Cardiovascular risk in patients with new gout diagnosis: is monosodium urate volume at ankles and feet on dual-energy computed tomography associated with previous cardiovascular events?

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AbSTRACT

Objective. *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.*

Introduction

An independent association (*i.e.* not dependent on classical risk factors) of gout and increased risk of cardiovascular disease (CVD) is fully recognised (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) (6, 7), 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 (8).

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 (9), included in a study on the value of DECT in early gout (10), also participated in this study. Between April 2016 and August 2018, 100 consecutive subjects meeting the entry criteria [previously undiagnosed mono or oligoarthritis (2–3 swollen joints)] were screened. Patients with MSU proven gout in history or on uric acid lowering therapy had been excluded. Two experienced (≥5 years clinical experience) rheumatologists performed index joint aspiration and polarisation microscopy on all adequate samples within one hour of sample acquisition at base line. Eleven of 100 screened patients dropped out, 2 because of no SF examination and 9 because of the lack of DECT imaging of the arthritic joint (see study flow in Fig. 1).

Of 89 patients, 76 were classified with gout, but of 8/76 patients, DECT volumes could not reliably be calculated because of artefacts, leaving 68 patients for analyses. None of the patients in our study had been diagnosed with another kind of inflammatory arthritis (*e.g.* rheumatoid arthritis, or psoriatic arthritis), which are known to increase

Table I. Characteristics of included gout patients.

	Total	(n=68)
Age in years, mean (SD)	61	(14.2)
Male	57	(83.8)
BMI in kg/m^2, mean (SD)	28.8	(3.8)
Normal (<26 kg/m^2)	16	(23.5)
Overweight (26-30 kg/m^2)	30	(44.1)
Obesity (≥30 kg/m^2)	22	(32.4)
CV risk factors present		
Hypertension	37	(54.4)
Diabetes mellitus	11	(16.2)
hypercholesterolaemia	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.

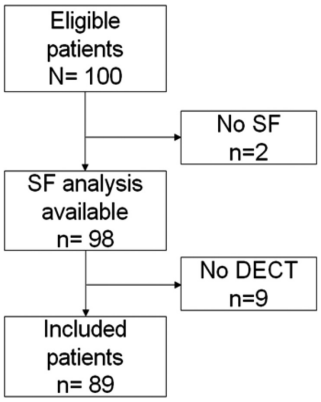

Fig. 1. Study flow chart.
SF: synovial fluid; DECT: dual-energy CT.

the risk of CVE. 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.

• *Collected data*

The data collected 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) online Supplementary Table S1).

• *Cardiovascular risk assessment*

The 10-year CV risk was estimated applying the Dutch SCORE risk chart (11), which uses gender, age, smoking status, systolic blood pressure and the TC:HDL ratio, and the Framingham risk score (FRS) (12). 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*

The subjects 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 (13) (see Supplementary file). A radiologist who was blinded to the subject's polarisation microscopy results evaluated the images. DECT images 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). Other DECT-findings, such as pixilation <3mm or erosive changes, which were not systematically assessed, were classified as negative. 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. 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 step-

wise 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, v. 22.0 (SPSS Inc., Chicago, IL, USA).

Results

The characteristics of the 68 patients are summarised in Table I.

Relationship between urate volume on DECT and CV events

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

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%).

Table II. Univariable regeression analyses of factors associated with CVE.

Variable	OR (95%CI)	*p*-value
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 III. Results of multiple logistic regression.[#]

Variable	OR (95%CI)	*p*-value
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.

Discussion

We found a trend of an independent positive relationship of DECT urate volumes at ankles and feet already and CVE in patients with gout, probably based on chronic inflammation as a risk factor for CVE.(14) However, the association could be also based on other mechanisms than inflammation, *e.g.* usage of non-steroidal anti-inflammatory drugs, which is also a risk factor for CVE.(15) 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-year risk of CVE (16). 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 (17). Biases inherent to the retrospective design, for example exclusion of subjects with incomplete data, may have affected the result of this study.

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 (18), 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. Third, at the stage of analyses of the data, we chose to analyse depositions in feet and ankles only, because depositions in other regions proved to be very scarce in our early arthritis population. Furthermore, in 29 of 89 subjects (32%), DECT imaging had not been performed of the knees (protocol violence), but in none of these patients the knees were clinically suspected of gout.

Regarding to the transferability of our results to a different DECT technique: more standardisation of postprocessing parameters and spectral imaging techniques is needed to improve the generalisability of DECT-results (19).

Other limitation in our study is the fact that we did not consider other factors that could influence the cardiovascular risk (*e.g.* the family history of CVE, inadequately controlled hypertension and diabetes).

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 at ankles and feet 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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