DECT Prognosis for Gout

Dual Energy CT Has Additional Prognostic Value over Clinical Measures in Gout Including Tophi: A Systematic Literature Review

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Key Indexing Terms (up to 6 and must be MeSH terms): Dual Energy Computed Tomography, gout, urate burden, monosodium urate, tophi, flares

The source(s) of support in the form of grants or industrial support:

This study was supported by Horizon Therapeutics plc, Deerfield, IL, USA.

Initials, surnames, appointments, and highest academic degrees of all authors (e.g., MD, PhD), and affiliated department(s) and institution(s):

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Conflict of interest:
Sally K. Stauder has no conflicts of interest. Paul M. Peloso is former employee of Horizon and holds company stock.

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Statement of ethics and consent:
Horizon Therapeutics funded the collection of retrospective de-identified chart data, contributed to the analysis, and data interpretation and the writing, review, and approval of the manuscript. Editorial assistance was provided by Amy Cohen, PhD, a Horizon employee.
Abstract: (250 words with Structured Objective, Methods, Results and Conclusion)

Objective. This Systematic Literature Review determined whether there is clinical utility for Dual Energy CT (DECT) to inform on prognosis for gout patients. With DECT, individualized treatment plans could be developed based on the patient’s unique urate burden, with DECT used as a clinical outcome measure in gout management.

Methods. To evaluate DECT as a reliable, valid, and sensitive prognostic instrument, a librarian-assisted search was undertaken in PubMed and EMBASE for articles on gout and DECT informing on reliability, validity (content, construct, criterion), sensitivity to change and minimum clinically important changes.

Results. This systematic literature review showed that DECT has high intra- and inter-rater reliability. Tophus burden correlates with functional loss to show content validity. DECT volume is positively correlated with death and cardiovascular risk factors, and the risk for future gout flares. DECT has excellent sensitivity to change with effective urate lowering therapies.

Conclusion. DECT is a promising prognostic tool based on its high reliability, sensitivity to change, and emerging validity. Additional large, well-designed prospective cohort studies are needed to fully evaluate its prognostic utility. This systematic review suggests it’s very likely DECT has additional prognostic information beyond clinical tophi assessment alone.
Introduction

Gout has a rising global prevalence with highest rates in the Pacific and a higher burden in the developed world; regional prevalence varies from 0.1% up to 10.0%.\(^{(1)}\) The United States has an estimated 9 million individuals with gout.\(^{(2)}\) The current gold standard for a gout diagnosis is detection of monosodium urate (MSU) crystals in joint fluid.\(^{(3)}\) Joint aspiration can be a painful, invasive process\(^{(4)}\) which not all healthcare providers are able to perform. Dual energy CT (DECT) scans are a non-invasive technique that may be an alternative diagnostic tool, especially in more established gout patients\(^{(5)}\) as DECT scans have excellent reliability.\(^{(6)}\)

The gout disease process is a continuum, starting with asymptomatic hyperuricemia, progressing to acute gouty attacks and then to persistent arthritis, joint destruction and subcutaneous tophi as urate deposits build.\(^{(6)}\) Crystals can deposit in multiple locations, including joints, tendons, cartilage, and skin.\(^{(7)}\) Higher urate burdens are associated with diabetes, hypertension, cardiovascular disease, and chronic kidney disease.\(^{(8-10)}\)

DECT scans provide an individualized volumetric urate burden and are a longitudinal outcome measure. DECT should be recommended as a standard clinical assessment if it can be proven to provide additional prognostic information beyond tophi counts alone. Tophi and DECT volumes are known independent predictors of mortality.\(^{(11)}\) and DECT reliability is better than clinical tophi assessment.\(^{(12)}\)

To have prognostic value, DECT should be reliable and valid, including content validity (results should represent truth), construct validity (results should move in predictable ways with other clinical measures of similar concept, like erosions) and criterion validity (results should predict disease features, like death, disability, and distress). DECT should provide more prognostic information than clinical tophi alone to warrant routine clinical use. DECT should also be
sensitive to change with effective urate lowering therapy with these changes correlating to other important health measures. The goal of this systematic review is to inform on the reliability and validity of DECT to understand its prognostic value in gout patients.

**Methods**

A systematic search was undertaken in PubMed and Embase databases from inception to February 29, 2022. Medical subject heading (MeSH) terms used were [(Dual Energy Computed Tomography OR DECT) AND (gout) AND (urate burden OR monosodium urate volume OR monosodium urate crystals)] with these keywords: [(Dual Energy Computed Tomography OR DECT), (Gout, tophaceous gout, chronic gout), (monosodium urate crystals OR monosodium urate burden OR tophi OR monosodium urate volume OR flares OR pain OR distress OR death OR disability OR function)]. Titles and abstracts identified were screened by both authors. A manual search of secondary sources included personal holdings, conference abstracts and review of identified articles’ references.

Inclusion criteria included original research on DECT, its reliability, validity, relationship to clinical outcomes and ability to detect change. Participants must have gout diagnosed by ACR/EULAR classification and/or crystal confirmation. Excluded papers included; editorials, narrative reviews, case reports, letters to the editor, and conference abstracts without complete methods and results. Non-human and non-English studies were excluded. Data selection and extraction were performed independently by both authors and final data presentation was based on consensus.

To assess study quality, two approaches were implemented. For systematic reviews of DECT reliability, the AMSTAR-2 tool was used, which was designed to critically appraise systematic reviews of randomized and non-randomized studies based on 16 elements. An
overall summary score is not provided, but each systemic review is rated based on weaknesses in critical domains. In the interest of space limitations, only the highest quality meta-analyses are represented in Table 1. For all other studies, we used the approach of the ILAR 2000-2010 Decade of the Bone and Joint Neck Pain Task Force. (15) Methodological quality was evaluated by considering selection bias, information bias, and confounding to inform on a study’s internal validity. No formal grading scale was used. No articles were excluded based on pre-defined cut points. Methodologic features of the included studies are summarized in Tables 1 and 2.

Reliability is interpreted based by the generally accepted standards as: ICC estimates from 0.00 to < 0.40 is poor agreement, 0.40-0.59 is fair agreement, 0.59-0.74 is good agreement and values from 0.75 to 1.00 represent excellent agreement. (16) Validity was assessed by construct and criterion validity. Construct validity is described by OMERACT as “do the results of the instrument agree with expected results of other instruments measuring the same construct/concept”. (17) Criterion validity is described by OMERACT as “does the result of the instrument predict or correlate with long term outcomes (e.g., death, disability, radiographic damage)?”. (17)
Results

MEDLINE and EMBASE yielded 393 potential citations. Full manuscripts of interest were retrieved and reviewed for 98 abstracts (24.0%). Forty-nine of 98 manuscripts (50.0%) were found to be relevant to our goals. A complete list of articles considered, along with the rationale for final selections is available from the authors. Articles on gout and DECT first appeared in English in 2007, denoting a nascent literature.

DECT is highly reliably, with excellent intra-class correlation coefficients varying from 0.86 to nearly 1.00 for both intra-rater and inter-rater reliability, summarized in Table 1 along with DECT performance characteristics [sensitivity, specificity, and area under the curve (AUC)].

Systematic reviews of highest quality are presented in descending order based on year of publication, followed by selected primary studies describing intra-rater reliability and then DECT studies in early gout showing the heterogeneity of DECT performance by gout duration.

[Place Table 1 on Summary of the Reliability, Sensitivity, Specificity of DECT imaging in gout patients] about here

Meta-analyses scoring best on the AMSTAR-2 tool were authored by Gamala, Chen, Newberry, Ogdie and Zhang.(19, 21, 23, 24, 30) The review by Ogdie(24) is among the oldest and Newberry(23) included only 3 studies. The Gamala(19) and Chen(21) meta-analyses differ in their inclusion of studies with and without a joint aspiration gold standard. Chen(21) summarized 5 articles and showed a pooled sensitivity of 0.88 (95% CI: 0.90-0.96), a pooled specificity of 0.85 (95% CI: 0.67-0.78) and pooled AUC of 0.93 (No 95%CI given), with joint aspiration used as the gold standard assessment. Gamala did not require joint aspiration to confirm gout in their included articles and included 10 articles with pooled sensitivity of 0.81 (95% CI: 0.77-0.86) and pooled specificity of 0.91 (95% CI: 0.85-0.95).(19) Two studies that used aspiration for gout
diagnosis had pooled sensitivity of 0.92 (95% CI: 0.81-0.97) and pooled specificity of 0.81 (95% CI: 0.69-0.90). Two studies using the ACR 1977 clinical criteria had pooled sensitivity of 0.89 (95% CI: 0.85-0.92) and pooled specificity of 0.88 (95% CI: 0.80-0.93) and suggested similar diagnostic performance with aspiration or clinical criteria. \(^{(19)}\)

Singh and colleagues studied a clinic-based cohort that confirms the comparable DECT test performance with either joint aspiration or a clinical diagnosis. \(^{(34)}\) In 147 patients, mean gout duration of 9 years and mean age 65 years, DECT and ultrasound were contrasted against joint aspiration (gold standard) and ACR-EULAR 2015 clinical classification (silver standard). \(^{(34)}\) DECT of feet and ankles had a sensitivity of 0.87 (95% CI: 0.82-0.92) and a specificity of 1.00 (95% CI: 1.00-1.00) versus joint aspiration. Against ACR-EULAR clinical criteria, DECT had a sensitivity 0.82 (95% CI: 0.79-0.85) and specificity 0.76 (95% CI: 0.72-0.80), similar to joint aspiration. Singh found that DECT of feet and ankles only was preferred to DECT of feet, ankles and knees combined or knees alone, based on better AUCs. \(^{(34)}\) In fact, DECT of feet and ankles out performed ultrasound against the gold standard of joint aspiration. \(^{(34)}\)

DECT in early gout patients has lower sensitivity, as suggested by Gamala \(^{(19)}\), Odgie \(^{(24)}\), Zhang \(^{(30)}\) and others. Zhang examined patients with early gout (<1 years from first symptoms) and contrasted DECT sensitivity to patients with mid and late gout. \(^{(30)}\) DECT scans showed sensitivity of 4/15 (0.27) in early gout, 8/12 (0.67) in mid gout and 9/10 (0.90) in late gout against joint aspiration. \(^{(30)}\) Ultrasound sensitivity was higher in early-stage gout compared to DECT at 0.66 versus 0.27, \(p<0.050\) \(^{(30)}\) Lee showed early gout patients sensitivities at 0.51-0.53 for two readers with specificity at 1.00 for both. \(^{(31)}\) Early gout was determined by excluding patients with tophi, erosions or use of urate-lowering therapy with 103 patients with 115 painful joints included while DECT was read by two experienced radiologists. Gout diagnosis was based on consensus of two rheumatologists using ACR/EULAR 2015 criteria.
Kravchenko suggested early gout had more false negatives with DECT. Of 36 subjects, DECT confirmed positive cases had a median disease duration of 43 months (IQR 5–103), whereas false negatives had a median duration of 4 months (IQR 2–33). (33) Shang defined early gout as disease <1 year, middle gout from 1-3 years, and late gout >3 years in a 196 subject cross-sectional study. The 49 early gout cases had DECT sensitivity (feet and ankles) of 0.38 (95%CI: 0.18- 0.62), with specificity 0.96 (95%CI: 0.82-0.99); late gout had sensitivity of 0.78 (95%CI: 0.68-0.85) and specificity 0.88 (95%CI: 0.84-0.99). (32) DECT reliability was not influenced by gout duration, with inter-reader agreements of 0.87 and 0.86 in early gout and late gout respectively. (32) Shang, in a separate study performed a meta-analysis of 28 studies with DECT and ultrasound, including early gout, defined as disease < 2 years. (18) DECT pooled sensitivity in early gout was 0.75 (95%CI: 0.60-0.86), pooled specificity was 0.85 (95%CI: 0.75-0.91); ultrasound had pooled sensitivity of 0.93 (95%CI: 0.72-0.99) and pooled specificity of 0.80 (95%CI: 0.71-0.86) when positive findings included the double contour sign and ultrasound detected tophi. (18) DECT was a better diagnostic test overall versus ultrasound when all disease durations were combined; DECT pooled sensitivity 0.89 (95%CI: 0.80-0.94), pooled specificity 0.91 (95%CI: 0.88-0.94) versus ultrasound pooled sensitivity 0.84 (95%CI: 0.73-0.91) and pooled specificity 0.84 (95%CI: 0.78-0.89). (18) Collectively, early stage gout appears to have reduced sensitivity (more false negatives) with preserved specificity (few false positives) compared to later gout.

Construct validity for DECT is demonstrated by its correlation with radiographic erosions in four studies. (35, 36, 37, 38) Dalbeth reported a cross-sectional study of 92 tophaceous gout patients undergoing radiographs and DECT of feet. An experienced rheumatologist scored 920 metatarsophalangeal (MTP) joints. DECT volume was correlated to radiographic damage, correlation coefficient 0.70, p<0.001. (35) Shi studied 27 gout patients retrospectively, cross-sectionally with a median age of 52 years and 84 months of disease. (36) Total erosions, defined...
on CT as a focal area of cortex loss with sharply defined margins in 2 planes and bone cortex breach in >1 plane, positively correlated with DECT volume (rs=0.55, p=0.003) in 52 individual foot joints across all participants. (36) Pecherstorfer studied 20 gout patients with a mean age of 59 years and a mean gout duration of 12 years. (37) The MTP1 joint, phalangeal base, and two sesamoid bones were assessed by DECT and CT. Erosions were defined as pathological juxta articular cortical breaks in at least two successive slices and vertical planes on CT. DECT volume correlated with erosions, r=0.60, p=0.005. (37) Yokose studied 153 patients with mean age of 59 years and 15 years of disease duration. (38) DECT and CT scans of the hands/wrists, feet/ankles and knees showed subcutaneous tophi were more likely when bone erosions were present (83.0% vs. 67.0%, p=0.040) with erosions 8 times more likely with abnormal DECT scans of the ankles and feet versus normal DECT scans (43.6% vs. 8.6%, OR= 8.10). (38)

Importantly, DECT has been shown to detect urate deposition in patients without clinical evidence of urate abnormalities. Dalbeth collected DECT scans on 152 patients with and without palpable tophi. (12) Patients were treated with allopurinol >300 mg/day for 5 years and DECT of the hands/wrists, feet/ankles/Achilles and knees were collected. DECT abnormalities was present in 47.0% of patients with normal serum uric acid (UA <6.0 mg/dL) without palpable tophi and increased to 90.0% when serum uric acid >6.0 mg/dL and tophi were palpable. (12) Therefore DECT volume correlates with bone erosions while DECT deposits exist in the absence of clinical urate abnormalities.

[Place Figure 1: Criterion Validity for DECT in Gout Patients Based on Stage of Gout, with and without Tophi, with and without DECT for Death and mortality prediction, Disability and Distress (gout flares).] about here.
Evidence for criterion validity is summarized in Figure 1 and in Tables 2a-c. Dalbeth found tophaceous joint disease strongly predicts loss of hand function.\(^{(39)}\) The number of joints with overlying tophi was found to be the best single predictor of the Sollerman Hand Function test, correlation coefficient 0.59, \(p<0.050\).\(^{(39)}\) No studies have examined DECT volume against hand or foot function or overall disability, but since joint erosions are a direct consequence of tophus invasion, such a relationship would be expected.\(^{(35)}\)

Perez studied a large clinical cohort and found that gout patients with an increasing burden of clinical tophi had a proportional increased risk of death, hazard ratio (HR) 2.05 (95%CI: 1.29-3.28).\(^{(40)}\) Vincent found that clinical tophi were the best predictors of all-cause and cardiovascular mortality in gout patients.\(^{(11)}\) Greater urate deposition on DECT also correlates with mortality and predictors of cardiovascular mortality. Marty-Ané followed a 135 patient gout cohort for 3 years and the cohort had a mean age of 61 years and gout duration of 11 years.\(^{(41)}\) Baseline DECT scans of feet, ankles and knees showed DECT volumes were the single best predictor of mortality, hazard ratio 1.02 (95%CI: 1.01-1.04).\(^{(41)}\) Survivors had smaller DECT volumes on average versus non-survivors (0.20 vs 0.40 cm\(^3\), \(p=0.045\)) and DECT volume was associated with mortality, but baseline clinical tophi were not, \(p=0.060\).\(^{(41)}\) DECT volume and predictors of cardiovascular mortality were assessed in six studies with 5 reporting a positive association.\(^{(8, 10, 41, 42, 43)}\) A retrospective cross sectional study by Gamala reported that a positive DECT scan was associated with the presence of CV disease, HR 2.39 (95%CI: 1.50-3.80).\(^{(8)}\) A 2020 Gamala study showed a positive, non-significant relationship on multivariate logistic regression between positive DECT volume and predicted CV events with odds ratios for mortality risk increased as DECT volume increased, from the first to the 3rd quartile, OR=4.60 (95%CI: 0.60-42.00) and the first to the 4th quartile OR = 6.40 (95%CI: 0.70-63.00), both \(p\)-values of 0.100.\(^{(42)}\) Lee performed a clinical case study and found a significant univariate association with DECT volume and the American Heart Association 10-year cardiovascular risk
score, correlation 0.22, p=0.040.\textsuperscript{(43)} A multivariable analysis showed DECT scores to be one of the strongest predictors, total model fit R\textsuperscript{2} = 0.761, p<0.001.\textsuperscript{(43)} Pascart initially found no significant association between DECT volumes of the knees and feet or both with cardiovascular risk on the Framingham Risk Score, with p-values of p=0.180, p=-0.010, and p =0.130 respectively.\textsuperscript{(44)} In a second study, Pascart studied 91 gout patients not previously on urate lowering therapy with baseline DECT scans of feet, ankles and knees. DECT volumes ≥1 cm\textsuperscript{3} were statistically associated with cardiovascular risk factors including age, gout duration, clinical tophi, hypertension, diabetes, and chronic heart failure.\textsuperscript{(10)} The median DECT volume (inter-quartile range) was 1.01 cm\textsuperscript{3} (IQR: 0.18, 2.66) for patients with hypertension, and 0.38 cm\textsuperscript{3} (IQR: 0.10, 0.62) without, p=0.020. For diabetes, median DECT volumes were 1.09 cm\textsuperscript{3} (IQR: 0.29, 2.63) versus 0.41 cm\textsuperscript{3} (IQR: 0.09, 2.11) without, p=0.050. Median DECT volume was 2.04 cm\textsuperscript{3} (IQR: 0.70, 2.95) for patients with chronic heart failure versus 0.42 cm\textsuperscript{3} (IQR: 0.12, 1.96) without, p=0.030.\textsuperscript{(10)} Those with ≥2 years of gout had a median DECT volume of 1.01 cm\textsuperscript{3} (IQR: 0.22, 3.00) versus 0.25 cm\textsuperscript{3} (IQR: 0.10, 0.70) if <2 years, p=0.007. In multivariable analysis, chronic heart failure was retained as a factor explaining DECT volume, adjusted R\textsuperscript{2}=0.21, F=5.60, p=0.002. Thus, DECT volume has been associated with cardiovascular mortality in a prospective cohort \textsuperscript{(41)} and with predictors of cardiovascular mortality in 5 of 6 studies.

Criterion validity includes the concept of distress, with measures including pain and disability of gout flares. Gout flare rates are positively correlated to DECT volume in four studies \textsuperscript{(8, 12, 45, 46)} Dalbeth followed patients over 2 years and found those with flares had mean DECT volumes of 2.60 cm\textsuperscript{3} (95%CI: 2.30-3.00) versus 2.10 cm\textsuperscript{3} (95%CI: 2.00-2.20) without flares, p=0.001.\textsuperscript{(45)} Pascart found that DECT volume predicted future gout flares.\textsuperscript{(46)} Patients with at least one flare between 0 and 6 months had a mean±SD DECT volume of 1.70±3.40 cm\textsuperscript{3} versus those without flares at 0.90±1.30 cm\textsuperscript{3}, p=0.006.\textsuperscript{(46)} Dalbeth demonstrated 83.3% of patients...
with abnormal DECT scans had flares in the past month, compared to a 63.6% of patients with abnormal DECT scans without flares, $p=0.020$.(12) Greater DECT volumes were associated with more palpable tophi, serum urate levels $>6$ mg/dL, more than 1 gout flare, and allopurinol doses $>300$ mg/day.(12) A retrospective analysis by Gamala showed a positive DECT scan was associated with more gouty attacks per year, (OR 1.23, 95%CI: 1.07-1.42) compared to patients without abnormal DECT scans.(8)

DECT is sensitive to change in urate volumes. Araujo and colleagues measured the tophus volume on DECT before and after pegloticase intravenous treatments.(47) A clinical cohort study of 152 gout patients assessed DECT of hands, wrists, feet, ankles, and knees. The mean DECT volume pre-treatment was $9.15$ cm$^3$ and post-treatment was $1.89$ cm$^3$ after a mean of 12 months, a 95% reduction.(47) Modjinou showed that DECT detected a 100% resolution of urate deposition in three index tophi over 6 months in a single patient clinical study.(48) Oral urate lowering therapy reduces the DECT urate burden in four prospective studies.(45, 49, 50, 51)

Chui demonstrated in 29 tophaceous gout patients that DECT volume (mean±SD) declined from $10.94±10.59$ cm$^3$ at baseline to $2.87±5.27$ cm$^3$ on allopurinol therapy, $p<0.001$, a 75.0% reduction after a mean 20 months. When serum urate (SU) was $>0.43$ mM/L (7.00 mg/dL), dissolution times approach infinity and when SU approached zero, DECT dissolution was modelled to take 4–8 months.(49). In the NOR-Gout 2-year clinical cohort study, DECT of feet and ankles were measured in 187 patients diagnosed by aspiration.(50) Patients were 95.0% male with a mean age of 57 years, disease duration of 8 years, and had a mean±SD baseline serum urate (SU) of $501±80$ mM/L.(50) Using allopurinol and febuxostat in a treat-to-target approach, SU values declined to $311±48$ mM/L at 12 months, and $322±67$ at 24 months. The percent of patients with clinical tophi declined from 16.6% at baseline, to 11.3% at 1 year and 9.1% at 2 years, DECT volumes declined in parallel with a study specific DECT scoring at 1
Dalbeth studied patients receiving allopurinol in a randomized trial comparing immediate titration to maintain SU <0.36 mM/L versus standard allopurinol dosing for 1 year then titration from year 1 to 2.\textsuperscript{(45)} DECT of feet and ankles were read by two independent readers blind to treatment, evaluated at baseline and year 2 in 87 subjects. There was a substantial reduction in SU, with >69.0% reaching SU targets of <0.36 mM/L, with DECT volume declining over 20.0% across the 2 years, p<0.001.\textsuperscript{(45)} Sun studied 44 gout patients treated with allopurinol or febuxostat with or without probenecid.\textsuperscript{(51)} Among 42 men and 2 women with gout duration between 1-9 years, baseline and follow up DECT feet scans were obtained up to 24 months. In concert with SU decreases, from a mean 516 to 360 µM/L, DECT volumes decreased approximately 50.0% from baseline, p<0.020; treatment duration was a significant predictor of DECT resolution, p<0.010.\textsuperscript{(51)}

Limited information is available on the definition of a clinically important DECT volume. Pascart estimated the minimum DECT volume related to excess mortality risk in patients with 11 years of disease, showed survivors had a mean DECT volume of 0.20 cm\textsuperscript{3} and non-survivors with volumes of 0.40 cm\textsuperscript{3}.\textsuperscript{(10)} They also reported that DECT volumes ≥1 cm\textsuperscript{3} predicted a higher burden of comorbid conditions (AUC 0.84). The 1 cm\textsuperscript{3} threshold separated gout patients with and without hypertension, diabetes, and chronic heart failure.\textsuperscript{(10)} Pascart showed DECT volume was related to future gout flares; DECT volumes (mean±SD) for patients with > 1 flare was 2.40±2.10 cm\textsuperscript{3} and without flares was 0.90±1.30 cm\textsuperscript{3}, p=0.006, and suggested the minimum DECT volume predicting flares was 0.81 cm\textsuperscript{3}.\textsuperscript{(46)} Dalbeth found that patients with flares over a 2-year interval had a mean DECT volume of 2.60 cm\textsuperscript{3} (95% CI: 2.30-3.00) versus those without had a volume of 2.10 cm\textsuperscript{3} (95% CI: 2.00-2.20), p<0.001.\textsuperscript{(45)} Thus a DECT volume difference of 0.50 cm\textsuperscript{3} may be important at a population level. Rajan has shown the smallest detectable difference in DECT of the feet over 12 months is 0.91 cm\textsuperscript{3}.\textsuperscript{(52)} Since the minimum important volume of DECT must be larger than the smallest detectable difference, a value of 1.00 cm\textsuperscript{3} is
tentatively proposed as the minimum important difference for DECT. The minimum clinically important DECT volume for improvement or worsening of disability has not been reported.

[Insert Table 2a-c: Study Details for studies supporting the relationships for DECT Criterion Validity in Gout against clinical outcomes of Death, Disability, Distress] about here.
Discussion

This systematic review showed that DECT images are highly reliably interpreted with intra-rater, intra-class correlation coefficients from 0.86 to 1.00. The stage of gout, (early, middle or late stage), does not influence this level of reliability. DECT overall has very good sensitivity and specificity in established gout against joint aspiration, with ranges from 0.78-0.89 and 0.84-1.00 respectively. DECT also performed very well against clinical criteria, with pooled sensitivities and specificities of 0.81 (95%CI: 0.77-0.86) and 0.91 (95%CI: 0.85-0.95).(19) Singh and colleagues reported that DECT of ankles and feet perform as well as, or better than DECT of multiple locations such as ankles, feet and knees combined.(34) This is consistent with Mallison showing DECT is most likely to be abnormal at the ankles and feet.(53) Further work should confirm whether DECT of the feet and ankles alone is preferred over scanning additional areas that are involved clinically.

DECT in early gout reduces sensitivity, but preserves specificity as compared to established gout. Lee reported sensitivities from 0.51-0.53 for two readers, with early gout defined by the absence of signs of established gout or lack of urate lowering therapy.(31) Zhang defined early gout as <1 years from first symptoms, and DECT sensitivity was 0.27, with mid gout of 0.75 and late gout of 0.90 (30). Zhang suggested ultrasound had better sensitivity than DECT in early gout, with values of 0.67 vs 0.27 respectively, using the gold standard clinical procedure of joint aspiration.(30). Shang and colleagues(18) showed DECT of early gout cases had a pooled sensitivity of 0.75 (95%CI: 0.60-0.86) and pooled specificity of 0.85 (95%CI: 0.75-0.91), whereas ultrasound had a pooled sensitivity of 0.93 (95%CI: 0.72-0.99) and pooled specificity of 0.80 (95%CI: 0.71-0.86).(18). It may be beneficial for future studies of early gout to use a standard definition such as time from first symptoms or the absence of clinical signs and symptoms. More head-to-head studies of DECT and ultrasound are needed in early gout, to confirm benefits. Ahn and colleagues suggest that DECT is less sensitive in early gout since
MSU crystals in synovial fluid have a low density, reducing resolution.\(^{(54)}\) To illustrate this, Ahn collected patient-derived solid and liquid tophi from three patients at surgery. DECT did not detect urate deposition in liquid tophi at any urate concentration, whereas solid tophi were easily detected.\(^{(54)}\) Based on the lower sensitivity of DECT in early gout and considering that more study of ultrasound is needed, when symptoms are less than two years in duration, it is recommended that clinicians aspirate joints preferentially, including when a DECT scan is negative.

Clinical tophi predict excess mortality, both cardiovascular and all-cause \(^{(11,40)}\) and DECT scans also predict \(^{(41)}\) cardiovascular and all-cause mortality in prospective cohorts. Since up to 50.0% of patients without clinical tophi or abnormal serum urates have abnormal DECT scans, confirming the mortality relationship to DECT is important. DECT was shown to be associated with CV risk scores in five of six studies examining this relationship.\(^{(8, 10, 41, 42, 43)}\)

Clinical tophi correlate with hand disability.\(^{(39)}\) We did not find studies on the relationship of DECT volumes to disability for the hands, feet, ankles or knees although a relationship seems probable. These studies should be performed.

A relationship between DECT volume and future gout flares was found in four studies.\(^{(8, 12, 45, 46)}\); DECT volumes predicting flares at 6 months \(^{(46)}\) and 2 years\(^{(45)}\). No studies were found on DECT volume and its relationship to chronic gouty arthropathy.

This systematic review found DECT volume to be very sensitive to change with effective urate lowering therapy. This supports DECT use in clinical studies and in the clinic as an outcome measure. The minimum important volume of DECT is tentatively set at 1.00 cm\(^3\), a value that
seems to predict death, cardiovascular risk factor burden and future gout flare risk although this threshold only considers DECT volume in the feet and ankles and not areas such as the hands, wrists, and knees. Further work on defining the minimum important value should be undertaken.

To the best of our knowledge, there are no prior systematic reviews of DECT volume and its prognostic ability. Still this systematic review has several limitations. The conclusions are limited by the quantity and quality of the current literature. Most of the literature relating to DECT reliability has shown it to be excellent. The diagnostic performance of DECT and ultrasound in early gout requires more study where DECT sensitivity appears lower. The prognostic value of DECT abnormalities in the absence of clinical tophi is not fully defined but is important as up to 50.0% of gout patients have an abnormal DECT scan without clinical tophi or abnormal serum urate levels. We found limited literature on the relationship of DECT to disability. We also found limited literature on the minimum important change in DECT.

A large, properly powered, prospective, cohort study should be performed, including early and established gout, patients with and without clinical tophi, with and without abnormal DECT scans, both males and females with and without controlled hyperuricemia to better understand DECT’s prognostic potential. DECT scans of the feet, ankles, knees, hands, and wrists could inform on near term outcomes such as joint pain (chronic pain and acute flares) and hand and foot disability. Better characterization of DECT measured urate volume with mortality would be welcomed; the large New Zealand gout cohort saw separation in mortality rates between participants with and without tophi as early as one year. Ideallly DECT and ultrasound would be contrasted further to better understand their respective prognostic abilities.

DECT is a promising prognostic tool in gout. It has excellent reliability with good diagnostic test performance in established gout. It is very sensitive to change with effective urate lowering
therapies, supporting its use as a clinical outcome measure. DECT appears to have a reduced sensitivity in early gout and joint aspiration should be undertaken preferentially when disease duration is less than two years, including when DECT is negative. Based on current evidence showing that DECT volumes predict mortality and gout flares, DECT should be used to stage gout patients, especially in established disease as 50.0% of patients have abnormal DECT scans with normal serum urate levels and no clinical tophi.

References

5) Dalbeth N, Doyle AJ. Imaging tools to measure treatment response in gout. Rheumatology 2018;57:i27-i34.
13) Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results, and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA 1994;271:703-7.


**Figure 1:** Construct Validity for DECT in Gout Patients Based on Stage of Gout, with and without Tophi, with and without DECT for Death, Disability and Distress (gout flares)

- **Gout with Hyperuricemia**

- **Gout, Abnormal DECT, No Tophi**

- **Gout, Abnormal DECT, Tophi present**

- **Gout with tophi present, DECT not measured**

<table>
<thead>
<tr>
<th>Authors, Journal, Year</th>
<th>Population (N)</th>
<th>Study Selection and Raters</th>
<th>Intra-rater Correlation ICC (95%CL)</th>
<th>Inter-rater Correlation ICC (95%CL)</th>
<th>Sensitivity (95%CL)</th>
<th>Specificity (95%CL)</th>
<th>AUC (95%CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic Reviews Reporting on DECT Reliability and Diagnostic Performance</strong></td>
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<tr>
<td>Shang J., Zhou L-P., Wang H., et al. <em>Acad. Radiol.</em> (2020)(18)</td>
<td>Systematic Review. Searched PubMed, EMBASE, Cochrane, Web of Science. 13 studies of DECT, 11 of ultrasound</td>
<td>Selection by 2 independent reviewers. Quality assessed by QUADAS-2. Subjects had possible or established gout</td>
<td>NR</td>
<td>NR</td>
<td>Pooled 0.89 (0.80-0.94)</td>
<td>Pooled 0.91 (0.88-0.94)</td>
<td>Pooled 0.94 (0.92-0.96)</td>
</tr>
<tr>
<td>Gamala M., Jacobs JWG, Van Laar JP., et al. <em>Rheumatology</em>, (2019)(19)</td>
<td>Systematic Review. Searched PubMed, EMBASE, Cochrane Library. 10 studies included</td>
<td>One reviewer screened titles, abstracts and full text. Final selection by consensus. Data extracted in a standard format</td>
<td>NR</td>
<td>NR</td>
<td>Pooled 0.81 (0.77-0.86)</td>
<td>Pooled 0.91 (0.85-0.95)</td>
<td>Pooled 0.95 (0.93-0.97, at joint level). Pooled 0.92 (0.81-0.95, at patient level).</td>
</tr>
<tr>
<td>Yu, Z., Mao, T., Xu, Y., et al. <em>Skeletal Radiology</em>, (2018)(20)</td>
<td>Systematic review. Searched Medline Pubmed, Embase, Cochrane Library. Seven studies included</td>
<td>Two investigators selected literature separately. More than one reviewer performed data extraction</td>
<td>NR</td>
<td>NR</td>
<td>Pooled 0.88 (0.84–0.90)</td>
<td>Pooled 0.90 (0.85–0.93).</td>
<td>Pooled 0.95 (0.94–0.96)</td>
</tr>
<tr>
<td>Chen, J., Liao, M., Zhang, H., et al <em>Zeitschrift Für Rheumatologie</em>, (2017)(21)</td>
<td>Systematic Review. Searched Web of science, PubMed, El Elsevier, Wiley Online, Cochrane Library, 2005- 02/2016. 11 studies, six of DECT, six of ultrasound, one of both</td>
<td>Data extraction and quality assessed by two independent investigators. Consensus used for disagreement</td>
<td>NR</td>
<td>NR</td>
<td>Pooled 0.88 (0.90-0.96)</td>
<td>Pooled 0.85 (0.67-0.78).</td>
<td>Pooled 0.93 (No 95%CL given)</td>
</tr>
<tr>
<td>Lee YH, Song GG <em>Semin Arthritis Rheum</em> (2017)(22)</td>
<td>Systematic review. Searched Medline, Embase, Cochrane Library to Oct. 2016. Reference lists reviewed. 8 DECT studies</td>
<td>Two data extractors and consensus used for discrepancies</td>
<td>NR</td>
<td>NR</td>
<td>Pooled 0.84 (0.81-0.87)</td>
<td>Pooled 0.93 (0.93-0.96)</td>
<td>Pooled 0.95 (0.94-0.96)</td>
</tr>
<tr>
<td>Newberry, S, FitzGerald J., Motala, A., et al <em>Ann Int Med</em> (2017)(23)</td>
<td>PRISMA guidelines followed; An Agency for Healthcare Research and Quality protocol published in 2014</td>
<td>Three studies on DECT evaluating 235 patients from 3 academic institutions</td>
<td>NR</td>
<td>NR</td>
<td>0.85-1.00 Two studies suggest early gout lower versus later gout</td>
<td>0.82-0.93</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Studies reporting on Intra-rater and Inter-rater reliability ICCs

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Description</th>
<th>ICCs</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayat, S., Aati, O., Rech, J. et al Arth Care &amp; Res, (2016)(25)</td>
<td>224 patients, 182 without gout, males 70.0%, mean age 61 yrs, mean gout duration 9 yrs</td>
<td>DECT scans scored by 2 independent readers: rheumatology fellow with no DECT experience and experienced rheumatologist</td>
<td>0.99 (0.98-1.00)</td>
<td>NR</td>
</tr>
<tr>
<td>Shi, D., Xu, J., Wu, H., et al Clinical Rheumatol, (2015)(26)</td>
<td>N=66 Median age 52 years, 92.0% male. Median gout duration 7 yrs (range 1-30)</td>
<td>Two independent observers measure tophus volumes and bone erosions using automated software</td>
<td>1.00 (1.00-1.00 for urate volume)</td>
<td>NR</td>
</tr>
<tr>
<td>Choi, H. K., Burns, L. C., Shojania, K., et al Ann Rheum Dis (2012)(27)</td>
<td>80 patients, 40 with gout, 40 without. Gout patients mean age 62 yrs, 89.0% males, mean BMI 30</td>
<td>Blinded radiologists read DECT with automated software. Inter-rater ICC of 2 independent radiologists on 17 patients</td>
<td>1.00 (1.00- 1.00)</td>
<td>0.78 (0.62-0.89). (Excludes 3 patients).</td>
</tr>
<tr>
<td>Pascart, T., Grandjean, A., Norberciak, L., et al Arth Res Ther. (2017)(28)</td>
<td>64 patients, 34 with &gt; 1 tophi on ultrasound. Mean age 65 yrs, 84.0% Male, mean gout duration 13 yrs</td>
<td>Prospective Patients with gout prospectively recruited to assess urate deposition on ultrasound and DECT. Images read by two radiologists</td>
<td>NR</td>
<td>0.69 (0.47-0.83, for tophi)</td>
</tr>
<tr>
<td>Dalbeth, N., Aati, O., Gao, A., et al J. Clin Rheumatol, (2012)(29)</td>
<td>25 gout patients, median age 64 yrs, 92.0% male, median gout duration 24 yrs</td>
<td>Two independent observers read DECT</td>
<td>1.00 (0.99-1.00)</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Studies reporting on early gout and DECT diagnostic performance
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Details</th>
<th>Patient Details</th>
<th>Imaging Details</th>
<th>Reader Details</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang B., Yang M., Wang H., et al</td>
<td>Clinical Radiol. 2020(30)</td>
<td>41 consecutive patients suspected of gout. 37 had crystal confirmation. 15 had early gout, (&lt; 1 year) 12 had mid-stage gout, (1-3 years), 10 had late gout (&gt;3 years)</td>
<td>DECT post joint aspiration. A single experienced DECT radiologist read images blinded to aspiration. Siemens device using Gout Syngo software</td>
<td>NR</td>
<td>0.27 in early gout, 0.75 in middle gout, 0.90 in late gout</td>
<td>Not provided.</td>
</tr>
<tr>
<td>Lee, S.K., Jung, J.Y., Jee, W.H.,</td>
<td>Eur Radiol (2019)(31)</td>
<td>67 gout patients with 72 involved joints, diagnosed by two rheumatologists on ACR/EULAR 2015 criteria. Controls were 36 non-gout patients with 43 involved joints</td>
<td>Two experienced MSK radiologists read DECT on 1st generation Somatom Definition64 Seimens. 4-point scale used to remove artifacts. Scores &gt;3 considered positive</td>
<td>NR</td>
<td>0.95 95%CL not reported</td>
<td>Reader 1, 0.53 Reader 2, 0.51 1.00 for both readers. Reader 1, 0.77 Reader 2, 0.82</td>
</tr>
<tr>
<td>Shang, J., Xiao-Hu, L., Shu-Qin L., et al</td>
<td>Advances in Rheumatol. (2021)* (32)</td>
<td>196 patients included. Mean age 55 yrs, mean disease duration 6 yrs 89.0% male, tophi in 17.0%</td>
<td>Two blinded musculoskeletal radiologists read DECT independently. One deposit in one joint sufficient for gout diagnosis</td>
<td>NR</td>
<td>Early gout &lt;1 yr: 0.87 Middle gout, 1-3 yrs: 0.88 Late gout, &gt;3yrs: 0.86</td>
<td>Early gout: 0.96 (0.54-1.00) Middle gout: 1.00 (0.54-1.00) Late gout: 0.88 (0.62-0.98) Early gout 0.97 (0.52-0.80) Middle gout 0.82 (0.64-0.93) Late gout 0.83 (0.74-0.89)</td>
</tr>
<tr>
<td>Kravchenko, D., Karakostas, P., Kuetting D., et al</td>
<td>Clinical Rheumatology (2022)(33)</td>
<td>36 of 42 patients in analysis. Mean age, 61 yrs, 92.0% male, mean symptom duration 20 months</td>
<td>Two blinded DECT readers with 3- &amp; 4-years' experience. Arthrocentesis, synovial fluid analysis by rheumatologist. Ultrasound by board certified MSK sonographer</td>
<td>NR</td>
<td>0.63 (0.41–0.81) 0.92 (0.62–1.00) NR</td>
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</table>

DECT, dual energy computed tomography; ICC, intraclass correlation coefficient; AUC, area under the curve; Yrs, years; NR, not reported.

*DECT performance results pooled results across two different single source DECT devices (Discovery CT, Revolution CT)
## Table 2a-c: Studies Supporting the Criterion Validity of DECT in Gout Patients for Death, Disability, Distress

### Table 2a: Death and Predictors of Mortality

<table>
<thead>
<tr>
<th>Authors, Journal, Year</th>
<th>Study Design</th>
<th>Population</th>
<th>Follow up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marty-Ané A., Norberciak L., Budzik J, Pascart T. et al, <em>Arth &amp; Rheum.</em> (2020)(41)</td>
<td>Prospective cohort. Baseline DECT of knees and ankles/feet with clinical assessment. Cardiovascular and metabolic events captured. Univariate and multivariate Cox regression models used to determine hazard ratios for mortality risk.</td>
<td>128 subjects Mean (SD) age 66 (14) years and 87.0% male. Mean gout duration 8 years.</td>
<td>Follow up visits at 1, 2 and 3 years based on phone calls to patients. Assessment of laboratory values. To confirm mortality, medical records searched, and phone calls were made to general practitioners.</td>
<td>DECT volume and serum uric acid were the only predictors of all-cause mortality. DECT volume univariate Hazard Ratio, 1.02 (95%CI: 1.01-1.03, p=0.004) DECT volume multivariate analysis Hazard Ratio = 1.02 (95%CI: 1.00-1.03, p=0.020)</td>
</tr>
<tr>
<td>Pascart T., Ramon A., Ottaviani S., et al <em>J Clin Med.</em> (2020)(10)</td>
<td>Cross-sectional study. DECT scans of knees and feet/ankles. Gout diagnosed by 2015 ACR/EULAR criteria in 3 French hospitals. Patients were not previously exposed to urate lowering therapy.</td>
<td>91 patients Mean(SD) age 63(16) years Mean(SD) gout duration 7(10) years 83.5% male</td>
<td>Consecutive patients during a first medical consultation with gout diagnosis and no prior ULTs enrolled. Demographic, gout history, comorbidities, and biological data collected. Association with DECT volume analyzed in bivariate and multivariate analyses.</td>
<td>Bivariate analysis, median DECT volume (cm³, interquartile range) for patients with clinical tophi was 2.68 (IQR: 0.71; 6.33), vs. without tophi 0.43 (IQR: 0.12; 1.90), p = 0.004. DECT volume for gout duration &gt; 2 years, 1.01 (IQR: 0.22; 3.00) and &lt;2 years 0.25 (IQR: 0.10; 0.70), p=0.007 Median DECT volume with hypertension HR 1.01 (IQR: 0.18; 2.66), vs. without 0.38 (IQR: 0.10; 0.62), p = 0.020 Diabetes mellitus DECT volume HR 1.09 (IQR: 0.29; 2.63) vs. without 0.41 (IQR: 0.09; 2.11), p=0.050 Chronic heart failure DECT volume HR 2.04 (IQR: 0.70; 2.95), vs. without 0.42 (IQR: 0.12; 1.96), p = 0.030</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Methods</td>
<td>Results</td>
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<tr>
<td>Gamala M., Jacobs JW, Linn-Rasker SP., et al. <em>Clin Exp Rheumatol</em> 2020;38(4):763-766. (42)</td>
<td>Cross sectional study of gout patients diagnosed by 2015 EULAR/ACR classification underwent DECT scan. Dutch Risk prediction SCORE and Framingham CV risk score calculated.</td>
<td>68 patients with mean(SD) age 61(14), 84.0% male</td>
<td>History and physical exam and DECT were taken within 6 months of initial joint aspiration. Bivariate and multivariate relationships explored on logistic regression.</td>
<td>Multiple logistic regression showed a positive, non-significant trend between abnormal DECT scores and higher CV event predictions. Comparing DECT volumes between the 1st and 3rd quartiles, OR=4.80 (95%CI: 0.60-42.00) p=0.100. Comparing 1st and 4th quartile OR 6.40, (95%CI: 0.70-63.00) p= 0.100.</td>
</tr>
<tr>
<td>Perez-Ruiz, F., Martínez-Indart L., Carmona, L., et al. <em>Ann Rheum Dis</em> (2013)(40)</td>
<td>Prospective clinical cohort study DECT was not assessed; clinical tophi reported on examination</td>
<td>706 patients enrolled with mean(SD) age 58(12) years, 94.0% male and mean(SD) gout duration 6(6) years.</td>
<td>Baseline evaluation and follow-up over 3 to 12 months with mean(SD) follow-up duration of 47(46) months. (range 1-204). Standardized mortality ratios (SMR) assessed magnitude of excess mortality among gout patients vs. general population.</td>
<td>Cox regression (unadjusted) analysis for tophi versus no tophi, HR 2.39 (95%CI: 1.50-3.80). Multivariate (adjusted) analyses for presence versus absence of tophi, HR 2.05 (95% CI: 1.29-3.28). Tophi remained significant for mortality risk after adjustment for baseline serum uric acid values. (HR 1.98; 95%CI: 0.24-3.20).</td>
</tr>
<tr>
<td>Gamala, M., Linn-Rasker S. P., Nix, M., et al <em>Clin Rheumatol</em> (2018)(8)</td>
<td>Retrospective clinical analysis of all adult patients with DECT imaging from January 2013- December 2014. DECT assessed by MSK radiologist.</td>
<td>147 patients with mean(SD) age 63(2) years and 68.0% males. Mean(SD) gout disease duration 3(7) years</td>
<td>Cross sectional analysis, no follow up. Variables with p&lt;0.100 in univariate analyses brought into multivariate models. DECT result as positive or negative was the outcome variable.</td>
<td>Multivariable regression model showed CV disease (OR 3.07, 95% CI: 1.26– 7.47), Gout duration (OR 1.01, 95% CI: 1.00–1.02), Frequency of attacks (OR 1.23, 95% CI 1.07–1.42), and creatinine clearance (OR 2.03, 95% CI: 0.91–1.00) all independently associated with positive DECT scans.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Follow-up</td>
<td>Risk Factors Examined</td>
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</tbody>
</table>
| Pascart, T., Capon, B., Grandjean, A. et al  
Arth Res. & Ther (2018)[44] | Cross Sectional Study  
DECT in knees and feet.  
American College of Cardiology CVD Risk Scores (FRS) calculated over 10-year horizon. | 42 patients with mean(SD) age 63(13) years.  
95.0% male.  
33/42 without prior CAD, PVD or CVA. | No follow up.  
Relationship between DECT and risk factors examined by correlation coefficients. | Correlations between DECT volumes in knees, feet, knees & feet, and FRS CV risk score were poor, at -0.12, -0.08, 0.11, respectively. All p-values > 0.050. |
| Vincent, Z., Gamble, G., House, M. et al  
Clinical tophi assessed; no DECT captured.  
Follow up at least ≥1 year | 295 subjects with mean(SD) age 59(15) years and 71.0% male.  
Mean(SD) gout duration 5(3) years. | Mean(SD) follow up 5(2) years with a 1 year minimum on all.  
Standardized mortality ratios compared to the general population and Cox proportional hazard risk models calculated. | 14.6% died at study end; SMR 1.96 (95%CI: 1.44-2.62).  
Clinical tophi only baseline variable independently associated with CV death (HR= 3.13, 95%CI, 1.38-7.10) and non-CV death (HR=3.48, 95%CI: 1.25-9.63). |
| Lee KA., Ryu SR., Park SJ., et al  
Clin Rheumatol. (2017)[43] | Retrospective Cohort Study  
DECT in 91 gout patients.  
Mean(SD) DECT volume for positive DECT scans was 8.10(21.00) cm³  
91 patients, 55 with positive DECT, 36 with negative DECT. All 13 patients with clinical tophi were DECT positive.  
Mean(SD) age 48(15) years, 98.0% male.  
Mean(SD) gout duration 5(5) yrs. | No follow up.  
Ten-year cardio-vascular risk estimated with Framingham Risk Score. | Framingham Risk Score was 2.8 times higher in patients with positive DECT in the highest quartile compared to lowest DECT quartile (24.7% vs 8.7%, p = 0.024)  
Multivariable linear regression showed DECT volume was an independent determinant of total FRS CV risk score, total R² = 0.76, p<0.001. |
### Table 2b: Disability

<table>
<thead>
<tr>
<th>Authors, Journal, Year</th>
<th>Study Design</th>
<th>Population</th>
<th>Follow up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalbeth, N., Collis, J., Gregory, K., et al <em>Rheumatology</em> (2007)[39]</td>
<td>Prospective clinical cohort in unselected rheumatology patient clinic</td>
<td>20 participants with initial baseline assessment. Hand function assessed on Sollerman hand function test, DASH instrument, fingertip to palm distance and grip strength. Number of tophi on hands counted and position recorded.</td>
<td>Data was analyzed cross-sectionally, both univariate and multiple linear regression.</td>
<td>Number of joints with tophi was the best predictor of the Sollerman hand function in both univariate analyses ($r^2 = 0.59$) and multivariate analyses ($F=3.94$, $r^2 = 0.81$, $P=0.024$). Hand tophus joint count also correlated to hand disability on the DASH instrument ($r=0.77$, $p&lt;0.0001$). Tophus counts and flares correlated over prior 6 months. ($r=0.63$, $p&lt;0.003$).</td>
</tr>
<tr>
<td>Dalbeth, N., Collis, J., Gregory, K., et al <em>Rheumatology</em> (2007)[39]</td>
<td>Prospective clinical cohort in unselected rheumatology patient clinic</td>
<td>20 participants with initial baseline assessment. Hand function assessed on Sollerman hand function test, DASH instrument, fingertip to palm distance and grip strength. Number of tophi on hands counted and position recorded.</td>
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</tr>
</tbody>
</table>
Table 2c: Distress (assessed by gout flares)

<table>
<thead>
<tr>
<th>Authors, Journal, Year</th>
<th>Study Design</th>
<th>Population</th>
<th>Follow up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalbeth, N., Billington, K., Doyle, A., et al <em>Arth &amp; Rheumatol</em> (2019)(45)</td>
<td>Cross sectional analysis nested in 2-year randomized trial. One group received allopurinol dose escalation to sUA target (&lt;6 mg/dL) from start. The second received conventional dosing for one year with dose adjustments after 1 year.</td>
<td>87 participants. Mean(SD) age 60(13) years, 92.0% male. Mean(SD) gout duration 19(14) years.</td>
<td>DECT was performed at baseline, year 1 and year 2.</td>
<td>DECT volumes were higher at 1 and 2 years in those without sUA control. At year 1, DECT volumes were 0.62 cm³ in patients without sUA control vs. 0.46 cm³ with. At year 2 DECT volumes were 0.77 cm³ in patients without sUA control vs. 0.20 cm³ with. Gout flares at year 2 showed DECT volume with flares of 2.60 (95%CI: 2.30-3.00) cm³ vs. 2.10 cm³ (95%CI: 2.00-2.20) without flares, p&lt;0.001.</td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Patients</td>
<td>Analysis</td>
<td>Key Findings</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Dalbeth, N., Nicolaou, S., Baumgartner, S., et al. <em>Ann Rheum Dis</em> (2017)(12)</td>
<td>Prospective Cohort study</td>
<td>Patients treated with allopurinol &gt;300 mg/day for &gt;3 months prior to entry. DECT of hands &amp; wrists, feet/ankles &amp; Achilles and knees done within 28 days. Patients from 9 USA and 1 New Zealand center.</td>
<td>223 patients eligible, 153 patients with interpretable DECT, 152 in analyses. Central DECT reading in Vancouver, Canada. Adults (18-85 yrs.), all met ARA Criteria for gout. Approximately 25.0% had palpable tophi and 50.0% had elevated sUA levels.</td>
<td>Analysis was correlational. Relationship of DECT volume against clinical variables examined. No multi-variable analysis. 83.3% of patients with abnormal DECT scans had flares in past 3 months vs. 63.6% with abnormal DECT but no flares, p=0.019. Greater DECT volume associated with 1). sUA levels ≥6 mg/dL. 2). &gt;1 gout flare 3). allopurinol dose &gt;300 mg/day DECT abnormal in 46.9% of patients with sUA &lt;6.0 mg/dL and no palpable tophi and up to 90.0% for those with sUA &gt;6.0 mg/dL and palpable tophi. DECT volume increased with increasing tophi counts.</td>
</tr>
<tr>
<td>Gamala, M., Linn-Rasker S. P., Nix, M., et al <em>Clin Rheumatol</em> (2018)(8)</td>
<td>Retrospective clinical analysis of all adult patients with DECT imaging from January 2013-December 2014. DECT assessed by MSK radiologist.</td>
<td>147 patients with mean(SD) age 63(2) years and 68.0% males. Mean(SD) gout disease duration 3(7) years.</td>
<td>Cross sectional analysis, no follow up. Variables with p&lt;0.100 in univariate analyses brought into multivariate models. DECT result as positive or negative was the outcome variable.</td>
<td>Multivariable regression model showed CV disease (OR 3.07, 95% CI: 1.26–7.47), Gout duration (OR 1.01, 95% CI: 1.00–1.02), Frequency of attacks (OR 1.23, 95% CI 1.07–1.42), and creatinine clearance (OR 2.03, 95% CI: 0.91–1.00) all independently associated with positive DECT scans.</td>
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Cohort study recruited gout patients
Urate burden assessed by DECT and ultrasound

36 of 78 patients had all assessments, including DECT performed.

Mean(SD) age of 64(14) years, 87.0% male.
Mean(SD) gout duration 12(12) years
Mean(SD) number of flares reported over past 12 months 4.10(1.30)

Patients followed at 3, 6 and 12 months.

Univariate and multivariate analyses using logistic regression.

At 6 months on univariate analysis, factors associated with flare risk (p≤0.100):

1). Hypertension: patients without flare=22 (66.7%), vs. patients with ≥ one flare= 5 (26.3%), chi-square, p=0.012.

2). Gout duration: patients without flare, yrs (SD), 10(11) vs. patients with ≥ 1 flare, yrs(SD) 15(13) t-test, p=0.061.

3). DECT volume(SD) in feet: patients without flare=0.90(1.30) vs. patients with at least 1 flare= 2.40(2.1), t-test p=0.006.

4). subcutaneous tophi: patients without flare=7 (21.2%) vs. patients with at least 1 flare= 9 (47.4%), chi-square, p=0.098.

On multivariable analysis, DECT volume was the only predictor of flares. DECT volume at feet cm\(^3\)(SD) was 2.10(1.9) with flares vs. 0.9(0.08) with no flares, p=0.050.

Flare risk was 2.03 times greater for each 1.00 cm\(^3\) increase in DECT volume in feet.