Effects of Conventional Uric Acid-Lowering Therapy on Monosodium Urate Crystal Deposits

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Objective. Few studies have systematically and quantitatively addressed the impact of urate-lowering therapy on monosodium urate (MSU) deposits. This study was undertaken to analyze the effect of lifestyle measures and conventional urate-lowering therapy on MSU deposits in patients with gout.

Methods. In this prospective study, subjects with gout according to the American College of Rheumatology/European League Against Rheumatism classification criteria and presence of MSU deposits seen on dual-energy computed tomography (DECT) scans received either lifestyle intervention or conventional urate-lowering therapy for a mean period of 18 months before a follow-up DECT scan. Detected MSU deposits were quantified by volumetric measurement and validated by semiquantitative scoring, and baseline and follow-up measurements were compared.

Results. Baseline and follow-up DECT scans were available for all 83 subjects. Six subjects discontinued treatment, and 77 subjects underwent a lifestyle intervention (n = 24) or were treated with allopurinol (n = 29), febuxostat (n = 22), or benzbromarone (n = 2) over the entire observation period. The mean serum uric acid (UA) level decreased from 7.2 to 5.8 mg/dl in the overall population. In patients who discontinued treatment, no change in MSU deposits or serum UA levels was observed. The burden of MSU deposits significantly decreased in patients undergoing lifestyle intervention (MSU volume P = 0.007; MSU score P = 0.001), and in patients treated with allopurinol (MSU volume and score P < 0.001) or febuxostat (MSU volume P < 0.001; MSU score P = 0.001). No significant decline in MSU deposits was noted in patients who discontinued treatment.

Conclusion. These data show that lifestyle intervention and xanthine oxidase inhibitors significantly decrease the MSU deposit burden. Hence, conventional gout therapy not only lowers serum UA levels, but also reduces pathologic MSU deposits.

INTRODUCTION

Gout is a musculoskeletal disease caused by an imbalance in purine metabolism (1,2). Due to impaired excretion, increased intake, or endogenous overproduction of purine, serum uric acid (UA) levels rise above the solubility concentration limit of 6.8 mg/dl, allowing the precipitation of monosodium urate (MSU) crystals in soft tissues and joints (3,4). This process triggers inflammation manifesting as arthritis and enthesitis (5). Identification of MSU crystals in synovial fluid is recognized as the gold standard for the diagnosis of gout (6). However, direct identification of MSU crystals is often impossible due to the lack of fluid to be aspirated. Furthermore, it does not provide an estimate of the burden of MSU deposits. Therefore, techniques have been developed that allow visualization of MSU deposits in a noninvasive manner (7–10).

Dual-energy computed tomography (DECT) can noninvasively quantify the deposits of MSU crystals with high sensitivity and specificity (11,12). Automated volume measurement of MSU deposits is feasible by DECT, allowing quantification of MSU deposits (7,12).

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A DECT-based scoring system for MSU deposits has been developed to cross-sectionally and longitudinally assess the distribution and severity of the MSU burden in anatomic regions most frequently affected by gout (13). Although DECT has been shown to reliably detect MSU deposits, data on how urate-lowering therapies affect MSU deposits are very limited. Therefore, we performed a longitudinal study to investigate the effect of different urate-lowering interventions on the MSU deposit burden using sequential DECT scanning followed by quantitative assessment of MSU deposits.

**PATIENTS AND METHODS**

**Patients and evaluated characteristics.** Patients were included consecutively in this prospective cohort study, if they had gout that fulfilled the 2015 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria (14) and had MSU deposits seen on the baseline DECT examination of both feet. Patients were recruited from the University Hospital Erlangen outpatient clinic after referrals from general, rheumatology, and orthopedic practices. All patients provided written informed consent. The study was approved by the Ethics Committee of the Medical University Erlangen-Nuremberg. All individuals received recommendations regarding lifestyle, which essentially followed the guidelines of the German Society of Rheumatology (15) and are in accordance with the EULAR recommendations for the management of gout (16). Briefly, patients were advised to avoid the consumption of alcohol, in particular beer (17), the ingestion of fructose-containing beverages, as well as the consumption of excessive meat and shellfish. Patients were also advised to use an online calculator for the energy (including purine) content of food, which is freely available in Germany (https://www.naehrwerterrechner.de/naehrwerttabelle). It was recommended that purine consumption be limited to 200 mg/day based on the published recommendations of the Technical University of Munich (www.mti.tum.de/sites/default/files/seiten/ernaehrungsempfehlung_gicht_2016.pdf).

In patients with recurrent gout attacks (≥2), additional pharmacologic therapy was initiated based on the ACR guidelines for the management of gout (18) and upon the decision of the treating physician and with the patient’s consent. First choice was given to allopurinol, which was initiated at a dosage of 100 mg/day and titrated to a maximal dosage of 600 mg/day if a minimum target level of serum UA <6 mg/dl was not reached (18). Patients with symptomatic gout or serum UA levels >6 mg/dl who were already receiving treatment with allopurinol at baseline, or those who reported previous intolerability of allopurinol, were treated with febuxostat at a dosage of 80 mg/day, which was titrated up to 120 mg/day to reach the serum UA target level. In addition, 2 patients with contraindications to xanthine oxidase inhibitors were started on treatment with benz bromarone at 25 mg/day, which was titrated to a maximum dosage of 100 mg/day. At baseline, age, sex, and disease duration were recorded for all subjects, and serum UA levels were measured.

**DECT scanning.** All subjects underwent DECT scanning at baseline examination using a Somatom Definition Flash CT scanner (Siemens Healthcare). Follow-up examinations were done an average of 18 months following the initial scan. Scans were performed on the day of clinical and serologic investigation. For scanning, patients were placed in a supine position with dorsal extension of both feet during the examination. Scans were run axially in a caudocranial direction and covered a range of ~150 mm, including both feet and ankles. Regarding the setting of the scanner, tube A was run with Sn140kV/115 ref. mAs and tube B was run with 80kV/210 ref. mAs. DECT images were retrieved with commercial software (Syngo.via). MSU deposits were visualized and color-coded using the Syngo Dual Energy Gout clinical software application.

**Statistical analysis.** The data set was analyzed using IBM SPSS Statistics (version 23). Changes in serum UA level, MSU volume, and MSU score before and after treatment were analyzed by Wilcoxon’s signed rank test. Differences between treatment groups were analyzed by the Kruskal-Wallis test. In the case of significance, Dunn’s post hoc test for pairwise comparisons was performed. Characteristics related to changes in MSU volume were evaluated by Spearman’s rank correlation. Interrater reliability was analyzed using the ICC (absolute agreement; two-way mixed). All tests were 2-tailed, and P values less than or equal to 0.05 were considered significant. Spaghetti plots were created using R (version 3.5.1). In
order to reduce overplotting, small random noise was added to equal y values. Urate volume was displayed logarithmically, and an artificial 0 point was marked with an asterisk. As \( \log(0) \) is not defined, 0.01 was added to all volume measurements.

### RESULTS

**Patient characteristics.** Ninety consecutive patients with gout were screened (Figure 1). Seven patients were excluded because they did not show MSU deposits at the baseline DECT. In the remaining 83 patients, 166 DECT scans of the feet (83 at baseline and 83 at follow-up) were assessed. Of these 83 patients, 16 were female (19.3%) and 67 were male (80.7%), with a mean ± SD age of 59.4 ± 11.4 years (Table 1). The mean ± SD disease duration was 2.5 ± 6.3 years, and the time to follow-up was 18.7 ± 10.8 months. Seventy-seven of the 83 patients received continuous gout treatment between the baseline and follow-up DECT examinations, while 6 patients discontinued treatment on their own decision, i.e. due to noncompliance. Of the 77 patients treated continuously, 24 received lifestyle intervention only, 29 patients were treated with allopurinol (mean dosage 316 mg/day), 22 patients were treated with febuxostat (mean dosage 87 mg/day), and 2 patients were treated with benzbromarone. Age, sex, disease duration, and baseline serum UA levels were comparable among the groups.

Serum UA levels significantly decreased in the entire population (\( P < 0.001 \)) and in the subgroups treated with xanthine

![Figure 1](image_url). Disposition of patients in the prospective longitudinal observational study of dual-energy computed tomography (DECT) findings in patients with gout fulfilling the 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria. Patients received either lifestyle intervention only or additional treatment with allopurinol, febuxostat, or benzbromarone. Baseline and follow-up DECT scans were compared, and decreases in monosodium urate deposit volume and scores were documented.

| Table 1. Demographic and disease-specific parameters and changes in serum UA levels* |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Total (n = 83)† | Lifestyle (n = 24) | Allopurinol (n = 29) | Febuxostat (n = 22) | Benzbromarone (n = 2) |
|----------|-----------------|-----------------|-----------------|-----------------|
| Male, % | 80.7 | 79.2 | 75.9 | 86.4 | 100 |
| Age, years | 59.4 ± 11.4 | 59.0 ± 9.2 | 59.0 ± 12.9 | 61.8 ± 12.6 | 62.5 ± 7.8 |
| Chronic kidney disease, % | 18.3 | 12.5 | 10.3 | 42.9 | 0 |
| GFR, ml/minute | 55.6 ± 10.4 | 59.1 ± 3.1 | 57.7 ± 6.5 | 48.6 ± 16.0 | 53.5 ± 9.2 |
| Disease duration, years | 2.5 ± 6.3 | 0.7 ± 2.0 | 2.0 ± 6.4 | 5.1 ± 8.8 | 1.0 ± 0.0 |
| Months between baseline and follow-up DECT | 18.7 ± 10.8 | 21.6 ± 10.9 | 18.0 ± 9.7 | 14.6 ± 9.0 | 11.4 ± 7.3 |
| Recurrent gout attacks between baseline and follow-up, % | 10.5 | 9.1 | 7.4 | 15.0 | 0 |
| Baseline serum UA, mg/dl | 7.2 ± 2.1 | 7.2 ± 1.7 | 7.0 ± 1.5 | 7.8 ± 3.0 | 5.9 ± 1.1 |
| Follow-up serum UA, mg/dl | 5.8 ± 2.2 | 6.7 ± 1.7 | 5.5 ± 1.8 | 5.1 ± 2.5 | 4.5 ± 0.8 |
| Change in serum UA, mg/dl | 1.4 ± 2.5 | 0.5 ± 2.0 | 1.3 ± 2.1 | 2.7 ± 2.9 | 1.4 ± 0.2 |
| Tophaceous gout, % | 65.1 | 54.2 | 58.6 | 81.8 | 100 |

* Except where indicated otherwise, values are the mean ± SD. UA = uric acid; GFR = glomerular filtration rate; DECT = dual-energy computed tomography.
† Includes 6 patients who discontinued treatment at some time during the follow-up period and whose data are not included within any of the 4 specific treatment groups.
Effects of treatment on the burden of MSU deposits.

Next, we measured the extent of MSU deposits seen on DECT images, by volume measurement and semiquantitative scoring. Both MSU volume and MSU score significantly declined in the overall patient population. Mean ± SD MSU volume declined from 0.33 ± 1.48 to 0.20 ± 1.10 cm³ and semiquantitative score from 4.2 ± 3.2 to 2.5 ± 3.1 (both \( P < 0.001 \)) (Table 2). MSU deposits significantly decreased in the groups receiving lifestyle intervention (MSU volume \( P = 0.007 \); MSU score \( P = 0.001 \)) or treatment with allopurinol (MSU volume and score \( P < 0.001 \)) or febuxostat (MSU volume \( P < 0.001 \); MSU score \( P = 0.001 \)). Absolute change in the extent of MSU deposits was higher in the febuxostat group than in the allopurinol group, which itself was higher than in the lifestyle intervention group. In contrast, patients who discontinued treatment did not show any decline in MSU deposits.

Regarding conversion from presence of MSU deposits to absence of MSU deposits, 58.3%, 41.4%, and 27.3% of patients undergoing lifestyle intervention, those receiving allopurinol treatment, and those receiving febuxostat treatment, respectively, were free of detectable MSU deposits after treatment. The likelihood of MSU absence at follow-up was associated with the baseline MSU burden, but not with the baseline serum UA level or the extent of decrease in serum UA level or other demographic factors (Table 3), indicating that it takes more time to reach complete resolution of MSU deposits if the baseline MSU burden is high.

Table 2. MSU volumes and scores before and after treatment, assessed by dual-energy computed tomography*

|                      | Total (n = 83)† | Lifestyle (n = 24) | Allopurinol (n = 29) | Febuxostat (n = 22) | Benzbromarone (n = 2) |
|----------------------|-----------------|--------------------|----------------------|---------------------|----------------------|
| **Volume-based assessment** |                 |                    |                      |                     |                      |
| Baseline MSU volume, cm³ | 0.33 ± 1.48     | 0.07 ± 0.09        | 0.11 ± 0.15          | 0.99 ± 2.80         | 0.14 ± 0.18          |
| Follow-up MSU volume, cm³ | 0.20 ± 1.10     | 0.05 ± 0.15        | 0.02 ± 0.04          | 0.64 ± 2.09         | 0.04 ± 0.04          |
| Change in MSU volume, cm³ | −0.14 ± 0.41    | −0.02 ± 0.09       | −0.09 ± 0.14         | −0.35 ± 0.74        | −0.11 ± 0.15         |
| Follow-up MSU volume 0 cm³, no. (%) | 34 (41.0) | 14 (58.3) | 12 (41.4) | 6 (27.3) | 0 (0.0) |
| \( P \), baseline vs. follow-up‡ | <0.001 | 0.007 | <0.001 | <0.001 | 0.317 |
| **Score-based assessment** |                 |                    |                      |                     |                      |
| Baseline MSU score, units | 4.2 ± 3.2       | 2.8 ± 2.0          | 3.6 ± 2.8            | 6.4 ± 3.9           | 5.0 ± 4.2            |
| Follow-up MSU score, units | 2.5 ± 3.1       | 1.5 ± 2.3          | 1.7 ± 2.1            | 4.3 ± 4.1           | 4.5 ± 5.0            |
| Change in MSU score, units | −1.7 ± 2.0      | −1.3 ± 1.4         | −1.9 ± 2.0           | −2.1 ± 2.6          | −0.5 ± 0.7           |
| Follow-up MSU score 0 units, no. (%) | 26 (31.3) | 10 (41.7) | 12 (41.4) | 2 (9.1) | 0 (0.0) |
| \( P \), baseline vs. follow-up‡ | <0.001 | 0.001 | <0.001 | 0.001 | 0.317 |

* Except where indicated otherwise, values are the mean ± SD. MSU = monosodium urate.
† Includes 6 patients who discontinued treatment at some time during the follow-up period and whose data are not included within any of the 4 specific treatment groups.
‡ By Wilcoxon’s signed rank test.

Table 3. Characteristics of patients with and those without complete resolution of MSU lesions assessed by DECT*

|                        | Follow-up MSU volume 0 cm³ (n = 34) | Follow-up MSU volume >0 cm³ (n = 49) |
|------------------------|-------------------------------------|--------------------------------------|
| Male, no. (%)          | 24 (70.6)                           | 43 (87.8)                            |
| Age, years             | 62.2 ± 11.2                         | 57.5 ± 11.2                          |
| Disease duration, years| 1.4 ± 5.5                           | 3.4 ± 6.7                            |
| Months between baseline and follow-up DECT | 19.0 ± 10.8               | 18.4 ± 11.0                          |
| Lifestyle intervention, no. (%) | 14 (41.2)                 | 10 (20.4)                            |
| Allopurinol, no. (%)   | 12 (35.3)                           | 17 (34.7)                            |
| Febuxostat, no. (%)    | 6 (17.6)                            | 16 (32.7)                            |
| Benzbromarone, no. (%) | 0 (0.0)                             | 2 (4.1)                              |
| Discontinuation, no. (%)| 2 (5.9)                            | 4 (8.2)                              |
| Baseline MSU volume, cm³ | 0.05 ± 0.06†                       | 0.53 ± 1.90                          |
| Baseline total MSU score | 2.3 ± 1.51                        | 5.6 ± 3.4                            |
| Baseline serum UA, mg/dl | 6.6 ± 1.7                          | 7.6 ± 2.2                            |
| Follow-up serum UA, mg/dl | 5.5 ± 1.7                          | 6.1 ± 2.4                            |
| Change in serum UA, mg/dl | 1.1 ± 2.0                         | 1.6 ± 2.7                            |

* Except where indicated otherwise, values are the mean ± SD. DECT = dual-energy computed tomography; UA = uric acid.
† \( P < 0.05 \) versus patients without complete resolution of monosodium urate (MSU) lesions (volume >0 cm³), by Mann-Whitney U test.
Change in MSU volume was significantly related to baseline MSU volume ($r_S = 0.776$, $P < 0.01$) and baseline MSU score ($r_S = 0.499$, $P < 0.01$). There was a weaker but still significant correlation with the change in serum UA level ($r_S = 0.261$, $P < 0.05$), while there was no correlation with disease duration ($r_S = 0.016$, $P = 0.889$). Intraclass correlation coefficients were $>0.99$ for the total urate score and between 0.95 and 1.0 for the subscores. The SDC for the automated MSU volume measurement was 0.03 cm$^3$. Spaghetti plots and DECT images depicting the decline in MSU deposits are shown in Figure 2.

**Distribution of MSU deposits across anatomic regions.** MSU deposits were most commonly found in the soft tissue (85.5% of all cases), followed by the toes (51.8%), MTP1 joint (47.0%), and the midfoot/ankle region (37.3%) (Table 4). Larger MSU deposits were most frequently found in the soft tissue, especially in the Achilles tendon, with the highest mean subscore (1.52) found in this region. The likelihood that MSU deposits completely dissolved differed among the regions, with 36.1% in soft tissue, 30.1% in the toes, 27.7% in the MTP1 joints, and 13.3% in the midfoot/ankle. New MSU deposits were found in the toes (4.8%), the soft tissues (3.6%), and the MTP1 joint or midfoot/ankle (1.2%). More detailed information on the local distribution of the MSU burden is provided in Table 4.

**DISCUSSION**

Understanding if and how MSU deposits resolve during treatment of gout is of seminal importance, since MSU deposits, as opposed to serum UA levels, are the central pathology in gout. Lowering the serum UA level without any impact on MSU deposits would reflect “laboratory cosmetics” rather than disease modification. Importantly, MSU deposits and serum UA levels are only weakly correlated (21), making it difficult to draw conclusions on the dynamics of MSU deposits by merely assessing serum UA levels. Such a concept suggests that state-of-the-art gout management would need to include the monitoring of resolution of the MSU deposits during treatment. In this longitudinal observational DECT study, we showed that implementation of relevant lifestyle measures and, even more pronounced, continuous treatment with xanthine oxidase inhibitors, lead to regression of MSU deposits. Our data also reveal that longitudinal DECT scanning is sensitive to change and allows monitoring of the regression of MSU deposits during therapeutic intervention. Both the volume and score of deposits significantly decreased during conventional gout treatment, supporting a disease-modifying effect of such intervention.

**DECT is a highly sensitive diagnostic tool that can detect even very small MSU deposits and allows the testing of anatomic sites that cannot be assessed by joint aspiration, ultrasound, or clinical**

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**Figure 2.** Change in monosodium urate (MSU) volume and score in individual patients with gout. Data shown on the spaghetti plots (left) represent the changes in MSU volume and MSU scores between baseline and follow-up. Dual-energy computed tomography images (right) show MSU deposits (arrowheads) in the first metatarsophalangeal joint (MTPJ1), the Achilles tendon, and the midfoot at baseline and the decline in MSU deposits with treatment.
LIFESTYLE INTERVENTION OR CONVENTIONAL URATE-LOWERING THERAPY IN GOUT

In the present longitudinal DECT study, we have now shown that both lifestyle intervention and continuous treatment with xanthine oxidase inhibitors lead to a significant decline in the volumes and the extent of MSU deposits. For patients treated with allopurinol, our data reflect recent findings by Dalbeth et al showing that appropriate dose-escalation of allopurinol treatment reduces MSU deposits. We additionally found that the magnitude of the effect on MSU deposits is higher with xanthine oxidase inhibitor therapy than with lifestyle intervention, even though the interval between the 2 DECT scans was slightly higher in the lifestyle intervention group. However, it is interesting that lifestyle intervention per se also resulted in a consistent and significant reduction in MSU deposits over time. Furthermore, in the limited number of patients with gout who did not comply with treatment and discontinued xanthine oxidase inhibitor therapy and presumably also lifestyle measures, no reduction in MSU deposits was found. These latter data and the observation that the effect on MSU deposits was more pronounced with xanthine oxidase inhibitors than with mere lifestyle measures suggest that adherence to xanthine oxidase inhibitor therapy was good, although no formal surveillance of drug adherence was applied in this study.

Our study also showed that most MSU deposits are localized in soft tissue rather than in the toes or in the ankle joints. These findings highlight the importance of DECT as a diagnostic tool, as these locations are not accessible for joint aspiration. Use of the semiquantitative scoring system also revealed that the regression of MSU deposits is faster in soft tissue than articular lesions, although no formal surveillance of drug adherence was applied in this study.

Table 4. Distribution pattern of MSU crystals

|                      | MTP1 | Toes | Midfoot/ankle | Soft tissue |
|----------------------|------|------|---------------|-------------|
| Positive MSU score at baseline | 39 (47.0) | 43 (51.8) | 31 (37.3) | 71 (85.5) |
| Subscore at baseline, mean ± SD | 0.92 ± 1.2 | 0.92 ± 1.1 | 0.89 ± 1.3 | 1.52 ± 1.1 |
| Dots                  | 17 (20.5) | 22 (26.5) | 7 (8.4) | 40 (48.2) |
| Single deposit        | 7 (8.4) | 9 (10.8) | 5 (6.0) | 7 (8.4) |
| Fused deposits        | 15 (18.1) | 12 (14.5) | 19 (22.9) | 24 (28.9) |
| Positive MSU score at follow-up | 17 (20.5) | 22 (26.5) | 21 (25.3) | 44 (53.0) |
| MSU score 0 at follow-up | 66 (79.5) | 61 (73.5) | 62 (74.7) | 39 (47.0) |
| New deposits          | +1 (1.2) | +4 (4.8) | +1 (1.2) | +3 (3.6) |
| Subscore at follow-up, mean ± SD | 0.43 ± 1.0 | 0.55 ± 1.0 | 0.58 ± 1.1 | 0.95 ± 1.1 |
| Dots                  | 7 (8.4) | 7 (8.4) | 6 (7.2) | 24 (28.9) |
| Single deposit        | 1 (1.2) | 6 (7.2) | 3 (3.6) | 5 (6.0) |
| Fused deposits        | 9 (10.8) | 9 (10.8) | 12 (14.5) | 15 (18.1) |

* Except where indicated otherwise, values are the number (%). MSU = monosodium urate; MTP1 = first metatarsophalangeal joint.
† By Wilcoxon's signed rank test.
that lowering serum UA levels is accompanied by partial regression of the tissue lesions in gout. Conversion from presence to absence of MSU deposits occurs only in some individuals and is more likely if the initial MSU deposit burden is limited. This observation supports data obtained from a study by Dalbeth and colleagues, showing that a substantial proportion of patients treated with allopurinol still have lesions seen on DECT (29). Thus, longer follow-up will be necessary to demonstrate whether a complete resolution of MSU deposits indeed occurs in the majority of patients, if urate-lowering treatment is continuously received.

**AUTHOR CONTRIBUTIONS**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ellmann had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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