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Musculoskeletal ultrasound abnormalities in asymptomatic hyperuricemic patients: Association with cardiovascular risk factors

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Abstract

To assess the relation between musculoskeletal ultrasound (MSUS) abnormalities and cardiovascular risk factors in asymptomatic and symptomatic hyperuricemic patients. The study included 66 hyperuricemic patients. 33 were asymptomatic and 33 were symptomatic. The socio-demographic features, body mass index (BMI), blood pressure measurement and musculoskeletal examination were recorded. Serum uric acid (SUA), serum creatinine (s.Cr.), total cholesterol, high density lipoprotein (HDL) and triglycerides (TG) were measured and estimated glomerular filtration rate (e GFR) was calculated using chronic kidney disease-epidemiology collaboration (CKD-EPI). Cardiovascular risk was calculated using Systematic Coronary Risk Evaluation of the European Society of Cardiology (SCORE/ESC) and Atherosclerotic Cardiovascular Disease of American College of Cardiology (ASCVD/ACC). MSUS of the knees, ankles and 1st metatarsophalangeal joints (MTPs) was performed and specific gout signs (aggregates, double contour and tophi) were assessed. There was no association between MSUS abnormalities and either individual or overall cardiovascular risk factors except the negative correlation between the age and the high density lipoprotein (HDL) level and the positivity of the patients (presence of at least one of the specific gout sign "aggregates, double contour or tophi" in at least one out of the six assessed joints "both knees, ankles and 1st MTPs" among the symptomatic group. The association between MSUS abnormalities and cardiovascular risk factors in the hyperuricemic patients is not yet clear and further studies are needed to introduce it as a screening modality for these patients.

Keywords: Musculoskeletal ultrasound, hyperuricemia, asymptomatic, cardiovascular.

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1. Introduction

Uric acid is the final product of hepatic purine metabolism. Hyperuricemia is defined as abnormally high serum uric acid (SUA) levels that exceed the renal excretion capacity withsubsequent formation of urate crystals in different body fluids [1]. In practice, it is defined asSUA level above 6.8 mg/dl [2]. The prevalence of hyperuricemia is obviously rising during thelast years [3]. Its damaging effects are not limited to joints and periarticular structures but extend to other systems as renal, hepatic and cardiovascular systems [4]. Clinically, hyperuricemia may be asymptomatic or symptomatic and gout is the commonest presentation [5]. Traditional staging system described two clinical stages of symptomatic hyperuricemia, acute gouty arthritis which is characterized by intermittent course of inflammatory arthritis [6] and chronic tophaceous gout [7]. Both asymptomatic and symptomatic hyperuricemia are subdivided into other two pathological subtypes or stages. Asymptomatic type is subdivided according to the evidence of monosodium urate (MSU) crystal deposition into stages A and B while symptomatic type is subdivided according to theevidenceof disease complications (as bone erosions and tophi) into stages C and D [8]. In the past, the relation between hyperuricemia and cardiovascular disease (CVD) was not well established [9]. The association between hyperuricemia and CVD became more prominent [10]. The SUA level may be considered one of the biochemical markers for CVD and may behelpful in the patient's follow up and detection of diseases prognosis [11, 12]. So, it is valuable to search for other CRFs in the hyperuricemic cases either asymptomatic or symptomatic. Proper management of these factors is required to lower the cardiovascular risk in these patients [13].Although hyperuricemia is one of the CRFs, treatment of asymptomatic hyperuricemia is controversy [4]. Musculoskeletal ultrasound (MSUS) is an important advanced modality in the management and follow up of several rheumatological diseases being safe, cheap and highly sensitive and specific [14]. MSUS helps detection of crystal deposition through guided joint aspiration and non invasively through recognition the specific signs of gout and hyperuricemia [15]. Moreover, it can discriminate between different types of crystal arthropathies [16]. There are two groups of gout MSUS findings, nonspecific like synovial proliferation, joint effusion and bone erosions and specific

like aggregates, double contour sign (DCS) and tophi [17]. The current study aims to assess the relation between MSUS abnormalities and cardiovascular risk factors in asymptomatic and symptomatic hyperuricemic patients.

2. Patients and methods

Hyperuricemic patients (SUA level > 6.8 mg/dl) symptomatic and asymptomatic cases were recruited from the Rheumatology and Internal medicine clinics of Beni-Suef University Hospital. Symptomatic cases had present or past history of acute gouty attack/s or clinically detected chronic tophaceous gout. Each group included 33 patients. Patients with another inflammatory arthritis such as rheumatoid arthritis, cases with hypercalcemia or advanced hepatic and renal diseases were excluded. It was extracted from an MD thesis. Ethical approval was obtained from ethical committee of Scientific Research, Faculty of Medicine, Beni-Suef University (FMBSURC/09072023/HUSSIEN). All participants gave an informed consent after explaining the purposes and the methodology of the study. The socio-demographic data and past history of medical diseases were recorded, body mass index (BMI) was calculated and blood pressure was measured for all patients. Thorough clinical examination of peripheral small and large joints was performed. SUA level and serumcreatinine (s.Cr) were measured; estimated glomerular filtration rate (eGFR) was calculatedusing chronic kidney disease-epidemiology (CKD-EPI) creatinine equation. Total cholesterol, triglycerides (TG) and high density lipoprotein (HDL) were assessed. Cardiovascular risk was calculated using well known scoring systems; Systematic Coronary Risk Evaluation of European Society of Cardiology (SCORE/ESC) [18] and Atherosclerotic Cardiovascular Disease of American College of Cardiology (ASCVD/ACC) that were further categorized into low, borderline, intermediate and high risk [19]. Knees, ankles and 1stMTPs were examined by MSUS searching for specific signs of hyperuricemia and gout including aggregates, DCS and tophi (LOGIQ P9 GE, Milwaukee, USA) with a 6-15 MHz matrix probe for the ankles and knees, and hockey-stick probe (8-18MHz) for the 1st MTPs. A patient and joint was considered positive when there is at least one specific MSUS signs of hyperuricemia and gout sign. Statistical analysis: It was performed using statistical package for social science (SPSS) v. 25. Variables were presented as mean ±standard deviation (SD) or numbers and percent (%). Independent T-test and Chi-square test were considered for comparison. Significance was set at $p<0.05$.

3. Results

The sex, smoking state, history of diabetes and BMI were comparable between asymptomaticand symptomatic groups. Symptomatic group was significantly older (p=0.021), hypertension was more frequent (p=0.003), SCORE and ASCVD risk scoring system showed higher cardiovascular risk (p=0.004 and p=0.002 respectively) (Table 1). Aggregates of the knee, DCS and tophi of the ankle in hyperuricemic patient are presented in figure1. MSUS revealed aggregates of right knee were more frequent in asymptomatic patients (p=0.039) and tophi of right 1stMTPs was more in the symptomatic (p=0.037). The asymptomatic group had 41 DCS, 8 aggregates and 40 tophi while the symptomatic had 44 DCS, 6 aggregates and 72 tophi (the maximal number of each gout sign in each group = number of the group patient "33" x number of the assessed joints "6" = 198). On comparing those with and without positive MSUS signs or joints (n=25 vs. n=8) There was no significant difference of the SCORE (p=0.58), ASCVD (p=0.971), age (p=0.49), cardiovascular risk factors and positivity of patients in asymptomatic group while the relation between age (p=0.04) and HDL level (p=0.04) with positivity of patients was significant in the symptomatic group. Comparisons of SCORE and ASCVD in hyperuricemic patients with and without positive MSUS signs are presented in tables 2 and 3 respectively. ASCVD risk score was applied in only 22 asymptomatic patients and 29 symptomatic as the score could not be calculated for patients whose age was outside the respective range ofapplicability and for participants with a prior history of coronary heart disease, peripheral arterial disease and stroke. Characteristics of asymptomatic and symptomatic patients with and without positive MSUS signs are presented in table 4 and 5 respectively. There was no significant association between the number of positive MSUS signs or positive joints with the cardiovascular risk factors, SCORE and ASCVD risk score in both groups but there was a significant association between the number of positive MSUS signs (r=0.47,p=0.006) and positive joints (r=0.44, p=0.01) with the SUA level in the asymptomatic patients.

4. Discussion

Although the identification of monosodium urate crystals (MSU) by polarized light microscopy is the gold standard for diagnosing gout, synovial fluid analysis is not always available. Earlydiagnosis and treatment allows avoiding irreversible structural damage, comorbidities, and asevere impact on the quality of life of patients [20]. In Egyptian patients with gout, the level ofSUA, severity and presenceof MTPpunched-out erosions were closely relatedto insulinresistance and metabolic syndrome [21]. Furthermore, in a nation-wide study it was reportedthat US features of the knees even in suspected gouty arthritis patients represent a potentially imperative window to encompass the disease spectrum [22]. Key progress in the clinical practice of rheumatology especially gout, is the innovation of advanced imaging modalities such as MSUS [23]. This noninvasive tool allows detecting aggregates of microcrystals at multiple anatomical sites to establish a diagnosis [20]. Recently, an exciting potential role of MSUS was suggested in the evaluation of subjects with asymptomatic hyperuricemia as MSU crystal deposits including aggregates, double contour sign and/or tophi in intra-and periarticular tissues has been demonstrated. Yet, the value and potential application of US in asymptomatic hyperuricemia remain to be clearly delineated [24]. Although individuals with asymptomatic hyperuricemia lack ultrasound features of inflammation or structural joint changes, a similar frequency of urate deposition to those in patients with gout have been demonstrated [25]. Attempts to develop MSUS features-based scoring system to evaluate theseverity of gout and asymptomatic hyperuricemia have been developed [26]. However, therelation between MSUS signs and cardiovascular risk factors in hyperuricemic patients is notyet well established.

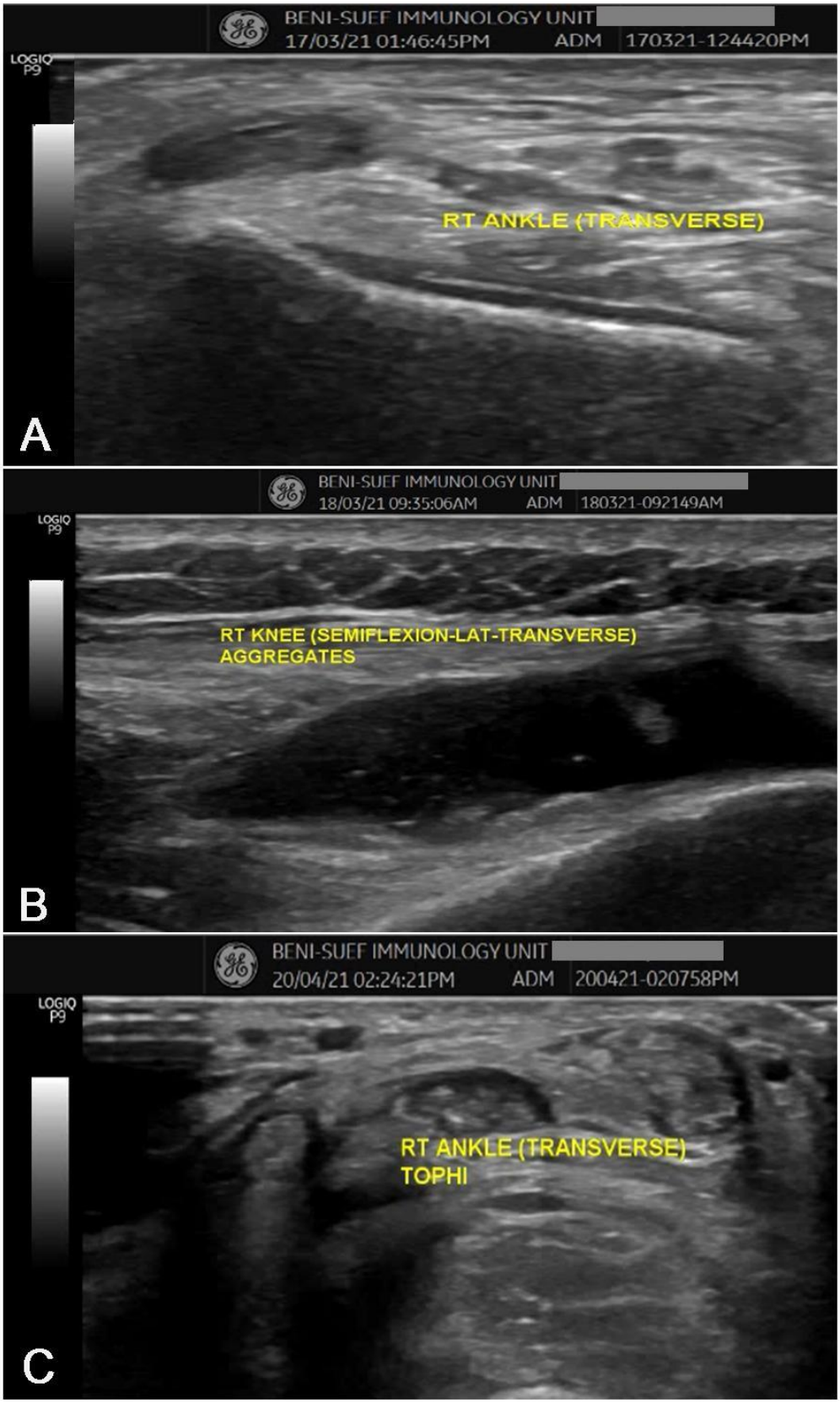

Figure 1: Musculoskeletal ultrasound of different patients in both group where (A) and (C) of asymptomatic hyperuricemic patients while (B) of symptomatic hyperuricemic patients.These joints abnormalities showing (A) Double contour sign (right ankle), (B) aggregates (right knee) and (C) Tophi (right ankle).

Table 1: Basic characteristics of the hyperuricemic patients; asymptomatic and symptomatic

Variable mean±SD or n(%)	Hyperuricemic patients (n=66)		p
	Asymptomatic (n=33)	Symptomatic (n=33)	
Age (years)	50.8±17.1	60.2±15.1	**0.02**
Males:Female	15:18 (0.83:1)	22:11 (2:1)	0.08
Duration of gout (years)	-	3.3±4.4	-
Smokers	2(6.1)	5(15.2)	0.23
Hx of hypertension	12(36.4)	24(72.7)	**0.003**
SBP (mmHg)	126.4±17.8	130.2±20.3	0.42
DBP (mmHg)	81.1±11.4	82.6±12.2	0.6
History of diabetes	6(18.2)	11(33.3)	0.16
Body mass index	31.3±9.8	31.2±7.3	0.95
SUA (mg/dl)	9.1±2.2	9.5±1.7	0.45
sCr.(mg/dl)	2.7±2.6	2±2.6	0.27
eGFR	50.2±39.6	54.4±31.6	0.64
Cholesterol (mg/dl)	193.1±55.6	187.9±55.9	0.71
Triglycerides (mg/dl)	196.5±115.7	184.3±155.77	0.72
HDL (mg/dl)	41.8±16.3	39.1±12.4	0.45
+ve joints	2±1.6	3±1.5	**0.02**
+ve MSUS signs	(2.91±2.4)	3.79±2.4	**0.04**
SCORE	2.1%±2.8%	4.4%±4.3%	**0.004**
ASCVD	8.9%±9%	19.8%±15.7%	**0.002**

SBP: systolic blood pressure, DBP: diastolic blood pressure, SUA: serum uric acid, sCr.: serumcreatinine, eGFR: estimated glomerular filtration rate, HDL: high density lipoprotein, SCORE: Systematic COronary Risk Evaluation, ASCVD: Atherosclerotic Cardiovascular Disease riskscore.Bold values aresignificant at $p<0.05$.

Table 2: Comparison of SCORE in asymptomatic and symptomatic hyperuricemic patients with and without positive musculoskeletal ultrasound signs

Joints *mean±SD*	SCORE according to MSUS findings in hyperuricemic patients (n=66)								
	DC		p	Aggregates		p	Tophi		p
	No	*Yes*		*no*	*Yes*		*no*	*yes*	
Asymptomatic group (n=33 patients)									
Knee (n=66)	Maximal number of each sign in the group= number of the patient in the group X both sides = 33 X 2 =66								
R	1.8±2.5	3.3±3.7	0.23	2.2±2.9	1.8±1.7	0.79	1.8±2.6	2.8±3.2	0.38
L	2.3±2.9	0.7±1.1	0.36	2.1±2.8	2(n=1)	0.97	2.2±3.1	1.7±1.4	0.23
Ankle (n=66)	Maximal number of each sign in the group= number of the patient in the group X both sides = 33 X 2 =66								
R	1.7±2.5	3.2±3.2	0.15	-	-	-	2.2±3	1.8±1.3	0.79
L	1.8±2.8	2.5±2.8	0.47	2.1±2.8	2 (n=1)	0.97	2.1±2.8	2(n=1)	0.97
1stMTP(n=66)	Maximal number of each sign in the group= number of the patient in the group X both sides = 33 X 2 =66								
R	2.1±2.8	2 (n=1)	0.97	2.2±2.9	1.5±0.7	0.76	2±2.5	2.6±3.9	0.65
L	2.4±2.9	0.3±0.5	0.16	-	-	-	1.5±1.7	3.5±4.3	0.07
Symptomatic group (n=33)									
Knee	Maximal number of each sign in the group= number of the patient in the group X both sides = 33 X 2 =66								
R	4.2±4.4	5.1±4.2	0.59	-	-	-	4.1±4.3	4.8±4.5	0.68
L	4.4±4.6	4.3±2.6	0.96	4.3±4	9(n=1)	0.29	4.3±4.2	4.7±4.7	0.59
Ankle	Maximal number of each sign in the group= number of the patient in the group X both sides = 33 X 2 =66								
R	4.3±4.8	4.7±3	0.85	-	-	-	4.6±4.6	3.8±3.2	0.72
L	5.3±5.2	3.5±2.9	0.24	-	-	-	4.5±4.6	4.2±3.3	0.9
1stMTP	Maximal number of each sign in the group= number of the patient in the group X both sides = 33 X 2 =66								
R	4.2±4.2	11(n=1)	0.13	4.8±4.3	0.7±0.5	0.12	4.6±4.5	4.3±4.3	0.85
L	4.6±4.4	2.3±2	0.39	4.5±4.4	3±2.8	0.64	4.9±5	4±3.7	0.57

SCORE: Systematic COronary Risk Evaluation, MSUS: musculoskeletal ultrasound, DC: double contour, R: right, L: left, MTP: metatarsophalangeal

Table 3: Comparison of ASCVD risk score in asymptomatic and symptomatic hyperuricemic patientswith and without positive musculoskeletal ultrasound signs

Joints *mean±SD*	ASCVD according to MSUS findings in hyperuricemic patients (n=66)								
	DC		p	Aggregates		p	Tophi		p
	No	*yes*		*no*	*yes*		*no*	*Yes*	
Asymptomatic group (n=33)									
Knee									
R	8.1±9	11.1±9.5	0.5	8.5±8.8	11.6±12.1	0.6	8.8±9.5	9.2±8.6	0.93
L	9.4±9.3	3.9±3.1	0.43	9.1±9.2	6.2 (n=1)	0.77	8.7±9.2	9.7±9.2	0.5
Ankle									
R	10.8±10.5	6.3±5.9	0.26	-	-	-	9.2±9.6	7.1±2.6	0.71
L	9±10.8	8.9±7.7	0.98	9.1±9.2	6.2 (n=1)	0.77	9.1±9.2	6.2(n=1)	0.77
1st MTP									
R	9.1±9.2	6.2 (n=1)	0.77	9.4±9.3	4.4±2.6	0.47	7.9±8.6	13.5±10.6	0.28
L	9.5±9.2	2.7±2.8	0.32	-	-	-	6.5±6.1	12.3±11.6	0.14
Symptomatic group (n=33)									
Knee									
R	20.3±17.8	18.8±10.5	0.96	-	-	-	19.1±15.6	20.5±16.3	0.81
L	20.1±17.4	18.7±7.3	0.85	19.5±15.9	29.1 (n=1)		18.9±15.2	21.3±17.2	0.82
Ankle									
R	18.9±17.6	21.9±10.9	0.64	-	-	-	19.4±16.1	21.7±15.1	0.77
L	26±19.9	14.8±9.1	0.05	-	-	0.31	19.8±16.3	20.2±13.6	0.96
1st MTP									
R	19.9±16	19.1 (n=1)	0.96	21.1±15.5	2.7±2.2	0.11	19.4±17.7	20.3±13.5	0.88
L	19.8±15.9	20.1±17.2	0.98	20.5±16	11.2±9.9	0.43	22.1±18.8	17.7±12.6	0.46

ASCVD: Atherosclerotic Cardiovascular Disease risk score, MSUS: musculoskeletal ultrasound, DC: double contour, R: right, L: left, MTP: metatarsophalangeal.

Table 4: Characteristics of asymptomatic patients with and without positive musculoskeletal ultrasound signs

Items mean±SD	MSUS signs in asymptomatic patients (n=33)		
	without (n=3)	with (n=30)	P
Age (y)	47±23.4	52±14.9	0.5
BMI	30.9±10.9	31.4±9.7	0.92
SBP (mmHg)	135±13.1	123.6±18.4	0.116
DBP (mmHg)	85±9.3	79.8±11.9	0.29
SUA (mg/dl)	8.6±1.6	9.2±2.3	0.15
sCr. (mg/dl)	4.1±3.4	2.3±2.3	0.1
eGFR	32.4±30.8	55.9±41.1	0.15
Cholesterol (mg/dl)	191.5±65.2	193.7±53.8	0.93
HDL (mg/dl)	42.4±17.8	41.7±16.2	0.9
TG (mg/dl)	162.8±114.7	207.3±116.3	0.35
SCORE	1.6%±2.1%	2.3%±3.1%	0.58
ASCVD score	9.1%±8.5%	8.8%±9.4%	0.97

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, SUA: serum uric acid, sCr.: Serum creatinine, eGFR: estimated glomerular filtration rate, HDL: high density lipoprotein, TG: triglycerides, SCORE/ESC: Systematic COronary Risk Evaluation, ASCVD/ACC: Atherosclerotic Cardiovascular Disease risk score. Bold values are significant at $p<0.05$.

Table 5: Characteristics of symptomatic patients with and without positive musculoskeletal ultrasound signs

Items mean±SD	MSUS signs in symptomatic patients (n=33)		
	without (n=3)	with (n=30)	P
Age (y)	77±11.1	58.5±14.4	**0.04**
Disease duration (y)	2.3±4	3.4±4.4	0.69
BMI	23.9±7.1	31.8±7.1	0.07
SBP (mmHg)	133.3±15.3	129.8±20.9	0.78
DBP (mmHg)	83.3±5.8	82.5±12.7	0.91
SUA (mg/dl)	9.4±2.1	9.5±1.7	0.95
s.Cr. (mg/dl)	1.9±0.9	2±2.7	0.95
eGFR	36.7±16.2	56.2±32.4	0.32
Cholesterol (mg/dl)	160.7±120.1	190.6±48.8	0.39
HDL (mg/dl)	53±16.5	37.8±11.3	**0.04**
TG (mg/dl)	112.7±41.4	191.4±161.5	0.41
SCORE	8.7%±7.4%	4%±3.8%	0.08
ASCVD score	36.4%±18.8%	17.9%±14.6%	0.052

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, SUA: serum uric acid, s.Cr.: Serum creatinine, eGFR: estimated glomerular filtration rate, HDL: high density lipoprotein, TG: triglycerides, SCORE/ESC: Systematic COronary Risk Evaluation, ASCVD/ACC: Atherosclerotic Cardiovascular Disease risk score. Bold values are significant at $p < 0.05$.

This study aimed to clarify that possible link and the relation between MSUS abnormalities "DCS, aggregates or tophi" and the summation of these signs in three joints bilaterally with the cardiovascular risk factors and scoring systems. Current result are in line with the work of Pascart et al. on high-risk gout patients, as there were weak correlations between the urate burden assessed with MSUS (DCS) or dual energy computed tomography (DECT) and the SUA level with and the individual cardiovascular risk components (as increased TG and decreased HDL). Also there was no association between thenumber of joints with DCS and the cardiovascular risk [27]. On the other hand, Lee et al. onpatients with and without tophaceous gout detected by DECT, there was a correlation between total urate volumes of the ankles and feet joints with the10-year Framingham risk for cardiovascular disease. Also there was significantly higher frequency of hypertension and impaired fasting glucose among DECT positive patients [28]. Furthermore, Gamala et al. found that the cardiovascular events history was associated with urate volumes already present at the time of diagnosis of gout detected by DECT [29]. The current results disagree with Andrés et al. who reported that the frequency of moderate-to-severe coronary calcification "which indicates more severe CAD" was significantly higher inasymptomatic hyperuricemia patients with MSU crystals compared to those without or those with normouricemia [30]. Andrés et al. in another study found that the majority of gout patients are at high CV risk with the presence of athermanous plaques [31]. In patients with intercritical gout, an association between sonographic crystal deposits and tophi of the examined joints and tendons with carotid atherosclerosis was detected [32]. Also patients with large tophi had higher levels of calprotectin and more frequent carotid plaque [33]. Recently Wang et al. found that the presence of at least two tophi (detected by MSUS in 2 different sites, joint or tendon, in ankles and foot regions) and carotid plaque could independently predict major adverse cardiovascular events (MACE) in addition to conventionalcardiovascular risk factors in gout patients [34]. Moreover, Lu et al. found that the incidence of hypertension and hyperlipidemia were significantly higher in tophaceous patients [35]. However Andrés et al. [30] showed no association between DCS and tophi detected during MSUS examination and coronary outcomes. On the contrary, others [36] showed that age and the presence of tophi (detected by MSUS) were independent risk factors for the presence of carotid plaques. Gouty arthritis bears a higher risk of atherosclerosis than both rheumatoid arthiritis and asymptomatic hyperuricemia. Perez-Ruiz et al. found that high baseline SUA level and the presence of subcutaneous tophi were both associated with an increased risk of mortality in patients with gout, in most cases attributed to a CV cause. This suggests a plausible pathophysiological link between greater total body urate load and CV disease [37]. Disveld et al. found that the crystal-proven gout was strongly associated with prevalent CVD [38]. In addition, gout patients had an increased association with all-cause disease mortality,especially attributed to CVD, cancer, and infectious diseases. This association is strongest in hyperuricemic and tophaceous patients and in those with a history of peripheral vascular disease, myocardial infarction, and heart failure [39]. We did not correlate MSUS abnormalities with either the gender or the drugs taken by the patients as we assumed that the association was with the final serum urate level. The cross-sectional study design, relatively small sample size, heterogeneity of patients, presence of significantly older symptomatic cases, absence of quantitative assessment of articular urate burden by MSUS and not measuring the tophi volume were limitations to this work. A larger scale longitudinal study is warranted. In conclusion, there was no association between the MSUS abnormalities in

asymptomatic or symptomatic hyperuricemic patients and either individual or overall cardiovascular risk factor except the negative correlation between age and HDL level with the positivity of MSUS signs in symptomatic patients. MSUS screening of asymptomatic hyperuricemic patients is recommended to predict future attacks.

Conflict of interest

The authors declare no conflict of interest.

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