Construct Validity of Radiographs of the Feet to Assess Joint Damage in Patients with Gout

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ABSTRACT. ***Objective.*** To investigate construct validity of radiographic damage of the feet in gout.

Methods. Radiographs of the feet were scored using the Sharp/van der Heijde method. Factors associated with damage were investigated by a negative binomial model, and contribution of damage to health by linear regressions.

Results. Age, disease duration, serum uric acid, and tophi were associated with being erosive and erosion score. Tophi were associated with joint space narrowing. Erosions were associated (β 0.47, 95% CI 0.09–0.84) with physical function, but damage was not associated with overall physical health.

Conclusion. Our results support construct validity for radiographs of the feet when assessing joint damage in gout. (First Release December 1 2016; J Rheumatol 2017;44:91–4; doi:10.3899/jrheum.160737)

Key Indexing Terms:

GOUT RADIOGRAPHIC DAMAGE IMAGING

PATIENT-REPORTED OUTCOME QUALITY OF LIFE

Gout is the most prevalent inflammatory arthritis worldwide[1]. It is therefore surprising that outcome research in gout is more limited when compared to other rheumatic diseases. To fill this gap, the Outcome Measures in Rheumatology (OMERACT) gout working group reached consensus on outcome domains that should be measured in clinical trials and studies in gout and proposed instruments to measure domains[2]. With joint damage being endorsed as a core outcome domain, joint imaging was proposed as an instrument[3].

To date, conventional radiography (XR) is still considered a feasible approach to measure joint damage because of its widespread availability, low patient burden, and easy scoring method. For scoring XR damage, a highly reliable method is available: the gout-modified Sharp/van der Heijde score (SvdH-mG)[4]. The SvdH-mG includes the same joints in hand and feet of the SvdH system for rheumatoid arthritis, plus the distal interphalangeal joints of the hand. Joints are scored for erosions and joint space narrowing (JSN), features that can be distinguished on XR[5].

While XR has intuitively high face validity to assess joint damage in gout, no comprehensive data on the construct validity of radiographic damage are available. Construct validity addresses the ability of the instrument to measure the "construct" it intends to measure. Although construct validity of XR to measure joint damage is supported by comparisons of damage scores assessed by other imaging modalities[6], there is only 1 study (20 patients) that assessed whether radiographic damage was associated with functioning[7]. It was shown that radiographic damage on XR affected hand function. Another aspect of construct validity can be found in the expectation that a series of biological factors that reflect the disease process [such as serum uric acid (sUA) or tophi] would be associated with radiographic damage, because it is generally assumed that joint damage is the result of progressive accumulation of uric acid. More evidence that radiographic damage relates in expected ways to physical function and biological factors would add confidence in the construct validity of XR and enhance the systematic inclusion of XR in any gout trial.

Therefore, the aim of our study was to evaluate the construct validity of radiographic damage in the feet by

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exploring which biological factors of gout contribute to radiographic damage and by investigating the relationship between radiographic damage and health outcomes.

MATERIALS AND METHODS

Patient population. Data from patients with gout were obtained from a cross-sectional study of 126 patients attending the outpatient clinic of rheumatology at the Maastricht University Medical Center (MUMC), which serves as a regional hospital for patients with gout. During the study visit, comprising a structured interview and clinical examination, demographic and disease characteristics were assessed, including disease duration, sUA level, use of uric acid–lowering therapy (ULT), location and number of clinical tophi, and confirmation of number of self-reported gout flares (past year). Based on physician-confirmed comorbidities, the Rheumatic Diseases Comorbidity Index (RDCI) was calculated[8]. Physical function was assessed using the Health Assessment Questionnaire–Disability Index (HAQ-DI; range 0–3) and physical health using the physical component score of the Medical Outcomes Study Short Form-36 questionnaire (SF-36 PCS)[9,10]. Plain radiographs of the feet were obtained as part of standard clinical care within 1 month before or after the study visit. The principles of the Declaration of Helsinki were followed and the study was approved by the ethics committee of the MUMC (NL39525.068.12/METC 12-2-013).

Radiographic damage. The radiographs were independently scored by 2 trained and experienced rheumatologists (CvD, TS) blinded to the clinical characteristics and to each other's score. Radiographs were scored using the SvdH-mG, assessing erosions in metatarsophalangeal I-V and interphalangeal I (score 0–10 per joint; 0–5 per articular surface) and JSN (score 0–4 per joint), resulting in a maximum combined score of 168 for both feet[5]. Intraobserver and interobserver ICC (2-way mixed, average measures) were calculated separately for erosion, JSN, and total damage scores.

Statistical analysis. The sample characteristics are presented as mean (SD) or median [interquartile range (IQR)] depending on the distribution of the data. To explore biological factors associated with radiographic damage, a negative binomial regression (NB) and a zero-inflated negative binomial regression (ZINB) were performed for JSN and erosion scores, respectively, because data were non-normally distributed with overdispersion (for JSN) and an excess of zeros (for erosions). In the multivariable models, age and sex were included by default, and the remaining variables were added using manual forward selection ($p < 0.05$). To explore the relative contribution of JSN and erosions to HAQ-DI and SF-36 PCS, linear regression analyses were performed, adjusted for age, sex, disease duration, and comorbidities. Data were analyzed using IBM SPSS statistics v19.0 and Stata Release 12 (for NB and ZINB).

RESULTS

Study population. Eighty-one patients with gout (81/126; 64.3%) had radiographs and were included. The demographic and clinical characteristics are presented in Table 1. No patient had an acute gout flare at the time of the study visit. The patients contributing to the current analyses did not differ significantly from the 45 patients with no radiographs with regard to age, sex, use of ULT, or presence of tophi.

Radiographic damage. The ICC (95% CI) for intraobserver reliability (of 10 radiographs) for erosion, JSN, and total scores were 0.98 (0.95–0.99), 0.87 (0.57–0.96), and 0.96 (0.87–0.99) for observer 1 and 0.92 (0.72–0.98), 0.71 (0.20–0.92), and 0.88 (0.60–0.97) for observer 2, respectively. For interobserver reliability, the total sample ICC (95% CI) for erosion, JSN, and total scores were 0.94 (0.90–0.96), 0.85 (0.76–0.90), and 0.93 (0.90–0.96).

Table 1. Demographic and disease characteristics of the sample (n = 81). Values are expressed as mean (SD) unless stated otherwise.

Characteristic	Value
Age, yrs	66.4 (10.5)
Male sex, n (%)	65 (80.2)
Ethnicity, n (%)	
White	79 (97.5)
Asian	2 (2.5)
Body mass index (kg/m^2)	29.4 (4.6)
Disease duration, yrs	11.1 (10.0)
No. gout flares last year, median (IQR)	1 (0–3)
Last flare in foot/ankle, n (%)	70 (86.4)
Currently taking ULT, n (%)	57 (70.4)
Uric acid level, mmol/l	0.40 (0.13)
Uric acid level < 0.36 mmol/l (independent of ULT), n (%)	38 (46.9)
Tophaceous gout, n (%)	38 (46.9)
Tophi in foot, n (%)	15 (18.5)
No. tophi, mean (median) [IQR]	2.0 (0) [0–2]
RDCI (0–9), mean (median) [IQR]	2.8 (3) [2–4]
Chronic kidney disease, n (%)	
MDRD < 60 ml/min/1.73 m^2	30 (37.0)
MDRD < 30 ml/min/1.73 m^2	11 (13.6)
Gout-modified SvdH-score, foot	
Total (0–168), mean (median) [IQR]	5.1 (4.5) [1.5–7.5]
Erosion (0–120), mean, (median) [IQR]	1.6 (0.5) [0.0–2.0]
JSN score (0–48), mean, (median) [IQR]	3.5 (3.0) [1.0–5.3]
HAQ-DI (0–3)	0.65 (0.59)
SF-36 PCS (0–100)	38.7 (11.9)
SF-36 MCS (0–100)	49.2 (12.7)

RDCI: Rheumatic Disease Comorbidity Index; MDRD: Modification of Diet in Renal Disease Study equation; SvdH score: Sharp/van der Heijde score; JSN: joint space narrowing; HAQ-DI: Health Assessment Questionnaire-Disability Index; SF-36 PCS: Medical Outcomes Study Short Form-36 questionnaire physical component score; SF-36 MCS: SF-36 mental component score; IQR: interquartile range; ULT: urate-lowering therapy.

Seventy-one patients (71/81, 87.7%) had radiographic damage, of which 38 (46.9%) had erosions (score > 0.5) and 63 (77.8%) had JSN (score > 0.5). Median (IQR) erosion, JSN, and total SvdH-mG scores were 0.5 (0–2), 3 (1.0–5.3), and 4.5 (1.5-7.5), respectively, for the entire group.

Factors associated with radiographic damage. Table 2 shows the final model of the NB and ZINB regression analyses. Older age and having not reached the sUA target level (i.e., sUA < 0.36 mmol/l) were significantly associated with being erosive. Older age, longer disease duration, and higher number of clinical tophi were positively associated with erosion scores. Presence of clinical tophi was associated with having more JSN.

The contribution of radiographic damage to outcome. In Table 3, the results are shown of the univariable and multivariable regression analyses to explore the effect of radiographic damage on HAQ-DI and SF-36 PCS. In multivariable analysis, higher erosion scores were significantly associated with higher HAQ-DI, although contribution to the variation in outcome (+6.0% after adjustment) was limited.

Table 2. Multivariable models exploring determinants of joint damage in patients with gout separately for (a) erosions using zero-inflated negative binomial regressions and (b) joint space narrowing (JSN) using negative binomial regressions.

(a)	Not Being Erosive*				Erosion Score (count)¥			
	β	OR†	95% CI (OR)	p	B	Exp(β)‡	95% CI [Exp(β)]	p
Age, yrs	–0.15	0.86	0.74–0.99	0.036	0.05	1.06	1.02–1.09	**0.002**
Sex, female	3.36	28.80	0.87–955.74	0.06	0.50	1.65	0.72–3.75	0.23
Disease duration, yrs					0.04	1.04	1.01–1.07	**0.018**
No. tophi					0.07	1.07	1.03–1.12	**0.001**
sUA ≤ 0.36 mmol/l, yes/no	4.39	80.53	1.25–5192.79	**0.039**				
(b)					JSN score (count)¥			
Age, yrs	#	#	#	#	0.01	1.01	0.99–1.02	0.63
Sex, female	#	#	#	#	–0.13	0.88	0.55–1.39	0.58
Tophaceous gout, yes/no	#	#	#	#	0.57	1.76	1.23–2.53	**0.002**

Significant values are shown in bold face. *Logistic model, predicting being nonerosive (erosion score being "certain zero"). ¥Negative binomial model, predicting expected count. †Factor change in odds for 1-unit increase in the independent variable. ‡Factor change in expected count for 1-unit increase in the independent variable. # No estimates, because a negative binomial model has no "certain zeros." sUA: serum uric acid.

Table 3. Uni- and multivariable linear regressions exploring the effect of radiographic damage on physical functioning and health-related quality of life, measured with HAQ-DI and SF-36 PCS.

	HAQ-DI				SF-36 PCS			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Erosion score, per 10 points worsening*	0.51 (0.10–0.91)	0.015	0.47 (0.09–0.84)	0.015	–2.02 (–10.28 to 6.22)	0.63	–1.44 (–9.46 to 6.58)	0.72
JSN score, per 10 points worsening*	0.02 (–0.43 to 0.46)	0.94	–0.09 (–0.32 to 0.49)	0.68	4.08 (–4.64 to 12.80)	0.36	3.03 (–5.39 to 11.44)	0.48
R^2 model, %			26				14	
Variance (R^2) explained by radiographic damage scores, %								
Erosion			6.0				0.2	
JSN			0.2				0.6	

*Tested separately in multivariable analysis. Multivariable analyses adjusted for age, sex, disease duration, and comorbidity (calculated by the Rheumatic Diseases Comorbidity Index). HAQ-DI: Health Assessment Questionnaire–Disability Index; SF-36 PCS: Medical Outcomes Study Short Form-36 questionnaire physical component score; JSN: joint space narrowing.

The multivariable analysis of SF-36 PCS revealed no significant influence of erosions or JSN.

DISCUSSION

Our current study further supports the construct validity of radiographic damage in the feet when assessing outcome in gout. Patients who were older, had longer disease duration, had not reached the sUA target level, and had more tophi were more likely to be erosive or to have more erosions. In addition, patients with tophaceous gout had higher JSN scores. Radiographic damage showed an association with physical function assessed by HAQ, but not with overall physical health measured by the SF-36.

The finding that age, disease duration, sUA level, and tophi were associated with radiographic damage was recently also reported by Dalbeth, *et al*, who found that sUA level, tophi, and disease duration were at least moderately associated with radiographic damage of hands and feet[11]. A study showing that profound reduction of sUA levels led to improvement of the SvdH-mG (erosion) score further supports the role of sUA and clinical tophi in the pathophysiology of erosions[12].

On the other hand, radiographic damage was not consistently associated with health outcome in our study. A reason for the inconsistent and at most moderate (for HAQ-DI) association might be that the natural course of gout is difficult to identify, because radiographic damage seems reversible with ULT. Another explanation might be the overall low scores of radiographic damage, but this is likely the clinical reality of unselected patients under care of a rheumatologist, because observed damage scores are in line with those reported in other studies by patients not selected for trials[13]. Further, self-reported HAQ-DI and SF-36 might insufficiently identify lower limb impairments. SF-36 in particular, a health-related quality of life instrument, is strongly influenced by different aspects of health such as vitality. Finally,

it is known that patients with slowly progressive disease, as is the case for chronic gout, can often adapt to impairments, indicating reference shift[14].

We recognize that this study has limitations. First, the sample size is small and patients were recruited from a university hospital, although for patients with gout it serves as a regional hospital. Although this would not hamper the internal validity, it might be possible that the relationship between radiographic damage and health outcomes is stronger in selected subgroups with more severe disease. Second, only radiographs of the feet were obtained in standard clinical care, because clinical manifestations occur most frequently in the feet. Third, we need to be cautious when interpreting our results, because joint damage scored with SvdH-mG might be attributable to osteoarthritis rather than gout, especially because both diseases often occur together[15]. The study by Dalbeth, *et al*[11] showed that JSN was the imaging feature least associated with crystal deposition (assessed using dual-energy computed tomography). Therefore, we believe that JSN, present in both gout and osteoarthritis, lacks discriminative validity and might be reconsidered in the future. Nevertheless, our study convincingly confirmed that the SvdH-mG is a highly reproducible method to score radiographic damage. Finally, this is a cross-sectional study and therefore knowledge about how radiographic damage evolves over time could not be obtained.

Our findings support the construct validity of XR to evaluate joint damage in gout. Together with widespread availability, low patient burden, and low cost, this suggests a role for XR to monitor joint damage in patients with gout. More research is needed to understand whether in clinical practice, information on XR would influence currently recommended treatment strategies.

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