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ORIGINAL ARTICLE

Musculoskeletal Ultrasonography Identifies Structural Damage in Chronic Kidney Disease Patients with Gouty Arthritis

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Background: Renal insufficiency reduces the excretion of uric acid and inflammatory factors and exacerbates the structural deformities caused by gouty arthritis. Musculoskeletal ultrasonography (MSKUS) is often used to evaluate the severity and inflammatory progression of gout. **Aim:** We aimed to determine whether ultrasound help to identify structural damage in patients with chronic kidney disease (CKD) and gout. **Methods:** This was a retrospective review of the clinical manifestations and abnormalities observed with MSKUS in 280 patients with gouty arthritis between August 2004 and April 2017. MSKUS identified intra-articular features, including joint effusion, synovial proliferation, Baker's cysts, double contour sign, tophi, and extra-articular tenosynovitis. Serum and synovial fluid were collected and analyzed. Significant differences were identified using the Pearson correlation coefficient and independent *t*-test. **Results:** This retrospective cohort included 257 men (91.8%) and 23 women (8.2%) with a mean age of 54.6 years. CKD stage correlated positively with the presence of joint Baker's cyst ($P = 0.004$). Notably, serum estimated glomerular filtration rate correlated negatively with serum C-reactive protein level in patients with CKD ($P < 0.001$), and more severe CKD correlated with a higher prevalence of Baker's cyst in CKD patients ($P = 0.0037$). **Conclusion:** Insufficient control of hyperuricemia can lead to chronic gouty arthritis and subsequent structural deformities. Reciprocally, acute inflammation of joints is downregulated as chronic gouty arthritis develops. Patients with hyperuricemia and CKD should receive regular MSKUS examination to avoid the progression of structural damage in the joints.

Key words: Gout, musculoskeletal ultrasonography, chronic kidney disease, synovial proliferation, Baker's cyst

INTRODUCTION

Gouty arthritis is the most common type of inflammatory arthritis and is associated with hyperuricemia and comorbidities.[1] The deposition of monosodium urate (MSU) crystals in the synovial tissues of joints is a major factor in the pathogenesis of gout.[2] The American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2015 Gout Classification criteria suggest that musculoskeletal ultrasonography (MSKUS) is a reliable technique for the diagnosis of gout. MSKUS is often used to evaluate the severity and to monitor the inflammatory progression of gout. The advantages of MSKUS over other imaging modalities include convenience, lack of radiation, reduced cost, and easy localization of structures during invasive procedures.[3]

The features of gouty arthritis identified with MSKUS include joint effusion, synovial proliferation, Baker's cysts, double contour (DC) sign, tophi, and tenosynovitis.[4] Synovial proliferation is often accompanied by joint effusion and often induces the subsequent development of Baker's cyst because of the persistent chronic inflammation of the joint space. Baker's cyst is an abnormal distension of the communicating

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gastrocnemius–semimembranosus bursa caused by joint effusion in the knee and may be asymptomatic or can present as pain over the popliteal fossa, stiffness of the knee, and limited range of motion.[5] Baker's cyst has been noted in patients with osteoarthritis, rheumatoid arthritis, and MSU- or pyrophosphate-induced arthritis.[6] DC sign and tophi can resolve after appropriate treatment of symptomatic hyperuricemia, which suggests that MSKUS may be a sensitive tool for monitoring disease activity and guiding therapy to lower uric acid (UA) level.[7] An inflammatory process characterized by fluid accumulation around a tendon sheath, tenosynovitis is induced either by infection or noninfectious causes such as trauma, gout, or tendon overuse.[8]

Gouty arthritis and hyperuricemia are commonly observed in patients with chronic kidney disease (CKD).[9] A lower serum estimated glomerular filtration rate (eGFR) in people with CKD is associated with a higher prevalence of hyperuricemia and gout.[10] There is no consensus about the timing of the initiation of treatment with urate-lowering agents in patients with asymptomatic hyperuricemia in patients with or without CKD, although some reports have mentioned a potential protective effect on the kidneys.[9] However, CKD patients with asymptomatic hyperuricemia do not routinely receive MSKUS, and this may impede the early diagnosis of structural joint damage induced by the deposition of intra-articular MSU crystals.

The presence of tophi in joints is associated with rapid deterioration of renal function.[11] However, the presence of CKD is a challenge in gout management because urate-lowering agents can be harmful or ineffective in most patients with CKD.[9] Only a few studies have investigated the clinical manifestations and ultrasonic features of gouty arthritis in patients with CKD. Using MSKUS to monitor the progression of the structural damage of joints in CKD patients is warranted because few data have been reported. The aim of this study was to examine the relationships between ultrasonic manifestations and common laboratory features identified in the analysis of serum and synovial fluid in patients with gout, such as the synovial fluid white cell count (SFWCC), blood white cell count (BWCC), and serum C-reactive protein (CRP), serum UA, and creatinine concentrations. Here, we demonstrate that the crystal-induced long-term localized inflammation contributes to the chronic structural damage in joints. We analyzed MSKUS features in patients with CKD and found that chronic inflammation induced by MSU crystals contributes to progressive joint damage in patients with renal insufficiency. We also report that the risk of Baker's cyst formation is significantly positively correlated with the severity of impaired renal function.

MATERIALS AND METHODS

Patient selection

In this retrospective study, we reviewed the records of 280 patients with gout and active arthritis treated between August 2004 and April 2017. All patients were diagnosed with gout according to the 2015 ACR/EULAR Gout Classification criteria. Gout was confirmed using the sufficient criterion of MSU crystals detected in the synovial fluid using blind arthrocentesis or a score of >8 points. Half of the patients in this cohort exhibited MSU crystals in their synovial fluid and met the sufficient criterion for gout. The remaining patients had a score of >8 points.[3] Laboratory data included analysis of SFWCC, BWCC, serum CRP, UA, and creatinine levels. eGFR was calculated using the serum creatinine level according to the Modification of Diet in Renal Disease equation.[7] This retrospective study has been approved by the Institutional Review Board of Tri-Service General Hospital with waiving of the informed consent form, TSGH IRB number: 1-106-05-174.

Musculoskeletal ultrasonography assessment

Two experienced rheumatologists with expertise in MSKUS performed the MSKUS examinations using a commercially available MSKUS real-time scanner (EnVisor, Philips) between August 2004 and December 2011 and an MSKUS real-time scanner (Acuson S1000, Siemens) between January 2012 and April 2017. Both scanners were equipped with a multifrequency linear transducer (7–12 MHz) and color Doppler imaging system. All MSKUS examinations were performed according to standardized scanning methods.[7] The knee joints of each enrolled patient in this cohort were exanimated and recorded in the MSKUS examination. Other inflamed joints, such as the finger, wrist, elbow, ankle, and toe joints, were inspected for clinical manifestations but were not analyzed in this study. The reading process was completely blinded, that is, readers had no knowledge of the patients' characteristics or other clinical and imaging data. To assess intra-reader reliability, Fleiss' kappa coefficients, and kappa values were compared to determine the concordance and were found to be >0.6.[12,13]

The literature indicates that the intra-articular damage of gouty arthritis in MSKUS includes joint effusion, synovial proliferation, Baker's cyst, DC sign, and tophi. Joint effusion was defined as the presence of an anechoic homogeneous widening protrusion from the joint space. Synovial proliferation was defined as a widening of the joint space with clusters of synovial thickening and hypertrophy with a bushy or villous appearance. Baker's cyst at the knee joint was defined as an enlargement of the gastrocnemius–semimembranosus bursa caused by the accumulation of an anechoic or hypoechoic

fluid.[5] DC sign was defined as the formation of hyperechoic linear-like bands above the anechoic cartilage. A tophus was defined as a heterogeneously echoic echotexture with a posterior acoustic shadow; a soft tophus does not produce a posterior acoustic shadow.[14] As the only extra-articular manifestation of gout, tenosynovitis was defined as a homogeneous hypoechoic or anechoic sheath or spindle-shaped thickening of the tendon sheath.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows software (version 22.0, IBM Corp, Chicago IL, USA). The correlations between all MSKUS findings were analyzed using the Pearson Chi-square and phi coefficient test. The independent *t*-test was used to analyze MSKUS features and laboratory examination results, and the Pearson correlation coefficient was used to analyze laboratory examination results. A two-tailed $P < 0.05$ was considered to indicate significance.

RESULTS

Demographics of serum and synovial examinations of patients

A total of 280 patients with gouty arthritis were included in this cohort: 257 men (91.8%) and 23 women (8.2%). Their mean age was 54.6 years (standard deviation (SD), 22.3; range, 20–95). The mean duration between the first diagnosis of gout and MSKUS examination was 2.2 years. Laboratory examinations showed a mean SFWCC of 26.4 × 10^3/L (SD, 26.1; range, 0.1–119.0); mean BWCC of 9.8 × 10^3/L (SD, 4.0; range, 2.5–29.1; normal value, 4.0–10.0); mean serum CRP level of 7.5 mg/dL (SD, 8.0; range, 0.11–37.2; normal value, <0.35); mean serum UA level of 8.1 mg/dL (SD, 3.8; range, 2.2–16.2); and mean eGFR of 72.4 mL/min/1.73 m^2 (SD, 36.7; range, 1.4–175.8) [Table 1]. As expected, leukocytosis was positively associated with increased serum CRP level ($P < 0.001$, Pearson correlation) but was not associated with serum UA level ($P = 0.42$). A significant negative correlation was observed between eGFR and serum CRP level ($P < 0.001$) [Table 2].

Two hundred and twenty patients underwent MSKUS examination, which revealed that 212 (96.3%), 127 (57.7%), 26 (11.8%), 120 (54.5%), 67 (30.4%), and 56 (25.4%), patients exhibited joint effusion, synovial proliferation, Baker's cysts, DC sign, tophi, and tenosynovitis, respectively [Table 1]. The correlations between MSKUS features were analyzed using the Phi correlation coefficient [Table 3]. The percentage of patients with synovial proliferation was significantly higher ($P < 0.001$) in those with than in those without joint effusion. Compared with patients without synovial proliferation, a significantly higher percentage of patients with synovial proliferation had joint effusion ($P < 0.001$), Baker's cyst ($P = 0.029$), and DC sign ($P = 0.023$) in the knee joints. By contrast, a significantly

Table 1: Demographics of abnormalities of serum parameters, synovial abnormalities, and musculoskeletal ultrasonography in patients with gout

Parameters	*N* (%) mean±SD
Demographics and laboratory results for synovial fluid and serum	
Number of patients	280
Age (years), mean±SD	54.6±22.3
Sex: Male, *n* (%)	257 (91.8)
Synovial fluid white blood cell count (10^3/μL), mean±SD	26.4±26.1
Blood white blood cell count (10^3/μL), mean±SD	9.8±4.0
Serum C-reactive protein level (mg/dL), mean±SD	7.6±8.0
Serum uric acid level (mg/dL), mean±SD	8.1±3.8
Serum creatinine level (mg/dL), mean±SD	1.8±2.4
eGFR value (mL/min/1.73 m^2), mean±SD	72.4±36.7
MSKUS manifestations	
Number of MSKUS examinations (patients)	220
Effusion, *n* (%)	212 (96.3)
Synovial proliferation, *n* (%)	127 (57.7)
Tenosynovitis, *n* (%)	56 (25.4)
Baker's cyst, *n* (%)	26 (11.8)
Double contour sign, *n* (%)	120 (54.5)
Tophi, *n* (%)	67 (30.4)

SD=Standard deviation; eGFR=Estimated glomerular filtration rate; MSKUS=Musculoskeletal ultrasonography

Table 2: Associations between serum and synovial abnormalities in gout (Pearson Chi-square and Phi scores)

	SFWCC	BWCC	CRP level
CRP			
Phi score	0.173	0.373	NA
P	0.065	<0.001***	
Serum UA			
Phi score	–0.059	–0.142	0.079
P	0.5	0.042*	0.269
eGFR			
Phi score	–0.010	0.054	–0.254
P	0.909	0.443	<0.001***

*P<0.05, ***P<0.001; Phi scores were used to assess the associations between binary variables. SFWCC=Synovial fluid white cell count; BWCC=Blood white cell count; CRP=C-reactive protein; UA=Uric acid; eGFR=Estimated glomerular filtration rate; NA=Not applicable

lower percentage of patients with synovial proliferation had extra-articular tenosynovitis ($P = 0.003$).

The associations between MSKUS abnormalities and laboratory examinations were analyzed using the independent *t*-test [Table 4]. In these 220 patients, serum CRP level correlated significantly positively with the presence of synovial proliferation in the inflamed knee joints but negatively with DC sign ($P = 0.006$ and $P = 0.001$, respectively). The CKD stage, as indicated by the eGFR, and the presence of joint Baker's cyst correlated significantly ($P = 0.004$). However, some patients had a normal serum CRP level regardless of whether they exhibited the DC sign. In patients with an abnormal serum CRP level, the CRP level was lower in patients with than in those without the DC sign ($P = 0.016$).

In the entire cohort classified according to CKD,[15] the eGFR was ≥90, 60–89, 30–59, 15–29, and <15 mL/min/1.73 m^2 for 90 (34.7%), 77 (29.7%), 53 (20.4%), 20 (7.7%), and 19 (7.3%) patients, respectively. Among patients with Stage V CKD, 5 patients received regular hemodialysis. The respective numbers of patients with Baker's cyst according to these categories were two, eleven, six, four, and three [Table 5]. The eGFR correlated negatively with the development of Baker's cyst ($P = 0.037$, independent *t*-test), that is, the more severe the CKD, the higher the prevalence of Baker's cyst in this group [Table 4].

Table 3: Associations between musculoskeletal ultrasonography manifestations (Pearson Chi-square and Phi scores)

	Joint effusion	Synovial proliferation	Tenosynovitis	Baker's cyst	DC sign
Synovial proliferation					
Phi score	0.508				
P	<0.001***				
Tenosynovitis					
Phi score	–0.034	–0.185			
P	0.585	0.003**			
Baker's cyst					
Phi score	0.052	0.135	0.084		
P	0.404	0.029*	0.178		
DC sign					
Phi score	0.089	0.142	0.028	−0.015	
P	0.153	0.023*	0.647	0.808	
Tophi					
Phi score	0.018	–0.049	0.048	–0.026	0.096
P	0.775	0.432	0.442	0.676	0.124

*P<0.05; **P<0.01; ***P<0.001. DC=Double contour

DISCUSSION

Gout, the most common inflammatory arthritis, is characterized by the deposition of MSU crystals in the synovial space of joints.[1,2] Dysregulation of UA metabolism induces hyperuricemia, which is a major risk factor for gouty arthritis.[16] Although many imaging tools are available for detecting gouty arthritis in joints, such as conventional radiography, conventional computed tomography, dual-energy computed tomography, and magnetic resonance imaging, MSKUS remains a reliable method and the most convenient tool for detecting inflammation and structural deformities.[16] In this retrospective study, we assessed the relationships between MSKUS abnormalities and serum and synovial abnormalities,

Table 4: Association and strength between the laboratory abnormalities and Musculoskeletal ultrasonography manifestations (independent *t*-test)

	SFWCC (×10^3/μL)	BWCC (×10^3/μL)	CRP (mg/dL)	Serum UA (mg/dL)	eGFR (mL/min/1.73 m^2)
Joint effusion					
−		9.5±0.6	5.9±1.1	7.9±0.3	78.8±4.6
+		9.9±0.3	7.9±0.6	8.4±0.3	70.5±2.6
P		0.505	0.118	0.289	0.120
Synovial proliferation					
−	29.8±3.3	9.9±0.4	6.0±0.7	7.9±0.2	76.5±3.1
+	24.3±3.0	9.8±0.4	9.1±0.9	8.7±0.5	67.6±3.4
P	0.228	0.946	0.006**	0.103	0.052
Tenosynovitis					
−	27.6±2.4	9.7±0.3	7.5±0.6	8.4±0.3	71.4±2.6
+	25.4±5.0	10.8±0.8	7.7±1.3	7.7±0.3	77.0±5.1
P	0.702	0.201	0.939	0.063	0.335
Baker's cyst					
−	27.5±2.4	9.9±0.3	7.5±0.6	8.2±0.2	74.0±2.4
+	22.4±6.6	9.7±0.8	7.7±1.9	8.8±0.5	57.6±6.0
P	0.487	0.869	0.919	0.238	0.016*
DC sign					
−	26.7±2.6	10.2±0.3	9.2±0.8	8.3±0.2	72.8±3.1
+	27.5±4.2	9.5±0.4	5.6±0.7	8.2±0.5	72.0±3.3
P	0.881	0.200	0.001**	0.765	0.849
Tophi					
−	27.1±2.5	9.7±0.3	7.1±0.6	8.1±0.2	73.2±2.6
+	26.7±4.9	10.4±0.6	9.3±1.5	8.6±0.8	70.3±4.9
P	0.950	0.331	0.115	0.343	0.607

*P<0.05; **P<0.01. MSKUS=Musculoskeletal ultrasonography; SFWCC=Synovial fluid white cell count; BWCC=Blood white cell count; CRP=C-reactive protein; UA=Uric acid; eGFR=Estimated glomerular filtration rate; DC=Double contour

such as the BWCC, serum CRP and UA concentrations, and eGFR in patients with symptomatic gouty arthritis, especially in the patients with CKD.[17]

Patients with leukocytosis exhibited increased serum CRP level, which might indicate that these patients exhibited more active inflammation and are consistent with previous reports.[18] We found that serum CRP levels correlated significantly negatively with eGFR. Impaired renal function and decreased eGFR reduce the renal excretion of inflammatory factors. The CRP levels were reported to be higher in patients with end-stage renal disease than in those with normal renal function.[19] Patients with impaired renal function and gouty arthritis often exhibit fever and oligoarthritis, and it is difficult for clinicians to distinguish MSU crystal-induced arthritis from septic arthritis or other infectious diseases. Serum procalcitonin level may be an alternative diagnostic tool for distinguishing inflammation from infection in patients with CKD. However, serum procalcitonin level is often influenced by severe renal failure associated with low eGFR, which makes it more difficult to identify real inflammation or infection in patients with severe CKD. Our data highlight the need for MSKUS examinations in CKD patients regardless of this presence or absence of symptoms. In the future, we will integrate the measurement of serum procalcitonin and CRP levels with the detection of MSKUS abnormalities to aid in the differential diagnosis for CKD patients with active oligoarthritis and a high serum CRP level.

In our study, patients with gout and joint effusion had a significantly higher chance of exhibiting synovial proliferation. Joint effusion is a major manifestation of gout, whereas chronic and recurrent inflammation of joint structures induces synovial proliferation.[20] Thus, we hypothesize that synovial proliferation is an interim characteristic connecting the acute and chronic stages of gout [Figure 1]. In our study, patients with an increased serum CRP level exhibited a high prevalence of synovial proliferation (P = 0.006), which indicates that patients with an abnormal CRP level exhibited more severe inflammation within the joint space and suggests that this may contribute to synovial proliferation.

Simultaneous long-term synovial inflammation and the presence of MSU crystal deposition in the joint contribute to the development of the DC sign, an indicator of the chronic structural damage of gouty arthritis. However, the DC sign is sometimes observed in patients with asymptomatic hyperuricemia.[21] In our study, synovial proliferation was associated with a higher risk of exhibiting the DC sign, and patients with the DC sign had lower serum CRP levels. Thus, we hypothesize that the levels of inflammatory factors may be downregulated as gouty arthritis progresses from the acute to the chronic stage. The serum CRP level is higher in patients with acute gout and gradually decreases when gouty arthritis evolves into the chronic phase. Therefore, a higher serum CRP level may indicate a higher risk of synovial proliferation and inflammation. Because synovial inflammation persists a long time, like the presence of the DC sign in joints, serum CRP levels may decrease reciprocally with progression to the chronic phase.

Table 5: Incidence of Baker's cyst according to chronic kidney disease stage

eGFR (mL/min/1.73 m^2)	Number, *n* (%)	Number and incidence rate of Baker's cyst, *n* (%)
≥90	77 (35.0)	2 (2.6)
60-89	64 (29.1)	11 (17.2)
30-59	45 (20.5)	6 (13.3)
15-29	17 (7.7)	4 (23.5)
<15	17 (7.7)	3 (17.6)

eGFR=Estimated glomerular filtration rate

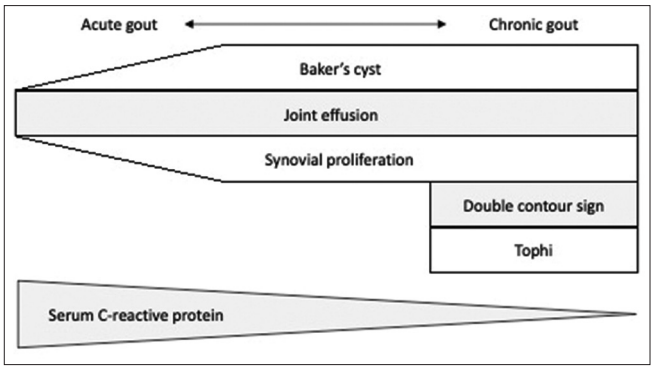

Figure 1: The different articular manifestations in acute and chronic gout. The synovial proliferation might be a bridge connecting acute and chronic gouty arthritis and induce chronic manifestation like double contour sign and tophi formation. The serum level of C-reactive protein is higher in acute phase and attenuate as chronic gouty arthritis develops

Synovial proliferation often occurs in combination with joint effusion and induces the formation of Baker's cyst, a secondary response to synovial inflammation in the knee joint.[5] Baker's cyst can be an incidental finding during imaging studies of articular diseases. Gout accounts for almost one-sixth of the total incidence of Baker's cyst. We found a higher prevalence of Baker's cyst in patients with synovial proliferation. Some patients may present with a ruptured cyst, a condition that mimics thrombophlebitis.[22] Baker's cysts can cause nerve compression neuropathy, which reduces the vascular flow or leads to compartment syndrome. MSKUS is a powerful technique for the detection of Baker's cyst, and ultrasound-guided aspiration has been used for the treatment of Baker's cysts.[23] To the best of our knowledge, no study has specifically discussed the associations between CKD and the incidence of Baker's cyst. Our study found that the risk of

Baker's cyst in gout was higher in CKD patients than in those with normal renal function ($P = 0.037$). This difference may be related to the reduced excretion of inflammatory factors in people with impaired renal function.[24] To prevent the development of Baker's cysts and associated articular complications, we recommend regular MSKUS examinations for patients with simultaneous gouty arthritis and CKD, regardless of the stage of CKD, and prompt initiation of urate-lower therapy.

The prevalence of tenosynovitis was lower in patients with than without synovial proliferation ($P = 0.003$). Tenosynovitis is an extra-articular inflammatory disorder that is not specific to gout and is detected in many diseases, such as mechanical injury, osteoarthritis, and infections.[6] MSU crystal deposition in the joint can induce tenosynovitis in people with gout.[25-27] MSKUS may help to identify extra-articular tenosynovitis and intra-articular structural damage, which may make the use of MSKUS critical in daily clinical practice. It remains unknown how tenosynovitis is relevant to the intra-articular features of gout, such as synovial proliferation or structural damage. A larger cohort study is warranted to elucidate the associations between tenosynovitis and synovial inflammation in gouty arthritis.

This study has several limitations. The sensitivity and specificity of MSKUS depend on the skill of the operator; hence, at least two experienced rheumatologists with the expertise and certification in MSKUS performed the image examinations for all patients in this investigation. Intra-reader variation was calculated and met the criteria. As mentioned in previous studies, rheumatologists experience difficulties in estimating the duration of gout when distinguishing between acute, intercritical, and chronic gout. Many patients are often unaware of their first onset of gout or have only asymptomatic hyperuricemia when actual structural damage has developed, and it can be difficult to determine the correct timing for initiating MSKUS examination. However, we recommend regular periodical MSKUS follow-up at the commonly involved joints, such as the knee, to identify insidious synovial inflammation or even chronic manifestations such as the DC sign. Finally, many patients who were enrolled in this retrospective study had received UA-lowering or anti-inflammatory agents, which makes it difficult to discern how medications can influence the appearance of gouty arthritis on MSKUS.

CONCLUSION

Insufficient control of hyperuricemia can lead to chronic gouty arthritis and subsequent structural joint deformities. Reciprocally, acute inflammation of joints is downregulated as chronic gout develops. Physicians should be aware of the risk of chronic structural deformities and arrange for regular MSKUS examination for patients with gout, regardless of whether the gout is in the acute or chronic stage. Physicians should prescribe prompt treatment in patients exhibiting synovial proliferation, such as Baker's cyst or the DC sign, which indicate a high risk of severe structural damage by chronic gouty arthritis. Patients with gout and CKD should receive intensive treatment and regular monitoring through MSKUS because they are at high risk of developing chronic structural joint deformities.

Ethics approval

The study was conducted in accordance with the declaration of Helsinki and was approved by the local ethics committee of the institute. Informed written consent was obtained from all participants and patients.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions:

Study concept and design: Zheng-Hao Huang, Acquisition and interpretation of data: Shu-Yi Lin, Drafting of the manuscript: Zheng-Hao Huang, Statistical analysis: Tony Szu-Hsien Lee,; Obtained funding: Chun-Chi Lu; Administrative, technical, or material support: all authors; Study supervision: Chun-Chi Lu, Submission: Chun-Chi Lu. All authors have read and approved the draft of manuscript.

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Data availability statement

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

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Conflicts of interest

There are no conflicts of interest.

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