Urate-lowering therapy (ULT) reduces non-episodic foot pain in patients who fail to meet ACR/EULAR 2015 gout classification criteria: an effect predicted by ultrasound and potential rationale for reclassification

Gout, which is caused by monosodium urate (MSU) deposition within joints in the presence of hyperuricaemia, is now the leading cause of inflammatory arthritis within developed countries.[1 2] Despite recent observations that urate-lowering therapy (ULT) should be considered early to reduce disease chronicity, diagnosis is frequently delayed, leading to suboptimal clinical outcomes.[2 3]

The current American College of Rheumatism (ACR)/European League Against Rheumatism (EULAR) 2015 gout classification entry criterion requires the history of a prior episode of swelling, pain or tenderness of a peripheral joint/bursa before confirmation either through MSU crystal identification in synovial fluid or through achieving a score of ≥8 using a predefined scoring system of radiological, laboratory and clinical features. One such feature, a gout 'episode', is clearly defined both in terms of its intensity (joint erythema, tenderness, reduced/inhibited walking ability) and duration (time to maximal pain from onset <24 hour; resolution to baseline <14 days).[4]

Emerging evidence that the joints of asymptomatic hyperuricaemic individuals contain MSU deposits and that alternative presentations of foot pain occur in hyperuricaemia suggests that preclinical and clinical phases may occur prior to a first episodic gout attack.[5 6] This case–control study evaluated urate deposition in hyperuricaemic individuals not fulfilling the current gout classification criteria, as well as a potential therapeutic role for ULT.

Following informed consent, hyperuricaemic individuals with persistent, non-episodic foot pain (n=16, mean±SE, pain duration 28±8.7 months), not fulfilling ACR/EULAR 2015 gout classification criteria, were compared with asymptomatic hyperuricaemic controls (n=15, online supplementary table S1). Ultrasound (US) of bilateral first metatarsophalangeal joints and features of MSU deposition including double contour (DC) sign, tophus and juxta-articular erosion were recorded. Cases only were treated with febuxostat 80 mg once daily for 3 months. Serum urate, 24 hours and 7 day visual analogue score (VAS) 0–100 mm pain scales and the Manchester Foot Pain and Disability Index (MFPDI) were recorded before treatment and after 1 and 3 months.[7] Statistical analysis was performed using SPSS V.25 software, mean and SE data shown.

DC sign, erosion and tophus occurred in 44%, 37% and 37% of cases, respectively (figure 1). No US features of gout occurred in controls. No significant difference was seen in baseline serum urate between cases (450±18 mg/dL) versus controls (426±7; p=NS). Serum urate in cases fell at 1 month (200±18; p<0.001) and 3 months (223±28; p<0.001). For cases, baseline 24-hour pain VAS (65±4.9) reduced at 1 month (41±6.6; p=0.001) and 3 months (33±7.2; p<0.001) of ULT. The 7-day pain VAS (70±4.7) decreased at 1 month (44±7.1; p<0.001) and 3 months (38±8; P<0.001). MFPDI (25±2.1) decreased at 1 month (21±2.9; p=0.019) and 3 months (17±2.8; p=012). When cases were grouped according to the presence (n=7) or absence (n=9) of DC sign on baseline US, no differences were observed for baseline pain scores (figure 2). Following ULT therapy, however, 24-hour pain VAS were significantly lower in DC positive patients at 1 month (26±8.4 DC positive vs 52±8.1 DC negative; p=0.046) and 3 months (14.3±4.2 vs 49±9.8; p=0.009). The 7-day pain VAS were significantly lower in DC positive patients at 1 month (27±7.6 vs 57±9; p=0.011) and 3 months (17.7±6.4 vs 56±10.6; p=0.01). No significant differences between DC positive and DC negative patients were seen in MFPDI or serum urate at 1 or 3 months of ULT.

These findings indicate that persistent, non-episodic foot pain in hyperuricaemia is both associated with US features of MSU deposition and is responsive to ULT. Symptomatic hyperuricaemia occurring prior to episodic gout therefore represents an

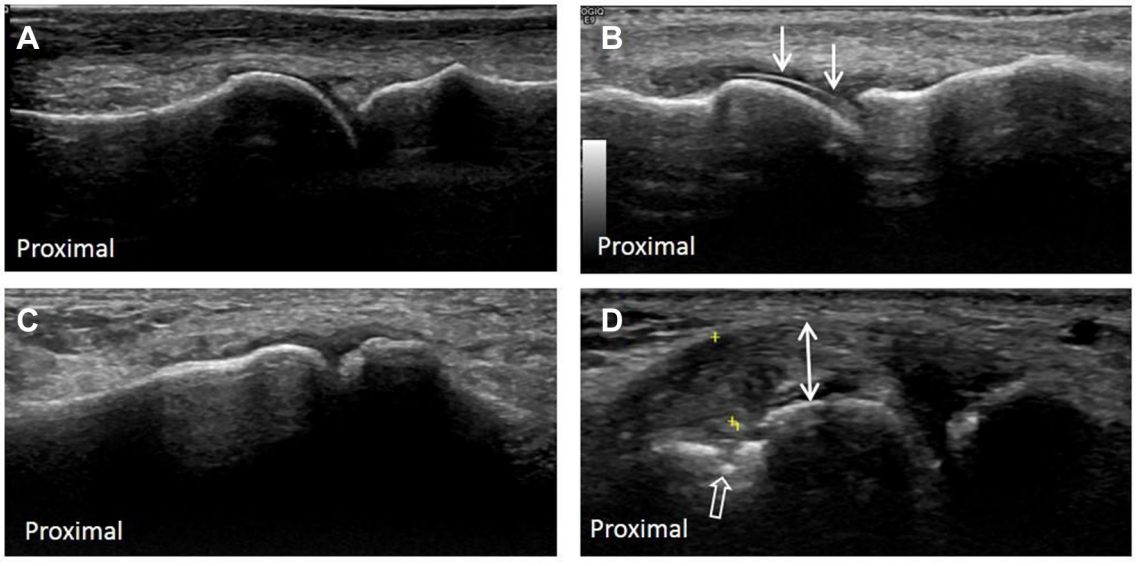

Figure 1 Ultrasound features in patients with hyperuricaemia. Dorsal longitudinal ultrasound of first metatarsophalangeal joints (MTP1) in (A) isolated hyperuricaemia and (B) hyperuricaemia with non-specific foot pain. The presence of double contour sign due to articular cartilage monosodium urate deposition (solid arrows) is shown in (C). Medial longitudinal ultrasound of MTP1 in (C) isolated hyperuricaemia and (D) hyperuricaemia with non-specific foot pain. The presence of tophus (double-headed arrow) and juxta-articular erosion (open arrow) over the medial surface of the first metatarsal is shown in (D). Greyscale images obtained using LogiqE9 at 15 MHz.

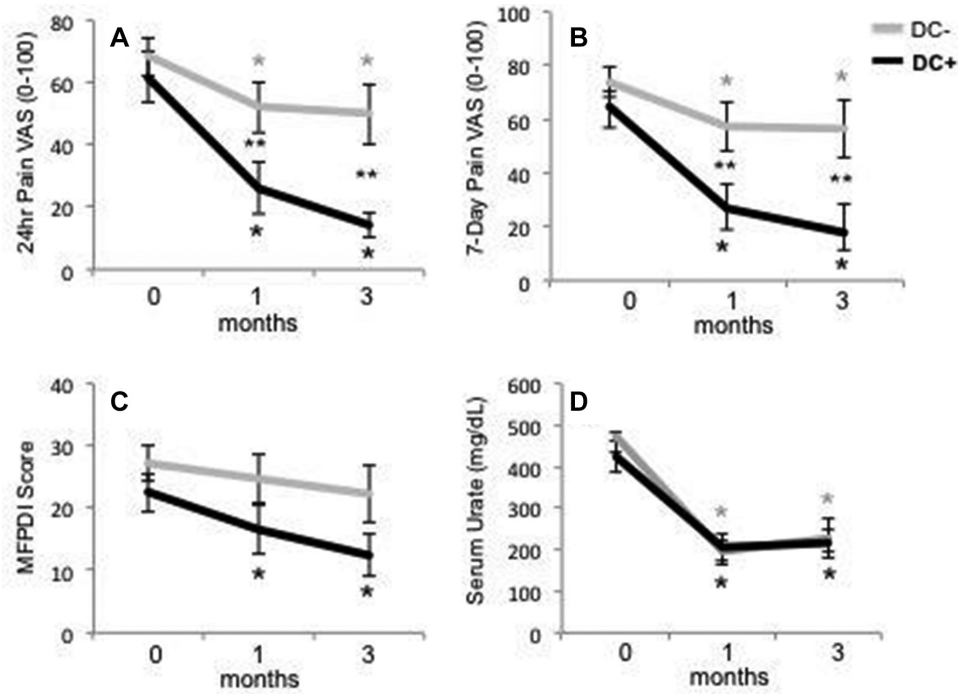

Figure 2 Baseline double contour (DC) sign is associated with a greater reduction in non-specific foot pain at 1 and 3 months. Patient reported (A) 24-hour pain visual analogue score (VAS) (0–100 mm), (B) 7-day pain VAS (0–100 mm), (C) Manchester Foot Pain and Disability Scores (MFPDI) and (D) serum urate concentration (mg/dL) at 0–3 months compared between patients with baseline positive DC sign (black line, n=7) or negative DC sign (grey line, n=9). Mean and SE values shown.*P<0.05, significant difference compared with baseline, paired t-test. **P<0.05 significant differences between groups, independent samples t-test.

earlier or alternative disease presentation. Changes to the ACR/EULAR classification criteria to include non-episodic foot pain in the presence of US features of gout may increase the sensitivity of disease classification at an early stage, leading to improved future treatment strategies and long-term outcomes.

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Contributors YA obtained informed consent from research participants, participated in follow-up visits and co-wrote this article. RM designed the study, performed the statistical analysis and wrote the article. YA and RM both performed baseline ultrasounds on all cases to reach consensus on the findings. DG assisted with patient recruitment. RF obtained baseline patient data. GB provided access to and performed serum urate analysis. DK provided mentorship on the acquisition of ultrasound images for this study. RM is responsible for the overall content as guarantor.

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