# Reduction but not disappearance of Doppler signal after two years of treatment for gout. Do we need a more intensive treatment?

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## Abstract Objective

We undertook this study to evaluate the responsiveness of Doppler ultrasound (US) to urate lowering therapy (ULT) in gout patients.

# Methods

Twenty-four consecutive patients were prospectively included from an outpatient clinic. The patients underwent clinical, and US assessment at baseline and after 6, 12 and 24 months of ULT. The US assessment was made by another rheumatologist blinded to the clinical data. Standardised examinations were performed in four joints (both first metatarso-phalangeals and knees) and the patellar tendons. The Doppler signals were scored. The mean and standard deviation were calculated for each parameter. The comparison between the quantitative values was performed by Student's t-test. Sensitivity to change in the US examinations was assessed by estimating the smallest detectable difference (SDD) in the total Doppler score.

# Results

A Doppler signal was detected in 95.8% of the patients at the baseline. A significant parallel improvement in the serum urate level, clinical parameters and in Doppler scores was found at the follow-up assessment. 62% of the patients had achieved a uric concentration level below 6 mg/dl at one year. At two years, persistence of a Doppler signal was found in 72.7% of the patients. The SDD in the Doppler score at 2 years was 1.92, lower than the difference achieved.

## Conclusion

The Doppler US findings show significant improvement and responsiveness after ULT in gout patients. The Doppler signal persistence after two years of treatment is marked. This finding introduces a reflection on the accuracy of the current outcome measures and treatments.

Key words ultrasonography, Doppler ultrasonod imaging, gout, drug monitoring

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#### Introduction

Gout is one of the most common forms of inflammatory arthritis in adult men. There are effective treatments that achieve remission of clinical manifestations in nearly all cases of gout. There are few chronic rheumatic diseases that can go into remission as well as be healed. This is the case with gout, in which uric deposits may disappear and any structural damage and inflammation can be stopped. However, in spite of such possibilities, gout is a considerable source of morbidity and disability (1).

The synovial fluid of patients, even in cases without clinically detectable arthritis, shows low-grade inflammation (2). Such a persistent inflammatory state could be associated with an increased cardiovascular risk as has been shown in other rheumatic diseases (3, 4). Doppler ultrasound (US) detects an increase in flow in the vascular synovium, tendons and other tissues in different conditions in inflammatory arthritis and correlates the flow with inflammatory activity, even in patients with clinical remission (5).

The accepted outcome measures in gout, according to the OMERACT proposals, are serum urate levels, a recurrence of gouty flares, tophus regression, health quality, functional disablement, pain, overall disease activity and joint damage imaging (6). In the last few years, US has been studied as a gout diagnostic tool (7, 8), and only a few studies have examined its usefulness as a monitoring tool, such as for assessing a reduction in tophi size or the disappearance of a double contour after treatment (9, 10).

To the best of our knowledge, there are no analyses of the responsiveness of the Doppler signal as a tool for therapeutic monitoring in gout; though, Doppler might be useful for assessing a response to treatment and for evaluating residual inflammatory activity. The aim of this long-term study was to evaluate the ability and responsiveness of Doppler US to monitor the response to urate lowering therapy (ULT) of patients with chronic gout.

### **Patients and methods**

#### Study population

A total of 37 consecutive gout patients with at least one symptomatic acute

attack in the three months prior to the basal visit were included in this longitudinal 2-year study. A definitive diagnosis was confirmed by the presence of monosodium urate crystals in aspirates from symptomatic joints using polarising light microscopy. Patients without microscopic confirmation or patients with other rheumatic diseases were excluded. Prior to their inclusion, the patients provided informed consent for participation, and local approval was obtained from the ethics committee and institutional review board of our hospital.

The patients underwent clinical assessment and ultrasound evaluation (on the same day) at baseline, 6 months, 12 months and 24 months. The demographic, clinical and laboratory characteristics of each patient were recorded. The patient global assessment of disease activity (PGA) was measured by a visual analogue scale range 0–100. The treatment was adjusted at each visit to achieve adequate clinical control.

### Ultrasonographic examinations

The US examinations were performed by a second rheumatologist within 2 hours of each clinical evaluation. This rheumatologist was unaware of the clinical and laboratory findings and was not involved in the treatment decisions. The assessment was completed using Logiq 9 equipment (General Electric Medical Systems, Milwaukee, WI, USA) with a 9-14 MHz probe for the grey scale and a 5-7.5 MHz probe for Doppler. The studies were performed by scanning across the joints and moving the probe from the medial to lateral aspect and from the proximal to distal aspect. The assessment included the Doppler signal in the following four joints: both first metatarsophalangeal (1<sup>st</sup> MTP) joints and both knees (medial and lateral recesses) and in the patellar tendons (PAT). The PRF was 0.4 hHz and the Doppler gain was adjusted to a level just below its disappearance under the bony cortex. The absence or presence of a Doppler signal was considered for the analysis, and also a score was calculated for each region. The score range was from 0 to 6 (0= without Doppler in right or left side; 6= Doppler signal 3 in left and right side). We calculated a global

*Competing interests: none declared.* 

score for each patient. The baseline reliability analysis in this cohort of patients was previously reported (11).

## 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 the quantitative values on successive visits was performed with Student's t-test for paired samples and the McNemar test for qualitative values. In statistical terms, the smallest detectable change (SDC) 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 SDC for the total Doppler score according to the following formula:  $SDC = 1.96 * \sqrt{2} * SEM$ ).

#### Results

Thirty-seven consecutive gout patients were prospectively recruited in the outpatient clinic as follows: 29 had crystalproven gout and were included in the study (in 8 patients we tried unsuccessfully to obtain synovial fluid). Five patients were lost during follow-up. We analysed 24 gout patients, 23 (95.8%) of whom were men, with a mean age of 60.8 years (±11 years). The median disease duration was 10.3 years (IQR: 2-15). At baseline, 10 patients (42%) were treated with allopurinol, 17 patients (71%) were treated with colchicine, and 12 patients (50%) were treated with non-steroidal anti-inflammatory drugs (NSAIDs). At the last visit, 17 patients (71%) were treated with allopurinol and 4 (16.6%) with a combination of allopurinol plus benzbromarone. The remaining percentage of patients without ULT is because of the lack of therapeutic compliance. Additionally, at the last visit, 3 patients were still treated with NSAIDs and 14 with prophylactic colchicine.

Forty-two percent and 62% of the patients achieved a blood uric concentration level of <6 mg/dl at six months and after 12 months, respectively. Similarly, the number of flares, the serum urate **Table I.** Clinical and laboratory parameters at the baseline and follow-up assessments, expressed by the mean  $\pm$  standard deviation or the median and interquartile range (IQR) value.

	Baseline	6 months	12 months	24 months
PGA (0–100 mm)	24.08 ± 19.5	$16.2 \pm 13.9$	$16.05 \pm 14.8$	$9.14 \pm 8.35^{*}$
SJC	1 (0, 1)	$0 (0,1)^*$	$0 (0, 0.5)^*$	0 (0, 0.25)*
TJC	1 (0, 2.75)	$0 (0, 0.75)^*$	$0 (0, 0.5)^*$	$0 (0, 0)^{***}$
ESR mm/h (IQR)	$14.24 \pm 15.85$	$9.29 \pm 8.48$	$7.47 \pm 6.17$	$8.47 \pm 7.5$
CRP (mg/dl)	10.66 ± 19.3	$2.97 \pm 2.39$	$2.88 \pm 2.02$	$5.83 \pm 10.4$
Serum urate (mg/dl)	$8.87 \pm 1.85$	$6.5 \pm 1.40^{***}$	$5.89 \pm 0.97^{***}$	$5.33 \pm 1.36^{***}$
Patients with urate <6 mg/dl (%)	0	10 (42%)**	13 (62%)***	13 (62%)***
Gout flares <sup>†</sup>	1	0.58	0.38***	0.41**

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

**Table II.** PDUS parameters at the baseline and follow-up assessments, expressed by the mean  $\pm$  standard deviation or the median and interquartile range (IQR) value.

	Baseline	6 months	12 months	24 months
Doppler score 1 <sup>st</sup> MTP	1.63 ± 1.69	$1.08 \pm 1.38$	0.5 ± 0.96***	$0.24 \pm 0.62^{***}$
% 1st MTP with Doppler signal	52%	35.4%	18.7%**	14.6%**
Doppler score PAT	$0.52 \pm 0.79$	$0.33 \pm 0.7$	$0.38 \pm 0.82$	$0.09\pm0.3^*$
% PAT with Doppler signal	21%	15.2%	15.2%	4.3%*
Doppler score Knee	$2.25 \pm 1.29$	$2.13 \pm 1.46$	$1.71 \pm 1.3$	$1.2 \pm 1.15^{**}$
% Knee with Doppler signal	76%	67.3%	63%	36.9%***
Doppler score Global	$4.38 \pm 2.39$	$3.46 \pm 2.47$	$2.54 \pm 2.1^{***}$	$1.55 \pm 1.54^{***}$
Number of regions with Doppler	$2.92 \pm 1.24$	$2.29 \pm 1.55$	$1.88 \pm 1.48^{**}$	$1.18 \pm 1.1^{***}$
% Patients with Doppler	95.8%	83.3%	91%	72.7%*

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

level, the PGA, SJC and TJC showed a significant and progressive decrease at the follow-up. The laboratory inflammatory markers such as ESR and CRP decreased in the successive visits, without achieving statistical significance (Table I).

Regarding the ultrasonographic parameters in the first visit, a Doppler signal was found in 50% of the total scanned regions in all the patients, and 95.8% of the patients had a Doppler signal in at least one scanned area. We found a Doppler signal in 52% of the 1<sup>st</sup> MTPs (66.7% of the patients had a Doppler signal in at least one 1<sup>st</sup> MTP), 76% of the examined knees had a Doppler signal (87.5% of the patients), and 21 of the examined patellar tendons had a Doppler signal (37.5% of patients) (Table II).

The Doppler global score and the number of regions with a Doppler signal significantly decreased at one and two years, and if we evaluate the evolution of the Doppler signal according to the different locations, the MTF joint appears more sensitive to change (Table II, Fig. 1). Persistence of the Doppler signal at two years was observed in a high percentage of patients (72%). This finding occurred, despite appropriate clinical controls: 62% of the patients had a uric concentration below 6 mg/dl, it was observed a significant decrease in levels of uric acid from 6 months, and a decrease in the percentage of patients with gout flares. No significant correlation between uricemia and the laboratory or PDUS parameters could be found. In an analysis of the patients achieving a serum urate level below 6 mg/ dl during the follow up, two patients, one patient, and four patients did not have a Doppler signal at six months, 12 months and 24 months, respectively. In this group of patients with a serum urate level below 6 mg/dl, one patient had a flare at the first visit, one patient had a flare at the second visit (six months and



# 12 months), and 2 patients had a flare at 24 months.

The significant decrease in the Doppler scores during the study is shown in Table II and Figure 1. To analyse whether that difference was independent of chance or measurement error, the minimum detectable change (SDC) was calculated. The analysis showed that at 2 years, the SDC for the Doppler score was 1.92, lower than the difference achieved between the baseline score and the two-year score (2.83).

The representative images of the PDUS changes at the different locations are shown in Figure 2.

#### Discussion

The accuracy of US in the diagnosis of gout is supported by previous studies. The following US features have demonstrated diagnosis validity: the double contour sign and the hyperechoic cloudy area in synovial joints with a sensitivity-specificity of 43.7%-99%, 79%–95% (12), respectively. and Additionally, two studies have shown the disappearance of these specific US features after ULT (9, 10). Regarding the Doppler signal, US studies in gout have revealed findings of synovitis in acute gout and a Doppler signal in the synovial fluid, around the tophi or within the erosions in chronic gout (12). A Doppler signal has been observed in symptomatic and asymptomatic joints in patients with gout and in patients with asymptomatic hyperuricemia and characteristic ultrasound urate deposits (13). This finding is in agreement with the presence of low- grade inflammation in the synovial fluid of gout patients during asymptomatic periods (2). In



Fig. 2. The Doppler signal at baseline, 12 (<sup>^</sup>) and 24 months (<sup>^</sup>). A. Hyperechoic cloudy area and the Doppler signal at the lateral recess of the knee. B. Hyperechoic cloudy area, erosion and the Doppler signal at the 1st MTP (longitudinal) C. Doppler signal and hyperechoic aggregate at the patellar tendon (longitudinal).

other inflammatory arthritis conditions, a Doppler signal has been shown to be a sensitive method to identify inflammation, even on the subclinical level, and to predict future structural damage (5). We studied the responsiveness of Doppler ultrasonography in response to hypouricemic treatment in patients with gout. Our hypothesis was that if patients achieved acceptable outcomes, such as a serum uric acid level below 6 mg/dl, the Doppler signal should disappear or decrease. Regarding this aspect, we found no previous studies, except one monitoring case in which the Doppler signal disappeared after treatment (14). To the best of our knowledge, this study is the first to systematically evaluate the Doppler signal evolution in chronic gout at the patient level.

In this work, a Doppler signal was detected in 95.8% of the patients at the baseline examination. Similar results were observed in other publications (12, 15). Regionally, 52% of the MTFs had inflammatory activity determined by Doppler, which is a slightly higher percentage than that in other references (15). In contrast to the study of Filipucci (16), our work detects a baseline Doppler in most of the knees, which could be because of a different assessment location (we explore the medial and lateral para-patellar recesses) or by clinical differences between the patients.

During the two years of our study, we could observe improvement in most of the clinical and laboratory parameters after starting treatment, as well as in the number of flares (Table I). A significant response in the global Doppler score, with a higher than minimal detectable change, was observed (Table II); no significant correlation with the serum urate level or laboratory parameters could be observed, most likely because of an insufficient number of patients. A Doppler signal at two years persists in a high percentage of the patients (72.7%), despite an obvious clinical improvement, with 62% of the patients achieving a uric concentration below 6 mg/dl, adequate symptom control and a significant improvement in the Doppler score. This finding could indicate the presence of persistent subclinical activity

and is in accordance with the presence of a Doppler signal in asymptomatic gout patients or in asymptomatic hyperuricemia patients (13); these results are also in agreement with data of synovitis observed by magnetic resonance (3). This finding could be supported by the hypothesis of a pathogenic granulomatous basis for gout (17), which would require resolution of uric acid deposits for the disappearance of a Doppler signal. Knowledge of new emerging issues is necessary, and ultrasound technology could facilitate our understanding of the disease, resulting in new reflections on the accuracy of current outcome measures and therapeutic uses. Evidence-based recommendations for gout management suggest that maintaining an SUA below the saturation point for monosodium urate crystals (6 mg/dl-360 mmol/l) is appropriate for promoting crystal dissolution. Recently published American College of Rheumatology guidelines (18) affirm that 5 mg/dl might be appropriate in some patients to strongly improve the signs and symptoms of gout. Our results most likely support this lower level because most patients did not achieve the disappearance of the Doppler signal. A pertinent question is whether reducing the recommended uric acid level has relevance for patients, because patients with gout have a higher independent risk for coronary heart disease and increased mortality, which could be related to clinical and subclinical goutassociated inflammation. This question should be answered in futures studies. One problem with introducing а

Doppler signal as an outcome measure in clinical practice and clinical trials is its feasibility. To solve this problem, we used a short assessment of four joints and two tendons. These locations were more valid for the detection of ultrasonographic gout findings, according to preliminary study results (11). The inter-reader reliability analysis of the Doppler signal was previously studied in each of the examined regions with good or excellent Kappa coefficients: 0.958, 0.790, and 0.860 for the 1<sup>st</sup> MTP, knee and PAT, respectively (11).

Some limitations of our study should be noted. The number of patients was low.

A larger cohort would be necessary to correlate the clinical and ultrasonography results. Another limitation is that this study was conducted in accordance with daily clinical practice; therefore, the patients were treated with different hypouricemic agents, colchicine and NSAIDs, at various dosage levels during the study. These differences in treatment might introduce bias into the study; however, the results are closer to normal clinical practice.

We found a significant improvement in the US Doppler signal scores in parallel with changes in the clinical and laboratory indices of disease activity throughout the follow-up period, which indicates the construct validity of the Doppler signal as an outcome in patients with gout. Sensitivity to change and responsiveness was shown to be valid for monitoring gout with an SDC below the observed level. The persistence of the Doppler signal, despite the clinical improvement, makes us reflect on the limitations in the accuracy of the current outcome measures in gout. Whether to include ultrasound as an outcome in gout treatment is to be considered in further studies.

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