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Musculoskeletal Ultrasound in Monitoring the Efficacy of Gout: A Prospective Study Based on Tophus and Double Contour Sign

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Background: In patients with gout receiving uric acid-lowering therapy, musculoskeletal ultrasound has the potential to observe changes in gout lesions.

Aims: To analyze the effectiveness of uric acid-lowering therapy in patients with gout over one year using musculoskeletal ultrasound as a monitoring technique.

Study Design: Prospective cohort study.

Methods: A total of 215 patients meeting the 1977 American College of Rheumatology gout classification criteria and treated with uric acid-lowering therapy were separated into two groups, treat-to-target and treat-to-non-target depending on the target serum urate levels. Lower extremity joints were evaluated by ultrasound before therapy (M_0), as well as three (M_3), six (M_6), and twelve (M_{12}) months after therapy. At various moments during uric acid-lowering therapy, the tophus size and the semiquantitative ultrasound scoring system of double contour sign were measured in the treat-to-target and treat-to-non-target groups.

Results: Ninety-five tophi (45 in treat-to-target and 50 in treat-to-non-target) and sixty-seven double contour sign (34 in treat-to-target and 33 in treat-to-non-target) were evaluated longitudinally. In both groups, the long diameter, short diameter, and area of tophus in treat-to-target decreased as the duration of uric acid-lowering treatment increased. Differences in the long diameter of tophus between M_{12} and M_0, M_3 and M_6 were statistically significant ($P < 0.05$), while differences between the other time points were not significant ($P > 0.05$). No statistically significant differences were observed in the short diameter and the area of tophus between M_0 and M_3 ($P > 0.05$), while there were statistically significant differences between other periods ($P < 0.05$). In treat-to-non-target, the long diameter, short diameter, and area of tophus showed a slight increase at different uric acid-lowering therapy time points. The differences in the long diameter, short diameter, and area of tophus at different uric acid-lowering therapy time points were not significant ($P > 0.05$). The semiquantitative ultrasound scoring system of double contour sign of treat-to-target and treat-to-non-target showed a decreasing trend with increasing uric acid-lowering therapy time, with a more pronounced drop in treat-to-target than treat-to-non-target. In treat-to-target, the difference in the semiquantitative ultrasound scoring system of double contour sign at each uric acid-lowering therapy time point was significant ($P < 0.05$). In treat-to-non-target, the difference in semiquantitative ultrasound scoring system of double contour sign scores between M^0 and M^3 was not statistically significant ($P >0.05$), but it was statistically significant for the remaining time points ($P < 0.05$).

Conclusion: After one year of uric acid-lowering therapy in patients with gout, an ultrasound indicated that the size of tophus and the semiquantitative ultrasound scoring system of double contour sign score decreased dramatically in the treat-to-target group. Semiquantitative ultrasound scoring system of double contour sign score was dramatically reduced in the treat-to-non-target group, but the size of the tophus remained the same. Therefore, musculoskeletal ultrasound is an effective tool to monitor the efficacy of uric acid-lowering therapy.

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INTRODUCTION

Gout is a crystal deposition-related disease caused by purine metabolism disorder.[1] The formation of monosodium urate (MSU) crystals and the activation of a nonspecific inflammatory response act as the central link in acute gout attacks.[2,3] Gout includes the hyperuricemia period, acute period of a gout attack, intermittent period, and chronic period of tophus formation.[4] Gout treatment drugs include those that reduce MSU production, increase renal MSU excretion, as well as anti-inflammatory drugs.[5,6] Longterm use of gout drugs may cause several adverse reactions in patients, such as damage to the liver and kidney function and even rhabdomyolysis, which can endanger life.[7] Uric acid-lowering therapy (ULT) is highly time-consuming, and clinicians and most patients want to know its therapeutic effect during treatment. Therefore, finding a suitable and reliable monitoring method to determine the therapeutic effect of ULT can help clinicians understand the effect of treatment, quickly adjust the treatment plan, and increase patients' confidence in treatment.

The most prominent curative effect in patients with gout is a clinical manifestation; however, clinical symptoms can improve in the intermittent period, which is not synchronized with the curative effect and cannot reflect the real effect of ULT. Regular detection of serum urate (SUA) is used in clinical treatment. However, SUA has the disadvantage of high volatility.[8,9] Multiple repeated measurements are conducted over a short period to increase the stability of SUA, although this approach is not preferred by most gout patients. Dual-energy CT measurement of MSU sediment volume is another effective method to monitor the therapeutic effect of ULT, though it is not suitable longterm due to the exposure to high radiation.[10,11] The 2015 American College of Rheumatology/European League Against Rheumatism classification of gout adopted DCS as a specific ultrasound sign for the diagnosis of gout. Several studies have confirmed that the disappearance of DCS and the reduction of tophus can be observed in ULT.[9,12-15] Therefore, musculoskeletal ultrasound (MSUS) could be implemented as a ULT efficacy monitoring method. However, reports on this are limited. In this study, we observed changes in tophus and DCS during ULT by MSUS to determine whether MSUS could be an effective tool to monitor the efficacy of ULT for gout.

MATERIALS AND METHODS

Patients and Sample Collection

The inclusion criteria were primary gout arthritis and were based on the gout diagnostic criteria of the 1977 American College of Rheumatology (ACR). All patients met the criteria for classifying primary gout arthritis. Patients with rheumatoid, reactive, psoriatic, spinal, or other inflammatory arthritis were excluded. Patients with gout arthritis received anti-inflammatory therapy during an acute episode and a standardized ULT in remission. All patients received a small dose of oral anti-inflammatory drugs during ULT to prevent paroxysm of gout arthritis. During treatment, SUA was measured monthly in all participants. SUA values of all participants were plotted as a continuous curve, and all gout patients were divided into treat-to-target (TTG) and treat-to-non-target (TNTG) groups. The TTG standard curve showed a decreasing trend; the lowest SUA was below 300 μmol/l. Other gout patients who did not meet the TTG criteria were included in the TNTG group (Figure 1).

All US investigations were performed by a doctor who had received formal musculoskeletal US training, using a Supersonic Imagine Aixplorer machine (French) with an SL15-4 linear array probe. Joints of both lower extremities (bilateral knee, ankle, tarsal, and metatarsophalangeal joints) and some tendons of both lower extremities (bilateral quadriceps tendon, pes anserinus tendon, patellar ligament, biceps femoris tendon, iliotibial band tibial attachment, and pollicis abductor tendon) were regularly checked. The MSUS examination was performed before treatment (M_0), three months after treatment (M_3), six months after treatment (M_6), and 12 months after treatment (M_{12}), and the DCS and tophus ultrasound images were recorded and stored for further use. DCS was scored based on the semiquantitative ultrasound scoring system (SQUS) of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) in 2021 double contour sign [(DCS)-SQUS]. The DCS-SQUS was divided into four grades as follows: 0: not at all; 1: possible; 2: definite, minor; 3: definite, severe. The maximum long diameter and the short diameter of tophus were measured based on two-dimensional ultrasound images, and the maximum area of tophus was determined using Image J. The SQUS-DCS of ultrasound images was assessed separately by two musculoskeletal ultrasonographers using a blinded method, and in case of disagreement, the two physicians consulted and reached a consensus.

Statistical Analysis

Continuous data following a normal distribution were presented as mean ± standard deviation. The differences between the data

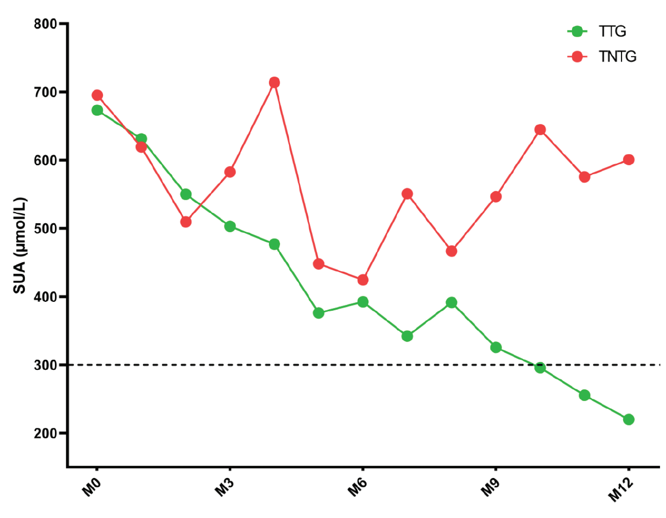


FIG. 1. Green curve (TTG standard curve): a 43-year-old gout patient with a gout duration of 5.5 years was included in the TTG group; blue curve (TNTG standard curve): a 48-year-old gout patient with a gout duration of 8.5 years was included in the TNTG group.
TTG, treat-to-target; TNTG, treat-to-non-target

groups were compared by performing the independent samples t-test. Nonnormally distributed data were presented as median (interquartile spacing), and the Mann-Whitney U test was performed to compare the differences between the data groups. A General Linear Model repeated measure analysis of variance (ANOVA) was used to analyze the longitudinal data before and after treatment, and the two-tailed tests were considered statistically significant at $P < 0.05$.

RESULTS

Clinical Data

A total of 215 gout patients who met the 1977 ACR gout classification criteria participated in the ultrasound examination (214 males and one female). During the treatment, follow-up ultrasound examinations were performed at M_0, M_3, M_6, and M_{12} for 162 lesions, including 95 tophi and 67 DCS. There were 79 lesions in the TTG group and 83 lesions in the TNTG group. The clinical data for the two groups are shown in Table 1. There were no significant differences in the SUA level before treatment (SUA_{M0}), disease duration, age, attack frequency, pain scores, and body mass index between TTG and TNTG ($P > 0.05$). Only the minimum value of SUA (SUA_{min}) during treatment significantly differed between the two groups.

Dynamic Changes in Tophus and DCS During ULT

The long diameter of tophus

The long diameter of tophus in TTG decreased as the ULT time point changed, while the long diameter of the tophus in TNTG showed a slight increase in the ULT time point (Figure 2a). ANOVA was performed to analyze the change in the long diameter of tophus. Since the difference in Mauchly's spherical test was significant ($P < 0.05$), a multivariate test was performed, which showed that the long diameter was significantly different at each time point of ULT ($F_{(3,91)} = 28.508$, $P < 0.05$). Then, the simple effects of the time points were analyzed, and in TTG, the results showed significant differences between M_{12} and M_0, M_3 and M_6. However, in TNTG, there were no significant differences in the long diameter at each time point (Figure 2b, Table S1-2, Supporting Information).

TABLE 1. Comparison of the Clinical Data of TTG and TNTG

	Tophus/DCS	SUA_{M0}	SUA_{min} #	Duration of the disease	Age	Attack frequency#	Pain scores	BMI
		μmol/L	μmol/L	Years	Years	Times/year	Score	kg/m²
TTG	45/34	599.15 ± 90.37	255.85 (236.68,275.75)	9.27 ± 5.29	48.75 ± 9.08	6.00 (4.00,11.75)	7.83 ±1.37	25.78 ± 3.05
TNTG	50/33	597.09 ± 104.41	345.45 (329.83,375.63)	12.75 ±7.83	43.34 ± 14.61	6.00 (5.00,12.00)	8.00 (7.00,9.75)	26.59 ± 3.82
Z/t		0.077	-6.358	-1.877	1.700	-0.433	-0.879	-0.856
P		0.939	0.001	0.066	0.095	0.665	0.379	0.396

#Indicates that the data do not obey the normal distribution by the SW test; SUA_{M0}, SUA level before treatment; SUA_{min}, the minimum value of SUA during treatment; BMI, body mass index

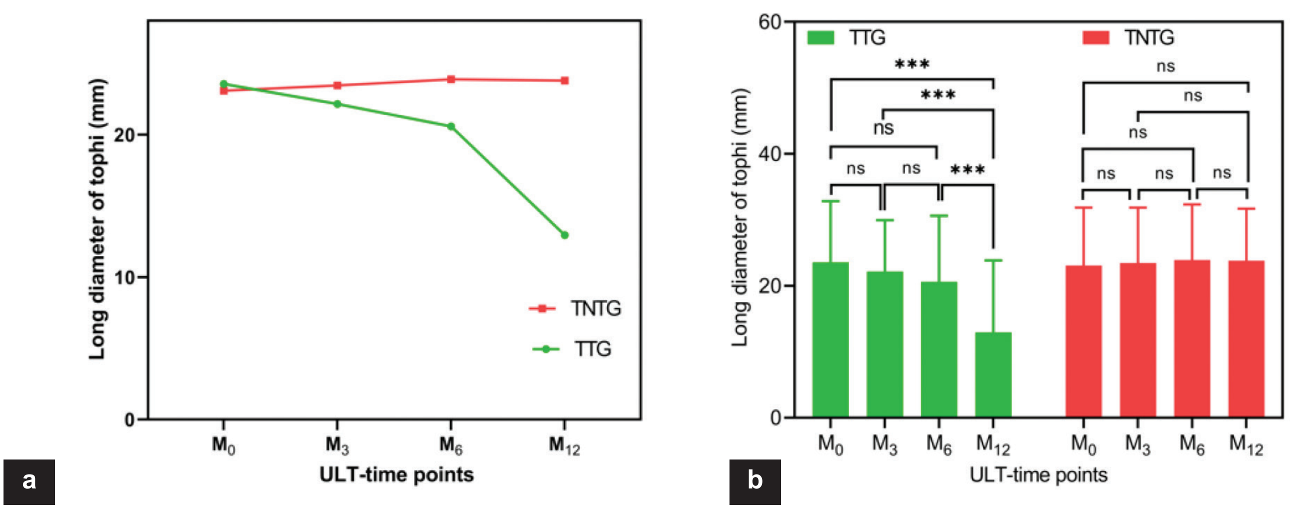


FIG. 2. (a) Distribution of the long diameter of tophus at different ULT time points in TTG and TNTG. (b) Statistical analysis of the long diameter of tophus at different time points in TTG and TNTG. ***$P < 0.001$.
TTG, treat-to-target; ULT, uric acid-lowering therapy; ns, not significant

The short diameter of tophus

The short diameter of tophus decreased significantly in TTG with the extension of ULT duration but increased slightly in TNTG with the extension of the ULT duration (Figure 3a). ANOVA was performed to analyze the change in the short diameter of tophus. Since the difference in Mauchly's spherical test was significant ($P < 0.05$), a multivariate test was performed, which showed that the short diameter of tophus was significantly different at each ULT time point ($F_{(3,91)} = 41.957$, $P < 0.05$). Subsequently, the simple effects of the time points were analyzed, and the results showed significant differences between M_{12} and M_0, M_3 and M_6, as well as between M_6 and M_0, M_3 in TTG. However, there were no significant differences in TNTG at each ULT time point (Figure 3b and Tables S3-4, Supporting Information).

The area of tophus

The area of tophus decreased with the extension of the ULT time point in TTG (Figure 4), while it showed a slight increase with the extension of the ULT time point in TNTG (Figures 4-5a). ANOVA was done to analyze the changes in the tophus area. Since the difference in Mauchly's spherical test was significant ($P < 0.05$), a multivariate test was performed, which showed that the area of tophus was significantly different at each ULT time point ($F_{(3,91)} = 10.703$, $P < 0.05$). Next, the simple effects of the time points were analyzed, and the results showed no significant differences in the tophus area between M_0 and M_3 in the TTG group ($P > 0.05$), but the differences at other time points were significant ($P < 0.05$). However, there were no significant differences in the area of tophus in TNTG between the ULT time points (Figure 5b, and Tables S5-6, Supporting Information).

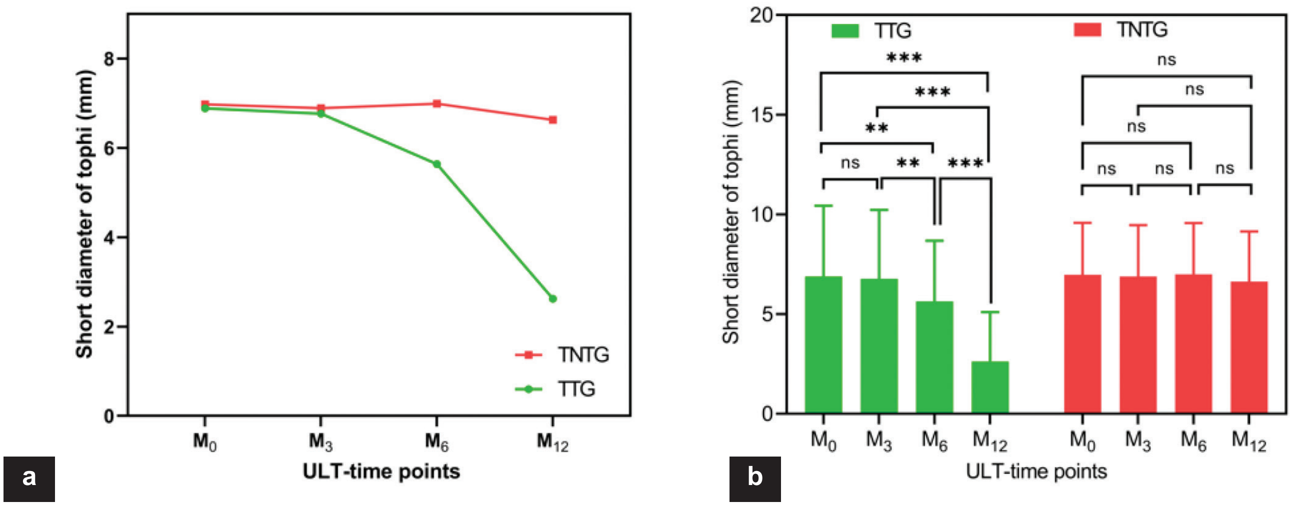


FIG. 3. (a) The distribution of the short diameter of tophus at different ULT time points in TTG and TNTG. (b) Statistical analysis of the short diameter of tophus at different time points in TTG and TNTG. **$P < 0.01$, ***$P < 0.001$.
TTG, treat-to-target; TNTG, treat-to-non-target; ULT, uric acid-lowering therapy; ns, not significant

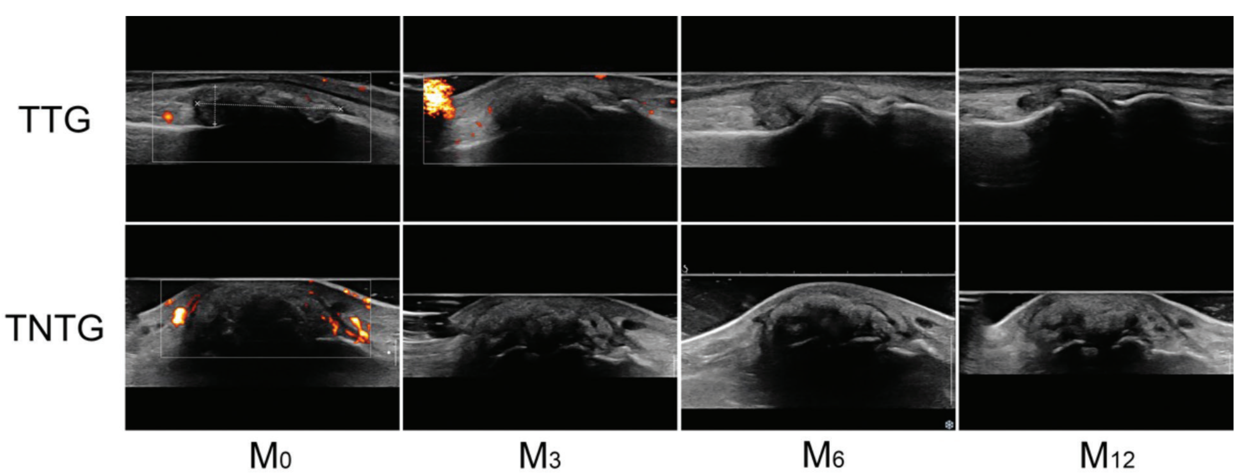
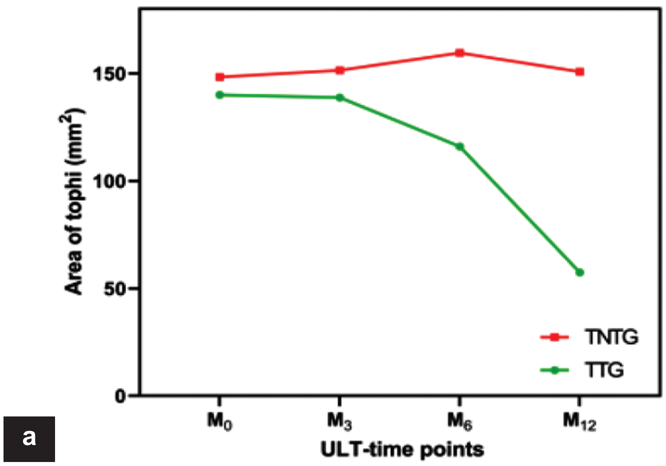


FIG. 4. MTP1 ultrasound: A longitudinal section of the dorsal tophus at each time point in TTG and TNTG. The area of tophus: A 51-year-old male with a five-year course of gout (TTG). A 41-year-old man with a history of gout for 12.5 years (TNTG).
TTG, treat-to-target; TNTG, treat-to-non-target



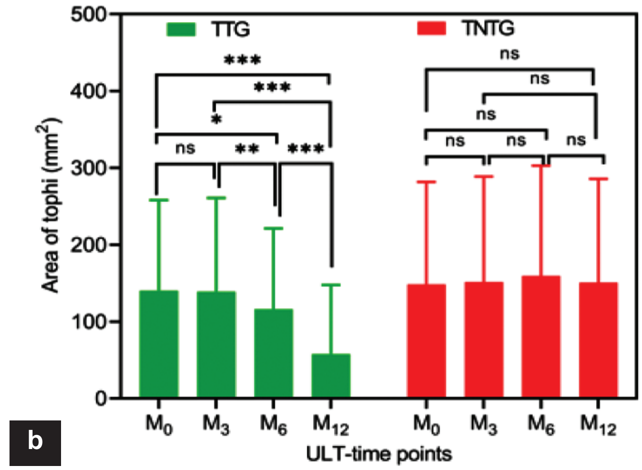


FIG. 5. (a) The distribution of the tophus area at different ULT time points in TTG and TNTG. (b) Statistical analysis of the area of tophus at different time points in TTG and TNTG.Dynamic changes of SQUS-DCS in ULT. *P < 0.05, **P < 0. 01, ***P < 0.001.
TTG, treat-to-target; TNTG, treat-to-non-target; ULT, uric acid-lowering therapy; DCS, double contour sign; ns, not significant

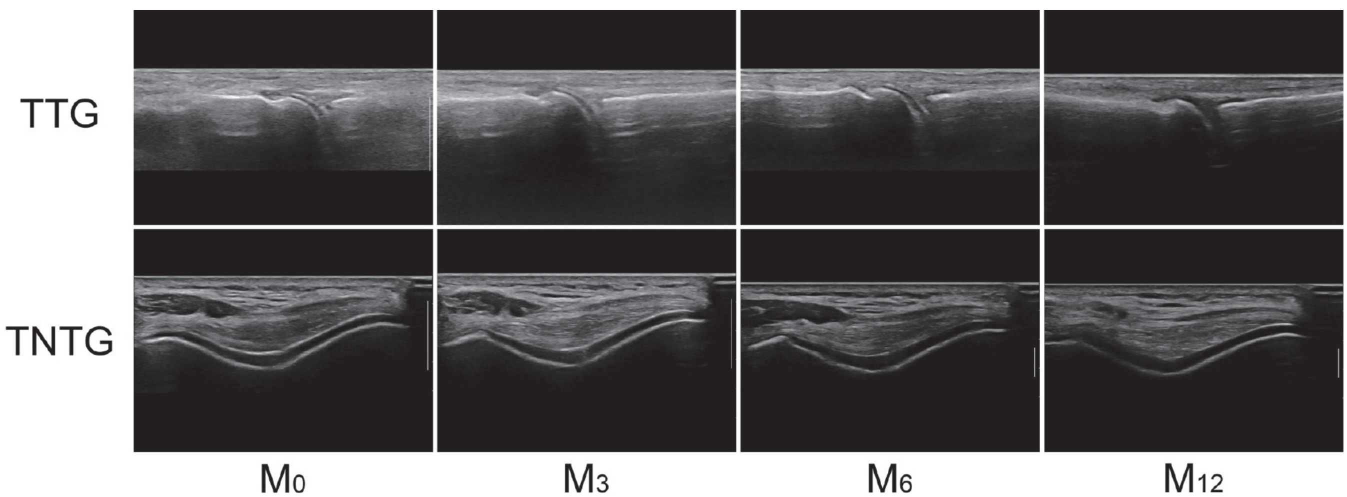


FIG. 6. Sonography of the dynamic changes in DCS at the different ULT time points in TTG and TNTG. MTP1 (dorsal longitudinal section) with DCS (TTG): A 45-year-old male with a gout course for over ten years; SUA_{M0}: 689.1 μmol/L and SUA_{min}: 191.6 μmol/L. Knee joint (cross-section in flexion position) with DCS (TNTG): A 37-year-old man with a course of gout for eight years; SUA_{M0}: 689.1 μmol/L and SUA_{min}: 382.7 μmol/L.
TTG, treat-to-target; TNTG, treat-to-non-target; ULT, uric acid-lowering; DCS, double contour sign

The SQUS-DCS

The SQUS-DCS evaluation was performed on 67 lesions, 34 in TTG and 33 in TNTG. The mean values of the SQUS-DCS of TTG and TNTG decreased with the extension of the ULT time point (Figures 6, 7). ANOVA was performed to analyze the changes in the SQUS-DCS. A multivariate test and a simple effects analysis showed that the SQUS-DCS of the TTG group were significantly different at different time points (P < 0.05) (Table S7, Supporting Information). However, there were no significant differences between M_0 and M_3, and between M_3 and M_6 in TNTG (P > 0.05), while the differences at other time points were significant (P < 0.05). Therefore, SQUS-DCS in TNTG also decreased after six months of ULT (Figure 7b, and Table S8, Supporting Information).

DISCUSSION

Tophus, DCS, and aggregates are the most characterized signs of MSU crystal deposition at the joint site.[16] The progressive disappearance of these signs is critical to monitoring the success of ULT in patients with gout. A study was conducted to determine whether tophus and DCS can change or dissipate during ULT in patients with gout. In total, 162 lesions (95 tophus and 67 DCS) were included in the current analyses. There were 79 lesions (45 tophus and 34 DCS) in TTG and 83 lesions (including 50 tophus and 33 DCS) in TNTG. During ULT, the DCS and the area, long and short diameters of tophus could be reduced in the TTG group (reduced speed: DCS > short diameter of tophus = area of tophus > long diameter of tophus). The DCS was reduced in the TNTG group, although the area, long and short diameters of tophus did

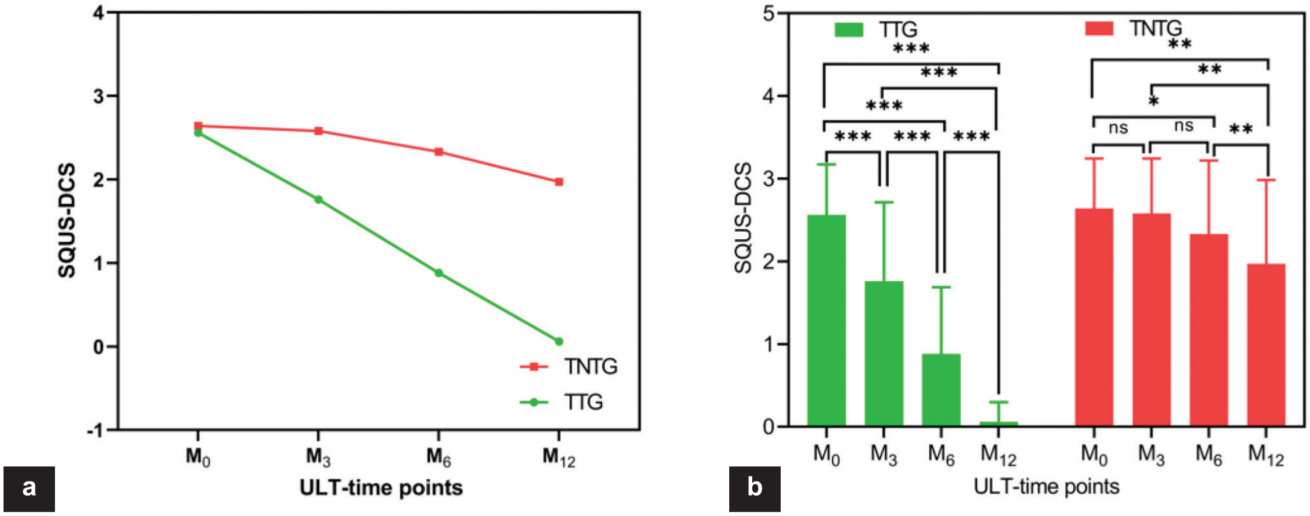


FIG. 7. (a) SQUS-DCS variation trend with different ULT time points. (b) The statistical analysis of the SQUS-DCS in TTG and TNTG at different time points. *P < 0.05 ***P* < 0. 01, ****P* < 0.001.
TTG, treat-to-target; TNTG, treat-to-non-target; ULT, uric acid-lowering therapy; SQUS-DCS, semiquantitative ultrasound scoring system of double contour sign; ns, not significant

not change significantly. The DCS reduced faster in TTG than TNTG.

We used the SQUS-DCS created by OMERACT in 2021 to examine the dynamic changes in the DCS of patients with gout.[17,18] The scoring system also determines the semiquantitative score for tophus. However, concepts, including specific scores of varying sizes, are not provided. Therefore, it is better to evaluate the therapeutic effect of ULT using the size change rather than the SQUS of tophus. Furthermore, we discovered that most tophi in M_0 and M_3 were accompanied by acoustic shadows, resulting in some aggregates eluding observation due to acoustic shadow occlusion. However, the tophi softened at M_6 and M_{12}, and the detection rate of aggregates increased significantly with the decrease in sound shadow, resulting in an upward trend of the SQUS of aggregates with ULT progression. This aggregate anomaly is not mentioned in 2021-OMERACT-SQUS' thus, it is not suitable for the monitoring of the efficacy of ULT.[17] Therefore, the SQUS of the aggregates was not evaluated in the ULT effectiveness monitoring in this study.

Changes in the same tophus in all directions were not coordinated during ULT. Thus, we evaluated the tophi's area, long diameter, and short diameter, respectively. The dynamic follow-up findings on tophus in this study revealed that the short diameter and the area of tophus changed consistently throughout ULT; however, the long diameter of tophus changed considerably later. After six months of ULT, the tophi in the TTG group revealed a significant reduction in area and short diameter. However, the area, long diameter, and short diameter of the tophi in the TNTG group did not change significantly within a year. Since the tophi significantly reduced in TTG but not in TNTG, a decrease in SUA is required for tophus reduction. Furthermore, we unexpectedly observed that the tophus dissolution rate in different parts of the same patient was not completely synchronous and could be related to different factors affecting tophus dissolution, such as blood supply and temperature. We could not perform a statistical analysis as we did not consider this point before beginning the investigation, and therefore, we did not have a fixed gain parameter in the ultrasound examination. Zhang et al.[8] reported that the difference clearance rates in tophus at different ULT time points were not statistically significant. However, in our research, tophus clearance between different ULT time points was statistically significant in the TTG group but not in the TNTG group. Possibly, the previous study only routinely observed patients without interventions, including ULT and dietary therapy. That study did not consider SUA decline as a prerequisite for the reduction of tophus and DCS, considering all patients with gout receiving ULT as a group for analysis, which may explain the statistically insignificant tophus clearance between different ULT time points. In our study, all gout patients receiving ULT and dietary management were separated into two groups based on whether SUA reached the target value after therapy. This may help identify patients for whom ULT is effective, allowing a more accurate usage of MUSU in efficacy monitoring.

SQUS-DCS was significantly reduced after three and six months of ULT in the TTG and TNTG groups, respectively. This result suggests that MSUS may be performed for the followup after three and six months of ULT for DCS in TTG and TNTG, respectively. Wang et al. reported that the time of disappearance of DCS was not related to the course of the disease, but to the baseline level of SUA, specifically the area under the curve during ULT.[9] In our study, the relationship between the baseline level of SUA (SUA_{M0}) and the decrease in DCS could not be identified as there was no significant difference in the baseline levels of SUA between TTG and TNTG. Wang et al.[9] also revealed that SUAmin in the DCS disappearance group was lower than that in the DCS retention group. According to Zhang et al.[8], the difference in the DCS clearance rates at different ULT time points was statistically significant, which is consistent with our findings. Therefore, MSUS is a suitable method to monitor the efficacy of ULT by observing DCS.

Two prior investigations compared tophus and DCS response sensitivity following ULT. Hammer et al.[19] found that DCS's response sensitivity was quicker than that of tophus, while Christiansen et al.[18] reported that DCS's response sensitivity was slower than that of tophus. In this study, for the TTG group, we found the response sensitivity of the gout lesions as follows: DCS (M_3) > short diameter of tophus (M_6) = area of tophus (M_6) > long diameter of tophus (M_{12}). This may be because Christiansen SN's research used semiquantitative scores to quantify tophus, whereas the present study used size to quantify tophus.

This paper has presented novel work. First, in this study, gout patients receiving ULT were divided into TTG and TNTG groups, and changes in tophus and DCS within each group were observed separately. Second, we applied the SQUS developed by OMERACT in 2021 to monitor ULT efficacy. Third, we evaluated the response sensitivity of the different parameters of DCS and tophus. However, this study also has some limitations. Since many patients were lost during the followup, the sample size was small.

MSUS is a low-cost, easy-to-operate, and nonradiation-damaged imaging examination. By examining the dynamic changes in tophus and DCS, this study confirmed the practical relevance of MSUS in evaluating the effectiveness of ULT. Moreover, the results of this paper might help doctors to understand the curative effect of ULT more intuitively and increase the confidence of gout patients to adhere to the therapy. In future studies, the correlation between the reduction in SUA levels and changes in tophus and DCS degree can be investigated to minimize the frequency of ultrasound examinations of patients. Additionally, in patients with gout with numerous tophi and DCS, determining the most sensitive joint location for ULT is essential to help reduce the time to perform an ultrasound during the followup.

After one year of ULT in patients with gout, the area, long diameter, and short diameter of tophus and SQUS-DCS in the TTG patient group reduced significantly (reduced speed: DCS > short diameter of tophus = area of tophus > long diameter of tophus). Although DCS decreased in TNTG, DCS decreased faster in TTG than in TNTG. Therefore, MSUS might be an effective tool for monitoring dynamic changes in tophus and DCS.

Ethics Committee Approval: the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (ethics number: 2021ER177-1), Dec. 2, 2021.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept- H.Y., Y.F., Y.Q.; Design- H.Y., Y.F.; Data Collection or Processing- Y.F., X.Y.; Analysis or Interpretation- Y.F.; Literature Search- X.M., X.T.; Writing- H.Y., Y.F.; Critical Review- W.Y., P.G.; Fundings- Q.Y., Y.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary: http://balkanmedicaljournal.org/uploads/pdf/2022-7-39-supplementarymaterials.pdf

REFERENCES

1. Huang Z, Xie N, Illes P, et al. From purines to purinergic signalling: molecular functions and human diseases. *Signal Transduct Target Ther*. 20216:162. [Crossref]
2. Yang QB, He YL, Zhang QB, Mi QS, Zhou JG. Downregulation of Transcription Factor T-Bet as a Protective Strategy in Monosodium Urate-Induced Gouty Inflammation. *Front Immunol*. 2019;10:1199. [Crossref]
3. Zhong L, Li S, Wen Y, et al. Expansion of Polymorphonuclear Myeloid-Derived Suppressor Cells in Patients With Gout. *Front Immunol*. 2020;11:567783. [Crossref]
4. Urits I, Smoots D, Franscioni H, et al. Injection Techniques for Common Chronic Pain Conditions of the Foot: A Comprehensive Review. *Pain Ther*. 2020;9:145-160. [Crossref]
5. Rezapour A, Alidoost S, Asgharzadeh A, et al. Cost-effectiveness of allopurinol versus febuxostat in the treatment of gout patients: A systematic review. *Med J Islam Repub Iran*. 2020;34:41. [Crossref]
6. Yu X, Zhang L, Zhang P, Zhi J, Xing R, He L. Lycium barbarum polysaccharides protect mice from hyperuricaemia through promoting kidney excretion of uric acid and inhibiting liver xanthine oxidase. *Pharm Biol*. 2020;58:944-949. [Crossref]
7. Barker T, Henriksen VT, Rogers VE, et al. Vitamin D deficiency associates with gamma-tocopherol and quadriceps weakness but not inflammatory cytokines in subjects with knee osteoarthritis. *Redox Biol*. 2014;2:466-474. [Crossref]
8. Zhang W, Zhao D, Wu M, Chen W, Jin Z, Zhang H. Ultrasound Evaluation of Three Outcome Domains in the Follow-up of Urate-Lowering Therapy in Gout: An Observational Study. *Ultrasound Med Biol*. 2021;47:1495-1505. [Crossref]
9. Wang Yu HW, Deng Xuerong, Zhang Zhuo-Li. Change of ultrasonographic signs during urate lowering therapy in patients with gout. *Chinese Journal of Practical Internal Medicine*. 2019;39:274-277. [Crossref]
10. Ahn SJ, Zhang D, Levine BD, et al. Limitations of dual-energy CT in the detection of monosodium urate deposition in dense liquid tophi and calcified tophi. *Skeletal radiology*. 2021;50:1667-1675. [Crossref]
11. Uhlig T, Eskild T, Karoliussen LF, et al. Two-year reduction of dual-energy CT urate depositions during a treat-to-target strategy in gout in the NOR-Gout longitudinal study. *Rheumatology (Oxford, England)*. 2022;61:Si81-si85. [Crossref]
12. Zou YD, Fei YN, Gao H, Xie LF, Zhong YC, Zhang X. Association between musculoskeletal ultrasonography and bone remodeling markers and the role of ultrasonography on monitoring treatment responsiveness in patients with gout and hyperuricemia. *Arthritis and Rheumatology*. 2018;70:1410. [Crossref]
13. Xiao L. Febuxostat for the treatment of urate deposits in goat: Ultrasound as a diagnostic tool. *International Journal of Rheumatic Diseases*. 2016;19:96. [Crossref]
14. Christiansen SN, Terslev L, Ostergaard M, Slot O. Gradual reduction of tophaceous deposits during urate-lowering therapy. *Joint bone spine*. 2021;88:105049. [Crossref]
15. Ebstein E, Forien M, Norkuviene E, et al. Ultrasound evaluation in follow-up of urate-lowering therapy in gout: the USEFUL study. *Rheumatology (Oxford)*. 2019;58:410-417. [Crossref]
16. Gutierrez M, Schmidt WA, Thiele RG, et al. International Consensus for ultrasound lesions in gout: results of Delphi process and web-reliability exercise. *Rheumatology (Oxford)*. 2015;54:1797-1805. [Crossref]
17. Christiansen SN, Filippou G, Scire CA, et al. Consensus-based semi-quantitative ultrasound scoring system for gout lesions: Results of an OMERACT Delphi process and web-reliability exercise. *Semin Arthritis Rheum*. 2021;51:644-649. [Crossref]
18. Christiansen SN, Østergaard M, Slot O, Fana V, Terslev L. Retrospective longitudinal assessment of the ultrasound gout lesions using the OMERACT semi-quantitative scoring system. *Rheumatology (Oxford)*. 2022;61:4711-4721. [Crossref]
19. Hammer HB, Karoliussen L, Terslev L, Haavardsholm EA, Kvien TK, Uhlig T. Ultrasound shows rapid reduction of crystal depositions during a treat-to-target approach in gout patients: 12-month results from the NOR-Gout study. *Ann Rheum Dis*. 2020;79:1500-1505. [Crossref]