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Time to redefine hyperuricemia? The serum uric acid cut-off level for precipitation might be lower: a pilot study

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Abstract

Background: Hyperuricemia is classically defined as serum uric acid (SUA) value higher than 6.8 mg/dL; between hyperuricemic patients, only 15–20% will develop gout. Our first goal was to find if there is a specificity of the "snowstorm" feature on ultrasound (US) for hyperuricemia. Moreover, we aimed to determine if there is a level of SUA from which the urates tend to appear in the synovial fluid, without generating a typical clinical gouty flare. *Patients, Materials and Methods*: We conducted a cross-sectional, transverse study, including 108 consecutive patients that displayed a set of clinical and imaging features, such as swollen knee and US proof for knee joint effusion. *Results*: Performing binary logistic regression, the relation between the explanatory variable (hyperechogenic spots) and the response variable (SUA) was demonstrated to be a significant one (p=0.005). The value of 0.397 for the statistical *phi* coefficient suggests a medium intensity association between the diagnosis of gout or asymptomatic hyperuricemia and whether the patients have hyperechogenic spots or not. We found the cut-off value for SUA equal to 4.815 mg/dL, regardless of gender, from which, the urate starts to precipitate. Values for men tend to be higher in comparison to the ones found for women (4.95 mg/dL *vs.* 3.9 mg/dL). *Conclusions*: The "snowstorm" aspect of the fluid might be the result of an increased level of SUA and more than this, the cut-off level for SUA to precipitate might be lower than the fore used values.

Keywords: asymptomatic hyperuricemia, snowstorm, hyperechoic spots, ultrasonography, precipitation.

Introduction

The diagnosis approach to microcrystals-related arthritis (MCRA), although heavily reliant on clinical history, physical examination and, especially, polarized light microscopy of synovial fluid, can benefit also from additional information obtained through ultrasonographic (US) examination of the joints. This has led, in the case of gout and calcium pyrophosphate deposition disease (CPPD), to the development of certain imaging features, *e.g.*, double contour sign (DCS), tophi, hyperechoic spots or "snowstorm" appearance, features which are routinely used by examiners to support the diagnosis or to differentiate from other non-MCRA [1]. Arthritis flares can be attributed to a variety of causes, both inflammatory and infectious. Thus, US can offer a fast insight into the joint damage until the diagnostic work-up is underway. Main joint diseases which can be differentiated from MCRA using US are rheumatoid arthritis (RA), osteoarthritis (OA), septic arthritis (SA) and spondyloarthropathies, such as reactive arthritis (ReA).

Problems arise when MCRA overlaps with another inflammatory joint disease, for example in the case of gout and RA [2]. CPPD, also has the propensity to complicate other joint pathologies, such as RA and OA, with significant prevalence among RA patients, up to 25.8% in one study [3]. When compared to plain radiography, US has demonstrated a superior detection rate of bone damage in gout patients [4], and better sensitivity for evidence of calcium deposits in CPPD [5]. Previous studies on the performance of US in gout generally yielded a moderate sensitivity with high specificity, of up to 99% for DCS [6, 7]. Even in early gout classification, using a specific set of four joints evaluation, US can be feasible and reliable [8]. Typically, research has been aimed at patients with confirmed diagnosis of MCRA, on which reliability of US features is tested using a set of the aforementioned criteria. The prevalence of the crystal deposit US criteria in

non-MCRA diseases and the general population has rarely been the main objective in research.

Aim

From this standpoint, we designed our pilot study in a somewhat reverse manner, starting from a pool of patients with various musculoskeletal diseases and specific clinical findings, which were randomly examined by US. Our first goal was to find if there is a relation between the "snowstorm" and hyperuricemia, as, for the moment, there are studies correlating this type of finding with confirmed diagnosis of gout [7]. Moreover, we aimed to determine if there is a level of serum uric acid (SUA) from which the urates tend to appear in the synovial fluid, without generating a typical clinical gouty flare.

Patients, Materials and Methods

Study design

This cross-sectional, two-center study (Emergency County Hospital, Craiova, and Dr. Avram Medical Center, Timişoara, Romania) was performed between 2017–2019. We included in our group all the patients that displayed a set of pre-determined clinical and imaging features, such as swollen knee and US proof for knee joint effusion, except the ones that had a trauma in the recent past. The study was approved by the Local Ethics Committees, being performed in accordance with the 1964 Declaration of Helsinki and its later amendments and the written informed consent was obtained from all patients before study entry. Thus, 108 consecutive patients, with swollen knee joints, regardless of the cause, except trauma, were included in the study, and underwent clinical, serological [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and SUA] and US examination. To mention, none of the patients known with gout was specifically in the acute phase when SUA was evaluated.

US examination was carried out using two US machines, an Esaote MyLab25 Gold (Genoa, Italy) and a GE Logiq S7 (General Electric, Boston, USA), with high frequency probes (Esaote 10–18 MHz and GE 6–15 MHz) at the level of the suprapatellar pouch, with the knee slightly flexed (approximately 30º) and at the level of the femoral cartilage, to identify any crystal deposits at this level, visible as a DCS. Definitions used for "snowstorm" or DCS were the previously known ones [9]. US was performed by two *European Alliance of Associations for Rheumatology* (EULAR) recognized, experienced examiners (AFV and CA), with more than 10 years of experience in musculoskeletal US. Findings were confirmed between the two examiners, to confirm inter-reader's reliability and to avoid intermachine variability related biases. The findings were noted in terms of presence and absence. Representative still images were stored on the hard drive of the machines.

Statistical analysis

Results for continuous clinical and demographic variables are reported as the mean ± standard deviation (SD) (for normally distributed variables) or median (interquartile range, for not normally distributed variables), and the results for categorical variables, reported as numbers (percentage per category). We divided the patients into two groups: patients with hyperechogenic spots (Group 1) and patients without hyperechogenic spots (Group 2). The two groups were compared using *t*-test (if normally distributed), Mann–Whitney *U*-test (if not normally distributed) or χ^2 (*chi*-squared) test. We used the receiver operating characteristic (ROC) curves analyses to evaluate the diagnostic efficiency of a diagnostic test (the dichotomous variable: hyperechogenic spots), the cut-off value for SUA (the maximum value of the Youden index). We used binary logistic regression to predict whether a patient is likely to have the presence of hyperechogenic spots. We generated a logistic regression model from which predictions can be made, with a probability, about the likelihood that a patient has or not hyperechogenic spots. Because at this moment, we know that SUA level is different in men and women, two models were assessed: regardless of gender (Model 1) and according to gender (Model 2). A cut-off was assessed for both models. The diagonal reference line is indicative of a 0 level for both specificity and sensitivity and thus, would not be a very good instrument – a good instrument would have high sensitivity and high specificity, with area under the curve (AUC) closer to 1. Significance tests were 2-tailed and *p*-value <0.05 was considered statistically significant. Tests were performed using GraphPad Prism 9.3.1 (GraphPad Software, San Diego, CA, USA).

Results

The demographic data and other characteristics for the 108 patients are summarized in Table 1. The mean age of the patients was 63 years old with SD=12.8 and range between 19 and 84 years old. There were more women than men in our study (72.2% *vs.* 27.8%).

Table 1 – *Demographic and diagnostic characteristics*

Characteristics	Hyperechogenic spots			*p*-value
	All (n=108)	*Yes (Group 1) n=76*	*No (Group 2) n=32*	
Age [years]	65.5 (±13.75)	66 (±12.75)	63.5 (±15.75)	0.527
Gender				0.321
Women	78 (72.2%)	57 (53%)	21 (19%)	
Men	30 (27.8%)	19 (18%)	11 (10%)	
ESR [mm/h]^	20 (±20)	20.5 (±19.75)	19 (±26.25)	0.925
CRP [mg/dL]^	2.27 (±4.895)	2.13 (±4.81)	2.9 (±5.18)	0.619
SUA [mg/dL]^	5.24 (±2.67)	5.5 (±2.46)	4.31 (±2.19)	0.006
Diagnosis				
OA	41 (38%)	27 (25%)	14 (13%)	0.528
Other arthritis	28 (26%)	19 (18%)	9 (8%)	0.816
Gout	20 (19%)	16 (15%)	4 (4%)	0.296
CPPD	8 (8%)	6 (6%)	2 (2%)	0.714
Hyperuricemia	9 (8%)	7 (6%)	2 (2%)	0.714
RA	2 (2%)	0	2 (2%)	0.091
DCS				0.838
Yes	6 (6%)	4 (4%)	2 (2%)	
No	102 (94%)	72 (67%)	30 (28%)	
Synovial fluid				
No	13 (12%)	12 (11%)	1 (1%)	0.065
Right knee	31 (29%)	15 (14%)	16 (15%)	0.0024
Left knee	25 (23%)	20 (19%)	5 (5%)	0.319
Both knees	39 (36%)	29 (27%)	10 (9%)	0.521

^: Not-normally distributed variables; CPPD: Calcium pyrophosphate deposition disease; CRP: C-reactive protein; DCS: Double contour sign; ESR: Erythrocyte sedimentation rate; *n*: No. of cases; OA: Osteoarthritis; RA: Rheumatoid arthritis; SD: Standard deviation; SUA: Serum uric acid. Mean (±SD) or *n* (%).

There were 76 patients in Group 1 and 32 patients in Group 2. There was the same distribution between the two groups for age (p=0.527) and gender (p=0.321). Of 76 patients with hyperechogenic spots, the mean age was 64.43 years old, 57 (53%) were women, and OA, other arthritis, gout, CPPD, hyperuricemia, and RA were present in 28 (26%), 19 (18%), 16 (15%), six (6%), seven (6%), and 0, respectively. Of 32 patients without hyperechogenic spots, the mean age was 61.22 years old, 21 (19%) were women, and OA, other arthritis, gout, CPPD, hyperuricemia, and RA were present in 14 (13%), nine (8%), four (4%), two (2%), two (2%), and two (2%), respectively. The values for ESR and CRP between the two groups weren't different. The distribution of diagnosis and the presence of DCS was the same between the two groups. Only the SUA was statistically significantly different between the two groups, with bigger values in Group 1, as in Figure 1.

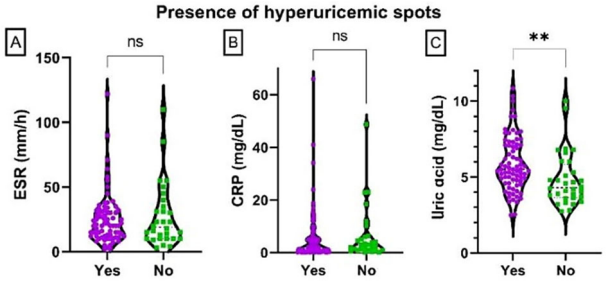

Figure 1 – ***Comparisons of the ESR (A), CRP (B) and uric acid (C) in patients with and without hyperechogenic spots. **: Statistically significant (p<0.05); CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ns: Not significant.***

As in Table 1, more synovial fluid is found in right knee at patients without hyperechogenic spots (p<0.05). Regarding the gender, no differences were observed between the patients with and without hyperechogenic spots (p=0.4726).

Evaluation of the relation between explanatory variable (hyperechogenic spots) and the response variable (age, gender, ESR, CRP, SUA) demonstrated a significant relation between SUA level and the presence of hyperechogenic spots (p=0.005). Considering this hypothesis as correct, we could imagine an equation that could also be applied to the inverted model, with hyperechogenic spots as response variable. The equation for this model would be as follows:

y = 3.37-0.02*gender+0.01*ESR+0.01*CRP-0.54*SUA

where y: *logit* [probability (hyperechogenic spots)].

Results of the multivariate logistic regression analysis proved a very good percentage of predicting patients with hyperechogenic spots: 97.4% (χ^2=13.552, df=5, p=0.019).

We used a ROC curve to evaluate the sensitivity and specificity of a diagnostic test (SUA level and the dichotomous variable: hyperechogenic spots). We assumed that the absence of hyperechogenic spots is the result of the fact that the SUA level isn't high enough. In this situation, we considered that a lower SUA level is predictive for the absence of hyperechogenic spots, and a high SUA value is predictive for the presence of hyperechogenic spots (Figure 2).

Results obtained for the two models, assessed according to the SUA level's differences in men and women, are presented in Figures 3 and 4.

The red line from Figure 3 is fairly far up toward the top left and this indicates we obtained a fairly good instrument, numerically attached in Table 2. The AUC is 0.698 [95% confidence interval (CI): 0.586–0.811], with a standard error (SE) of 0.057 and p<0.01. We obtained statistically significant results, and we considered the cut-off value for the SUA level equal to 4.8 mg/dL, regardless of gender, as a fair test for the presence of hyperechogenic spots.

When separated on gender variable, we found the cut-off value for the SUA level for men equals to 4.95 mg/dL (AUC: 0.726, 95% CI: 0.546–0.961) and for women a value of 3.9 mg/dL (AUC: 0.713, 95% CI; 0.582–0.845), as in Table 2 and Figure 4.

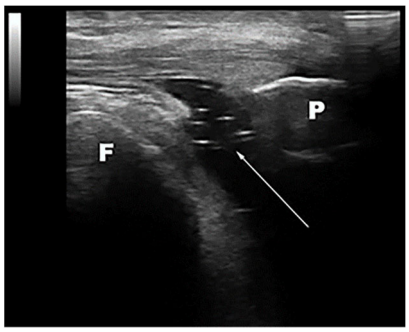

Figure 2 – ***Ultrasound gray-scale image of the para-patellar lateral recess, with anechoic effusion and hyper-echoic spots (arrow). F: Femur; P: Patellar.***

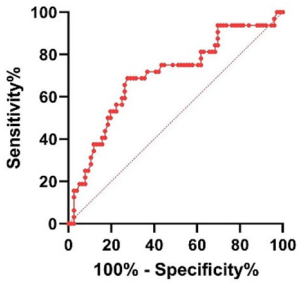

Figure 3 – ***Area under the receiver operating characteristic curve for Model 1, regardless of gender.***

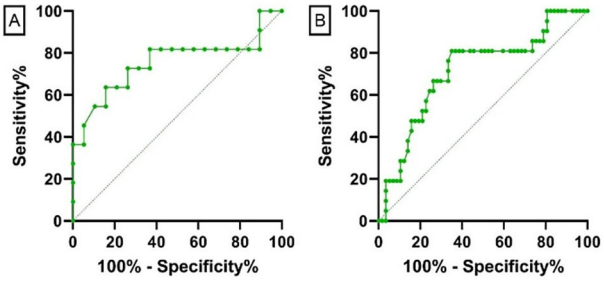

Figure 4 – ***Area under the receiver operating characteristic curve for Model 2: (A) The analysis for men; (B) The analysis for women.***

Table 2 – ***Performance of the two models***

Model	Description		AUC (95% CI)	*p*-value	Cut-off point of the SUA level
1	Regardless the gender		0.698 (0.586–0.811)	0.001	4.8150
2	With gender differences	Male	0.726 (0.511–0.941)	0.036	4.95
		Female	0.713 (0.582–0.845)	0.004	3.9

AUC: Area under the curve; CI: Confidence interval; SUA: Serum uric acid.

AUC is quite high (0.726 for men and 0.713 for women), with a SE of 0.11 for male patients and 0.067 for women; $p<0.05$ suggested statistically significant results. Evaluating the AUC value, we considered those values for cut-off as a fair test for the presence of hyperechogenic spots.

We found a week relation between gender and the presence of the hyperechogenic spots, without statistical significance ($p=0.373$).

For the DCS, we found no association with hyperechogenic spots, but this might be related to the low number of patients with the gout specific sign and the low number of patients with high SUA level ($p=0.839$).

Discussions

In the terms of an increasing prevalence of hyperuricemia over the last 20 years, due to ageing population and to increasing prevalence of the diseases associated with it, such as obesity, hypertension, frequent use of thiazide diuretics, and chronic kidney disease (CKD) [10, 11], and considering that hyperuricemia alone predicts major cardiac events and death in patients with acute coronary syndrome [12], and it represents a risk factor for one-year overall survival [13], we might consider a lower SUA value as normal, than the fore used, of 6 mg/dL [12] in patients with gout and not only.

Hyperuricemia is classically defined as SUA value >6.8 mg/dL (404 μmol/L) without symptoms secondary to crystal deposition [14, 15]. However, each laboratory calculates the SUA threshold as the mean SUA for the local healthy population value, plus 2 SDs and this is calculated separately according to gender [16, 17]. This value is more related to physiological issues since at this level and with a pH of 7.4, at a temperature of 37ºC, 98% of uric acid (UA) is ionized as urate and this is the highest concentration to stay dissolved. *In vivo*, it is not so clear what is the level of SUA that is clinically significant, but usually, only 15–20% of all patients with asymptomatic hyperuricemia, will develop gout [18]; still, our study findings suggest that the urate precipitation might start at lower values than considered before.

US diagnosis of gout is based on the identification of crystalline material which exhibits intense echogenicity and can be visualized in and around the joint. Crystalline deposits can, thus, be detected in the joint space, on the surface of hyaline cartilage, in the tendon sheets or subcutaneous tissue. Suggestive US features of gout include the "snowstorm" appearance, DCS and tophi formations. Gout-related joint damage based on imaging also includes synovial hypertrophy and bone erosions. The "snowstorm" appearance is described as multiple hyperechoic foci visible within the synovial fluid and is considered highly specific for gout. Nevertheless, there are also other conditions in which a similar US pattern can develop. These other causes include: CPPD, deposits of fibrin or rice bodies, presence of gas bubbles and even in infections [19].

Several studies have reported the prevalence of subclinical US lesions related to crystal deposition in hyperuricemic individuals [20–23]. In a 2011 study, Pineda *et al.* observed features of DCS at the metatarsophalangeal joint in 25% of asymptomatic subjects with hyperuricemia and they also describe other types of lesions, such as tophi and enthesophytes, but with smaller prevalence [20]. Similarly, in a 2021 study, Cao *et al.* described the prevalence of monosodium urate (MSU) crystals in 25% of patients with asymptomatic hyperuricemia [22], while in very recent study in 2023, Shao & Wang reported a less frequent occurrence of crystal deposition lesions, which were visible in only 17 individuals out of a group of 81 asymptomatic subjects with hyperuricemia [23]. Common sites at which subclinical crystal depositions occurred include the metatarsophalangeal joint, ankles, and peroneus tendons [23].

Importantly, cardiovascular prognosis can also be influenced by the association of crystal deposits in asymptomatic hyperuricemia. Andrés *et al.* reported a significantly increased risk for moderate to severe coronary calcification in asymptomatic hyperuricemic patients with crystal deposits, compared to patients with hyperuricemia alone [24]. It thus becomes essential to detect early crystal formation through imaging in the setting of hyperuricemia. Some authors have analyzed the risk factors to develop crystal deposits in hyperuricemic patients. In a pilot study, Min *et al.* identified class II obesity and non-alcoholic fatty liver disease as being associated with a significantly higher risk of developing DCS in patients with asymptomatic hyperuricemia [25].

Some studies found high gout specificity and high positive predictive value for the diagnosis of gout, for the US findings, such as DCS, "snowstorm" type joint effusion and US tophus aspect, in clinically symptomatic joints, especially in patients with long standing disease, but they concluded that those results cannot be applied in patients with asymptomatic hyperuricemia [7]. Still, there is some evidence that the knee and first metatarsophalangeal joint might, in a low percentage, express DCS in asymptomatic hyperuricemic patients, but with a mean value of SUA of 8.139 mg/dL [26].

Thus, our pilot study, which was centered on the presence/absence of the hyperechoic spots, firstly, generated a descriptive analysis for the occurrence of certain US features suggestive for possible joint crystal presence also in non-MCRA patients and, secondly, tried to find some correlations with demographic characteristics and laboratory findings.

Our pilot study found a possible relation between the "snowstorm" type effusion and asymptomatic hyperuricemia as this seems to be the earliest US finding in those patients [27]. We demonstrated a medium intensity association between the diagnosis of gout or asymptomatic hyperuricemia and whether the patients have hyperechogenic spots or not.

Since there is evidence of US findings, even if not very specific, before the onset of gouty arthritis, we decided to search for a cut-off value for the SUA level that could be associated with "snowstorm" appearance of the synovial fluid. We found the cut-off value for the SUA level equal to 4.815 mg/dL, regardless of the gender, value from which the urate starts to precipitate into the synovial fluid. Values for male subjects tend to be higher in comparison to the ones found for female subjects (4.95 mg/dL *vs.* 3.9 mg/dL). Keeping the SUA levels lower might prevent MSU crystal formation, prevent inflammation [28], reduce progressive debilitating joint and tissue damage, reduce the likelihood of flares and tophus formation and thus, the likelihood of gouty arthritis.

The study limitations are related to the fact that we don't have the confirmation by polarized light of the urates in the joint fluid and to possible selection bias, as some of the subjects may in fact have been developing gout but the

active, swollen joint was related to a different diagnosis and the SUA level was lower than the cut-off generally used value. More than this, we are aware that the appearance of crystals in a joint is not immediate, but something that is happening gradually. In other words, just a determination of UA might not be enough to establish a cut-off value, an average of the SUA levels in several determinations being, maybe, more appropriate.

Extended studies, with higher number of patients and with a good comparator, such as polarized light microscopy examination of the synovial fluid and maybe with multiple SUA evaluation, are required to confirm the relationship between high SUA level and hyperechoic spots inside the fluid. Future studies could also focus on evaluating the possibility to determine the future development of gout in individuals with "snowstorm" appearance of the synovial fluid on US examination, in association with a level of SUA higher than our newly found values.

Conclusions

To conclude, the "snowstorm" aspect of the synovial fluid might be the result of an increased level of SUA and more than this, the cut-off level for SUA to precipitate might be lower than the fore used values.

Conflict of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interests.

Authors' contribution

Ananu Florentin Vreju and Cristina Dorina Pârvănescu equally contributed to this article.

AFV, CDP, AT-Ş, PLC and CA completed the research and manuscript writing. AFV, CDP, AT-Ş, ŞCD, RAI and HVP contributed the analysis of the data. SCF, ALB, ABC, CEG, RMD, CGE and FLG contributed to the collection of the data. All authors contributed to the article and approved the submitted version.

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