Ultrasound sensitivity to changes in gout: a longitudinal study after two years of treatment

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Abstract

Objective

The goals of our study are to evaluate the urate-lowering therapy (ULT) effect on gout ultrasound (US) lesions and to explore US sensitivity to change in gout patients.

Methods

Patients with chronic and symptomatic gout, confirmed by crystal identification, were prospectively included. Clinical and US assessments were performed at baseline and after 6, 12 and 24 months of ULT. The presence of double contour sign (DCS) and US- detectable tophi were assessed in the first metatarsophalangeals, the knees and patellar tendons. The mean and standard deviation were calculated for each parameter. The correlation between the clinical and US parameters was assessed by calculating Pearson's correlation coefficient. Sensitivity to change in the US examinations was assessed by estimating the smallest detectable difference (SDD).

Results

Twenty-three consecutive patients were included (96% men; mean age 59 ± 11 years). DCS and US tophi were detected in 73.9% and 91.3% of patients at baseline. A significant parallel improvement in the serum urate, clinical parameters and US lesions was found at the follow-up assessment. The SDD values for the global DCS and tophi were 0.52 and 0.69, respectively, which were smaller than the differences achieved over the course of the two years. A significant correlation between DCS and clinical parameters was observed (r =0.49, p=0.038).

Conclusion

Ultrasound findings in gout patients show sensitivity to change and concurrent validity with uric acid reduction after ULT in gout patients. US can be a useful tool for gout tophus burden monitoring.

Key words

ultrasonography, tophus burden, gout, drug monitoring, double contour sign

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Background

Gout is one of the most common forms of inflammatory arthritis in adult men, with a prevalence of up to 7% in men aged over 65 (1, 3). This pathology is caused by the deposition of monosodium urate crystals in tissues, and the aim of urate-lowering therapy is to avoid crystal formation and dissolve them by reaching a subsaturating serum urate concentration (2). An inverse correlation between serum urate and the speed of reduction of subcutaneous tophi has been demonstrated (4), and one of the proposed OMERACT outcome measures for chronic gout is the evaluation of tophi burden (5).

In recent years, different imaging modalities have begun to be used in gout diagnosis. Ultrasound (US) can detect crystal deposition in the cartilage, synovial joint and tendons with good sensitivity, specificity and reliability for gout diagnosis (6). The two gout US elementary lesions that are most assessed and utilised are the double contour sign (DCS) and the ultrasonographic tophi. A recent meta-analysis showed that the pooled (95% CI) sensitivity and specificity of DCS were 0.83 (0.72 to 0.91) and 0.76 (0.68 to 0.83), respectively, and the pooled (95% CI) sensitivity and specificity for tophus on US were 0.65 (0.34 to 0.87) and 0.80 (0.38 to 0.96), respectively (6). In fact, in the most recent EULAR/ACR diagnostic criteria, DCS has been included as a criterion with the same value as the presence of clinical tophus (7). Nevertheless, there are few studies that evaluate the monitoring usefulness of ultrasound in gout (4, 8, 9). Ultrasound may monitor the disease more directly and accurately than other laboratory or clinical parameters because it can inform us about the presence or size of the urate deposits. We hypothesise that in the future, US will be the tool used to assess the success of outcomes in gout treatment by evaluating the disappearance of these deposits.

The goal of our study is to analyse the sensitivity of US to changes in patients with gout. To achieve this objective, we evaluated the clinical and US parameters of a symptomatic gout patient cohort treated for two years.

Materials and methods

This study evaluated a cohort of consecutive adult gout patients. The patients included had to display recurrent attacks or symptomatic gout with a duration of symptoms longer than four months, independent of treatment. In all patients, a definitive diagnosis was established by the presence of urate monosodium crystals in the aspirates of affected regions. Needle aspiration of synovial fluid on the symptomatic joint was performed, or in the absence of symptoms, aspiration of the first metatarsophalangeal joint (1MTP) synovial fluid was performed. The aspirates were examined with polarising light microscopy, and the patients without the presence of UMS crystals or with calcium pyrophosphate dehydrate crystals were excluded. Patients with other rheumatic diseases were excluded. Prior to inclusion, all the patients provided informed consent for participation, and the study was approved by the Ethics Committee at our institution.

The clinical examinations were performed by a rheumatologist (AVY) during subsequent visits over a period of two years. The demographic and clinical characteristics of each patient, including age, gender, and disease duration as well as current treatment with NSAIDs, hypouricemics or colchicine were recorded at each visit. The patients underwent a complete clinical and laboratory assessment, including scores for joint pain and number of tender and swollen joints. Blood and urine samples were collected to determine the serum urate and erythrocyte sedimentation rate (ESR). Patients were treated according to the standard guidelines.

Ultrasonographic examination

Every 6 months, US examination was performed by a US rheumatologist (DPL) who was blind to all other study findings. The assessment was completed using a Logiq 9 instrument (General Electric Medical Systems, Milwaukee, WI, USA) with a 9- to 14-MHz probe for grey scale and Doppler. All patients underwent US of both knees (medial and lateral recesses), 1MTP joints, and patellar tendons. The sites for monitoring in our cohort were those in which a higher prevalence and reliability of

US gout findings had been demonstrated, according to preliminary study results (10). All studies were performed by scanning across the joints in a medial-lateral sweep and proximal-distal sweep. In the knee, a transversal suprapatellar view in maximal flexion was also performed to examine the condylar cartilage. The typical US signs considered for the evaluation were the double contour sign and the ultrasonographic tophus. The 'double contour sign' was recently defined by the OMERACT group as an "Abnormal hyperechoic band over the superficial margin of the articular hyaline cartilage, independent of the angle of insonation and which may be either irregular or regular, continuous or intermittent and can be distinguished from the cartilage interface sign." (11). Ultrasonographic tophus is defined as "A circumscribed, inhomogeneous, hyperechoic and/or hypoechoic aggregation (which may or may not generate posterior acoustic shadow), which may be surrounded by a small anechoic rim"(11). In the course of the ultrasound examination, the sonographic images for each subject were stored, and the presence of different types of lesions was determined.

Statistical analysis

The mean and standard deviation or the median with interquartile range was used to describe the demographic characteristics of the patients and the ultrasonographic features of the group in consecutive visits. The comparison between quantitative values on successive visits was performed using Student's *t*-test for paired samples and the Wilcoxson test/McNemar test for qualitative values. In statistical terms, the smallest detectable difference (SDD) shows which changes fall outside the measurement error of the health status measurement (based on the internal or test-retest reliability in stable persons). We calculated the SDD for the US parameters (total number of DCS and total number of tophi) according to the following formula: SDD= $1.96 * \sqrt{2} *$ SEM (standard error of measurement). The correlation between the clinical and US parameters was assessed by calculating Pearson's correlation coefficient.

Table I. Clinical and laboratory parameters at the baseline and follow-up assessments, expressed by the mean ± standard deviation or the median and interquartile range (IQR) value.

	Baseline	6 months	12 months	24 months
PGA (0–100 mm)	23.6 ± 19.8	13 ± 14.1*	14.5 ± 14.7	8.8 ± 7.7**
SJC	1 (0, 1)	0 (0, 1)*	0 (0, 0.75)**	0 (0,1)*
TJC	1 (0, 3)	0 (0, 1)*	0 (0, 75)*	0 (0, 0)**
ESR mm/h (IQR)	15 (16)	9.3 (8)	6.9 (6.2)*	8.2 (6.2)
CRP (mg/dl)	11.3 ± 20	2.8 ± 2.8	3 ± 2.2	4.3 ± 7.4
Serum urate (mg/dl)	8.8 ± 1.9	6.5 ± 1.4***	5.9 ± 1***	5.3 ± 1.2***
Percentage of patients with Us<6 mg/dl	4.5%	41%**	65%***	58%***
Percentage of patients with Us<7 mg/dl	13%	90%***	77%***	89%***
Gout flares†	1 ± 0	0.19 ± 0.4***	0.24 ± 0.4***	0.33 ± 0.5**

PGA: Patient global assessment of disease activity; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Us: serum urate; †: Gout flares since previous visits. *p<0.05, **p<0.01, ***p<0.001.

Table II. US parameters at baseline and follow-up assessments, expressed by the mean ± standard deviation.

		Baseline	6 months	12 months	24 months
DCS in 1MTPS	Number	18	11	5	3
	Mean ± SD	0.78 ± 0.85	0.48 ± 0.66*	0.24 ± 0.44**	0.14 ± 0.36**
	% patients	52.2%	39.1%	23.8%	14.3%
DCS in knees	Number	16	11	7	6
	Mean ± SD	0.70 ± 0.82	0.48 ± 0.79	0.33 ± 0.65*	0.29 ± 0.64*
	% patients	47.8%	30.4%	23.8%	19%
DCS global	Number	34	22	12	9
	Mean ± SD	1.5 ± 1.2	0.9 ± 1.2*	0.6 ± 0.8**	0.4 ± 0.8**
	% patients	73.9%	56.5%	38.1%	28.6%
Tophi in 1MTPS	Number	30	24	16	14
	Mean ± SD	1.3 ± 0.8	1 ± 0.9	0.7 ± 0.8**	0.7 ± 0.8***
	% patients	78.3%	65.2%	52.4%	47.6%
Tophi in knees	Number	46	45	36	35
	Mean ± SD	2 ± 1.5	1.9 ± 1.5	1.7 ± 1.5	1.7 ± 1.5*
	% patients	73.9%	69.6%	72.4%	71.4%
Tophi in patellar tendon	Number	19	17	17	16
	Mean ± SD	0.8 ± 0.8	0.7 ± 0.8	0.8 ± 0.8	0.7 ± 0.8
	% patients	56.5%	47.8%	52.4%	52.4%
Tophi global	Number	95	86	67	65
	Mean ± SD	4.1 ± 2.5	3.7 ± 2.7*	3.3 ± 2.5**	3.1 ± 2.3***
	% patients	91.3%	82.6%	81%	81%

PAT: patellar tendon. *p<0.05, **p<0.01, ***p<0.001

Results

Demographic characteristics

Twenty-three consecutive patients were included (96% men; mean age 59.4±11.3). The mean disease duration was 10.1±9.4 years. The baseline mean of serum urate was 8.85±1.89 mg/dl, with reactive C protein (RCP) and erythrocyte sedimentation rate (ESR) means of 11.3±20 and 15±16, respectively. The median tender regions count (TRC) and the median swollen regions count (SRC) were 1 (IQR 0-3) and 1 (IQR 0-1), respectively, and the mean patient global assessment of disease activity (PGA) was 23.6±19.8. At the first visit, 52.1% of patients were being treated with NSAIDs, 73.9% with colchicine, 43.3% with allopurinol (although 61% with doses lower than 300 mg) and none with another urate-lowering therapy (ULT).

Ultrasonographic results at baseline

A total of 52.2% of patients had DCS in 1MTF (26.1% in both 1MTFs), while 47.8% of patients had DCS in the knees (21.7% in both knees). Globally, 73.9%

of patients had DCS in at least one region. A total of 78.3% of patients had ultrasonographic tophi in 1MTF (52% bilateral), 73.9% of patients had US tophi in the knee joint (39.1% bilateral), 56.5% of patients had tophi in the patellar tendon, and 91.3% of patients had US tophi in at least one region.

Monitoring results: ULT was adjusted in all patients according to the usual clinical practice. Allopurinol was started in 13 patients (56.5%), and the dose was increased in 15 (65%). Benzobromarone was started in 3 patients (13%). At the last visit, 19 patients (87%) were being treated with allopurinol and 3 (13%) with a combination of allopurinol and benzbromarone. One patient had no ULT treatment because of the lack of therapeutic adherence. Additionally, at the last visit, two patients were still being treated with AINEs and 14 with prophylactic colchicine.

Table I shows the evolution of the clinical and laboratory parameters during the follow-up.

The percentage of patients with a serum urate concentration lower 6 mg/dl significantly increased from 5 to 60%, rising to 90% if we consider a serum urate under 7 mg/dl. The number of flares and PGA also showed significant and progressive decreases during the follow-up, and physical examination improved with tender or swollen joints medians of 0, since 6 months. The laboratory inflammatory markers such as ESR and CRP decreased in successive visits, but without achieving statistical significance.

Table II shows the results of ultrasound assessment throughout the two years.

The presence of DCS significantly decreased at one and two years. This decrease was earlier and more significant in the 1MTPs than in the knees (Table II, Fig. 1). After two years, the global number of DCSs was reduced from 34 (in 74% of patients) to 9 (in 28.6% of patients). Interestingly none of the patients with DCS persistence had reached the therapeutic goal of serum urate below 6mg/dl at the 12th or 24th month.

Regarding the presence of US tophi, there was a significant decrease in the knee and MTF tophi but not in the patellar tophi. Again, the 1MTF was more sensitive to change in the tophi resolution than the knees. The global number of tophi significantly decreased from 95 to 65, however a high percentage of patients with persistent tophi despite treatment were noted (81%). We analyse the persistence of tophi exclusively in the patients who reached and maintained serum urate levels under 6 mg/dl in the successive visits, and the percentage of patients with persistence of tophi (83%), was similar to results in the complete cohort.

The SDD values at two years for the global DCS and the global tophi were 0.52 and 0.69, respectively. Both numbers were lower than the differences achieved throughout the two years, which were 1.05 for DCS and 1.03 for tophi.

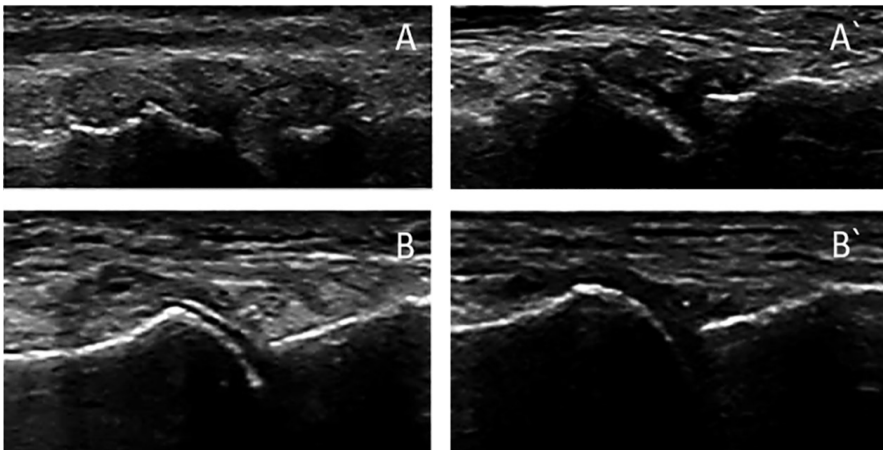

Fig. 1. A: Baseline tophi in 1MTP. A´: Resolution of tophi at 18 months. **B**: Baseline double contour sign (DCS) in 1MTP. B´: Resolution of DCS at 12 months.

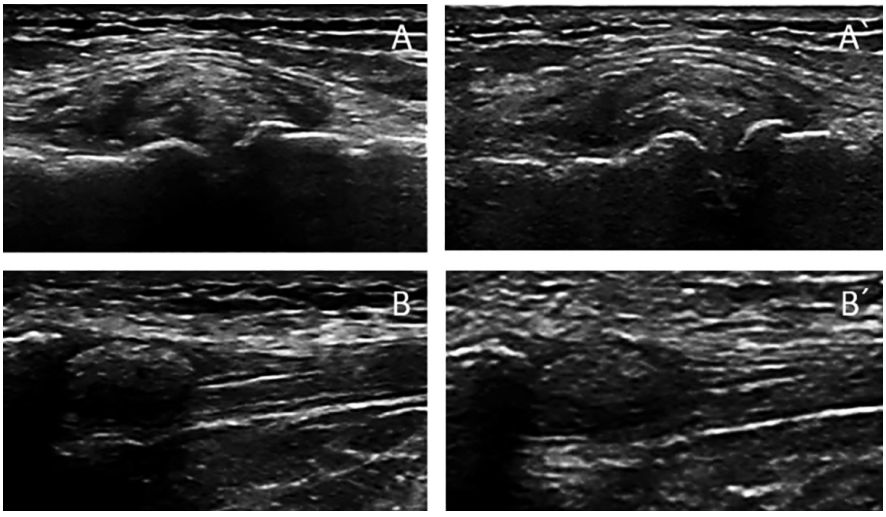

Fig. 2. A: Baseline tophi in medial recess of knee. A´: Persistence of tophi at two years. B: Baseline tophi in proximal insertion of patellar tendon. B´: Persistence of tophi at two years.

Relationship with serum urate

In the analysis of the correlation between US and clinical parameters, we observed that the decrease in serum urate during the two years had a significant correlation (r =0.49, p=0.038) with the reduction in the locations with double contour sign. In contrast, no correlation was found between tophi reduction and the decrease in uric acid.

Figure 1 and 2 show representative images of the evolution of the deposits.

Discussion

Various studies have shown an association between gout and different comorbidities such as renal or cardiovascular diseases (12, 13). In fact, a high baseline SU level and the presence of subcutaneous tophi were both associated

with an increased risk of cardiovascular mortality in patients with gout, which suggests a possible pathophysiological link between greater total body urate load and cardiovascular disease (14) (15). This information shows the necessity for better disease control and more accurate monitoring. A physical exam evaluating joint or tendon inflammation or the presence of tophi remains indispensable. Nevertheless, considering the presence of deposits in the asymptomatic joints of gout patients and in asymptomatic hyperuricaemia (16) (17), other possibilities for monitoring should be assessed and the usefulness of imaging tools in monitoring disease should be evaluated. In fact, the OMERACT working group identified "tophus burden" as one of the seven essential domains for therapeutic monitoring in chronic gout (5) and later identified 3 relevant domains for imaging in gout studies: urate deposition (tophus burden), joint inflammation, and structural joint damage (18).

Few studies have evaluated the use of ultrasound as a tool for therapeutic drug monitoring. One previous report observed the disappearance of the knee double contour sign in five cases (8). Another study measured the presence and size of 38 tophi. In this report, after one year of treatment, 20 tophi were reduced in size, and 9 disappeared. An inverse correlation was observed between serum urate concentrations and the change in the baseline measurement of tophi. This study also demonstrated that the US measurement of tophi satisfied the OMERACT criteria for an outcome measure (4). More recently, Ottaviani performed an US examination of knees and 1MTPs in patients treated during 6 months. The results showed that the DCS disappeared in most of the patients achieving urate levels <360 μM (6 mg/dl); in addition, knee and 1MTP tophi disappeared in 37% and 75% of these patients, respectively (9).

Our study confirms the significant decrease in the presence of DCS at one and two years (from 34 to 9 DCS), with earlier and better results in the 1MTPs than in the knees. The percentage of patients with DCS was reduced from 74% to 28.6% at 2 years. Interestingly, none of the patients who maintained DCS had reached the therapeutic target.

A significant decrease is also displayed in the presence of US tophi in the knees and 1MTPs but not in patellar tendon. Similar to DCS, the US examination of tophi was more sensitive to change in the 1MTP than in the knees, probably due to the lower volume of the tophi or cartilage surface in the MTP than in the knee. We speculate, also, that the limited reduction in patellar tophi may be due to greater difficulty in crystal clearance caused by the lower vascularisation of the tendon tissue. The number of tophi decreased from 95 to 65 (31.5% clearance), which is similar to results from other studies (4). However, it is important to note that after two years, around 80% of patients still had US tophi in at least one location, even if we consider exclusively the patients with maintained serum urate levels under 6 mg/dl. This persistence of tophi in the different US monitoring studies casts doubt on whether the current therapeutic objectives are the most appropriate, and supports a stricter therapeutic objective for patients with US-detectable deposits, similar to the tophaceous gout recommendations (19). In addition, our findings and the Ottaviani´s results allow us to speculate that it is probably much easier to clear the cartilage deposits than the tophi (9).

We initially proposed the analysis of the tophi size, but finally we didn't perform it because the tophi were very heterogeneous and with poorly defined limits. This made the tophi size analysis very complex, and we decided to be more rigorous and to consider only the presence or complete disappearance of tophi. However, our impression is that most of tophi reduced their size and changed their echogenicity along the two years of treatment, becoming more heterogeneous and more blurred (see Figures). But it is not an aspect that we analysed systematically.

Our work also demonstrates the US exhibits sensitivity to change in gout, by calculating SDD, and shows a significant correlation between the decrease in uric acid and the DCS reduction (r =0.49, p=0.038), which has not been previously reported.

Various issues in gout US monitoring remain unresolved. The first is determining which US test to perform, in which joints or tendons, and including or not including the symptomatic locations. We consider that in any case, gout monitoring should include the deposits burden and also the inflammatory activity by the Doppler signal (18) (20). Another unresolved question is the clinical interpretation of these findings, when to identify disease activity or remission, and how the results should influence therapeutic decisions. The knowledge of these new concepts is necessary, and imaging can facilitate our understanding of the disease.

Some limitations have to be mentioned in our study. First, the number of patients is relatively low. Second, the treatment was performed according to standard guidelines but without strict search of the therapeutic target, so the percentage of patients with serum uric acid levels lower than 6 mg/dl is not the most appropriate and can influence the US lesions evolution.

In conclusion, ultrasound can be a useful tool for treatment monitoring in gout, as it shows sensitivity to change and concurrent validity with uric acid reduction in patients.

Significance and innovations

- Our study shows that US is sensitive to change for monitoring response to urate-lowering therapy in gout; and also demonstrate a significant correlation between the decrease in uric acid and the DCS reduction (r =0.49, p=0.038), not previously reported.
- The high percentage of patients with tophi persistence after two years of treatment, despite the clinical control, introduces a reflection on the accuracy of the current outcome measures and treatments.
- Our results show that it is probably much easier to clear the cartilage urate deposits than the tophi.

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