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Original Article

Relationship between Metabolic Syndrome and Uric Acid Levels in Patients with Familial Mediterranean Fever

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Abstract

Background: This study aims to investigate the prevalence of metabolic syndrome (MetS) in familial Mediterranean fever (FMF) and the relationship between serum uric acid (SUA) concentrations and MetS status by sex in patients with FMF.

Methods: This cross-sectional study included all attack-free patients previously diagnosed with FMF who referred to the rheumatology clinic for follow-up between October 2018 and January 2019. This study included 154 patients with FMF (66 males and 88 females) and 154 controls (62 males and 92 females) with similar age and sex.

Results: MetS was more prevalent among the FMF patients compared to the controls (42.90% [95% CI: 34.9–51.1%) vs. 28.57% [95% CI: 21.6–36.4%); OR=1.88, 95% CI: 1.17–3.01, $P=0.009$]. In the FMF group, we found higher SUA, number of MetS components, body mass index (BMI), waist circumference (WC), and insulin compared to the control group ($P<0.001$, $P<0.001$, $P=0.018$, $P=0.002$, $P=0.008$, respectively). The prevalence of MetS (men: $P<0.001$, women: $P<0.001$) and number of MetS components (men: $P<0.001$, women: $P<0.001$) were significantly increased with increasing SUA quartiles in both sexes.

Conclusion: The prevalence of MetS was higher in patients with FMF, and the prevalence of MetS and number of MetS components were significantly increased with increasing SUA quartiles in both men and women with FMF. SUA levels, as a biochemical marker, could be a strong and independent predictor of MetS in patients with FMF, and may provide substantial help with early diagnosis and management of MetS.

Keywords: Body mass index, Familial Mediterranean fever, Metabolic syndrome, Uric acid, Waist circumference

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Introduction

Familial Mediterranean fever (FMF) is characterized by abdominal and chest pain, recurrent fever, and arthritis occurring as a result of inflammation of serous membranes.[1] Pyrin protein, which has anti-inflammatory activity, is encoded by the Mediterranean fever (*MEFV*) gene.[2,3] *MEFV* gene mutations lead to acute attacks of inflammation caused by inflammatory activation, causing spontaneous release of interleukin-1beta (IL-1β), which is a major inflammatory cytokine in the pathogenesis of harmful cardiometabolic outcomes of FMF.[4-6] In the literature, few studies addressing the cardiometabolic outcomes of FMF have shown that the systolic function of the right ventricle as well as the diastolic function of left and right ventricles are impaired,[7] endothelium-dependent flow-mediated dilation is reduced,[8] intima media thickness of the carotid arteries is increased,[8,9] aortic stiffness is increased,[10] coronary flow reserve is reduced and coronary microvascular function is impaired[11] in patients with FMF when compared with controls. In patients with FMF, serum levels of IL-1β and TNF-α are elevated during acute attacks and remission compared with healthy individuals, and are therefore defined as indicators of ongoing subclinical inflammation.[12]

Metabolic syndrome (MetS) encompasses a group of risk factors such as hyperglycemia, lower high-density lipoprotein cholesterol (HDL-C), obesity, hypertension (HT), and higher triglyceride (TG) levels.[13] Diabetes mellitus (DM), cardiovascular disease (CVD), and CV mortality risk are increased with MetS.[14,15] Considering its high prevalence in both developing and developed countries, MetS is a critical public health problem and is also considered as a challenge in clinical practice.[16,17] Therefore, the earliest possible identification and management of patients with MetS will help decrease the burden of MetS-associated diseases.

In humans, uric acid is the end-product of purine metabolism.[18] Hyperuricemia stems from increased formation or decreased excretion of uric acid as a consequence of purine metabolic abnormalities associated with gout, HT, dyslipidemia, type 2 DM, and MetS. Recently, hyperuricemia has been shown to play a role in MetS pathophysiology.[19,20] Although MetS is not evaluated on the basis of hyperuricemia, cross-sectional and

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longitudinal studies have reported a positive correlation between MetS and its components and increased serum uric acid (SUA) levels when different ethnic and age populations are considered.[21-24] Qin et al[25] have voiced the possibility that hyperuricemia might be a new component of MetS.

To date, no evaluation has been conducted on MetS prevalence, SUA levels, and the correlations between MetS prevalence and SUA levels in patients with FMF. This study aims to investigate the prevalence of MetS in FMF and the relationship between SUA concentrations and MetS status by sex in patients with FMF.

Materials and Methods

This cross-sectional study included all attack-free FMF patients who referred to the rheumatology outpatient clinic of Kahramanmaras Sütcü Imam University (KSU) for follow-up between October 2018 and January 2019. These patients were previously diagnosed with FMF according to the diagnostic criteria of Livneh et al.[26] This study included 154 patients with FMF (66 males and 88 females) and 154 controls (62 males and 92 females) with similar age and sex. The control group consisted of individuals who referred to the rheumatology outpatient clinic of KSU with complaints of arthralgia and myalgia and who did not have any rheumatologic disease based on physical examinations and laboratory findings, who were not diagnosed with any chronic disease previously, who were not receiving any medical therapy, and who were similar in age and sex to the patient group. We excluded patients with systemic inflammation other than FMF, those on corticosteroids, thiazide diuretics, and SUA-lowering medications, and those with active or chronic infections and cancer. All analyses of physical variables and blood tests were conducted close together within the same period. Systolic (SBP) and diastolic blood pressure (DBP) and waist circumference (WC) were measured. Body mass index (BMI) was calculated.

At the end of a minimum 8 hour fasting, blood samples were taken in the morning. All participants' data were collected regarding their SUA, creatinine, fasting blood glucose (FBG) and insulin levels. An autoanalyzer was used to obtain serum lipid profile including TG, low-density lipoprotein cholesterol (LDL-C), HDL-C, and total cholesterol (TC).

The evaluation of the presence of MetS was based on the criteria of consensus approved recently by Alberti et al.[27] The patients were considered as having MetS if they met three or more of the following criteria: reduced HDL-C (<40 mg/dL for men, <50 mg/dL for women), increased TG (≥150 mg/dL), increased WC (≥80 cm for women, ≥94 cm for men), hyperglycemia (FBG level ≥100 mg/dL or use of antidiabetic agents), and SBP ≥130 mm Hg or DBP ≥ 85 mm Hg.[27,28] Patients were also classified in terms of SUA categories. Men and women had separate quartiles categorized by SUA concentrations. As a result, the categories pertaining to the men were as follows: (Q1) <4.8 mg/dL, (Q2) 4.8-5.5 mg/dL, (Q3) 5.6–6.4 mg/dL, and (Q4) ≥6.5 mg/ dL. The categories pertaining to the women were: (Q1) <3.8 mg/dL, (Q2) 3.8–4.2 mg/dL, (Q3) 4.3-5 mg/dL, and (Q4) ≥5.1 mg/dL.

Statistical Analysis

The findings obtained from the experiments were analyzed using "SPSS 15.0 for Windows and Minitab 17". Normal distribution of the data was tested using Kolmogorov-Smirnov Test. In the case of normally distributed data, the difference between the groups was assessed using the Independent Samples *t* test; otherwise, the difference was assessed using the Mann-Whitney U and Kruskal-Wallis tests. For analysis of qualitative data, the chi-square test was used. In order to analyze the correlation between parameters, Spearman' correlation coefficient was used. Continuous numeric variables were given as mean ± standard deviation (95% confidence interval [CI]) or median (interquartile range) (IQR) (25%–75%). Categorical variables were given as numbers and percentages. Prevalence estimates of MetS were given as percentages (95% CI). Furthermore, in order to evaluate the effect of SUA level on the prediction of MS, multivariate binary regression analyses were performed by adjusting for potential confounders. Moreover, in order to evaluate the effect of SUA level on the prediction of the number of MS components, multivariate linear regression analyses were performed by adjusting for potential confounders. Also, $P<0.05$ was considered statistically significant.

Results

A total of 154 patients with FMF (66 men, 88 women) aged between 18 and 68 years and 154 healthy controls (62 men, 92 women) aged between 18 and 66 years were included in the study. The biochemical and clinical findings and demographics of the groups are given in Table 1. Regarding sex and age distribution, there was no difference between the groups ($P=0.421$, $P=0.644$, respectively) (Table 1). The prevalence of MetS was statistically significantly higher in the FMF group than in the control group (66/154 [42.90%]; 95% CI: 34.9–51.1% vs. 44/154 [28.57%]; 95% CI: 21.6–36.4%, respectively; $P=0.009$]. Patients with FMF were at an increased risk of having MetS (OR = 1.88, 95% CI =1.17–3.01, $P=0.009$). When the SUA levels of FMF and control groups were compared, the SUA level of the FMF group was higher than that of the control group (4.70 mg/dL [IQR: 3.70-5.60] vs. 4.10 mg/dL [IQR: 3.50–4.63], respectively; $P<0.001$). Additionally, in patients with FMF, the number of MetS components, BMI, WC, and fasting insulin levels were also significantly higher compared to the control group ($P<0.001$, $P=0.018$, $P=0.002$ [mean differences with 95% CI: 1.864–7.954), $P=0.008$, respectively] (Table 1).

Table 1. Baseline Clinical and Biochemical Characteristics of the Patients with FMF and Healthy Controls

Variables	FMF (n = 154)	Control (n = 154)	*P* Value
Age (y)	35 (25–46)	35 (26–45)	0.996
Sex, No. (%)			0.644
Male	66 (42.9)	62 (40.3)	
Female	88 (57.1)	92 (59.7)	
Metabolic syndrome, No. (%)	66 (42.9)	44 (28.6)	0.009
(95% CI)	(34.9–51.1)	(21.6–36.4)	
Number of MetS components	2 (1–3)	1 (0–3)	<0.001
BMI (kg/m^2)	25.70 (21.95–29.78)	24.20 (21.60–27.97)	0.018
Waist circumference (cm)	89.42 ± 15.06	84.51±11.93	0.002*
(95% CI)	(87.02–91.81)	(82.61–86.40)	(1.864–7.954)
SBP (mmHg)	110 (100–120)	110 (100–120)	0.207
DBP (mmHg)	70 (60–80)	70 (60–80)	0.334
TC (mg/dL)	178.00 (152.00–196.50)	175.00 (151.75–196.00)	0.516
TG (mg/dL)	135.00 (88.75–173.75)	125.00 (90.50–149.00)	0.269
HDL cholesterol (mg/dL)	45.00 (38.00–51.00)	46.00 (40.00–51.00)	0.377
LDL cholesterol (mg/dL)	101.00 (81.50–127.25)	100 (79.25–126.25)	0.554
FPG (mg/dL)	91.00 (85.00–101.00)	89.00 (85.00–97.00)	0.088
Fasting insulin level	14.00 (9.45–17.73)	12.00 (9.00–15.00)	0.008
Creatinine (mg/dL)	0.60 (0.60–0.80)	0.60 (0.60–0.80)	0.541
SUA (mg/dL)	4.70 (3.70–5.60)	4.10 (3.50–4.63)	<0.001

Abbreviations: FMF, Familial Mediterranean fever; MetS, metabolic syndrome; BMI, body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TC, Total cholesterol; TG, triglycerides; SUA, serum uric acid; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Continuous variables with normal distributions are expressed as mean ± standard deviation (95% CI), whereas continuous variables with non-normal distributions are expressed as median (IQR) (25%–75%). Categorical variables are expressed as percent n(%). Groups were compared using Independent sample *t* test (*P* value is given with mean differences with 95% confidence intervals between groups) or the Mann-Whitney U-test for continuous variables and the chi-squared test for categorical variables.

MetS was present in 28 of 66 men (42.4%), in 38 of 88 women (43.2%), and in 66 of the total 154 patients (42.9%) with FMF. No significant difference was found between female and male patients with FMF with respect to the prevalence of MetS ($P=0.925$). MetS was present in 10 of 62 men (16.1%), in 34 of 92 women (37.0%), and in 44 of the total 154 healthy controls (28.6%). MetS prevalence was statistically higher in females compared with males in the control group ($P=0.005$). The prevalence of MetS was significantly higher in men with FMF compared with the male controls ($P=0.001$). There was no statistically significant difference between women with FMF and women in the control group ($P=0.394$).

The SUA levels of men with FMF who had MetS were higher than those of men with FMF without MetS ($P<0.001$). Similarly, the SUA levels of women with FMF who had MetS were higher than those of women with FMF without MetS ($P<0.001$) (Table 2). The number of MetS components, BMI, WC, SBP, DBP, TG, and FBG levels of men and women with FMF who had MetS were higher than those of men and women with FMF without MetS (for men: $P<0.001$, $P<0.001$, $P<0.001$ (mean differences with 95% CI: 18.133–28.897), $P=0.009$, $P=0.004$, $P=0.029$, $P<0.001$, respectively; for women: $P<0.001$, $P<0.001$, $P<0.001$, $P=0.044$, $P<0.001$, $P<0.001$, $P<0.001$, respectively), but their HDL-C levels were lower (for men: $P<0.001$, for women: $P<0.001$) (Table 2). LDL-C levels of women with FMF who had MetS were higher than those of women with FMF without MetS ($P=0.023$), but their creatinine levels were lower ($P=0.009$) (Table 2).

The clinical characteristics and demographics of the patients with FMF according to sex-specific SUA quartiles are given in Table 3. The MetS prevalence ($P<0.001$) and numbers of MetS components ($P<0.001$) were significantly increased with increasing SUA quartiles in both sexes. BMI, WC, TC, TG, and FBG were significantly increased with rising SUA levels in both sexes (for men: $P<0.001$, $P<0.001$, $P=0.030$, $P=0.007$, $P<0.001$, respectively; for women: $P<0.001$, $P<0.001$, $P=0.035$, $P=0.005$, $P=0.015$, respectively). LDL was significantly increased ($P=0.039$) and creatinine was significantly decreased ($P<0.001$) with rising SUA levels in women, and the levels of HDL was significantly decreased ($P=0.009$) with rising SUA levels in men. The correlation between SUA levels of men and women with FMF and metabolic risk factors are given in Table 4. SUA levels showed a statistically significant positive correlation with WC, SBP, DBP, TG, and FBG ($P<0.001$, $P=0.007$, $P=0.001$, $P<0.001$, $P=0.004$, respectively) but a negative correlation with HDL-C in men with FMF ($r=-0.424$, $P<0.001$). Also, SUA levels were positively correlated with WC, DBP, TG, and FBG in women with FMF ($P<0.001$, $P=0.012$, $P=0.013$, $P=0.001$, respectively).

Table 2. Clinical and Biochemical Characteristics of 154 Patients with FMF with and without Metabolic Syndrome

Variables	MetS (*n* = 66)	Non-MetS (*n* = 88)	*P*-Value
Men *n*(%)	**28 (42.42)**	**38 (57.58)**	
Age (y)	43 (35–50)	40 (30–52)	0.421
Number of MetS components	3.5 (3–4)	1 (0–1)	<0.001
BMI (kg/m²)	31.45 (28.20–33.30)	22.90 (20.90–27.50)	<0.001
WC (cm)	108.36 ± 6.37	84.84 ± 13.14	<0.001
(95% CI)	(105.89–110.83)	(80.52–89.16)	(18.133–28.897)
SBP (mm Hg)	120 (120–130)	110 (100–120)	0.009
DBP (mm Hg)	80 (70–85)	70 (60–80)	0.004
TC (mg/dL)	190.00 (178.00–211.00)	186.00 (161.00–200.00)	0.377
TG (mg/dL)	156.50 (106.00–200.00)	115.00 (91.00–147.00)	0.029
HDL cholesterol (mg/dL)	37.50 (35.00–39.00)	47.00 (40.00–58.00)	<0.001
LDL cholesterol (mg/dL)	125.00 (103.00–132.00)	109.00 (83.00–131.00)	0.125
FPG (mg/dL)	102.50 (91.00–123.00)	85.00 (83.00 - 92.00)	<0.001
Fasting insulin level	14.65 (12.40–20.00)	12.40 (7.10–16.80)	0.077
Creatinine (mg/dL)	0.7 (0.70–0.90)	0.80 (0.70–0.80)	0.406
SUA (mg/dL)	6.30 (5.40–6.60)	4.50 (4.00–5.40)	<0.001
Women *n*(%)	**38 (43.18)**	**50 (56.82)**	
Age (y)	33 (28–44)	25 (21–36)	0.017
Number of MetS components	3 (3–4)	1 (0–1)	<0.001
BMI (kg/m²)	28.90 (26.80–31.60)	23.00 (19.68–25.23)	<0.001
WC (cm)	95.00 (89.00–98.00)	78.00 (69.75–83.75)	<0.001
SBP (mm Hg)	110 (100–130)	110 (100–111)	0.044
DPB (mm Hg)	70 (70–80)	70 (60–70)	<0.001
TC (mg/dL)	170.00 (151.00–198.00)	160.00 (133.00–188.50)	0.066
TG (mg/dL)	152.00 (133.00–192.00)	89.00 (68.50–149.75)	<0.001
HDL cholesterol (mg/dL)	40.00 (37.00–47.00)	51.00 (43.00–70.00)	<0.001
LDL cholesterol (mg/dL)	105.00 (75.00–142.00)	93.00 (66.50–106.50)	0.023
FPG (mg/dL)	101.00 (88.00–102.00)	88.00 (83.75–93.25)	<0.001
Fasting insulin level	14.60 (10.30–19.20)	12.00 (8.38–16.63)	0.051
Creatinine (mg/dL)	0.50 (0.50–0.60)	0.60 (0.50–0.63)	0.009
SUA (mg/dL)	4.90 (4.10–5.70)	3.70 (3.25–4.30)	<0.001

Abbreviations: WC, Waist circumference; FMF, Familial Mediterranean fever; MetS, metabolic syndrome; BMI, body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TC, Total cholesterol; TG, triglycerides; SUA, serum uric acid; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Continuous variables with normal distributions are expressed as mean ± Standard deviation (95% CI), whereas continuous variables with non-normal distributions are expressed as median (interquartile range) (IQR) (25%–75%). Categorical variables are expressed as percent n(%). Groups were compared using Independent sample *t* test (P value is given with mean differences with 95% confidence intervals between groups) or the Mann-Whitney U-test for continuous variables and the chi-squared test for categorical variables.

Finally, multivariate binary regression analysis showed that MS was predicted by serum uric acid levels independent of age, sex and other potential confounders (Table 5) and multivariate linear regression analysis showed that number of MS components were predicted by serum uric acid levels independent of age, sex and all other potential confounders (Table 6).

Discussion

This is the first study to investigate the prevalence of MetS and the correlation between presence of MetS and sex-specific SUA levels in patients with FMF. According to the results of our study, MetS prevalence was found higher in patients with FMF, and the prevalence and number of MetS components were significantly increased with increasing SUA quartiles in all patients with FMF (both sexes). We found a positive correlation between SUA and FBG, SBP, DBP, WC, BMI, TG, and LDL-C, and a negative correlation with HDL-C in male patients with FMF, and a positive correlation between SUA and BMI, WC, DBP, TC, TG, and FBG in female patients with FMF. Furthermore, we found that MS and the number of MS components were predicted by serum uric acid levels independent of age, sex and all other potential confounders.

Sarkis et al[29] showed that MetS prevalence was 17% in patients with FMF and 0% in healthy controls. In our study, MetS prevalence was found to be 42.90% (95% CI: 34.9–51.1%) in patients with FMF and 28.57% (95% CI: 21.6–36.4%) in the control group (OR = 1.88, 95% CI = 1.17–3.01, P = 0.009); MetS prevalence was higher in female patients with FMF (43.2%) than in men (42.4%), but the difference was not statistically significant. Bayram et al[30] demonstrated that MetS prevalence in healthy subjects was 40.1% in females and 25.2% in males, with an overall rate of 34.9%. Turkish MetS research data suggested that the prevalence of MetS was 28.8% in males and 41.1% in females, with an overall rate of 35%.[31] In our study, MetS

Table 3. Clinical and Biochemical Characteristics of the Patients with FMF According to Sex-Specific Serum Uric Acid Quartiles

Variables	Q1	Q2	Q3	Q4	*P*-Value
Men (n)	**24**	**16**	**14**	**12**	
MetS, No. (%)	3 (12.5)	7 (43.75)	9 (64.29)	9 (75.00)	<0.001
Number of MetS components	0.50 (0.0–1.75)	1.50 (1–3)	3.00 (1–4)	3.50 (3–4)	<0.001
SUA (mg/dL)	4.05 (3.53–4.48)	5.30 (4.88–5.40)	6.10 (5.70–6.30)	6.65 (6.60–6.90)	<0.001
Age (years)	37 (26–52)	35.5 (34.3–47.5)	44 (33–52)	46 (42–49)	0.418
BMI (kg/m^2)	22.35 (20.94–29.15)	24.10 (20.40–28.48)	30.70 (28.30–33.70)	32.15 (30.70–33.30)	<0.001
WC (cm)	81.50 (73.25–93.50)	90.00 (72.25–102.8)	104.00 (103.0–109.0)	110.50 (109.0–114.0)	<0.001
SBP (mm Hg)	110 (100–120)	120 (112.5–135.0)	130 (110–140)	120 (110–130)	0.057
DBP (mm Hg)	70.0 (60.0–77.5)	77.5 (70.0–96.3)	80.0 (70.0–90.0)	70.0 (70.0–80.0)	0.002
TC (mg/dL)	168.00 (142.25–195)	189.50 (182.3–189.5)	190.00 (187.0–200.0)	191.00 (175.0–217.0)	0.030
TG (mg/dL)	104.50 (76.0–145.25)	127.50 (98.0–148.5)	179.00 (115.0–224.0)	156.00 (106.0–204.0)	0.007
HDL cholesterol (mg/dL)	46.50 (41.00–52.00)	41.50 (36.00–67.25)	39.00 (37.00–47.00)	36.50 (34.00–38.00)	0.009
LDL cholesterol (mg/dL)	97.50 (61.5–126.75)	116.50 (88.0–207.25)	127.00 (109.0–132.0)	121.00 (109.0–126.0)	0.071
FPG (mg/dL)	87.50 (82.75–97.00)	86.50 (83.25–91.00)	92.00 (83.00–97.00)	113.00 (102.0–147.0)	<0.001
Fasting insulin level (μU/mL)	14.60 (7.43–33.60)	14.85 (7.25–16.68)	13.70 (12.20–16.00)	13.30 (12.40–30.50)	0.903
Creatinine (mg/dL)	0.80 (0.70–0.80)	0.85 (0.70–0.98)	0.80 (0.70–0.80)	0.75 (0.60–0.90)	0.209
Women *(n)*	**32**	**16**	**22**	**18**	
MetS, No. (%)	5 (15.63)	8 (50.0)	12 (54.55)	13 (72.22)	<0.001
Number of MetS components	1.00 (0–2)	2.50 (1–3)	2.00 (1–3)	3.00 (3–4)	<0.001
SUA (mg/dL)	3.50 (3.03–3.68)	4.00 (3.93–4.10)	4.80 (4.70–4.90)	5.80 (5.58–6.30)	<0.001
Age (y)	24 (20–35)	37 (22–44.75)	32 (28–36)	35 (39–46.25)	0.022
BMI (kg/m^2)	21.60 (18.40–25.15)	25.80 (21.88–28.95)	25.50 (23.70–28.60)	29.20 (28.28–33.00)	<0.001
WC (cm)	74.00 (68.25–79.75)	86.50 (81.25–94.50)	93.00 (82.00–98.00)	96.00 (92.00–104.5)	<0.001
SBP (mm Hg)	110 (100–118.75)	110 (100–117.50)	110 (100–130)	110 (90–130)	0.672
DBP (mm Hg)	70 (50–70)	70 (62.50–81.25)	70 (60–70)	80 (60–80)	0.042
TC (mg/dL)	159.00 (129.0–178.8)	152.50 (137.8–191.8)	170.00 (158.0–207.0)	186.00 (140.8–214.5)	0.035
TG (mg/dL)	110.00 (78.8–164.8)	77.50 (59.50–157.8)	152.00 (120.0–192.0)	148.00 (119.3–183.5)	0.005
HDL cholesterol (mg/dL)	49.00 (40.00–60.00)	48.00 (39.00–54.00)	45.0 (37.00–70.00)	45.00 (35.25–53.50)	0.654
LDL cholesterol (mg/dL)	97.50 (68.5–118.0)	75.00 (62.75–115.0)	97.00 (72.00–128.0)	119.00 (82.75–155.3)	0.039
FPG (mg/dL)	88.00 (84.00–93.75)	92.50 (85.50–101.8)	92.00 (87.00–97.00)	101.00 (93.00–101.3)	0.015
Fasting insulin level	14.70 (8.63–21.00)	12.45 (8.28–19.05)	10.40 (9.20–15.40)	14.50 (10.10–18.08)	0.567
Creatinine (mg/dL)	0.55 (0.50–0.60)	0.55 (0.50–0.60)	0.60 (0.60–0.70)	0.50 (0.50–0.60)	<0.001

Abbreviations: WC, waist circumference; FMF, familial Mediterranean fever; MetS, metabolic syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; SUA, serum uric acid; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
The categories pertaining to men were Q1) <4.8 mg/dL Q2) 4.8–5.5 mg/dL Q3) 5.6–6.4 mg/dL and Q4) ≥ 6.5 mg/dL; and those pertaining to women were Q1) <3.8 mg/dL Q2) 3.8–4.2 mg/dL Q3) 4.3–5 mg/dL and Q4) ≥ 5.1 mg/dL. Continuous variables with normal distributions are expressed as mean ± standard deviation, whereas continuous variables with non-normal distributions are expressed as median (interquartile range) (IQR) (25%–75%). Categorical variables are expressed as percent *n*(%). Groups were compared using Kruskal–Wallis test for continuous variables and the chi-squared test for categorical variables.

Table 4. Correlation between SUA Levels of Men and Women with FMF and Metabolic Risk Factors

Variables	Men (*n* = 66) r (95% CI)	*P*	Women (*n* = 88) r (95% CI)	*P*
WC (cm)	0.709 (0.564–0.811)	<0.001	0.756 (0.650–0.833)	<0.001
SBP (mm Hg)	0.327 (0.093–0.527)	0.007	0.077 (-0.134–0.281)	0.478
DBP (mm Hg)	0.388 (0.162–0.575)	0.001	0.266 (0.060–0.450)	0.012
TG (mg/dL)	0.360	0.003	0.276	0.009
HDL cholesterol (mg/dL)	-0.424 (-0.604/–0.203)	<0.001	-0.191 (-0.385–0.019)	0.075
Fasting plasma glucose (mg/dL)	0.348 (0.116–0.544)	0.004	0.337 (0.138–0.510)	0.001

Abbreviations: WC, waist circumference; FMF, familial Mediterranean fever; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, Total cholesterol; TG, triglycerides; SUA, serum uric acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

prevalence was found to be 37.0% in women and 16.1% in men, with an overall rate of 28.6% in the control group; MetS prevalence was higher in women than in men.

Balkarli and colleagues[32] investigated the genetic distribution of the *MEFV* gene in their study, and they found that the heterozygous R202Q mutation was more

Table 5. Multivariate Binary Regression Analysis of Uric Acid Level (mg/dL) as a Predictor for Metabolic Syndrome

	Beta (95% CI)	*P* Value
Simple	3.806 (2.479 – 5.842)	<0.001
Model 1	5.897 (3.359 – 10.352)	<0.001
Model 2	2.098 (1.072 – 4.104)	0.031

Model 1: Adjusted for sex and age; Model 2: Adjusted for all other confounders.

frequent in patients with MetS. Although the diagnosis of FMF was not made clinically in the patients, the authors proposed that the mutation in the *MEFV* gene caused this condition by leading to subclinical inflammation. In our study, the genetic distribution of the *MEFV* gene in our patients was not analyzed, but the results showed that MetS prevalence was higher in patients with FMF compared to the control group. We believe that a mutation in *MEFV* gene may increase the prevalence of MetS by increasing the release of inflammatory markers (e.g., IL-1β, TNF-α) in patients with FMF more actively in the active period, but also in the subclinical period.

Age, lifestyle-related factors, and a family history of disease are well-known risk factors leading to the development of MetS and affecting SUA.[33-35]

A wide range of epidemiologic researches have observed a positive correlation between MetS prevalence and SUA levels. Nevertheless, whether increased levels of UA are a risk factor or only a biomarker in terms of MetS development and its progression is a question of ongoing debate.[36,37] In this study, we demonstrated that MetS prevalence increased progressively in both women and men with FMF as SUA levels increased.

Clinical and animal studies conducted recently show that increased SUA levels may assume a pathogenic role in MetS development.[38] It has been verified in basic research that SUA plays a causal role in the onset of MetS and it is beneficial to decrease SUA levels for prevention or reversion of MetS.[39-41] The protective impact of lowered levels of SUA in MetS development has also been confirmed by a clinical trial.[42] A recent analysis of National Health and Nutrition Examination Survey (NHANES III) demonstrated that the MetS prevalence increased considerably with increasing levels of SUA. MetS prevalence (NCEP criteria) ranged from 18.9% for UA levels <6.0 mg/dL, to 70.7% for levels ≥10.0 mg/dL. In the subgroups classified in terms of age, sex, BMI, alcohol consumption, HT and diabetes, the increasing trends showed continuity.[43] The correlation between SUA and MetS may be interpreted by a number of possible mechanisms. First, an experimental study conducted previously suggested that SUA might stimulate redox-dependent signaling and oxidative stress.[44] Paneni et al[45] reported that oxidative stress had a notable effect on insulin resistance, which could pave the way for glucose metabolic disorder. Secondly, glucose uptake in skeletal muscle is to some extent dependent on the increase in blood flow regulated by insulin, which prompts endothelial cells to excrete nitric oxide.[46] It was shown that there was a greater chance for mice that lacked endothelial nitric oxide synthase to develop MetS components.[47] Thirdly, SUA has been depicted to mediate systemic inflammation and endothelial dysfunction.[48,49]

To the best of our knowledge, this is the first study in Turkey to report the prevalence of MetS in FMF and the relationship between SUA concentrations and MetS status by sex in patients with FMF. We believe that the results of this study may guide future prospective studies. However, several limitations of the present study should be mentioned. First, the small sample size of our study and its cross-sectional design limit the ability to describe causal relationships. Second, factors such as diet, alcohol consumption or mental health, which have not been evaluated in this study, may be confounders in this relation.

In conclusion, MetS prevalence was found to be higher in patients with FMF, and the prevalence of Mets and the number of MetS components were significantly increased with increasing SUA quartiles in both men and women with FMF. SUA levels, as a biochemical marker, could be a strong and independent predictor of MetS in patients with FMF, and could provide substantial help with early diagnosis and management of MetS.

Authors' Contribution

Study design: HG, NSA, GYC; Data collection: HG, GYC; Data analysis: NSA; Drafting the manuscript: HG, NSA, GYC; Critically revising the manuscript: All authors. All authors have read the manuscript and approved its final version.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

This study was approved by the Ethics Committee of Kahramanmaras Sütcü Imam University (No. 2017/17-05), Kahramanmaras, Turkey.

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