CLINICAL UTILITY OF DUAL ENERGY CT IN GOUT

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CLINICAL UTILITY OF DUAL ENERGY-CT IN GOUT

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(met een samenvatting in het Nederlands)

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door

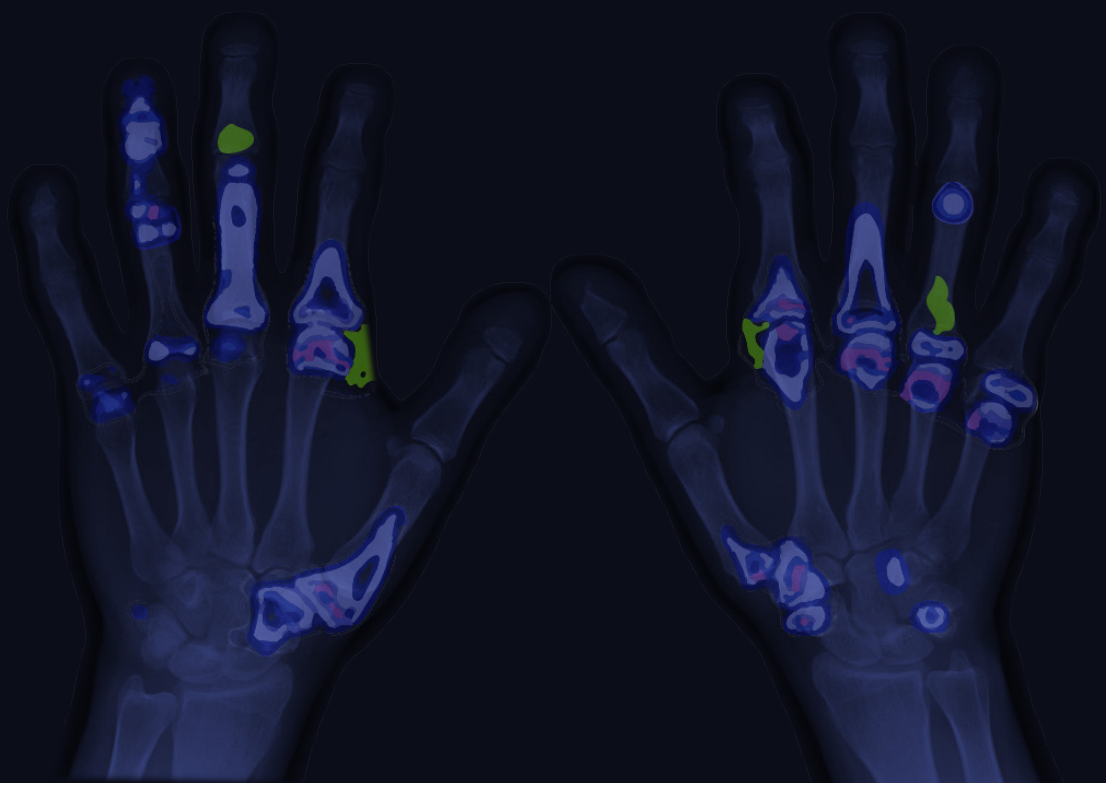
Mihaela Gamala

geboren op 3 september 1975
te Turnu Severin, Roemenië

Promotor: Prof.dr. J.M. van Laar
Copromotoren: Dr. J.W.G. Jacobs
Dr. R. Klaasen

TABLE OF CONTENTS

Chapter 1



General introduction

INTRODUCTION

Gout is a monosodium urate (MSU) deposition disease, especially in joints but also frequently at periarticular structures, such as tendons.[1] Gout is the most common form of inflammatory arthritis, the reported prevalence of gout worldwide ranges from 0.1% to approximately 10%, and the incidence from 0.3 to 6 cases per 1,000 person-years.[2] The prevalence in the Netherlands has been estimated 3.7% among men and 2.3% among women.[3] Gout is associated not only with joint damage but also with increased cardiovascular (CV) morbidity and mortality.Therefore is important to diagnose and treat gout early.

DIAGNOSIS OF GOUT

The diagnosis of acute gout is based on clinical features of arthritis and/or tenosynovitis, and confirmed by demonstration of MSU crystals in synovial fluid (SF).[1] However, results may be false negative due to a sampling error (incorrect placement of the needle in the affected joint), or an extra-articular location of the MSU deposits, (e.g. near tendons around the joint) or incorrect microscopy technique,[4] or true negative in case of other causes of arthritis (e.g. infection, reactive arthritis). In addition, joint aspiration may be technically difficult or impossible to perform.

CLASSIFICATION CRITERIA OF GOUT

In an attempt to achieve a more uniform system for reporting and comparing studies on gout, the American College of Rheumatism (ACR) and the European League against Rheumatism (EULAR) formulated criteria in 2015 for the classification of gout. The entry criterion for the new classification criteria is the occurrence of at least one episode of peripheral joint or bursal swelling, pain, or tenderness. The presence of MSU crystals in SF of a symptomatic joint/bursa or in a tophus is a sufficient criterion for classification of the subject as having gout, and does not require further scoring. The new classification criteria include 4 clinical, 2 laboratory (serum urate and SF analysis) and 2 imaging (dual-energy-CT (DECT) OR ultrasonography, and conventional radiography) criteria, see Table 1.[5] The maximum possible score of the criteria is 23. A score of ≥8 classifies an individual as having gout.[5]

DECT leads to low radiation exposure, 0.5 mSv per region scanned, (e.g., 0.5 mSv for both hands and wrists, which are scanned together)[9] and there is no need to use contrast fluids.[6] Several studies with various methodological designs have investigated the accuracy of DECT for gout.[7,9-15] These studies primarily involved subjects with established disease, in whom the diagnosis is clinically obvious without using DECT. Only 3 studies

Table1. The 2015 ACR/EULAR classification criteria for gout

Domain	Criteria (to be used if sufficient criterion not met)	Categories	Score
CLINICAL	**Pattern of joint/bursa involvement during symptomatic episode(s) ever**	Joint(s) or bursa(e) other than ankle, mid-foot or first metatarsophalangeal (MTP) joint (or their involvement only as part of a polyarticular presentation)	0
		Ankle or mid-foot joint(s) as monoarticular or part of an oligoarticular presentation without first MTP joint involvement	1
		MTP joint involvement as monoarticular or part of an oligoarticular presentation	2
	Characteristics of symptomatic episode(s) ever: i) Great difficulty with walking or inability to use the affected joint(s) during a symptomatic episode ever (patient-reported) ii) Can't bear touch or pressure to the affected joint during a symptomatic episode ever (patient-reported) iii) Erythema overlying affected joint during a symptomatic episode ever (patient-reported or physician-observed)	No characteristics	0
		One characteristics	1
		Two characteristics	2
		Three characteristics	3
	Time course of symptomatic episode(s) ever: i)Time to maximal pain <24 h ii) Resolution of symptoms in ≤14 days iii) Complete resolution (to baseline level) between symptomatic episodes	No typical episodes	0
		One typical episode	1
		Recurrent typical episodes	2
	Clinical evidence of tophus: Appearance: draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity. Location: classic locations—joints, ears, olecranon bursae, finger pads, tendons (e.g, Achilles)	Absent	0
		Present	4
LAB	**Serum urate:** highest reading on record, of urate-lowering therapy Special considerations: Ideally, the serum urate level should be scored if tested at a time when the patient was not receiving urate-lowering therapy and it was >4 weeks from the start of an episode; *if* practicable, retest under those conditions. If serum urate level is ≥10 mg/dL, no need to retest	<4 mg/dL (0.24 mmol/L)	-4
		4–<6 mg/dL (0.24–<0.36 mmol/L)	0
		6–<8 mg/dL (0.36–<0.48 mmol/L)	2
		8–<10 mg/dL (0.48–<0.60 mmol/L)	3
		≥10 mg/dL (≥0.60 mmol/L)	4
	Synovial fluid analysis of asymptomatic (ever) joint or bursa: should be assessed by a trained observer	Note done	0
		MSU negative	-2

IMAGING	**Imaging evidence of urate deposition in symptomatic (ever) joint or bursa:** double-contour sign on ultrasound *OR* urate deposition on dual energy-CT	Absent OR Not done	0
		Present (either modality)	4
	Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrate at least one erosion.	Absent OR Not done	0
		Present	4

DECT is a new technique to diagnose gout.[6-8] This technique enables one to visualize and quantify MSU depositions[8], see Figure 1.

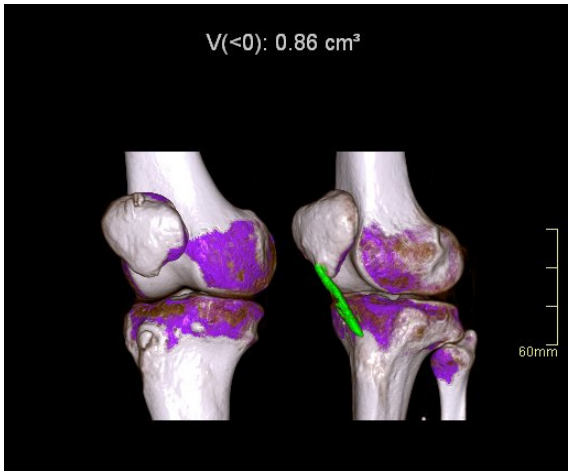


Figure 1. Urate deposition on DECT.

Legend: green pixilation of patella tendon represents urate deposition

assessed subgroups with recent onset disease and no prior diagnosis of gout;[7,16,17] these suggest that DECT may have limited sensitivity for detection of MSU deposition in recent onset gout in previously undiagnosed patients. However, these studies included relatively low numbers of subjects and showed marked variability in study design, reference standards and withdrawals, making it difficult to draw firm conclusions. The two studies with meta-analyses did not discriminate for person-based and joint-/localisation-based evaluations.[18,19] In person-based evaluations, DECT at multiple sites is performed in a single person for diagnostic purpose, while in joint-/localisation-based evaluations, DECT is performed only for the symptomatic joints/localisations. Second, these reviews did not separate findings for gout of short and long duration, which is important because gout is a deposition disease, with more depositions over time.[7,16]

Altogether, although DECT seems a promising modality, its utility in classifying and diagnosing recent onset gout requires further assessment. In addition, the impact of DECT results on diagnosis and therapy of gout in clinical practice needs further evaluation.

ASSOCIATED MORBIDITY IN GOUT

There is an increasing interest in the association of gout with other diseases. Although the causal relationship remains to be elucidated,[20] multiple studies report the association of gout with CV risk factors and diseases.[21,22] The independent association of gout and CV disease (CVD) is fully recognised,[23,24] and likely relates to persistent inflammation.[25] The EULAR recommends treating as soon as possible after diagnosis to avoid further gout attacks and growing crystal load and to possibly prevent CVD.[26] However, if at the time of diagnosis, MSU deposition is present, detectable and quantifiable by DECT, this may indicate longstanding hyperuricaemia and a start of urate deposition, long before diagnosis, increasing the risk of CVD.

The Dutch SCORE,[27] a modified version of the Systematic COronary Risk Evaluation (SCORE),[28] estimates the 10-year risk of fatal and nonfatal CVD based on gender, age, smoking, blood pressure and the total cholesterol/HDL-cholesterol ratio (see Figure 2). In it, a correction for rheumatoid arthritis (RA),[29] but not for gout, can be taken into account. To account for RA or diabetes as risk factor, the CV Dutch risk management guideline adds 15 years to the actual age to calculate the 10-year CV risk. However, gout was found a risk factor with similar weight compared to diabetes for both incident myocardial infarction and incident stroke.[30] Screening and aggressive treatment of risk factors for CVD may be warranted in patients with gout, although the efficacy of this strategy needs confirmation in future studies.

AIMS AND OUTLINE OF THIS THESIS

This thesis consists of two parts that together address the utility of DECT in classifying, diagnosing and assessing CV morbidity in gout. The first part will deal with the utility of DECT in classification, diagnosis and therapy decision making in gout. The second part will deal with CV morbidity in new gout patients and the role of DECT in assessing this morbidity.

Part I: The utility of DECT in classification, diagnosis and treatment decisions in gout

In **chapter 2**, a systematic review and a meta-analysis to assess the utility of DECT for diagnosing gout was performed. Data from person-based and joint-/localisation-based evaluations were pooled separately, and subgroup analyses for short disease phase/duration were performed, avoiding the flaws of the previous reviews, and providing clinicians with clinically more applicable data. **Chapter 3** studied if DECT improves the performance of the 2015 ACR/EULAR clinical set of classification criteria at group and at patient level in subjects with unclassified mono and oligoarthritis. **Chapter 4** studied the additive value of DECT in diagnosis and therapy outcomes of gout in subjects with unclassified mono and oligoarthritis after one-year follow-up. In **chapter 5**, a patient

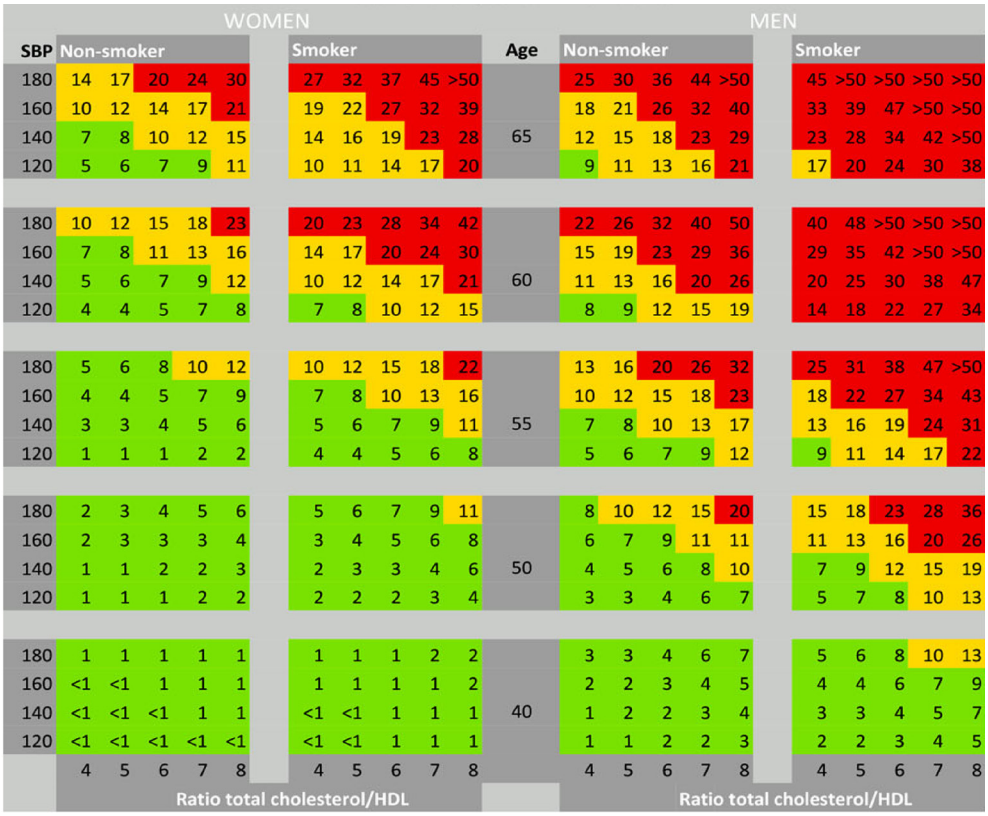


Figure 2. The Dutch Score chart estimating the 10-year risk of fatal and nonfatal CV diseases in percentages[31]

Legend: green represents low risk (no therapeutic intervention necessary), orange represents moderate risk (conditionally therapeutic intervention is necessary. e.g. depending on family history of CVD) and red represent high risk (therapeutic intervention necessary). SBP: systolic blood pressure This figure was published in cardiovascular risk management guidelines.[31]

history is described to illustrate the value of DECT in diagnosing axial gout. In **chapter 6**, the impact of DECT results on therapy adjustments of gout in clinical practice and predictability of DECT results by clinical and laboratory variables were assessed.

Part II: Associated morbidity in gout and the utility of DECT in assessing cardiovascular risk

Chapter 7 summaries the recent literature on hyperuricaemia, gout burden and the associated morbidity. **Chapter 8** explored whether urate deposition on DECT already present at the diagnosis of gout is associated with a history of CV events. **Chapter 9** theoretically explored the effect of adding gout as a chronic inflammatory disease as risk factor with a weight as RA to the Dutch SCORE.

In **chapter 10**, the main findings of this thesis are discussed, methods and limitations considered, and recommendations made for daily practice and future research.

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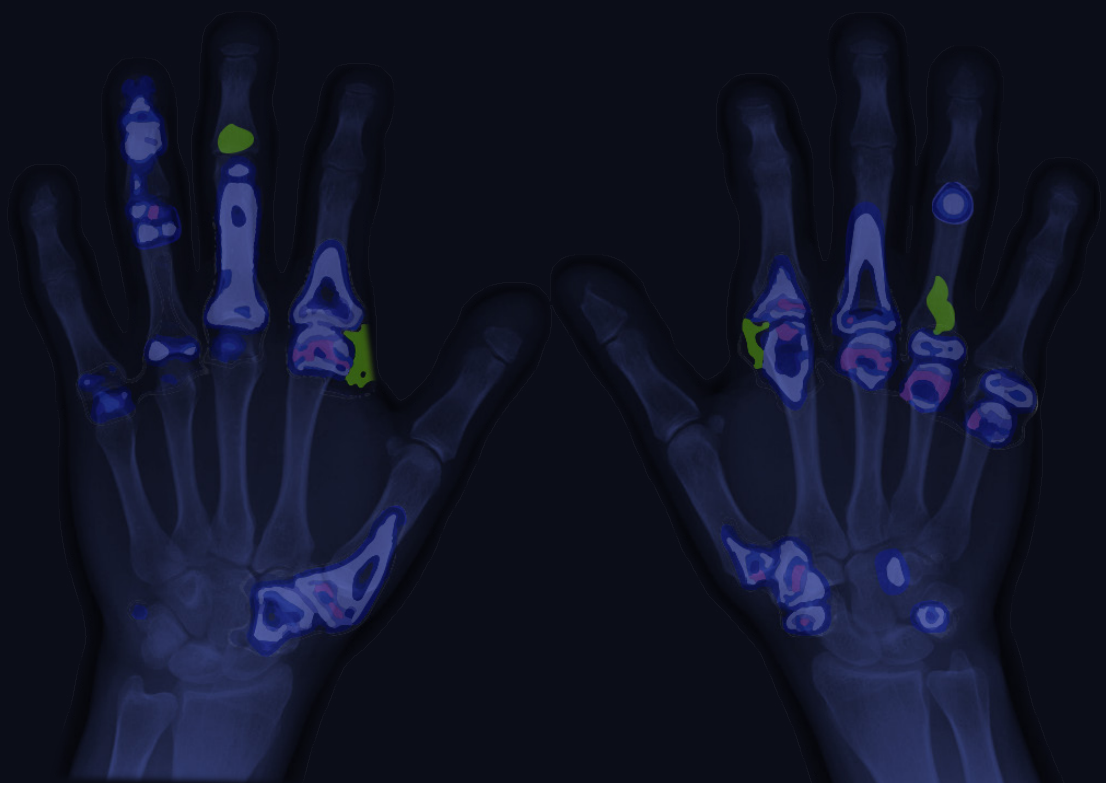
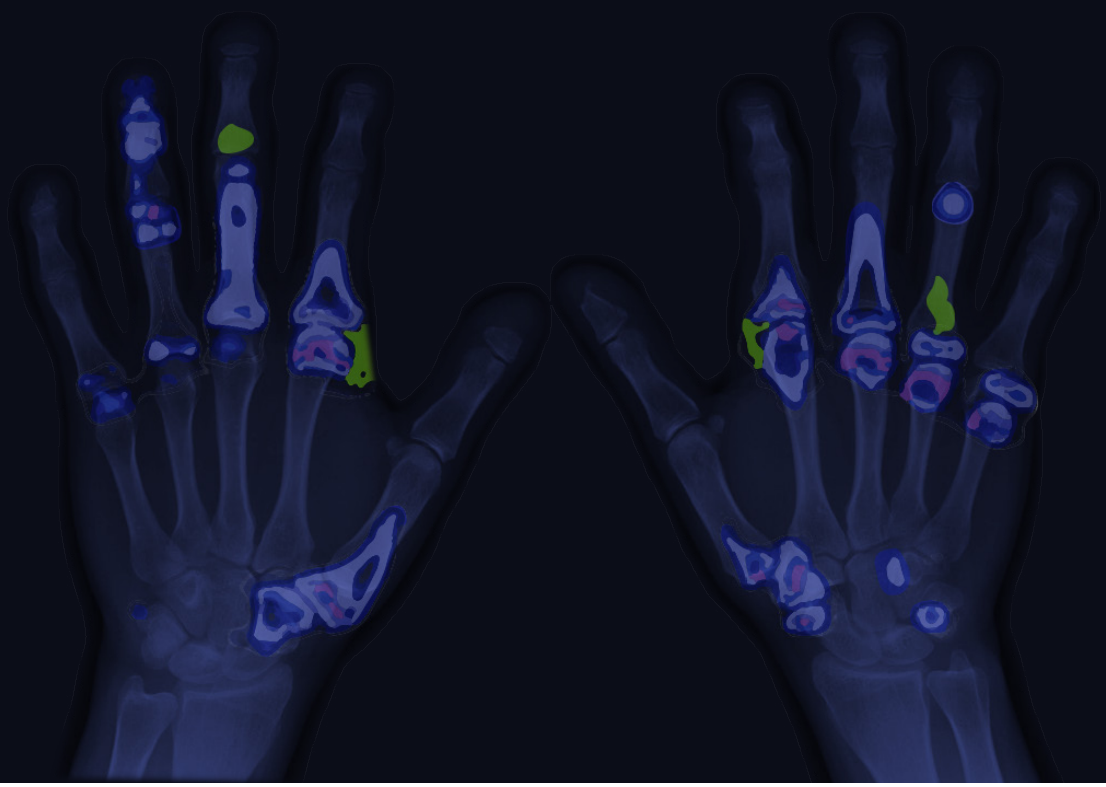
Part I



DUAL ENERGY CT IN CLASSIFICATION, DIAGNOSIS AND TREATMENT DECISIONS IN GOUT

Chapter 2



The diagnostic performance of Dual Energy CT for diagnosing gout: a systematic literature review and meta-analysis

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J.W.G. Jacobs
J. M van Laar

Rheumatology (Oxford). 2019 July 11. [Epub ahead of print]

Abstract

ABSTRACT

Objective: to assess the utility of Dual Energy CT (DECT) for diagnosing gout.

Methods: A systematic literature search was performed in PubMed, Embase and Cochrane. Studies evaluating the utility of DECT for diagnosing gout were included. Reference standards were detection of monosodium urate crystals at synovial fluid assessment or a validated set of criteria. The methodological quality of studies was evaluated according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 criteria. Data from person-based and joint-/localisation-based evaluations were pooled separately, and subgroup analyses for disease stage/duration and reference standard were performed.

Results: 10 studies were included; in person-based evaluations, the pooled (95% CI) sensitivity and specificity were 0.81 (0.77 to 0.86) and 0.91 (0.85 to 0.95), respectively. In joint-based evaluations, they were 0.83 (0.79 to 0.86) and 0.88 (CI 0.83 to 0.92), respectively. At short disease duration (≤ 6 weeks), the pooled (95% CI) sensitivity and specificity at the joint level were 0.55 (0.46 to 0.64) and 0.89 (CI 0.84 to 0.94), respectively.

Conclusion: DECT has a high diagnostic accuracy in established gout, but its diagnostic sensitivity is low in subjects with recent onset gout.

Keywords: Gout, DECT, Review, Utility

INTRODUCTION

Gout is a disease characterized by accumulation of monosodium urate (MSU), especially in joints but also frequently at peri-articular structures, such as tendons.[1] Diagnosis is based on clinical presentation, and confirmed by demonstration of MSU crystals in synovial fluid (SF).[1] However, joint aspiration may be technically difficult or impossible to perform. In addition, SF assessments may not reveal MSU crystals in up to 25% of patients with gout.[2] A new modality to image MSU deposits is Dual Energy CT scan (DECT).[3] DECT scanning is incorporated in the 2015 EULAR/ACR classification criteria.[4] Several studies with various methodological have investigated the diagnostic accuracy of DECT for gout; some systematic reviews evaluated these studies.[5-7] However, in these reviews, analyses did not differentiate between person-based evaluation and joint-/location-based evaluations, of which sensitivity and specificity might differ. In person-based evaluations, DECT is performed on multiple joints in a single person for diagnostic purpose, while in joint-/localisation-based evaluation DECT is performed only for symptomatic joints/ localisations. Second, these reviews did not separate findings for gout of short and long duration, which is important because gout is a deposition disease, with more depositions in time.[3,8]

In the present systematic review and meta-analysis, we pooled data from person-based and joint-/localisation-based evaluations separately, and performed subgroup analyses for short disease phase/duration, to provide clinically more applicable data for clinicians.

METHODS

Literature search

This study was conducted according to the Proffered Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. [9] This study was registered in Prospero (https://www.crd.york.uk/PROSPERO/; CRD42018116415). All analysed data were extracted from published studies. Therefore, no ethical approval was required. Study selection was performed by one reviewer (M.G.) who screened titles, abstracts and full text. The final selection of a study was based on consensus of all authors.

Search strategy

September 22, 2018, we performed a systematic literature search with no time restriction in PubMed, EMBASE (OVID version) and COCHRANE Library. The search strategy consisted of the Boolean "AND" combination of two main concepts: gout, and Dual Energy CT. For the different concepts, all relevant search terms variation was used, see Supplementary file textbox.

Screening for relevant papers

For the steps taken for the selection of papers, see Supplementary file Figure 1 (selection flowchart). First, duplicates were removed. Subsequently, titles and/or abstracts were screened for selection of relevant papers, using the following inclusion criteria:

(i) the publication was a full-text paper; reviews, editorials, meta-analyses, and case-reports were excluded.
(ii) the publication concerned research in humans, written in English language.
(iii) the study population consisted of subjects with a suspicion of gout.
(iv) the reference standard was synovial fluid assessment for MSU crystals or meeting a validated set of diagnostic or classification criteria. [4,10,11]

The papers selected were given a full-article review with the following inclusion criteria:

(i) the topic was the performance of DECT in for the diagnosis of gout.
(ii) data on true-positive (TP), false-positive (FP), false-negative (FN) and true-negative (TN) cases were reported.

Data extraction

From the papers included in the last step, the following data were systematically extracted: first author, year of publication, study-design (case-control, cross-sectional, or cohort study), subjects recruitment or selection criteria, number of gout subjects, average age (years), number of male patients (%), average disease duration (years), localization of imaged joints, whether person-based or joint-localisation-based evaluations had been applied, and the reference standard. Reported values for TP, FP, FN and TN for each study were collected for quantitative pooling.

Assessment of methodological quality

The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) was used to assess the quality of each study. [12] The results of the methodological quality assessment were summarized with RevMan version 5.3.5 (The Cochrane Collaboration, Copenhagen, Denmark), see Supplementary file Figure 2.

Pooling, statistical analysis

Data from person-based and joint-localisation-based evaluations were pooled separately. Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood radio (NLR), diagnostic odds ratio (DOR), and their 95% confidence intervals (CIs) of DECT for imaging MSU-depositions were obtained using random-effects models. A pooled DOR ranges from zero to infinity and a higher pooled DOR represents better accuracy. Summary receiver operating characteristic (sROC) curves were created to obtain area under the curve (AUC) and Q-index (Q), which both reflect diagnostic accuracy. Furthermore, subgroup analyses for different reference standards for the diagnosis gout and disease

duration were performed. The pooling analyses were performed using Meta-DiSc version 1.4 (Unit of Clinical Biostatistics team of the Ramon y Cajal Hospital, Madrid, Spain).

RESULTS

Selected study characteristics

According to the procedures outlined in the PRISMA statement [9], we selected 10 studies [3,8,13-20] for quantitative analysis from three electronic databases, see Supplementary file textbox (search terms) and Supplementary file Figure 1 (selection flowchart). In general, quality of the studies was adequate with low risk of bias. Among the 10 studies, 5 presented data from joint-/localisation-based evaluation,[3,8,13,17,20] and 5 data from person-based evaluations.[14-16,18,19] Only 3 studies [3,8,13] assessed subgroups of participants with recent onset disease (≤6 weeks). Details of the 10 included studies and involved participants are presented in Table1.

Table1. Characteristics of included studies

Author, year	Design	Inclusion interval	Reference standard	Scanned joints	Index joint only	Radiologist blinded	Evaluation method	Clinical manifestation	Gout			Controls		Arthro-centesis
									N	Age in years	Disease duration	N	Age in years	
Lee, 2018[13]	retrospective, cross-sectional	April 2015-August 2017	EULAR/ACR 2015	MTP1	no	yes	joint / localisation	joint pain and/or swelling	67	50*, SD 13.2	2.9 years, range 1-4.3	43	53*, SD 14	yes
Jia, 2017[8]	prospective, case-control	May 2013-Dec. 2016	ACR 1977	affected joint	yes	yes	joint / localisation	painful joint	136	49*, SE 1.6	4.8 years, SD 0.5	85	NR	no
Kiefer, 2016[14]	retrospective, cross-sectional	Febr 2011-July 2013	ACR 1977	feet	no	yes	patient	acute arthritis of feet	21	63*, SD 12	NR	23	63*, SD 9	no
Ahmad, 2016[15]	prospective, cross-sectional	April 2011-March 2013	ACR 1977 or/ and MSU-detection	feet, knees	no	NR	patient; joint / localisation	joint pain and/or swelling	54	21-75**	6.1 years	36	21-75**	yes
Hu, 2014[16]	retrospective, cross-sectional	Oct. 2010-Dec. 2013	MSU-detection	hands, wrists, elbows, knees, ankles, feet	no	yes	patient	joint pain and/or swelling	161	51*, SD 15	55 months, SD 71	40	55*, SD 19	yes
Bongartz, 2014[3]	prospective, case control	Oct. 2010-Sept. 2012	ACR 1977	affected joint	yes	yes	joint / localisation	joint pain and/or swelling	40	62*, SD 13	NR	41	58*, SD 13	yes
Wu, 2014[17]	prospective, case control	NR	ACR 1977	feet, hand, knee	no	NR	patient	acute joint swelling	143	51*, SD 13	74 months SD 68	48	50*, SD 15	no
Huppertz, 2014[18]	retrospective, case-control	August 2011-March 2012	MSU-detection or Janssens' score	feet, knees, hands, elbows	no	yes	patient	joint pain and/or swelling	39	62*	NR	21	62*	yes
Choi, 2012[19]	prospective case-control	Dec. 2009-July 2011	MSU-detection	feet, ankles, knees, elbows, hands, wrists	no	yes	patient	joint swelling	40	62*	13 years	40	53*	NR
Glazebrook, 2011[20]	retrospective, cross-sectional	April 2008-Febr. 2010	MSU-detection	affected joints	yes	yes	joint / localisation	joint pain and/or swelling	12	29-89**	NR	19	28-89**	yes

NR, not reported; MSU, monosodium urate; ACR, American College Rheumatology; EULAR, European League Against Rheumatism; N, number; SD: standard deviation, SE: standard error; *, mean; **, range

Diagnostic accuracy of DECT

Patient based and joint-/localisation-based evaluations

For patient based evaluations, the pooled sensitivity and specificity were 0.81 (95% CI 0.77-0.86) and 0.91 (95% CI 0.85-0.95), and for joint-/localisation-based evaluations, they were 0.83 (95% CI 0.79-0.86) and 0.88 (95% CI 0.83-0.92), respectively, see Supplementary file Table 1 and Figure 1 (summary ROC curves). Because one study included only patients with recent onset gout (disease duration range 1-4.3 weeks),[13] we performed also an analysis without including this study, see Supplementary file Table 1. This yielded no major changes.

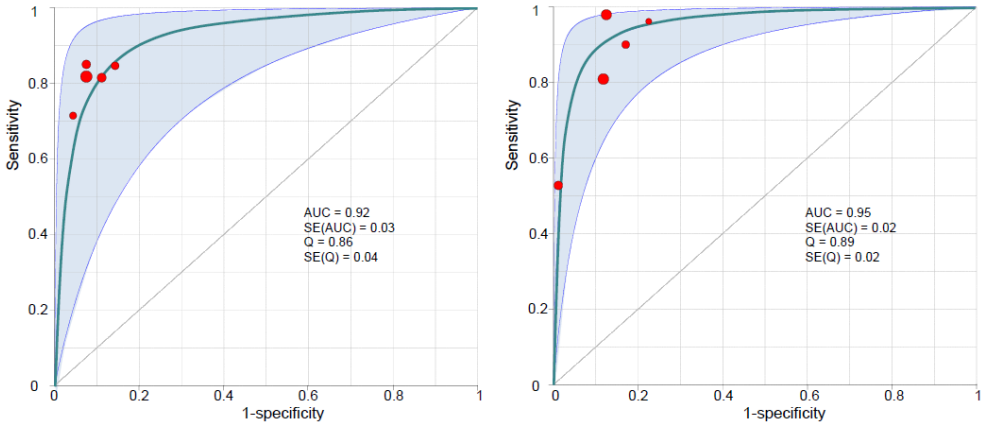

Figure 1. Left: patient based evaluation; right: joint/localisation based evaluation

Legend: The circles indicate individual studies and their diameters the study sizes. The blue areas indicate 95% confidence intervals. AUC: area under the ROC curve; SE(AUC): standard error of area under the ROC curve, Q: Q-index, the point where sensitivity and specificity are equal, which is the point closest to the ideal top-left corner of the ROC space; SE(Q): standard error of the Q-index.

Analyses for different reference standards for gout

Additionally, subgroup analyses were performed for different reference standards for gout (Supplementary file Table 2). In the 5 patient-based evaluations, three (sub)studies used the ACR 1977 criteria as reference standard; [14-16] the pooled sensitivity and specificities were 0.80 (95% CI 0.74-0.85) and 0.91 (95% CI 0.84-0.96), respectively. Two used MSU-detection,[15,19] with pooled sensitivity and specificities of 0.91 (95% CI 0.82-0.96) and 0.75 (95% CI 0.63-0.85), respectively. One used MSU-detection [18] and a Janssens' score ≥8; [11] sensitivity and specificity were 0.84 and 0.85, respectively. In the 5 joint / localisation based evaluations, two studies used the ACR 1977 criteria as reference standard;[8,17] the pooled sensitivity and specificity were 0.89 (95% CI 0.85-0.92) and 0.88 (95% CI 0.80-0.93), respectively. Two studies used MSU-detection [3,20] with pooled sensitivity and specificity of

0.92 (95% CI 0.81-0.97) and 0.81 (95% CI 0.69-0.90), respectively; one used the EULAR/ACR 2015 criteria,[13] with a sensitivity and specificity of 0.52 and 0.1, respectively.

Diagnostic accuracy of DECT in recent onset disease (≤ 6 weeks)

Three studies, all joint / localisation based, assessed subgroups of patients with recent onset disease (≤ 6 weeks). [3,8,13] Subgroup analyses were performed for recent onset disease (Supplementary file Table 3). Especially sensitivities were lower in comparison with those of other analyses, ranging from 0.35 to 0.85, pooled 0.55 (95% CI 0.46-0.64) indicating a relatively higher occurrence of false negatives.

DISCUSSION

We found that DECT has good sensitivity and specificity for diagnosing longstanding gout, with no major differences for the different reference standards used. In the subgroups with gout of short term duration, sensitivity seems too low to assume that DECT is clinically reliable enough to exclude gout. However, the subgroups only consisted of limited numbers of subjects and showed marked variability in study design, reference standards and withdrawals. Therefore, more research of DECT in recent onset gout is warranted. Although the objective of our review was to assess the utility of DECT for diagnosing gout, the performance of DECT in asymptomatic hyperuricaemia also is interesting. The value of DECT in the ankles/feet of subjects with asymptomatic hyperuricaemia was assessed in two studies;[21,22] urate deposits were observed in 6/25 (24%) and 7/46 (15%), respectively, of these subjects.

We found no major differences in pooled sensitivities and specificities between joint / localisation based evaluations and patient based evaluations; it thus remains unknown which and how many joints must be scanned by DECT to strike a balance between diagnostic accuracy, radiation exposure, efficiency and economic costs.

There are some limitations to the present literature review. First, although 10 studies were included in the meta-analysis, sub-group analyses were based on a small number of studies. Second, we included cross-sectional and case-control studies, with varying quality of the studies. Some studies were conducted in established (somewhat advanced) gout patients in whom the diagnosis was established. The inclusion criteria of the control groups were different among the case-control studies included in this meta-analysis. Duration of symptoms, the number of examined joints in person-based evaluations, the device used and other methodological characteristics varied across studies. Furthermore, the use of uric acid lowering treatment would affect the deposition of urate, and thus DECT-results. However, whether urate-lowering therapy was used or not by included patients with established gout was not specified in six of the included studies;[3,14-17,20] it was specified that this therapy had been used in two of the studies;[18,19] one study study included only patients who were not on urate-lowering therapy.[8]

Because of these limitations, future studies are needed to refine the study design and investigate the performance of DECT at specific sites and at specific time points in the disease course of gout, in particular recent onset gout.

CONCLUSION

DECT generally has a good diagnostic accuracy in established gout. However, DECT seems to have low diagnostic sensitivity in recent onset gout patients.

Key messages:

- Dual energy-CT (DECT) has a high diagnostic accuracy in established gout.
- DECT seems to have low diagnostic sensitivity in recent onset gout.
- Further research is needed to establish how many joints must be scanned to strike a balance between diagnostic accuracy and efficiency.

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Supplementary file

Textbox: search

Combined search terms:
(gout OR podagra OR toph$), (dual-energy computed tomography OR dual-energy CT OR DECT)

Search strategy:
((“gout”[MeSH Terms] OR “gout”[All Fields]) OR podagra[All Fields] OR toph$[All Fields]) AND ((dual-energy[All Fields] AND (“tomography, x-ray computed”[MeSH Terms] OR (“tomography”[All Fields] AND “x-ray”[All Fields] AND “computed”[All Fields]) OR “x-ray computed tomography”[All Fields] OR (“computed”[All Fields] AND “tomography”[All Fields]) OR “computed tomography”[All Fields])) OR (dual-energy[All Fields] AND (“J Comput Tomogr”[Journal] OR “Commun Theory”[Journal] OR “Cancer Ther”[Journal] OR “ct”[All Fields])) OR DECT[All Fields])

Figure 1. Flowchart of literature selection process of relevant papers

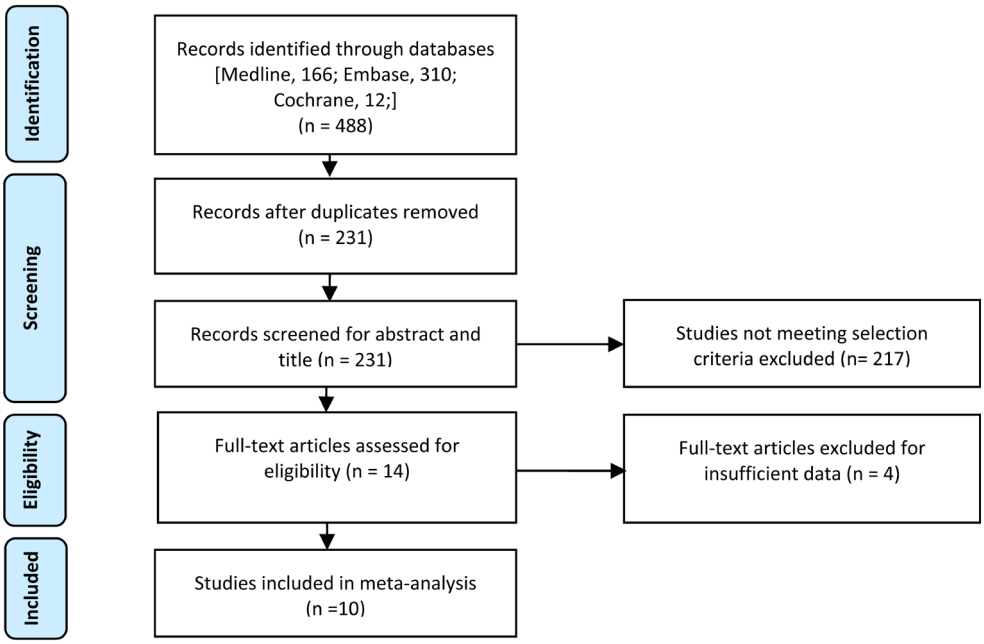


Figure 2. The methodological quality assessment according to The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2)

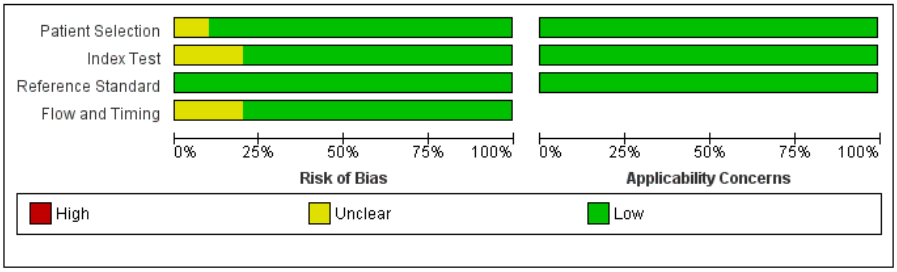


Table 1. Diagnostic accuracy of DECT for diagnosing gout, for patient based versus joint / localisation based analyses

Evaluation method	Study: first author	TP	FP	FN	TN	Sens	Spec	Pooled Sens (95%CI)	Pooled Spec (95%CI	Pooled PLR (95%CI)	Pooled NLR (95%CI)	Pooled DOR (95%CI)	AUC (SE)	Q (SE)
patient based	Kiefer[14]	15	1	6	22	0.71	0.96	0.81 (0.77-0.86)	0.91 (0.85-0.95)	8.8 (5.3-14)	0.20 (0.16-0.26)	47 (24-89)	0.92 (0.03)	0.85 (0.04)
	Ahmad[15]	44	4	10	32	0.82	0.89							
	Hu[16]	121	3	27	37	0.75	0.93							
	Hupertz[18]	33	3	6	18	0.85	0.86							
	Choi[19]	34	3	6	37	0.78	0.93							
joint / localisation based	Lee[13]	38	0	34	43	0.53	1	0.83 (0.79-0.86)	0.88 (0.83- 0.92)	6.3 (4.4-9.0)	0.13 (0.04-0.37)	71 (26-194)	0.95 (0.02)	0.89 (0.02)
	Jia[8]	110	10	26	75	0.81	0.88							
	Bongartz[3]	36	7	4	34	0.90	1							
	Wu[17]	140	6	3	42	0.98	0.97							
	Glazebrook [20]	12	4	0	15	1	0.89							
joint / localisation based, excluding one study on recent onset gout	Jia[8]	110	10	26	75	0.81	0.88	0.90 (0.86-0.93)	0.86 (0.80-0.90)	6.1 (4.3-8.6)	0.08 (0.02-0.28)	71 (22-222)	0.93 (0.01)	0.87 (0.02)
	Bongartz[3]	36	7	4	34	0.90	1							
	Wu[17]	140	6	3	42	0.98	0.97							
	Glazebrook [20]	12	4	0	15	1	0.89							

TP, true positive; FP, false positive; FN, false negative; TN, true negative; Sens, sensitivity; Spec, specificity; PLR, positive likelihood ratio; NLR, negative likelihood ratio, DOR, diagnostic odds ratio; AUC, area under the receiver operating characteristic curve, Q: Q-index, the point where sensitivity and specificity are equal, which is the point closest to the ideal top-left corner of the ROC space; SE: standard error

Table 2. Subgroup analyses of diagnostic accuracy of DECT for diagnosing gout, for different reference standards for gout

Evaluation method	Reference standard	Study	TP	FP	FN	TN	Sens	Spec	Pooled Sens (95%CI)	Pooled Spec (95%CI)	Pooled PLR (95%CI)	Pooled NLR (95%CI)	Pooled DOR (95%CI)	AUC (SE)	Q (SE)
patient based	ACR 1977	Kiefer[14]	15	1	6	22	0.71	0.96	0.80 (0.74-0.85	0.91 (0.84-0.96)	9.4 (4.8-18)	0.21 (0.16-0.28)	45 (20-103)	0.92 (0.05)	0.85 (0.06)
		Ahmad[15]	44	4	10	32	0.82	0.89							
		Hu[16]	121	3	27	37	0.75	0.93							
	MSU-detection	Ahmad[15]	30	13	0	12	1	0.48	0.91 (0.82-0.96)	0.75 (0.63-0.85)	4.4 (0.5-41)	0.12 (0.03-0.42)	66 (18-247)	NA	NA
		Choi[19]	34	3	6	37	0.78	0.93							
	Janssens/or MSU-detection	Huppertz[18]	33	3	6	18	0.85	0.86	0.84	0.85	NA	NA	NA	NA	NA
joint based	EULAR/ACR 2015	Lee[13]	38	0	34	43	0.53	1	0.52	1	NA	NA	NA	NA	NA
	ACR 1977	Jia[8]	110	10	26	75	0.81	0.88	0.89 ().85-0.92)	0.88 (0.81-0.93)	7.3 (4.6-11)	0.07 (0.00-0.74)	94 (9.6-919)	NA	NA
		Wu[17]	140	6	3	42	0.98	0.97							
	MSU-detection	Bongartz[3]	36	7	4	34	0.90	1	0.92 (0.81-0.97)	0.81 (0.69-0.90)	4.8 (2.9-8)	0.11 (0.04-0.26)	48 (15-162)	NA	NA
		Glazebrook [20]	12	4	0	15	1	0.89							

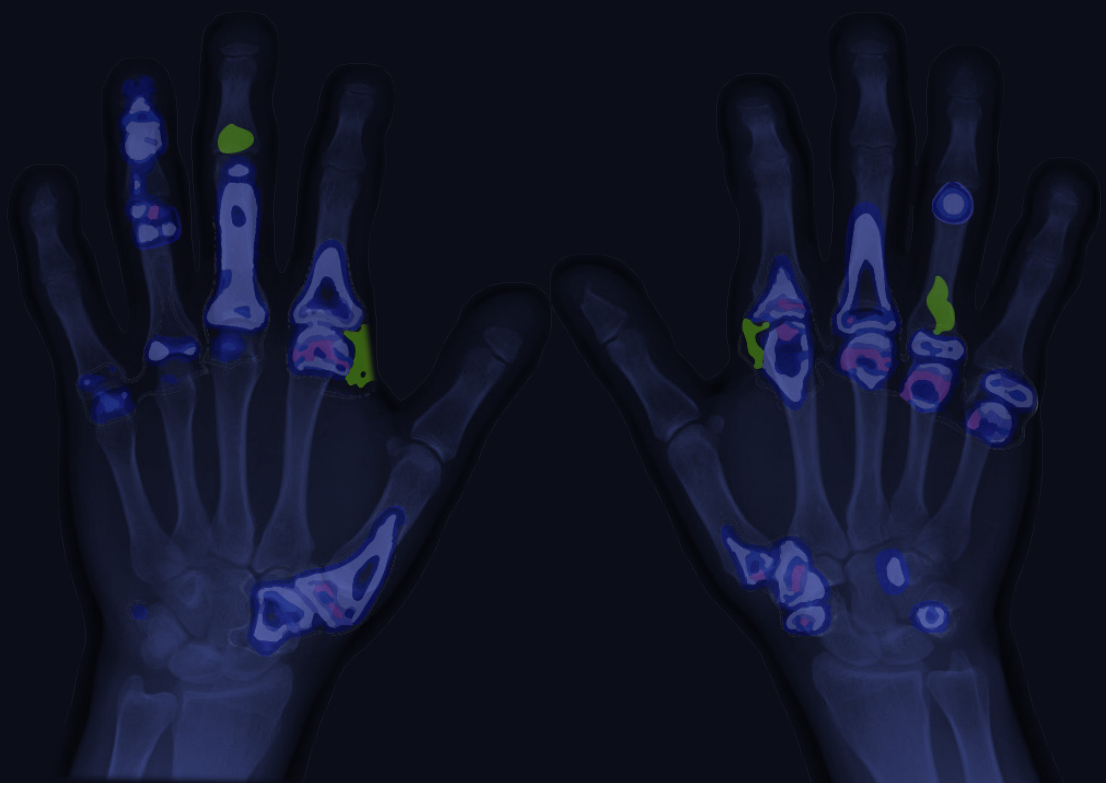
TP, true positive; FP, false positive; FN, false negative; TN, true negative; Sens, sensitivity; Spec, specificity; PLR, positive likelihood ratio; NLR, negative likelihood ratio, DOR, diagnostic odds ratio; AUC, area under the receiver operating characteristic curve; MSU, monosodium urate, ACR, American College Rheumatology criteria set, EULAR, European League Against Rheumatism criteria set; NA, not applicable, Q: Q-index, the point where sensitivity and specificity are equal, which is the point closest to the ideal top-left corner of the ROC space; SE: standard error

Table 3. Diagnostic accuracy of DECT in subgroup recent onset gout (≤ 6 weeks).

Study: first author	Reference standard	TP	FP	FN	TN	Sens	Spec	Pooled Sens (95% CI)	Pooled Spec (95% CI)	Pooled PLR (95% CI)	Pooled NLR (95% CI)	Pooled DOR (95% CI)
Lee[13]	EULAR/ACR 2015	38	0	34	43	0.53	1	0.55 (0.46-0.64)	0.89 (0.84-0.94)	5 (1.80-15)	0.46 (0.27-0.79)	17 (2.7-109)
Jia[8]	ACR 1977	10	10	18	75	0.36	0.88					
Bongartz[3]	MSU-detection	23	7	4	34	0.85	0.83					

TP, true positive; FP, false positive; FN, false negative; TN, true negative; Sens, sensitivity; Spec, specificity; 95% CI, 95% confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio, DOR, diagnostic odds ratio; MSU, monosodium urate, ACR, American College Rheumatology criteria set, EULAR, European League Against Rheumatism criteria set. Heterogeneity of studies prohibited calculation of area under the receiver operating characteristic curve. All studies are joint-based evaluation.

Chapter 3



The performance of Dual-energy CT in the classification criteria of gout: a prospective study in subjects with unclassified arthritis

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Abstract

ABSTRACT

Objective: To establish the performance of (subsets of) the 2015 ACR/EULAR gout classification criteria in patients with unclassified arthritis, and to determine the value of Dual-Energy-CT (DECT) herein. Reference was the monosodium urate (MSU) crystal detection result in synovial fluid (SF) at polarization microscopy.

Methods: We included subjects with acute, unclassified mono or oligoarthritis, who underwent SF analysis and DECT. Performance was assessed by calculating area under the receiver operating characteristic curve (AUROC) of 1) the clinical criteria subset, 2) the clinical+serum urate subset, and 3) the full set (including DECT).

Results: Of the 89 subjects enrolled, 40 met the clinical+serum urate subset criteria, and 49 (55%) subjects did not. Of these 49, 30 had a negative microscopy result, of whom 15 had positive DECT; of these 15, 14 met the full set criteria only after adding the positive DECT result. For the clinical-only subset, AUC's were 0.68 and 0.69 without and with DECT result, respectively and for the clinical+serum urate subset without and with DECT, AUC's were 0.81 and 0.81, respectively (results n.s.).

Conclusion: Adding the serum urate results to the clinical subset improves the performance, but adding the DECT result does not, neither does adding the DECT results to the clinical+serum urate subset. However, DECT seems to have an additive value in gout classification, especially when microscopy of SF is negative; 14/89 of patients (16%) only met the classification criteria with the use of DECT.

KEYWORDS: Gout, DECT, additive value, diagnostic accuracy, unclassified arthritis

INTRODUCTION

Gout is a monosodium urate (MSU) deposition disease, especially in joints but also frequently at periarticular structures, such as tendons.[1] Diagnosis is based on clinical presentation, and typically confirmed by demonstration of MSU crystals in synovial fluid (SF) or periarticular depositions.[1] However, results may be false negative due to sampling error (no SF obtained because of incorrect placement of the needle in the affected joint, or an extra-articular location of the MSU deposits, e.g. at tendons around the joint) or due to incorrect microscopy.[2] In addition, not all joints can (easily) be aspirated. Early and accurate diagnosis of gout is crucial, since the treatment is distinctly different from that of other types of inflammatory arthritis.

A relatively new modality to image MSU deposits is Dual-Energy CT scan (DECT).[3] DECT scanning is incorporated into the 2015 ACR/EULAR classification criteria, which consist of 4 clinical, 2 laboratory (serum urate and SF fluid analysis) and 2 imaging (DECT OR ultrasound, and conventional radiography) criteria.[4] Several studies with various methodologies have investigated the accuracy of DECT for gout.[3,5-11] These studies have primarily involved subjects with established disease, in whom the diagnosis is clinically obvious without using DECT. Only 3 studies assessed subgroups with recent onset disease and no prior diagnosis of gout;[3,12,13] these suggest that DECT may have limited sensitivity for detection of MSU deposition in recent onset gout in previously undiagnosed patients. However, these studies included relatively low numbers of subjects and showed marked variability in study design, reference standards and withdrawals, making it difficult to draw firm conclusions. Altogether, although DECT is a promising modality, its utility in recent onset gout requires further assessment. To date, to the best of our knowledge, no study has evaluated the additive value of and performance of DECT in subjects with unclassified arthritis with an indication for joint aspiration and no prior diagnosis of gout.

We aimed to establish the performance of (subsets of) the 2015 ACR/EULAR gout classification criteria in patients with unclassified arthritis, and to determine the value of Dual-Energy-CT (DECT) herein. Reference was the monosodium urate (MSU) crystal detection result in synovial fluid (SF) at polarization microscopy. Additionally, we explored subject and disease characteristics associated with a positive DECT result in patients with unclassified arthritis and indication for joint aspiration.

METHODS

Study subjects

We screened subjects age> 18 years, who presented to the Rheumatology outpatient clinic of Meander Medical Center, Amersfoort, the Netherlands because of mono- or

oligoarthritis (1-3 swollen joints) with an indication for joint fluid aspiration. Subjects with MSU proven gout in history or on uric acid lowering therapy were excluded. The study was conducted according to the ethical principles of the declaration of Helsinki and approved by the Medical Research Ethics Committee - United on research involving human subjects (MEC-U) at Nieuwegein, the Netherlands. The study was registered at the Netherlands trial register with number 5826 and at the ClinicalTrials.gov with number NCT03038386. All included subjects provided informed consent.

Clinical data and covariates of interest

The following variables were collected: patient demographic data; DECT results (positive or negative); clinical, laboratory and imaging features known from the literature as predictor variables of DECT results: gender, body mass index (BMI in kg/m^2), disease duration (the period from start of arthritis symptoms till the DECT investigation), uric acid levels between flares, creatinine clearance, joint involvement at the moment of DECT: type of joint involved (for regression analyses classified as MTP1 or other joint), result of microscopy (MSU crystals yes/no).

Interventions

Testing of SF

Polarization microscopic detection of MSU crystals in SF is generally regarded as the most specific, though not very sensitive, method to diagnose gout.[14] If subjects presented with more than one swollen joint, the clinically most prominently involved joint was aspirated and chosen as index joint. Per protocol we also intended to perform ultrasonographic guided joint aspiration in those with negative blind aspiration result and positive DECT, but only 2 patients consented at that stage.

Two experienced (≥5 years clinical experience) rheumatologists performed polarisation microscopy on all adequate samples within one hour of sample acquisition; a definite classification (and diagnosis) of gout was made if needle-shaped, negatively birefringent crystals were seen.[15]

DECT

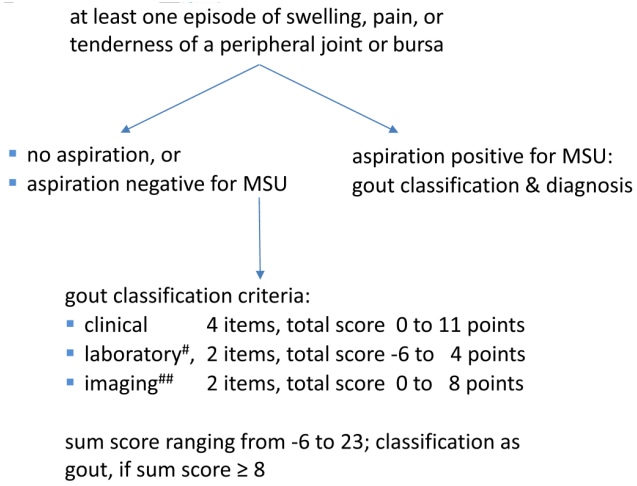
Subject were scanned within 6 weeks of joint aspiration according to the protocol, comprising three sets of DECT images with limbs scanned in pairs; the hands/wrists, feet/ankles, and knees. The technical details of DECT have been described elsewhere.[5] In brief, the SOMATOM Definition Flash Dual Source CT scanner (Siemens Healthcare) was used, with 140 kV/ 55 mA for one tube and 80 kV/ 243 mA for the other. Collimation of 0.6 mm was reconstructed to 0.75 mm slices and a 2 material decomposition algorithm performed on a multi-technique CT workspace (SW-Version VA20 Siemens Healthcare) using Syngo dual-energy Siemens Healthcare software. The urate-specific difference in attenuation

between the two energy levels allows accurate detection of MSU, which is then color coded as green and fused with the standard greyscale cross-sectional and 3D CT images.

A musculoskeletal experienced (≥5 years clinical experience) radiologist who was blinded to the subject's microscopy results evaluated the images, which were classified as positive for gout if green pixilation ≥3 mm was observed in or around (e.g. at tendons) the index joint (positive at the joint level) or at other locations (positive at the patient level). Artifacts known to produce green pixels near a joint, e.g. nail beds and metal prostheses, were excluded for classification as gout.

Gout classification criteria

We used subsets of the 2015 ACR/EULAR classification criteria; [4] the subsets and their subscores are summarised in Figure 1.



Legend Figure 1. The 2015 ACR-EULAR classification criteria. MSU, monosodium urate; DECT, dual-energy computed tomography.

First, a clinical-only subset (gout clinical score), in which laboratory domain and imaging were not included, mimicking the daily practice of primary care at the first presentation, where SF analysis is very infrequently performed and the timing of the urate assessment may be an issue. Second, a clinical+serum urate subset, consisting of clinical domain and intercritical serum urate level, in which imaging was not included, mimicking the situation often present at the time of the first visit to a rheumatologist. DECT imaging results were added to both subsets to assess if this improved their performance. As only 6 patients had joint erosions, we chose not to include radiography. We used consensus labels and definitions for gout. [16]

Analyses

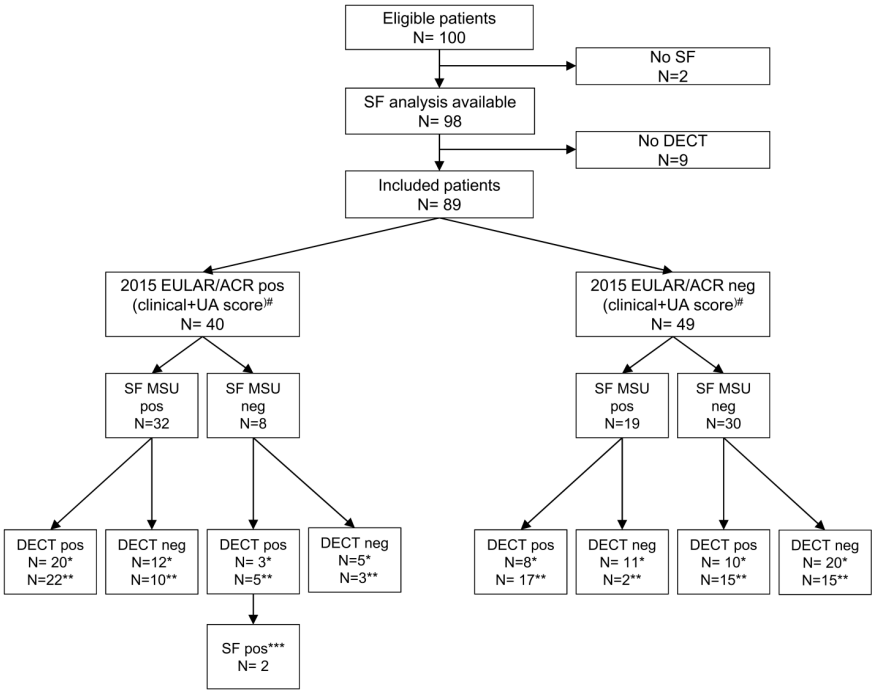
The relationships between the gold standard (MSU crystals in SF) and the criteria subsets were assessed in multivariable logistic regressions; the probabilities of the regressions were used for receiver operating characteristic analyses and curves and areas (AUROCs). For the clinical subset, the score of the 4 items were used, for serum urate an actual intercritical value, and for DECT a score of 0 (negative) or 1 (positive). The AUCROCs of the subsets were compared using a Z-test. Additionally, the 2015 EULAR/ACR full set gout classification criteria was used to score the patients (cut-off 8 points), with or without DECT results at patient level.

The following test characteristics of DECT in (subsets of) gout classification criteria with MSU in SF as reference standard were calculated on the joint-/localisation level and patient level: the overall accuracy and sensitivity, specificity, positive predictive value, negative predictive value; for these the values at the maximum sum of sensitivity and specificity were chosen.

Standard descriptive statistics were used: numerical data are given as mean and standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) in case of skewed distribution. DECT result and microscopy result were analysed as dichotomous data. Univariable and multivariable logistic regressions were used to identify factors associated with positive DECT result, see Supplementary Table S1 and Supplementary Data S1. A manual backward stepwise technique was performed, removing variables with p values > 0.1, starting with the highest p-values, until all p values were ≤ 0.1. All statistical analyses were performed with SPSS v22.0 for Windows (SPSS, Chicago, Illinois, USA) and NCSS v12 (NCSS, LLC. Kaysville, Utah, USA). All tests were two-sided; p values < 0.05 were considered statistically significant.

RESULTS

Between April 2016 and August 2018, 100 consecutive subjects meeting the entry criteria were screened, 11 of these dropped out, because of unavailable SF or DECT imaging of the arthritic joint (2 and 9, respectively), see study flow in Figure 2.



Legend Figure 2. Study flow. SF, synovial fluid; ACR-EULAR American College Rheumatology/ European League Against Rheumatism; #, EULAR/ACR-EULAR clinical+serum urate subset score; pos, positive; neg, negative; DECT, dual-energy computed tomography; MSU, monosodium urate, *, joint-based evaluation; **, patient based evaluation;*** SF positive for MSU crystals at ultrasound guided aspiration after positive DECT result.

The demographic and clinical characteristics of the subjects included in the analyses are summarized in Table 1.

89 patients were analysed. Of them, 51 (57%) were classified as having gout based on detection of MSU crystals in SF. The SF analysis for MSU was negative in 38 subjects (43%). DECT was positive in 59 subjects, in 55 of them (93%) in feet or ankles.
Of the 31 subjects with the index joint cranially of feet/ankles and of the 58 subjects with index joint at feet or ankles, DECT was positive at person level in 19 and 40 subjects, respectively; of these, 15/19 and 40/40 had DECT positive at feet or ankles.

Additive value of DECT in gout classification

Additive value of DECT to the clinical and the clinical+serum urate subsets

The performance of the clinical-only and the clinical+serum urate subsets of the 2015 ACR/EULAR gout classification criteria without and with DECT results are shown in Table 2.

Table 1. Demographics and characteristics of the subjects (N=89) included in analysis#

	SF MSU positive (N=51)	SF MSU negative (N=38)
Age, mean (SD), years	60 (16)	64 (12)
Male, N (%)	44 (86.3%)	28 (73.7%)
Symptom duration:*		
• median (IQR), months	12 (0.9-48)	5.5 (0.2-36)
• <3 month,	20 (39.2)	19 (50)
• 3-24 month	8 (15.7)	9 (23.7)
• >24 month	23 (45)	10 (26.3)
Index joint, N (%):		
• MTP1	32 (67.7)	8 (21.1)
• IP1 foot	3 (5.9)	1 (2.6)
• Mid-tarsal/ankle	5 (9.8)	9 (23.7)
• knee	6 (11.8)	13 (34.2)
• wrist	2 (3.9)	3 (7.9)
• MCP/PIP hand	3 (5.9)	4 (10.5)
BMI in kg/m^2, mean (SD)	29 (4)	28 (4)
Serum uric acid in mg/dl, mean (SD)	499 (88)	411 (101)
creatinine in µmol/L, mean (SD)	99 (36)	86 (20)
DECT imaging area		
• hands/wrists, feet/ankles, knees, N (%)	26 (56.7)	34 (86.2)
• hands/wrists, feet/ankles, N (%)	25 (43.3)	4 (13.8)

#, MTP1 joint was significantly more involved in SF MSU positive subjects than in MTP1 negative subjects. There are no other significant differences between the two subgroups.

*,self-reported; MTP, metatarsophalangeal; IP, interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal; DECT, dual-energy CT; BMI, body mass index

The addition of the DECT result to the clinical and clinical+serum urate subset did not significantly improve the performance, AUCROCs were similar, 0.68 and 0.69 and 0.81 and 0.81, respectively, see also Figure 3.

Additive value of DECT at patient level

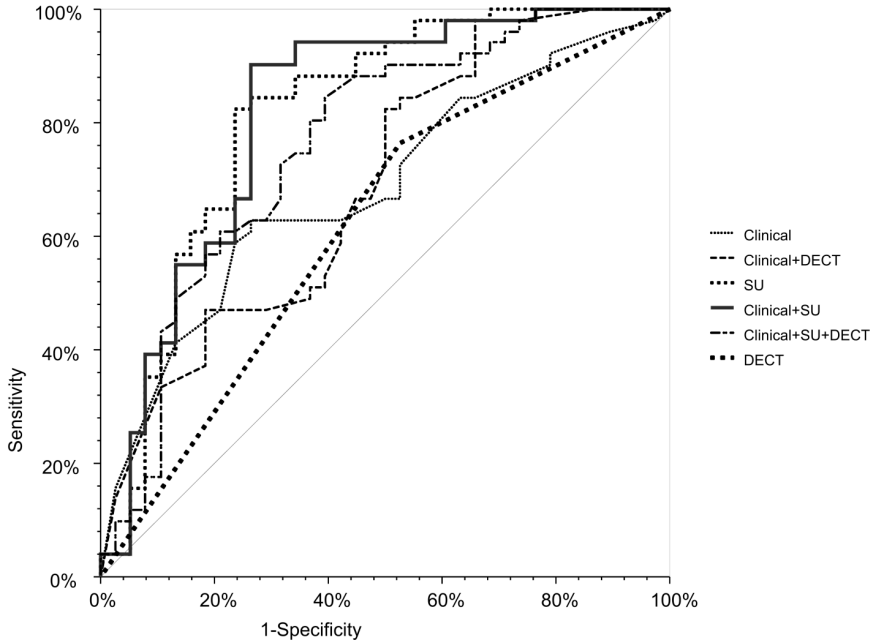
Of the 89 included subjects, 45% had a positive gout clinical-serum urate score and 55% had a negative gout clinical-serum urate score, see also Figure 2; of patients with a negative gout clinical-serum urate score, 61% had a negative microscopy result, but 31% had a positive DECT result at the patient level and 21% also at the index joint level. Of the 89 included subjects, 16% met the full set criteria only after adding the positive DECT result.

Finally, 68 of the 89 subjects (76.4%) who underwent DECT were classified already as having gout based on the MSU crystals in SF (51 patients) or fulfilling the 2015 ACR/EULAR classification criteria full set for gout (17 patients).

Table 2. The performance of clinical-only and clinical+serum urate subsets of the 2015 EULAR/ACR gout classification criteria without and with DECT

Subset 1	Subset 2	AUC 1	AUC 2	Difference in AUC's	95% CI of difference	Z-value	p-value
clinical-only	clinical-only + DECT	0.68	0.69	0.01	-0.06 to 0.05	-0.17	0.8
clinical+serum urate	clinical+serum urate + DECT	0.81	0.81	0.001	-0.02 to 0.2	0.26	0.8

AUC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; Monosodium urate crystal identification in synovial fluid is reference standard



Legend Figure 3. Receiver Operating Characteristic (ROC) curve analysis.

Area under the ROC curve (AUROC) for scores: clinical-only subset; clinical-only+DECT subset, clinical+serum urate (SU) subset score; clinical-SU-DECT, clinical+SU+DECT subset; DECT, dual-energy computed tomography. Reference standard: monosodium urate crystal detection in synovial fluid.

Test characteristics of DECT

Joint based and patient based evaluations

DECT was positive at the index joint in 28 of the 51 subjects with proven gout by MSU aspiration (55%). Among the 38 subjects in whom SF analysis was negative for MSU crystals, DECT demonstrated MSU deposition around the index joint in 13 cases. The index joint in these cases was: MTP1 (four cases), mid-foot (two cases), ankle (three cases), knee (three cases) and wrist (one case). Importantly, MSU deposits were located mainly in periarticular structures of the index joint of these subjects.

For joint based evaluation using MSU crystals in SF as reference standard, the sensitivity and specificity of DECT for detection of MSU deposits were 0.55 (95%CI 0.40 to 0.69) and 0.66 (95%CI 0.49 to 0.80), respectively, and for patient based evaluations, they were 0.77 (95% CI 0.63 to 0.87) and 0.47 (95%CI 0.31 to 0.64), respectively, see Table3.

Table 3. Test characteristics of DECT; reference standard monosodium urate crystal identification in synovial fluid

Subjects	DECT evaluation method	TP	FP	FN	TN	Sensitivity (95%CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95%CI)
All (N=89)	joint based	28	13	23	25	0.55 (0.40- 0.69)	0.66 (0.49 - 0.80)	0.57 (0.46-0.68)	0.52 (0.43-0.61	0.60 (0.49- 0.70)
	patient based	39	20	12	18	0.77 (0.63- 0.87)	0.47 (0.31- 0.64)	0.66 (0.58-0.73)	0.60 (0.45-0.73)	0.64 (0.53- 0.74)
Those with disease duration<3 months* (N=39)	joint based	11	7	9	12	0.55 (0.32- 0.76)	0.63 (0.38- 0.84)	0.61 (0.44-0.76)	0.57 (0.42-0.70)	0.59 (0.42- 0.74)
	patient based	16	10	4	9	0.80 (0.56- 0.94)	0.47 (0.24- 0.70)	0.62 (0.50-0.72)	0.69 (0.45-0.86)	0.64 (0.46-0.78)
Those with a neg. clinical+serum urate subset score (N=49)**	joint based	8	10	11	20	0.42 (0.20-0.67)	0.67 (0.47-0.83)	0.44 (0.28-0.62)	0.65 (0.53-0.74)	0.57 (0.42-0.71)
	patient based	17	15	2	15	0.89 (0.67-0.99)	0.50 (0.31-0.69)	0.53 (0.43-0.63)	0.88 (0.66-0.97)	0.65 (0.50-0.78)

*, self-reported; **, only clinical parameters and serum urate, i.e., without scoring synovial fluid and imaging DECT, dual-energy CT; TP, true positive; FP, false positive; FN, false negative; PPV, positive predictive value; NPV, negative predictive value; TN, true negative; 95% CI, 95% confidence interval. Values at the maximum sum of sensitivity and specificity are reported.

The sensitivity and specificity of DECT detection using MSU as the reference standard for the subgroup of subjects reporting joint symptoms ≤ 3 months, are shown in Table 3.
The test characteristics of DECT in subjects with negative gout clinical+serum urate subset of the classification criteria are shown in Table 3,

Clinical, laboratory and imaging variables associated with the DECT result
Positive DECT results were significantly associated with MTP1 joint involvement, positive results for MSU crystals in SF of the index joint, serum uric acid levels between flares, and serum creatinine. In contrast, self-reported joint symptoms duration, BMI and gender showed no significant associations, see Supplementary Table S1.

At multiple logistic regression, MTP1 joint involvement was the only variable of those mentioned above remaining in the model at a cut-off selection level of p≤0.1, but not statistically significantly (OR 2.31, p=0.09).

The urate volume on DECT was calculated in 52 of the 59 DECT positive subjects after exclusion of artifacts. The median urate volume on DECT was 0.11 (IQR 0.05-0.38) cm^3; the median urate volume in the feet and ankles was 0.07 (IQR 0.03-0.26) cm^3. For patients with a self-reported symptom duration ≤ 3 months (n=23), median urate volume was 0.11 (IQR 0.05-0.45) cm^3; for 3-12 month (n=5), it was 0.10 (0.03-0.45) cm^3, for 12-24 months (n=5), it was 0.27 (IQR 0.10-3.02) cm^3 and for > 24 months (n=19), it was 0.08 (IQR 0.04-0.25) cm^3.

DISCUSSION

In the studied population of patients with unclassified mono and oligoarthritis, the performance of clinical-only and clinical+serum urate subsets of the 2015 ACR/EULAR gout classification criteria was fair and good, respectively. Addition of DECT to these scores did not significantly improve the performance. We found a lower performance of the clinical-only and clinical+serum urate subsets compared to the SUGAR study [17], (0.68 vs 0.89, and 0.81 vs 0.89, respectively), probably because of the lower disease severity (e,g, fewer flare recurrences, absence of tophi) in subjects with short disease duration.
Our results demonstrate that DECT has an additive value to clinical algorithms in subjects with unclassified arthritis when microscopy of SF fails to demonstrate the presence of MSU crystals: 14/30 of those subjects met the 2015 EULAR/ACR full set classification criteria for gout only after a positive DECT result. Importantly, MSU deposits were mainly located in periarticular structures of the index joint in the majority of these subjects, explaining the negative SF-results. Although classification criteria are not intended to make diagnoses in individuals in daily medical practice,[4] MSU crystal detection in SF as classification criterion also establishes the diagnosis gout in an individual. As per protocol we intended to perform ultrasonographic guided joint aspiration in those with negative blind aspiration

result and positive DECT, but only 2 patients consented at that stage. The SF of these 2 patients was positive for MSU crystals.

All 40 subjects with positive DECT result at the patient level and the index joint at feet/ankles had a positive DECT result at least at feet/ankles. Of the 19 subjects with positive DECT result at the subject level and an index joint cranially of feet/ankles, 15 (79%) (also) had a positive DECT result at the feet/ankles. Therefore, we suggest that scanning of the index joint and of feet/ankles in all patients with mono/oligoarthritis suspected of gout would be a clinically rational choice.

The availability, cost, and the need for trained personnel limit use of DECT in routine clinical practice. Safety concern includes potential long term effect (e.g., from accumulated radiation exposure). DECT's radiation dose is estimated to be 0.5 mSv per region scanned (eg, 0.5 mSv for both hands and wrists, which are scanned together).[6] Note that the average annual natural background radiation dose is approximately 2.4 mSv.[18] This radiation exposure issue should be weight against the potential effects of misdiagnosis, including delay in initiating of failure to initiate appropriate treatment for gout.

As gout is a deposition disease, we expected disease duration to be correlated with the urate volume on DECT and the chance of a positive DECT result. However, no major difference in MSU volume on DECT between subjects reporting shorter or longer reported disease duration was found, nor a significant association of the chance of a positive DECT result and reported disease duration. Similarly, we found no major difference between accuracy of DECT in the subjects with a disease duration shorter than 3 months and overall accuracy. An explanation could be that the disease duration was based on recall of the patients; it might be difficult for them to differentiate between the symptoms of gout or of other joint condition such as osteoarthritis, especially as gout predominantly manifests in osteoarthritic joints.

Our study has some limitations. Patients were included with mono- or oligoarthritis (1-3 swollen joints); this could have yielded a biased sample: gout could be polyarticular at onset and also could be present at atypical localizations, such as the spine; we only made DECT images of the hands/wrists, feet/ankles, and knees. In 29 of 89 subjects (32%), DECT imaging was not performed of the knees (protocol violence), but in none of these patients the knees were clinically suspected of gout. Only 2 of 60 subjects with complete DECT results had urate deposition limited to the knee joint area. There is no inter-reader and intra- reader reliability testing performed regarding the evaluation of the DECT imaging. However, the radiologist were experienced (≥5 years clinical experience) and artifacts known to produce green pixels near a joint, e.g. nail beds and metal prostheses, were excluded for classification as gout. Finally, our study represents the results of a single center. Experience of the rheumatologist performing the SF aspirations and polarization microscopy may impact the likelihood of detecting MSU crystals.[2]

Strengths of our study are that it was prospective, and that, in contrast to several studies in literature, we included only patients with undiagnosed gout and a short disease

duration, not patients with established, diagnosed gout. Furthermore we analysed results separately on the patient and joint level.

CONCLUSION

DECT seems to have additive value in gout classification in subjects with undifferentiated arthritis when microscopy of SF is negative. Based on our study results, we recommend that not only the index joint is scanned, but also the feet/ankles in all patients with mono/oligoarthritis suspected of gout, in whom microscopy of SF is negative.

KEY MESSAGES

- DECT has additive value in gout classification in subjects with periarticular monosodium urate deposits
- DECT did not improve the performance of clinical criteria in new gout at group level
- Scanning of index joint and feet/ankles in patients suspected of gout would be a clinically rational choice

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Supplementary file

Univariable and multiple logistic regression to identify factors associated with positive DECT result

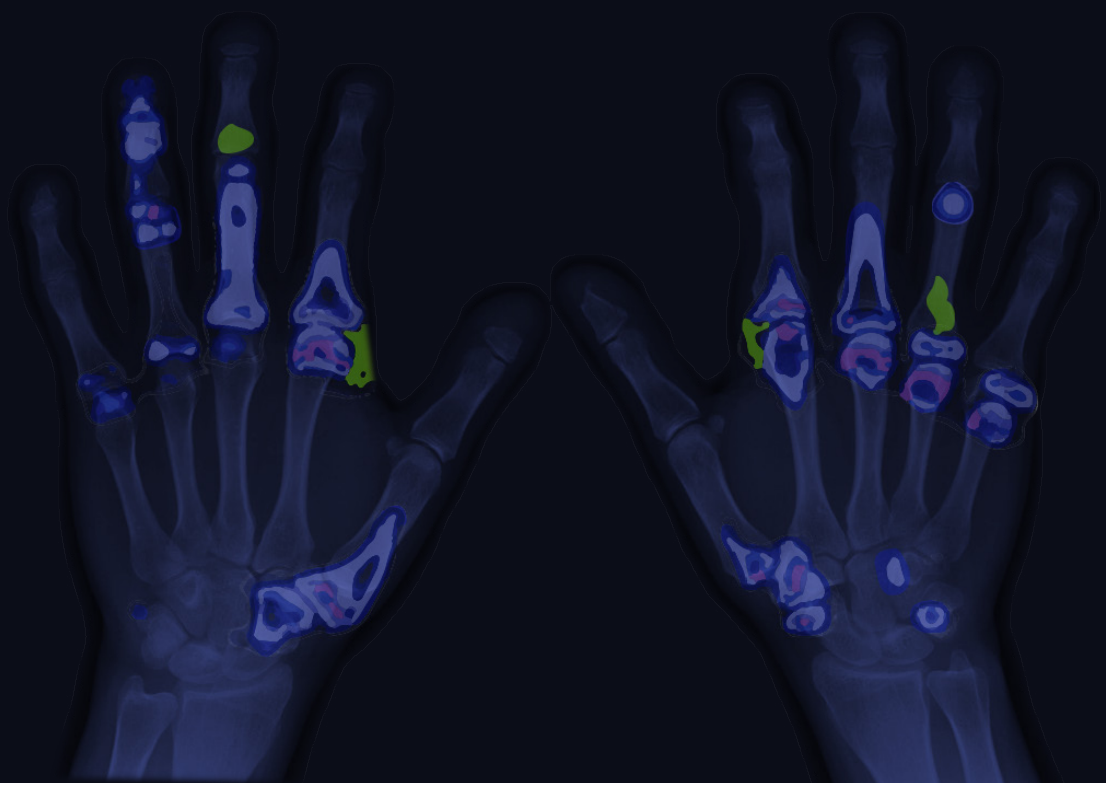
Univariable logistic regression was used to identify factors associated with positive DECT result, entering the variables mentioned in Table 1 below. Odds ratios (OR) were computed with corresponding 95% confidence intervals (CI). Variables with p< 0.10 in these univariate analyses were entered in a multiple logistic regression model as independent variables, with the DECT result (positive/negative) as dependent variable. A manual backward stepwise technique was performed, removing variables with p values > 0.1, starting with the highest p-values, until all p values were ≤ 0.1. All statistical analyses were performed with SPSS v22.0 for Windows (SPSS, Chicago, Illinois, USA). A p value of < 0.05 is considered statistically significant.

Table S1. Univariate regression analyses of factors associated with positive DECT result

Variable	OR (95% CI)	p
gender (reference: male gender)	0.67 (0.22-1.97)	0.4
BMI (per kg/m^2)	1.01 (0.90-1.14)	0.7
disease duration in month*	1 (0.99-1.01)	0.9
intercritical serum uric acid levels (per µmol/l)	1.006 (1.001-1.011	0.01
serum creatinine (per umol/l)	1.032 (1.002-1.062)	0.03
joint involvement at the moment of DECT: MTP1 vs other joints (reference: other joints)	3.43 (1.43-8.29)	0.006
MSU crystals in SF yes/no (reference: no)	2.95 (1.18-7.25)	0.02

*, self-reported; OR, odds ratio; 95%CI, 95% confidence interval; DECT, dual-energy computed tomography; MTP1, metatarsophalangeal joint 1; BMI, body mass index; MSU, monosodium urate; SF, synovial fluid.

Chapter 4



Diagnostic and therapy outcomes in gout using dual-energy CT: one-year follow-up study in daily practice

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Abstract

ABSTRACT

Objective: to establish the performance of the 2015 ACR/EULAR gout classification criteria in patients with unclassified arthritis, with as reference the clinical gout diagnosis yes/no after 1-year follow-up. Additionally, to explore the use and efficacy of uric acid lowering therapy (ULT) in daily clinical practice in the new gout patients.

Methods: A cross-sectional 1-year follow-up study was performed in subjects with unclassified arthritis, who at baseline were screened for gout applying the gout classification criteria, including imaging with dual-energy CT, but without ultrasonography and joint X-rays.

Results: 71 patients were included; all 63/71 patients diagnosed as having gout at baseline also had a gout diagnosis after one year, and vice versa, no patient not diagnosed with gout at baseline had the clinical diagnosis of gout at one year. Sensitivity, specificity, positive and negative predictive value, and accuracy values (95% CI) of the classification criteria were 0.91 (0.80-0.96),1 (0.63-1) 1, 0.57 (0.38-0.74) and 0.92 (0.83-0.97), respectively. The area under the receiver operating characteristics curve (95% CI) was 0.95 (0.91-0.99).
ULT was started in 49/63 (78%) of gout patients; 45/49 (92%) of them had serum uric acid (SUA)≤ 360 µmol/l and no recurrent gout attacks at/during one-year follow-up.

Conclusion: The 2015 ACR-EULAR gout classification criteria performed well for the diagnosis gout in clinical practice. Most gout patients had been treated successfully according to the current guidelines.

INTRODUCTION

Gout is a monosodium urate (MSU) deposition disease, especially in joints but also frequently at periarticular structures, such as tendons.(1) Diagnosis is based on clinical presentation, and confirmed by demonstration of MSU crystals in synovial fluid (SF).(1) However, joint aspiration may be technically difficult or impossible to perform. In addition, SF aspirations may not reveal MSU crystals in up to 25% of patients with gout.(2) Early and accurate diagnosis of gout is crucial for targeted treatment, since the treatment of gouty arthritis is distinctly different from that for other types of inflammatory arthritis. With ultrasonography and Dual Energy CT (DECT) scanning,(3) MSU deposits can be visualised. Both are incorporated in the 2015 EULAR/ACR gout classification criteria.(4) Classification criteria are not intended to make diagnoses in individuals in daily medical practice,(5) but MSU crystal detection in SF is a gout classification criterion and establishes the diagnosis gout in an individual. A question of importance is the place of the 2015 EULAR/ACR classification criteria for gout diagnosis. The aim of this study was to establish the performance of the 2015 ACR/EULAR gout classification criteria in patients with undifferentiated arthritis, with as reference the clinical gout diagnosis yes/no, according to the rheumatologist after 1-year follow-up. Additionally, to explore the use and efficacy of uric acid lowering therapy (ULT) in daily clinical practice in newly diagnosed gout patients.

METHODS

Study subjects

The study population involved 71 patients with unclassified arthritis who had participated in an earlier study on the value of DECT in early gout,(6). They had been included at the Rheumatology outpatient clinic of the Meander Medical Center, The Netherlands between April 1, 2016 and Augustus 31, 2018 with previously undiagnosed mono or oligoarthritis (2-3 swollen joints). Patients with MSU proven gout in history or ULT had been excluded. Of 18/89 patients, we did not receive informed consent for this follow-up study; these patents were not included, leaving 71 patients for analyses. The study was conducted according to the ethical principles of the declaration of Helsinki and approved by the Medical Research Ethics Committee - United (MEC-U) at Nieuwegein, the Netherlands. The study was registered at the trial register of the Netherlands (NTR) with number 5826 and at the ClinicalTrials.gov with number NCT03038386.

Material and methods

Baseline

The details of the study on the value of DECT haven been reported previously.(6) Briefly, the following variables were collected: patient demographic data, gender, body mass index (BMI in kg/m^2), disease duration (the time from start of arthritis symptoms till the

DECT investigation), uric acid levels between flares and type of joint involvement at baseline. Patients underwent blind diagnostic aspiration of SF from the inflamed joint. Testing of SF was performed on all adequate samples. We applied the 2015 ACR/EULAR full-set classification criteria (cut-off 8 points) consisting of clinical domain, laboratory (intercritical serum urate level, synovial fluid analysis), but for imaging only DECT,(4) excluding radiography (as only 3 patients had joint erosions) and ultrasonography (not performed because of feasibility reasons).
Patients underwent DECT scan of hands/wrist and ankle/feet and knees within 6 weeks. The technical details of our imaging method have been described elsewhere.(7) We chose to analyse depositions in feet and ankles only, because depositions in other regions were very scarce.
Patients clinically diagnosed as having gout according to the rheumatologist were treated according to the guidelines according to treated to target approach, serum uric acid (SUA) target≤360 µmol/l.

One-year follow-up
Data on clinical diagnosis (according to the treating rheumatologist), arthritis attacks and ULT use were collected after 1-year from the medical records in the rheumatology outpatient clinic and from questionnaires in case of patients were followed-up by the general practitioner.
In the case of a recurrent attack during the follow-up in patients with SF negative for MSU at baseline, microscopic SF analysis was repeated.

Analyses
Standard descriptive statistics were used: continuous data are given as mean and standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) in case of skewed distribution. DECT, microscopy result and the clinical diagnosis were analysed as dichotomous data. To test for significant differences between gout subjects using and no using ULT, we used chi-square test for categorical data and Mann-Whitney U or unpaired t- test for continuous data. Statistical tests were 2-sided, and p-values <0.05 were considered significant. All statistical analyses were performed with SPSS v22.0 for Windows (SPSS, Chicago, Illinois, USA).

Results
Demographic and clinical characteristics of the 71 included subjects are summarized in Table 1.

All 63/71 patients diagnosed as having gout at baseline also had a gout diagnosis at one year and of the patients not diagnosed with gout at baseline none had the clinical diagnosis of gout at one year. Of three patients with no diagnosis at baseline after all

Table 1. Characteristics of the subjects (N=71) included in analysis

	Diagnosis**	
	gout (n=63)	**no gout (n=8)**
age in years, mean (SD)	62 (14)	59 (14)
male gender, N (%)	53 (84)	5 (63)
symptom duration* at baseline in months, median (IQR)	12 (1-48)	8 (0.5-33)
joint involvement at baseline N (%):		
MTP,	33 (52)	1 (12)
ankle/midfoot	12 (19)	1 (12)
other joint	18 (29)	6 (76)
SUA intercritical in µmol/l, mean (SD)	484 (63)	337 (71)
2015 ACR/EULAR criteria baseline score, mean (SD)	10.3 (2.5)	2.6 (1.5)
2015 ACR/EULAR criteria ≥8 points, N (%)	57 (90)	0 (0)
MSU crystal positive, N (%)	44 (70)	0 (0)
DECT positive, N (%)	49 (78)	0 (0)

* self-reported; **, all patients diagnosed with gout at baseline also had a gout diagnosis after one year

MTP, metatarsophalangeal; SUA, serum uric acid; DECT, dual-energy CT; MSU, monosodium urate;.

diagnostic procedures, at one year two had the diagnosis psoriatic arthritis and one Lyme's disease. The other 5 patients with no gout at one year had been diagnosed with osteoarthritis (n=3), Baker's cyst (n=1), and reactive arthritis (n=1). One patient with the clinical baseline diagnosis of gout in spite of negative results for SF-exam and DECT, had a positive SF-exam for MSU at an attack during follow-up.

Results (95% CI) for sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the gout classification criteria with the clinical gout diagnosis at 1 year as a reference standard were 0.91 (0.80-0.96),1 (0.63-1), 1, 0.57 (0.38-0.74) and 0.92 (0.83-0.97), respectively; the area under the receiver operating characteristics curve (95% CI) was 0.95 (0.91-1).

ULT therapy and arthritis attacks

Characteristics and therapy outcomes of subjects diagnosed as having gout are shown in Table 2.

Table 2. Characteristics and therapy outcomes at 1-year follow-up in gout subjects

	ULT use (n=49)	no ULT use (n=14)	p
subjects with gout attack during 1-year follow-up, N (%)	2 (4)	4 (29)	0.01
intercritical SUA at baseline in µmol/l, mean (SD)	505 (81)	411 (85)	0.002
baseline DECT volume at ankle/feet in mm^3, median (IQR)	0.10 (0.03-0.3)	0.05 (0.03-0.1)	0.1
baseline joint symptom duration* in months, median (IQR)	24 (1-66)	10 (0.1-36)	0.1
baseline frequency attacks per year, median (IQR)	2 (1-3)	1 (1-2)	0.3
subjects with SUA ≤360 µmol/l at 1-year, n (%)	45 (92)	n.a.	n.a.
subjects using colchicine at 1-year, n (%)	43 (88)	2 (14)	0.01

*, according to the patient; SUA, serum uric acid level; DECT, dual-energy computed tomography; SD, standard deviation; IQR, interquartile range; n.a, not applicable.

ULT (allopurinol, febuxostat or benzbromaron) was started in 49/63 (78%) patients diagnosed as having gout according to the rheumatologist; 8/63 patients choose not to start ULT; the rheumatologist did not recommend ULT in 6/63 patients because of negative SF and DECT result (1 patient) and very small urate depositions on DECT (volume<0.1 cm^3) in 5 patients; none of these 5 had arthritis attacks during one-year follow-up.
Of the 2/49 patients starting ULT discontinued the therapy because of adverse-effects; 45/49 (92%) had SUA≤ 360 µmol/l and no recurrent gout attacks during one-year follow-up.

Discussion

The 2015 ACR/EULAR gout classification criteria perform well for the diagnosis gout in clinical practice in patients with undifferentiated mono and oligoarthritis, with a very high sensitivity, specificity, PPV and moderate NPV. We found a higher performance of the 2015 ACR/EULAR gout classification criteria, compared to in a previous study (8), in which DECT was not performed.
According to the EULAR recommendations, ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation, and it is indicated in all patients with recurrent flares, tophi and urate arthropathy.(9) At one year, we found that in 78% of the gout patients in our study, ULT therapy had been initiated, of whom 92% had achieved the target of SUA⩽360 µmol/l. In a recent study,(10) only 45% of gout patients using ULT achieved this target at one year. An explanation could be the stricter treat-to-target approach applied at our rheumatology clinics.
The finding that the 5 patients without ULT, because of very small urate depositions, had no further arthritis attacks during one year follow-up; further research is warranted on the appropriate treatment approach in this patient group.
There are limitations to our study. First, patients were included with mono- or oligoarthritis (1-3 swollen joints); this could have yielded a biased sample: gout could be polyarticular at

onset and also could be present at atypical localizations, such as the spine. Second, 80% of the patients included at the baseline study, confirmed to participate in this follow-up study. Final, the relatively small sample size precludes drawing firm conclusions regarding ULT prescription in patients with no or scarce urate depositions on DECT.

Conclusion

The 2015 ACR-EULAR gout classification criteria performed well for the diagnosis gout in clinical practice. Most gout patients had been treated successfully according to the current guidelines.

KEY MESSAGES

- The 2015 ACR-EULAR gout classification criteria performed well for the diagnosis gout in clinical practice.
- The EULAR treatment aim of gout is in practice very feasible. Most aspects of gout management concorded well with published guidelines.

Footnotes

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- Competing interests: All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work.

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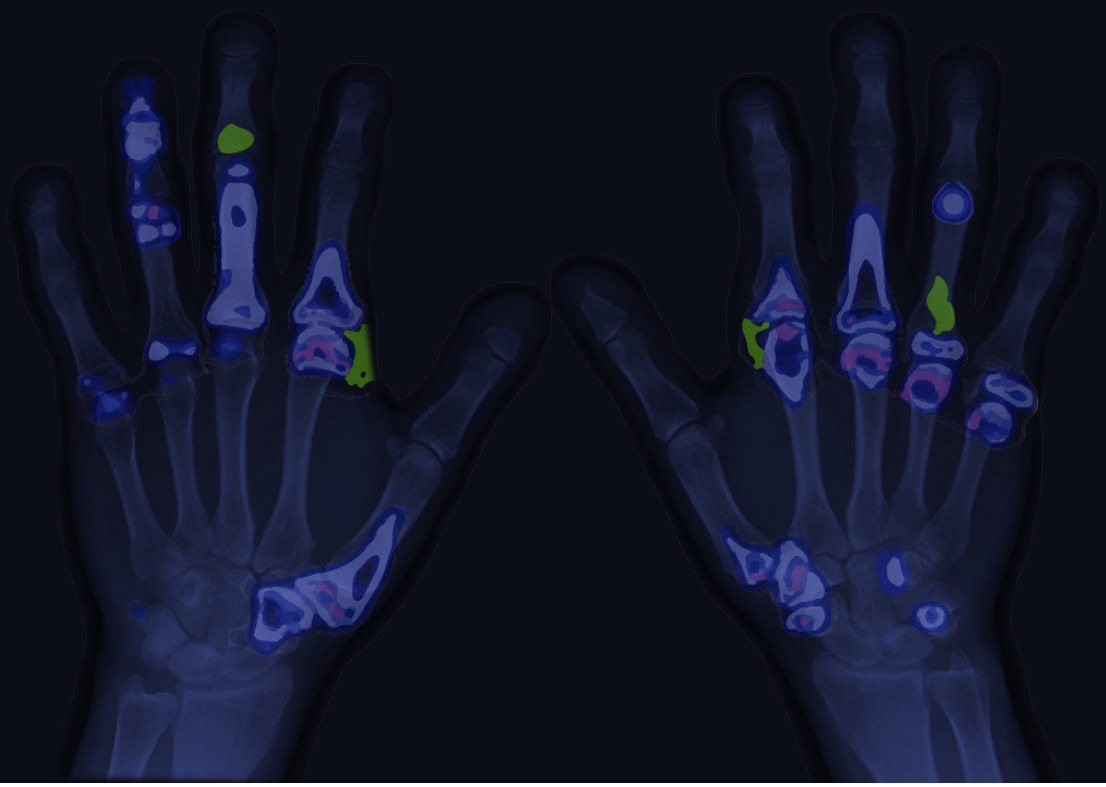
Chapter 5



Clinical vignette. An unexpected manifestation of gout

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A 76-year old woman without a prior diagnosis of gout was seen because of pain in her neck and arms and tingling in her shoulder regions during several months.
Examination revealed decreased mobility of neck and shoulder joints, no arthritis. MRI showed degenerative changes of facet joints and lesions suspected for metastases in the spine. SPECT-CT and PET-CT yielded lytic lesions and high FDG uptake, respectively, at cervical, thoracal, lumbar spine and acromioclavicular (AC) joints. Cervical spine and AC lesions were aspired; histology revealed fibrillar material, surrounded by histiocytes and multinucleate giant cells, strongly suggestive of a gout tophus,[1] but the aspirate was not fit for polarization microscopy. Lab showed a serum urate of 940 µmol/l. Dual-energy CT (DECT) was performed,[2] showing urate deposition at the cervical spine (Figure) and AC joints. The diagnosis of atypical gout with axial involvement was confirmed. Following treatment with allopurinol, alleviation of symptoms was achieved; serum urate after 6 year of follow-up still is ≤300 µmol/l.
Our case illustrates the importance of DECT in differentiating in the spine between tophaceous gout and other osteolytic lesions, such as malignancy.

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The authors declare no conflicts of interest.

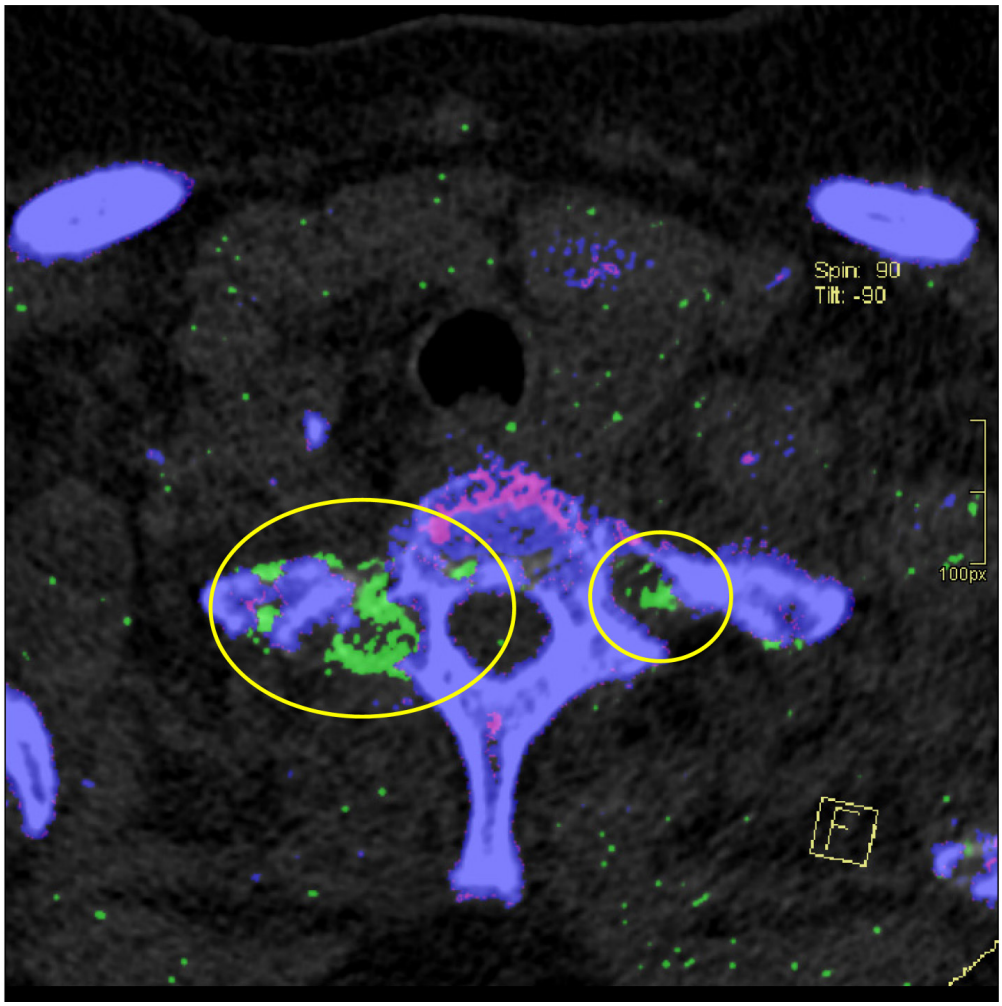
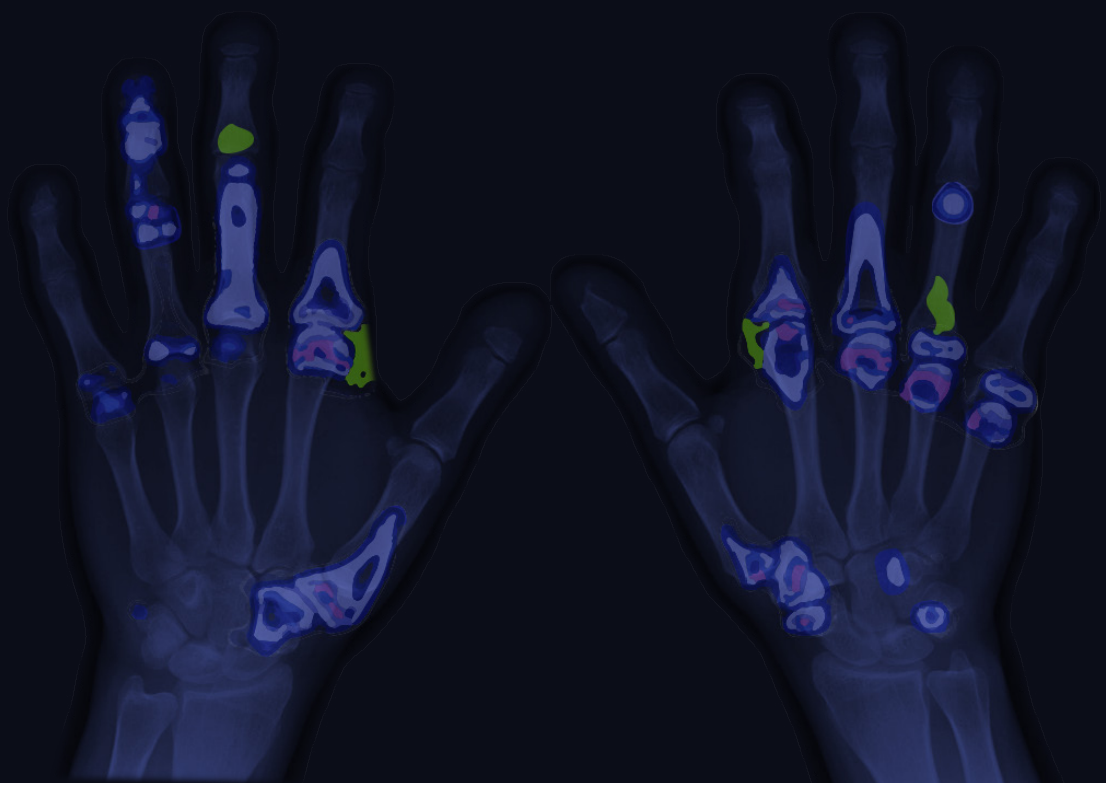


Figure legend: transversal image at level of 7th cervical vertebra; green pixilation>3 mm in diameter represent urate depositions (yellow circles)

Chapter 6



Gouty arthritis: decision making following dual energy CT in clinical practice, a retrospective analysis

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Clinical Rheumatology 2018 Jul;37(7):1879-1884.

Abstract

ABSTRACT

Objective: To establish whether DECT is a diagnostic tool, i.e. associated with initiation or discontinuation of a urate lowering drug (ULD). Secondly, to determine whether DECT results (gout deposition y/n) can be predicted by clinical and laboratory variables.

Methods: Digital medical records of 147 consecutive patients with clinical suspicion of gout were analyzed retrospectively. Clinical data including medication before and after DECT, lab results and results from diagnostic joint aspiration and DECT were collected. The relationship between DECT results and clinical and laboratory results was evaluated by univariate regression analyses; predictors showing a $p< 0.10$ were entered in a multivariate logistic regression model with the DECT result as outcome variable. A backward stepwise technique was applied.

Results: After the DECT 104 of these patients had a clinical diagnosis of gout based on the clinical judgment of the rheumatologist, and in 84 of these patients the diagnosis was confirmed by demonstration of monosodium urate (MSU) crystals in synovial fluid (SF) or by positive DECT. After DECT the current ULD was modified in 33 (22,4 %) of patients; in 29 of them ULD was started and in 1 it was intensified. Following DECT, the current ULD was stopped in 3 patients. In the multivariable regression model cardiovascular disease (OR 3.07, 95% CI 1.26-7.47), disease duration (OR 1.008, 95% CI 1.001-1.016), frequency of attack (OR 1.23, 95% CI 1.07-1.42), creatinine clearance (OR 2.03, 95% CI 0.91-1.00) were independently associated with positive DECT results.

Conclusion: We found that the DECT result increases the confidence of the prescribers in their decision to initiation or discontinuation of urate lowering therapy regimen in of mono- or oligoarthritis. It may be a useful imaging tool for patients who cannot undergo joint aspiration because of contraindications or with difficult to aspirate joints, or those who refuse joint aspiration. We also suggest the use of DECT in cases where a definitive diagnosis cannot be made from signs, symptoms and MSU analysis alone.

INTRODUCTION

Gout is a disease characterized by accumulation of monosodium urate (MSU) in joints and tissues [1]. The clinical presentation varies from arthritis of one joint e.g. the first metatarsophalangeal (MTP1), to severe polyarthritis and subcutaneous tophi and sometimes tophi around tendons [2]. Gout is associated with joint damage and increased cardiovascular morbidity and mortality [3-5].

Attacks of arthritis caused by gout are very painful, and the affected persons are often not able to perform normal daily activities and work [6,7]. Prevention with uric acid lowering drugs (ULD) of new attacks of gout and thus joint damage is an important goal of the treatment. ULD are very effective, especially if started early in the course of the disease [8-10]. Therefore, an early and accurate diagnosis of gout is crucial for targeted treatment and rapid alleviation of symptoms.

Diagnosis usually is based on clinical presentation, and confirmed by demonstration of monosodium urate (MSU) crystals in synovial fluid (SF) [2,11]. In daily clinical practice this is usually done by blind diagnostic joint aspiration [12,13], followed by polarized microscopy. Microscopic demonstration of MSU crystals in SF during an acute arthritis attack has sensitivity of 0.84 (95% CI, 0.77-0.92) and specificity of 0.99 to 1.00 [14,15]. However correct identification of crystals using polarized light microscopy in SF can be challenging [16].

Often though, the clinical presentation can be strongly suggestive of gout, whereas the aspiration is a dry tap or microscopy of the needle aspirate of SF is negative for MSU [14]. Results may be false negative due to a sampling error (no SF obtained because of incorrect placement of the needle in the affected joint, or an extra-articular location of the gout, (e.g. near tendons around the joint) or incorrect microscopy, or true negative in case of a different cause of arthritis (e.g. infection, reactive arthritis).

Furthermore, aspiration may be difficult or impossible to perform in some joints.

The newest modality to image MSU deposits is Dual Energy CT scan (DECT)[17-20].The examination findings are classified as positive if urate deposition is observed on any place, and as negative if no urate deposition is observed. In a systematic review [21], the pooled (95% CI) sensitivity and specificity of DECT for detecting gout, were 0.87 (0.79-0.93) and 0.84 (0.75-0.90), respectively with microscopic demonstration of MSU crystals in SF as a reference standard. DECT scanning is incorporated in the 2015 EULAR/ACR classification criteria [22]. The purpose of the current study was to analyze the clinical impact of dual-energy computed tomography (DECT) results on treatment regimen as measured by start or stop of ULD therapy after the DECT in patients with mono- or oligoarthritis possibly caused by gout. In addition, we investigated whether DECT results can be predicted by clinical, laboratory and imaging features. Furthermore, we analyzed the false negative DECT results, i.e. the percentage of patients with negative DECT results but a crystal proven gout diagnosis after one year.

METHODS

Study design

We retrospectively evaluated medical charts of all adult patients of our outpatient clinic who underwent DECT imaging between January 2013 and December 2014 because of mono- or oligoarthritis possibly caused by gout. For patients with negative DECT result a medical charts review was performed 1 year after DECT. The study was approved by the institutional review board of Meander Medical Centre, Amersfoort, the Netherlands (15-05).

Patients

Patient inclusion criteria were as follows: age> 18 years, DECT examination performed between January 2013 and December 2014 according to our gout protocol (see below) for clinical purposes to check the presence of uric acid crystals in or around the most affected (swollen or painful) joints.

Study outcomes:

Primary outcome: change in ULD defined by initiation or discontinuation of one or more of the following drugs: allopurinol, benzbromarone, febuxostat.
Secondary outcomes:

1. prediction of DECT results by clinical, laboratory and imaging variables.
2. comparison of disease duration between patients with positive and negative DECT result.
3. percentage of false negative DECT results defined as the clinical diagnosis crystal-proven gout after 1 year follow-up.
4. frequency of gouty attacks and uric acid levels between flares in patients with changes in therapy based on DECT.

Interventions of selected patients

DECT

All patients underwent DECT following the clinical suspicion of gouty arthritis by the outpatient clinic. Scans of the most affected joints and regions were made, using a dual source DECT scanner (SOMATOM Definition Flash Dual Source CT scanner; Siemens Healthcare). The following scanning parameters were used: 140 kV and 55 mA for the one tube and 80 kV and 243 mA for the other. A 2 material decomposition algorithm was performed on a multi-technique CT workspace (SW-Version VA20 Siemens Healthcare) using Syngo dual-energy Siemens Healthcare software. The material-specific difference in attenuation of urate between the two voltages allowed accurate detection of the MSU. This was color coded as green and fused with the standard greyscale CT image. DECT's radiation dose was estimated to be 0.5 mSv per region scanned (eg, 0.5 mSv for both

hands and wrists, which are scanned together)[20]. Images were recorded as both cross-sectional and 3D images. Imaging results were classified as positive for gout if green pixilation was observed around the index joint and/or in other locations of the imaged area. A musculoskeletal radiologist, previously informed about the clinical indications for imaging, evaluated the dual-energy CT images and recorded the locations of urate deposition(s). Artifacts known to produce green pixels near a joint, i.e., naillbeds, metal prostheses, beam hardening, were excluded.

Testing of SF

Experienced rheumatologists (5 years or more of clinical practice) examined the synovial fluid within one hour of sample acquisition using polarized microscopy

Statistical analysis

The following variables were collected: patient demographics, DECT results (positive or negative), initiation or discontinuation of ULD, frequency of gouty attacks and uric acid levels between flares in patients with changes in therapy based on DECT. In addition we registered clinical, laboratory and imaging features known from the literature as predictor variables of DECT results, i.e., gender, body mass index (BMI in kg/m^2), cardiovascular disease, diabetes mellitus, disease duration (the time in month from the start of the arthritis symptoms till the DECT), frequency of attacks (attacks per year over the past year before the DECT), uric acid levels between flares, creatinine clearance, joint involvement at the moment of DECT, MTP1 joint involvement in the past, result of microscopy (MSU crystals yes/no) around the date of the DECT, scanned joints by DECT: hands, feet, knees, elbows and other joints.

The 2015 EULAR/ACR classification criteria were used to score the patients (cut-off 8 points), with or without DECT [22]. In case of missing data by domain number 2 (characteristics of symptomatic episodes ever) 3 points were given.

Standard descriptive statistics were used: numerical data are given as mean ± standard deviation (SD) if normally distributed, or median and interquartile range (IQR) in case of skewed distribution. DECT and microscopy results were analysed as dichotomous data. Mann-Whitney U test was used to compare disease duration between patients with positive and negative DECT result. Univariable logistic regression was used to identify factors associated with positive DECT result, entering the predictors mentioned above. Odds ratios (OR) were computed with corresponding 95% confidence intervals (CI). Predictors showing a $p < 0.10$ in these univariate analyses were entered in a multiple logistic regression model with the DECT result as dependent variable. A manual backward stepwise technique was performed, removing stepwise the predictors with highest p-value, until all p values were ≤ 0.1.

Mann-Whitney U test was used to test for statistically significant difference of disease duration between patients with positive and negative DECT result.

All statistical analyses were performed with SPSS v22.0 for Windows (SPSS, Chicago, Illinois, USA). A p value of < 0.05 is considered statistically significant.

RESULTS

Between 1 January 2013 and 31 December 2014 a total of 147 DECT were performed in patients with mono- or oligoarthritis possibly caused by gout. The demographic and clinical characteristics of the patients at the time of DECT are summarized in Table 1.

Table1. The demographic and clinical characteristics of the patients (n=147) at the time of DECT

Age, mean (SD), years	**63.3 (13.6)**
Sex (N, %)	
Male	100 (68)
Female	47 (32)
Body Mass Index, mean (SD), kg/m^2	28.5 (4.9)
Cardiovascular disease (N, %)	57 (39)
Diabetes Mellitus (N, %)	21 (14.4)
Disease duration median (IQR), years	3 (6.6)
Frequency of attack during the past year (N, %)	
0-2	51 (34.5)
≥3	80 (54.1)
unknown	17 (11.5)
Uric acid levels between flares, mean (SD), (µmol/L)	442.5 (124.0)
Joint involvement at the moment of DECT (N, %)	
MTP1	52 (62.8)
other joints	93 (35.1)
unknown	3 (2.0)
Result microscopy of the index joint	
Diagnostic joint aspiration of the index joint (N, %)	86 (58.5)
MSU crystals present (N, %)	25 (17.0)
MSU crystals absent (N, %)	61 (41.5)
Clinical evidence of tophi N, (%)	26 (17.8)
Urate lowering therapy (Allopurinol, Benzbromarone, Febuxostat) use at the moment of DECT) (N,%)	
yes	28 (19.3)
no	115 (80.0)
unknown	4 (0.7)

DECT: dual energy computed tomography; MSU: monosodium urate; MTP, metatarsophalangeal.

Following DECT, 104 of these patients had a clinical diagnosis of gout based on the clinical judgment of the rheumatologist and in 84 of these patients the diagnosis was confirmed by demonstration of monosodium urate (MSU) crystals in synovial fluid (SF) or by positive

DECT result. The DECT and joint aspiration results of the index joint are summarized in Table 2.

Table 2. DECT and joint aspiration results

	joint fluid MSU positive (N,%)	joint fluid MSU negative (N,%)	no joint fluid aspiration (N,%)	2015 ACR/ EULAR positive (N,%)	2015 ACR/ EULAR negative (N, %)	Total
positive DECT	16 (10.88)	25 (17.0)	34 (23.12)	67 (45.6)	8 (5.5)	75 (51)
negative DECT	9 (6.12)	36 (24.48)	27 (18.4)	17 (11.5)	55 (37.4)	72 (49)
Total	25 (17.0)	61 (41.5)	61 (41.5)	84 (57.1)	63 (42.9)	147 (100)

DECT: dual energy computed thomography; MSU, monosodium urate.

Eighty-six of 147 patients underwent aspiration of the index joint. Joint fluid was MSU positive in 25 patients and MSU negative in 61 patients. Twenty-five patients with synovial fluid aspirate negative for MSU had positive DECT of the index joint.
Eighty-four of 147 patients (57.14%) fulfilled the 2015 EULAR/ACR criteria for gout, 54 (36.7 %) of which without taking DECT into consideration and 30 (20.4 %) meeting the criteria only after a positive DECT result.

DECT scans of the most affected joints were made. Other regions were scanned too if the treating rheumatologist had requested this, e.g. based on a history of joint inflammation in this region. Table 3 shows the distribution of scanned area and the DECT results.

Table 3. Distribution of DECT scanned area and DECT results of 147 patients (N, %)

DECT scanned area	N, %	Positive DECT (N,% of all patients)
ankles+ feet	70 (47.6)	36 (24.5)
ankles+ feet+ hands+ wrists	28 (19.0)	13 (8.8)
hands+ wrists	17 (11.6)	5 (3.4)
ankles+ feet+ hands+ wrists+ elbow	10 (6.8)	8 (5.4)
ankles+ feet+ knees	8 (5.4)	7 (4.8)
knees	5 (3.4)	3 (2.0)
elbow	3 (2.0)	0 (0)
other (sterno-clavicular, shoulders)	3 (2.0)	0 (0)
ankles+ feet+ knees+ hands+ wrists+ elbow	2 (1.4)	1 (0.7)
hands+ wrists+ elbow	1 (0.7)	1 (0.7)
Total	147 (100)	74 (50.3)

DECT: dual energy computed thomography.

Therapeutic impact of results of DECT

The DECT result increases the confidence of the prescribers in their decision to modify urate lowering therapy regimen in 33 (22.4%) of patients. Three patients had negative DECT and no MSU crystals at joint aspiration and the urate lowering therapy was discontinued. No gouty attacks were registered in these patients after 1-year follow-up. In 29 patients the urate lowering therapy was started and in 1 patient this was intensified based on the positive DECT result. 1-year follow-up data were available in 21 of these patients in our outpatient clinic. In 15 of these 21 patients the serum urate level was below 360 µmol/l (6 mg/dl) and no gouty attacks were registered in 13 of these patients.

The clinical, laboratory and imaging variables associated with the DECT result are presented in table 4.

Table 4. Univariate model analyses of factors predictive of positive DECT result

	OR (95% CI)	p
gender (reference: male gender)	0.48 (0.24-0.99)	0.04
Body Mass Index (per kg/m^2)	1.03 (0.96-1.11)	0.36
cardiovascular disease yes/no	2.72 (1.36-5.42)	0.04
diabetes mellitus yes/no	3.69 (1.26-10.71)	0.01
urate lowering therapy use at the moment of DECT yes/no	2.6 (1.15-6.28)	0.02
disease duration years	1.01 (1.005-1.02)	0.01
frequency of attacks per year	1.2 (1.08-1.33)	0.01
uric acid levels between flares (per µmol/L)	1.004 (1.001-1.007)	0.008
creatinine clearance (per ml/min)	0.95 (0.92-0.99)	0.01
joint involvement at the moment of DECT: MTP1 or other joints	1.69 (1.05-3.37)	0.1
past first metatarsophalangeal (MTP1) joint involvement yes/no	3.37 (1.69-6.72)	0.01
MSU crystals at microscopy yes/no	1.62 (1.23-2.17)	0.001

DECT: dual energy computed tomography; MSU: monosodium urate; DECT, dual-energy computed thomography; MTP, metatarsophalangeal; MSU, monosodium urate.

Positive DECT result were significantly associated with male gender, cardiovascular disease, diabetes mellitus, ULD use at the moment of DECT, MTP1 joint involvement at the time of DECT or in the past, positive results for MSU crystals of the index joint, disease duration, frequency of attack, and uric acid levels between flares and creatinine clearance. The results of the multiple logistic regression analysis are shown in table 5.

Table 5. Results of logistic regression with manual backward selection procedure

Variable	OR (95% CI)	p
cardiovascular disease yes/no	3.07 (1.26-7.47)	0.01
disease duration, years	1.008 (1.001-1.016)	0.03
frequency of attack per year	1.23 (1.07-1.42)	0.01
creatinine clearance ml/min	2.03 (0.91-1.00)	0.10

Disease duration in the DECT positive group (median 50 months, IQR 74.7) was statistically significantly longer (p=0.001) than in the DECT negative group (median 12 months, IQR 46).

During 1-year follow-up, 25 patients (17 % of the whole group, 34.2 % of the DECT negative group) with a negative DECT were diagnosed with gout based on the presence of MSU crystals in joint aspiration performed after the DECT. The mean disease duration of these patients was 2.5 years, versus 6.2 years for the remaining patient group. All patients with positive DECT results were still considered to have gout after 1 year follow-up.

Discussion

We found that the DECT result increases the confidence of the prescribers in their decision to initiation or discontinuation of urate lowering therapy regimen in of mono- or oligoarthritis in 33 (22.4 %) patients with possible gout. Thus DECT led to earlier initiation or intensification of adequate ULD therapy 30 patients, resulting in subjective and objective relief of symptoms in 24 patients. In 3 patients, DECT led to avoiding unnecessary treatment. Our data suggest that for patients with uncertain diagnosis of gout, i.ie, recurrent attacks of inflammatory monoarthrities or oligoarthritis butno fluid available for aspiration, negative MSU results or joint aspiration refusal, DECT may be a useful adjunct to clinical algorithms.

To date no study has evaluated the impact of DECT results on ULD therapy decisions in patients with suspected gouty arthritis in the outpatient clinic. Finkenstaedt et al [23] et al evaluated the diagnostic impact of DECT in patients with known hyperdense soft-tissue deposits on radiographs or conventional computed tomography (CT) images, so patients with high suspicion for gout. This study showed that the therapy was changed in 23/43 (53%) of the patients, with a low incidence of gouty attacks in the following year. This higher percentage compared to our study might be explained by the higher chance of gout based on prior imaging results.

In agreement with the study of Bongartz [19], we found that patients with a positive DECT had longer disease duration, which seems logical in the light of gout being a deposition disease. The diagnostic value of DECT in early gout had not yet been clearly established [19,20]. After 1-year follow-up, 25 patients (17 % of the whole group) with a negative DECT were diagnosed with gout based on the finding of MSU crystals in joint aspiration. The mean disease duration of these patients was 2.5 years compared to 6.2 years for the other patients, indicating a higher risk for false negative DECT results in patients with shorter disease duration. This has also been found by others: in one study [19], DECT appeared to have limited sensitivity in patients with acute gout and no prior episodes of gouty arthritis.

We have to acknowledge the following study limitations: this is a retrospective study and thus diagnostic and therapeutic impact as well as follow-up data were registered through

digital patient charts, with some missing data. Furthermore, there was no control group of patients who did not undergo DECT. The selection of patients undergoing DECT and the locations scanned were based on the judgment of the rheumatologist and not on well-defined criteria as the decision was made in daily clinical practice. In 61 patients it was not possible to determine false-positive or false-negative DECT findings because of lack of the gold standard, i.e., joint aspiration. The rheumatologist tended to propose DECT more often to patients afraid of joint aspiration. In agreement with the study of Taylor [24] we reported no adverse events associated with aspiration of synovial fluid for MSU analysis. Another limitation of our study was the lack of data on the duration of ULD therapy. Finally, our study represents the experience of a single center and the diagnostic and therapeutic approach may differ in other centers. However, in our center the therapy of patients with gout is in accordance with the current guidelines [9,25].

In conclusion, dual-energy CT provides additional useful information to joint fluid aspiration, with impact on ULD therapy. We suggest the use of DECT in cases where a definitive diagnosis cannot be made from signs, symptoms and MSU analysis alone. It may also be a useful diagnostic imaging modality/tool for patients who do not undergo joint aspiration because of difficult to aspirate joints, or those who refuse joint aspiration.

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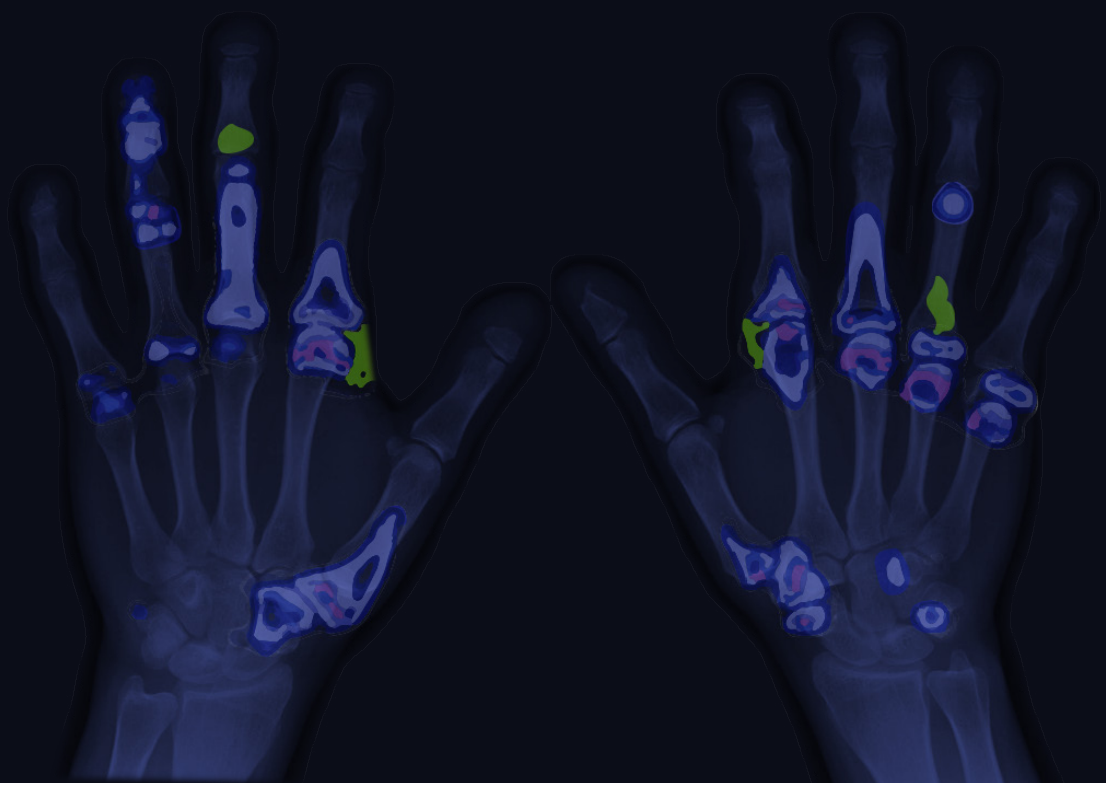
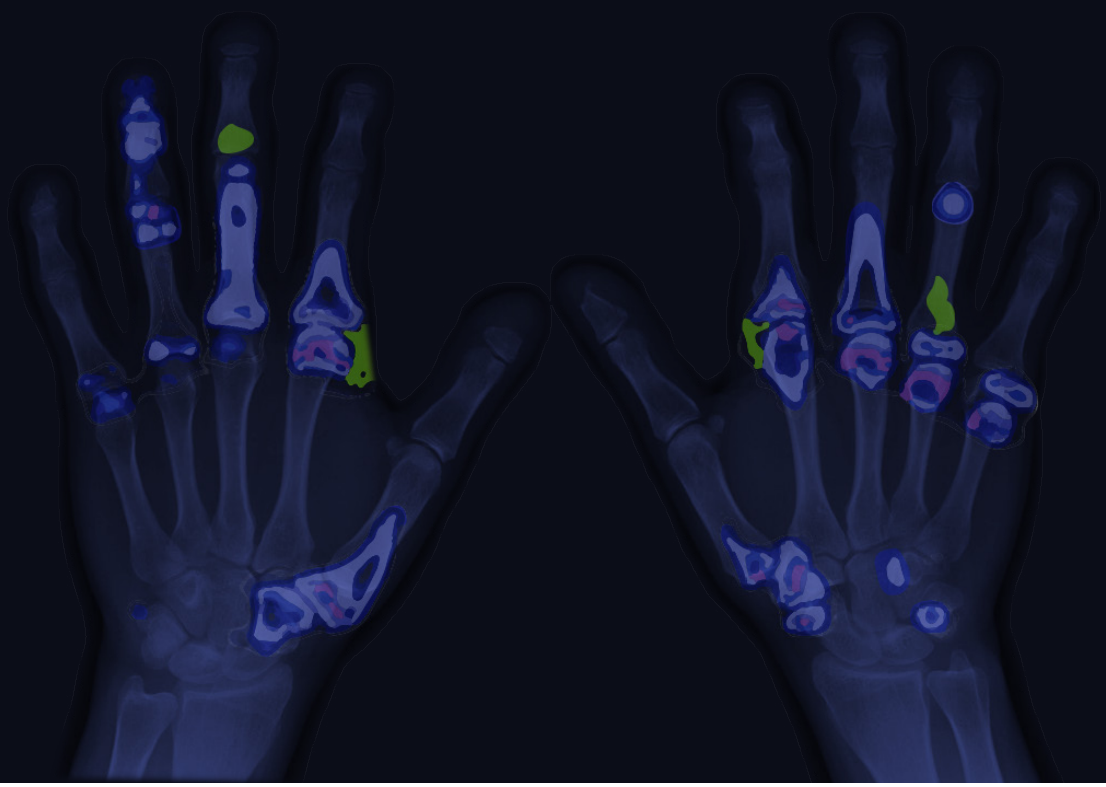
Part II



ASSOCIATED CARDIOVASCULAR MORBIDITY IN GOUT AND THE UTILITY OF DUAL ENERGY-CT

Chapter 7



Gout and hyperuricaemia: a worldwide health issue of joints and beyond

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In this issue, Singh et al. report from their observational cohort study using the NHANES database, the prevalence of reported gout and of hyperuricaemia among US adults in 5 periods of one year each: 2007-08, 2009-2010, 2011-2012, 2013-2014, and 2015-2016. Hyperuricaemia was defined as serum urate level > 0.40 mmol/dl (6.8 mg/dl), at which there is at 37 degrees Celsius saturation in the extra-cellular fluid. The authors also looked at other cut-offs: 0.36 mmol/l (6.0 mg/dl), and 0.48 mmol/l (8.0 mg/dl). They found no statistically significant trends in the age-adjusted prevalence of gout and hyperuricaemia and concluded that gout and hyperuricaemia are still a considerable burden in the increasingly aging US population. There are no good reasons to assume this will be very different for the rest of the western world. While hyperuricaemia is not a disease, the rationale to consider hyperuricaemia a burden is that it is associated with several systemic complications.

No increase found in prevalence of gout and hyperuricaemia

No statistically significant trends in the age-adjusted prevalence of gout and hyperuricaemia over the 5 year periods is surprising, given the increasing prevalence worldwide of obesity and metabolic syndrome, also referred to as "globesity".[1] Gout and hyperuricaemia are clearly associated with obesity and metabolic syndrome, but these and dietary factors may be relative mild risk factors in comparison with genetic factors. In a meta-analysis, dietary factors e.g. explained a much smaller proportion of the variation in serum urate levels (≤ 0.3%) than common genetic variants (23.9%).[2] Furthermore, despite the strengths of the study of Singh et al, including a large sample size, the study's findings must be interpreted in the light of two limitations. First, some people with gout may not seek care due to infrequent arthritis flares, or the experienced stigma from the societal misconception that gout is caused by unhealthy dietary habits and lifestyle.[3] Second, the diagnose of gout was self-reported.

Self-report of gout

In a study of McAdams et al,[4] of which the conclusions were reported by Singh et al, reliability and sensitivity of self-report of physician-diagnosed gout were evaluated in two big cohorts: the Campaign Against Cancer and Heart Disease (CLUE II) cohort and the Atherosclerosis Risk in the Community (ARIC) cohort. In ARIC, sensitivity of self-reported physician-diagnosed gout (defined as a hospital discharge diagnosis of gout or use of gout-specific medication) was 84%. In repeated questionnaires, of the 437 CLUE II participants who self-reported physician-diagnosed gout in 2000 and subsequently answered the 2003 questionnaire, 75% reported gout in 2003. Of the 271 participants who reported gout in 2000, and subsequently answered the 2007 follow-up questionnaire, 73% again reported gout in 2007. So, first, gout was not self-reported consistently in 25-27% of

patients. Second, study participants with less severe gout, i.e., those neither hospitalized nor treated with gout-specific medication, would not satisfy the definition for gout in this study of McAdams, of which the reliability and sensitivity findings of self-reported gout thus may not be generalizable to milder gout cases. This indicates the limitations of (validation of) self-reported gout.

Hyperuricaemia and gout: beyond joints: cardiovascular disease

The spectrum of gout includes, next to arthritis, tophi, urate stones and kidney disease, which we will not go into, and cardiovascular complications. Substantial data show an increased risk of cardiovascular disease in patients with hyperuricaemia and gout, above and beyond that attributable to the traditional risk factors for cardiovascular disease.[5] Several issues exist.

Is gout an independent risk factor for cardiovascular disease?

Gout is associated with the metabolic syndrome, a complex of cardiovascular risk factors overweight, hypertension, dyslipidemia and diabetes. The increased prevalence of cardiovascular disease in gout patients might only reflect these associations, see Figure. These intercorrelations make it difficult to answer the question above, but support the recommendation that in every individual with hyperuricaemia or gout, a cardiovascular screen is indicated.[6] Arthritis, whatever the cause, is a risk factor for cardiovascular disease by systemic inflammation. However, gout most frequently is characterised by intermittent arthritis flares. An independently increased risk for cardiovascular disease seems to be more based on, or associated with hyperuricaemia.

Is hyperuricaemia a pathophysiologic mechanism of cardiovascular disease?

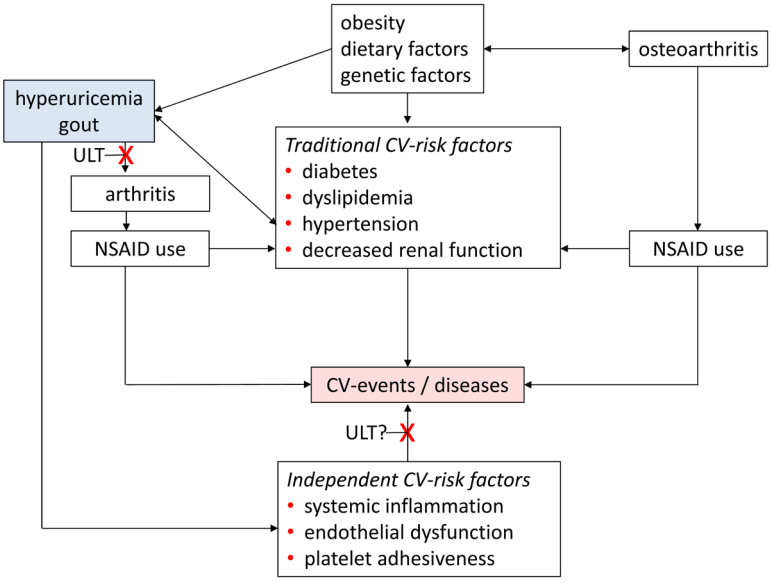
Hyperuricaemia and uric acid deposition are thought to lead (via several mechanisms) to a pro-oxidative and pro-inflammatory state,[7] associated with systemic inflammation, endothelial dysfunction, and platelet adhesiveness, all increasing the risk of cardiovascular disease, see Figure. One of these mechanisms might involve xanthine oxidase: hyperuricaemia leads to increased activity of this enzyme, that also generates radical oxygen species.[7] A study among patients with rheumatic diseases suggested that baseline serum uric acid in the upper range is a stronger predictor of first cardiovascular events than traditional cardiovascular risk factors for, or parameters of, inflammation,[8] which suggests that hyperuricaemia indeed has an independent contribution to cardiovascular risk. Generally, current opinion is that hyperuricaemia is not only associated with traditional risk factors for, and outcomes of, cardiovascular disease, but also is an independent risk factor.[7]

Should asymptomatic hyperuricaemia be treated?

So, there would be arguments for cardiovascular protection by urate lowering therapy also in subjects with asymptomatic hyperuricaemia.[9] But is there evidence for such strategy? First, cardiovascular protection by urate lowering therapy in gout patients should be demonstrated. However, a systematic review showed that a positive effect of this therapy on cardiovascular outcomes in patients with chronic gout cannot yet be proven,[10] although many of the included studies had drawbacks. Lack of evidence of an effect is not the same as evidence of the lack of an effect: in the future evidence might emerge. Till that time, treatment of asymptomatic hyperuricaemia seems not to be indicated.

Conclusion

We agree with Singh et al. that there is still a considerable burden of gout and hyperuricaemia, probably not only regarding arthritis, but also cardiovascular disease. The best strategy seems to diagnose gout early, and treat early to a prespecified serum urate target level. Each gout patient and individual with hyperuricaemia should be screened for traditional cardiovascular risk factors. It seems (yet) not be justifiable to treat asymptomatic hyperuricaemia.



Figure

ULT: urate lowering therapy; CV: cardiovascular; NSAID: non-steroidal anti-inflammatory drug

Footnotes: authors declare no conflict of interests.

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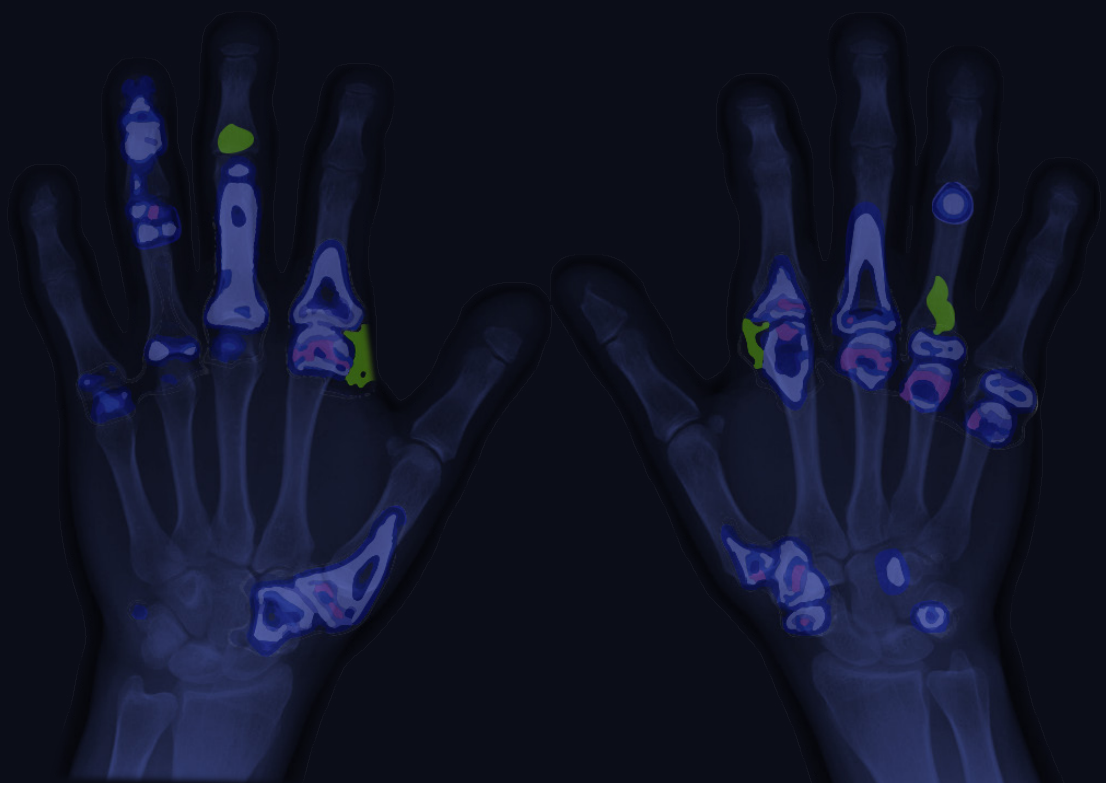
Chapter 8



Cardiovascular risk in patients with new gout diagnosis: is monosodium urate volume on Dual-Energy CT associated with previous cardiovascular events?

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Abstract

ABSTRACT

Objectives: Chronic inflammation associated with hyperuricaemia and urate deposition may contribute to an increased risk of developing cardiovascular (CV) events (CVE) in patients with gout. The aim of this study was to explore whether urate deposition on dual-energy CT (DECT) present at the diagnosis of gout is associated with a history of CVE.

Methods: Patients from a study on clinical value of DECT with mono or oligoarthritis who had gout according the 2015 EULAR/ACR classification criteria were included in this cross-sectional study. Urate volume on DECT was calculated. Patients underwent a structured CV consultation, including assessment of CVE-history and of CV risk factors, scored with the Dutch risk prediction SCORE and the Framingham score. The data were analysed using logistic regression analyses.

Results: Sixty-eight patients were included. In the multivariable model, -next to significant associations of age (OR per year 1.1, 95% CI 1.04 to 1.02, p=0.02), HDLc per mmol/l (OR 0.04, 95% CI 0.002 to 0.8, p=0.03), and diabetes yes/no (OR 4, 95% CI 0.8 to 20.9, p=0.09)-, urate volumes at ankles/feet on DECT in the third and fourth quartile with first quartile as reference showed a trend of association (OR 4.8, 95% CI 0.6 to 42, p=0.1 and 6.4, 0.7 to 63, 0.1, respectively) with past CVE events (yes/no). This association could be bidirectional. Almost two-third of newly classified gout patients had a high or very high CV risk.

Conclusion: CVE history probably is associated with urate volumes already present at the time of diagnosis of gout. Our data corroborate the need of assessing and treating CV risk factors when diagnosing gout.

Keywords: gout, DECT, cardiovascular risk

INTRODUCTION

An independent association (i.e. not dependent on classical risk factors) of gout and increased risk of cardiovascular disease (CVD) is fully recognized.(1;2) A higher monosodium urate (MSU) load is associated with increased cardiovascular (CV) mortality,(3) and asymptomatic hyperuricaemia with coronary atherosclerosis.(4) The European League Against Rheumatism (EULAR) recommends assessing and treating CV risk factors when diagnosing gout, and treating gout as soon as possible after diagnosis to avoid further gout attacks and growing crystal load, and to possibly prevent CV events (CVE).(5) However, if at the time of diagnosis, MSU deposition is present, detectable and quantifiable by dual-energy computed tomography (DECT), this would indicate a start of slow urate deposition before diagnosis and probably longstanding hyperuricaemia, with increased risk of CVE long before the diagnosis of gout.
The aim of this study was to explore whether MSU deposition on DECT present at the diagnosis of gout is associated with a history of CVE.

METHODS

Study subjects

Patients with a new classification of gout according the 2015 EULAR/American College of Rheumatology (ACR) gout classification criteria,(6) included in a study on the value of DECT in early gout, participated also in this study. In the DECT study, 89 patients with previously undiagnosed mono or oligoarthritis (2-3 swollen joints) had been recruited at the Rheumatology outpatient department of the Meander Medical Center, The Netherlands between April 1, 2016 and September 30, 2018. Patients with MSU proven gout in history or on uric acid lowering therapy had been excluded. Of 89 patients, 76 were diagnosed with gout, but of 8/76 patients, DECT volumes could not reliably be calculated because of artefacts, leaving 68 patients for analyses. The study was conducted according to the ethical principles of the declaration of Helsinki and approved by the Medical Research Ethics Committee - United on research involving human subjects (MEC-U) at Nieuwegein, the Netherlands. The study was registered at the trial register of the Netherlands (NTR) with number 5826 and at the ClinicalTrials.gov with number NCT03038386. All included subjects provided informed consent.

Material and methods

Collected data (supplementary table S1) were: patient characteristics, joint symptom duration, serum uric acid levels, and a structured assessment, including, but not limited to, conventional CV risk factors, and CVE (by review of medical records; CVE including coronary heart disease, peripheral artery disease and stroke).

Cardiovascular risk assessment

The 10-year CV risk was estimated applying the Dutch SCORE risk chart,(7) which uses gender, age, smoking status, systolic blood pressure and the TC:HDL ratio, and the Framingham risk score (FRS).(8) For this latter score, patients with a prior CVE or an age over 80 years are excluded. According to these methods, a risk of <10% is classified as low, of 10–20% as intermediate and of ⩾20% as high.

DECT

Subject underwent DECT within 6 weeks of joint aspiration, comprising three sets of DECT images with the index (symptomatic) joint and limbs scanned in pairs; hands/wrists, feet/ankles, and knees. The technical details of our imaging method have been described elsewhere.(9), see Supplementary file. A radiologist who was blinded to the subject's polarization microscopy results evaluated the images. The radiologist excluded artefacts known to produce green pixels near a joint: e.g. nail beds and metal prostheses, before classifying DECT results as positive or negative. The automated volume software allowed determining the total MSU volume with a high degree of reproducibility. We chose to analyse depositions in feet and ankles only, because depositions in other regions were very scarce.

Statistical analyses

Numerical data are given as mean and standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) in case of skewed distribution, and as frequencies for categorical variables. Univariable logistic regression was used to identify factors among the collected data described above -excluding GFR <50 ml/min as only 5% of the patients had this-, associated with a $p \leq 0.1$ with CVE (y/n) as dependent variable. These were independent variables in a multiple logistic regression model with the same dependent variable. A manual backward selection technique was performed, removing stepwise the variables with highest p-value, until all p values were ≤ 0.1. P-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The characteristics of the 68 patients are summarized in Table 1.

Table 1. Characteristics of included gout patients

	Total (N=68)
Age in years, mean (SD)	61 (14.2)
Male	57 (83.8)
BMI in kg/m2, mean (SD)	28.8 (3.8)
CV risk factors present	
Hypertension	37 (54.4)
Diabetes mellitus	11 (16.2)
hypercholesterolemia	57 (83)
Smoking (yes/no, n= 66 patients)	6 (8)
History of CV disease	16 (23.5)
Coronary heart disease	8 (10.5)
Peripheral artery disease	2 (2.6)
Stroke	6 (7.8)
GFR <60 ml/min	8 (11.7)
Use of medication	
diuretics	17 (25)
treatment for hypertension	32 (47.1)
hypolipidaemic treatment	32 (47.1)
antidiabetic treatment	8 (11.8)
Lipid spectrum	
TCh, mmol/l, mean (SD)	5 (1.2)
TG, mmol/l, median (IQR)	1.9 (1.4-2.6)
HDLc, mmol/l, mean (SD)	1.2 (0.4)
LDLc, mmol/l, mean (SD)	3 (0.9)
Urate burden, urate volumes on DECT	
serum uric acid, mmol/l, mean (SD)	481 (94)
urate volume at ankles/feet, cm^3, median (IQR) (n= 68)	0.04 (0.01- 0.17)
urate volume at knee, cm^3, median (IQR) (n= 44)	0 (0- 0.08)
urate volume at wrists/hands, cm^3, median (IQR) (n= 68)	0 (0-0.01)
Gout characteristics	
MSU cystal proven gout, N patients (%)	47 (70)
joint symptom duration* in month, median (IQR)	12 (0.5-36)

Data shown as n (%) unless otherwise specified. BMI, body mass index, calculated as weight:$(height)^2$; CV, cardiovascular; GFR, glomerular filtration rate; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; TCh, total cholesterol; TG, triglycerides; DECT, dual-energy computed tomography; MSU, monosodium urate; *, according to the patient.

Relationship between urate volume on DECT and CV events

The results of variables tested with univariable analyses are presented in Table 2; of those, age, male gender, HDLc, diabetes mellitus and gout duration met the selection criterion of p≤ 0.1. Of those, only age and HDLc were statistically significant in the multivariable model, see Table 3.

Table 2. Univariable regeression analyses of factors associated with CVE

Variable	OR (95%CI)	p
age, per year	1.09 (1.02-1.15)	0.005
male gender	3.4 (0.9-13)	0.07
diabetes mellitus y/n	3.4 (0.9-13)	0.07
gout duration, per month	1 (0.9-1.02)	0.06
Smoking y/n	1.2 (0.8-1.5)	0.5
BMI, per kg/m^2	1.04 (0.9-1.2)	0.5
systolic blood pressure, per mm/Hg	1 (0.9-1.01)	0.2
total serum cholesterol, per mmol/l	0.7 (0.5-1.2)	0.2
HDLc, per mmol/L	0.3 (0.03-1.8)	0.1
serum uric acid, per mmol/l	1 (0.9-1.01)	0.2

BMI, body mass index, calculated as weight:(height)^2; HDLc, high-density lipoprotein cholesterol

Table 3. Results of multiple logistic regression#

Variable	OR (95%CI)	p
diabetes mellitus yes/no	4.0 (0.8-20.9)	0.09
age per year	1.1 (1.04-1.2)	0.02
serum HDLc per mmol/l	0.04 (0.002-0.8)	0.03
DECT urate volume at ankle/feet per cm^3, 2nd quartile	0.9 (0.1-7)*	0.9
DECT urate volume at ankle/feet per cm^3, 3rd quartile	4.8 (0.6- 42)*	0.1
DECT urate volume at ankle/feet per cm^3, 4th quartile	6.4 (0.7-63)*	0.1

HDLc, high-density lipoprotein cholesterol; DECT, dual-energy computed tomography.
outcome variable cardiovascular events y/n, results after a stepwise manual backward selection procedure, removing variables with p>0.1
* 1st quartile urate volume ankle/feet as reference

CV risk stratification

For prediction of CVE, 16 patients (23.5%) were excluded because of a prior major CVE and 2 (3.1%) because of age over 80 years; thus the 2 risk prediction tools were applied to 50 patients (73.5%). Median (IQR) 10-year CVE risk scores were 14% (5%-34%) according the Dutch SCORE and 21% (12%-31%) according the FRS, corresponding to a moderate and a high risk, respectively. The 10-year CVE risk scores according to the Dutch SCORE were high in 23 patients (46%), moderate in 4 (8%) and low in 23 (46%), and according to FRS, they were high in 26 patients (52%), moderate in 15 (30%) and low in 9 (18%).

DISCUSSION

We found a trend of an independent positive relationship of DECT urate volumes and CVE in patients with gout, probably based on chronic inflammation as a risk factor for CVE.(10) However, the association could be also based on other mechanisms than inflammation. e.g. usage of non-steroidal anti-inflammatory drugs for gouty arthritis, which is also a risk factor for CVE.(11) Furthermore, the association could be bidirectional, e.g. the CVE risk factor diabetes could via nephrosclerosis cause gout.

Two other studies investigating the relationship between urate volumes on DECT and CVE showed contradictory results. A cross sectional study in 42 subjects with gout found a very weak correlation between urate volumes on DECT and the estimated 10-years risk of CVE.(12) However, this study did not correct for traditional risk factors, associated with gout, and included patients with longer gout duration (mean 8 years), in contrast to our study. A retrospective study with a multivariable analysis including traditional CV risk factors and urate volumes on DECT as predictors among 55 subjects with gout showed an independent contribution of the urate volumes predicting the 10-year FRS for CVE. (13) Biases inherent to the retrospective design , for example exclusion of subjects with incomplete data, may have affected this study's result.

Our study demonstrated that almost two of every three patients with newly classified gout were classified as having a high or very high CV risk. Our results are in line with those of a previous study,(14), reporting high CV risk in patients with early gout, however with a median disease duration of 4 years, compared to the 1 year in our study. These results suggest that the trend we found of a relationship of DECT urate volumes and CVE is real; the relatively small sample size and low frequency of CVE may have prohibited finding statistical significance.

Thus, the CV risk in new diagnosis of gout requires attention, since relatively simple lifestyle and/or pharmacological interventions may prevent future CV disease in this group of patients.

There are limitations in our study. First, the relatively small sample size as mentioned above. Had patients with longstanding untreated or inadequately treated gout been included, we probably would have found a stronger association between MSU volumes and CVE, but that design diverged from the aim of our study. Second, our study was based on the hypothesis that preceding the definite diagnosis of gout, urate deposition already might have taken place, with some systemic inflammation increasing the risk of CVE. A long-term prospective study after the diagnosis of gout assessing the incidences of CVE in those not or insufficiently treated for hyperuricaemia would have been scientifically more sound. Strengths of our study are that all participants underwent a structured CV assessment that can be reproduced in clinical practice and that DECT scans were obtained systematically in 68 patients all meeting ACR/EULAR classification criteria for gout.

CONCLUSION

MSU volumes already present at the time of diagnosis may be associated with a history of CVE, and a large proportion of patients already has a high CV risk when diagnosed with gout. These results corroborate the current opinion that the CV risk in diagnosed gout patients requires full attention.

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Supplementary file

Table S1 Study variables collected

Demographic variables	age, years
	Gender, male/female
Measures	blood pressures (mm/Hg)
	BMI, kg/m^2
CV risk factors present	hypercholesterolaemia
	hypertension
	diabetes mellitus
	smoking habit
History of CV disease	(signs of) coronary heart disease (including angina pectoris, myocardial infarction, coronary artery stenosis, ischemic heart failure)
	peripheral artery disease
	stroke (including ischaemic stroke cerebrovascular accidents, transient ischaemic attack and carotid endarterectomy)
Use of medication, N patients (%)	diuretics
	treatment for hypertension
	hypolipidaemic treatment
	antidiabetic treatment
Lab tests	estimated glomerular filtration rate <60 ml/min and <50ml/min
	total serum cholesterol, mmol/l
	serum triglycerides, mmol/l
	serum HDLc, mmol/l
	serum LDLc, mmol/l
	serum uric acid, mmol/l
	serum glucose, mmol/l
Gout related variables	symptom duration (time of first arthritis attack according to the patient)
	Index joint at presentation

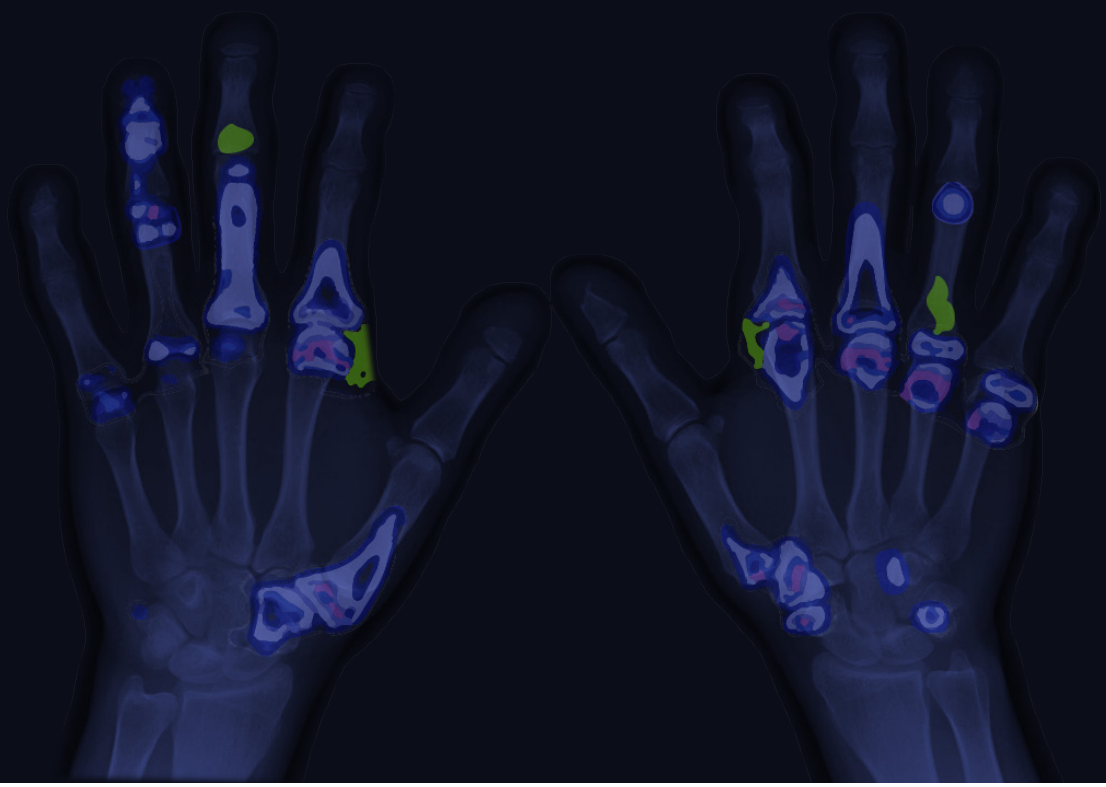
BMI, body mass index, calculated as weight:(height)^2; CV, cardiovascular; GFR, glomerular filtration rate; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; SUA, serum uric acid; TCh, total cholesterol; TG, triglycerides

DECT-protocol

Scans were performed using a dual source dual energy CT scanner (SOMATOM Definition Flash Dual Source CT scanner; Siemens Healthcare). Parameters were 140 kV and 55 mA for one tube and 80 kV and 243 mA for the other. Collimation of 0.6 mm was reconstructed to 0.75-mm slices. A 2 material decomposition algorithm was performed on a multi-

technique CT workspace (SW-Version VA20 Siemens Healthcare) using Syngo dual-energy Siemens Healthcare software. The material-specific difference in attenuation of urate between the two energy levels at 80- and 140-kV energy levels allows accurate detection of MSU, which is then colour coded as green and fused with the standard greyscale CT images. These can be reviewed as both cross-sectional and 3D images.

Chapter 9



Cardiovascular risk in patients with new gout: should we reclassify the risk?

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Abstract

ABSTRACT

Objectives: Chronic inflammation, as seen in gout, may contribute to an increased risk of developing cardiovascular (CV) events (CVE). The aim of the study was to explore the effect of adding gout as a chronic inflammatory disease to the Dutch SCORE, a tool predicting 10-years CV mortality and morbidity.

Methods: This was a cross-sectional substudy including new patients with gout according the 2015 EULAR/ACR classification criteria who had participated in a trial on diagnostic accuracy of DECT with mono or oligoarthritis. Patients underwent a structured CV consultation, including assessment of CVE-history and of CV risk factors with the Dutch risk prediction SCORE. Chi-square test for trends was used to test for significance reclassification of the CV risk before and after adding gout to the Dutch SCORE.

Results: Seventy-six gout patients were included. SCORE was applied in 60 patients; 16 patients had experienced a prior CVE. The 10-year risk scores without gout as risk factor were high in 29 patients (48.3%), moderate in 6 (10%) and low in 25 (41.7%); with gout, the risk of 23/60 patients (38.3%) was reclassified from low to moderate in 6 patients (10%), from low to high in 11 (18.3%) and from moderate to high in 6 (10%), $p<0.001$ for trend.

Conclusion: Adding gout to the risk prediction tools led to significant and clinically relevant reclassification of CV risk in new gout patients. Studies with large follow-up are warranted to validate these findings.

Keywords: Gout, DECT, cardiovascular risk.

INTRODUCTION

It is well established that gout is associated with an increased risk of cardiovascular disease (CVD)[1,2] and likely relates to persistent inflammation.[3,4] As inflammation present in chronic diseases such as rheumatoid arthritis (RA), gout, diabetes is a contributor to the hallmark oxidative stress associated with most CVD [5], gout would be a CV risk factor comparable to RA and diabetes. In a study in new gout patients,[6] those initially not classified as 'very high' risk underwent carotid ultrasound; 56% had their risk upgraded, and 46% moved in the 'very high' risk stratum, based on atheroma plaque. The European League Against Rheumatism recommends treating gout as soon as possible after diagnosis to prevent gout attacks, and possibly cardiovascular events (CVE).[7]
In the Dutch SCORE,(5) a modification of the Systematic Coronary Risk Evaluation (SCORE), estimating the 10-year risk of fatal and nonfatal CVD,(6) (RA) is a risk factor because of its chronic inflammatory action, but gout is not.
The objective of this study was to explore the theoretical effect of adding gout as risk factor to the Dutch SCORE for patients with gout.

METHODS

Study subjects

Seventy-six patients from a study on accuracy of dual energy-CT (DECT) with undifferentiated mono and oligoarthritis (1-3 swollen joints) who were classified with gout according the 2015 EULAR/ACR gout classification criteria,[8] between 1 April 2016 en 30 September 2018 at the Rheumatology outpatient clinic of the Meander Medical Center, The Netherlands were included in the current substudy. The study was conducted according to the ethical principles of the declaration of Helsinki and approved by the Medical Research Ethics Committee - United on research involving human subjects (MEC-U) at Nieuwegein, the Netherlands and is registered at the trial register of the Netherlands (NTR) with number 5826 and at the ClinicalTrials.gov with number NCT03038386. All included subjects provided informed consent.

Material and methods

Gender, age, body length and weight, joint symptom duration, conventional CV risk factors (CRF), CVE (via review of medical records), and serum urate levels) were assessed; for details, see supplementary table S1.

Gout classification criteria

These criteria consist of clinical symptoms and signs, detection of urate cristals in joint fluid and DECT results.(8) Testing of Syncytial Fluid (SF) with polarisation microscopy was performed on all samples. Two experienced rheumatologists performed this examination

within one hour of sample acquisition. A definite diagnosis of crystal proven gout was made if needle-shaped, negatively birefringent crystals were seen.[9] For DECT, subjects were scanned within 6 weeks of joint aspiration. Scans of index joint and, in addition, of hands/wrists, feet/ankles, and knees, all bilaterally, were performed. The technical details of our imaging method have been described elsewhere.[10] A radiologist who was blinded to the subject's polarization microscopy results evaluated the images. The radiologist excluded artefacts known to produce green pixels near a joint: e.g. nail beds and metal prostheses, before classifying DECT results as positive or negative.

Cardiovascular risk assessment

The 10-year CV risk was calculated using the Dutch SCORE table [11], which uses gender, age, smoking status, SBP, the TC:HDL ratio and rheumatic disease (rheumatoid arthritis). In this score, patients with a prior CVE are automatically classified as having the highest risk, and for patients over 70 years the score of a 70 year old patient is calculated. To account for RA or diabetes as risk factor, the Dutch CVRM guideline adds 15 years to the actual age to calculate the 10-year CV risk. A risk <10% is classified as low, 10-20% as intermediate and ⩾20% as high. Risk scores were calculated separately without gout and after adding gout to the algorithm, based on hypothesis that gout is an independent risk factor for CVE, with an overall impact similar to that of RA or diabetes. According to the Dutch CVRM guideline, preventative treatment with an antihypertensive drug or statin is indicated in high risk patients with a systolic blood pressure >140mmHg or an LDL>2.5 mmol/l.
In addition, the 10-year CV mortality risk was calculated using the European Systematic Coronary Evaluation (SCORE), stratified as low (<1%); moderate (1-4%); high (5-9%) and very high (>9%).[12]

Statistical analysis

Standard descriptive statistics were used: numerical data are given as mean and standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) in case of skewed distribution, and categorical variables as frequencies and percentages. Chi-square trend test was used to compare the CV risk stratification before and after adding gout to the risk tool. Differences in patient characteristics between reclassified and non-reclassified patients were assessed through Student t, Mann-Whitney U, dependent of normal distribution or not, and chi-square, or Fisher's exact tests. Statistical analyses were performed using SPSS for Windows, Version 22.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered as statistically significant.

Results

Seventy-six patients with new gout according to the EULAR/ACR 2015 classification criteria were included; patients' characteristics are summarized in Table 1.

Table 1. Characteristics of included patients (N=76)

	Total (N=76)
Age in years, mean (SD)	61.4 (14.3)
Male	63 (82.9)
BMI, kg/m², mean, SD	28.7 (3.7)
CV risk factors present	
Hypertension	42 (55.3)
Diabetes mellitus	13 (17.1)
hypercholesterolemia	64 (72)
Smoking habit (n= 73)	9 (12)
History of CV disease	
Coronary heart disease	8 (10.5)
Peripheral artery disease	2 (2.6)
Stroke	6 (7.8)
GFR <60 ml/min	10 (13.1)
Use of medication	
diuretics	19 (25)
treatment for hypertension	37 (48.7)
hypolipidemic treatment	33 (43.4)
antidiabetic treatment	10 (13.2)
Lipid spectrum	
TCh, mmol/l, mean (SD)	5 (1.2)
TG, mmol/l, median (IQR)	1.9 (1.5-2.7)
HDL, mmol/l, mean (SD)	1.7 (0.3)
LDL, mmol/l, mean (SD)	3 (0.9)
Urate burden	
serum urate, mmol/l, mean (SD)	484.1 (95.1)

Data shown as n (%) unless otherwise specified. BMI, body mass index, calculated as weight:(height)^2;

CV, cardiovascular; GFR, glomerular filtration rate; HDLc, high-density lipoprotein cholesterol;

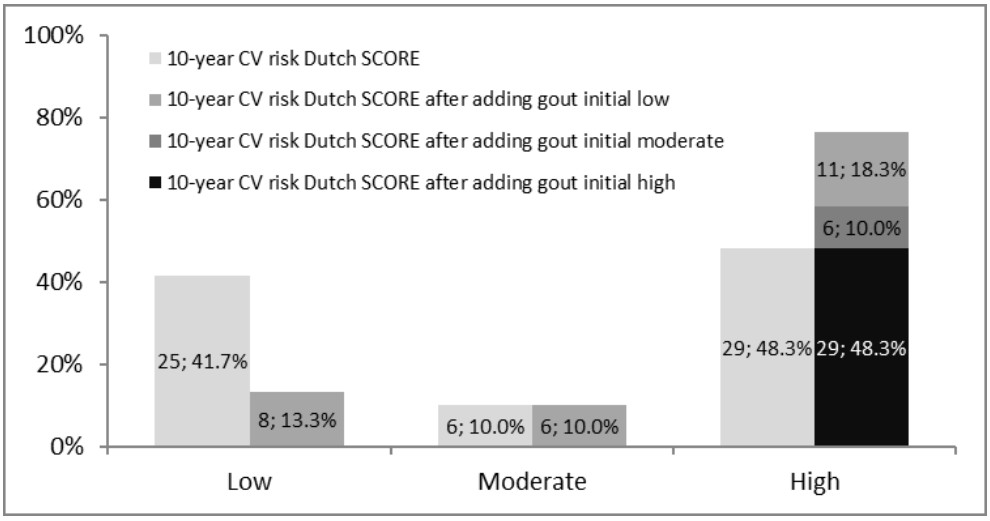
LDLc, low-density lipoprotein cholesterol; SUA, serum uric acid; TCh, total cholesterol; TG, triglycerides;

DECT, dual-energy computed tomography;

Median symptom duration suggestive of intermittent gout was 12 month (IQR 0.7-48). Fifty-three (70%) subjects had MSU crystal proven gout. Sixty-four (84%) subjects had a positive DECT result.

CV risk stratification

The Dutch SCORE was applied to 60 patients (79%) as all other 16 patients (21%) had a history of CVE, classifying them in the highest risk score, which prohibits reclassification. Median risk score was 18% (IQR 6%-34%). The 10-year risk scores were high in 29/60 patients (48%), moderate in 6 (10%) and low in 25 (42%). After adding gout as risk factor, the risk of 23/60 patients (38%) was upgraded: from low to moderate in 6 patients (10%), from low to high in 11 (18%) and from moderate to high in 6 (10%). Figure 1 shows the CV risk reclassification, which is statistically significant (p<0.001 for trend test); before reclassification, 29/60 patients (48%) were at high CV risk level and after reclassification, 46/60 patients (77%).



Legend Figure 1 Cardiovascular (CV) risk stratification of included new diagnosed gout patients.

Left light grey bars in each category show the risk before adding gout to the Dutch SCORE, while right dark grey bars show the CV risk after adding gout to the Dutch SCORE, mentioning how many patients moved in a higher category.

Data shown as number of patients per each subgroup and percentage of total sample.

The patients with CV risk reclassification had a significantly higher BMI (p=0.04), used antihypertensive and hypolipidemic drugs less frequently (p= 0.02 and 0.04, respectively) and were significantly younger (p=0.01). Frequency of diabetes, smoking habits and lipid levels did not differ significantly between the reclassified en not reclassified patients group (for details see supplementary table S2). According to the European SCORE, the 10-year CV mortality risk score was very high in 3/60 patients (5%), high in 15/60 patients (25%), moderate in 34/60 patients (57%) and low in 8/60 patients (13%). After adding gout as risk factor, by multiplying the score by 1.5 according to guidelines,[13] the risk of 23/60

patients (38%) was reclassified: from moderate to high in 11 patients (18%), from high to very high in 12 (20%).

DISCUSSION

After adding gout as risk factor to the Dutch SCORE, 23/60 (38%) of patients with new gout according to the 2015 EULAR/ACR classification criteria had their CV risk upgraded; 17/60 (28%) of the patients moved into the high risk class. The patients group who did not have their risk upgraded used antihypertensive and hypolipidemic treatment more often, lowering the risk of presence of the traditional CV risk factors, i.e., hypertensive and hyperlipidaemic states, respectively. The non-reclassified patients were also older; an explanation is that in the higher risk group before reclassification, patients predominantly were old, prohibiting many older patients to be upgraded more (ceiling effect). Our results that the Dutch SCORE classifications were upgraded when including gout as risk factor corroborate with the results of SCORE for the 10 year CVE mortality risk, when taking gout as risk factor into account.

In another study in patients with new gout diagnosis,[6] 142 patients not initially classified as 'very high' risk underwent carotid ultrasound; 80 (56%) had their risk upgraded, 66 (46%) moved in the 'very high' risk stratum, based on atheroma plaques.

Our findings indicate that if gout is a CV risk factor comparable to RA, the consequences are clinically very relevant; our findings reinforce the recommendation to screen gout patients at diagnosis. The goal is to prevent the onset of CVE in patients with gout.

There are limitations to our study. First, the relatively small sample size with relatively low statistical power and the cross sectional design. Second, our study was based on the hypothesis that gout is an independent risk factor for CVE, with an overall impact similar to that of RA and diabetes[14]. A long-term prospective study after the diagnosis of gout assessing the incidences of CVE and validating the reclassification would be warranted.

A strength of our study is that we highlighted the clinical relevance of considering gout as CV risk factor comparable to RA in patients with new gout diagnosis.

In RA patients in whom CVD risk is substantially elevated compared with the general population [15], anti-rheumatic treatment lead to switch in CV risk category and preventive treatment advice in 13% of the patients in a recent study.[16] The presence of gout should alert physicians to screen, diagnose, and promptly treat cardiovascular risk factors (hypertension, hyperlipidemia) in addition to treat gout early.

CONCLUSION

Adding gout as risk factor to the Dutch risk prediction tool leads to relevant reclassification of CV risk. Studies with large follow-up are warranted to validate our results.

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Supplementary file

Table S1. Study variables collected

Demographic variables	age, years
	Gender, male/female
Measures	blood pressures (mm/Hg)
	BMI, kg/m2, mean, SD
CV risk factors present	hypercholesterolemia
	hypertension
	diabetes mellitus
	smoking habit
History of CV disease	coronary heart disease (including angina pectoris, myocardial infarction, percutaneous coronary intervention and coronary artery bypass surgery, heart failure)
	peripheral artery disease
	stroke (including ischaemic stroke cerebrovascular accidents, transient ischaemic attack and carotid endarterectomy)
Chronic kidney disease	GFR <60 ml/min
Use of medication	diuretics (N,%)
	treatment for hypertension N, (%)
	hypolipidemic treatment N,(%)
	antidiabetic treatment N, (%)
Lab tests	estimated gloemrular filtration rate, eGFR
	total cholesterol, mmol/l
	triglycerides, mmol/l
	HDL, mmol/l
	LDL, mmol/l
	serum urate, mmol/l
	glucose, mmol/l
Gout related variables	symptom duration (time of first attack according to the patient)

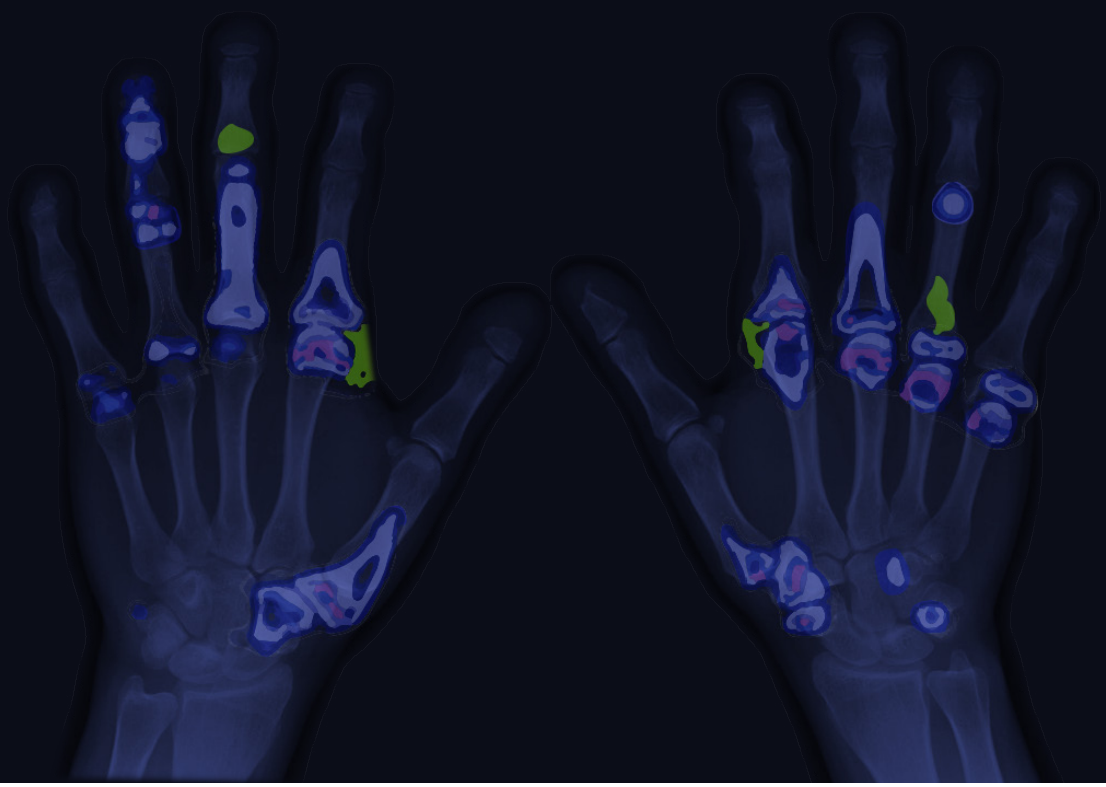
BMI, body mass index, calculated as weight:(height)^2; CV, cardiovascular; GFR, glomerular filtration rate; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; SUA, serum uric acid; TCh, total cholesterol; TG, triglycerides

Table S2. Differences between reclassified and non-reclassified patients after adding gout to the Dutch Score

Variables	reclassification*,N=23	non- reclassification*,N=37	p
Male	21 (91)	31 (84)	**0.4**
age, years, mean (SD)	53.2 (7.3)	62.6 (16.6)	**0.01**
BMI, kg/m2, mean (SD)	27.5 (3.4)	30.4 (4)	**0.04**
Hypertension	8 (34.7)	23 (62.2)	**0.04**
Diabetes mellitus	1 (4.3)	7 (18.9)	**0.1**
Smoking habit	2 (8.7)	7 (18.9)	**0.3**
TCh, mmol/l, mean (SD)	5.2 (1.2)	5.1 (1.2)	**0.8**
TG, mmol/l, median (IQR)	1.7 (1.5-2.6)	1.9 (1.4-2.7)	**0.8**
HDL, mmol/l, mean (SD)	1.1 (0.3)	1.2 (0.4)	**0.2**
LDL, mmol/l, mean (SD)	3.3 (1.1)	3 (0.9)	**0.2**
antihypertensiva	7 (30.4)	20 (54.1)	**0.07**
diuretica	1 (4.3)	10 (27.4)	**0.02**
hypolipidemic treatment	4 (17.4)	16 (43.2)	**0.04**

*,after adding gout to the Dutch Score; BMI, body mass index, calculated as weight:(height)^2; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; TCh, total cholesterol; TG, triglycerides.

Chapter 10



Summary
General discussion

Summary

Gout is associated with joint damage and cardiovascular (CV) morbidity making an early diagnosis, appropriate treatment and screening for CV morbidity very important. The aim of this thesis was to establish the utility of Dual-Energy-CT (DECT) in the classification, diagnosis and treatment choice in gout. The associated CV morbidity in gout and the utility of DECT herein were also investigated.

This thesis presents the results of the DEteCTing gout study exploring the clinical utility of dual energy CT in gout. In this study, 100 patients with undifferentiated mono and oligoarthritis and indication for diagnostic joint aspiration were recruited in a rheumatology outpatient clinic setting. Patients underwent blind diagnostic aspiration of synovial fluid (SF) from the inflamed joint. An ultrasound guided diagnostic aspiration was performed in several patients because no fluid was obtained by blind aspiration. Testing of SF on the presence of monosodium urate (MSU) crystals was performed on all adequate samples. Patients underwent DECT scan of hands/wrist and ankle/feet and knees. The 2015 ACR/EULAR gout classification criteria were applied. These consist of clinical domain, lab domain (intercritical serum urate level and synovial fluid analysis) and imaging (in our study only DECT).[1] Patients underwent a structured CV consultation, including assessment of the CV events (CVE) history via review of medical records and the CV risk factors. The Dutch risk prediction SCORE and the Framingham score were applied. Patients diagnosed with gout by the rheumatologist were treated according to the guidelines, with a treat to target approach, i.e., the target of serum uric acid (SUA) ≤360 µmol/l. After 1 year, data on the rheumatologic diagnosis (according to the treating rheumatologist), arthritis attacks and urate lowering therapy (ULT) use were collected.
Additionally, a systematic review and a meta-analysis to assess the utility of DECT for diagnosing gout, a retrospective study looking into the value of DECT in the clinical practice and a review of the recent literature on hyperuricaemia, gout burden and associated morbidity were performed.
The main findings of this thesis are summarized below, followed by a general discussion with future perspectives.

Part I: The utility of DECT in classification, diagnosis and treatment decision in gout
In **chapter 2**, the results of a systematic review and a meta-analysis to assess the utility of DECT for diagnosing gout are presented. Data from person-based and joint-/localisation-based evaluations were pooled separately, and subgroup analyses for short disease phase/duration were performed. DECT has good sensitivity and specificity for diagnosing longstanding gout, with no major differences for the different reference standards used for gout. In the subgroups with gout of short term duration, sensitivity was low (high percentage false negatives) and therefore DECT is clinically not reliable to exclude gout.

However, these patient subgroups were small and showed too much variability in study design, reference standards and withdrawals to draw firm conclusions.

In **chapter 3**, the performance of (subsets of) the 2015 ACR/EULAR gout classification criteria in patients with unclassified arthritis was established and the value of DECT herein was determined. The detection results of MSU crystals in the SF at polarization microscopy was the reference. The median duration of joint symptoms was 12 and 6 month in gout en non-gout patients, respectively. Adding the serum urate to the clinical subset improved the performance, whereas adding DECT to both the clinical set alone and to the combined clinical plus serum urate subset did not significantly influence the performance. An explanation could be the short disease duration accompanied by low volume urate deposition. However, DECT seems to have an additive value in gout classification, especially when microscopy of SF is negative: 21% of patients classified as having gout fulfilled the 2015 ACR/EULAR gout classification criteria only after adding the DECT result. Especially patients with periarticulair urate depositions and patients in whom joint aspiration is not feasible could benefit from using DECT. As 93% of patients had urate deposition in ankles/feet, we suggest that scanning of these regions, together with the index joint, could be a well-balanced cost-effective choice. Although classification criteria are not intended to make diagnoses in individuals in daily medical practice,[2] MSU crystal detection in SF as classification criterion also establishes the diagnosis gout in an individual. As per protocol we intended to perform ultrasonographic guided joint aspiration in those with negative blind aspiration and positive DECT, but only 2 patients consented at that stage. The SF of these 2 patients was positive for MSU crystals.

In **chapter 4**, the performance of the 2015 ACR/EULAR gout classification criteria in 100 patients with undifferentiated arthritis, using as reference the clinical gout diagnosis yes/no, according to the rheumatologist after 1-year follow-up is described. Additionally, the use and effectiveness of ULT in daily clinical practice in newly diagnosed gout patients were explored.
The 2015 ACR-EULAR gout classification criteria performed well and have a high discriminating value for the diagnosis gout in clinical practice. A very high sensitivity, specificity and PPV, indicating that these criteria have an excellent performance, were found. Most gout patients had been treated according to the current guidelines, meeting the treat to target cutoff of SUA ≤360 µmol/l. The treating rheumatologists gave life-style advice to all patients, and did not initiate ULT in some patients with scarce urate depositions at DECT scanning. Interestingly, none of those patients had further arthritis attacks during one year follow-up. Longitudinal follow-up of patients with new gout and scarce urate deposition in whom ULT therapy is started or not started will help to establish the appropriate management in this patient group.

In **chapter 5**, a patient history is described, illustrating the value of DECT in diagnosing axial gout and in differentiating between tophaceous gout and other osteolytic lesions such as malignancy.

In **chapter 6**, the clinical impact of DECT results on treatment regiments in clinical practice is described based on a retrospective study including 144 patients with mono- or oligoarthritis, possibly caused by gout. This was assessed by looking at starting of ULT or stopping of it by their treating rheumatologists, after DECT had been performed. After DECT, the regimen regarding ULT was modified in 22 % of patients, indicative of confidence of the prescribers in the DECT result.
DECT is a useful imaging tool for patients with contraindications for joint aspiration, with difficult to aspirate joints, or those who refuse joint aspiration. In addition, it was investigated whether DECT results can be predicted by clinical, laboratory and imaging features. In a multivariable regression model, CV disease, disease duration, frequency of gout attack and creatinine clearance were independently associated with positive DECT results.

Part II: Associated cardiovascular morbidity in gout and the utility of DECT
Chapter 7 summarizes the recent literature about hyperuricaemia, gout burden and the associated morbidity. Gout and hyperuricaemia represent a burden, not only with regard to arthritis, but also to associated CV disease. The best strategy seems to be early diagnosis, and treatment to a prespecified low SUA target level. Each gout patient and each individual with hyperuricaemia should be screened for traditional CV risk factors. It seems not yet justifiable to treat asymptomatic hyperuricaemia to prevent CV disease.

Chapter 8 explores whether presence of the urate deposition on DECT at the diagnosis of gout is associated with a history of CVE. Urate volumes at ankles/feet on DECT in the third and fourth quartile respectively, with first quartile as reference at the time of diagnosis seem independently associated with CVE (yes/no) in history: odds ratio's of 4.8 and 6.4, respectively, although the p-values were not significant, only indicating a trend (p=0.1), probably due to the small simple size. This association might indicate a bidirectional causality: CV-diseases and their medications might negatively impact the renal function, increasing the risk of gout, and, the other way round and not excluding the first mechanism, longstanding hyperuricaemia in patients with gout has been shown to be a CV-risk factor. Almost two-third of newly classified gout patients had a high or very high CV risk.

In **chapter 9**, the effect of adding gout as a risk factor to the Dutch SCORE, weighing it as a chronic inflammatory disease similar to rheumatoid arthritis, is discussed. Adding gout to the risk prediction tool led to significant and clinically relevant reclassification of CV risk

in new gout patients. The presence of gout (and asymptomatic hyperuricaemia) should alert physicians to screen, diagnose, and promptly treat CV risk factors (e.g., hypertension, hyperlipidaemia).

General discussion

From part I of this thesis we conclude that DECT has an additional value in gout classification, especially when microscopy of SF is negative. In these cases, results may be false negative due to sampling error (incorrect placement of the needle in the affected joint, or an extra-articular location of the MSU deposits, e.g. at tendons around the joint) or due to incorrect microscopy[3]. The additional value at group level seems less in patients with short duration of joint symptom. Yet, it cannot be neglected as 93% of these patients with the final classification of gout had urate deposition at ankles/feet. Although there are potential artifacts related to DECT, ways to minimize them and avoid false-positive interpretations have been described.[6]

The cost and the need for trained personnel might limit the use of DECT. In daily clinical practice, the use of DECT examination could be limited to patients in whom MSU has not been confirmed by polarized light microscopic examination of joint aspirates. Safety concerns include potential long term adverse effects (e.g., from accumulated radiation exposure). DECT's radiation dose is estimated to be 0.5 mSv per region scanned (e.g., 0.5 mSv for both hands and wrists, which are scanned together)[7]. Note that the average annual natural background radiation exposure is approximately 2.4 mSv.[9] and that the radiation dose at typical commercial airline flight altitude is about 0.036 mSv per 12 hours. The DECT radiation exposure issue should be weighed against the potential effects of misdiagnosis, including delay in initiating of failure to initiate appropriate treatment for gout.

A recent study showed that combined analysis of DECT and non-contrast CT (NCCT) improved sensitivity without a significant decrease in the specificity in symptomatic early gout.[4] However, the sole use of NCCT has limited specificity for gout because the hyperdense deposits it detects can also be attributed to other crystal arthropathies like calcium pyrophosphate deposition disease.[5] More research is needed to better assess the diagnostic approach in early gout.

We did not use ultrasonography as diagnostic modality for gout, because of feasibility reasons. However, ultrasonography to establish gout may be very useful, both during an acute inflammatory episode or an intercritical period.

Part II of this thesis adds evidence to the body of knowledge regarding the association of gout with CV comorbidity. Given this dependent and independent association, we propose to take gout into account as risk factor for cardiovascular disease in cardiovascular risk scores. However, follow-up research is necessary to better assess the incidences of CVE

and to determine which CV risk screening model is optimal in gout patients. Of interest would be to see which CV risk model best predicts the CV outcome of the present cohort in ten years and how additional correction for gout associated factors can improve this risk prediction model. Obviously, this model should be validated in other cohorts with long follow-up.

Each gout patient and individual with hyperuricaemia should be screened for traditional CV risk factors. To date, a benefit of treatment of asymptomatic hyperuricaemia has not been proven.[9]

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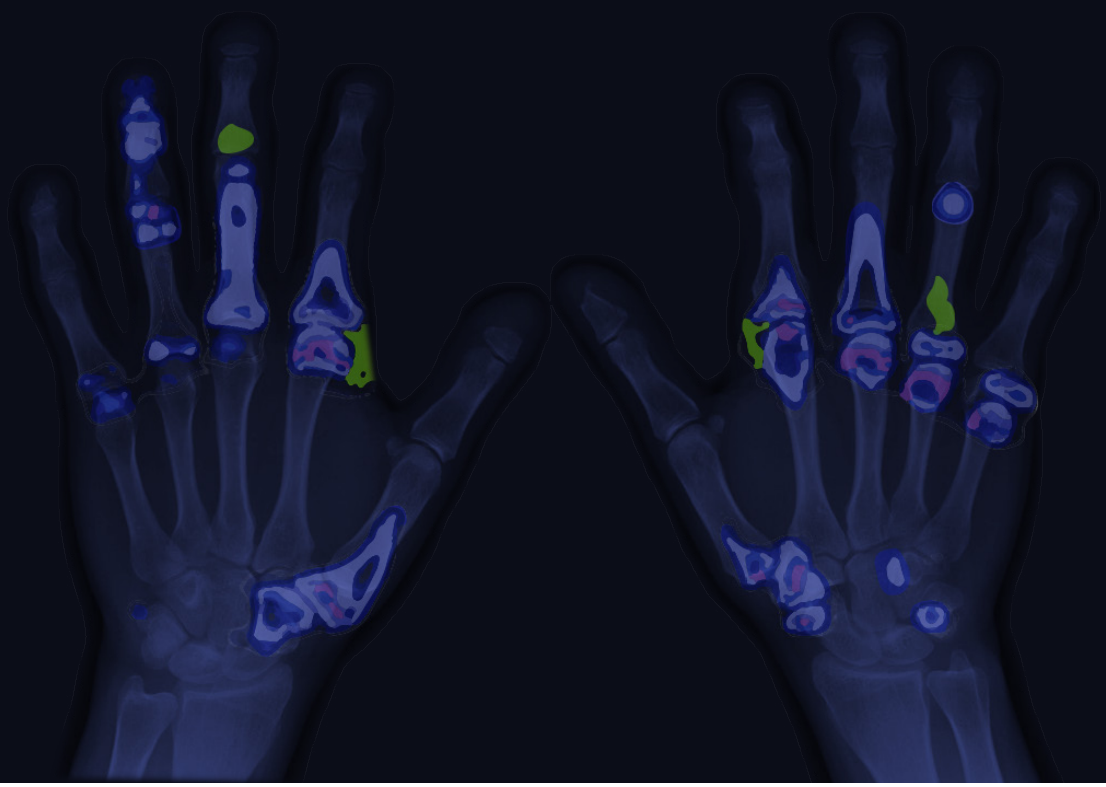
Addendum



Nederlandse samenvatting
List of publication
Dankwoord
Curriculum vitae

Nederlandse samenvatting

Jicht is geassocieerd met beschadiging van gewrichten en cardiovasculaire morbiditeit (ziekte); een vroegtijdige diagnose, behandeling en screening op cardiovasculaire morbiditeit zijn belangrijk. Het doel van dit proefschrift was om de klinische utiliteit (het nut) van de Dual-Energy-CT (DECT) scan vast te stellen bij de classificatie, diagnose en behandeling van jicht. Bovendien werden de cardiovasculaire morbiditeit van jicht en de klinische utiliteit DECT daarbij, onderzocht.

Dit proefschrift laat onder andere de resultaten van het "DEteCTing gout" onderzoek zien, dat de klinische utiliteit van DECT bij het classificeren (vaststellen binnen groepen) van jicht onderzoekt. In dit onderzoek werden 100 patiënten met ongedifferentieerde (nog niet nader gediagnosticeerde) mono- en oligoartritis (respectievelijk ontsteking van een en van 2-4 gewrichten) en indicatie voor diagnostische aspiratie (opzuigen van vocht voor onderzoek) van het ontstoken gewricht gescreend op de polikliniek reumatologie. Een "blinde" (zonder hulp van beeldvorming, zoals echografie) diagnostische aspiratie van gewrichtsvloeistof uit het ontstoken gewricht werd verricht; een tweede aspiratie met hulp van echografie werd verricht bijn enkele patienten omdat geen vloeistof werd verkregen na de "blinde" aspiratie; gewrichtsvloeistof werd nagekeken op jicht (urinezuurkristallen). Patiënten ondergingen ook een DECT-scan van handen/pols en enkel/voeten en knieën. De internationale (ACR/EULAR) classificatie criteria voor jicht uit 2015 werden toegepast. Deze bestaan uit klinische criteria, laboratoriumcriteria (urinezuurspiegel in het bloed (serumuraat) geprikt buiten de jichtaanval, en resultaat van analyse van gewrichtsvloeistof op jicht) en beeldvorming (in ons onderzoek alleen DECT).[1] Patiënten ondergingen daarnaast een gestructureerd cardiovasculair consult, met nagaan van doorgemaakte cardiovasculaire "events" (CVE, zoals hartinfarct en cerebrovasculair incident) en met scoren van cardiovasculaire risicofactoren met de Nederlandse predictie SCORE en met de Framingham-score. Patiënten bij wie de reumatoloog de diagnose jicht stelde, werden behandeld volgens de genoemde internationale richtlijn, waarbij gestreefd wordt naar een lage urinezuurspiegel in het bloed (≤360 µmol/l). Een jaar na het eerste polikliniekbezoek werden gegevens over de klinische diagnose (volgens de behandelende reumatoloog), artritisaanvallen en het gebruik van urinezuurverlagende therapie (ULT) verzameld.
Verder beschrijft dit proefschrift een systematische review met meta-analyse (analyse van reeds gepubliceerde onderzoeken) over de utiliteit van DECT voor de diagnose van jicht. Ook werden een retrospectief onderzoek naar de waarde van DECT in de klinische praktijk uitgevoerd en een overzicht van de recente literatuur over hyperurikemie (verhoogde urinezuurspiegel in het bloed), klachten van jicht en bij jicht behorende morbiditeit gegeven.
De belangrijkste bevindingen van dit proefschrift zijn hieronder per hoofdstuk samengevat, gevolgd door een algemene discussie.

Deel I: Utiliteit van DECT bij classificatie, diagnose en behandelbeslissing bij jicht

In **hoofdstuk 2** worden de resultaten van een systematische review en een meta-analyse betreffende de utiliteit van Dual Energy CT (DECT) voor de diagnose van jicht gepresenteerd. Patiënt-gebaseerde en gewrichten/lokalisatie-gebaseerde resultaten werden door ons apart geanalyseerd en er werden subgroepanalyses voor korte ziekteduur uitgevoerd. DECT heeft een goede sensitiviteit (detectiegevoeligheid) en specificiteit voor het diagnosticeren van lang bestaande jicht, zonder grote verschillen voor de verschillende gebruikte gouden standaarden (referentiestandaarden) voor jicht. In de subgroepen met kort bestaande jicht was de sensitiviteit laag (hoog percentage fout-negatieven) en daardoor is DECT onvoldoende betrouwbaar om jicht uit te sluiten. Deze subgroepen van patiënten waren echter klein en vertoonden te opmerkelijke variabiliteit in onderzoeksopzet en gouden standaarden voor jicht om definitieve conclusies te trekken.

In **hoofdstuk 3** werden de "performance" van (subsets van) de ACR/EULAR-classificatiecriteria voor jicht 2015 bij patiënten met niet-geclassificeerde artritis nagegaan en werd de waarde van DECT hierin bepaald. Het onderzoeksresultaat van urinezuurkristallen in de gewrichtsvloeistof was de gouden standaard. De mediane duur van gewrichtssymptomen was 12 en 6 maanden bij respectievelijk jicht- en niet-jichtpatiënten. Het toevoegen van de urinezuurspiegel in het bloed aan de klinische subset verbeterde de "performance", terwijl het toevoegen van DECT aan zowel de klinische subset alleen, als aan de klinische subset gecombineerd met de urinezuurspiegel in het bloed, de performance niet significant beïnvloedde. Een verklaring kan de korte ziekteduur zijn, die gepaard gaat met maar nog weinig stapeling van urinezuur, en dus een negatieve DECT-uitslag. DECT lijkt echter toegevoegde waarde te hebben bij de classificatie van jicht, vooral als er geen urinezuurkristallen in de gewrichtsvloeistof worden gevonden: 21% van die patiënten voldeden pas aan de 2015 ACR/EULAR criteria voor jicht nadat het DECT-resultaat was toegevoegd. Vooral patiënten met periarticulaire (rond gewrichten) urinezuurafzettingen (uraatafzettingen) en patiënten bij wie gewrichtspunctie niet haalbaar is, kunnen baat hebben bij het ondergaan van DECT. Aangezien 93% van de patiënten urinezuurafzetting in/rond enkels/voeten had, suggereren wij dat het scannen met DECT van deze gebieden, samen met het ontstoken gewricht, een goed gebalanceerde en kosteneffectieve keuze zou kunnen zijn. Hoewel classificatiecriteria niet bedoeld zijn om diagnoses te stellen bij individuele patiënten in de dagelijkse medische praktijk,[2] is het vaststellen van urinezuurkristallen in de gewrichtsvloeistof tegelijkertijd een classificatie criterium en diagnostisch criterium voor jicht.

Volgens protocol waren we van plan echografisch geleid aspiratie van gewrichtsvloeistof uit het ontstoken gewricht uit te voeren bij patiënten bij wie "blinde" aspiratie niet was gelukt, en die een positieve DECT-uitslag voor jicht hadden, maar slechts 2 patiënten

stemden in dat stadium daarmee in. Beide patiënten bleken urinezuurkristallen in de gewrichtsvloeistof te hebben.

In **hoofdstuk 4** zijn de performance van de 2015 ACR/EULAR jicht classificatiecriteria bij 100 patiënten met ongedifferentieerde artritis vastgesteld, met als gouden standaard de klinische jicht diagnose (ja of nee) volgens de reumatoloog na 1 jaar follow-up. Bovendien werden het gebruik en de effectiviteit van ULT in de dagelijkse klinische praktijk bij nieuw gediagnosticeerde jichtpatiënten geëvalueerd. De 2015 ACR-EULAR classificatie criteria voor jicht presteerden goed en hebben een hoge onderscheidende waarde voor jicht in de klinische praktijk. Een zeer hoge sensitiviteit, specificiteit en PPV werden vastgesteld. De meeste jichtpatiënten bleken te zijn behandeld volgens de huidige richtlijn met streven naar een urinezuurspiegel in het bloed ≤360 µmol/l. De reumatologen gaven levensstijladviezen aan alle patiënten en hadden bij sommige patiënten met minimale urinezuurafzettingen op de DECT-scan geen ULT gestart. Interessant is dat geen van deze patiënten gedurende het jaar follow-up, artritisaanvallen (jichtaanvallen) had. Langdurige follow-up van meerdere patiënten met jicht en minimale urinezuurafzettingen, bij wie ULT-therapie is gestart of niet gestart, zal helpen om het juiste management in deze patiëntengroep te evalueren.

In **hoofdstuk 5** wordt een patiënt beschreven bij wie de waarde van DECT bij het diagnosticeren van jicht in wervels (zeldzaam) en bij het onderscheid met andere oorzaken van osteolytische laesies (botverdringende afwijkingen) zoals (uitgezaaide) kanker wordt geïllustreerd.

In **hoofdstuk 6** werd de invloed van DECT-resultaten op de beslissing ULT te starten of stoppen in de klinische praktijk onderzocht in een retrospectief onderzoek onder 144 patiënten met mono- of oligoartritis, mogelijk veroorzaakt door jicht. Het DECT-resultaat verhoogde het vertrouwen van de voorschrijvers in hun beslissing om ULT te starten of te stoppen bij mono- of oligoartritis. Na DECT werd het ULT-regime bij 22% van de patiënten aangepast. DECT is een nuttig aanvullend onderzoek bij patiënten met contra-indicaties voor gewrichtsaspiratie, moeilijk te aspireren gewrichten of degenen die gewrichtspunctie weigeren. Daarnaast werd onderzocht of DECT-resultaten kunnen worden voorspeld door klinische parameters en laboratoriumwaarden. In een multivariabel regressiemodel (statistische techniek die onafhankelijke verbanden kan aantonen) bleken cardiovasculaire aandoeningen, ziekteduur, frequentie van jichtaanvallen en creatinineklaring (nierfunctie) onafhankelijk geassocieerd te zijn met positieve DECT-resultaten.

Deel II: Geassocieerde cardiovasculaire comorbiditeit bij jicht en de utiliteit van DECT

Hoofdstuk 7 is een overzicht de recente medische literatuur over hyperurikemie, klachten van jicht en de bij jicht behorende morbiditeit (comorbiditeit). Jicht en hyperurikemie veroorzaken een belangrijke ziektelast, niet alleen wegens artritis, maar ook wegens de bijbehorende cardiovasculaire comorbiditeit. De beste strategie is het stellen van de diagnose in een vroegtijdig stadium, en dan met ULT een vastgestelde, lage urinezuurspiegel in het bloed bewerkstelligen. Elke jichtpatiënt moet worden gescreend op cardiovasculaire risicofactoren, zoals hypertensie en hoog cholesterol. Het lijkt (nog) niet te verdedigen om asymptomatische hyperurikemie te behandelen om hart- en vaatziekten te voorkomen.

Hoofdstuk 8 onderzocht of de aanwezigheid van urinezuurafzetting op het moment van het stellen van de diagnose jicht al zijn geassocieerd met een voorgeschiedenis van CVE. Urinezuurvolumes bij enkels/ voeten op DECT in het derde en vierde kwartiel, met het eerste kwartiel als referentie (dus hoge waardes vergeleken met lage waardes) lijken onafhankelijk geassocieerd met CVE (ja/nee) in de geschiedenis: odds ratio's (mate waarmee de risico's verhoogd zijn, 1= niet verhoogd) van 4,8 en 6,4, respectievelijk, hoewel de p-waarden niet statistisch significant waren, alleen een trend aangaven ($p = 0,1$), waarschijnlijk vanwege de kleine aantallen patiënten met CVE. Deze associatie kan wijzen op een bidirectionele causaliteit (oorzakelijk verband in twee richtingen): de waarschijnlijk al langer bestaande hyperurikemie kan CVE hebben veroorzaakt, en cardiovasculaire ziekte kan door verminderde nierfunctie en door bepaalde medicijnen ervoor, het risico op jicht hebben verhoogd. Bijna tweederde van de pas gediagnosticeerde jichtpatiënten had een hoog of zeer hoog cardiovasculair risico.

In **hoofdstuk 9** werd het effect van het toevoegen van jicht als risicofactor aan de Nederlandse SCORE geëxploreerd, waarbij jicht, als chronische ontstekingsziekte vergelijkbaar met reumatoïde artritis, het risico evenveel als reumatoïde artritis verhoogt. Het zo toevoegen van jicht als risicofactor leidde tot klinisch relevante herclassificatie van het geschatte cardiovasculair risico bij nieuwe jichtpatiënten. De aanwezigheid van jicht moet artsen aanzetten om cardiovasculaire risicofactoren (bijvoorbeeld hypertensie en hyperlipidemie=verhoogd vetgehalte in bloed) te screenen, en zo nodig te behandelen.

Discussie

Uit deel I van dit proefschrift concluderen we dat DECT toegevoegde waarde heeft bij de classificatie van jicht, vooral wanneer het onderzoek op urinezuurkristallen in de gewrichtsvloeistof negatief is. Deze negatieve resultaten kunnen fout- negatief zijn, door een "sampling" fout (onjuiste plaatsing van de naald in het gewricht, of bij urinezuurafzetting buiten het gewricht, bijvoorbeeld op pezen rond het gewricht) of door

een onjuiste techniek van onderzoek op urinezuurkristallen in de gewrichtsvloeistof.[3] De toegevoegde waarde op groepsniveau van DECT lijkt minder bij patiënten met een korte duur van gewrichtssymptomen. Toch is de waarde van DECT dan ook niet te verwaarlozen, gezien het feit dat 93% van deze patiënten met korte duur van gewrichtssymptomen, als zij voldoen aan de classificatie voor jicht, urinezuurafzetting had in/aan enkels/voeten. Hoewel er ook fout-positieve interpretaties van DECT kunnen zijn, zijn er manieren beschreven om deze zoveel mogelijk te voorkómen.[4] De kosten en beperkte beschikbaarheid van opgeleid personeel en specifieke DECT apparatuur kunnen beperkende factoren zijn voor het toepassen van DECT. Wij kunnen aanbevelen in de dagelijkse klinische praktijk alleen DECT-onderzoek te doen bij patiënten bij wie onderzoek op urinezuurkristallen in de gewrichtsvloeistof negatief is en bij wie er toch verdenking is op jicht, en bij hen bij wie onderzoek op urinezuurkristallen in de gewrichtsvloeistof niet mogelijk is of door de patiënt afgewezen wordt.

Nadeel van DECT is blootstelling aan straling met mogelijk nadelige effecten op de lange termijn daarvan. De stralingsdosis van DECT wordt geschat op 0,5 mSv per gescand gebied (bijvoorbeeld 0,5 mSv voor zowel handen als polsen, die samen worden gescand),[5] maar de gemiddelde jaarlijkse blootstelling aan natuurlijke straling is ongeveer 2,4 mSv;[9] en de stralingsdosis tijdens een vlucht is ongeveer 0,003 mSv per uur. Het blootstellen aan extra bestraling door DECT, hoe weinig ook, dient afgewogen te worden tegen mogelijke negatieve effecten van een verkeerde diagnose, inclusief vertraging bij het starten of het niet starten van de juiste behandeling voor jicht, als DECT geïndiceerd is, maar niet wordt verricht.

Een recent onderzoek toonde aan dat gecombineerde analyse van DECT en non-contrast computer tomografie (CT-scan: NCCT) de diagnostiek van kort bestaande jicht verbetert: verhoogde sensitiviteit zonder significante afname van specificiteit.[6] Maar NCCT alleen heeft maar beperkte specificiteit voor jicht, doordat de gevonden afzettingen niet alleen kunnen passen bij jicht, maar ook bij andere aandoeningen met afzetten van kristallen, zoals calciumpyrofosfaat bij calciumpyrofosfaatziekte.[7] Zoals altijd: meer onderzoek is nodig.

We hebben, vanwege praktische problemen, echografie in ons onderzoek niet gebruikt als diagnostisch middel om jicht vast te stellen. Maar echografie is daar wel geschikt voor, tijdens de acute aanval vooral om te helpen bij de gewrichtspunctie, en buiten aanvallen om, om de urinezuurafzettingen weer te geven.

Deel II van dit proefschrift bevestigt de associatie van jicht met cardiovasculaire comorbiditeit. Dit is deels een afhankelijke (samenhangend met andere risicofactoren, zoals overgewicht) en deels onafhankelijke associatie. Het is derhalve ons voorstel, jicht als risicofactor voor hart- en vaatziekten in cardiovasculaire risicoscores op te nemen. Vervolgonderzoek is echter nodig om de incidentie (het vóórkomen) van CVE beter vast te leggen en om te bepalen welk cardiovasculair risicoscreenings- en schattingsmodel

optimaal is voor jichtpatiënten. Met andere woorden: welk cardiovasculair risicomodel het beste de cardiovasculaire uitkomst van jichtpatiënten voorspelt en hoe jicht als risicofactor in dit risicovoorspellingsmodel opgenomen moet worden.
Elke jichtpatiënt moet worden gescreend op cardiovasculaire risicofactoren. Tot op heden is een voordeel van behandelen van asymptomatische hyperurikemie niet bewezen,[8] maar het tegendeel, dat er geen voordeel zou kunnen zijn, is evenmin bewezen: er is meer onderzoek nodig.

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List of publication

Publications related to this thesis

Gamala M, Jacobs JWG, Heggelman BGF, Klaasen R. Clinical vignette. An unexpected manifestation of gout**.** 2019 Sept 24 [Epub ahead of print]

Gamala M, Jacobs JWG, Linn-Rasker SP, Nix M, Heggelman BGF, van Laar JM, Pasker-de Jong PCM, Klaasen R. The performance of Dual-energy CT in the classification criteria of gout: a prospective study in subjects with unclassified arthritis. Rheumatology (Oxford). 2019 Sept 5 [Epub ahead of print]

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Submitted

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Curriculum vitae

Mihaela Gamala was born September 3, 1975 in Turnu Severin, Romania. After graduating high school in 1994 at the Traian National College in Turnu Severin, she started with Physics-Chemistry studies at the Bucharest University and passed her propaedeutic examination in 1995.
That year she was admitted at the Faculty of Medicine, University Carol Davila in Bucharest. In 2001 she obtained her medical degree. In 2002 she started as resident at the department of Internal Medicine of the University Hospital in Bucharest.
After moving to the Netherlands, she followed several medical internships at Maastricht University in 2006 and 2007. In 2007 she received her Dutch medical degree at Maastricht University. Subsequently, she worked in 2007 and 2008 as resident internal medicine/cardiology at the Vie Curie Hospital in Venlo. She followed her Internal Medicine residency program at the Academic Medical Center Amsterdam and Tergooi Hospital Hilversum and Blaricum from 2008 to 2011, and from 2011 to 2014 she followed her rheumatology fellowship program at the Academic Medical Center Amsterdam and Reade Amsterdam. During the fellowship, she specialized in the musculoskeletal ultrasonography and after passing the exam, she became in 2014 EULAR recognized international trainer in musculoskeletal ultrasonography.
She started with her master Epidemiology at the VU University of Amsterdam in 2014 and graduated (MSc) in 2016. Thereafter, she became 'Epidemiologist A' at the 'Vereniging voor Epidemiologie' (VVE).
Since 2014 she has worked as a rheumatologist at the Northwest Clinics in Alkmaar and Den Helder.
Her PhD project on the clinical utility of Dual-Energy CT in gout was started September 2014 at the Department of Rheumatology & Clinical Immunology of the University Medical Center Utrecht, under supervision of prof. dr. J.M. van Laar, dr. J.W.G. Jacobs and dr. R. Klaasen. She also taught musculoskeletal ultrasonography to rheumatology fellows at University Medical Center Utrecht from 2014 to 2018. The results of the years of research are described in this thesis. The present work has been published in peer-reviewed international medical journals, and led to several presentations at (inter)national rheumatology congresses.
Mihaela Gamala is member of the Auditing Committee (Commissie Kwaliteitsvisitaties), the Professional Interests Committee (Beroepsbelangencommissie), the Gout Workgroup and the Osteoarthritis Workgroup, all of the Dutch Society for Rheumatology. She will represent the Dutch Society for Rheumatology in the "LOGEX model" Committee and

Professional Interests Council (Raad Beroepsbelangen) of the Dutch Federation of Medicals Specialists in January 2020.
Mihaela Gamala was appointed as Vice President of the Dutch Society for Rheumatology in September 2019.