Performance of Ultrasound in the Clinical Evaluation of Gout and Hyperuricemia

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Research article

Keywords: Gout, Hyperuricemia, Ultrasound, MSU

Posted Date: March 9th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-16419/v1

Version of Record: A version of this preprint was published at Journal of Immunology Research on April 5th, 2021. See the published version at https://doi.org/10.1155/2021/5550626.

Abstract

Objective Evaluation of monosodium urate (MSU) crystal deposition and related lesion in joints using ultrasound in gout and hyperuricemia patients.

Methods Total 202 gout patients and 43 asymptomatic hyperuricemia patients were included, the clinical data and ultrasounic assessment results were collected and statistically analyzed.

Results Deposition of MSU crystals were found in 25.58% (11/43) of the patients with asymptomatic hyperuricemia and 76.24% (154/202) of the patients with gout. In the all examined 1082 joints from gout patients, 33.09% (358/1082) of them were detected MSU crystals. In MSU crystal positive joints, 77.37% (277/358) of them had history of attacks. Among the joints of gouty arthritis, 56.88% (277/487) of them were found MSU crystals. Double contour sign (DCS), hyperechoic aggregate (HAG) and Tophi were found in 32.65% (159/487), 7.80% (38/487) and 24.64% (120/487) of the joints, respectively. DCS and Tophi, but not HAG, appeared inceasingly in gout duration extension. In the patients with more than 15 years of gout history, DCS, Tophi and HAG were found in 48.18%, 40.00%, 6.36% of US assessed joints, respectively. In the gout patients, synovial lesion and bone erosion were found in 17.74% (192/1082) and 7.58% (82/1082) of joints, respectively. Synovial lesion was related with HAG, while bone erosion was related to tophi and DCS.

Conclusion HAG is the early sign of MSU crystal deposition in joints. Early urate lowering therapy (ULT) may reduce HAG and ameliorate synovitis and synovial hypertrophy. DCS and tophi are the risk factors of bone erosion. Early ULT should be considered in the gout patients with DCS or tophi.

Background

Gout is a common inflammatory disease induced by deposition of monosodium urate (MSU) crystals in joints and surrounding soft tissues. Although hyperuricemia is required for development of symptomatic gout, majority of patients with hyperuricemia do not suffer gouty arthritis, even MUS crystals are detected in joints (1, 2). Chronic pain, soreness or numbness in the joints are reported in some patients without convincing clinical evidence of gouty attack. It is difficult to differentiate gout from osteoarthritis or other chronic arthritis. In the undistinguishable situation, noninvasive imaging evidence of urate deposition in joint is valuable and helpful for differential diagnosis (3).

Ultrasound (US), the non-invasive, free of ionizing radiation, convenient and less expensive approach, has recently been applied to identify MSU crystal deposits for diagnosis of gout(4, 5). A standardized definition of ultrasound lesions with the elementary morphostructural changes in gout have been established in an international consensus(6). Double contour sign (DCS), hyperechoic aggregates (HAG) and tophi are generally considered as characteristic US abnormalities of MSU crystal deposits. In addition, synovial lesion (i.e., synovial hypertrophy and synovitis) and bone erosion are also regularly detected by ultrasound in gout and hyperuricemia patients(2).

In clinic, US findings are usually known to be a crucial evidence for the diagnosis or differential diagnosis for gout (7, 8). The various US phenomena may indicate a variety of joint injuries. Tophus detected by US is reported to be associated with worse foot pain and disability(9). However, US evidence of MSU crystal deposition can be found in asymptomatic joints in gouty patients while MSU crystals may not always be detected in the gouty joints with attacks (10). Furthermore, joint US may show the sign of MSU crystal deposition in asymptomatic hyperuricemia and normal person(11). These findings suggest that the reliable correlation between MSU crystal deposition and gouty attack or erosion remains to be further elucidated.

In this study, we retrospectively analyzed the US results of the joints from the patients who were diagnosed gout or hyperuricemia, to validate the US assessment of MSU crystal deposition and lesion in joints, and to evaluate the clinical value of US application in the diagnosis and prevention of gout and hyperuricemia.

Methods

Study cohort and methods

Age between 18-75 years old patients diagnosed gout or asymptomatic hyperuricemia in gout specialized clinic in Huashan Hospital from Aug 1st, 2016 to Feb 28th, 2019 were eligible for this study. Patients with visible tophi were not included. Total 245 patients (202 gout, 43 asymptomatic hyperuricemia) were included in the study. All 202 gout patients matched the gout classification criteria of the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) (2015). Urate level in fasting serum in all 43 hyperuricemia patients was greater than 420μmol/L, and was confrmed at least twice. Besides the US results, all the following data including demographics (i.e., sex, age and disease duration), body mass index (BMI) and the clinical feature of affected joints were collected.

In the 202 gout patients, totally 1082 joints including first metatarsophalangeal joint (MTP1), ankle, knee, acrotarsium, elbow, wrist and hands joints were detected with US. In the 43 hyperuricemia patients, total 256 joints were examined, most of the joints were the three vulnerable pairs of lower joints (MTP1, ankle, knee), and the others were the joints with mild clinical manifestation, including numb, slight pain or discomfort. The rheumatologist decided which and how many joints underwent US examination based on clinical judgement (the joints with symptoms and potentially affected joints).

US assessment

The US examination was performed by the skilled sonographers who had more than 10 years of experience in the musculoskeletal US in Huashan Hospital. Aplio i900 color ultrasonic diagnostic apparatus (probe frequency 5-18 MHz) was used for the US examination. According to the international consensus of the standardized definition of US gout lesion published by OMERACT (Outcome Measures

in Rheumatology) US Gout Task Force was employed(6, 12), MSU crystal deposition in Joints was diagnosed based on double contour sign (DCS), hyperechoic aggregates (HAG) and Tophi. Synovial hypertrophy, synovitis and bone erosion was considered as joint damage.

Statistical analysis

The analysis was performed with SPSS 19.0 (IBM). All data were presented as mean ± SD or proportions. Comparisons of baseline data between two groups were tested for statistical significance using a *t* test or one-way analysis of variance test with a least significant difference multiple comparison test. *P* values <0.05 were considered as significant. Pearson's correlation coefficient was calculated to examine correlations between variables.

Results

Demographics and clinical characteristics of the study population

Demographics and clinical characteristics were summarized in Table 1. Among the 202 gout patients, 191(94.55%) were male. The average age was 46.90 years old. Among the 43 hyperuricemia patients, 31(72.09%) were male. The average age was 44.47 years old. BMI in both gout (25.59±3.48) and hyperuricemia (25.64±3.03) patients were higher than normal value (18.5~23.9), and there was no significant difference between the two groups. Serum uric acid (SUA) in gout patients (524.24±79.68) was higher than that in hyperuricemia patients (493.40±66.85), which might be due to the longer course of hyperuricemia in gout group.

The urate crystal deposits in the kidney directly result in chronic urate nephropathy. In table 1, creatinine clearance rate (Ccr) in gout patients (95.55±2.55ml/minute) is lower than that in hyperuricemia patients (106.42±5.54ml/minute). Ccr□80ml/minute were detected in 39.60% (80/202) of gout patients and in 20.93% (9/43) of hyperuricemia patients. Hyperlipidemia and hyperglycemia were known to co-exist with hyperuricemia and gout. In our study, both fasting blood glucose (GLT) and triglyceride (TG) were found higher in gout patients than those in hyperuricemia patients (Table 1). Our results showed more common comorbidities, such as kidney damage and metabolic disorder in gout patients.

Clinical characteristics of gouty attacks in the gout population

We further analyzed the clinical characteristics of the joints with ultrasound abnormalities in the gout population (Table 2). Totally 531 joints including 187 (35.22%) of MTP1, 155 (29.19%) of ankles, 100 (18.83%) of knees, 45 (8.47%) of acrotarsium, 21 (3.95%) of hand joints, 12 (2.26%) of wrist and 11 (2.07%) of elbow in the 202 patients had clinical attacks. There were more right joints showed attacks than left ones although there was no statistical significance. Of the 202 gout patients, the headmost involved joints were 99 (49.01%) on MTP1, 61 (31.20%) on ankle, 21(10.40%) on acrotarsium, 14(6.93%)

on knee, 3(1.49%) on wrist and 4(1.98%) on hand joints. The results indicate that attacks more likely occurred on MTP1, ankle and acrotarsium.

Global US findings in the patients with gout and hyperuricemia

In the 202 gout patients, 76.24% (154/202) of patients were detected MSU crystals in at least one of the joints, and 23.76% (48/202) of patients did not present any MSU crystals in the examined joints. MSU crystals were detected in 358 (33.09%) joints of total 1082 examined joints among the gout patients (Table 3.1). There were 277 (77.37%) of the 358 joints with MSU crystals had attacks. In the hyperuricemia patients, MSU crystals were detected in 11 joints among 256 joints underwent US examination and the positive rate was 4.3% (11/256). Interestingly, these 11 joints belonged to 11 patients and each patient had only one joint with positive US signs of MSU crystal deposition (Table 3.1).

In the 1082 joints of the gout patients, 487 joints had at least one attack, while no attacks were reported in 541 joints (Table 3.2). In the 487 joints, 56.88% (277/487) of joints were found MSU crystals using US. Among these joints, 32.65% (159/487), 7.80% (38/487) and 24.64% (120/487) were DCS, HAG and Tophi, respectively.

Synovial lesion and bone erosion in the patients with gout

Beside the US signs of MSU crystal deposition, synovial lesion (i.e., synovial hypertrophy and synovitis) and bone erosion were regularly detected in the patients. In the gout patients, synovial lesion was found in 192 (17.74%) joints and bone erosion was found in 82 (7.58%) joints among total 1082 joints. In the 192 joints with synovial lesion, 24.48% (47/192), 11.98% (23/192), 12.50% (24/192) joints were simultaneously detected DCS, HAG and tophi, respectively. In the 82 joints with bone erosion, 56.10% (46/82), 7.69% (4/82), 75.61% (62/82) of joints were simultaneously detected DCS, HAG and Tophi, respectively (Table 4.1). We further analyzed the correlation between synovial lesion and bone erosion with three different US assessments. The results showed that synovial lesion was related to HAG ($p<0.01$) (Table 4.2), bone erosion was related to tophi ($p<0.001$) and DCS ($p<0.01$) (Table 4.3).

Course time and the MSU crystals in gout patients

Hyperuricemia is the pathogenesis of gout. When the urate level in serum exceeds its saturation concentration, the precipitated urate crystals deposit in joints and soft tissues. In this study, we found that MSU crystal deposition was correlated with serum uric acid (SUA) level ($p<0.01$) and the duration ($p<0.01$). Furthermore, a large proportion of patients had no awareness of their SUA level prior to seeking clinical specialists. In the 202 gout patients, only 17.33% (35/202) of the patients came for treatment at their early stage (course<1 year). Majority of them had more than one year gout history (Table 5.1).

In the gout patients, the proportion of US positive signs of MSU crystal deposition were gradually increased, especially DCS and tophi during the process of gout. In the patients with more than 15 years of gout history, DCS and Tophi were detected in 48.18% and 40.00% of joints respectively, while in the patients with less than 1 year of gout history, DCS and Tophi were only found in 6.29% and 5.03% of

joints respectively. HAG appeared no notable rising as gout duration extension. HAG was found in 5.03% (8/159) of joints of the patients who had less than one year gout course, and it was 6.36% (7/110) in the patients with more than 15 years of gout course (Table 5.1).

In the 35 patients at early stage (gout course was less than 1 year), 28 patients came to clinic at their first gout attack and the affected joints were MTP1 (17), ankles (6), knee (1), acrotarsium (2) and hand joints (2). In the 17 affected MTP1 joints, 8 (47.06%) joints were detected MSU crystal deposition (3 DCS, 3 HAG, 2 Tophi, 1 DCS+Tophi) (Table5.2).

Correlation of joint MSU crystal deposition with nephrolithiasis

Gout patients were reported prone to have nephrolithiasis, acute renal colic or hematuria although it is difficult to determine the type of the crystal in kidney. In this study, we further analyzed the US data of kidney. Nephrolithiasis was defined as US signs of calculus or crystal deposition in kidney. We found that nephrolithiasis was detected in 20.30% (41/202) of gout patients and 4.65% (2/43) of hyperuricemia patients, indicating nephrolithiasis occurred in more gout patients than in hyperuricemia patients. The findings also showed that nephrolithiasis was remarkably relevant to MSU crystal deposition in joints in gout patients (p<0.05) (Table 6).

Discussion

The demographics of cohorts in this study show the average ages of the gout and hyperuricemia patients in this study were 46.90 and 44.47 years old, respectively, which were younger than the previously reported 52.69 years old of average age from hyperuricemia data in a Chinese national cross-sectional survey in 2014(13). It may suggest that gout and hyperuricemia are increasing in younger population due to the changes in life style (14). Our results are also consistent with the previous reports that high-BMI, hyperlipidemia and hyperglycemia are notably complicated with gout and hyperuricemia, especially gout (15). Hence, middle-aged males with certain metabolic syndromes should be listed in the attention-demanding high-risk population of gout and hyperuricemia.

Our data indicate that lower limb joints are more vulnerable in gout patients. MTP1 (49.01%), followed by ankle (31.20%) and acrotarsium (10.40%), are the most affected joints. The upper limb joints, including hands, wrist and elbow are rarely involved. This result strongly supports the gout diagnostic value of MTP1 and ankle attacks, especially at the early stage.

For the patients without classic symptoms, MSU crystal deposition could be identified by image-based examination, such as dual-energy computed tomography (DECT) and US. It has been reported that MSU burden volume, which is predictive of the risk of flares (16) can be measured using DECT (17). Due to the advantage of non-invasion, free of ionizing radiation, and convenience with less expensive, US is more widely used in clinic. Our study show that MSU deposition can be detected by US and the most frequently affected joint is MTP1 in the gout patients. This result is consistent with clinical findings reported by other groups(7).

Previous research suggested that MSU deposition in joint is the crucial factor of gouty arthritis attack(4). In this study, 28 gout patients came to outpatients at their first acute attack, and took joint examination by US. Only 39.29% (11/28) attacked joints were found MSU deposition in the 28 patients. Furthermore, among the total 11 gouty joints with initial attack, big joints such as knee and ankle were majority of MSU deposition positive joints. Only one MTP1 was positive of MSU crystal deposition detected by US. Moreover, of the 17 patients who were headmost attacked on MTP1 at early stage (course < 1 year), 47.06% (8/17) of them were detected with MSU crystal deposition in the MTP1. These results rise a serious question about how sensitive US is to the detection of MSU crystal deposition in joints, particularly in smaller joints of lower extremities at early stage. But surprisingly, 77.37% of total US-detected MSU crystal deposited joints had gouty attacks in the past. Due to practical reasons, the selection of joints for US examination is based on rheumatologist personal judgement in this retrospective study and the certain bias cannot be ruled out. It is consistent with previous research, ultrasound features of MSU crystal deposition had high positive predictive value but more limited sensitivity for early gout(18). Further investigation is warranted to validate the sensitivity and specificity of US in detection of MSU crystal deposition in various joints.

According to “2018 updated European League Against Rheumatism evidence-based recommendations for the diagnosis of gout”(19), MSU crystal deposition is a crucial evidence for gout diagnosis. In our study, DCS and tophi were frequently detected by US in gout patients. The detection rate of them was notably increased with the disease history of gout, but not the HAG. HAG was reported to be the most common sign at early stage, especially in asymptomatic joints(20). In animal experiment, MSU was injected into the knees of rabbits, HAG was found frequently displayed in 75% knees at early stage (day 7 after MSU injection)(21). Collectively, our data support that HAG is the US sign for early MSU crystals deposition, while DCS and tophi are the useful signature of MSU crystal deposition for chronic gout.

HAG was found associated with synovial lesion in this study. We found synovial lesion was notably detected at the early stage, and gradually increased with the gout course extension. It is reported that urate lowering therapy (ULT) with febuxostat for 24 months reduced synovitis detected by MRI in patients with acute gout(22). ULT may diminish HAG and ameliorate synovitis or synovial hypertrophy. Bone erosion was known to be an irreversible injuriousness in gout(23). In our study, Tophi and DCS were both found to be correlated with bone erosion. Timely ULT may minimize Tophi and DCS and block bone injury in the gout patients.

Male, diabetes, obesity, low pH in urine, hyperuricosuria and low urine volume are reported to be the main etiologic factors of nephrolithiasis (24, 25). It is not surprising that higher prevalence of nephrolithiasis is found in gout patients as well due to oversaturated urate and deposition of its crystals in kidney (26). In this study, nephrolithiasis is remarkably relative to MSU crystal deposition in gouty arthritis. The result suggests that the patients with MSU crystal deposition in joints may prone to suffer nephrolithiasis. Since MSU crystal deposition is related to hyperuricemia and it is not a focal event (27), systemic conditions such as genetic predisposition, geographical location, dietary indiscretion, and various metabolic

characteristics should be considered as risk factors (28, 29). Howsoever the pathogenesis of gout should be assessed and treated earlier.

Conclusion

Ultrasound is a clinically convenient approach to detect MSU crystal deposits in joints for supporting diagnosis of gout. HAG is considered as an early sign of MSU crystal deposition in joints, early ULT might be effective in reduction of HAG and partially protect synovitis and synovial hypertrophy. DCS and tophi are correlated with bone erosion. However, the sensitivity and specificity of the ultrasound application remains to be further validated.

Abbreviations

MSU:monosodium urate;DCS:Double contour sign ;HAG:hyperechoic aggregate; ULT:urate lowering therapy;US:Ultrasound;ACR:American College of Rheumatology; EULAR:European League Against Rheumatism;BMI:body mass index ;MTP1:first metatarsophalangeal joint;Ccr:creatinine clearance rate; GLT: fasting blood glucose;TG:triglyceride;SUA:serum uric acid;DECT:dual-energy computed tomography

Declarations

Ethics approval and consent to participate

Ethical approval for the study was obtained from the Institutional Review Board for Human Studies at Huashan Hospital, Fudan University (approval number: 2012137). All the included patients had provided fully informed written consent form prior to data collection.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81302573; No. 81671588), Research Funding from Shanghai Hospital Development Center (No. SHDC12016227; No. 16CR3012A), Medical Health Projects from BaoShan District, Shanghai (No. 18-E-27).

Authors' contributions

Ling Cao contributed to data collection, acquisition of data .Tianyi Zhao contributed to data interpretation.Chunmei Xie contributed to test the patient.Shucong Zheng contributed to experimental design. Weiguo Wan contributed to computational data analysis.Hejian Zou and Xiao xia Zhu contributed to manuscript drafting and conceived the study.All authors contributed to manuscript review.All authors read and approved the final manuscript.

Acknowledgements

The funders had no role in the study design, data collection and analysis, decision to publish and manuscript preparation.

Reference

1. Stewart S, Maxwell H, Dalbeth N**.** Prevalence and discrimination of OMERACT-defined elementary ultrasound lesions of gout in people with asymptomatic hyperuricaemia: A systematic review and meta-analysis. Semin Arthritis Rheum. 2019;49(1):62-73.Pubmed PMID:30709689
2. Stewart S, Dalbeth N, Vandal AC, Allen B, Miranda R, Rome K**.** Ultrasound Features of the First Metatarsophalangeal Joint in Gout and Asymptomatic Hyperuricemia: Comparison With Normouricemic Individuals. Arthritis Care Res (Hoboken). 2017;69(6):875-83.Pubmed PMID:27635596
3. Durcan L, Grainger R, Keen HI, Taylor WJ, Dalbeth N**.** Imaging as a potential outcome measure in gout studies: A systematic literature review. Semin Arthritis Rheum. 2016;45(5):570-9.Pubmed PMID:26522139
4. Naredo E, Uson J, Jimenez-Palop M, Martinez A, Vicente E, Brito E, et al. Ultrasound-detected musculoskeletal urate crystal deposition: which joints and what findings should be assessed for diagnosing gout? Ann Rheum Dis. 2014;73(8):1522-8.Pubmed PMID:23709244
5. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2015;74(10):1789-98.Pubmed PMID:26359487
6. Gutierrez M, Schmidt WA, Thiele RG, Keen HI, Kaeley GS, Naredo E, et al. International Consensus for ultrasound lesions in gout: results of Delphi process and web-reliability exercise. Rheumatology (Oxford). 2015;54(10):1797-805.Pubmed PMID:25972391
7. Zufferey P, Valcov R, Fabreguet I, Dumusc A, Omoumi P, So A**.** A prospective evaluation of ultrasound as a diagnostic tool in acute microcrystalline arthritis. Arthritis Res Ther. 2015;17:188.Pubmed PMID:26198435
8. Norkuviene E, Petraitis M, Apanaviciene I, Virviciute D, Baranauskaite A**.** An optimal ultrasonographic diagnostic test for early gout: A prospective controlled study. J Int Med Res. 2017;45(4):1417-29.Pubmed PMID:56255526

9. Stewart S, Dalbeth N, Vandal AC, Allen B, Miranda R, Rome K. Are ultrasound features at the first metatarsophalangeal joint associated with clinically-assessed pain and function? A study of people with gout, asymptomatic hyperuricaemia and normouricaemia. J Foot Ankle Res. 2017;10:22.Pubmed PMID:28539973
10. Di Matteo A, Filippucci E, Cipolletta E, Musca A, Di Donato E, Martire V, et al. Ultrasound and clinical features of hip involvement in patients with gout. Joint Bone Spine. 2019;86(5):633-6.Pubmed PMID:30779966
11. Zhang Q, Gao F, Sun W, Ma J, Cheng L, Li Z. The diagnostic performance of musculoskeletal ultrasound in gout: A systematic review and meta-analysis. PLoS One. 2018;13(7):e0199672.Pubmed PMID:29979706
12. Cazenave T, Martire V, Reginato AM, Gutierrez M, Waimann CA, Pineda C, et al. Reliability of OMERACT ultrasound elementary lesions in gout: results from a multicenter exercise. Rheumatol Int. 2019;39(4):707-13.Pubmed PMID:30539275
13. Liu R, Han C, Wu D, Xia X, Gu J, Guan H, et al. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. Biomed Res Int. 2015;2015:762820.Pubmed PMID:26640795
14. Chen JH, Wen CP, Wu SB, Lan JL, Tsai MK, Tai YP, et al. Attenuating the mortality risk of high serum uric acid: the role of physical activity underused. Ann Rheum Dis. 2015;74(11):2034-42.Pubmed PMID:25053714
15. Zhu C, Cui R, Gao M, Rampersad S, You H, Sheng C, et al. The Associations of Serum Uric Acid with Obesity-Related Acanthosis nigricans and Related Metabolic Indices. Int J Endocrinol. 2017;2017:5438157.Pubmed PMID:28367214
16. Bhadu D, Das SK, Wakhlu A, Dhakad U, Sharma M. Ultrasonographic detection of double contour sign and hyperechoic aggregates for diagnosis of gout: two sites examination is as good as six sites examination. Int J Rheum Dis. 2018;21(2):523-31.Pubmed PMID:29210196
17. Pascart T, Grandjean A, Capon B, Legrand J, Namane N, Ducoulombier V, et al. Monosodium urate burden assessed with dual-energy computed tomography predicts the risk of flares in gout: a 12-month observational study : MSU burden and risk of gout flare. Arthritis Res Ther. 2018;20(1):210.Pubmed PMID:30223875
18. Ogdie A, Taylor WJ, Neogi T, Fransen J, Jansen TL, Schumacher HR, et al. Performance of Ultrasound in the Diagnosis of Gout in a Multicenter Study: Comparison With Monosodium Urate Monohydrate Crystal Analysis as the Gold Standard. Arthritis Rheumatol. 2017;69(2):429-38.Pubmed PMID:27748084
19. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda J, et al. 2018 updated European League Against Rheumatism evidence-based recommendations for the diagnosis of gout. Ann Rheum Dis. 2020;79(1):31-8.Pubmed PMID:31167758
20. Zhu L, Zheng S, Wang W, Zhou Q, Wu H. Combining Hyperechoic Aggregates and the Double-Contour Sign Increases the Sensitivity of Sonography for Detection of Monosodium Urate Deposits in Gout. J

Ultrasound Med. 2017;36(5):935-40.Pubmed PMID:28240795

21. Pineda C, Fuentes-Gomez AJ, Hernandez-Diaz C, Zamudio-Cuevas Y, Fernandez-Torres J, Lopez-Macay A, et al. Animal model of acute gout reproduces the inflammatory and ultrasonographic joint changes of human gout. Arthritis Res Ther. 2015;17:37.Pubmed PMID:25889158
22. Collison J. Crystal arthritis: Febuxostat reduces synovitis in early gout. Nat Rev Rheumatol. 2017;13(12):694.Pubmed PMID:29051626
23. Wu M, Liu FJ, Chen J, Chen L, Wei C, Hu ZM, et al. Prevalence and Factors Associated With Bone Erosion in Patients With Gout. Arthritis Care Res (Hoboken). 2019;71(12):1653-9.Pubmed PMID:30474923
24. Roughley MJ, Belcher J, Mallen CD, Roddy E. Gout and risk of chronic kidney disease and nephrolithiasis: meta-analysis of observational studies. Arthritis Res Ther. 2015;17:90.Pubmed PMID:25889144
25. Landgren AJ, Jacobsson LTH, Lindstrom U, Sandstrom TZS, Drivelegka P, Bjorkman L, et al. Incidence of and risk factors for nephrolithiasis in patients with gout and the general population, a cohort study. Arthritis Res Ther. 2017;19(1):173.Pubmed PMID:28738835
26. Shimizu T, Hori H, Umeyama M, Shimizu K. Characteristics of gout patients according to the laterality of nephrolithiasis: A cross-sectional study using helical computed tomography. Int J Rheum Dis. 2019;22(4):567-73.Pubmed PMID:30485677
27. Chhana A, Lee G, Dalbeth N. Factors influencing the crystallization of monosodium urate: a systematic literature review. BMC Musculoskelet Disord. 2015;16:296.Pubmed PMID:26467213
28. Martillo MA, Nazzal L, Crittenden DB. The crystallization of monosodium urate. Curr Rheumatol Rep. 2014;16(2):400.Pubmed PMID:24357445
29. Sakhaee K. Epidemiology and clinical pathophysiology of uric acid kidney stones. J Nephrol. 2014;27(3):241-5.Pubmed PMID:24497296

Tables

Table 1: Demographics and clinical characteristics of study population

Variable	Gout	HUA	*p*-value
Total number	202	43	-
Male/Female	191/11	31/12	-
Age (years)	46.90±14.82	44.47±18.18	0.35
BMI (kg/m2)	25.59±3.48	25.64±3.03	0.93
SUA (mmol/L)	524.24±79.68	493.40±66.85	0.018*
Ccr (ml/min)	95.55±2.55	106.42±5.54	< 0.0001
TG (mmol/L)	2.91±1.42	1.80±1.29	0.0051*
GLU (mmol/L)	5.73±0.62	4.92±1.68	0.0031*
Cholesterol (mmol/L)	4.97±1.04	4.70±0.65	0.34

HUA: Asymptomatic hyperuricemia; BMI: Body Mass Index; SUA: serum uric acid; Ccr: creatinine clearance rate; TG: triglyceride; GLU: fasting blood glucose

*significantly difference ($p<0.05$)

Table 2: Clinical characteristics of gouty attacks in the gout population

Flared joint	Total	Left	Right	*p*-value
MTP1	35.22% (187/531)	16.20% (86/531)	19.02% (101/531)	0.148
Ankle	29.19% (155/531)	13.93% (74/531)	15.25% (81/531)	0.496
Knee	18.83% (100/531)	9.04% (48/531)	9.79% (52/531)	0.671
Acrotarsium	8.47% (45/531)	4.71% (25/531)	3.76% (20/531)	0.399
Hands	3.95% (21/531)	1.88% (10/531)	2.07% (11/531)	1
Wrist	2.26% (12/531)	0.75% (4/531)	1.51% (8/531)	0.220
Elbow	2.07% (11/531)	0.94% (5/531)	1.13% (6/531)	1

MTP1: First metatarsophalangeal joint

Table 3.1: Global US findings in patients with gout and hyperuricemia

	Patients			
	Gout	HUA	*p*-value	X^2
Total patient	202	43	-	-
Positive patient *	154 (76.24%)	11 (25.58%)	0.001	41.369
	Joints			
	Gout	HUA	*p*-value	X^2
Total Detected Joints	1082	256	-	
Positive Joint	358 (33.09%)	11 (4.30%)	0.001	85.913
DCS	228 (21.07%)	6 (2.34%)	0.001	50.320
HAG	64 (5.91%)	5 (1.95%)	0.04	4.168
Tophi	159 (14.70%)	0	0.001	42.693

*Positive patient: MSU crystal deposits in at least one joint of the patient;

Table 3.2: US findings and clinical attacks in the joints of gouty patients

	Ever Attacked	Never Attacked
Total Detected Joints	487	595
Positive Joints	277/487 (56.88%)	67/595 (11.26%)
DCS	159/487 (32.65%)	43/595 (7.23%)
HAG	38/487 (7.80%)	16/595 (2.69%)
Tophi	120/487 (24.64%)	16/595 (2.69%)

Table 4.1: Synovial lesion and bone erosion in the patients with gout

	Joints
	Gout
Total Detected Joint	1082
Synovial Lesion	192/1082 (17.74%)
DCS	47/192 (24.48%)
HAG	23/192 (11.98%)
Tophi	24/192 (12.50%)
Bone Erosion	82/1082 (7.58%)
DCS	46/82 (56.10%)
HAG	4/82 (7.69%)
Tophi	62/82 (75.61%)

Table 4.2: Synovial lesion is related to HAG

Synovial Lesion	Number	*p*-value
DCS	47	0.385
HAG	23	0.01*
Tophi	24	0.316

*significantly difference ($p<0.05$)

Table 4.3: Bone erosion is related to Tophi and DCS

Bone Erosion	Number	*p*-value
DCS	46	0.01*
HAG	4	1
Tophi	62	0.001*

*significantly difference ($p<0.05$)

Table 5.1: Clinical course and the MSU deposition in gout patients

	Course (years)				
	≤1	1-5	5-10	10-15	≥15
Patients	35	70	50	28	19
Total Detected Joints	159	380	283	150	110
Positive Joints	13.84% (22/159)	20.79% (79/380)	39.93% (113/283)	48.00% (72/150)	65.45% (72/110)
DCS	6.29% (10/159)	12.89% (49/380)	23.32% (66/283)	33.33% (50/150)	48.18% (53/110)
HAG	5.03% (8/159)	4.74% (18/380)	8.48% (24/283)	4.67% (7/150)	6.36% (7/110)
Tophi	5.03% (8/159)	6.05% (23/380)	14.49% (41/283)	27.33% (41/150)	40.00% (44/110)
Synovial Lesion	12.58% (20/159)	15.26% (58/380)	19.08% (54/283)	22.67% (34/150)	23.64% (26/110)
Bone Erosion	0	2.11% (8/380)	6.36% (18/283)	18% (27/150)	26.36% (29/110)

Table 5.2: US assessment in patients at first acute attack

Attacked Joints (28)	MSU crystal deposition	
	Total	US signs
MTP1 (17)	8	3 DCS; 3 HAG; 2 Tophi; 1 DCS+Tophi
Ankle (6)	2	1 DCS; 1 HAG
Knee (1)	0	0
Acrotarsium (2)	1	1 HAG
Hand joints (2)	0	0

Table 6: Correlation of joint MSU deposition with nephrolithiasis

Joint Kidney	Positive	Negative	Total
Positive	37	4	41
Negative	117	44	161
Total	154	48	404

X^2=5.571, p=0.018 (p<0.05, considered as significantly difference)