



Review

Imaging Follow-Up of MSU Crystal Depletion

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Abstract: Imaging modalities such as ultrasonography (US) and dual-energy computed tomography (DECT) have been recognized for their abilities to detect monosodium urate (MSU) crystals. The main described features of gout detected by DECT (tophus) or US (tophus, double contour [DC] sign and aggregates) are very specific for the diagnosis of gout, but the impact of imaging on the follow-up of MSU deposits is not well known. US and DECT allow for visualization of the disappearance of MSU crystals under adequate urate-lowering therapy (ULT). An OMERACT US score and a DECT urate score have been described. The dissolution of the DC sign is detectable on US after 3 months, whereas a decreased size or volume in tophus can be observed on US or DECT after 6 months of ULT. Serum urate level decrease is associated with a reduction in MSU crystal deposition. Finally, the risk of gout flare is associated with the baseline MSU burden and with the degree of dissolution of crystal deposition. All these data confirm that imaging could be useful in managing gout, even if its exact place in routine practice remains unclear.

Keywords: gout; urate-lowering therapy; imaging; ultrasonography; dual-energy computed tomography



Citation: Ottaviani, S. Imaging Follow-Up of MSU Crystal Depletion. *Gout Urate Cryst. Depos. Dis.* **2024**, *2*, 34–44. <https://doi.org/10.3390/gucdd2010003>

Academic Editor: John D. FitzGerald

Received: 13 September 2023

Revised: 10 January 2024

Accepted: 17 January 2024

Published: 24 January 2024



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1. Introduction

Gout is a joint disease characterized by the deposition of monosodium urate (MSU) crystals in joints, tendons and/or soft tissues secondary to chronic hyperuricemia [1]. Experts from the gout, hyperuricemia and crystal-associated disease network previously defined gout as MSU crystal deposition associated with at least the following clinical manifestations: flares, persistent arthritis or tophi [2]. During the first disease stages, gout is characterized by recurrent self-limited flares. In the absence of or insufficiency of treatment, chronic arthritis with structural damages and tophi can appear, leading to disabilities and an impaired quality of life [3,4]. An increase in hospitalizations for gout has been observed in some countries [5,6]. Moreover, gout patients are at increased risk of cardiovascular disease and mortality [7], which is associated with the burden of MSU crystal deposition [8]. All these complications of gout can be reduced with appropriate treatment. The management of gout includes treating flares with colchicine, non-steroidal anti-inflammatory drugs or corticosteroids; preventing flares with colchicine; and dissolving MSU crystals with adequate urate-lowering therapy (ULT). The urate target depends on the guidelines of each country but is usually <0.30 mmol/L [9] or 0.36 mmol/L [10,11].

Although gout is a curable disorder, the disease is not well managed worldwide because of several factors: poor adherence to ULT, low or inefficient prescription of ULT by physicians [12], as well as an occasionally difficult diagnosis. Indeed, the gold standard for gout diagnosis is the identification of MSU crystals on synovial fluid analysis or in tophus aspiration in the absence of joint fluid. In the absence of joint effusion or tophus, the diagnosis of gout can be challenging. In such cases, imaging to detect MSU crystal deposition is recommended [13]. Because plain radiographs have limited value for gout diagnosis, the main imaging modalities are ultrasonography (US) and dual-energy CT (DECT).

In this review, we analyze the relevance of using imaging for managing gout, particularly the follow-up of ULT.

2. The Imaging Features of Gout

2.1. Ultrasonography

Several US features of gout have been described [14]. Non-specific signs including synovitis, joint effusion, synovial hypertrophy and erosions can be observed but have a low utility for diagnosis. Three specific features of gout need to be searched for to establish the gout diagnosis: the double contour (DC) sign, tophus and aggregates. The prevalence of these features varies depending on the stage of disease and the joint location. These US features have a high specificity (>90%) [15–19]. Despite this high specificity for gout, the same US detection of the DC sign can sometimes occur in calcium pyrophosphate disease (CPPD), for a pseudo-DC sign [20]. A recent study provided an anatomic explanation for this pseudo-DC sign [21]. On the dissection of elbows of CPPD patients, calcifications were present within the annular ligament but not the surface of the hyaline cartilage of the radial head. On US dynamic scanning, the pseudo-DC sign appears mobile and dissociated with the cartilage, whereas in gouty patients, the DC sign follows the movement of the cartilage. The importance of the dynamic evaluation of the DC sign was confirmed in another study. The addition of dynamic scanning assessment to static assessment increased the specificity of the DC sign for the diagnosis of gout, without a loss of sensitivity [22].

The outcome measures in rheumatology (OMERACT) US group validated a consensus-based definition of these US features of gout [23]. The interobserver reliability was good for tophus and DC but only fair to moderate for aggregates [24]. The OMERACT group recently proposed a new definition of aggregates, which resulted in increased interobserver reliability [25]. The definitions of the features are as follows:

- Double contour sign: “abnormal hyperechoic band over the superficial margin of the anechoic cartilage, independent of the angle of insonation and which may be irregular, continuous, or intermittent and can distinguished from the cartilage interface sign” (Figure 1A,C). The DC sign must be searched preferentially at the first metatarsophalangeal joints (MTP1s), the trochlear cartilage of knees (suprapatellar plane in maximal flexion) and the talar cartilage.
- Tophus: “a circumscribed, inhomogenous, hyperechoic and/or hypoechoic aggregation (which may or may not generate a posterior acoustic shadow)” (Figure 1E,F). The main locations for detecting US tophus are the MTP1s and quadriceps and patellar tendons.
- Aggregates: “bright hyperechoic, isolated spots too small to fulfil the tophus definition and characterized by maintaining their high degree of reflectivity when the insonation angle is changed”.

2.2. Dual-Energy CT

DECT relies on the combined attenuation properties of two X-ray beams of different energies projected at right angles [26]. The obtained difference in attenuation of the analyzed tissue allows for distinguishing urate and calcium in soft tissues surrounding bone. MSU crystals appear as color-coded images (Figure 2A). The ability of DECT to detect soft-tissue MSU crystal deposition is well known. DECT allows for the visualization of MSU crystal deposition in the vessels, kidneys and spine but also provides an automatic calculation of MSU crystal volume that could be useful for quantitative analysis. As for US, DECT had an important weight in the American College of Rheumatology/European Alliance of Associations for Rheumatology gout classification [27]. Some studies suggest that the accuracy for gout diagnosis by DECT differs by disease duration. Sensitivity is lower in patients with recent-onset disease. DECT is able to detect all MSU crystal depositions, except for the DC sign. This could be related to the required minimum amount of MSU deposits in tophi that could be detected by US (~50–100 µm) and DECT (~250 µm) [28,29]. Some data suggest a correlation between MSU burden and renal [30] or cardiovascular complications [8]. The overall sensitivity of DECT in the gout diagnosis ranges from 71% to 97% and specificity 84% to 95% [13].

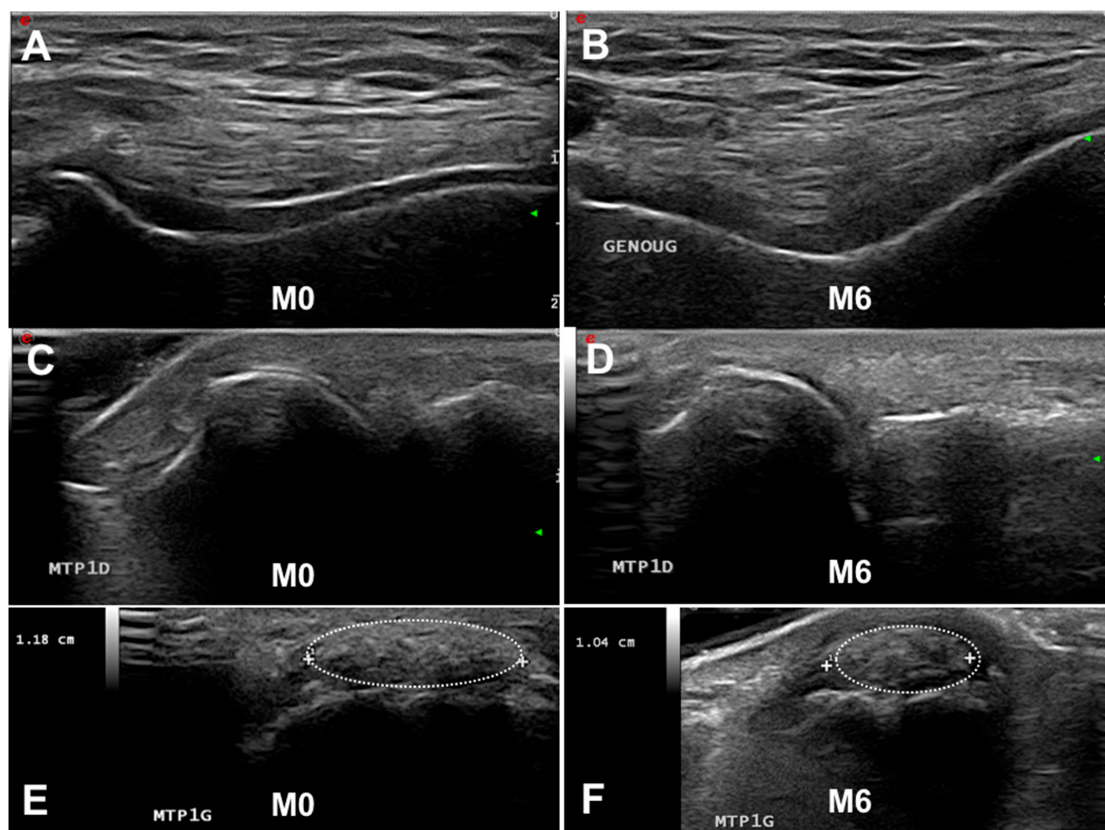


Figure 1. Follow-up of ultrasonography (US) and dual-energy CT gout lesions. (A,C,E). Baseline US features of gout with a double contour (DC) sign on the knee (A) and first metatarsophalangeal joints (MTP1s) (C) and a tophus on the MTP1s ((E), dotted oval). After 6 months of urate-lowering therapy, the disappearance of the DC sign (B,D) and slow decrease in tophus volume (F). M, month.

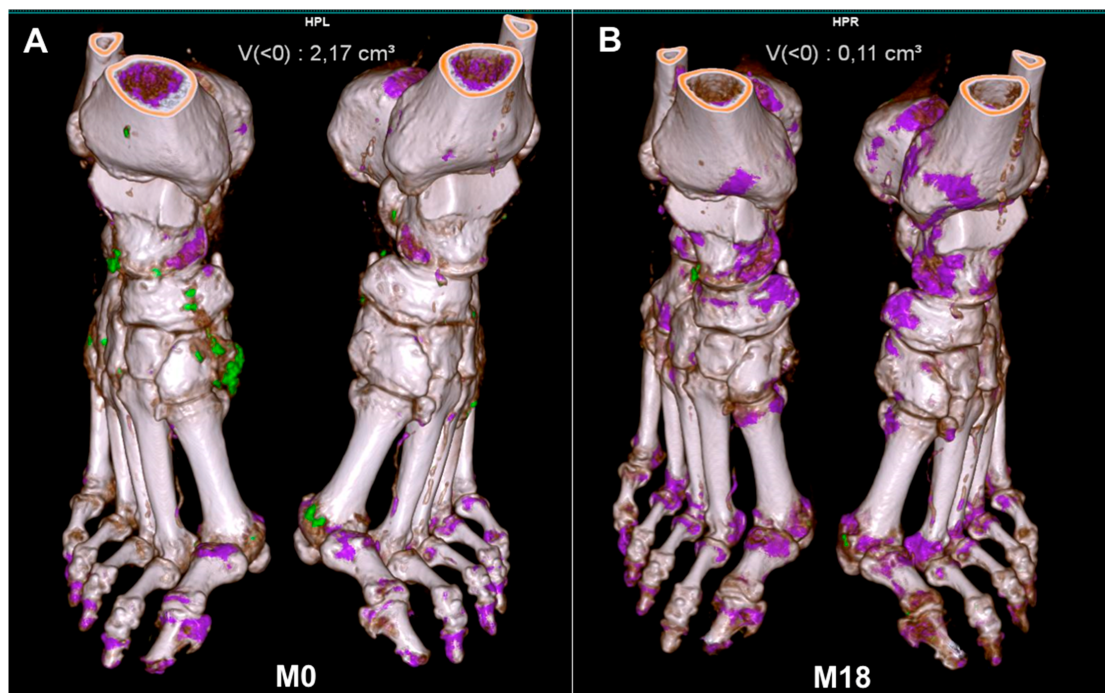


Figure 2. Follow-up of dual-energy CT-detected gout lesions. Disappearance of gout deposits (in green) after 18 months of urate-lowering therapy. M, month. (A): 0 months; (B): 18 months.

3. Scoring Imaging Features of Gout

The ability of the two imaging modalities to detect MSU crystals suggests that the follow-up of MSU crystal dissolution under ULT is possible. However, the physician needs a practical imaging score allowing for intra-individual follow-up, as well as homogenization of the evaluation. Other unresolved questions are which and how many joints to analyze.

3.1. Ultrasonography

3.1.1. Scoring

Multiple scores have been used to monitor gout lesions during ULT. Most studies used a binary approach (present or not) for the DC sign. Regarding tophus scoring, a binary approach or measuring the size was most often used. The OMERACT initially validated the binary score for DC, tophus and aggregates for the follow-up of gout lesions [31]. Hammer et al. proposed a semi-quantitative score [32], which was incorporated in the OMERACT score and validated by the group [25]. For this score, the DC sign, tophus and aggregates are assessed according to OMERACT definitions. Each lesion is classified into four categories with scores as follows: 0 = absent; 1 = possible, 2 = definite but minimal and 3 = definite and severe.

The intra-reader reliability for the three gout lesions was >90%, but the inter-observer reliability was 0.61, 0.63 and 0.67 for aggregates, the DC sign and tophus, respectively [25]. The OMERACT group proposed scoring aggregates only when patients also had other US features of gout, thus emphasizing that aggregates are non-specific lesions of gout.

Of note, the benefit of the US monitoring of gout lesions in clinical practice has not been demonstrated. There is no study suggesting that such a US follow-up of gout decision might help the clinician change or stop ULT.

3.1.2. Which Joint to Analyze

As detailed in Table 1, the most-used sites for US analysis are the knees (cartilage and tendons) and MTP1s. Indeed, in clinical practice, these joints are the most affected, although any joints or the spine could also be affected [33,34]. A previous study evaluated by US the prevalence of tophus and the DC sign on 10 joints (MTP1-2, knees and MCP2-3). The frequency of the DC sign and tophus in MTPs, knees and MCPs was 67% and 74%, 57% and 42%, and 21% and 22%, respectively [14]. The OMERACT NOR-gout study assessed 28 joints and 26 tendons [32]. The DC sign and US tophus were mostly found in MTP1s. However, in clinical practice, screening a large number of locations is time-consuming. Some studies assessed the knees and MTP1s for the DC sign and measured the larger tophus as the index tophus, thus avoiding time-consuming US evaluation [35–37]. The Naredo et al. study used US analysis of 26 joints, 6 bursae, 8 tendons and 4 ligaments in patients with gout and controls [38]. The presence of intratendinous or intraarticular aggregates and the DC sign was recorded. The most involved joints for intraarticular aggregates were MTP1 and radiocarpal joints. Tendon abnormalities were most frequently found in the patellar (60%) and triceps tendon (42%), and the MTP1s were the main location for the DC sign. The combined assessment of one joint (radiocarpal joint), two tendons (patellar and triceps tendons) and three hyaline cartilages (MTP1, talar and femoral condyle cartilages) had the best balance between sensitivity (85%) and specificity (83%) [38]. Recently, Cipolletta et al. evaluated a targeted US protocol for the diagnosis of crystal diseases [39]. Patients with acute mono/oligoarthritis underwent a systematic US scanning protocol: MTP1s, ankles, knees, hip, shoulders, elbows, MCP2s and hips, searching for the DC sign, tophus or CPP deposits. The US assessment of two joints bilaterally (knees and MTPs for gout, wrists and knees for CPPD) and the targeted joints had an excellent sensitivity and specificity [39].

Table 1. Ultrasonography studies with follow-up of monosodium urate (MSU) crystal deposition.

References	No. of Patients	Follow-Up	Analyzed US Features of Gout	Scoring System	Location	Results	Correlation with Urate Serum Level
[37]	22	12 months	Tophus	Tophus size	Knee, ankle	↓ Tophus size	Yes
[18]	5	7–18 months	DC sign	Binary	MCP2, Knee MTP1	Disappearance of DC sign (80% patients)	Yes
[36]	16	6 months	DC sign	Binary	Knee, MTP1	Disappearance of DC sign (75% patients)	Yes
			Tophus	Index tophus size	Knee, MTP1	↓ Tophus size (75% patients)	Yes
[40]	23	24 months	DC sign	Binary	Knee, MTP1	↓ Number of DC signs	Yes
			Tophus	Binary	Knee, MTP1, patellar tendon	↓ Number of tophus (except patellar tendon)	No
[35]	79	6 months	DC sign	Binary	Knee, MTP1	↓ Number of DC signs	Yes
			Tophus	Index tophus size	Knee, MTP1	↓ Tophus size	M3: No M6: Yes
[32]	209	12 months	DC sign	Semi-quantitative (0–3)	Wrist, knee, MTP1, MCP2	↓ DC sum score (4.3–1.3)	Yes
			Tophus		Wrist, knee, MTP1, MCP2 Achilles, triceps tendons	↓ Tophus sum score (6.5–3.8)	No
			Aggregates		Wrist, knee, MTP1, MCP2	↓ Aggregates sum score (9.3–6.7)	No
[31]	50	6 months	DC sign	Binary	28 joints and 26 tendons:	↓ DC sum score (3.2–1.3)	Yes
			Tophus	Binary	MCP1–5, wrist, elbow, MTP1–5,	↓ Tophus sum score (2.7–1.8)	No
			Aggregates	Binary	tibiotalar, knee, tendons	↓ Aggregates sum score (6.1–5.0)	No
			Erosion	Binary	(triceps, quadriceps, patellar, Achilles, finger extensors, peroneus, tibial posterior)	No decrease in erosion score	No

DC, double contour; MCP1–5, metacarpophalangeal joints 1–5; MTP1s, first metatarsophalangeal joints.

3.2. Dual-Energy CT

3.2.1. Scoring

As seen below, DECT cannot detect a DC sign, but its ability to measure the tophus volume allows for a quantitative measure of the tophus. Thus, most studies used the quantification of tophus volume as a primary criterion. A semi-quantitative score (DECT urate score) was proposed in 2016 by Bayat et al. [41]. This score included four locations of MSU crystal deposits: MTP1s, toes (proximal and distal interphalangeal joints, metacarpophalangeal joints 2–5), midfoot/ankle and soft tissue. MSU crystal deposition was quantified in each location as follows: 0 = no deposits, 1 = single deposit < 2 mm, 2 = single deposit > 2 mm and 3 = fused deposits.

The scores for each region were added to produce a score range of 0–12. The DECT urate score validated the OMERACT filter, and the inter-reader intraclass correlation coefficient was 0.98, with very high correlation between the score and volume quantification.

DECT also allows for quantifying urate volume and bone erosion. In a recent study, Dalbeth et al. associated DECT measurement of the urate volume in both feet with a semi-quantitative assessment of bone erosions [42]. The authors used the gout CT bone erosion scoring system to analyze seven bones: MTP1 head, 2nd–4th MTP base, cuboid, middle cuneiform and distal tibia. Each site was scored by using a semi-quantitative scale (0–10 according to the percentage of bone involvement).

3.2.2. Which Joint to Analyze

Because gout deposits mainly involve feet, most studies using DECT analyzed this region. Although US allows for multiple joint analysis, DECT is often restricted to one region. However, DECT allows for measuring all tophus occurrences in one region, which is more difficult with US. Moreover, measuring the tophus with US can be imprecise. Indeed, DECT only visualizes MSU crystals, whereas US visualizes the tophus and the cellular inflammatory processes around the tophus, for an approximate measure [43].

4. The Ability of Imaging to Visualize the Dissolution of MSU Crystal Deposition
4.1. Ultrasonography

US is able to visualize the disappearance of MSU crystals. Table 1 summarizes the main results of studies on this subject. Perez-Ruiz et al. first demonstrated that measuring tophus size by US was possible and fulfilled the OMERACT filter [37]. Other studies suggested that under efficient ULT, the DC sign could disappear [36,44] and the number of US-detected tophi might decrease [40]. Larger studies confirmed that the decrease in tophus volume and the number of DC signs was observable by US whatever the score used for measurement (OMERACT, tophus size, binary approach) [31,32,35]. Of note, the dissolution of the DC sign is detectable after 3 months of ULT, whereas the decrease in tophus size is observed after at least 6 months [35]. Most studies found a correlation between the decrease in serum urate level and dissolution of the DC sign but with discrepancies between studies in the correlation between the serum urate level and tophus size measured by US. These data suggested that (1) US is an interesting imaging modality for MSU deposition follow-up, (2) the DC sign represents an early sign of ULT efficacy (Figure 1A–D), and (3) the decrease in tophus size could be a late sign of MSU crystal dissolution (Figure 1C,D).

4.2. DECT

With its ability to detect MSU deposition and to automatically calculate the volume of the tophus, DECT seems a good imaging technique for MSU crystal follow-up (Table 2). As detailed in Table 2, all studies analyzed the tophus volume at the feet [42,45–49]. Sun et al. also used a semiquantitative approach with the quantification of small and large MSU crystals. Two studies used the DECT urate score (described below) [45,48]. Whatever the score used to quantify gout lesions, all DECT studies found a decrease in MSU crystal deposition under ULT. Of note, this decrease was correlated with a decrease in serum urate level only in ULT-naïve patients [42,48,49] or in patients not reaching the target serum urate level and switching to pegloticase [47]. Patients not reaching the serum urate level target (<0.36 mmol/L) did not show a reduced DECT-detected urate volume [42,48]. Laurent et al. demonstrated that gouty patients reaching the <0.30 mmol/L SU target showed more extensive and rapid dissolution of MSU deposits than those reaching the <0.36 mmol/L target [50]. Only one study did not find any correlation between the change in tophus volume and serum urate level, but those patients were already under ULT [46]. Recently, Dalbeth et al. reported two gouty patients receiving pegloticase and methotrexate [51]. Serial DECT revealed the rapid depletion of MSU deposits associated with bone erosion remodeling. These data suggest that DECT is an appropriate imaging modality for monitoring MSU crystal deposition (Figure 2) but also for bone remodeling evaluation.

Table 2. Dual-energy CT (DECT) studies with follow-up of MSU crystal deposition.

References	No. of Patients	Follow-Up	ULT-Naïve at Baseline	Scoring System	Location of DECT Analysis	Results	Correlation with Urate Serum Variation
[46]	73	12 months	No	Tophus volume	Feet	↓ Volume of 0.01 cm ³	No
[47]	10	13.3 weeks	Yes (switch to pegloticase)	Tophus volume	Feet (n = 10) Hands (n = 2)	↓ Volume of 74%	Yes
[48]	83	18 months	Yes	Tophus volume	Feet	↓ Volume (0.33–0.2 cm ³)	Yes
				DECT urate score		↓ Score (4.2–2.5)	Yes
[49]	44	6–24 months	Yes	Number of crystals < or >3 mm	Feet	↓ Number of crystals	Yes
				Maximal tophus volume		↓ Maximal volume (3.5–2.7 cm ³)	Yes
[42]	87	24 months	Yes	Index tophus volume	Feet	↓ Volume	Yes
[45]	187	24 months	Yes	DECT urate score	feet	↓ Score (4.6–1.5)	Yes

MSU, monosodium urate.

5. The Impact of Imaging on Relapse

5.1. Ultrasonography

In the 2-year NOR-gout study [45], MSU deposits were measured by DECT but also by US with the semi-quantitative score developed by Hammer et al. (see below) [32]. Colchicine was given for 3–6 months to prevent relapse. The sum-score at baseline was associated with the risk of flare after 9 months of ULT and up to 2 years [45]. Another study evaluated the risk of flare according to the MSU burden evaluated by US [52]. In this 1-year study, 71 patients with gout who had at least 6 months of stable ULT underwent US of the knees, elbows, MTP1s, wrists and second metacarpophalangeal joints. MSU crystal deposits (aggregates, the DC sign and tophus) were assessed with a binary score, with the calculation of a sum-score. Baseline US findings were independent predictors of gout flare over 12 months. The multicenter 1-year USEFUL-2 study [53] used another approach: 79 gouty patients starting ULT were followed by US (months 0, 6 and 12), with quantification of the number of joints with the DC sign and tophus but also the measurement of tophus size. Colchicine was given during the first 6 months and then stopped. The primary outcome of the second phase of the study was the proportion of patients experiencing a relapse between Months 6 and 12. The probability of relapse during this period was increased for patients with a decrease in tophus size < 50%. Finally, in a 12-month study, Cipolletta et al. found that US estimation of the MSU burden before initiating ULT could predict the fulfillment of the 2016 remission criteria for gout [54]. These data suggest that the duration of flare prophylaxis could be guided by changes in US-measured tophus size and that the ability to achieve remission can be affected by the initial amount of MSU deposits.

5.2. Dual-Energy CT

Some studies measured the impact of the MSU burden measured by DECT. In a 12-month longitudinal study, Pascart et al. compared the MSU burden measured by DECT and US of 78 gouty patients according to the occurrence of flare during this period [55]. The risk of flare was not associated with the number of joints with the DC sign at baseline but was associated with the DECT-detected MSU volume of the feet. With each 1-cm³ increase in MSU volume, the risk of flare was increased two-fold at 6 months [55]. Another study did not find any association between gout flare and DECT findings at 1 year but rather after 2 years [42]. In the treat-to-target NOR-gout study, the DECT urate score at baseline predicted flare after 9 months of ULT and up to 2 years [45]. Regarding the change in MSU crystal deposition measured by DECT and risk of flare, Hammer et al. published the results of the US and DECT assessment in the 2-year NOR-gout study that had been communicated at the 2023 EULAR congress. Patients experiencing flares had higher baseline US and DECT scores. US and DECT scores decreased in parallel during follow-up, and baseline DECT depositions predicted flare at 3 and 12 months [56].

6. Perspectives

Thus, imaging is playing an important role in the management of gout. US and DECT can detect MSU deposition with great sensitivity and specificity. The change in the US- or DECT-detected features of gout under ULT is well associated with urate level changes. The advantages and limitations of each imaging modality are summarized in Table 3. The main advantage of US is its availability. It is an inexpensive exam without irradiation that allows for full-body analysis and a dynamic approach. US features of gout are quite specific, even if some false-positive results in CPPD are possible (pseudo-DC sign). Other limitations are the inability to analyze some sites such as the spine or inaccessible ligaments and only a semiquantitative estimation of urate burden. In contrast, DECT allows for a direct quantification of MSU burden and analysis of spine or other inaccessible structures. However, its feasibility in clinical practice seems less than with US and the availability is limited. DECT analysis is limited to one site and the cost varies depending on the

country, but it is higher than with US. Thus, the choice of imaging modality depends on all these variables.

Table 3. Advantages and limitations of US and DECT.

	Ultrasonography	DECT
Advantages	Availability Cost Feasibility in clinical practice Possible whole-body assessment No irradiation Good sensibility to changes Associated with changes in serum urate level	Good sensibility to change Associated with changes in serum urate level Direct quantification of urate volume Able to analyze bone erosion Able to analyze spine
Limitations	Operator-dependent Some sites are not accessible (e.g., spine) False positive results: pseudo-DC sign Semi-quantitative measure of urate deposition	Availability Cost Feasibility in clinical practice Irradiation One analyzed site False positive results (e.g., nail artefact)

Although imaging is a sensitive tool for quantifying MSU deposits under ULT, improved management of gout with systematic imaging follow-up has not been demonstrated as compared with classical follow-up (blood tests and clinical screening). In rheumatoid arthritis studies, systematic US follow-up failed to demonstrate a better rate of remission than usual management [57,58]. The scanning protocol for US varied according to the studies. A clear imaging approach is mandatory for routine practice. In this sense, the EULAR recommendations for the use of imaging in gout will soon be proposed. Finally, the close monitoring of urate load change could have some benefit of patient education. The absence of a decrease in gout deposits might reflect a low adherence to ULT. In some patients, ULT could be taken with irregularity and the available SU level may not be reflecting the exact urate load. Of those, the determination of urate load or slow decrease in the tophus size might help the physician to detect low adherence. Thus, the ability to visualize the dissolution of crystal deposits might help gouty patients to better understand their disease and improve their adherence to ULT.

7. Conclusions

DECT and US are performant imaging modalities allowing for visualizing changes in MSU crystal deposition. With US, the number of joints with the DC sign and measuring the index tophus volume seem the best features to follow. DECT is the modality of choice for measuring the tophus volume at the feet or calculating the urate score for quantifying gout lesions. The change in gout lesions under ULT measured by US and DECT seem to be correlated with the change in the serum urate level, the DC sign being the earlier gout lesion to disappear. Additionally, the risk of relapse is associated with the baseline MSU burden or the degree of change in gout lesions. All these data confirm that imaging could be useful in managing gout even if its exact place in routine practice remains unclear.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The author thanks Laura Smales for copyediting.

Conflicts of Interest: The author declares no conflicts of interest.

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