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Concise report

Two-year reduction of dual-energy CT urate depositions during a treat-to-target strategy in gout in the NOR-Gout longitudinal study

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Abstract

Objectives. There is a lack of large longitudinal studies of urate deposition measured by dual-energy CT (DECT) during urate lowering therapy (ULT) in people with gout. We explored longitudinal changes in DECT urate depositions during a treat-to-target strategy with ULT in gout.

Methods. Patients with a recent gout flare and serum-urate (sUA) >360 μmol/l attended tight-control visits during escalating ULT. The treatment target was sUA <360 μmol/l, and <300 μmol/l if presence of tophi. A DECT scanner (General Electric Discovery CT750 HD) acquired data from bilateral forefeet and ankles at baseline and after one and two years. Images were scored in known order, using the semi-quantitative Bayat method, by one experienced radiologist who was blinded to serum urate and clinical data. Four regions were scored: the first metatarsophalangeal (MTP1) joint, the other joints of the toes, the ankles and midfeet, and all tendons in the feet and ankles.

Results. DECT was measured at baseline in 187 of 211 patients. The mean (S.D.) serum urate level (μmol/l) decreased from 501 (80) at baseline to 311 (48) at 12 months, and 322 (67) at 24 months. DECT scores at all locations decreased during both the first and the second year (P <0.001 for all comparisons *vs* baseline), both for patients achieving and not achieving the sUA treatment target.

Conclusions. In patients with gout, urate depositions in ankles and feet as measured by DECT decreased both in the first and the second year, when patients were treated using a treat-to-target ULT strategy.

Key words: DECT, deposition, gout, treat to target, urate lowering treatment

CLINICAL SCIENCE

Rheumatology key messages

- Dual-energy CT is a sensitive measure of urate deposition in gout patients.
- A treat-to-target urate lowering strategy reduced urate depositions over 2 years.
- Successful gout management needs to be long-term to reduce crystal depositions in joints and tendons.

Introduction

Gout is a prevalent inflammatory joint disease [1–3] in which hyperuricaemia leads to depositions of monosodium urate crystals in joints and other tissues. A key strategy for effective gout management is the treat-to-target serum urate (sUA) strategy with urate-lowering therapy (ULT) [4, 5]; this approach leads to crystal dissolution, prevention of gout flares and regression of tophi and joint damage.

Dual-energy CT (DECT) is an imaging modality that allows excellent detection of urate depositions in gout [6–8]. A semi-quantitative DECT scoring system for measurement of urate depositions in gout has been developed; this system has high inter-reader reliability, construct validity and feasibility [9]. DECT methodology has been developed mainly using one type of scanner (Siemens). While larger longitudinal

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studies reporting the efficacy of ULT on DECT urate depositions are lacking [10], some studies found reductions in DECT volume or score [11–13] after ULT, which could affect future subsequent gout flare [14].

In this study, we assessed changes in the DECT scoring system over two years in a large patient group from clinical practice.

Methods

Study design and participants

NOR-Gout (Gout in Norway) is a prospective, observational single-centre study in a hospital-based rheumatology clinic [15, 16]. All patients had crystal proven gout and fulfilled the ACR/EULAR classification criteria for gout [17]. They were included after a recent flare with gout, had sUA >360 μmol/l and started ULT with allopurinol or febuxostat with frequent follow-up visits during the first year and a final visit after year 2. During this treat-to-target strategy, ULT was escalated to achieve sUA <360 μmol/l (or <300 μmol/l if clinical tophi were present) as recommended in international guidelines [4]. The study (ACTRN12618001372279) was registered at https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370430. The Norwegian Regional Committee for Medical and Health Research Ethics South East (reference number 2015/990) approved the study and participants gave their written informed consent.

Demographic, clinical and laboratory assessment

All patients were assessed by a study nurse and/or a rheumatologist at baseline, after 1, 2, 3, 6, 9, 12 and 24 months and with additional monthly visits until the sUA target was achieved. Demographics, clinical, laboratory analyses and questionnaires addressing health status were assessed, including joint assessment and clinical subcutaneous tophi.

DECT semi-quantitative scoring system

DECT was performed at baseline and at one and two years. A DECT scanner (General Electric Discovery GE CT750 HD, United States) acquired data from bilateral forefeet and ankles at 80 KW and 140 KV, processed with a GE AW server software with a 2-material decomposition algorithm, which colour codes urate depositions using threshold values: Uric acid-HAP (Hydroxyapatite): 1236,6–1378 and HAP- Uric acid: −5–130. The applied scanner method did not provide volumetric data as is available in other scanners, for example by Siemens.

Images were scored using the semiquantitative Bayat method [9] in known order by an experienced radiologist (T.E.) who was blinded to serum urate and clinical data. Each scan assessed four regions: the first metatarsophalangeal (MTP1) joint, the other joints of the toes, the ankles and midfeet, and tendons in the feet and ankles. Each region was then scored according to the maximum amount of urate depositions observed on visual inspection (0 = no deposits, 1 = dots, 2 = single deposit, 3 = more than one deposit). Common artefacts (nail bed, skin, motion, submillimetre and beam hardening) were excluded from the analysis. A total DECT sum score was derived by adding all values from the four regions, with a maximum score of 12.

DECT images from one patient with decreasing depositions are shown in Supplementary Fig. S1, available at *Rheumatology* online.

Statistics

Descriptive measures of baseline variables are presented using absolute and relative frequency, means (S.D.) and medians with interquartile ranges. Differences between groups were explored by use of independent samples *t* test, Mann–Whitney *U* test, and by the McNemar–Bowker test. Changes in DECT scores over time were explored by paired samples *t* test and Wilcoxon signed-rank test. Statistical analyses based on normal or skewed distribution did not alter the results. As a measure of effect size for we calculated mean change divided by the S.D. of the change for of change in DECT scores. $P < 0.05$ was defined as significant. Calculations were performed with IBM SPSS statistics (version 27).

Results

Patients and laboratory variables

Of 211 patients included in NOR-Gout, 187 patients were recruited for DECT measurement of ankles and feet at baseline, 157 patients at 1 year and 166 patients at 2 years. Mean (S.D.) age in these patients was 56.7 (13.7) years, disease duration 8.1 (7.9) years and 95.3% were males, see baseline characteristics in Supplementary Table S1, available from *Rheumatology* online. After 2 years, all patients measured with DECT at baseline were still receiving ULT, either allopurinol (88%, mean dose 276 mg/d) or febuxostat (12%, mean dose 58 mg/d).

The mean (S.D.) sUA level (μmol/l) decreased from 501 (80) at baseline to 311 (48) at 1 year and 322 (67) at 2 years; the treatment target <360 μmol/l was achieved by 86% at 1 year and 81% at 2 years. The percentage of patients with clinical tophi was 16.6% at baseline, 11.3% at 1 year and 9.1% at 2 years.

Baseline localization and frequencies of depositions

In 21.2–29.9% in each region, depositions were present, most frequently at the MTP1 joint, and depositions were equally distributed between the left and right side (Supplementary Table S2, available at *Rheumatology* online).

Changes in DECT scores

DECT scores at the different regions and sum scores decreased from baseline during the first year and continued to decline during the second year ($P < 0.001$ for

all within-patient comparisons *vs* baseline), displayed as Table 1 and Supplementary Table S3 (available at *Rheumatology* online). Reductions in DECT scores after 1 and 2 years were seen no matter whether patients achieved the sUA target <360 μmol/l or not after year 2. Patients not achieving the 2-year treatment target had an increase in sUA during year 2, but still a reduction in overall DECT score in year 2.

The frequency of depositions improved in all regions during follow-up. At baseline, depositions in MTP1 joints were present in in 41.7% of patients, decreasing to 30.6% after 1, and to 21.1% after 2 years. Corresponding percentages were for toes 33.6–21.5–10.8, for ankles/midfeet 35.8–21.7–13.9 and for tendons 33.6–20.1–13.9.

Patients with clinical tophi at baseline had higher baseline total DECT scores than those without clinical tophi (12.6 *vs* 3.4, $P < 0.001$), but DECT scores were reduced during the first and the second year both in patients with and without baseline tophi (all $P < 0.001$).

Effect sizes for DECT changes

Effect sizes for decrease in DECT depositions at the different locations after 1 and 2 years, and during year 2 (Fig. 1) were moderate (0.52–0.70), and seen over one and two years, and were similar for all locations. They demonstrated reduction of depositions also during the second year of ULT.

Discussion

This is to date the largest prospective DECT study following gout patients in real-life practice over 2 years. Patients received treat-to-target ULT with dose escalation during frequent visits until they achieved sUA < 360 μmol/l (300 μmol/l if presence of tophi). DECT of ankles and feet showed changes in depositions both during the first and the second year, demonstrating continuous structural modification during recommended ULT [4, 5, 18]. Even patients who did not achieve the sUA target at 2 years had a reduction in total DECT scores during year 2, indicating that the tight control schedule with ULT during year 1 had prolonged effects on DECT findings in year 2. DECT urate depositions were, however, still present after 2 years, supporting the need for long-term therapy applying urate lowering drugs.

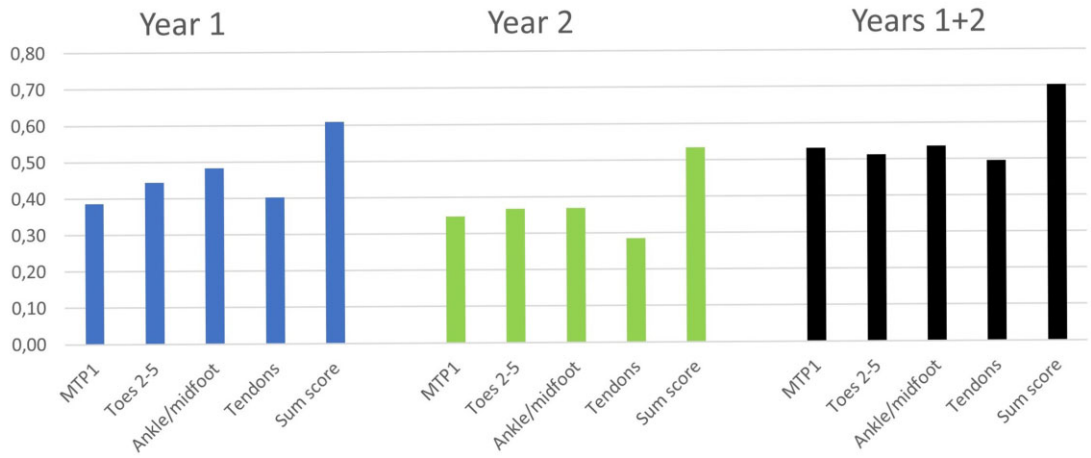
Our study is the first to demonstrate in a non-Siemens scanner the reduction of depositions during ULT and provides further validation for the DECT semi-quantitative scoring system described by Bayat *et al.* [9]. Reductions in depositions were seen at the four joint and tendon sites at a similar rate during the first and second year indicating effect

Table 1 Baseline and follow-up dual-energy CT scores for different locations over 2 years

	Baseline ($n = 187$) mean (S.D.)	1 year ($n = 157$) mean (S.D.)	*P*	2 years ($n = 166$) mean (S.D.)	*P* 2 years *vs* baseline	*P* 2 years *vs* 1 year
All						
MTP1 (0–3)	1.4 (2.0)	1.0 (1.7)	<0.001	0.6 (1.3)	<0.001	<0.001
Toes (0–3)	1.0 (1.8)	0.6 (1.4)	<0.001	0.3 (1.0)	<0.001	<0.001
Ankle/Midfoot (0–3)	1.2 (2.1)	0.7 (1.6)	<0.001	0.3 (1.0)	<0.001	<0.001
Tendons (0–3)	1.0 (1.7)	0.5 (1.2)	<0.001	0.3 (0.8)	<0.001	<0.001
Sum score (0–12)	4.6 (6.4)	2.8 (4.7)	<0.001	1.5 (3.2)	<0.001	<0.001
Target achieved at 2 years ($n = 133$)[a]						
Serum urate (μmol/l)	492 (77)	310 (47)	<0.001	297 (34)	<0.001	0.01
MTP1 (0–3)	1.4 (2.1)	1.0 (1.7)	<0.001	0.6 (1.3)	<0.001	<0.001
Toes (0–3)	1.1 (1.9)	0.5 (1.3)	<0.001	0.3 (1.0)	<0.001	<0.001
Ankle/Midfoot (0–3)	1.3 (2.1)	0.7 (1.6)	<0.001	0.3 (1.0)	<0.001	<0.001
Tendons (0–3)	1.0 (1.7)	0.5 (1.3)	<0.001	0.3 (0.8)	<0.001	<0.01
Sum score (0–12)	4.8 (6.6)	2.7 (4.6)	<0.001	1.4 (3.2)	<0.001	<0.001
Target not achieved at 2 years ($n = 32$)[a]						
Serum urate (μmol/l)	523 (97)	321 (50)	<0.001	426 (69)	<0.001	<0.001
MTP1 (0–3)	1.2 (1.9)	0.8 (1.8)	0.02	0.5 (1.3)	0.001	0.16
Toes (0–3)	1.0 (1.8)	0.9 (1.8)	0.17	0.5 (1.3)	0.02	0.05
Ankle/Midfoot (0–3)	1.1 (2.1)	0.7 (1.7)	0.04	0.5 (1.2)	0.01	0.20
Tendons (0–3)	0.8 (1.4)	0.8 (1.8)	0.07	0.2 (0.6)	0.01	0.08
Sum score (0–12)	4.1 (5.9)	2.8 (5.2)	<0.01	1.8 (3.5)	<0.001	0.03

Paired samples *t* test and independent samples *t* test. [a]All DECT comparisons for all time points between groups 'Target achieved' and 'Target not achieved' were non-significant. DECT: dual-energy CT.

FIG. 1 Effect sizes (mean change divided on S.D.) for the decrease in dual-energy CT sum scores in the first, second and both years of follow-up



sizes around 0.3 and 0.4, and with similar resolution between joint and tendon sites.

In a previous study, a 2-year RCT [11] found volumetric reductions of depositions both in patients achieving and not achieving the sUA target, and our study found that this was the case also when applying the DECT score. In other studies, reduced DECT burden was observed for both volume and semiquantitative score after mean 18 months [12], and in volumetric scores until 24 months follow-up in patients treated with ULT [13]. A 1-year prospective follow-up of patients on stable ULT showed no decline in DECT volumetric scores [19].

One limitation of our study is that the DECT scoring was performed by only one reader, but this reader is an experienced radiologist who scored all images. Prior work has demonstrated good intra-reader agreement using the DECT scoring system [20]. Further, the lack of a control group does not allow causal inferences. In addition, patient recruitment occurred in one study centre, but gout patients met relatively easy access to specialized rheumatology care. Strengths of the study are inclusion of patients with a broad range of disease severity, including many patients without severe disease, high retention of participants over the two-year period, and protocolised approaches to treat-to-target care.

In conclusion, this large prospective follow-up study in gout patients found that treat-to-target ULT over 2 years led to sustained reductions in DECT urate depositions in the feet and ankles during the first and the second year.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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