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High-resolution ultrasound evaluation in the follow-up of treat to target urate-lowering therapy in gout: an observational study

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Abstract

Background: The monitoring of treat-to-target (T2T) urate-lowering therapy (ULT) for gout is crucial for the assessing treatment response. However, evidence is lacking about clinical remission on ultrasound (US). The aim of this study was to observe the changes in three outcome domains (urate deposition, joint inflammation and bone erosion) in patients with ULT within 1 year, evaluate the effect of target treatment and analyse the relationships between clinical factors and US features.

Methods: The elementary lesions of the bilateral knee, ankle and first metatarsophalangeal joints were evaluated by US before and after 3,6 and 12months of treatment. Urate deposition was assessed by the maximum long and short axis diameters of the tophi and dichotomous data of the double-contour (DC) sign and aggregates. After each follow-up, the most obvious lesions were selected for repeated observation. The effective clearance rates of these three signs in different time groups were compared. A Global OMERACT–EULAR Synovitis Score (GLOESS) was calculated for these three paired joints to observe the remission and recurrence of inflammation. Bone destruction was scored at each time point. The correlation between serum uric acid (sUA) levels and tophi size changes was analysed.

Results: This cohort contained 79 patients. The long and short axis diameters of tophi showed a different descending tendency. The decrease of sUA levels correlated with the decrease of long axis values, but not with the short. For tophi, there was no significant difference in the clearance rate between different time groups, while for DC sign and aggregates, significant differences were found by paired comparison. The GLOESS was significantly lower after 6 months of therapy. Bone erosion had not been improved after 1 year of ULT.

Conclusion: The decrease in sUA levels was not completely parallel to the decrease in tophi size. ULT with different intensities should be formulated according to different crystal deposition conditions under US assessment. Subclinical inflammation was gradually controlled after 6 months of therapy and can be sensitively observed by US. Joint damage was relatively stable within 12 months of ULT.

Trial registration: ChiCTR1800015043

Keywords: Gout, Ultrasound, Urate-lowering therapy, Outcome measures

Introduction

Gout is a chronic disease that seriously damages human health. Patients without treatment will eventually have a reduced quality of life, decreased capacity to work and increased risk of death due to joint damage, kidney impairment and an increase in cardiovascular events[1]. Timely and effective treatment and monitoring may control disease progression, avoid

adverse events and ultimately reduce mortality. Urate-lowering therapy (ULT), as an effective gout management strategy, has been widely recognized as crucial in delaying the disease progression and reducing damage to the functions of certain viscera. Unfortunately, direct best-quality evidence is not available for the treat-to-target (T2T) approach. Different therapeutic targets may depend on the severity of the disease and the stage of treatment[2]. There is an overall agreement to consider serum uric acid(sUA) levels below 6 mg/dL (360 μmol/L) as the minimum target and below 5 mg/dL (300 μmol/L) for severe gout. These therapeutic targets have been endorsed by both the 2016 European League Against Rheumatism (EULAR)[3] and 2012 American College of Rheumatology (ACR) [4] recommendations. However, the sUA level is affected by many factors and changes over time, so it cannot truly reflect the whole-body urate burden. In addition, it takes several months for monosodium urate (MSU) crystals deposited in the joint capsule to dissolve with normal sUA, and the dissolution rate is correlated with other factors, such as disease duration[5]. To date, there are no remission criteria established for gout[6]. Considering that and the endpoints of ULT vary greatly, imaging evidence of MSU is feasible for the guidance of clinical medication because the disappearance or decrease of MSU in imaging may reflect the effectiveness of treatment to some extent.

To date, the impact of urate-lowering drugs on the changes in imaging

during the T2T approach is not very clear. The Outcome Measures in Rheumatology (OMERACT) gout working group identified three key domains for imaging modalities to assess: urate burden, joint inflammation and structural damage[7]. Different modalities have superiority and insufficiency for different domains[8]. Dual energy computed tomography (DECT) has the potential for urate deposition and bone damage observation but is not recommended for joint inflammation assessment[9, 10]. MRI is good at showing bone erosion and synovitis, however, for most clinically apparent tophi, measurement using MRI has little advantage over less expensive, safer and faster methods of physical measurement[8].

Compared with other imaging modalities, ultrasound (US) has the highest performance for all three domains[7], and is expected to help clinicians evaluate the intensity of ULT, increase the treatment compliance of patients, and guide them to achieve more ideal clinical and imaging outcomes.

Few studies have been reported on high-frequency US evaluation in the follow-up of ULT. Previous studies suggested that US had a high specificity and positive predictive value in the diagnosis of gout[11], and played a certain role in the monitoring of therapy[12-14]. However, most of these studies focused on the sensitivity of US features (such as double-contour (DC)sign and tophi) to ULT[14, 15] and evidence is lacking about the specific changes of those features during different treatment periods.

Meanwhile, MSU deposition is often associated with joint inflammation and structural damage, but there are few reports on the response to treatment of these two domains by US.

The primary objective of this study was to describe the progression of US features from those three aspects before and 3, 6, and12 months after T2T therapy. Other objectives included identifying whether the observed changes in imaging in response to treatment are associated with changes in clinical data and providing a perspective on the role of US imaging for measuring treatment response in patients with gout.

Methods

Study design

We designed a 1-year prospective, observational US study involving gouty patients initiated to receive regular ULT. All patients were treated according to clinical routine and no intervention was conducted during the whole treatment. Patients could also take colchicine, NSAIDs or corticosteroids if needed. US assessment was performed at baseline and at 3, 6 and 12 months after ULT initiation. The study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (No.2018-013-01) and all the enrolled patients signed an informed consent form.

Patients

Participants were selected consecutively form outpatients in our hospital between July 2017 and March 2018. Patients were eligible if they were

positive for MSU crystals in synovial fluid. The exclusion criteria included the following: (1)age<18 or >80 years old; (2)presence of other rheumatic diseases; (3) administration of regular ULT or corticosteroid injection within the previous 3 months; and (4) creatinine clearance of <20 ml/min or severe liver function lesions (liver enzymes 3 times the upper limit of normal). Participants who took medicine irregularly and had no follow-up records were also excluded from the final statistical analysis. To evaluate medication adherence, the proportion of days covered (PDC) was used, and PDC ≥80% was considered adherent[16]. At baseline, all patients underwent a detailed clinical evaluation, including disease history (disease duration, number of gout flares, duration of attack, comorbidities, etc.), demographics and clinical characteristics (age, sex, BMI, tender joint count (TJC) and swollen joint count (SJC)), and laboratory testing (sUA levels, serum creatinine levels, serum urea nitrogen levels) (table 1) .Some of the clinical data and laboratory testing were assessed at 3, 6 and 12 months after treatment.

Primary and secondary outcomes

The primary outcome was the reduction or disappearance of specific US features (tophi, DC sign and aggregates) after 12 months of ULT. The secondary outcome was that two measurements of sUA stayed below 360μmm/L at least six months apart.

US assessment

US examinations were performed by a single sonographer experienced in musculoskeletal US, who was unacquainted with the clinical data. The examinations were conducted using a Toshiba Aplio500 scanner (Toshiba, Tokyo, Japan) with a 4-12 MHz linear array transducer. The power Doppler (PD) frequency was 4.4–6.1 MHz. A medium wall filter was used and the gain was adjusted until the background noise was suppressed. The joints in which gout lesions were detected included the bilateral knee, ankle and first metatarsophalangeal (MTP) joints of each patient. Suprapatellar longitudinal and transverse planes as well as medial and lateral longitudinal planes were scanned with the knee in the 30° flexion position, while the femoral cartilage was examined in the axial plane with full knee flexion. To scan the ankle, the patients were asked to place their feet flat on the examination bed. The anterior, medial and lateral regions were scanned sequentially along the longitudinal and transverse axes. The first MTP joint was examined from the dorsal, plantar and medial views in the longitudinal and transverse planes according to the scanning technique described in the European guidelines for musculoskeletal ultrasound[17].

Urate deposition was represented as tophi, DC sign and aggregates on US, which were defined by recently formed OMERACT consensus-based definitions[18]. At baseline, these three items were systematically examined for each joint. The DC sign and aggregates were recorded as dichotomous data (presence or absence) at each visit. For tophi, we selected the most

obvious one (usually in the MTP1 joint for the high detection rate[19]) as the target at baseline, measured the longest diameter on the longitudinal and transversal axes from the medial side and repeated the measurement at 3,6, and 12 months of follow-up.

PDUS evaluation was performed at each site 4 times. The PDUS assessment consisted of an evaluation of greyscale synovial hyperplasia (SH) and intrasynovial PD signal. Each single component of joint inflammation (SH and PD) was scored separately using a semiquantitative scale of 0–3[20]. To monitor disease activity, we used the composite PDUS score according to the OMERACT–EULAR PDUS composite semiquantitative scale (0–3) at the joint level[21], which is analogous to the composite scoring system used in rheumatoid arthritis (RA). The Global OMERACT–EULAR Synovitis Score (GLOESS) for these 3 paired joints was then calculated using the sum of the composite PDUS scores for all joints examined[22], ranging from 0-18.

At baseline, the presence of erosion was also recorded with a 0-3 scale for each joint[20] and confirmed on longitudinal and transverse scans. At each follow-up, the same joint with the most obvious bone destruction was selected for reevaluation. All images were saved and stored in the hard drive of the US machine for further analysis.

Statistical analysis

Statistical analyses were performed using SPSS Version 23.0 (IBM,

Armonk, NY, USA). Normally distributed variables are reported as the mean (SD), and categorical variables are reported as the frequencies. Student's t test was used for quantitative variables, and the chi-square test or Fisher's exact test was used for categorical data. Repeated measurement data of sUA and tophi size were compared using one-way analysis of variance (ANOVA). Correlations between US findings and clinical characteristics were estimated by the Spearman correlation coefficient. Changes in clinical and US inflammatory indicators from baseline to month 12 were investigated by several related samples tests (Friedman's M test). Bone erosion before and after treatment was compared by the Wilcoxon matched-pairs signed rank test. $P<0.05$ was considered statistically significant.

Intra- and interobserver agreement

The interobserver reliability of the US features of gout (erosion, SH and PD) and tophi size measurement were calculated by two sonographers with more than 5 years of experience in musculoskeletal US using 30 images from 10 randomly selected patients. Two weeks after the initial assessment, one of the sonographers under blinded conditions re-analysed the images to evaluate the intraobserver reliability. For the measure of tophi size, a discrepancy >20% between the two measures of two US operators (interobserver) or between the same operator (intraobserver) was considered different. The concordance for US was estimated as the kappa

coefficient, with κ>0.8, almost perfect; 0.6-0.8, good; 0.4-0.6, moderate, 0.2-0.4, fair, and ≤0.2, poor.

Results

Clinical characteristics

A total of 79 individuals with regular ULT were recruited. The patient demographics are shown in table 1. Seventy-five (94.9%) patients received febuxostat for the treatment, with a mean dose of 35.2±12.2 mg/d, and another 4 (5.1%) subjects chose benzbromarone, with a mean dose of 39.7 ±14.7 mg/d. The number of patients who completed treatment at months 3, 6 and 12 were 67 (85.9%), 64 (81%) and 57 (72.2%), respectively.

With treatment, the symptoms of the patients were gradually relieved. We found that SJC, TJC, number of gout flares and duration of attack differed at different time points（P<0.001）. The paired comparison results showed that SJC was significantly reduced by 6 months (P=0.043), while TJC decreased by 3 months (P=0.006). The number of gout flares decreased significantly by 12 months compared with that at baseline and 3 months (P<0.001 and P=0.002, respectively), and the duration of attack gradually shortened from 3 months (P≤0.01) (table1).

Urate deposition changes in response to ULT

At baseline, tophi was found in 48 patients (60.8%), and the mean changes in the long and short axes of diameters are listed in table 2. The DC sign was present in 53 patients (67.1%) and hyperechoic aggregates were

detected in 44(55.7%) participants. The proportion of patients with these three features observed at different time points is shown in table 2.

Interobserver and intraobserver agreement

The interobserver agreement for the measure of tophi and US feature scoring were as follows: tophi: 0.45 (95% CI: -0.124 to 1.024); bone erosion: 0.616 (95%CI: 0.249 to 0.983); SH: 0.853 (95%CI: 0.579 to 1.127); and PD: 0.902 (95%CI: 0.716 to 1.088). The intraobserver agreement for all those features were as follows: tophi: 0.633 (95%CI: 0.004 to 1.262); bone erosion: 0.732 (95%CI: 0.407 to 1.057); SH: 0.874 (95%CI: 0.637 to 1.111); and PD: 0.920 (95%CI: 0.767 to 1.073).

Changes in sUA levels and tophi size over 12 months

Overall, the level of sUA showed decreasing tendency, and the difference was statistically significant ($F[2.349,77.530]=25.863$，$P<0.001$). After 6 months of treatment, the level of sUA remained basically stable. Twenty-four patients (42.1%) reached the sUA objective (<360 μmol/l) at month 12.

Both the long and short axis diameters of tophi decreased significantly at follow up (for long axis: $F[1.616,42.003]=7.41$, $P=0.003$; for short axis: $F[2.187,56.855]=10.95$, $P<0.001$). However, the long and short axes of tophi showed different trends. The maximum long axis diameter displayed a significant reduction until month 12. Compared with that at baseline and month 3, the long axis diameter measured at month 12 decreased by 0.22

cm(P=0.018) and 0.17 cm(P=0.02), respectively. The earliest reduction in the short axis diameter of the tophi was observed as early as month 3 and then gradually declined. The short axis values at months 3,6 and 12 dropped by 0.072 cm(P=0.038),0.111 cm(P=0.003) and 0.156 cm(P=0.02) respectively, compared with the baseline value (figure 1).

The changes in sUA levels were positively correlated with the changes in the long axis value of tophi (r=0.335, P=0.043); however, no correlation was found between the decrease of sUA level and the short axis value (r=0.287, P=0.085).There was no significant correlation between disease duration and the reduction in long and short axis diameters.

Urate deposition clearance follow-up after ULT

To evaluate the effectiveness of ULT, we introduced the concept of the effective clearance rate, which was defined as the proportion of subjects with DC signs or aggregates from presence to absence or with both the long and short axis diameters of tophi decreasing by 20% before and after ULT. The efficacy of the treatment for tophi was 5% (2/40), 12.5% (5/40) and 5.4% (2/37) at months 3, 6 and 12, respectively, and the clearance rate did not differ significantly between the different time groups (χ^2=1.76, P=0.392). Throughout the whole study period, 2 patients (5%) had their tophi totally dissolved at month 6. The differences in the effective clearance rate for the DC sign and aggregates among the three follow-up groups were statistically significant (DC sign: χ^2=21.48, P<0.001;

aggregates: χ^2=7.75, P=0.018). No patients were observed with the DC sign disappearing by 3 months of follow-up. However, the DC sign clearance rate significantly improved at month 6 (19.1%) and month 12 (34.2%) (P<0.001). Aggregates disappeared as early as 3 months in 7% of the patients (3/43). There were no significant between-group differences in the clearance rate at the neighbouring time point; however, the month 12 rate was higher than the month 3 rate (32.2% (10/31) vs 7% (3/43), P=0.01) (figure 2).

Disease activity follow-up

There were a total of 65 patients (82.3%) with joint inflammation at baseline. Thirty-four (52.3%) of them had only one joint involved, with 3 patients (8.8%) involved in the knees, 16 (47.1%) in the ankles and 15 (44.1%) in MTP1, while the rest had multiple joints affected. A reduction trend was observed after the initiation of ULT, and the proportion of patients with detected joint inflammation was 76.1% (51/67), 70.3% (45/64) and 57.9% (33/57) at months 3, 6 and 12, respectively. The GLOESS at each time point was significantly different (χ^2=32.316, P<0.001). Paired comparisons suggested that the values at baseline (range 0-11, median 3) were significantly higher than those at 6 months (range 0-10, median 1) (P=0.004) and 12 months (range 0-6, median 1) (P<0.001). That is, inflammation became gradually controlled after 6 months of treatment (figure 3).

Bone erosion follow-up

Forty-eight patients (60.8%) had bone erosions, 27 (56.3%) of whom had only one joint involved, and the others had multiple. The majority of those were located at MTP1 followed by the ankle. At baseline, we found that 10.1% of the patients had grade 1 erosions, and the proportions for grades 2 and 3 were 13.9% and 36.7%, respectively. At month 12, the corresponding values for grades 1, 2 and 3 were 8.8%, 15.8% and 40.3%, respectively. After 1 year of treatment, the rating increased in 3 patients (1 was upgraded from grade 0 to grade 1), while the other 54 subjects had their score remained unchanged, and no rating downgrade was found. There was no significant difference in the US rating of bone erosions before and after 1 year of treatment (Z=-1.633, P=0.102) (figure 4).

Discussion

There is a considerable amount of indirect evidence that T2T treatment for gout is clinically effective in real practice[2]. The ultimate goal is to lower sUA levels, which is beneficial for promoting the dissolution of MSU in tissue. Theoretically, effective treatment strategies will sufficiently reduce sUA levels to prevent further crystal formation and dissolve existing urate crystals, thus eliminating the causative agent and effectively ‘curing’ the disease[23]. Therefore, it is necessary to monitor the dissolution of MSU in vivo to better evaluate the efficacy of therapy, and a newly published meta-analysis demonstrated that US offers good diagnostic accuracy with high

specificity that may play an important role in the monitoring of disease[24]. We conducted a 12-month follow-up study to evaluate the disappearance of the US features of gout under efficient ULT. Three elementary lesions of urate crystal deposits on US: DC sign, tophi and aggregates[18] were mainly observed.

Clearance of crystal deposits

Patients with advanced gout usually present with large tophaceous deposits. Many challenges still exist in quantitating them on US. We found that the short axis diameter was significantly decreased by month 3 and then maintained a steady decline. The long axis diameter fell slowly, and the difference was statistically significant until month 12 compared with that at baseline, which was not completely consistent with the short axis diameter. This is possibly due to the smaller base of the short axis diameter, and the acoustic shadow of the tophi may also affect the measurement accuracy. Therefore, the long axis diameter rather than the short axis diameter is more suitable to reflect tophi size changes considering system bias.

In our study, the mean size of the tophi shrank; however, some patients had an enlarged tophus during ULT. A previous study has demonstrated that some tophi enlarge before beginning to resolve[25]. Such enlargement represents tophi remodelling during the early phases of resolution, which may result in reduction slowing[26].The sUA level is the most important

indicator in monitoring disease. There is ample evidence of the effect of sUA normalization on tophi resolution[15, 27, 28]. However, the concrete relationship between the sUA level and MSU clearance rate is unclear. The present study showed that the sUA level fell sharply by month 3 and then decreased moderately. This conclusion agrees with a previous report that sUA levels fell significantly from baseline through the 4th month of follow-up and plateaued thereafter[29]. Overall, our findings indicate that the changes in sUA levels were not exactly parallel to the tophi diameter changes. At the end of 12 months, there were still 13 patients (54.2%) achieving therapeutic goals observed with tophi. Therefore, we suggest that continuous monitoring by US is needed even for those who have achieved clinical remission until the tophi completely vanishes.

Our results showed that the dissolution rates of those three lesions were different. The clearance rate of tophi did not differ significantly between the different time groups. As mentioned above, the crystal structure was stable and hard to be dissolved. For the DC sign, Das et al[29] demonstrated that it disappeared mostly by 6 months. Peiteado et al[30] suggested that it was probably much easier to clear cartilage urate deposits than tophi. These results are consistent with our findings. Compared with tophi, a lighter MSU load within the DC sign and disappearance seemed to appear earlier. Among the three signs, aggregates showed the fastest clearance at as early as 3 months of treatment, indicating that under the

same treatment conditions, the curative effect of aggregates is better than that of DC sign and tophi. The difference may be relevant to critical size and time. The smaller the critical size is with a short deposition time, the faster the clean-up and vice versa. These results support the idea that different therapeutic intensities are demanded according to different US-detectable deposits, and intense treatment is needed for patients with tophaceous gout.

In addition, there is still a controversial issue about the association of the clearance rate and disease duration. Pascual et al[5] reported that the disappearance time of urate crystals from synovial fluid was correlated with the duration of gout, and a longer time was required in those patients with a longer duration. However, Ebstein et al[15] considered that disease duration was not associated with the modification of DC sign and tophi. In this study, we found no significant correlation between the course of disease and the changes in both the long axis and short axis diameters of tophi, in part because tophi solubility can be affected by variable factors, related to the drug used and the degree of sUA level decrease. Moreover, tophi represents a complex structure with inflammatory tissue located adjacent to the central core of the MSU crystal[31]. The heterogeneity itself and the individual variation may also be relevant.

Inflammation

Previous studies have confirmed that PDUS is able to globally measure the

perfusion changes with high sensitivity in other inflammatory arthritis conditions[32-34]. To the best of our knowledge, few studies have reported disease activity follow-up by US in gout to date. It is unclear whether additional value to clinical examination can be provided by PDUS in establishing true gout remission. A previous MRI study showed that ULT with febuxostat improved MRI synovitis and reduced gout flares in subjects with early gout over a 2-year period[35]. Another study demonstrated that a Doppler signal at two years persisted in a high percentage of patients (72.7%), despite an obvious clinical improvement[13]. The present study evaluated the reduction trend of GLOESS and found that inflammation became gradually controlled at 6 months of treatment. In the early weeks and months of treatment, patients using antihyperuricemic drugs usually experience more frequent gout attacks, and then the incidence is reduced afterwards[36]. After 12 months of treatment, although most of the patients were in the interictal stage with clinical indicators including SJC and TJC, the number of flares and duration of attack were significantly reduced. The presence of US synovitis in one or more joints was still observed in 56.9% of subjects. This low-grade inflammation in the joint might be associated with the deposition of tophi, which contributes to a cycle of chronic inflammation, attempted resolution, and tissue remodelling[31]. These results support the hypothesis that the disappearance of a Doppler signal requires for the entire dissolution of

MSU deposits. Furthermore, the subclinical activity of gout is often ignored by patients for they have no symptoms, resulting in the interruption of treatment thereafter. Thus, it is necessary to monitor inflammation by PDUS in target areas until no PD signal is found in follow-up visits. Further studies are needed to elucidate the predictive value of the underlying inflammation observed by US and the feasibility of introducing a Doppler signal as an outcome measure in clinical practice.

Bone erosion

The US technique was found to be superior to conventional radiographs in evaluating small bone changes[37]. According to experienced sonographers, the inter- and intraobserver reliability of bone erosion on US ranged from good to excellent[38]. However, a longitudinal analysis of bone erosions in response to treatment in gouty patients by US is lacking. A previous observational study evaluating radiographic joint damage in longstanding gout patients showed that most of them had stable radiographic damage scores over the 3-year follow-up period and baseline erosion was strongly associated with progressive radiographic damage[39].

Consistent with the findings of the previous study, we observed that no significant change was found in the US score of bone erosions after 1-year of treatment. This result was expected, mainly because the most powerful factor, tophi[40, 41], contributes to progressive bone erosion by promoting osteoclast activation[42] and reducing osteoblast viability and function[43].

Another possible explanation is sustained synovitis, such as RA. Wu et al[41] conducted a logistic regression analysis and showed that bone sites affected by erosion were 1.87-fold more likely to lie adjacent to regions of synovial hypertrophy than not. Synovitis stimulated by long-term inflammation rather than acute inflammation is a risk factor for bone erosion. So far, it is unknown whether gouty erosions reliably repair after effective ULT. A small case series demonstrated improvement in radiographic bone damage scores with profound urate lowering in pegloticase responders with severe gout[44]. In contrast, no erosion regression occurred in our cohort, at least during the 1-year observational period. The difference may be due to the intensity of ULT. Compared with first-line antihyperuricemic drugs, pegloticase therapy leads to a profound reduction in sUA levels that rapidly relieves patients. This finding could be supported by the hypothesis that the more intensive treatment[45] is and the longer the duration of sustained remission is, the greater the likelihood of radiographic erosion repair. Furthermore, to achieve the prevention or healing of bone erosion, early diagnosis and treatment would also be important, while US may provide a strong imaging basis for timing selection.

Limitations

This study has some limitations. First, it is difficult to accurately measure the size of tophi due to heterogeneity and irregular shape. A self-control approach with fixed sections and sites was employed to reduce the bias.

However, since the measurement was taken only from the two-dimensional plane, future investigation of three-dimensional ultrasonography is needed to possibly provide accurate volume measurements for tophus. Second, there are limits to observing the intraarticular damage due to the bone cortex resistance of penetration of the US beam. US can identify only erosions and cartilage damage compared with other modalities[7]. It is practical to assess treatment response with its advantages of cost, availability, and safety[46]. Furthermore, at the end of 12 months, most patients did not reach sUA levels (<360 μmol/l). The influential factor may be the relatively low dose of medication (a starting dose of 40 mg/d, then increased to 80 mg/d)[47] received by our subjects, which could postpone the achievement of the sUA target. In fact, we chose to perform a US assessment in a real-life condition with no intervention conducted, to better determine the role of US follow-up in clinical practice. Finally, we did not consider diet and lifestyle factors, and the influence on US changes remains unclear. Future long-term studies with larger cohorts are needed to provide more comprehensive explanations.

Conclusions

Our study indicates that the effective clearance rate of aggerates is highest, followed by DC sign, and then tophus. To control the disease effectively, different intensities of ULT should be chosen according to the different MSU burdens detected by US, which can objectively reflect urate crystal

dissolution and provide reliable imaging evidence under efficient ULT. In addition, our results provide a rational basis for the sensitivity of PDUS in detecting the subclinical activity of gout. Although inflammation was gradually reduced after 6 months of treatment, complete control needed for the complete dissolution of MSU deposits. Finally, bone erosions observed on US were stable during the 1-year follow-up period; therefore, early diagnosis and treatment would suggest that US may provide a strong imaging basis for the treatment timing. In summary, US plays an important role in assessing three outcome domain changes in response to effective ULT in patients with established gout.

Abbreviations

MTP1: First metatarsophalangeal joint; DCS: Double contour sign; ULT: Urate-lowering therapy; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; GFR: Glomerular filtration rate; BMI: Body mass index; TJC: Tender joint count; SJC: Swollen joint count; OMERACT: Outcome Measures in Rheumatology; T2T: treat to target; GLOESS: Global OMERACT–EULAR Synovitis Score; PDC: Proportion of days covered; BSR: British Society for Rheumatology; MSU: Monosodium urate: NSAID: Nonsteroidal anti-inflammatory drug

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (No.2018-013-01) and all the enrolled patients signed the informed consent form (Trial registration number: ChiCTR1800015043).

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.

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Authors' contributions

WZ wrote the initial manuscript; ZJ and HZ was responsible for the study design; WZ and DZ made a contribution to the arrangement of follow-up visit; MW and DZ were responsible for data acquisition and analyses. All the authors have been contributed in revising the manuscript and approved

the final manuscript.

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Figures

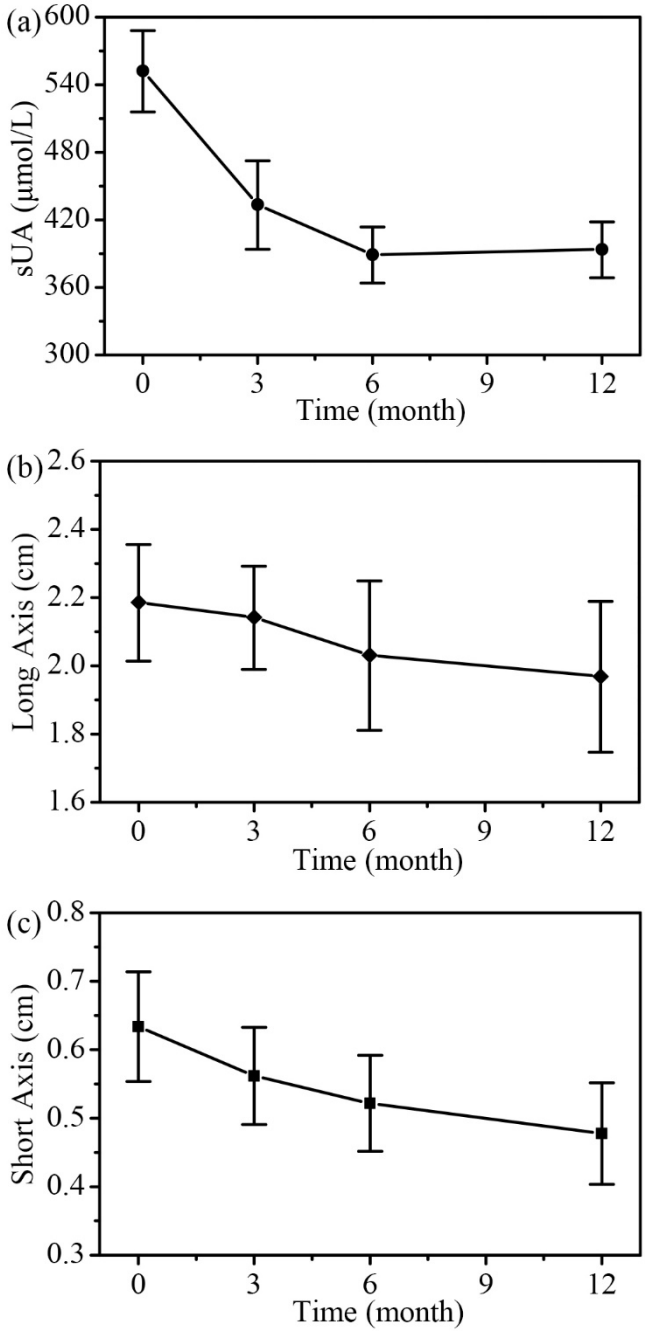

Fig 1. The decline trend of serum urate level (a), long axis (b) and short axis (c) diameter of tophi after receiving 3, 6 and 12 months of urate-lowering treatment.

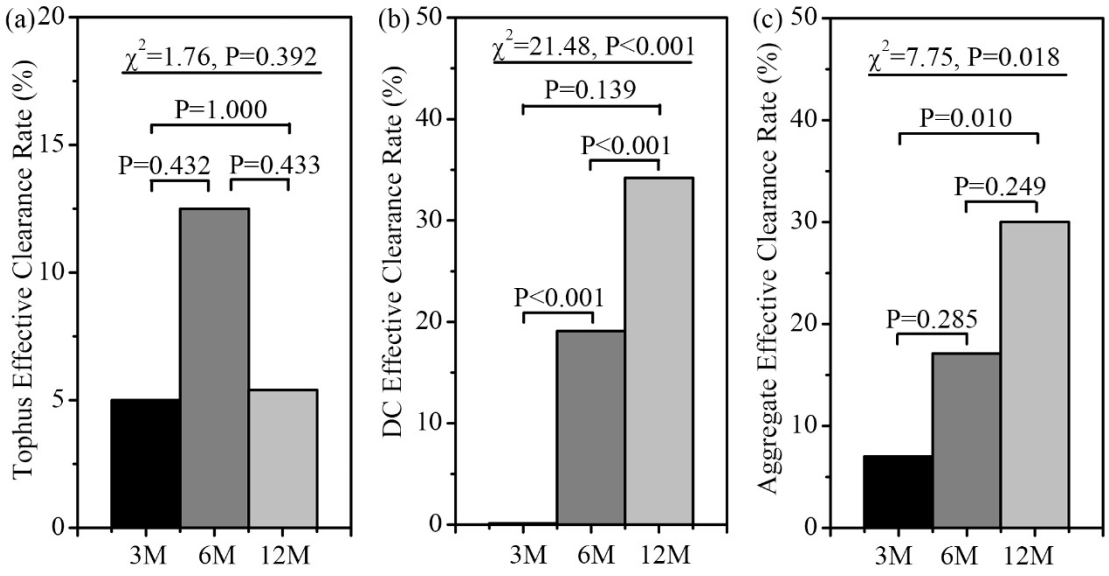

Fig. 2 Comparison of effective clearance rates of tophi, DC and aggregates between different time period

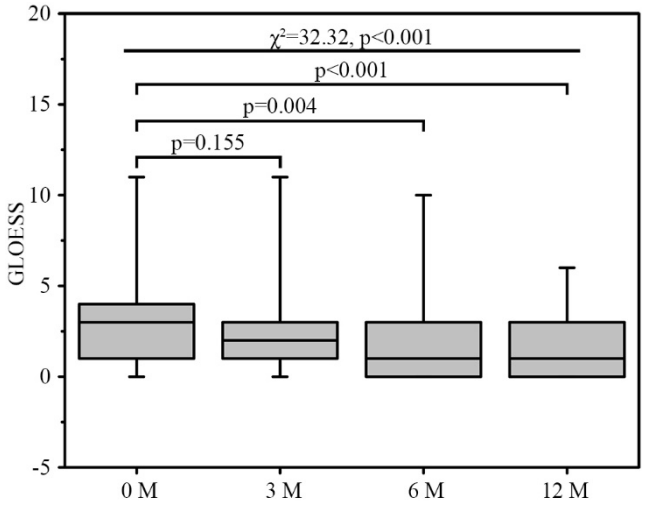

Fig. 3 Comparison among groups of GLOESS between different time period

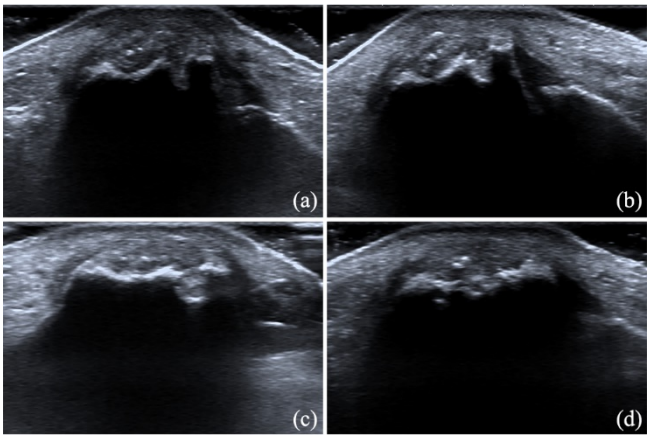

Fig. 4 lateral longitudinal view of the first metatarsophalangeal joint. There was no significant change in bone erosion at baseline period (a), 3 (b), 6 (c) and12 months (d) that the scores were all

graded 3.

Tables

Table1 Baseline demographics and clinical characteristics

	Baseline	Month 3	Month 6	Month 12
Family history	36（45.6）	/	/	/
High purine diet	45（57）	/	/	/
Drinking history	47（59.5）	/	/	/
Hyperlipidemia	22（27.8）	/	/	/
Hypertension	29（36.7）	/	/	/
Diabetes	7（8.9）	/	/	/
Coronary heart disease	3（3.8）	/	/	/
BMI ($\bar{x}$±s, kg/m^2)	26.5±2.9	/	/	/
SJC(M/QR)	1（0，2）	0（0，1）	0（0，0）▲	0（0，0）&
TJC(M/QR)	1（1，2）	0（0，1）&	0（0，1）&	0（0，0）*
Frequency of attacks (number/year，M/QR)	5（2，15）	4（0，12）	4（0，11）	0（0，4）*#
Duration time (day, M/QR)	7（3，7）	2（0，5）&	2（0，3）&	0（0，2）*
sUA level ($\bar{x}$±s, μmol/L)	552.1±103.4	433.3±112.5*	388.9±71.1*	393.5±71.2*
BUN ($\bar{x}$±s, mmol/L)	5.4±1.9	5.2±1.3	5.6±1.4	5.6±1.8
Scr ($\bar{x}$±s, μmol/L)	90.7±23.2	85.3±27.9	84.3±22.1	90.2±28.0

Data are number (%) unless indicated. BMI, body mass index；SJC, swollen joint count；TJC, tender joint count；M：median；QR：interquartile range; sUA, serum uric acid; BUN, blood urea nitrogen; Scr, serum creatinine*,compared with baseline data, P≤0.001；&,compared with baseline data, P≤0.01;#, compared with month 3, P<0.01；▲,compared with baseline data, P<0.05

Table2 modification of tophi, DC and aggregates during the follow-up process

	Baseline N=79	Month 3 N=67	Month 6 N=64	Month 12 N=57
Tophi, n (%)	48(60.8)	40(59.7)	38(59.4)	35(61.4)
Long axis diameter of tophi ($\bar{x}$±s, cm)	2.2±0.43	2.1±0.38	2.0±0.55	1.9±0.56
Short axis diameter of tophi ($\bar{x}$±s, cm)	0.63±0.20	0.56±0.18	0.52±0.18	0.48±0.19
DC, n (%)	53(67.1)	48(71.6)	38(59.4)	19(33.3)
Aggregates, n (%)	44(55.7)	39(58.2)	29(45.3)	17(29.8)

Figures

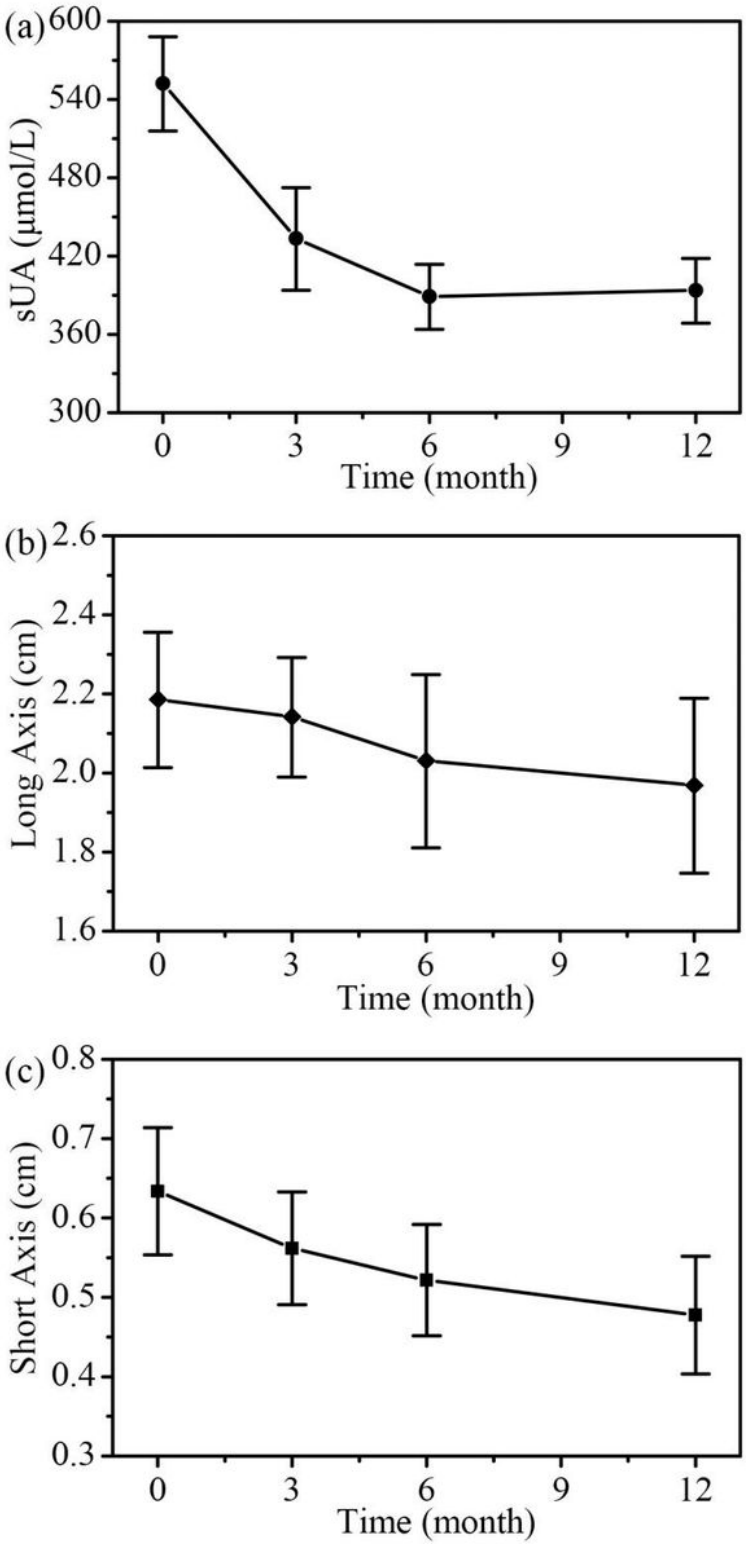

Figure 1

The decline trend of serum urate level (a), long axis (b) and short axis (c) diameter of tophi after receiving 3, 6 and 12 months of urate-lowering treatment.

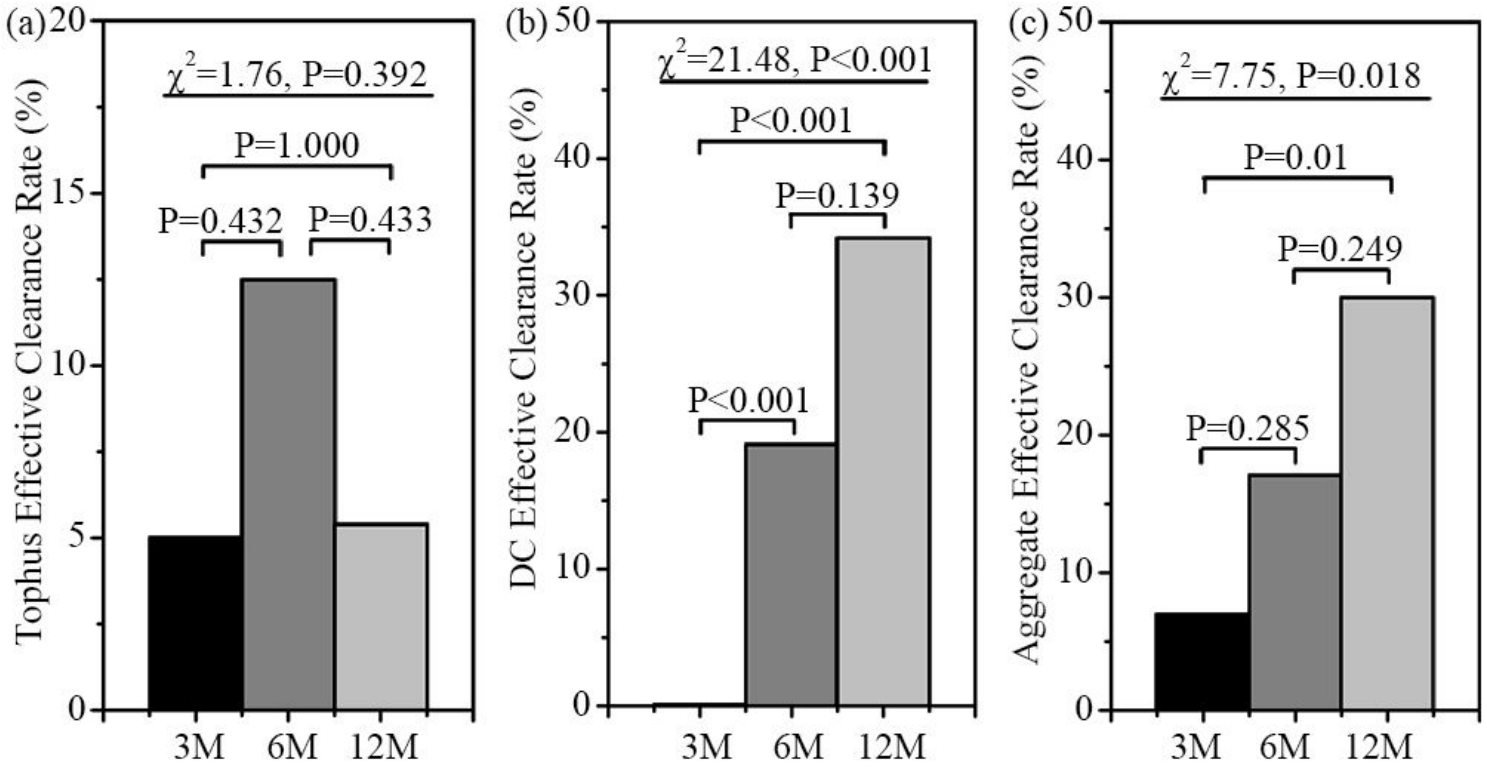

Figure 2

Comparison of effective clearance rates of tophi, DC and aggregates between different time period

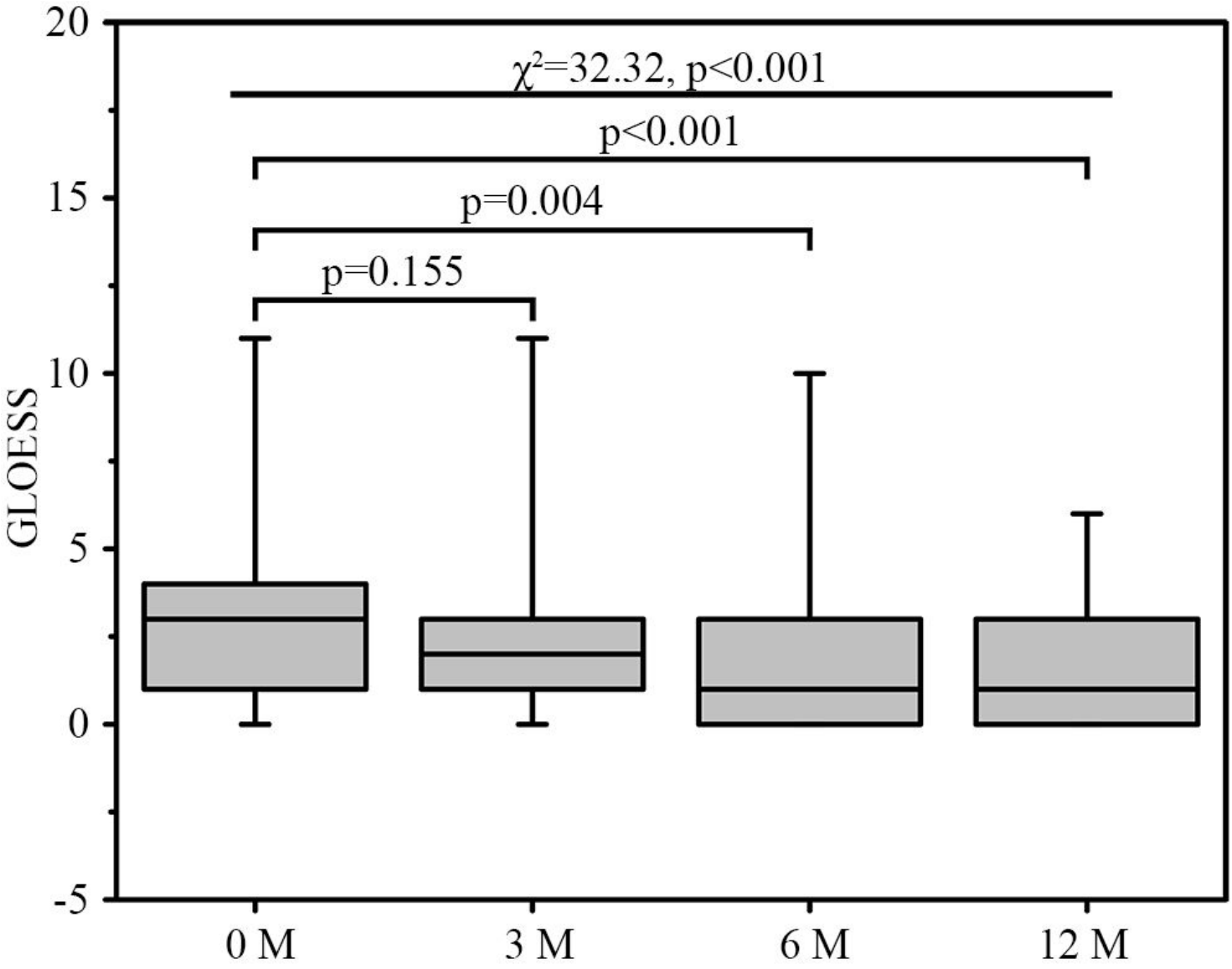

Figure 3

Comparison among groups of GLOESS between different time period

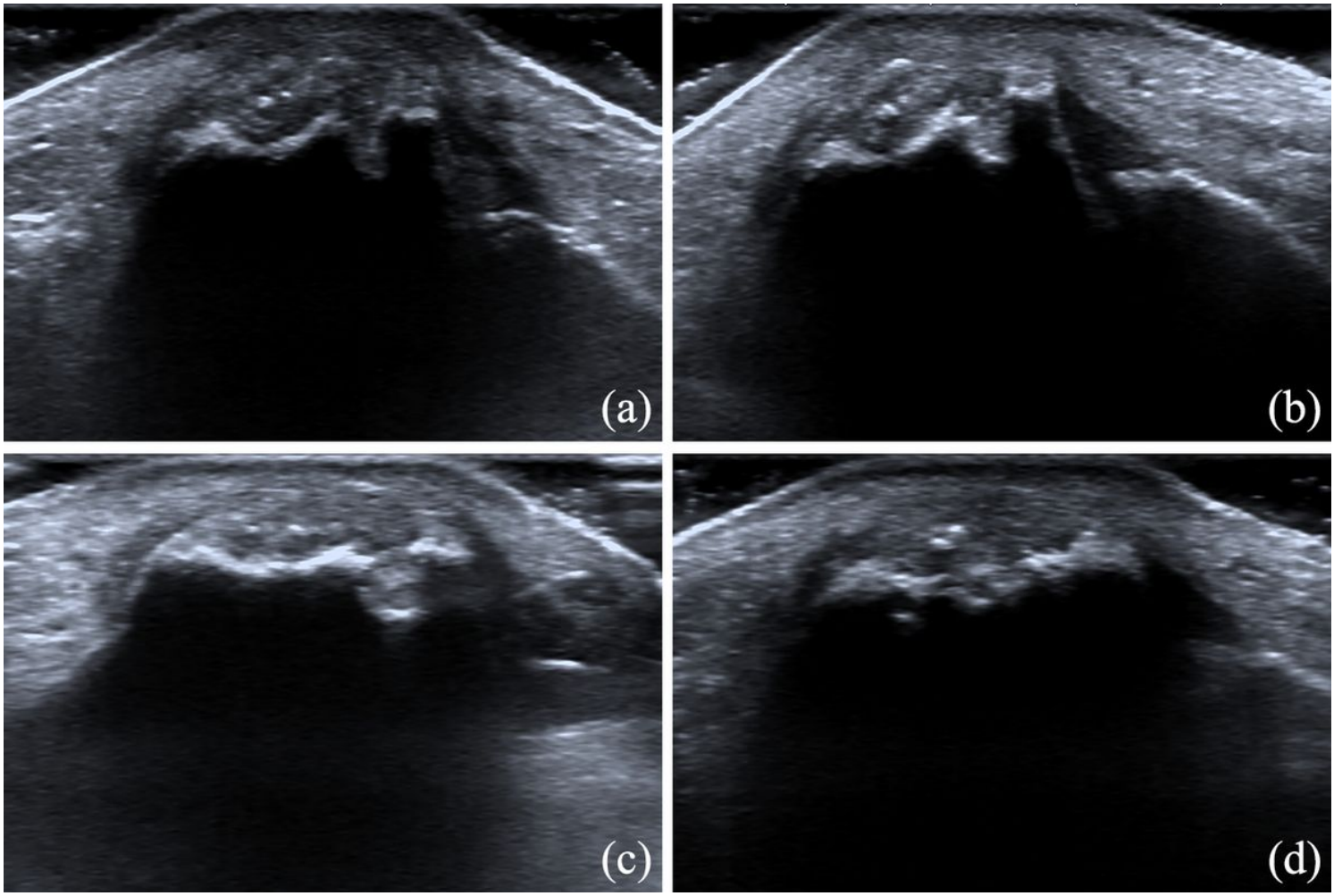

Figure 4

lateral longitudinal view of the first metatarsophalangeal joint. There was no significant change in bone erosion at baseline period (a), 3 (b), 6 (c) and12 months (d) that the scores were all graded 3.