An analysis of MRI and ultrasound imaging in patients with gout who have normal plain radiographs

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Objective. The aim of this study was to analyse the prevalence of occult destructive arthropathy in subjects with gout and normal plain radiographs by utilizing MRI and ultrasound (US).

Methods. The study consisted of two visits. At Visit 1, a plain radiograph of the ‘index joint’ was obtained. The ‘index joint’ was defined as a joint that has had the most acute attacks of gout historically. The index joint plain radiograph had to be free of erosive damage in order for the subject to qualify for Visit 2. At Visit 2, the subject had an MRI with contrast and an US of the index joint. Each subject also had an MRI and US of an ‘asymptomatic joint’. The ‘asymptomatic joint’ was defined as a joint that had never experienced an acute attack of gout (determined by standard protocol). The primary endpoint was erosive changes on the MRI and/or US of the index joint. Secondary endpoints included erosive changes on the asymptomatic joint as well as bone marrow oedema (BME) (on MRI), synovial pannus (SP), soft tissue tophi (STT) or oedema (STE) on either the index or asymptomatic joint.

Results. Twenty-seven subjects (26 males; 1 female) completed both visits. Their average age and disease duration were 55.1 years (range 21–75 years) and 6.8 years (range 0.25–25 years), respectively. The subjects’ average serum uric acid level over the past 5 years was 6.8 mg/dl (range 4.1–12.8 mg/dl); their average on the day of Visit 1 was 7.96 mg/dl (range 4.6–13.9 mg/dl). The first MTP was the most common index joint (17) followed by the ankle (5), mid-tarsal (2), knee (2) and wrist (1). The knee was the most common asymptomatic joint (21) followed by the wrist (3), MTP (2) and ankle (1). All subjects had both MRIs; one subject refused the US. Out of 27 subjects, 15 (56%) included erosive changes on the asymptomatic joint as well as bone marrow oedema (BME) (on MRI), synovial pannus (SP), soft tissue tophi (STT) or oedema (STE) on either the index or asymptomatic joint.

Conclusions. A large percentage of patients with gout and normal plain radiographs have occult destructive arthropathy that is only detected by advanced imaging such as MRI and/or US. However, MRI appears to be much more sensitive than US at detecting these findings.

Key words: Gout, MRI, Ultrasonography, Synovial pannus, Joint destruction, Plain radiograph, X-ray.

Introduction

As is the case with other inflammatory arthritides, gout will often lead to significant destructive skeletal changes if left untreated. Our current standard of care to determine the presence or absence of these destructive bony changes is a plain radiograph of the involved joint. However, these radiographic changes are thought to be irreversible and often are only detectable after many years of disease.

Surprisingly, there is a paucity of data in the literature regarding the bony changes of gout on MRI. The existing data focus primarily on the appearance of gouty tophi [1–6]. These tophi typically have low to intermediate signal intensity on T1 and variable intensity on T2-weighted images with a variable enhancement pattern depending on the amount of calcifications. One study of seven patients did suggest that MRI may be able to detect early ‘subclinical’ tophaceous deposits [5]. There is little attention paid to the MRI appearance of erosive changes or other potential findings associated with gout. Further, there has been very little effort to look for these changes in patients who were determined to have normal plain radiographs.

As is the case with MRI, there are few data in the literature regarding the ultrasound (US) findings in gout, but these data are rapidly expanding. The data available primarily assess the US appearance of soft tissue nodules, erosive changes and other potentially diagnostic signs of gout [6–11]. One study comparing gouty tophi to rheumatoid nodules suggested that the gouty tophi cause more cortical bone destruction than rheumatoid nodules [7]. Unique US features of gout, including the double-contour sign (hyperechoic band over the superficial margin of the articular cartilage indicative of MSU crystal deposition), have been described as potentially diagnostic signs [8–10]. Other studies describe the presence of erosive changes on US, but only one suggested that high-resolution US might detect these erosive changes earlier than plain radiography [9]. This study also was not restricted to patients with normal plain radiographs and other advanced imaging modalities were not studied.

Asymptomatic hyperuricaemia is a possible harbinger of clinical gout. Not surprisingly, the incidence of gout increases with the degree of hyperuricaemia [12]. Further, any body fluid with a urate level of >6.8 mg/dl exceeds the soluble concentration of MSU, thereby leading to MSU deposition [13], and MSU crystals have been demonstrated to be present in asymptomatic joints of patients with gout [14]. Therefore, it is quite possible that ‘silent’ deposition of MSU crystals as a result of hyperuricaemia may lead to early destructive skeletal changes.

This study was designed to assess patients with known gout and normal plain radiographs for occult skeletal damage. Specifically, we sought to determine the percentage of patients who had erosive changes on MRI or US that were not apparent on plain radiography. We also examined these patients for the presence of other characteristic findings of gout. Finally, each patient also had an asymptomatic joint examined in similar fashion to analyse for ‘silent’ disease.
Patients and methods

Patients and study design

This was a single-centre, prospective trial performed at the University of South Florida (USF) in Tampa, Florida. All of the MRIs and USs were performed at Tower Imaging, Inc. by Radiology Associates of Tampa, Florida. Ethical approval was obtained from the USF Institutional Review Board and all patients gave informed consent before undergoing any screening procedures. The trial was registered with ClinicalTrials.gov, identifier: NCT00584311.

Eligible patients were 18–80 years of age with a known history of gout. To be included in the study, the patient’s diagnosis of gout was defined by one of the three criteria: current or previous documentation of intracellular MSU crystals in SF, a tophus proved to contain MSU crystals; or at least 6 of the 12 ACR diagnostic criteria for gout [15]. Patients were excluded if they had a history of any other inflammatory arthritis, another crystal-induced arthritis, contraindication to receiving an MRI or gadolinium contrast dye, or a serum creatinine of >1.8 mg/dl at their screening visit.

Study subjects had two study visits. Visit 1 was their screening visit, whereas advanced imaging (MRI and US) was performed at Visit 2. The study procedures performed at each visit are outlined as follows:

Visit 1:
- Informed consent process
- Inclusion and exclusion criteria reviewed
- Detailed history (including number and exact location of previous acute gouty attacks)
- Physical examination
- Chart review: documentation of any serum urate level for the past 5 years
- Serum uric acid, CRP and creatinine obtained
- Any female study subject of child-bearing potential: urine β-human chorionic gonadotropin
- Plain radiograph of ‘index’ joint obtained

The ‘index’ joint was defined as a joint that has had the most acute attacks of gout historically. The index joint plain radiograph was assessed independently by two readers (one radiologist and one rheumatologist); both readers had to agree that there was no evidence of erosive damage in order for the subject to qualify for Visit 2. Study subjects were permitted to have mild osteoarthritic changes on their screening plain radiograph. Specifically in those cases where the index joint was the knee, the study subject could not have a Kellgren–Lawrence scale of arthritis on their screening plain radiograph.

Visit 2:
- MRI (1.5 tesla) (with and without gadolinium contrast) of the ‘index’ joint
- Color Doppler US (8 MHz) of the ‘index’ joint
- MRI (1.5 tesla) (with and without gadolinium contrast) of the ‘asymptomatic’ joint
- Color Doppler US (8 MHz) of the ‘asymptomatic’ joint
- Visit 2 was scheduled within 2 weeks of Visit 1

The ‘asymptomatic’ joint was defined as a joint that had never experienced an acute attack of gout. This joint was determined by a standard protocol in each subject. The asymptomatic joint protocol read as follows: the asymptomatic joint examined will be the ipsilateral knee. If the index joint is the knee, the subject will have the contralateral knee serve as the asymptomatic joint. If both knees have been involved in previous gouty attacks, the asymptomatic joint will be chosen from the following list (in order of decreasing preference): contralateral foot, ipsilateral wrist, contralateral wrist, ipsilateral elbow, contralateral elbow, ipsilateral ankle, contralateral ankle, ipsilateral hand and contralateral hand.

Each MRI and US was also read independently by two radiologists trained in musculoskeletal radiology. The radiologists who read the MRI and US were different than the radiologist who read the screening plain radiograph and were blinded to the joint designation; i.e. ‘index’ joint vs ‘asymptomatic’ joint. These radiologists did not perform the US, rather they read recorded real-time images. They were instructed to assess for the presence of erosions, synovial pannus (SP), bone marrow edema (BME) (MRI only since this cannot be detected on US), soft tissue edema (STE) or soft tissue tophi (STT) on all advanced imaging studies. They were not instructed to assess for the ‘double-contour’ sign previously reported in gout. SP was included in the pre-defined secondary endpoints because it had been previously documented in one small study [4], and it is a common finding on advanced imaging in other types of inflammatory arthritis.

Study objectives

The primary endpoint was to determine the presence of erosive changes on the MRI and/or US of the index joint in these subjects with gout who had no erosive changes on their plain radiograph of this same joint. Secondary endpoints included erosive changes on the asymptomatic joint, as well as BME (MRI only), SP, STT or STE on either the index or asymptomatic joint. Potential correlations of serum urate levels, disease duration, number of gouty attacks and gout medications with erosive changes on advanced imaging were also assessed.

Statistical analysis

The sample size of 27 study subjects was calculated assuming that ≥30% of the study subjects will exhibit skeletal damage on these advanced imaging techniques. Twenty-seven subjects with normal plain radiographs studied with MRI and US would provide 80% power to detect a difference of 30% between the X-rays and the advanced imaging studies at the 5% significance level.

The primary endpoint was analysed as categorical data (presence or absence of erosive changes on either MRI or US) compared with plain radiograph by the Fisher’s exact test. These data (i.e. the presence of erosions) were also analysed in the same fashion but by MRI and US independently, and in a head-to-head fashion. The secondary endpoints of SP, STT and STE were directly compared on MRI and US categorically with the Fisher’s exact test. Both radiologists had to agree on the finding (i.e. the presence of an erosion, SP, BME, STT and STE) in order for it to count for purposes of comparison.

Inter-reader agreement between the two radiologists on the MRI and US studies was also assessed. This was accomplished by calculating a k-coefficient between the radiologists with regard to the presence of erosions, SP, STT and STE on MRI and US, as well as the determination of BME on the MRI.

Results

Characteristics of the study population

A total of 33 study subjects were screened for this trial; of these 33 subjects, 4 were excluded at their screening visit and 29 qualified for Visit 2. Regarding the four study subjects that were excluded, two were excluded because of erosive changes on their screening plain radiograph and two were excluded because of a contraindication to receiving an MRI (both had residual bullet fragments from previous gunshot wounds). Two of the remaining subjects failed to present for Visit 2 so they were excluded leaving 27 subjects who completed both visits. Study subject demographics of the 27 study subjects are listed in Table 1.

Eight subjects (30%) had documented MSU crystals and the other 19 met at least 6 of the 12 diagnostic criteria for gout. The most common ‘index’ joint was the first MTP joint (n = 17)
and the most common ‘asymptomatic’ joint was the knee (n = 21). For more details regarding the ‘index’ and ‘asymptomatic’ joints and the subjects’ previous articular involvement of their gout, see Table 2.

In terms of gout medications, 10 (37%) subjects were on both allopurinol and colchicine, 7 (26%) were on allopurinol only, 3 (11%) were on colchicine only, and 7 (26%) were not on allopurinol, colchicine or any other serum urate-lowering medication.

**MRI and US results**

All 27 of the study subjects had both MRIs (‘index’ joint and ‘asymptomatic’ joint) and 26/27 subjects had both USs performed (‘index’ joint and ‘asymptomatic’ joint). One subject refused the US due to the length of time necessary to be at the advanced imaging facility. All of the study subjects had their MRI and US performed on the same day; 23/27 subjects had these advanced imaging studies within 2 weeks of their screening visit. Of the four subjects who did not have Visit 2 within 2 weeks of Visit 1, three had Visit 2 within 1 month and one within 2 months.

Regarding the primary endpoint, 15/27 (56%) of these gout subjects with normal plain radiographs had evidence of erosions on the index joint by MRI and/or US (P < 0.0001). Specifically, 15/27 (56%) of the subjects had erosions on their index joint detected by MRI and 1/26 (4%) had erosions on their index joint detected by US. The subject with erosions detected by US also had these erosions detected by MRI. The screening plain radiograph of the study subject is shown in Fig. 1. Typical erosions on MRI are demonstrated in Figs 2–5 (the corresponding screening plain radiograph can be seen in Fig. 1) and those detected on US are seen in Fig. 6. Interestingly, there were also erosive changes detected by MRI in one subject’s asymptomatic joint.

Other findings in the index and asymptomatic joints, including BME, STE and STT, were also observed. Quite unexpectedly, a high percentage of subjects [n = 13 (48%)] had SP detected by MRI on their index joint. See Table 3 for complete MRI and US results. Although there was a difference in the mean disease duration in those subjects who had erosions detected on advanced imaging compared with those who did not (7.8 vs 5.6 years, respectively), this did not reach statistical significance (P = 0.36). Similarly, there was a trend regarding the number of attacks of gout involving the index joint and the presence of erosive disease (7.3 vs 4.8 attacks in those with and without erosions, respectively; P = 0.19). There was no correlation between the presence of erosive changes on MRI or US with the use of allopurinol and/or colchicine. Rather surprisingly, there was also no correlation with serum urate levels (either the 5-year average or at the time of screening) and the presence of SP on MRI of the index or asymptomatic joint.
Inter-reader agreement between the two radiologists’ interpretation of the MRI and US was assessed by determining $\kappa$-coefficients. Radiologist 1 determined that 16/27 (59%) of the subjects had erosions on their index joint by MRI and radiologist 2 felt that 18/27 (67%) of these subjects had erosions on this same joint by MRI; they agreed on 15/27 subjects. The $\kappa$-coefficients for the determination of erosions on the index joint by MRI between the two radiologists was 0.68, which indicates very good agreement. Regarding erosions detected on the index joint by US, the $\kappa$-coefficient was 1.0 indicating perfect agreement.

The $\kappa$-coefficients for the determination of SP, BME and STE on the index joint by MRI were 0.46, 0.33 and 0.46, respectively. This indicates moderate to good agreement. Radiologist 2 determined that there were two STTs around the index joint on MRI and Radiologist 1 documented none revealing poor agreement. The $\kappa$-coefficients for the US on the index joint were 0.25, 0.0 and 1.0 for SP, STE and STT, respectively. The $\kappa$-coefficients for the MRI readings of the asymptomatic joint ranged from 0.24 to 1.0 and the range on the US readings of this same asymptomatic joint was from 0.0 to 1.0.

Regarding inter-reader agreement on the initial X-ray performed at Visit 1, both readers had to agree that this X-ray was free of erosive damage in order for the study subject to qualify for Visit 2; therefore, the $\kappa$-coefficient on the 27 subjects’ initial X-ray was 1.0 (perfect agreement). Two subjects of the 33 screened were deemed screen failures at Visit 1, because of erosive changes on their screening plain radiograph. These two X-rays were not read by the second reader.

**Discussion**

Gout often leads to significant destructive skeletal changes, particularly if left untreated. Our current standard of care for monitoring these structural changes is the plain radiograph. It is well known that progressive radiographic structural joint damage correlates with decreased functional ability, and even mortality, in other types of inflammatory arthritis, such as RA [16]. Although not as well studied in gout, a breadth of clinical experience suggests a similar correlation between radiographic damage and functional disability. Recent data suggest that tophaceous joint disease has a major impact on functional capacity in gout [17]. Therefore, earlier detection of skeletal damage could improve the long-term outcomes of gout. This study suggests that more than half (56%) of subjects with gout have skeletal damage (i.e. erosions) on advanced imaging that is not detected on plain radiography. Not only were erosive changes detected on MRI and US that were not appreciated on plain radiography, other pathological

| Table 3. The complete MRI and US results of the study subjects |
|-----------------|-----------------|-----------------|
| Index joint     | MRI, $n = 27$   | US, $n = 26$   |
| Erosion, n (%)  | 15 (56)         | 1 (4)          | $< 0.0001$ |
| SP, n (%)       | 13 (48)         | 1 (4)          | 0.0003    |
| BME, n (%)      | 4 (15)          | NA*            | NA        |
| STE, n (%)      | 3 (11)          | 0 (0)          | 0.24      |
| STT, n (%)      | 0 (0)           | 1 (4)          | 0.49      |

<table>
<thead>
<tr>
<th>Asymptomatic joint</th>
<th>MRI, $n = 27$</th>
<th>US, $n = 26$</th>
<th>$P$-value, MRI vs US</th>
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</thead>
<tbody>
<tr>
<td>Erosion, n (%)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>SP, n (%)</td>
<td>3 (11)</td>
<td>0 (0)</td>
<td>0.24</td>
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<tr>
<td>BME, n (%)</td>
<td>3 (11)</td>
<td>NA*</td>
<td>NA</td>
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<tr>
<td>STE, n (%)</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>0.49</td>
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<td>STT, n (%)</td>
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* BME cannot be detected by US.
sequela of inflammatory arthritis were observed in these gout patients on advanced imaging. These included SP, BME, STE, and STT. Several of these are indicative of an ongoing inflammatory process that could potentially lead to more skeletal damage. There was only one study subject (out of the 27) in whom both radiologists agreed that there were no pathological findings (i.e. erosions, SP, BME, STE or STT) on either MRI or US. It is important to note that the patients studied have relatively early gout and all of the patients had normal plain radiographs. These pathological findings could be even more prevalent in gout patients with more chronic disease.

Unexpectedly, nearly half of the study subjects had evidence of SP in their index joint on advanced imaging. It should be stressed that the MRI and US studies were not performed during acute attacks, rather these subjects had their advanced imaging studies performed during intercritical (i.e. asymptomatic) gout. Somewhat surprisingly, the presence of SP did not correlate with serum urate levels, although this study was not powered to answer that question directly. SP, the hypertrophic changes of the synovium indicative of chronic inflammation, has almost exclusively been associated with RA. To our knowledge, SP has only been documented in one other small study of nine patients with gout [14]. The clinical history of untreated gout suggests that, at some point, gout will progress to a chronic inflammatory arthritis. This tells us that gout will lead to a chronic synovial-based inflammation at some point. However, the data presented herein raise several questions. When does the synovial-based inflammation of gout resolve in between acute attacks? Does it ever completely resolve? These important questions deserve further study.

Pathological features of gout, including erosions, were also detected on the ‘asymptomatic’ joint in this study. This mirrors other data demonstrating MSU crystals in the SF of asymptomatic joints from patients with gout [14], and is consistent with the fact that MSU crystals develop in any body fluid when the soluble concentration is exceeded. The most common findings in the asymptomatic joints were SP and BME. Although BME can be observed on MRI in other common conditions such as OA, particularly in the knee (most common asymptomatic joint assessed), SP would not be typical of OA. These findings suggest that subclinical low-grade inflammation might precede acute inflammatory attacks.

There was a significant difference comparing MRI to US in this study, particularly in the index joint. Specifically, the MRI was a much more effective tool at detecting early erosive changes. In general, there was good to very good inter-reader agreement between the radiologists with both MRI and US interpretation. In some of the findings with US, specifically there was perfect agreement between radiologists. This suggests that the differences between modalities are real. Other studies suggest that US is a very effective tool for detecting characteristic, even diagnostic, findings of gout [8–10]. One suggested that it is more effective than MRI specifically [18]; however, the endpoint was other diagnostic features (i.e. the ‘double-contour’ sign) rather than early structural damage. Also, patients with normal radiographs were not studied. Conversely, these other studies generally used a higher resolution US (12–14 MHz) than the one we studied (8 MHz). It is possible that a higher frequency US would have fared better in this study. As stated, our radiologists were not instructed to assess for the ‘double-contour’ sign. However, one radiologist retrospectively reviewed several USs from these patients and this feature was not observed. The explanation could be the relatively low-resolution US utilized or that this is a finding in patients with more advanced gout. This deserves further study.

Utilizing our current standard of care, all of the patients in this study would have no evidence of structural joint damage as evidenced by their normal plain radiographs. However, advanced imaging modalities suggest that more than half of the subjects have erosive damage in their joint most often affected by gout. Nearly all had some pathological findings on either MRI or US in this same joint. Evidence of chronic inflammation (i.e. SP) was also seen even in the absence of acute attacks. Several patients even had occult findings in asymptomatic joints. Such findings are likely to be a harbinger of adverse long-term outcomes. These data demonstrate that skeletal damage occurs earlier than we might expect and that MRI might be the best advanced imaging modality to discover these changes.

### Rheumatology key messages

- Many patients with early gout have destructive bone changes (erosions) that are not detected on plain radiography.
- MRI might be superior to US at detecting these erosive changes.
- Other findings are common in these patients, including SP.

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