Clinical and Experimental Health Sciences

Does the Presence of Metabolic Syndrome Alter Serum Uric Acid Concentrations, Pain, and Well-Being in Patient with Chronic Musculoskeletal Pain?

Seyda Toprak Celenay[1], Derya Ozer Kaya[2], Senem Sas[3]

[1] Ankara Yildirim Beyazit University, Health Sciences Faculty, Department of Physiotherapy and Rehabilitation, Ankara,Türkiye.
[2] Izmir Katip Celebi University, Health Sciences Faculty, Department of Physiotherapy and Rehabilitation, Izmir,Türkiye.
[3] Erciyes University, Medical Faculty, Department of Physical Medicine and Rehabilitation, Division of Rheumatology, Kayseri, Türkiye.

Correspondence Author: Seyda Toprak CELENAY
E-mail: sydtoprak@hotmail.com

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ABSTRACT

Objective: To compare serum uric acid concentrations, pain and well-being in patients having chronic musculoskeletal pain with and without MetS, and investigate cut-off values.

Methods: Patients having chronic musculoskeletal pain with (MetS group, n=48) and without MetS (control group, n=52) were included. The serum uric acid concentration, pain intensity, body composition, physical activity level, quality of life, and psychological status were evaluated by a uric acid blood test, Visual Analogue Scale, Bio-impedance Analyzer, International Physical Activity Questionnaire-7 (IPAQ-7), Nottingham Health Profile, and Hospital Anxiety and Depression Scale, respectively.

Results: Uric acid level, fat mass, waist/hip ratio were found higher in the MetS group in comparison to the control group ($P<0.05$). It was seen that patients in the MetS group had lower physical activity levels than those in the control group ($P<0.05$). The cut-off points of the uric acid level, fat mass, waist/hip ratio, and physical activity level for detecting MetS were found as 5.25 mg/dl, 37.50 kg, 0.91, and 247.25 METs-minutes/week, respectively.

Conclusion: Patients with MetS had a greater uric acid level, fat mass, waist/hip ratio, and a lower physical activity level than those without MetS. The increase of uric acid level, fat mass, and waist/hip ratio, and the decrease of physical activity may be critical for patients having musculoskeletal pain with MetS. These results should be considered for the management of these patients.

Keywords: Metabolic syndrome, pain, uric acid, body composition, quality of life

1. INTRODUCTION

The musculoskeletal pain and metabolic syndrome (MetS) with the related burden of the problems have become two recent global health challenges (1). Musculoskeletal pain is originated from musculoskeletal conditions such as joint problems, musculoskeletal injuries, or inflammatory diseases (2). Regional or widespread musculoskeletal pain is more common in patients with MetS, and the relations between MetS and musculoskeletal disorders were declared for intervertebral disk degeneration, knee osteoarthritis, shoulder adhesive capsulitis, neck pain, and tendinopathies (3-6). Musculoskeletal disorders trigger major inflammatory reactions and similarly, MetS are strongly associated with chronic low-grade inflammation or proinflammatory state. Systemic and chronic inflammation changes body chemistry over time, causes nociception in musculoskeletal tissues, leads to the expression of chronic disease, and prevents tissue healing (7,8).

MetS is a cluster of disorders with the combination of visceral obesity, hyperglycemia or insulin resistance, hypertension, and dyslipidemia (1). The NCEP ATP III criteria is used widely for diagnosis including measurements and laboratory tests. The level of serum uric acid, the final metabolism product of endogenous purine catabolism, was also assosiated with an increased risk for impaired MetS and oxidative stress (9). The oxidant-antioxidant paradox was declared for the serum uric acid levels (10). While the visceral fat area was declared to be the strongest contributor to elevated serum uric acid concentration, serum uric acid level increase was related to bone mineral density increase (11). The difference and impact of the serum uric acid concentration in musculoskeletal patients with and without MetS are questionable.

In addition to serum uric acid alterations, pain, fatigue, sleep disturbances, disability, physical inactivity, and impairments in quality of life (QoL) and psychological well-being are common in musculoskeletal disorders and MetS patients (12). Nowadays, more and more patients with musculoskeletal pain conditions have been consulting outpatient physical therapy clinics and seeking physiological and psychological well-being**.** The prevalence of MetS in these patients seems to be high, and it is a very well-known that the treatment of those patients with MetS is more difficult (13). However, to our

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knowledge, the clinical differences for physical activity habits, body composition, pain intensity, QoL, and psychological well-being, and laboratory features such as serum concentrations in patients having chronic musculoskeletal pain with and without MetS have not been researched up to now.

Thus, the current study aimed to compare serum uric acid concentrations, pain and well-being in patients having chronic musculoskeletal pain with and without MetS, and investigate cut-off values. The hypotheses of the current study were as below: 1. There are differences in serum uric acid level, pain intensity and well-being of patients having chronic musculoskeletal pain with MetS compared to those without MetS, 2. There would be cut-off values between the occurrence of serum uric acid level, pain intensity and well-being characteristics.

2. METHODS

2.1. Participants

One hundred and ten patients, referred to the department of physiotherapy and rehabilitation, were assessed. The inclusion criteria were to be a volunteer between 20 to 70 years of age with a chronic non-specific musculoskeletal pain disorder for more than six months. Exclusion criteria were the presence of cancer history, chronic heart failure, renal and/or liver dysfunction, pregnancy, alcohol consumption, and being unable to complete the assessment. Moreover, the volunteers using medications for pain control, anxiety, and depression were excluded.

The present study was planned by a case-control study design. The Ankara Yildirim Beyazit University's Ethics Committee approved the protocol of the present study (Approval number: 32) and conducted within the framework of the Helsinki Declaration principles. Written informed consent forms were provided to participants.

2.2. Assessments

All the patients included in the study as having a musculoskeletal disorder were assessed by the same physician (SS). The physician collected demographic and physical data, revealed the musculoskeletal disorder with the consideration of exclusion criteria. Moreover, the diagnosis of MetS was carried out by the examination and blood test results according to the diagnostic criteria guidelines of NCEP-ATP III (14). During examinations, blood pressure was measured with a sphygmomanometer (Erka, Perfect Aneroid, Germany) on the same arm (right) after having a 30-minutes rest. The weight, height, hip, and waist circumferences were measured with a meter. The blood samples were collected from the patients after one night of fasting. The following routine blood tests included: serum uric acid levels, glucose, high-density lipoprotein cholesterol (HDL-C), and triglyceride. After getting the exact MetS diagnosis the suitable and voluntary patients were assigned to the MetS and control groups. The flowchart of the cases was presented in Figure 1. The other assessments related to physical and psychological well-being were conducted by the same physiotherapist blinded to the group allocations (STC). Body composition, physical activity level, musculoskeletal pain complaints and general well being such as QoL and psychological distress were examined.

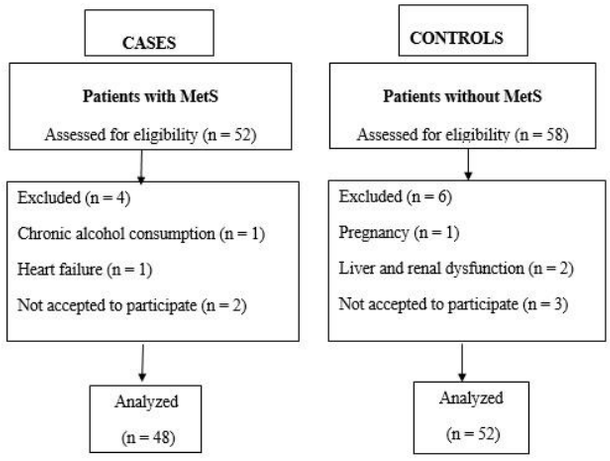

Figure 1. *The flowchart diagram for the participants.*

Body composition: The body composition was measured with Bio-impedance Analyzer (Bodystat®1500, Bodystat Ltd, Douglas, Isle of Man, UK). Patients' physical characteristics were entered into the analyzer. For the whole-body measurement, two electrodes were placed on the right hand and the other two electrodes were placed on the left foot. Within seconds by passing a safe signal at a low 400 µA and a frequency of 50 kHz through the body the results related to the body composition were displayed on a screen of the device and they were recorded (15).

Physical activity level: International Physical Activity Questionnaire-7 (IPAQ-7) Turkish version was used to assess the physical activity levels of the participants (16). The total score of the IPAQ-7 is obtained based on the duration and frequency of weekly vigorous and moderate-intensity physical activities and walking activities.

Musculoskeletal pain complaints: The musculoskeletal pain complaints were questioned. The patients were asked to mark their painful areas on a body diagram. Afterward, the pain intensity was questioned with the Visual Analog Scale (VAS) (17). This scale consists of a 10 cm horizontal line in length, in which "0" remarks "no pain" and "10" remarks "excruciating pain''.

Quality of life: Nottingham Health Profile (NHP) Turkish version was used to assess the QoL (18). The profile contains 38 items with 6 dimensions. The specific dimensions focus on pain, energy, emotional reactions, social isolation, sleep, and physical mobility. The scores of each part ranged from 0 (the best QoL) to 100 (the worst QoL). The total scores have been summed from all dimensions.

Psychological distress: Hospital Anxiety and Depression Scale (HADS), 14 items divided into anxiety (HADS-A) and depression (HADS-D) dimensions, was used for evaluating psychological distress. It is a valid and reliable questionnaire in Turkish (19).

The scores of each demension ranged from 0 to 21. The higher score indicated the deterioration of anxiety and depression.

2.3. Sample Size and Statistical Analyses

G*Power program (G*Power Version 3.0.10, Franz Faul, Universität Kiel, Germany) was used for the sample size calculation. For the pilot study, ten patients from each group were randomly recruited. According to the the IPAQ-7 scores of the pilot study, the sample with 90 participants (45 per group) was needed to obtain 80% power (d = 0.6 effect size and α = 0.05 type I error).

IBM SPSS Statistics 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, New York: IBM Corp.) was used for the analyses. The normal distributions of the variables were assessed with visual and analytical methods. Descriptive data was demonstrated with mean ± standard deviation (SD) values, median, minimum (min), and maximum (max) values, frequency (n) and percentage (%). Independent samples t-test, Mann-Whitney U test, and Chi-square test were used to compare the group differences. The statistical significance level was accepted as $p<0.05$.

The cut-off values for predicting the presence of MetS were analyzed using the receiver operating characteristic (ROC) curves. The determined area under the curve (AUC) according to ROC graphics and 95% confidence intervals of the area were investigated. When a significant cut-off value was observed, the sensitivity and specificity were calculated. While evaluating the AUC, a 5% type-I error level was used to accept a statistically significant predictive value of the measurements.

3. RESULTS

One hundred patients completed the study. There was no difference between the groups in terms of the demographic and physical data ($P > 0.05$), except MetS components ($P < 0.05$) (Table 1).

Table 1. *Demographical characteristics of the groups.*

Characteristics	MetS group (n = 48)	Control group (n = 52)	P
Age (years, Mean ± SD)	57.58 ± 11.02	52.76 ± 13.39	0.054[a]
Gender (n, %)			
Female	35, 72.9	40, 76.9	0.644[c]
Male	13, 27.1	12, 23.1	
Smoking (n, %)			
No	46, 95.8	45, 86.5	0.105[c]
Yes	2, 4.2	7, 13.5	
Musculoskeletal pain localization (n, %)			
Neck	11, 22.9	13, 25.0	0.994[c]
Low back	26, 54.2	27, 51.9	
Hip	1, 2.1	1, 1.9	
Knee	8, 16.7	8, 15.4	
Shoulder	2, 4.2	3, 5.8	
MetS components			
Waist circumferences (cm, Mean ± SD)	108.01 0± 11.91	98.90 ± 12.82	< 0.001[a]*
Serum glucose (mg/dL, Mean ± SD)	115.50 ± 39.14	95.67 ± 19.86	0.002[a]*
Triglyceride (mg/dL, Median (Min; Max))	200.50 (95.0; 348.0)	115.00 (36.0; 392.0)	< 0.001[b]*
HDL-C (mg/dL, Mean ± SD)	38.46 ± 8.03	49.34 ± 14.86	< 0.001[a]*
SBP (mmHg, Mean ± SD)	126.77 ± 12.65	117.30 ± 12.38	< 0.001[a]*
DBP (mmHg, Mean ± SD)	77.91 ± 9.66	72.69 ± 8.42	0.005[a]*

**P < 0.05, SD: standart deviation, Min: minimum, Max: maximum, MetS: metabolic syndrome, HDL-C: high-density lipoprotein cholesterol, SBP: systolic blood pressure, DBP: diastolic blood pressure, [a]Independent sample t-test, [b]Mann Whitney U test, [c]Chi-square test.*

It was found that the uric acid level, fat mass, waist/hip ratio increased and the IPAQ-7 scores decreased in the MetS group in comparison to the control group ($P < 0.05$). No differences were shown for the other parameters regarding lean mass, water, BMI, pain intensity, QoL, HADS-A, and HADS-D scores between the groups ($P > 0.05$) (Table 2).

The uric acid level, fat mass, waist/hip ratio, and IPAQ-7 values were analyzed for cut-offs. According to the ROC analysis, the areas under the curve (AUC = 0.708, AUC = 0.677, AUC = 0.707, and AUC = 0.888) were significant for the uric acid, fat mass, waist/hip ratio and IPAQ-7 scores, respectively ($P < 0.001$, $P = 0.002$, $P < 0.001$ and $P = 0.008$, Table 3). The cut-off points of the uric acid, fat mass, waist/hip ratio, and IPAQ-7 scores were detected at 5.25 mg/dl, 37.50 kg, 0.91, and 247.25 METs-minutes/week, respectively. In the study, 64.60% sensitivity and 71.15% specificity were observed for ≥ 5.25 mg/dl of the uric acid, 33.30% sensitivity and 80.70% specificity were observed for ≥ 37.50 kg of the fat mass, and 64.60% sensitivity and 73.08% specificity were observed for ≥ 0.91 of the waist/hip ratio (Table 3, Figure 2a). Furthermore, 31.30% sensitivity and 82.69% specificity were observed for ≤ 247.25 METs-minutes/week of the IPAQ-7 scores (Table 3, Figure 2b).

Table 2. *Differences between Serum concentrations, physical and psychological well-being of groups'.*

Values	MetS group (n = 48)	Control group (n = 52)	P
Serum concentrations			
Uric acid (mg/dl, Mean ± SD)	5.70 ± 1.13	4.72 ± 1.30	< 0.001[a]*
Physical well-being			
Fat mass (kg, Median (Min; Max))	34.95 (20.0; 70.40)	30.65 (6.40; 60.10)	0.002[b]*
Lean mass (kg, Median (Min; Max))	46.05 (34.50; 71.50)	49.05 (34.40; 68.30)	0.440[b]
Water (lt, Median (Min; Max))	37.40 (29.70; 54.90)	36.85 (8.20; 49.30)	0.722[b]
Waist/hip ratio (Median (Min; Max))	0.97 (0.78; 1.20)	0.87 (0.70; 1.27)	< 0.001[b]*
BMI (kg/m², Median (Min; Max))	32.60 (24.73; 51.44)	31.79 (17.01; 45.79)	0.053[b]
IPAQ-7 (METs-minutes/week, Median (Min; Max))	396.0 (148.0;2376.0)	672.0 (148.5;2772.0)	0.008[b]*
Pain intensity (VAS, cm, Median (Min; Max))	5.70 (1.67;9.33)	5.0 (0.17; 9.57)	0.121[b]
NHP-energy (Median (Min; Max))	63.20 (0.0; 100.0)	63.20 (0.0; 100.0)	0.237[b]
NHP-pain (Median (Min; Max))	70.77 (0.0; 100.0)	53.63 (0.0; 100.0)	0.065[b]
NHP-emotional reactions (Median (Min; Max))	41.80 (0.0; 100.0)	42.47 (0.0; 100.0)	0.923[b]
NHP-sleep (Median (Min; Max))	39.16 (0.0; 100.0)	39.83 (0.0; 100.0)	0.960[b]
NHP-social isolation (Median (Min; Max))	22.01 (0.0; 100.0)	21.07 (0.0; 100.0)	0.868[b]
NHP-physical mobility (Median (Min; Max))	54.46 (0.0; 100.0)	43.35 (0.0; 100.0)	0.303[b]
NHP-total (Median (Min; Max))	302.23 (0.0; 567.14)	283.61 (22.42; 544.54)	0.381[b]
Psychological well-being			
Anxiety (Mean ± SD)	9.54 ± 4.67	8.40 ± 3.91	0.189[a]
Depression (Mean ± SD)	8.25 ± 4.78	7.78 ± 3.58	0.589[a]

**P < 0.05; SD: standard deviation, Min: minimum, Max: maximum, MetS: metabolic syndrome, IPAQ-7: International Physical Activity Questionnaire-7; VAS: Visual analog scale; NHP: Nottingham Health Profile, [a]Independent sample t-test, [b]Mann Whitney U test*

Table 3. *The Area Under the curve regarding uric acid, fat mass, waist/hip ratio and ipaq-7 values.*

Parameters	AUC ± SE	95 % Confidence Interval	p	Cut-off Point *	Sensitivity (%)	Specificity (%)
Uric acid (mg/dl)	0.708 ± 0.051	0.607 – 0.809	**< 0.001**	≥ 5.25	64.60	71.15
Fat mass (kg)	0.677 ± 0.053	0.573 – 0.782	**0.002**	≥ 37.50	33.30	80.77
Waist/hip ratio	0.707 ± 0.052	0.605 – 0.809	**< 0.001**	≥ 0.91	64.60	73.08
IPAQ-7 (METs-minutes/week)	0.653 ± 0.054	0.546 – 0.760	**0.008**	≤ 247.25	31.30	82.69

** It was detected to determine MetS according to youden index. IPAQ-7: International Physical Activity Questionnaire-7, SE: standard error, AUC: area under the curve, METs: metabolic equivalent*

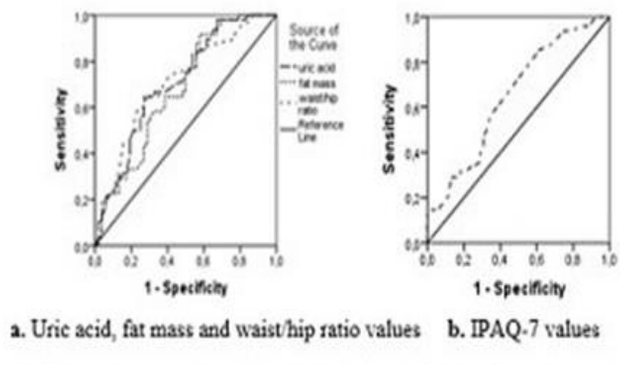

Figure 2a, b. *Receiver operating characteristic curve of uric acid, fat mass, waist/hip ratio and International Physical Activity Questionaire-7 (IPAQ-7) values.*

4. DISCUSSION

The present study yielded the following the results: (i) Patients with MetS showed greater uric acid level, fat mass, waist/hip ratio, and a lower physical activity level than those without MetS, (ii) no differences were detected for the other parameters of body composition, pain intensity, QoL, anxiety, and depression between the groups, (iii) the cut-off points for the uric acid, fat mass, waist/hip ratio and IPAQ-7 for detecting MetS were found as 5.25 mg/dl, 37.50 kg, 0.91 and 247.25 METs-minutes/week, respectively.

The serum uric acid is drawing increased attention as an inflammatory marker. Many studies reported higher serum uric acid concentration as a significant marker predicting the risk of developing cardiovascular diseases, stroke, cancer, and musculoskeletal pain (9,10,20,21). Afzal et al. (20) found that mean serum uric acid levels were higher in patients with chronic non-specific musculoskeletal pain in comparison to healthy controls, with 25% of patients showing hyperuricemia. They also declared that abnormalities of the uric acid profile may be an underlying biochemical abnormality in a significant number of patients. Furthermore, the increased serum uric acid level has also been reported to be associated with MetS and its components (21). However, the role of uric acid in the diagnosis of the MetS has not been established. Similar to

these studies, we also studied the uric acid level in patients having chronic musculoskeletal pain with and without MetS, and found increased uric acid levels in patients with MetS. These findings should be considered by clinicians to improve various symptoms of the patients having musculoskeletal pain with MetS.

MetS and musculoskeletal disorders may influence both physical and psychological well-being. Some parameters including physical inactivity, obesity, and depression are strong and independent predictors for the onset of an episode of intense and/or disabling musculoskeletal disorders; especially low back, neck, and knee pain, and these parameters have also been interrelated to the development of the MetS. Park et al. (22) reported that prevalence rates of MetS increased with BMI and physical inactivity. Lee et al. (23) put forward that increased physical activity levels were significantly correlated to decreased MetS. Similar to these studies, we also investigated physical well-being parameters including pain intensity, physical activity level, and body composition in patients having musculoskeletal pain with and without MetS, and found the increased fat mass and waist/hip ratio, and decreased physical activity in patients with MetS in comparison to those without MetS. There was no difference in parameters related to pain intensity. These findings should be considered for further studies to investigate the pain threshold and perception of the patients with MetS. Moreover, QoL is an important manifestation of both physical and psychological well-being. Several components of MetS and MetS-related adverse events have been associated with decreased QoL. Although different studies reported the impaired QoL in the MetS (24,25), a study by Vetter et al. (26) suggested that MetS itself was not related to impaired QoL. Therefore, the impact of MetS on QoL is less predictable and has not been clearly defined. In our study, no difference was shown between QoL and having MetS in patients with chronic musculoskeletal pain.

Besides, MetS has been found to be a significant predictor of some psychological disorders (27) and the reverse has also been reported (28). The evidence provided that depression was linked to MetS and its components (29). In contrast, according to a study by Hildrum et al. (30), no such association between depression and MetS was observed. Thus, the findings of these studies have been inconsistent regarding the association between psychologic status and MetS. We also compared the psychologic status in patients having musculoskeletal pain with and without MetS and put forward that no differences were detected for the anxiety and depression status between the groups. These results could be occurred due to the existence of chronic musculoskeletal pain.

Moreover, it may be substantial to determine the cut-off points of the uric acid, the fat mass, the waist/hip ratio, and the IPAQ-7 for the prevention and diagnosis of MetS. Thus, it was calculated these points for the uric acid (5.25 mg/dl), fat mass (37.50 kg), waist/hip ratio (0.91), and IPAQ-7 (247.25 METs-minutes/week) in this study. In literature, there were several studies related to the uric acid level, body composition values, and physical activity level in the MetS (21-23). However, there is no standard value for the uric acid, the fat mass, the waist/hip ratio, and the IPAQ-7 parameters. In health checkups, it may be beneficial to consider these values of the parameters.

The first limitation of the present study, different musculoskeletal pain patients included. More than 75 % of the individuals were non-specific low back or neck pain patients. The rest had joint problems. This should be taken into account. Secondly, body composition and general fat mass were presented. Especially, local fat mass related to the trunk, upper and lower extremities could be investigated in further studies due to the existence of MetS.

5. CONCLUSION

In conclusion, the current study demonstrated that patients with MetS had a greater uric acid level, fat mass, waist/hip ratio, and a lower physical activity level than those without MetS. Pain intensity, health profile characteristics, and psychological well-being did not differ in chronic musculoskeletal pain patients with and without MetS. Therefore, increased uric acid level, fat mass, and waist/hip ratio, and decreased physical activity level should be considered for the management of patients having musculoskeletal pain with MetS. Moreover, the increase of uric acid level, fat mass, and waist/hip ratio more than 5.25 mg/dl, 37.50 kg, 0.91 and the decrease of physical activity level more than 247.25 METs-minutes/week may be critical for MetS patients. The obscure relations need further attention during the treatment and healing processes of the patients.

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