Ultrasonographic Measurement of Tophi as an Outcome Measure for Chronic Gout

FERNANDO PEREZ-RUIZ, IÑAKI MARTIN, and BEGOÑA CANTELI

ABSTRACT. ***Objective.*** To validate the usefulness of measuring tophi with ultrasonography (US) as an outcome measure for chronic tophaceous gout.

Methods. Patients with crystal-proven gout were included. To evaluate validity, intraarticular and articular deep tophi were evaluated with both magnetic resonance imaging (MRI) and US. Tophi were punctured with US guidance to evaluate face validity. Interobserver and intraobserver measurement studies were done to evaluate reliability, and to estimate the smallest detectable difference. Sensitivity to change was evaluated with a 12-month followup observational study of urate-lowering therapy.

Results. US detected at least one tophus in all joints where MRI found nodules considered to be tophi. There was a good correlation, but just fair agreement between measurements with US and MRI. Puncture of nodules suspected of being tophi recovered urate crystals in 83% of the procedures. Intraobserver intraclass correlation was > 0.90 for diameters and volume, while it was 0.71 to 0.83 in the interobserver study. US was found to be sensitive to change, and there was an inverse correlation between serum urate concentrations and change from baseline measurement of tophi.

Conclusion. US measurement of tophi fulfilled the OMERACT filter for an outcome measure, although it should be tested further in randomized clinical trials. (First Release July 15 2007; J Rheumatol 2007;34:1888–93)

Key Indexing Terms:
GOUT ULTRASONOGRAPHY OUTCOME MEASURE GOUT SUPPRESSANTS

Gout is a deposition disease, and chronic depositions of monosodium urate (MSU) crystals aggregate to form macroscopic nodules called tophi[1]. Tophi appear most frequently in the subcutaneous tissue, but also in intraarticular and articular structures[2].

The aim of urate-lowering therapy (ULT) is to promote the dissolution of MSU crystals when a subsaturating concentration for serum urate (sUr) is achieved. Proper subsaturating sUr levels have been shown to be associated with reduction, and ultimate disappearance, of tophi[3-5]. Further, an inverse correlation between sUr during ULT and the speed of reduction of subcutaneous tophi has been reported[6].

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) 7 conference included evaluation of tophi within the proposals for the core set of outcome measures for chronic gout[7]. We evaluated whether measurement of articular tophi using ultrasonography (US) fulfilled the OMERACT filter requirements[8] to become an outcome measure for the efficacy of ULT in patients with chronic tophaceous gout.

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MATERIALS AND METHODS

Our study was evaluated and accepted by the Ethics and Clinical Investigation Committee at Hospital de Cruces. All patients were recruited from patients consecutively attending a gout clinic who agreed to be included in the study. All had a diagnosis of gout (by FPR) based on the observation of MSU crystals using polarized light, with first-order compensating red filter, as encouraged recently for studies in chronic gout[7].

Either a knee or an ankle joint was selected in each patient as the target joint. The target joint was selected by a clinician (FPR) based on the presence of restricted joint range of motion, in the absence of acute inflammation or extensive radiographic involvement suggesting severe chronic gouty arthropathy.

US was compared with magnetic resonance imaging (MRI) in each target joint, to evaluate accuracy for the detection of tophaceous nodules. MRI was used as the gold standard technique due to its availability in our clinical setting, and absence of radiographic exposure. Patients underwent US (IM) and MRI (BC) examination consecutively, on the same day, and operators were blind to the other imaging modality findings. Patients with an acute gouty episode at examination were excluded during the acute phase due to the interference of pain, swelling, and synovial effusion for examination, especially for intolerance to examination, and the possibility that this could affect the results. The knee joint was studied in the maximal extension possible, in order to have the same positioning for both US and MRI examinations, and the ankle joint in neutral position. The number, location, and diameters of nodules suspected to be tophi were recorded, and put in a database unavailable for US and MRI observers. MRI was considered to be the gold standard examination.

When comparing US with MRI, for US evaluation we used an Esaote Technos MPX (Esaote SpA, Florence, Italy), using a linear multifrequency probe (5.5 to 12.5 MHz). US scanning was carried out in longitudinal and transverse axes of the joint in B-mode gray-scale using 7.5 MHz frequency. Measurements were made longitudinally to the maximal diameter of nodules considered to be tophi, and transversal to the maximal diameter plane of the nodule. Volume was calculated with the integrated software in the US machine using the maximal longitudinal diameter of the nodule and 2 per-

pendicular transversal (coronal and sagittal) diameters. Volume was not evaluated in the presence of calcifications that generate an acoustic shadow that makes it difficult to obtain the 3 diameters needed to estimate volume.

MRI was performed with a 1.5 T unit (Philips Gyroscan Intera), with the following imaging protocol: T1-weighted sagittal spin-echo images (repetition time ms/echo time = 495/18, 2 signals acquired, 3 mm section thickness); T2-weighted axial fast spin-echo images (repetition time ms/echo time ms = 3158/100, 2 signals acquired, 4 mm section thickness); short-tau inversion recovery (STIR) sagittal images (repetition time ms/echo time ms = 2500/70, inversion recovery 170, 2 signals acquired, 4 mm section thickness); and T2-weighted coronal gradient-echo images (repetition time ms/echo time ms = 400/14, FLIP angle 30, 2 signals acquired, 4 mm section thickness). Intravenous gadolinium enhancement was not used. The best imaging result with any sequence was used for evaluation.

To evaluate face validity, a 21G needle set in a 1 cc syringe was guided with US into the nodule suspected to be a tophus, using standard sterile setting, to obtain a sample for the observation of MSU crystals with polarized and contrast-phase microscopy. For our study, patients were selected from consecutive patients with a clinical diagnosis of gout, but not yet confirmed by crystal observation due to ethical considerations. After puncture, a droplet of isotonic saline 0.9% was aspirated in the syringe, and then examined for crystals with polarized, red-compensated light microscopy (FPR). Only one puncture per patient and target tophi was allowed.

Reliability was evaluated by intraobserver and interobserver agreement; statistical analysis included multiple regression, intraclass correlation, and agreement analysis. Two authors evaluated the same target joint twice in a week. Measurements were included into analysis of regression, intraclass correlation, and agreement analysis. The smallest detectable difference (SDD) of the change for paired observations was calculated[9,10]. For the interobserver study, a second examiner used a Sonosite Plus machine with a multifrequency probe (5.5 to 10 MHz) with B-mode gray-scale. This machine is commonly used in the clinical setting, and it proved to be useful to evaluate subcutaneous nodules in patients with rheumatic diseases including tophaceous gout[11].

Sensitivity to change was evaluated comparing the measurement of tophaceous nodules during a 12-month period of ULT. Patients were prescribed ULT according to the National Agency for Medicines guide. All the patients took the prescribed urate-lowering drug at noon, and blood samples for analysis were obtained 20 hours (8 A.M.) after the intake. sUr was measured every 3 months, and the average sUr during the whole 12-month period calculated. In case a patient could not attend the 3-month schedule visits due to unexpected situations, the average was calculated using a trapezoidal method. The US examiner was blinded for baseline results and clinical followup. To further blind the examiner to identification of patients during the US imaging acquisition, patients who agreed to be included in the followup study were randomized to be assorted with patients with tophaceous gout for baseline examination, but who were not included in our study.

Change in tophi size was defined as any change from baseline to 12-month ULT that exceeded the calculated SDD for change. For analysis, tophi with baseline measurement under the SDD were not included for categorical comparisons, as in no case could there be a change over SDD in such tophi. Proper control of sUr was considered to be 6 mg/dl or less as an average during the 12-month followup period[7]. For comparison, patients with changes in tophi size over or under SDD were tabulated with patients who had average sUr over or under 6 mg/dl.

Correlation, regression, comparisons of paired means, chi-square or Fisher test when applicable, and intraclass correlations were calculated with an SPSS 13.0 statistical package (SPSS, Chicago, IL, USA). Sensitivity to change was evaluated using Guyatt's size effect[12]. It was calculated as the mean paired difference of the measurements in patients with proper control of sUr while receiving ULT, divided by the standard deviation of the paired difference of measurements in patients with improper control of sUr while on ULT.

RESULTS

Twenty-five patients were evaluated with US and MRI. Five patients had no subcutaneous tophus on examination, and 3 of these 5 showed no tophus on physical and imaging examinations. Other findings such as chronic tenosynovitis or joint synovitis were responsible for the restriction of joint range of motion in these patients. In the 22 patients available for analysis, 50 nodules suspected to be tophi were detected: 46 with US, 41 with MRI, and 37 with both imaging techniques. Nodules were mostly related to either ligament or tendon structures, and were mostly intraarticular (under collateral ligaments) in the knee joints. Thus, US detected 37/41 (90%) of the nodules reported to be tophi in MRI. Three of the nodules detected by MRI were located under or near the patella, and were missed by US scanning. MRI confirmed 37/46 (81%) of the nodules reported by US (Table 1). The 9 nodules observed by US and not by MRI showed a mean maximal diameter of 9.6 ± 3.6 mm, compared to 23.2 ± 10.1 mm for those detected by both MRI and US ($p < 0.001$). Five tophi (10%) were not measured for volume due to hard calcifications.

The correlation between US and MRI for maximal diameter was good ($r^2 = 0.65$; Figure 1), and the paired difference was 1.55 ± 7.20 mm (median 2 mm). Although the mean difference from measurement was small, agreement was high, estimated as the 95% CI limits for the variability according to the Bland and Altman[10] method (Figure 2): from –12.84 to 15.95 mm.

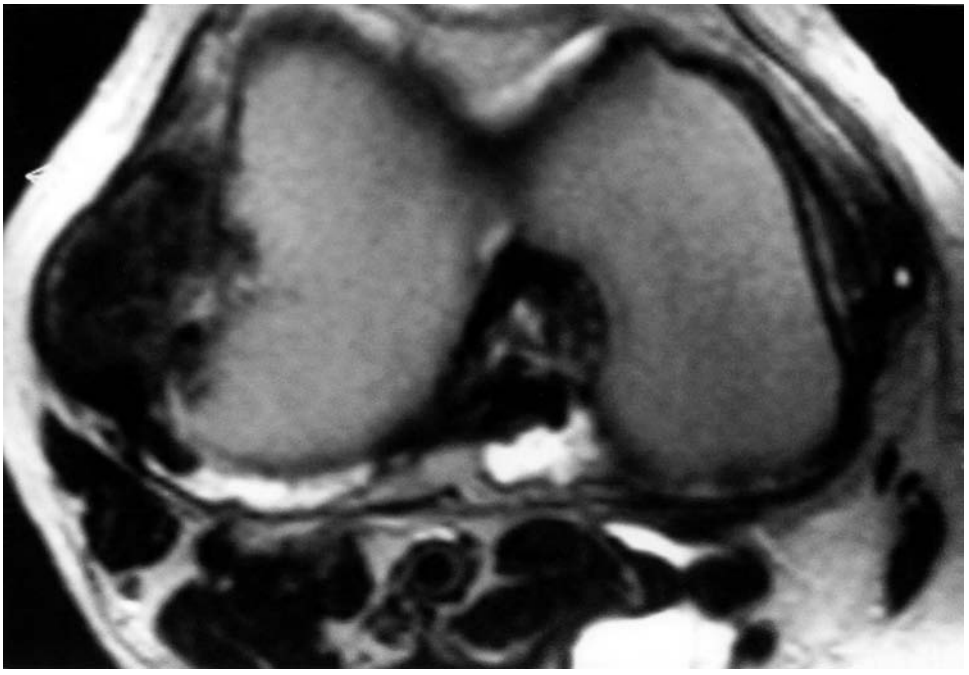
US-guided puncture was used to evaluate the presence of MSU crystals. Twelve out of 20 patients agreed to undergo US-guided puncture for diagnosis. Twelve nodules (8 in collateral knee ligaments, 2 in anterior tibial tendon, and 2 in posterior tibial tendon) suspected to be tophi were found in patients with hyperuricemia and chronic arthritis who had not yet been diagnosed by crystal observation in synovial fluid samples. MSU crystals were observed in 10/12 nodules: all the nodules over 10 mm in maximal diameter and all the nodules under collateral ligaments of the knee were positive for MSU crystals. The 2 patients in whom MSU crystals could not be recovered after nodule puncture afterwards had the diagnosis of gout confirmed by observation of MSU crystals in synovial fluid samples.

Intraobserver reliability was evaluated assessing 27 tophi in 14 patients. The measurements for maximal and minimal diameters and volume are displayed in Table 2. The SDD was calculated to be 5.5 mm for maximal (23% of average), 3.5 mm (35% of average) for minimal diameter, and 1.27 cc (34% of average) for volume. Intraclass correlation for absolute agreement was 0.96 (95% CI 0.93–0.98) for maximal diameter, 0.95 (95% CI 0.88–0.97) for minimal diameter, and 0.98 (95% CI 0.96–0.99) for volume.

Interobserver reliability was evaluated assessing 22/24 tophi in 8 patients concordant for both examiners. The results are shown in Table 3. The SDD was 6.51 mm for maximal diameter (27% of average) and 4.67 mm for minimal diameter (51% of average). Intraclass correlation for absolute agreement was 0.83 for maximal diameter (95% CI 0.41–0.95) and 0.71 (95% CI 0.26-0.91) for minimal diameter.

Table 1. Results from US vs MRI study (all data in mm).

Measurement	US Maximum	US Minimum	MRI Maximum	MRI Minimum
Number				
Valid	46	46	41	41
Missing	4	4	9	9
Mean	21.16	10.82	24.34	13.19
SD	10.19	5.80	12.01	6.44
Minimum	6.00	3.00	5.00	4.00
Maximum	43.00	26.00	50.00	35.00



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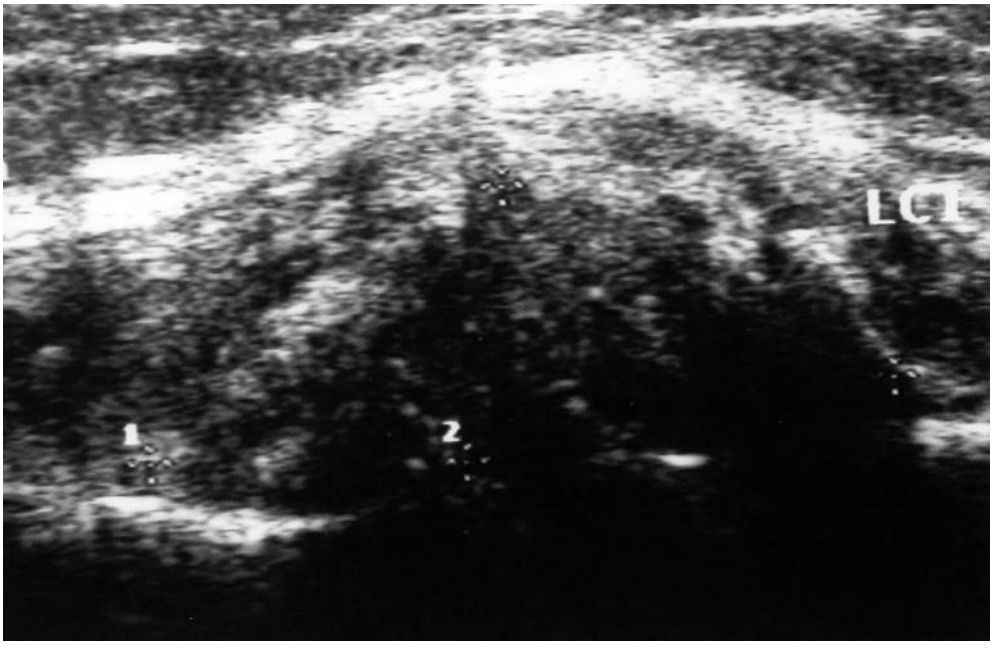

B

Figure 1. Tophi observed in the knee joint with MRI (A) and US (B), lying deep to the inner collateral ligament.

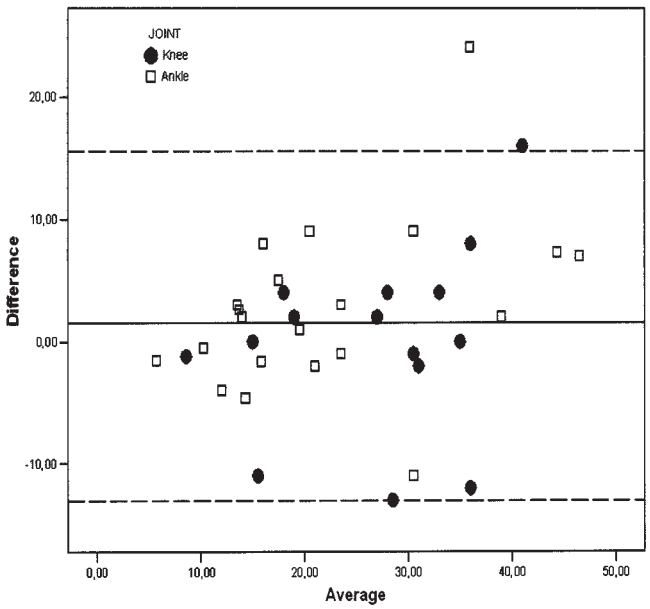

Figure 2. Bland and Altman plot for variability beween US and MRI.

Fourteen patients accepted a second US examination after 12-months' ULT. Allopurinol 150 to 450 mg/day was initially prescribed to all patients and 3 of them changed to benzbromarone 100 mg/day at 6-month followup due to poor control of hyperuricemia (following the Spanish National Drug Agency guidelines for the management of tophaceous gout). sUr at baseline was 9.47 ± 1.47 mg/dl (median 9.10, range 7.80–12.30), and final average sUr was 5.52 ± 0.99 mg/dl (median 5.65, range 3.75–7.20). These patients showed 38 tophi at baseline and 29 tophi at 12-month followup. Data for maximal diameter and volume at baseline and final US examination are displayed in Table 4.

The correlation between baseline and final measurements was good: r = 0.846 and 0.852 for maximal and transversal diameters, respectively, and 0.874 for volumes. Taking a reduction over the SDD for maximal diameter (5.5 mm) as a real change, 20/38 tophi showed a reduction from baseline to 12-month followup. Patients with a reduction in maximal diameter > SDD had a mean average sUr of 5.04 ± 0.79 mg/dl, compared to 6.03 ± 0.62 mg/dl in patients whose tophi showed no reduction ($p < 0.01$). In patients with average sUr < 6 mg/dl, 19/28 (68%) tophi showed reduction, while only 1/10 (10%) tophi in patients with sUr > 6 mg/dl showed changes. Considering volume change, 17 tophi were over SDD (1.27 cc). The mean average sUr was 5.23 ± 1.07 mg/dl for patients with reduction of tophi versus 6.26 ± 0.66 mg/dl for those with no reduction ($p = 0.039$). Patients with an average sUr < 6 mg/dl showed reduction in 9/12 (75%) tophi, while only 1/5 (20%) patients with sUr > 6 mg/dl showed reduction in tophi ($p = 0.10$). In addition, 19/20 (95%) tophi with reduction of maximal diameter and 9/10 tophi with reduction in volume had average sUr < 6 mg/dl. There was also a correlation between the reduction in maximal diameter and the volume of tophi ($r^2 = 0.47$ and $r^2 = 0.41$, respectively, both $p < 0.001$) and the average sUr on ULT (Figures 3 and 4). The Guyatt's size effect was 1.7 for maximal diameter change and 1.93 for volume change.

A separate analysis was made using just one target tophus for each patient and joint, with no significant change in results, except for a reduction in statistical significance due to the parallel reduction of the number of tophi analyzed (data not shown).

DISCUSSION

Imaging techniques have been shown to be useful for evaluating subcutaneous nodules. MRI, computed tomography (CT), and US have been used to evaluate the presence of tophaceous deposits in patients with gout[2,11,13-16] that are frequently not detectable on examination[15,17].

The OMERACT filter[8] for an outcome measure includes truth, discrimination, and feasibility. Measurement of tophi during ULT was included in the core set of outcome measures for chronic gout that deserve evaluation to be included for testing in clinical trials[7]. Measurement of subcutaneous tophi may be accomplished by physical methods, but a high variability for intraobserver reliability has been observed[18]. To avoid the variability in repeated measurement, a 100% change may be used in clinical practice[6], but this approach is not feasible for outcome measures in clinical trials, as a long period of observation should be required[6]. Measurement of tophi during ULT may also be made with imaging techniques, but US seems to be the most feasible, as it is a nonradiating technique, is less expensive than MRI or CT, and is also available in the clinical setting[11].

To evaluate validity, MRI was used as the gold standard technique to detect tophi due to feasibility and lack of radiation exposure, although limited experience with it is available from the literature[13-17], but also due to the lack of any defini-

Table 2. Intraobserver reliability was evaluated assessing 27 tophi in 14 patients (all data in mm).

	Maximal Diameter 1	Minimal Diameter 1	Maximal Diameter 2	Minimal Diameter 2	Volume 1	Volume 2	Difference, Maximal Diameter	Difference, Minimal Diameter	Difference, Volume
Mean	23.6	10.6	24.2	10.6	3.52	3.23	–0.54	–0.02	–0.15
SD	10.9	5.0	11.0	5.6	3.93	3.65	2.81	1.80	0.65
Minimum	6.4	3.1	7.3	3.8	0.10	0.10	–8.00	–4.00	–2.10
Maximum	43.0	26.0	41.0	29.0	11.50	9.60	3.00	5.00	0.80

Table 3. Paired samples statistics for interobserver study (all data in mm).

	Mean	SD	Paired Mean Difference	SD for Difference
Maximal diameter				
Observer 1	24.50	9.74	1.06	4.71
Observer 2	23.44	8.48		
Minimal diameter				
Observer 1	9.36	3.14	0.24	2.86
Observer 2	9.11	2.90		

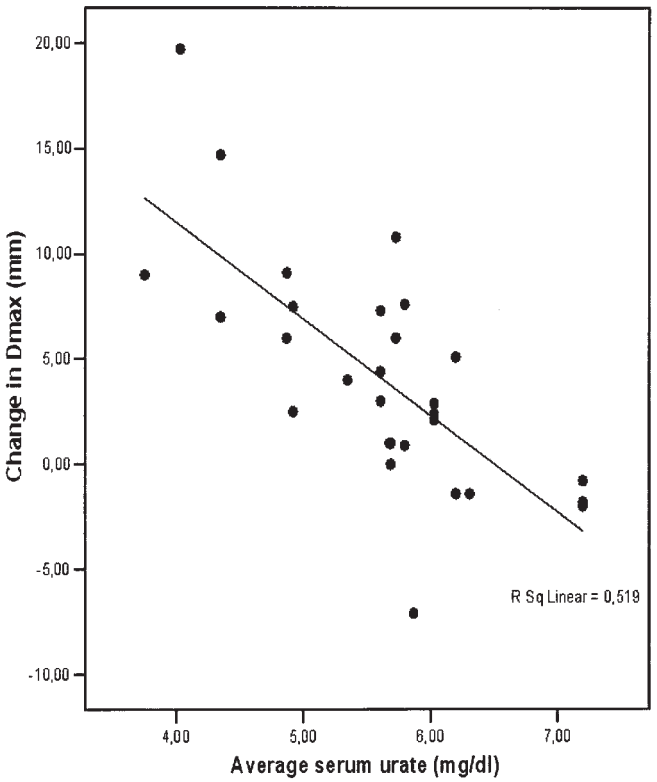

Figure 3. Change in maximal diameter measured with US during a 12-month followup on urate-lowering therapy.

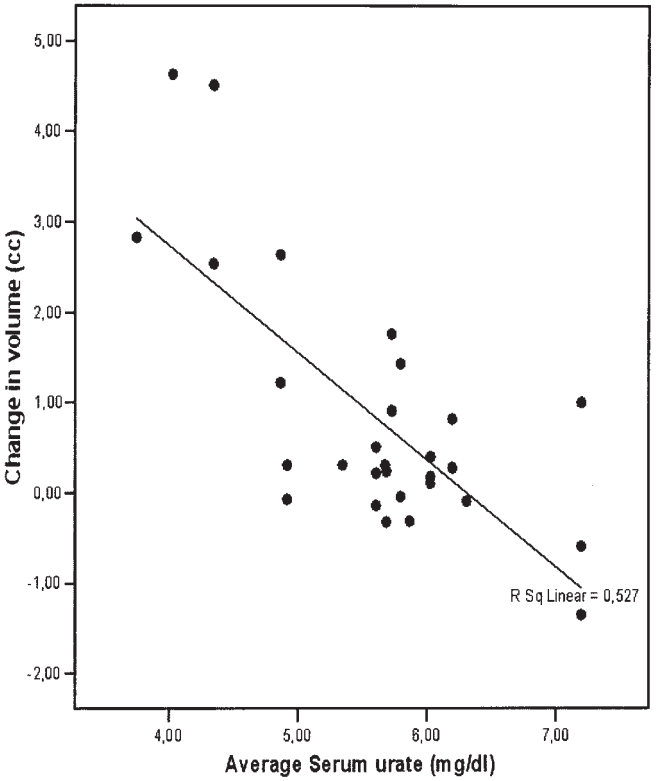

Figure 4. Change in volume measured with US during a 12-month followup on urate-lowering therapy.

Table 4. Maximal diameter and volume at baseline and final US examinations in the ULT study.

	Baseline Maximal Diameter, mm	Final Maximal Diameter, mm	Baseline Volume, cc	Final Volume, cc
Number valid	38	38	38	38
Mean	21.51	15.36	2.20	1.46
SD	10.66	12.25	2.56	2.16
Minimum	6.00	0.00	0.03	0.00
Maximum	42.00	41.00	10.40	9.40

tively proved gold standard in the literature. Most of the nodules observed by US were also observed by MRI, showing acceptable sensitivity and specificity, but there was not good agreement for measurements of diameters with the 2 techniques. Positioning of the limb, size and location of nodules, the presence of intranodule calcifications, or the MRI sequences used for evaluation[13,16] may explain this variability. Recently, spin-echo sequences have been considered to be the most appropriate to evaluate tophi with MRI, gadolinium enhancement adding nothing to evaluation[14]. In any case, US detected at least one tophus in all the joints in which MRI disclosed the presence of tophi. By contrast, our study shows that although there is good correlation between US and MRI measurement, the range of variability is high.

Face validity was confirmed when puncture of tophi revealed MSU crystals in 10/12 (83.3%) cases. Patients with not-yet crystal-proven gout were selected for our study, as previous knowledge of a crystal-proven diagnosis could bias the result, and also because of ethical concerns that the procedure would be similar to puncture of joints or subcutaneous tophi.

Discrimination was evaluated through inter- and intrareader accuracy. There was good reliability in both studies, but the intrareader results were, as one might expect, somewhat better, especially in order to calculate the SDD. By contrast, our results are somewhat better than those reported recently for MRI[14], where the interreader comparison showed statistically different measurements.

Sensitivity to change was shown to occur during the 12-

month ULT observation period. As reported[6], a correlation between average sUr while on ULT and reduction of tophi was shown — but with US for the first time — allowing us to estimate as a real change that change from baseline that was greater than the SDD. Methods of direct physical measurement using a tape measure have shown a high variability, and the SDD was not reported[18]. Most of the tophi that showed change in maximal diameter or volume were in patients with proper control of sUr[7], although they were infrequently observed in patients with higher sUr levels, as reported by others[19]. This may be due to pharmacokinetic differences between patients, as the half-life of urate-lowering drugs may vary from one patient to another, and the evaluation of serum urate levels is mostly done early in the morning, 24 h after the intake of the urate-lowering drugs. To avoid these kinds of biases in our study, drug intake was at noon, so that analyses were all obtained early in the morning, but within the half-life of any drug used as ULT.

Some limitations lay within the design of our study. Patients were not randomized for ULT, as we intended, not to initiate a clinical trial, but to evaluate the usefulness of US for measuring tophi during ULT in an observational study, and the US observer was blinded to clinical and biochemistry results during our whole study. We did not analyze volumes with MRI, as we found the variability in the measurement of diameters to be high compared to US, and these results discouraged us from going into further evaluation. The use of a thin 21G needle to avoid unnecessary trauma may constitute a limitation for crystal observations during US-guided puncture of tophi, and they could have been even better if a thicker needle was used, if tophi > 10 mm in diameter were selected, or if patients with a previous positive crystal-proven diagnosis were selected. In addition, if the same US equipment was used for interobserver reliability, and this may have biased for worse the results. Finally, near half of the tophi lay at baseline under the SDD thus limiting statistical power of analysis.

US seems to be a feasible, valid, and discriminative measurement technique to evaluate changes of tophi during ULT. In our opinion, US deserves further testing in randomized clinical trials with urate-lowering drugs. Some suggestions for the applicability of US in designing clinical trials may come from our results: one target tophus may be selected at screening, instead of measuring any tophus observed. This would make consecutive examinations more simple and feasible. Also, the target tophus can be measured both at screening and at baseline to evaluate intrareader correlation, and further calculation of the SDD. Also, US hardware can record and store images, allowing paired randomized post-trial evaluation. In this way, the smallest detectable change could also be estimated. It has recently been suggested that this method could even reduce the variability of measurements, thus improving detection of changes[20], an issue of outstanding importance in randomized clinical trials.

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