Diagnostic accuracy of dual-energy computed tomography and joint aspiration: a prospective study in patients with suspected gouty arthritis

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Abstract

Objective

To validate the diagnostic benefit of dual-energy computed tomography (DECT) and synovial fluid aspiration in suspected gout.

Methods

A total of 43 patients with suspected gout underwent aspiration and DECT (320-row CT; Canon Medical Systems, Japan). The patients were assessed (gout vs. non-gout) based on the 2015 ACR/EULAR gout classification criteria using clinical and laboratory findings. The results were analysed by comparing two scenarios using McNemar test:
Scenario A: ACR/EULAR criteria, followed by DECT results and aspiration findings.
Scenario B: ACR/EULAR criteria, followed by aspiration and DECT results.

Results

15/43 patients (34.9%) were positive for MSU crystals, and 16/43 patients (37.2%) for gouty tophi (DECT). 26/43 patients (60.5%) were diagnosed with gout and fulfilled the ACR/EULAR criteria. The diagnostic performance of either synovial fluid aspiration or DECT was similar with sensitivity of 58% and specificity of 100% and 94%, respectively. Combination of both modalities (at least one of them positive), resulted in increased sensitivity of 85% and unchanged specificity (94%). Based only on clinical and laboratory findings, 13/43 patients (30.2%) were classified as gout according to ACR/EULAR criteria. In scenario A, additional 8 out of 30 (26.7%) patients were diagnosed as gout by DECT findings, and another 5/22 (22.7%) patients by aspiration findings. In scenario B, initial consideration of aspiration findings resulted in 10 out of 30 (33.3%) additionally identified patients, and another 3 (15%) patients by DECT findings. There was no relevant difference between scenarios A and B (p=0.508).

Conclusion

Combination of joint aspiration and DECT improves the diagnostic algorithm for gout. In our attempt to establish an optimal sequence of diagnostic tests, we did not identify an advantage for either synovial fluid analysis or DECT as the initially better modality after clinical examination and analysis of blood tests.

Key words

single-source dual-energy computed tomography, joint aspiration, gout, diagnostic procedure

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Received on December 11, 2017; accepted in revised form on March 19, 2018.

Funding: this study was supported by Canon Medical Systems that subsidised the patient acquisition and joint aspiration and programmed and provided the software for DECT evaluation.
J. Mews is a coworker of Canon Medical Systems Europe and was involved in planning the study. The company did not authorise nor influence the scientific results.

Competing interests: E. Feist received research suport from Toshiba;
J. Mews is employed by Canon Medical Systems;
B. Hamm received grants Kendle/MorphoSys AG on behalf of the Department of Radiology, has board memberships for Deutsche Röntgengesellschaft, European Congress of Radiology, European Society of Radiology, ESMRMB, European School of Radiology, travel support from Deutcshe Forschungsgemeinschaft, and consultancy honoraria from Toshiba;
the other co-authors have declared no competing interests.

Introduction

Gouty arthritis is the most common inflammatory joint disease in the industrialised world and is characterised by sudden attacks due to activation of the innate immune system by monosodium urate (MSU) crystals (1-4). Furthermore, deposition of monosodium urate crystals in the joints and soft tissue can cause a destructive course of disease (5). The diagnosis is usually made on the basis of clinical findings in conjunction with laboratory tests especially elevated levels of uric acid. Additional diagnostic tests may be needed in patients with an atypical clinical presentation. The ACR/EULAR working group has proposed a set of criteria for the diagnosis of gout (6) based on the analysis of synovial fluid obtained by joint aspiration as the gold standard (7, 8). Accordingly, the demonstration of birefringent urate crystals on polarising microscopy is considered to be diagnostic of gout. However, joint aspiration is invasive, involves discomfort to the patients, and may not be feasible in all cases (9). Therefore, a reliable imaging modality is highly desirable to confirm the diagnosis of suspected gout noninvasively. Dual-energy computed tomography (DECT) has recently emerged as a beneficial imaging modality in these patients (10-15). While DECT was initially established on CT scanners with two x-ray tubes (dual-source systems) (16-18), more recently, there have been attempts to develop approaches for also performing DECT on single-source CT scanners (19-23). A recent study has investigated the impact of DECT on the therapeutic management of patients with gout (24). In the study presented here, we systematically compared synovial fluid analysis (MSU positivity) and DECT (demonstration of tophi) to define their diagnostic performance after initial evaluation of patients based on clinical findings and laboratory testing according to the 2015 version of the ACR/EULAR criteria for the diagnosis of gout. Our ultimate aim in conducting this study was to possibly establish a diagnostic algorithm for the use of DECT and synovial fluid aspiration in confirming the diagnosis of gout in a clinical setting.

Methods

Patients

This prospective study enrolled patients presenting with unclear arthritis and suspected gout from December 2013 through December 2016. The affected joint had to be accessible to synovial fluid aspiration. Exclusion criteria were age below 18 years and pregnancy.
Eligible patients were screened and enrolled by an experienced rheumatologist. The study was approved by the local ethics committee (EA1/151/13) and authorised by the Federal Office for Radiation Protection (ref. Z5-22462/2-2013-107). Written informed consent was obtained from all participants. The results are reported according to the STAndards for Reporting Diagnostic accuracy (STARD) (25).

Diagnostic procedures

All patients included underwent ultrasound-guided joint aspiration, which was performed by an experienced rheumatologist, and DECT. The order of these two diagnostic tests was not fixed and primarily depended on availability of the methods. Therefore, part of the patients underwent DECT first, followed by synovial fluid aspiration, while others first underwent aspiration and then DECT. The actual order in which the supplementary tests were performed had no effect on the order of analysis according to the algorithm presented in Figure 1. The 2015 ACR/EULAR gout classification criteria served as the standard of reference for all steps of analysis (6).

DECT

DECT examinations were performed on a 320-row CT scanner with 16 cm detector width (Aquilion ONE, then Aquilion ONE Vision, Canon Medical Systems, Japan) using the dual-energy volume scan mode without table movement. Scans were acquired with 80 and 135 kVp (19). A fixed tube current without dose modulation was used, depending on the joints examined and the availability of iterative reconstruction (see Table I). Rotation time was 0.275 s (Aquilion ONE Vision) to 0.5 s (Aquilion ONE) with a switching time of 0.5 s, resulting in a total scan duration

Table I. Parameters of DECT by joint examined.

Joint	Tube voltage of 80 kVp [mA]	Tube voltage of 135kVp [mA]	Exposure time [sec]	Total mAs	CTDIvol [mGy]	DLP [mGy*cm]	Conversion factor	EED [mSv]
Hand	140	25	0.55	45	2.4	38.5	0.0008	0.031
Elbow	200	35	0.55	64	3.1	48.8	0.0008	0.039
Knee*	230	40	0.55	74	3.5/ 3.9	56.0/ 62.2	0.0004	0.022/0.025
Ankle joint*	200	35	0.55	64	3.1/ 3.4	48.8/ 54.6	0.0002	0.010/0.011
Foot	140	25	0.55	45	2.4	38.5	0.0002	0.008

*Exposure parameters are provided with and without scanogram. EED is calculated by multiplying the DLP by the respective conversion factor: 0.0008 for the hand and elbow, 0.0004 for the knee, and 0.0002 for the ankle joint and foot (33). CTDIvol: computed tomography dose index; DLP: dose-length product; EED: estimated effective dose.

Table II. Patient characteristics.

	Gout (n=26)	Non-gout (n=17)	*p*-value
Mean age	56.85 ± 14.66	57.12 ± 12.03	0.950
Men	22/26 (84.6%)	14/17 (82.4%)	
Women	4/26 (15.4%)	3/17 (17.7%)	
ACR/EULAR score	10.42 ± 3.37	0.88 ± 3.16	
Uric acid [mg/dl] (♀:2.3-6.1 ♂:3.6-8.2)	8.59 ± 1.66	6.12 ± 1.96	<0.001
CRP [mg/l] (>5)	58.93 ± 84.14	84.33 ± 105.82	0.404
Leukocytes [/nl)] (3.9-10.5)	10.79 ± 5.11	10.1 ± 10.18	0.782

CRP: C-reactive protein, *p*-values were calculated 0using an unpaired *t*-test.

of 1.05 to 1.5 s. The datasets were analysed using the commercial dual-energy CT analysis software (v. 6, Canon Medical Systems, Japan). While only the affected elbow, ankle joint, and foot were scanned, bilateral scans were obtained of the knees and hands (26). A scanogram for planning was only acquired when the knee or ankle joints were examined. The DECT datasets were analysed in consensus by two radiologists with 6 years (TD) and 17 years of experience (KH) in musculoskeletal imaging. Both readers were blinded to the results of synovial fluid analysis and the clinical and laboratory findings.

Polarisation microscopy of synovial fluid

Polarisation microscopy of synovial fluid was performed by experienced rheumatologists or pathologists. Failure to obtain synovial fluid by aspiration was classified as "not done" in the analysis according to the ACR/EULAR criteria and as "negative" in the contingency analysis.

Gold standard

The ACR/EULAR gout classification system of 2015 served as the gold standard (6). According to this classification system, gout is diagnosed in patients with a score ≥8 or MSU positivity.

Diagnostic algorithm

To establish a possible diagnostic algorithm for the clinical use of DECT and synovial fluid aspiration, all patients were initially classified (gout *vs*. non-gout) by scoring them according to the ACR/EULAR criteria. This first step served to identify those patients who were positive for gout based on the ACR/EULAR criteria alone (score of ≥8) without taking the results of DECT or synovial fluid analysis into account. In a second step, all patients negative for gout based on these criteria were reclassified by adding either the results of DECT (Scenario A) or the results of synovial fluid aspiration (Scenario B). Positive DECT findings (evidence of urate deposition) were considered by adding 4 points to the score. In a third step, patients who were still negative for gout were reclassified again by additionally taking synovial fluid aspiration (Scenario A) or DECT findings (Scenario B) into account. The diagnostic procedure is presented in Figure 1 (including results).

Statistical analysis

All data were compiled in an Excel table, followed by a descriptive statistical analysis of the patient population. Patients' characteristics in the group of gout versus non-gout were compared using an unpaired *t*-test. A contingency analysis for calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) was performed for DECT, synovial fluid analysis and a combination of both (at least one positive) using the ACR/EULAR criteria as standard of reference. Scenarios A and B were tested for significant differences using the McNemar test. All analyses were conducted using IBM SPSS Statistics, v. 24. A *p*-value of less than 0.05 was considered significant.

Results

Patients

A total of 43 patients were included in the study after providing informed consent. 26 patients were diagnosed with gout (one patient in addition to a known rheumatoid arthritis). Of the remaining 17 patients five had the final diagnosis of undifferentiated arthritis, four of calcium-pyrophosphate-dehydrate arthropathy, three of osteoarthritis (one secondary after radiosynoviorthesis), two of a peripheral spondyloarthritis, one of rheumatoid arthritis, one of infectious arthritis and one of acute myeloid leukaemia. A description of the study population is shown in Table II and the joints examined are listed in Table III.

Results of synovial fluid analysis, DECT, and ACR/EULAR criteria

There were no complications related to synovial fluid aspiration or DECT. Microscopy of synovial fluid demonstrated MSU crystals in 15/43 patients (34.9%) and no crystals in 20/43 patients (46.5%). Aspiration was unsuccessful in 8/43 (18.6%) cases (punctio sicca). DECT demonstrated signs of gout in 16/43 patients (37.2%) (Fig. 2)

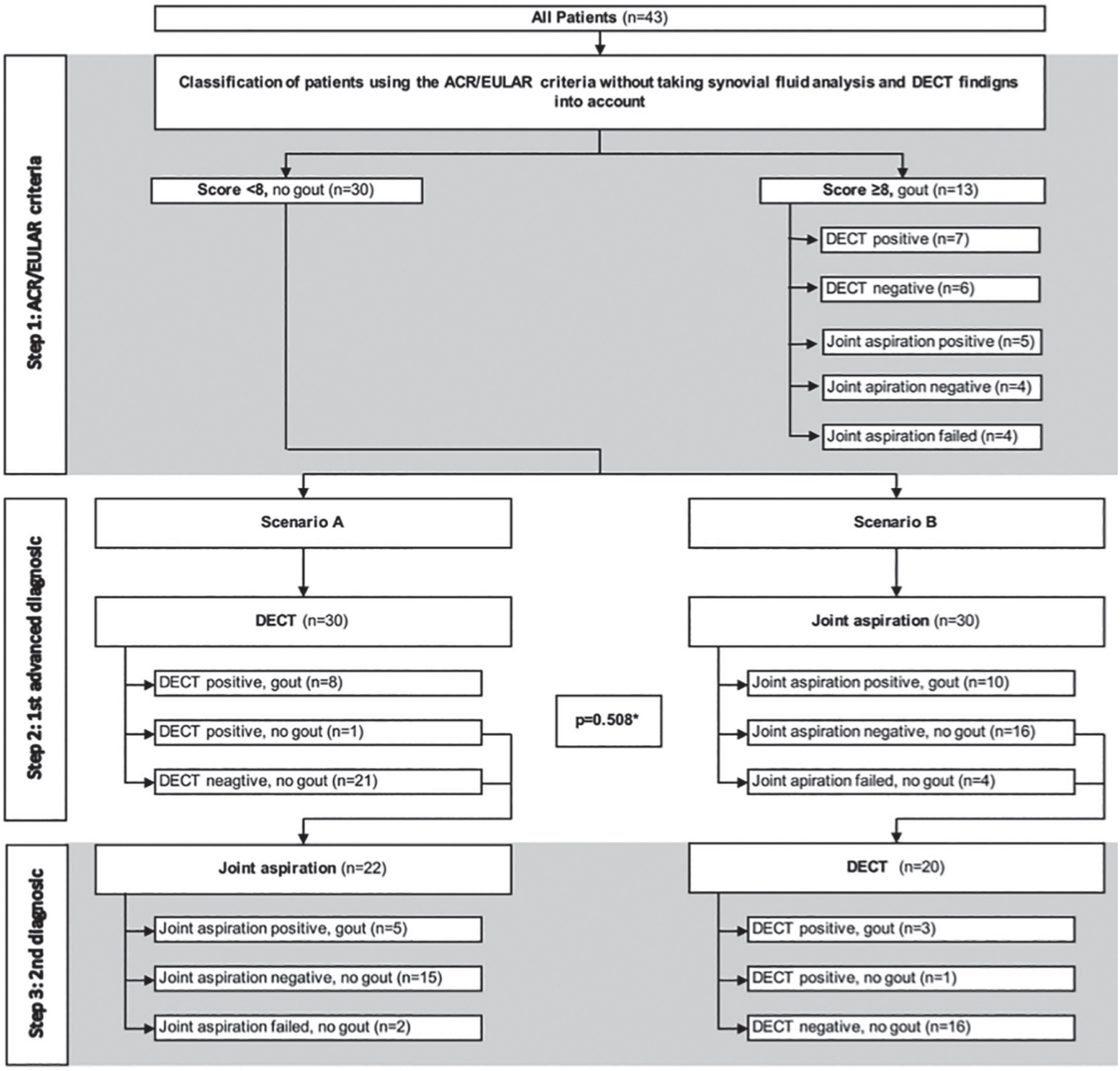

Fig. 1. Diagnostic algorithm and results for the two scenarios investigated (either DECT or joint aspiration as first supplementary diagnostic test following scoring of patients based on clinical and laboratory findings). Scenario A presents the results for first adding the DECT findings and then the synovial fluid analysis. Scenario B presents the results for first adding the synovial fluid analysis results and then the DECT findings. *p calculated according to McNemar: there is no significant difference between the two scenarios.

Table III. Distribution of joints examined in the patient population. In three of the 43 patients (7%), different joints were examined by synovial fluid analysis and DECT.

Joint region	Synovial fluid analysis positive	Synovial fluid analysis negative	Joint aspiration failed	Total number of joint aspirations	DECT positive	DECT negative	DECT total
Knee	7/20 (35%)	13/20 (65%)	0/20 (0%)	**20**	6/17 (35%)	11/17 (65%)	**17**
Foot	3/8 (37,5%)	2/8 (25%)	3/8 (37,5%)	**8**	3/8 (37,5%)	5/8 (62,5%)	**8**
Hand	3/8 (37,5%)	4/8 (50%)	1/8 (12,5%)	**8**	2/9 (22%)	7/9 (78%)	**9**
Ankle joint	1/5 (20%)	1/5 (20%)	3/5 (60%)	**5**	4/7 (57%)	3/7 (43%)	**7**
Elbow	1/2 (50%)	0/2 (0%)	1/2 (50%)	**2**	1/2 (50%)	1/2 (50%)	**2**
Total	**15**	**20**	**8**	**43**	**16**	**27**	**43**

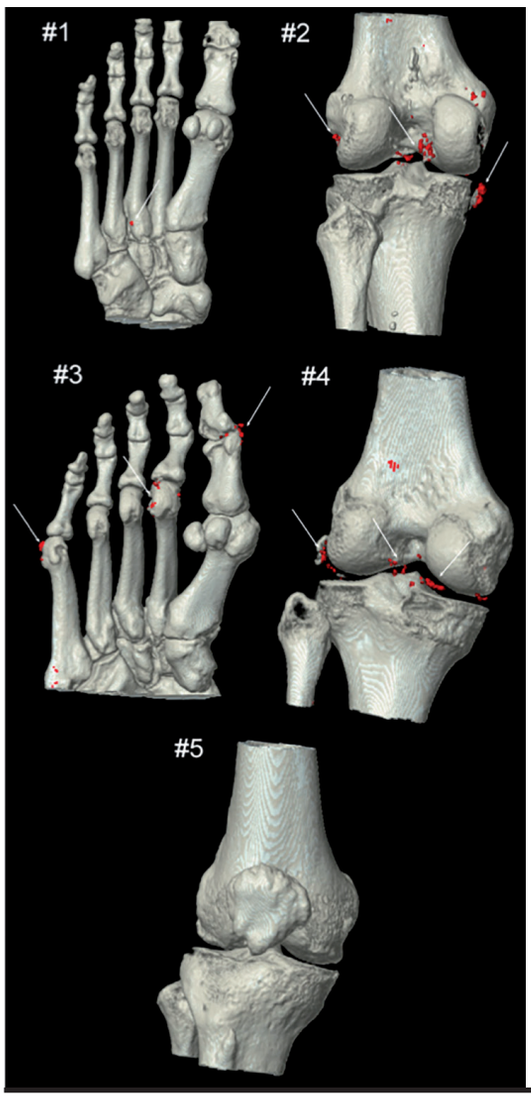

Fig. 2. 3D reconstructions of DECT scans obtained in 5 patients. The ACR/EUAR scores are provided as clinical score + DECT (4 points if positive) and the total score in brackets.
#1: 36-year-old man with a final diagnosis of gout. The reconstruction shows a gouty tophus of the right foot (white arrow). Positive joint aspiration and ACR/EULAR score of 7+4 (11).
#2: 69-year-old woman with a final diagnosis of gout. Multiple gouty tophi of the left knee (white arrows). Negative joint aspiration and ACR/EULAR score of 6+4 (10).
#3: 56-year-old man with a final diagnosis of gout. The reconstruction shows multiple gouty tophi of the right foot (white arrows). Joint aspiration failed and the ACR/EULAR score was 4+4 (8).
#4: 52-year-old man with a final diagnosis of pseudogout. There are false-positive gouty tophi of the left knee joint (white arrows). Joint aspiration negative, and ACR/EULAR score of 1+4 (5).
#5: 60-year-old woman with a final diagnosis of gout. Negative for gouty tophi of the right knee. Joint aspiration positive, and ACR/EULAR score of 7+0 (7).

and no signs of tophi in 27/43 patients (62.8%). Overall, 26/43 patients (60.5%) were diagnosed with gout based on the ACR/EULAR criteria.

Analysis of sensitivity and specificity

Table IV summarises the results of the contingency analysis for calculation of sensitivities, specificities, PPVs, and NPVs of DECT, synovial fluid analysis, and the combination both (at least one positive).

Diagnostic algorithm

In the first step, 13 of 43 patients (30.2%) were diagnosed with gout on the basis of the ECR/EULAR criteria alone. The results for the procedure according to Scenario A (DECT before synovial fluid analysis) were as follows: 8/30 patients (26.7%) with positive DECT findings were reclassified as positive for gout. One patient with positive DECT findings was still negative for gout (based on the total score), and 21 patients remained negative because DECT findings were also negative. By considering the results of synovial fluid aspiration for these 22 patients, 5 additional cases were reclassified as positive for gout (22.7%). The results for the procedure according to Scenario B (synovial fluid analysis before DECT) were as follows: the results of synovial fluid analysis gave a diagnosis of gout in 10 of the 30 patients with initially negative results (33.3%). Three of the 20 patients who were negative for gout after addition of the synovial fluid analysis results (15%) were reclassified as positive based on additionally taking DECT findings into account. Two of the three patients reclassified after addition of DECT had a dry puncture (see Fig. 2). The results of the different diagnostic algorithms are summarised in Figure 1 with no relevant differences between both scenarios (p=0.508).

Discussion

The results of our study show that both DECT and synovial fluid analysis have low sensitivity (58%) but high specificity (94%/100%) in diagnosing gout. The combination of both diagnostic tests continues to have high specificity (94%) while sensitivity is increased to 85%. Hence, our analysis did not reveal

Table IV. Contingency analysis; sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) with 95% confidence interval (CI) of synovial fluid aspiration, DECT, and combined aspiration/DECT: Note that synovial fluid aspiration and DECT, when analysed alone, have similar results for sensitivity, specificity, and PPV and NPV and that all parameters increased for combined synovial fluid aspiration/DECT.

Examination	Outcome	Gout	Non-gout	Sensitivity (CI)	Specificity (CI)	PPV (CI)	NPV (CI)
Joint aspiration	positive	15	0	0.58	1	1	0.61
	negative	11	17	(0.39 – 0.74)	(0.82 – 1)	(0.8 – 1)	(0.42 – 0.76)
DECT	positive	15	1	0.58	0.94	0.94	0.59
	negative	11	16	(0.39 – 0.74)	(0.73 – 1)	(0.72 – 1)	(0.41 – 0.75)
Joint aspiration/DECT	positive	22	1	0.85	0.94	0.96	0.8
	negative	4	16	(0.66 – 0.94)	(0.73 – 1)	(0.79 – 1)	(0.58 – 0.92)

a clear advantage for either of the two tests and, therefore, we cannot derive a recommendation as to whether synovial fluid analysis or DECT should be used as the next diagnostic test following clinical examinations and laboratory tests in patients with suspected gout. While supplementary synovial fluid aspiration from the joint space confirmed the diagnosis of gout in more patients compared with supplementary DECT (10 *vs*. 8 of 30), a limitation is that it is an invasive procedure that can only be performed by experienced clinicians. Furthermore, the risk of complications has to be taken into account. Therefore, the choice of the next diagnostic modality following clinical examination and laboratory testing should be made depending on the local availability of CT and joint aspiration. In case that both tests are equally assessable, the less invasive procedure (DECT) should be preferred. By using this approach, the risks of the joint aspiration can be avoided in patients with positive DECT results. Interestingly, there was a higher proportion of patients with positive DECT findings than with positive synovial fluid findings among the patients already diagnosed with gout based on the ACR/EULAR clinical and laboratory criteria. Compared with the literature, the observed sensitivity of 58% for DECT in our study is below the published range of 64% to 100%, while the specificity of 94% was is in the range reported by others (83-96%) (27-30). Overall, the patients included in our study had an unclear clinical presentation. Such complex cases are a challenge for both therapeutic and diagnostic management. This may explain the poor sensitivity of both supplementary diagnostic tests in our study and at the same time corroborates the clinical experience with complex cases requiring extended diagnostic workup for confirmation of the diagnosis.

The DECT was performed on a special CT machine that allows for the acquisition of two sequential volume scans (with 16 cm z-axis coverage) without table movement. This is a unique approach for dual-energy imaging. Other vendors have different solutions, *e.g*. dual-source systems that are equipped with two x-ray tubes, fast-kVp-switching or dual-layer detectors. Those techniques allow a simultaneous image acquisition, however, that is not necessary for the tophus detection. All techniques have certain advantages and disadvantages regarding energy-separation and quality of the basic images. Nonetheless, until now, no vendor has proven superiority for gout diagnostics or radiation dose. However in principle, our results can be transferred to conventional CT machines with sequential dual-energy image acquisition, *e.g*. two sequential spiral scans and co-registration by a software. Although our cohort of 43 patients is relatively small, the number allows adequate and valid analysis. Published studies are based on similar patient numbers (10, 29). Moreover, our population included patients with different stages of gout. And we also included patients with failed aspiration into the analysis. This reflects the clinical situation and might help in transferring our results into clinical practice. The ACR/EULAR gout criteria primarily rely on joint aspiration and clinical data, while imaging examinations such as DECT are of minor relevance. This is in line with the one false-positive DECT result in our study. In our study, we did not include ultrasound imaging that proved its value in previous studies. (31, 32). Whereas the majority of patients underwent sonography before joint aspiration, we focused on the DECT as primary subject to our analysis. Further studies may focus on a comparison of sonography and DECT for the diagnosis of gout in a similar way. A possible bias might result from the distribution of joints that were punctured for synovial fluid aspiration: in nearly half of the patients, puncture was performed for synovial fluid aspiration from knee joints (20/43; 46.5%), which are easier to puncture than smaller joints. The CT protocol used in our study has a lower radiation exposure than protocols used by other investigators (10, 27-29); however, the protocol has been established in an earlier study (30). In conclusion, our results show that DECT, in conjunction with synovial fluid aspiration from an affected joint, has the potential to achieve high specificity in the diagnosis of gout. Our findings further suggest that DECT cannot replace synovial fluid aspiration but should rather be regarded as a supplementary diagnostic test. Overall, DECT has an important role as a noninvasive modality in the diagnostic cascade of suspected gout, especially in unclear cases or when synovial fluid aspiration has failed or is not possible. In our attempt to establish an optimal sequence of diagnostic tests, we did not identify an advantage for either synovial fluid analysis or DECT as the best modality to use after clinical examination and analysis of blood tests. Our data thus suggest that the two diagnostic modalities investigated here are similar, and the decision to use either synovial fluid aspiration or DECT as the next diagnostic test should be based on the rheumatologist's experience and local availability. Even if either of the two modalities is negative, it is worthwhile to use the other modality as well, as it will enable confirmation of the diagnosis in an additional 15 to 22% of cases. However, in view of invasiveness and possible complications, we would recommend using a DECT scan before escalating to the synovial fluid aspiration.

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