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Do Metabolic Syndrome Components and Psoriatic Arthritis Affect the Uric Acid Level?

Metabolik Sendrom Komponentleri ve Psoriatik Artrit Ürik Asit Seviyelerini Etkiler mi?

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ABSTRACT Objective: Hyperuricemia is common in psoriatic arthritis (PsA). The aim of this study is to investigate the effect of PsA and metabolic syndrome (MS) components on serum uric acid (SUA). **Material and Methods:** A total of 102 adult individuals (53 females and 49 males) participated in this study. Fifty-one consecutive PsA patients followed and treated in the outpatient clinic between April 2011 and 2012 were enrolled in this study retrospectively. The control group consisted of 51 patients who have arthralgia but not arthritis. Insulin resistance was calculated according to the homeostasis model of assessment insulin resistance (HOMA-IR) formula. Patients were classified as having MS according to the National Cholesterol Education Program/Adult Treatment Panel definition. **Results:** SUA levels were higher in MS (p=0.016), but when adjusted for age, this difference was not found to be statistically significant. It was found that hypertension (HT), triglyceride (TG) and HOMA-IR which are important components of MS had an effect on SUA level but the effect of PsA on SUA was not found. SUA level was higher in patients with HT, TG and HOMA-IR elevation than those without (respectively, p=0.009, p=0.005, p=0.001). It was observed that PsA had no effect on SUA, but when adjusted for age, the UA level in PsA was found to be significantly higher (p=0.027). **Conclusion:** MS, which is a major risk factor for atherosclerosis, is increased in PsA. However, this increase may also be associated with higher age in PsA patients. It is known that there is a relationship between cardiovascular events and high SUA levels. SUA is known to play a potential role as a risk factor for atherosclerosis and related diseases. More studies are needed to investigate the effects of PsA and MS components on SUA levels.

Keywords: Metabolic syndrome; psoriatic arthritis; uric acid; insulin resistance

ÖZET Amaç: Hiperürisemi, psöriyatik artritte (PsA) yaygın görülmektedir. Bu çalışmanın amacı, PsA ve metabolik sendrom (MS) bileşenlerinin, serum ürik asit (SUA) üzerindeki etkisini incelemektir. **Gereç ve Yöntemler:** Bu çalışmaya, toplam 102 (53 kadın ve 49 erkek) erişkin birey katıldı. Çalışmaya, Nisan 2011-2012 tarihleri arasında poliklinikte takip ve tedavi edilen 51 ardışık PsA hastası retrospektif olarak alındı. Kontrol grubu, artraljisi olan ancak artriti olmayan 51 hastadan oluşuyordu. İnsülin direnci, insülin direncini değerlendirme (HOMA-IR) formülünün homeostaz modeline göre hesaplandı. Ulusal Kolesterol Eğitim Programı/Yetişkin Tedavi Paneli tanımına göre hastalar MS'li olarak sınıflandırıldı. **Bulgular:** SUA seviyeleri MS'de daha yüksekti (p=0,016), fakat yaşa göre düzeltme yapıldığında bu farkın, istatistiksel olarak anlamlı olmadığı tespit edildi. MS'nin önemli bileşenleri olan hipertansiyon (HT), trigliserid (TG) ve HOMA-IR'nin SUA düzeyi üzerine etkisi olduğu, ancak PsA'nın SUA üzerine etkisinin olmadığı bulundu. SUA düzeyi HT, TG ve HOMA-IR yüksekliği olan hastalarda, olmayanlara göre daha yüksekti (sırasıyla; p=0,009, p=0,005, p=0,001). PsA'nın SUA üzerine etkisinin olmadığı, ancak yaşa göre düzeltme yapıldığında PsA'da, SUA düzeyinin anlamlı şekilde yüksek saptandığı görüldü (p=0,027). **Sonuç:** Ateroskleroz için önemli bir risk faktörü olan MS, PsA'da artmıştır. Fakat bu artış, PsA hastalarındaki yüksek yaşla da ilişkili olabilir. Kardiyovasküler olaylar ile yüksek SUA seviyeleri arasında ilişki olduğu bilinmektedir. SUA'nın, ateroskleroz ve ilgili hastalıklar için bir risk faktörü olarak potansiyel bir rol oynadığı bilinmektedir. PsA ve MS bileşenlerinin, SUA seviyeleri üzerindeki etkilerini araştırmak için daha fazla sayıda çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Metabolik sendrom; psöriyatik artrit; ürik asit; insülin direnci

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Psoriatic arthritis (PsA) is a usually rheumatoid factor negative, chronic inflammatory type of arthritis associated with psoriasis.[1] Cardiovascular diseases (CVD) morbidity and mortality risk is raised in PsA patients. Chronic inflammation in PsA patients is generally related to increased atherosclerosis incidence. The raised atherosclerosis and CVD incidence associated with PsA has been reported in many studies.[2,3]

Metabolic syndrome (MS) is a major preventable risk factor for atherosclerosis and comprises components such as obesity, hypertriglyceridemia, hypertension (HT) and insulin resistance (IR).[3-5] These components are associated with greater cardiovascular morbidity than the sum of the risks associated with each component.[4]

It implies a potential role for serum uric acid (SUA) as a risk factor for atherosclerosis and associated diseases.[6] Patients with HT and hyperuricemia compared to patients who have normal SUA levels have more than 3-5 times the risk of cardiovascular or cerebrovascular disease. SUA is an indicator of increased oxidative stress. High SUA concentrations show high probability in coronary artery disease, heart failure and cardiovascular mortality.[7]

In literature, many studies have shown the relationship between the components of MS and SUA levels.[8,9] SUA is an independent MS indicator.[10,11] Hyperuricemia in psoriasis is closely associated with obesity and hyperlipidemia that are components of MS.[7,12,13] IR is the main mechanism linking visceral obesity and the MS, and determine the SUA increase in MS.[8] The increased relationship between SUA with MS and PsA have been reported previously but the effect of MS and PsA on SUA levels have not been investigated together.[14] In the study, we planned to explore the relationship of PsA with MS; to examine the effect of PSA and MS components on SUA.

MATERIAL AND METHODS

PARTICIPANTS

In the study, the patients who were followed and treated in the rheumatology outpatient clinic between April 2011 and 2012 were enrolled retrospectively. Patients who had PsA according to classification criteria for psoriatic arthritis were accepted in the PsA group and who had arthralgia but not arthritis like ankylosing spondylitis, rheumatoid arthritis, osteoarthritis, spondyloarthritis etc. were accepted in the control group.[15] Those with myocardial infarction, stroke, psychiatric disorder and renal failure (serum creatinine >1.4 mg/dL) history were excluded.

Demographic characteristics (age, height, weight, gender), history of diabetes mellitus (DM), HT, medication, and smoking habits, waist circumference (WC), blood pressure, fasting blood glucose, insulin, lipid profiles, uric acid (UA), blood urea and creatinine were registered from their files. IR was computed according to Homeostasis Model of Assessment Insulin Resistance [(HOMA-IR) formula: Fasting insulin (μu/mL) x Fasting glucose ((mg/dL)/405)]. HOMA value in normal individuals has been reported as lower than 2.7, more than 2.7 reflects the varying degrees of IR.[16] The study protocol was approved by the Haydarpaşa Numune Training and Research Hospital, Clinical Research Ethics Committee (decision number: 2012/14, date: 09.04.2012) dated ethical committee. Permission was obtained from the patients or, if necessary, their legal representative. The present study was planned according to the Declaration of Helsinki Principles.

METABOLIC SYNDROME DEFINITION

Subjects were grouped as having MS or not by following per under the National Cholesterol Education Program (NCEP)/Adult Treatment Panel III definition. According to the NCEP guidelines, individuals were diagnosed with MS if they had at least three of the components: (I) Increased waist circumference (WS) (WC >102 cm in males and >88 cm in females); (II) HT: ≥130/85 mmHg or receiving antihypertensive drugs; (III) Impaired fasting glucose ≥110 mg/dL or receiving antidiabetic drugs; (IV) Low high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in males or <50 mg/dL in females; (V) Elevated triglycerides >150 mg/dL.[17]

STATISTICAL ANALYSIS

The IBM-SPSS for windows version 20 software (IBM Corp., Armonk, NY, USA) was used for analyses. Descriptive statistics were given as mean and

standard deviation for numerical data and categorical variables were expressed as percentages. The normal distribution of the numerical variable was identified with analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Pearson chi-square was used to analyse sex and independent t-test was used to analyse age and body mass index (BMI) between groups. MS criteria were investigated by the chi-squared test or/and Ficher's exact chi-squared test between groups. The effects of each of the MS components on SUA separately and the effect of the PsA on SUA were analyzed by one-way ANOVA. The effect of PsA interaction with MS components on UA was tested with two-way ANOVA. Statistical significance was accepted at $p \leq 0.05$.

RESULTS

In present study, 102 elderly participants (53 females 49 males) participated. Fifty-one consecutive PsA patients followed and treated in the outpatient clinic between April 2011 and 2012 were enrolled in this study retrospectively. The control group consisted of 51 patients who have arthralgia but not arthritis. There was no difference in sex and BMI ($p>0.05$). There was a difference in age between groups ($p<0.001$). Mean age of the PsA group was higher. Demographic characteristics were given in Table 1.

There was a difference in the current smoker, MS, HT between groups ($p=0.005$, $p=0.004$, $p=0.050$, respectively). But when adjusted for age, this differences were not found to be statistically significant. The number of smokers in the control group (54.9%) were higher than in the PsA group (27.5%) and the number of patients who were diagnosed with MS and/or HT were higher in the PsA group. There was no difference in DM, IR, increased WC, low HDL-C, high triglyceride (TG) and hyperglycemia in patients between groups ($p>0.05$) (Table 2).

The mean SUA levels were higher in patients with MS than without (respectively 5.20±1.6 and

TABLE 1: Differences in demographic characteristics between groups.

n=51		PsA group n (%)/Mean±SD	Control group n (%)/Mean±SD	p value
Sex	Male	23 (45.1%)	25 (49.0%)	0.552*
	Female	28 (54.9%)	26 (51.0%)	
Age (year)		46.68±11.28	38.05±10.19	**0.000¥**
BMI (kg/m^2)		28.97±4.90	26.94±6.43	0.760¥

PsA: Psoriatic arthritis; BMI: Body mass index; kg: Kilogram; m: Meter; SD: Standart deviation; *: Pearson chi-square; ¥: Independent t-test;
Bold values mean significant statistically; $p \leq 0.05$.

TABLE 2: Differences in demographic characteristics and metabolic syndrome criteria between groups.

	PsA goup (n=51)	Control group (n=51)	p value	p^{ad}
Current smoker	14 (27.5%)	28 (54.9%)	**0.005**	0.946
Metabolic syndrome	20 (39.2%)	7 (13.7%)	**0.004**	0.185
Hypertension	11 (21.6%)	4 (7.8%)	**0.05**	0.380
Diabetes mellitus	7 (13.7%)	2 (3.9%)	0.163*	0.248
Insulin resistance	19 (37.3%)	17 (33.3%)	0.679	0.226
Increased waist circumference	25 (49.0%)	21 (42.0%)	0.479	0.104
High triglycerides	14 (27.5%)	8 (15.7%)	0.149	0.160
Low HDL-C	33 (64.7%)	35 (68.6%)	0.674	0.306
Hyperglycaemia	9 (17.6%)	7 (13.7%)	0.584	0.197

PsA: Psoriatic arthritis; HDL-C: high-density lipoprotein-cholesterol; *:Fisher's exact test, all the others chi-square test; p^{ad}: ANCOVA adjusted for age;
Bold values mean significant statistically; $p \leq 0.05$.

4.39±1.4; p=0.016). But when adjusted for age, this difference was not found to be statistically significant (p=0.735). Mean SUA levels were statistically significantly higher in PsA when adjusted for age (p=0.027). There was no difference in mean SUA between groups. When the interaction of MS and PsA groups on SUA was analyzed, no difference was found (p=0.552) (Table 3).

The effect of interaction with the PsA group separately for each of the MS subgroups on the SUA level was analyzed by two-way ANOVA. In two-way ANOVA analyze, MS components did not affect SUA levels in patients with or without PsA. When main effect of MS components on SUA, analyzed by one-way ANOVA, it was found that HT, TG and HOMA-IR affected SUA level. SUA level was found to be higher in patients with HT, TG elevation, HOMA-IR elevation than those without (p=0.009, p=0.005, p=0.001, respectively) (Table 4).

DISCUSSION

The aim of this study is to analyze the relationship of PsA with MS; to examine the effect of PSA and MS components on SUA. In the study, the prevalence of MS is higher in PsA but when adjusted for age, this difference was not found to be statistically significant. Similar to the literature, in our study, the average age of patients with PsA was higher than those without PsA.[7] In our study, SUA levels were higher in MS but this difference was not found to be statistically significant. However PsA did not affect SUA levels, when adjusted for age, mean SUA levels were statistically significantly higher in PsA in the study. When the interaction of MS and PsA groups on SUA was analyzed, no difference was found. While there was no difference in sex, BMI, DM, IR, increased WC, increased TG, low HDL-C, and hyperglycemia, there was a difference in age, the current smoker, MS, HT between groups. It was found that HT, TG and HOMA-IR which are important components of MS had a one-way main effect on SUA levels. However, there was no one-way main effect of BMI, WC, HDL, fasting blood glucose on SUA levels. When we analyzed the effect of interaction with the PsA group separately for each of the MS components on the SUA levels, any of the MS components did not affect SUA levels in PsA.

Raychaudhuri SK. et al. reported that half of PsA patients had MS in his study population.[7] In this study, the MS prevalence is higher in PsA at 40% but when adjusted for age, this difference was not found to be statistically significant. This is because the mean age of the PsA patients was higher in our study and it's known that prevelance of MS is increased with age.[18,19] Similarly, in our study, the frequency of MS was found to be 3 folds higher in patients with PsA. The incidence of MS increases with age.[18,19] The reason for the high MS prevalence reported by Smriti et al. may be the higher mean age than our population. The high MS prevalence in the present study emphasizes the need for close monitoring of PsA patients for concomitant diseases such as dyslipidemia, DM and HT. Also, patients have an increased risk of

TABLE 3: The mean SUA levels between patients with and without MS and PsA.

			Uric acid		
		n	Mean±SD (mg/dL)	p value	p¥
PsA	(-)	51	4.32±1.6	0.057*	**0.027**
	(+)	51	4.89±1.4		
MS	(-)	75	4.39±1.4	**0.016***	0.735
	(+)	27	5.20±1.6		
MS	MS (-)	PsA (-)	44	4.19±1.5	0.552** 0.072
		PsA (+)	31	4.68±1.3	
	MS (+)	PsA (-)	7	5.16±1.9	
		PsA (+)	20	5.21±1.5	

SUA: Serum uric acid; MS: Metabolic syndrome; PsA: Psoriatic arthritis; SD: Standard deviation; mg: Milligram; dL: Deciliter; *: One-way ANOVA; **: Two-way ANOVA; Bold values mean significant statistically; Independent t-test: p≤0.05; p¥: ANCOVA adjusted for age.

TABLE 4: The difference of mean SUA levels between MS components in patients with and without PsA.

		PsA group		Control group			
	MS components	**n**	**Mean±SD**	**n**	**Mean±SD**	**p sig***	**p sig****
HT	(-)	40	4.82±1.5	47	4.16±1.4	0.059	**0.009**
	(+)	11	5.15±1.1	4	6.20±1.7		
BMI	<25 kg/m^2	11	4.50±1.3	23	3.99±1.3	0.87	0.094
	25-29.9 kg/m^2	20	4.65±1.3	12	4.42±1.7		
	≥30 kg/m^2	20	5.34±1.4	16	4.73±1.7		
WC	≤102 cm in male ≤88 cm in female	26	4.80±1.3	29	4.19±1.3	0.653	0.309
	>102 cm in male >88 cm in female	25	4.97±1.5	21	4.62±1.8		
HDL -C	<50 mg/dL in male <40 mg/dL in female	18	5.11±1.2	16	3.86±1.0	0.104	0.588
	≥50 mg/dL in male ≥40 mg/dL in female	33	4.77±1.5	35	4.54±1.7		
Glucose	<110 mg/dL	42	4.91±1.5	44	4.13±1.5	0.051	0.097
	≥110 mg/dL	9	4.79±1.0	7	5.57±1.7		
Triglyceride	<150 mg/dL	37	4.72±1.3	43	4.10±1.4	0.259	**0.005**
	≥150 mg/dL	14	5.34±1.7	8	5.53±1.8		
HOMA-IR	<2.7	32	4.56±1.2	34	3.95±1.3	0.684	**0.001**
	≥2.7	19	5.44±1.5	17	5.07±1.8		

PsA: Psoriatic arthritis; MS: Metabolic syndrome; SD: Standard deviation; HT: Hypertension; BMI: Body mass index; WC: Waist circumference; HDL-C: High-density lipoprotein-cholesterol; HOMA-IR: Homeostasis Model of Assessment Insulin Resistance; kg: Kilogram, m: Meter; cm: Centimetre; mg: Milligram; dL: Deciliter; *: Two-way ANOVA for PsA and MS components interactions; **: One-way ANOVA for MS components main effects; Bold values mean significant statistically.

CVD. If necessary, lifestyle changes and medication treatments for individual risk factors can be recommended for PsA patients.

The mean of the SUA levels was higher in MS, but when adjusted for age this difference was not found to be statistically significant. It's shown that the elevated levels of SUA are associated with MS risk factors like dyslipidemia, HT, abdominal obesity and IR in several studies.[8,9,20-23] In Tae Woo Yoo's study, SUA levels are elevated in direct proportion to MS criteria. Also, there was a positive correlation between the SUA and fasting blood glucose, fasting serum insulin, serum triglyceride, HOMA-IR, BMI, waist/hip ratio, although a negative correlation between SUA with age and serum HDL.[24] In the study of Hansol Choi, he also found positive correlations of SUA levels with fasting glucose, WC, TG and HT and a negative correlation with HDL-C.[25] Similar to the literature, SUA levels were higher in patients with elevated HT, TG and HOMA-IR in the present study. However, the mechanisms of its relationship should be explored by further studies. SUA elevation is associated with higher IR.[20-22] Insulin, besides regulating the systemic glucose homeostasis, modulates vascular tone by the role of a vasoactive hormone.[21] As a result of the investigational study in mice, SUA has been shown to have a clear action on IR by an increasing mechanism in oxidative stress and reactive oxygen species leading to aberrant glucose metabolism.[26] In this study, no relation was found between BMI, WC, HDL, fasting blood glucose and SUA, which are important components of MS. Although it is known that obesity and SUA are related, no relation was found between BMI, WC and SUA in this study.[27,28] This contradiction should be re-investigated by new studies in a larger population. Despite these and similar studies investigating the relationship between SUA and MS, we have not found any study investigating the relationship between MS and SUA in PsA.

The prevalence of hyperuricemia is significantly higher in men and there is a relationship between PsA

and hyperuricemia.[29] In AlJohani's study, the male population is higher than the female population and PsA had a significant effect on UA.[14] However, in our study similar to other studies in the literature, we could not have shown the effect of PsA on UA but when adjusted for age, we found that mean SUA levels were statistically significantly higher in PsA, since the female population is higher than the male population.[30]

In the general population other than psoriasis, smoking interacts with an increased PsA risk. There was a negative association between smoking and psoriasis, but smoking strongly interacted with the risk of PsA in the general population in a large United Kingdom cohort.[31] However the smoking rate in the control group was higher than the PsA group in this study. Also, there was a difference in MS and HT between groups but when adjusted for age, these results were statistically not significant in this study. Smoking lowers HDL-C, increases blood pressure and causes IR, smoking rates were lower in the PsA group, but HT and hyperlipidemia were higher. However, besides smoking, some factors playing a role in the pathogenesis of PsA may be considered to be effective in the development of HT and hyperlipidemia.[3] It is necessary to study in a larger population to explain this contradiction.

The study has some limitations. First, the mean ages of PsA and control groups are statistically different. It is possible that age affects metabolic syndrome and SUA levels. The SUA concentration may be affected by the dietary habits but this condition was not able to be investigated in the present study population and so could not be evaluated about to with concerning SUA concentration. Second, recording only one evaluation of SUA level may result in missclassification of subjects. However, the effects of non-differential missassortment would have resulted in bias toward the null. Third, our study population was limited. Therefore, it cannot be generalized to society.

CONCLUSION

In the present study with a limited number of patients, we showed that the frequency of MS increased in patients with PsA, but when adjusted for age this difference was not found to be statistically significant. Also we showed the effect of HT, TG and IR on SUA, but we could not show the effect of the relationship between PsA and MS directly on SUA. So more studies are needed to investigate the effect of MS components on SUA in PsA. Rather, it is time to recommend precise large-scale clinical trials to determine whether lowering SUA in PsA is useful in the prevention and treatment of HT, IR, DM, hyperlipidemia, obesity and CVD.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Nurhan Sayaca, Seval Pehlevan;* ***Design:*** *Nurhan Sayaca, Seval Pehlevan, Çetin Sayaca;* ***Control/Supervision:*** *Refik Dermirtunç;* ***Data Collection and/or Processing:*** *Nurhan Sayaca, Seval Pehlevan, Yasemin Özgür;* ***Analysis and/or Interpretation:*** *Çetin Sayaca, Yasemin Özgür, Nurhan Sayaca;* ***Literature Review:*** *Nurhan Sayaca;* ***Writing the Article:*** *Nurhan Sayaca, Çetin Sayaca, Yasemin Özgür;* ***Critical Review:*** *Çetin Sayaca, Yasemin Özgür.*

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