ratio

Table 3 analyses the factors affecting SUA level and SUA/Cre ratio by multiple linear regression analysis. There is a negative relationship between SUA level and age. This indicates that SUA level

Table 2. Comparison of the groups based on the presence or absence of metabolic syndrome within the patient group

Parameters	Metabolic syndrome negative (n=63)	Metabolic syndrome positive (n=57)	p value
Age	44.8 ± 9.8	45.8 ± 10.9	0.588*
BMI (kg/m2)	24.6 ± 4.0	32.3 ± 5.0	0.001**
Systolic blood pressure (mmHg)	120.8 ± 7.8	128.2 ± 11.6	0.001*
Diastolic blood pressure (mmHg)	75.4 ± 6.4	82.4 ± 7.9	0.001*
Fasting blood glucose (mg/dL)	96.8 ± 20.4	131.5 ± 35.7	0.001**
Triglyceride (mg/dL)	149.8 ± 88.6	239.3 ± 167.6	0.001**
HDL (mg/dL)	43.8 ± 11.0	38.0 ± 7.2	0.001*
Waist circumference(cm)	84.7 ± 10.4	101.1 ± 10.1	0.001**
SUA (mg/dL)	5.4 ± 1.2	6.0 ± 1.4	0.009*
Creatinine (mg/dL)	0.9 ± 0.1	1.0 ± 0.2	0.267*
SUA/Cre ratio	5.8 ± 1.5	6.3 ± 1.6	0.067*
PANNS Negative Score	24.2 ± 9.6	26.5 ± 10.5	0.208*
PANNS Positive Score	17.1 ± 7.5	19.4 ± 8.1	0.107*
PANNS General Score	41.7 ± 15.9	47.6 ± 15.2	0.039*
PANNS Total	82.9 ± 30.1	93.5 ± 29.9	0.056*
Age at disease onset	22.1 ± 5.6	21.5 ± 5.2	0.566*
Age at first treatment	24.7 ± 6.8	23.8 ± 6.0	0.424*
Age at first hospitalization	25.9 ± 6.7	24.8 ± 5.8	0.378*
Disease duration(years)	22.8 ± 9.0	24.3 ± 10.5	0.381*
Time until treatment	2 (0 – 15)	1 (0 – 16)	0.388*
Number of hospitalizations	3 (0 – 12)	5 (0 – 20)	0.005*

Data were given as mean± SD. * independent t test, **Mann Whitney U test

BMI: Body Mass Index, HDL: High Density Lipoprotein, SUA: Serum Uric Acid, SUA/Cre: Serum Uric Acid/ Creatinine, PANSS: Positive and Negative Syndrome Scale, p <0.05 was considered significant.

Table 3. Regression analysis for SUA and SUA/Cre ratio between age, sex, metabolic syndrome, BMI, smoking and groups

Dependent variable: SUA	B	SE		95%Cl (LL/UL) for B	p-value
Age	-.032	.009	-.228	-.050 / -.015	0.001
Gender	.204	.188	.070	-.167 / .575	0.279
Metabolic syndrome	.142	.243	.048	-.338 / .621	0.561
BMI	.023	.023	.085	-.022 / .069	0.308
Smoking	-.223	.193	-.076	-.604 / .159	0.251
Group	.382	.189	.130	.010 / .754	0.044
Dependent variable: SUA/Cre ratio	B	SE		95%Cl (LL/UL) for B	p-value
Age	-.043	.010	-.276	-.062 / -.024	0.001
Gender	-.073	.203	-.023	-.473 / .327	0.719
Metabolic syndrome	-.158	.262	-.049	-.675 / .359	0.547
BMI	.050	.025	.164	.001 / .098	0.046
Smoking	-.050	.209	-.016	-.461 / .361	0.811
Group	.536	.204	.167	.135 / .937	0.009

For SUA: R square; 0,10, Adjusted R Square; 0,79

For SUA/Cre ratio: R square; 0,125, Adjusted R Square; 0,102

BMI: Body Mass Index, SUA: Serum Uric Acid, SUA/Cre: Serum Uric Acid/ Creatinine

decreases with increasing age. No significant relationship was found between SUA level and gender, metabolic syndrome, BMI and smoking. There was a positive correlation between SUA level and group. This shows that SUA levels in schizophrenia patients are significantly higher than the healthy control group. There was a negative relationship between SUA/Cre ratio and age,

which indicates that the SUA/Cre ratio decreases as age increases. No significant relationship was found between the SUA/Cre ratio and gender, metabolic syndrome and smoking. There was however a positive relationship between SUA/Cre ratio and BMI, which shows that as BMI increases, the SUA/Cre ratio also increases. There was also a positive relationship between the SUA/Cre ratio and the group, which in turn indicates that the SUA/Cre ratio of schizophrenia patients is significantly higher than the healthy control group.

Discussion

In our study, SUA levels and SUA/Cre ratios were found to be high in patients with schizophrenia. As far as the available literature indicated, our study is the first study showing the relationship between schizophrenia patients and SUA/Cre ratio.

SUA levels have been investigated in psychiatric and many other diseases due to their activity via antioxidant mechanisms. There is a possible connection between SUA and mental problems, according to the findings of several studies [5, 7]. A study conducted in Egypt examined the levels of SUA as a biomarker in patients diagnosed with schizophrenia, major depressive disorder, and bipolar affective disorder. The study revealed that SUA levels were elevated specifically in patients with schizophrenia [15]. Similar to our study, when fifty-five schizophrenia patients and a healthy control group were analysed in a 5-year follow-up study, high SUA levels were found in the stable stage of schizophrenia compared to healthy controls when standardized according to age, gender and smoking habits [6]. Yao et al. found that the levels of SUA were notably reduced in patients with schizophrenia when compared to healthy individuals, which contradicts our own results [4]. Similarly, in a meta-analysis conducted in 2020, no significant difference was found in SUA levels between schizophrenia patients and healthy controls [16].

In the literature, there are also studies investigating SUA levels according to the clinical phases of schizophrenia patients [16-18] Reddy et al. found that patients with first-episode schizophrenia had significantly lower SUA levels than healthy controls [17]. In contrast to this study, Malewska-Kasprzak et al. found no difference in SUA concentration between schizophrenia patients in the acute and remission phases [18]. When the studies conducted to date are evaluated, it remains unclear whether SUA levels are elevated at the onset of schizophrenia or because of the progression of the disease. These studies show that SUA levels may be associated with schizophrenia, but this relationship is not related to the etiology. Studies have also shown that elevated SUA levels are associated with higher oxidative stress and more inflammation in patients with schizophrenia. Nevertheless, the exact relationship between schizophrenia, oxidative stress and endogenous antioxidant levels remains unclear and requires further studies [6].

At the same time, it should not be forgotten that SUA levels may be affected by antipsychotics [19]. It was not possible to explain the clear effects of antipsychotic drugs on SUA for the reason that the patient population in our study consisted of patients with chronic schizophrenia, multiple drug use, duration of drug use and dose changes during the treatment process.

In our study, the SUA/Cre ratio was found to be high in patients with schizophrenia. In the literature, the SUA/Cre ratio has been investigated in many clinical conditions such as hypertension, diabetes, kidney diseases and heart diseases in recent years [11, 20]. Some studies even show that the SUA/Cre ratio may be a better prognostic marker than the SUA level in the diagnosis, prognosis and treatment of diseases. Similarly, the SUA/Cre ratio was found to be a better marker than the SUA in our study. This was associated with the fact that SUA/Cre ratio better reflects endogenous uric acid production [20].

In our study, the SUA/Cre ratio was also found to be associated with the negative score of PANNS, which is an indicator of clinical severity. However, this relationship was not found with the SUA level. There are no studies in the literature examining the SUA/Cre ratio and clinical severity; however, there are studies examining SUA and clinical severity [7, 15, 18, 21]. Like our study, no correlation was observed between SUA levels and PANSS scores in these studies [7, 15, 18]. However, Borovcanin et al. found a relationship between SUA level and clinical severity in their

study [21]. Negative symptoms are one of the indicators of poor prognosis in schizophrenia that may be resistant to treatment. It includes important symptoms affecting functioning such as social withdrawal, decreased emotional expression, lack of motivation, anhedonia, and avolition. Many studies emphasize the role of inflammation and oxidative stress in contributing to the severity of negative symptoms in schizophrenia [22]. It suggests that patients with worse clinical findings have higher oxidative stress and more inflammation.

It should be borne in mind that uric acid disorders may not only be a consequence of the disease but also of metabolic abnormalities such as smoking, weight gain, abdominal obesity, dyslipidemia, hypertension or insulin resistance [11, 23]. There is significant evidence in the literature supporting the relationship between metabolic syndrome and SUA levels [24]. Various research has examined the association between SUA levels and metabolic syndrome, highlighting the possible influence of uric acid on metabolic syndrome [24, 25]. In our study, when schizophrenia patients were examined according to the association of metabolic syndrome, SUA level was found to be significantly higher in schizophrenia patients with metabolic syndrome, while there was no difference between the two groups in terms of SUA/Cre ratio. In a study investigating the relationship of SUA concentration with metabolic syndrome in schizophrenia and schizoaffective disorder, it was found that metabolic syndrome was more common in patients with high SUA levels [25].

Our study had some limitations. The medications and doses of the patients for schizophrenia treatment were different from each other. It was challenging to assess the impact of antipsychotic medications since the research was carried out with a group of patients with varying levels of therapy. Eating habits and life activities such as exercise may differ for the patient and control groups. Larger sample groups and longitudinal studies are needed.

Conclusion

SUA and SUA/Cre ratios were found to be higher in schizophrenia patients. In addition, the SUA/Cre ratio was found to be higher in schizophrenia patients with negative symptoms. Therefore, we think that SUA concentrations and SUA/Cre ratio may be a biomarker that can be used in diagnosis or treatment follow-up.

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