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Original article

Health-related quality of life in gout: a systematic review

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Abstract

Objectives. To identify the instruments that have been used to measure health-related quality of life (HRQOL) in gout and assess their clinimetric properties, determine the distribution of HRQOL in gout and identify factors associated with poor HRQOL.

Methods. Medline, CINAHL, EMBASE and PsycINFO were searched from inception to October 2012. Search terms pertained to gout, health or functional status, clinimetric properties and HRQOL. Study data extraction and quality assessment were performed by two independent reviewers.

Results. From 474 identified studies, 22 met the inclusion criteria. Health Assessment Questionnaire Disability Index (HAQ-DI) and Short Form 36 (SF-36) were most frequently used and highest rated due to robust construct and concurrent validity, despite high floor and ceiling effects. The Gout Impact Scale had good content validity. Gout had a greater impact on physical HRQOL compared to other domains. Both gout-specific features (attack frequency and intensity, intercritical pain and number of joints involved) and comorbid disease were associated with poor HRQOL. Evidence for objective features such as tophi and serum uric acid was less robust. Limitations of existing studies include cross-sectional design, recruitment from specialist clinic settings and frequent use of generic instruments.

Conclusion. Most studies have used the generic HAQ-DI and SF-36. Gout-specific characteristics and comorbidities contribute to poor HRQOL. There is a need for a cohort study in primary care (where most patients with gout are treated) to determine which factors predict changes in HRQOL over time. This will enable those at risk of deterioration to be identified and better targeted for treatment.

Key words: gout, health-related quality of life, clinimetrics.

CLINICAL SCIENCE

Introduction

Gout is the most prevalent inflammatory arthritis, affecting 1.4% of adults in Europe [1]. Health-related quality of life (HRQOL) may be adversely influenced by the excruciating pain, chronic arthropathy, associated co-morbidities (renal and cardiovascular disease, metabolic syndrome and OA) and frequent suboptimal management in gout [2]. The UK Department of Health and the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group have identified HRQOL as a key component of patient outcome assessment alongside the more traditional markers such as survival rates, symptoms and cost of resources [3, 4]. HRQOL can be measured using generic instruments, which allow HRQOL to be compared between different disease states, or by disease-specific instruments, which account for the specific facets of individual diseases [5]. Recent interest in HRQOL in gout patients has resulted in the development of a disease-specific measure, the Gout Assessment Questionnaire 1.0 [6], which was subsequently revised, resulting in the Gout Assessment Questionnaire 2.0 and its subscale, the Gout Impact Scale (GIS) [7]. The aims of this systematic review were to (i) describe which instruments have been used to measure HRQOL in gout in existing studies, (ii) describe the clinimetric properties of these instruments, (iii) describe the distribution of HRQOL in gout and (iv) identify which factors associate with poor HRQOL in gout.

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Methods

Search strategy

A systematic search was undertaken using the following databases from inception to October 2012: Medline, EMBASE, CINAHL, PsycINFO and Cochrane database of systematic reviews. The search aimed to identify studies of self-reported HRQOL in gout as well as those evaluating the clinimetric (measurement) properties of instruments used to assess HRQOL in gout patients. Clinimetrics is defined as a methodological discipline focused on measurement issues [8, 9]. The clinimetric properties of an instrument describe the quality of its clinical measurements, e.g. validity, reliability and responsiveness. Search terms included gout, health or functional status and HRQOL. These domains were combined with filters for measurement properties, such as elicitation method (scale, measure and questionnaire) and measure of scientific quality (psychometrics, validity, responsiveness, reliability) [10].

To increase the recall of the search results, all terms were typed as synonyms and free text and mapped to a thesaurus. Truncated terms and wildcards were used specific to each database.

Eligibility criteria

The following inclusion criteria were applied: (i) adults aged >18 years with gout, (ii) assessment of HRQOL or evaluation of the clinimetric properties of one or more instruments and (iii) publication in English. Both primary care and secondary care studies were included. Publications without empirical data (such as commentaries, editorials and reviews), randomized controlled trials deemed to be non-representative of a typical population with gout and articles not available as full text were excluded.

Study selection

Titles and abstracts of identified articles were independently reviewed against the criteria above by two reviewers (PC, LC). Articles that could not be excluded based on title and abstract screening alone were included for full-text review, carried out independently by the same two reviewers. Further exclusions were made based on reapplication of the inclusion and exclusion criteria. The references of all full-text papers were examined for relevant studies. Disagreements at all stages were arbitrated through consensus meetings.

Data extraction

The following data were extracted: study design (length and method of recruitment, inclusion and exclusion criteria, controls), participants (sample size, geographic location, setting, mean age, gender, ethnicity, method of gout diagnosis), study response rate or attrition, methods of measurement (follow-up, statistical analysis), HRQOL scores and factors associated with poor HRQOL. The Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) checklist was used to extract data on the clinimetric properties of questionnaires [11].

Methodological assessment

The quality of the following clinimetric properties of HRQOL instruments was assessed against a modified version of the quality criteria for measurement properties by Terwee *et al.* [12]—validity (content, known group, floor or ceiling effects, construct and concurrent), reliability (internal consistency and test–retest) and responsiveness. Qualitative studies were assessed against the criteria set by the Critical Appraisal Skills Programme (CASP) [13]. Cohort studies were assessed against the standards set by the Newcastle Ottawa Scale (NOS) for assessing the quality of non-randomized studies [14]. Assessment of the methodological quality of cross-sectional studies included modified components such as the baseline associates of HRQOL, response rate and a measure of association between poor HRQOL in gout compared with controls, in addition to the NOS quality assessment scale.

Results

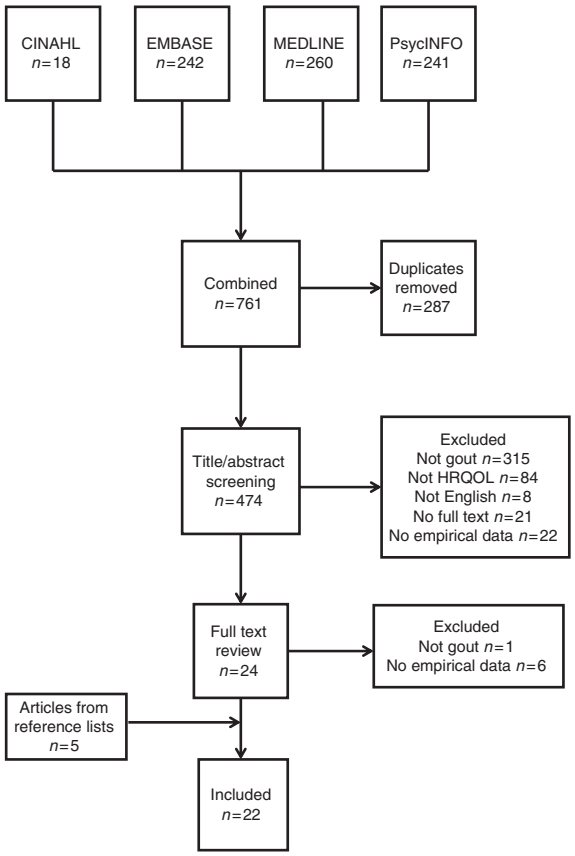
Study selection

A total of 761 potentially relevant articles were identified: 474 articles were included in title and abstract screening after removal of duplicated papers. After full-text review of the remaining 24 articles as well as 5 articles identified from reference lists, 22 articles met the inclusion criteria. Reasons for exclusion are described in Fig. 1. Included studies are summarized in Table 1.

Study characteristics and methodological quality

Of the 22 included studies, 8 evaluated clinimetric properties of instruments used to measure HRQOL [4, 6, 7, 15–19] and the remainder focused on self-reported HRQOL or health care utilization [20, 21–32]. One study reported both the measurement properties as well as the scores of HRQOL as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) and Short Form 36 (SF-36) [33]. All studies were published in or after 2006. A total of 13 cross-sectional [4, 7, 18, 20–24, 26–30], 7 cohort [6, 15–17, 19, 25, 33] and 2 qualitative studies [31, 32] were identified. The median sample size of the 20 quantitative studies was 134 (range 49–70 334). Only four studies [17, 18, 22, 33] used the diagnostic gold standard of MSU crystal identification from joint or tophus aspirate [34]. Other methods of gout diagnosis in studies included hyperuricaemia ($n = 3$) [6, 18, 19], ACR classification criteria [35] ($n = 11$) [4, 7, 15, 16, 23, 25, 26, 28, 29, 31, 35], self-reported gout ($n = 4$) [19, 21, 22, 30], physician diagnosis ($n = 2$) [22, 24] and ICD-9 codes ($n = 1$) [20]. The follow-up period in cohort studies ranged from 8 weeks [16, 19] to 2 years [17]. Five cross-sectional studies reported response rates of >60% [7, 18, 22, 24, 29]. Quality assessment of cohort and cross-sectional studies is summarized in Table 2 (for qualitative studies, see supplementary Table S1 available as supplementary data at *Rheumatology* Online).

FIG. 1 Systematic search and study selection.



Instruments used to measure HRQOL in gout

Twelve different instruments to measure HRQOL were identified (five studies employed more than one instrument) [16, 18, 23, 25, 33]. Most commonly used were the HAQ-DI ($n = 6$) [4, 15, 18, 23, 27, 33], SF-36 ($n = 5$) [17, 20, 22, 23, 33], GIS ($n = 4$) [7, 19, 24, 26] and Health Assessment Questionnaire II (HAQ II, $n = 2$) [18, 25]. The Gout Assessment Questionnaire 1.0 (GAQ 1.0) [6], Arthritis Impact Measurement Scale (AIMS) [16], Medical Outcomes Survey 20 (MOS 20) [16], Brief Illness Perception Questionnaire (BIPQ) [25], SF-36 Physical Function 10 (PF10) [18], Short Form 12 (SF-12v2) [30], HAQ [28], EuroQOL 5D (EQ5D) [23], Short Form 6D (SF-6D) [30] and World Health Organisation Quality of Life (WHOQOL)-BREF [21] were each used once.

Clinimetric properties of instruments used to measure HRQOL in gout

Values of the measurement properties of identified instruments are available in Table 3. Supplementary Tables S2 and S3 (available at *Rheumatology* Online) present quality ratings assigned to the measurement properties assessed against the modified guidelines by Terwee *et al.* [12]. Content validity was only established for the gout-specific GIS and GAQ 1.0, which received patient and health care provider input during the development of the questionnaires [6, 7]. The generic SF-36 (except PF10 [18]) and the HAQ-DI [4, 15–17, 33] performed well in the known-group analysis based on self-reported general health, comorbidities and correlation with disease characteristics. The HAQ-DI, HAQ II and SF-36 had significant floor (HAQ-DI 20.5%) and ceiling (HAQ-DI 34%, HAQ II 25.8%, SF-36 18.4%) effects, indicating a weakness in the ability to differentiate between participants at the extreme ends of the scale (no disability and severe disability), leading to limited content validity and responsiveness to change [4, 17]. The GIS showed poor construct validity, with low correlations between the subscales of GIS (except unmet treatment need) and physician-rated severity ($r = 0.02$–0.34), although moderate correlations were seen with patient-rated severity ($r = 0.31$–0.45) [7, 19]. Correlations of the SF-36 Mental Component Summary (MCS) ($r = -0.17$ to -0.43) with the GIS were generally higher than those seen with the Physical Component Summary (PCS) ($r = -0.10$ to -0.20) (NB correlation coefficients are negative, as higher scores indicate better health status on the SF-36 but worse health status on the GIS [5]). The GAQ 1.0 had better correlation with the MOS health distress questionnaire ($r = 0.03$–0.46) than the SF-36 (PCS, $r = 0.02$–0.34; MCS, $r = -0.01$ to 0.23) [6]. The HAQ-DI and HAQ II correlated with each other ($r = 0.87$) as well as the SF-36 (HAQ-DI, $r = -0.41$ to -0.67; HAQ II, $r = -0.35$ to 0.72) [15, 18]. Most instruments had good or excellent internal consistency (Cronbach's $\alpha = 0.4$–1.0), except the GIS (weak correlation between items of the gout medication side effects and unmet treatment needs) [7]. Test–retest reliability was low for the AIMS [intraclass correlation coefficient (ICC) = 0.11–0.70] and the MOS 20 (ICC = 0.27–0.65) [16] but acceptable for the HAQ-DI (ICC = 0.68–0.84) [15]. Responsiveness to clinical change was elicited by the Minimal Clinically Important Difference (MCID) of 5–8 points for the subscales of the GIS [19], SF-36 [17] and GAQ 1.0 (in all subscales except well-being anchored to pain frequency) [6] and a 20% change in scores of the AIMS and MOS 20 [16]. Effect sizes (ESs) of the PCS (SF-36) improved from small (0.3) in the treatment with colchicine only to large (0.99) in the urate lowering treatment (ULT) and colchicine group [17]. The magnitude of the ES was lower for the GIS (0.218–0.376 in the minimally improved and 0.129–0.682 in the markedly improved groups) [19] and moderate (0.62) for the HAQ-DI [15].

The distribution of HRQOL in gout

No studies were identified that defined or used a cut-off value for poor HRQOL in gout. Higher scores indicate worse HRQOL in the GIS, GAQ 1.0, HAQ-DI, AIMS and BIPQ and better HRQOL in the WHOQOL-BREF, SF-36 including PF10, MOS 20 and SF-12v2. Four studies identified instruments with scores lower than controls (SF-36 physical functioning, role physical, bodily pain, general health, role emotional, PCS $P < 0.001$ [20]; WHOQOL-BREF $P = 0.003$ [21]) and USA normative distribution (SF-36 PCS $P = 0.007$ [22], $P < 0.001$ [30]), representative

Table 1 Characteristics of studies providing data on HRQOL in gout

Reference	Study period	Publication year	Location	Source of data/recruitment	Study type	Sample size	Questionnaire to measure HRQOL
Singh and Strand [20]	1996–98	2008	USA	Veterans Affairs database	Cross-sectional	70 334	SF-36 (veterans)
Colwell *et al.* [6]	NR	2006	USA	Phase 2 clinical trial of febuxostat	Nested prospective cohort	126	GAQ 1.0
Taylor *et al.* [4]	NR	2008	New Zealand	Study of hand function in gout and rheumatology clinics	Cross-sectional	73	HAQ-DI
Hirsch *et al.* [24]	NR	2010	USA	Multispecialty clinics (physician, poster and newspaper advertisement recruitment)	Cross-sectional	371	GIS
Hirsch *et al.* [7]	NR	2008	USA	Multispecialty clinics (physician, poster and newspaper advertisement recruitment)	Cross-sectional	371	GIS
Roddy *et al.* [21]	NR	2007	UK	Two GP practices	Cross-sectional	13 684	WHOQOL-BREF
Dalbeth *et al.* [25]	NR	2011	New Zealand	Advertisements in the community and secondary care clinics	Prospective cohort	142	BIPQ, HAQ II
Alvarez-Hernandez *et al.* [16]	NR	2009	Spain	Not described	Prospective cohort	49	AIMS, MOS 20
Lee *et al.* [22]	NR	2009	USA	Advertisements in primary and secondary care clinics	Cross-sectional	371	SF-36
Sarkin *et al.* [26]	NR	2010	USA	Advertisements in community clinics and newspapers	Cross-sectional	260	GIS
Becker *et al.* [33]	NR	2009	USA	Academic and private rheumatology clinics	Prospective cohort	110	SF-36 and HAQ-DI
ten Klooster *et al.* [18]	2005–08	2011	Netherlands	Outpatient rheumatology clinics	Cross-sectional	102	HAQ-DI, HAQ II and SF-36 PF10
Khanna *et al.* [23]	NR	2008	USA	Private clinic and University of Cincinnati Veterans Affairs Medical Center	Cross-sectional	80	SF-36, EQ5D and HAQ-DI
Alvarez-Hernandez *et al.* [15]	NR	2008	Mexico	Eight rheumatology departments	Prospective cohort	206	HAQ-DI
Khanna *et al.* [17]	NR	2011	Spain	Gout clinic	Prospective cohort	99	SF-36
Lindsay *et al.* [31]	NR	2011	New Zealand	Primary and secondary care clinics	Qualitative interviews	11	None
Khanna *et al.* [19]	NR	2011	USA	RCT of rilonacept vs placebo	Nested prospective cohort	73	GIS
van Groen *et al.* [27]	2005–08	2010	Netherlands	Outpatient rheumatology clinic	Cross-sectional	102	HAQ-DI
Alvarez-Nemegyei *et al.* [28]	1999	2005	Mexico	Primary care	Nested case-control in a cohort	90	HAQ
Harrold *et al.* [32]	2005–10	2010	USA	Multispecialty practice (Fallon clinic)	Qualitative	26	None
Singh *et al.* [29]	NR	2011	USA	Multispecialty clinics (physician, poster and newspaper advert recruitment)	Cross-sectional	298	Healthcare utilization frequency
Khanna *et al.* [30]	2010	2012	USA, UK, Germany, France	National Health and Wellness Survey, Lightspeed Research panel	Cross-sectional	1936	SF-12v2, SF-6D

NR: not reported; RCT: randomized controlled trial.

Table 2 Modified NOS quality assessment for cross-sectional and cohort studies

Study details	Selection				Comparability		Assessment of HRQOL in addition to self-reported data		
	Cohort representative of average gout patient in community	Controls from same source as cases	HRQOL associations (CS) or predictors/ change (Cht)	Diagnosis of gout: MSU crystals, ARA criteria (35) or record linkage	Controls matched for age/ gender	Measure of association between gout and HRQOL (OR or RR)	Independent physician assessment, secure records or record linkage	Adequate follow-up period (Cht only)	Response rate >60% (CS) or attrition <30% (Cht)
CS									
Singh and Strand [20]	+	+	+	+	–	NR	+	Not relevant	–
Hirsch *et al.* [24]	+	NR	+	+	NR	NR	+	Not relevant	+
Hirsch *et al.* [7]	+	NR	+	+	NR	NR	+	Not relevant	+
Roddy *et al.* [21]	–	+	+	–	–	NR	+	Not relevant	–
Lee *et al.* [22]	+	NR	+	+	NR	NR	+	Not relevant	+
Sarkin *et al.* [26]	+	NR	+	+	NR	NR	+	Not relevant	NR
ten Klooster *et al.* [18]	–	NR	+	+	NR	NR	–	Not relevant	+
Khanna *et al.* [23]	+	NR	+	+	NR	NR	+	Not relevant	NR
Taylor *et al.* [4]	–	NR	+	+	NR	NR	–	Not relevant	NR
van Groen *et al.* [27]	–	+	NR	+	–	NR	–	Not relevant	NR
Alvarez-Nemegyei *et al.* [28]	+	+	+	+	–	NR	+	Not relevant	NR
Singh *et al.* [29]	+	NR	+	+	NR	NR	+	Not relevant	+
Khanna *et al.* [30]	+	NR	+	–	NR	NR	–	Not relevant	–
Cht									
Colwell *et al.* [6]	–	NR	+	–	NR	NR	+	+	+
Dalbeth *et al.* [25]	+	NR	+	+	NR	NR	+	+	+
Alvarez-Hernández *et al.* [16]	–	NR	+	+	NR	NR	+	–	+
Becker *et al.* [33]	–	NR	+	+	NR	NR	+	+	–
Alvarez-Hernández *et al.* [15]	+	NR	+	+	NR	NR	+	+	+
Khanna *et al.* [17]	–	NR	+	+	NR	NR	+	+	–
Khanna *et al.* [19]	–	NR	+	–	NR	NR	–	–	+

+: positive rating; –: negative rating; Cht: cohort study; CS: cross-sectional study; MSU: monosodium urate; NR: not reported; RR: relative risk.

Table 3 Measurement values of instruments used to measure HRQOL

	Reliability		Validity				Scale development		Responsiveness
Measurement instrument	Internal consistency (Cronbach's α)	Test–retest (ICC)	Content	Construct (Pearson or Spearman's *r*)	Concurrent (Pearson or Spearman's *r*)	Hypothesis *a priori*	Confirmatory factor analysis	Rasch analysis	MCID, SDC, ES, Guyatt's RR or >20% change in scores
GIS [7, 19]	0.54–0.94	0.77–0.89	Patients and rheumatologists	Patient severity ($r = 0.31$–0.45), attack freq. ($r = 0.06$–0.51), attack pain ($r = 0.13$–0.47), physician severity ($r = 0.02$–0.34), PCS ($r = -0.10$ to -0.20), MCS ($r = -0.17$ to -0.43)	NR	Yes	Yes	Yes	ES 0.218–0.376 in the minimally improved and 0.129–0.682 in the markedly improved groups
GAQ 1.0 [6]	0.78–0.97	NR	Patients and Rheumatologists	PCS ($r = 0.02$–0.34), MCS ($r = -0.01$ to 0.23), MOS ($r = 0.03$–0.46)	NR	Yes	Yes	No	GRR 0.030 (1 month) to 1.142 (6 months). MCID 1.88–12.33 (not significant in well-being for pain freq.)
HAQ-DI [4, 15, 18, 33]	0.81–0.97	0.68–0.84	Floor 20.5%, Ceiling 34%	Freq. of flares ($r = 0.41$), physician global ($r = 0.42$–0.77), swollen joints ($r = 0.40$–0.62), painful joints ($r = 0.46$–0.650), joints with limited mobility ($r = 0.36$), VAS pain ($r = 0.56$), tophi ($r = 0.42$), excellent/very good health = 0.16, good = 0.33, fair/poor = 1.25	SF-36 ($r = -0.41$ to -0.67), PCS ($r = -0.71$), MCS ($r = -0.56$), DASH ($r = 0.81$), Sollerman ($r = -0.79$), ACR functional class ($r = 0.79$), HAQ II ($r = 0.87$), PF 10 ($r = -0.75$)	Yes (55.5% true)	Yes	Yes	Mean ES = 0.62 (moderate), SDC = 0.59 and GRR = 1.91
SF-36 [17, 33]	0.75–0.97	0.40–0.90	Ceiling RP = 18.4%, SF = 32.7%, RE = 58.6%	PCS: tophi ($r = 0.277$), swollen joints ($r = -0.334$), painful joints ($r = -0.544$), flares last year ($r = -0.369$); MCS: painful joints ($r = -0.436$), freq. of flares ($r = -0.321$)	NR	NR	NR	NR	Colchicine: ES for PCS = 0.3 (small), ES for MCS = 0.16 (negligible) Colchicine + ULT: ES for PCS = 0.99 (large) ES for MCS = 0.08 (negligible), MCID (all subjects) 70% for PCS and 38% in MCS
MOS 20 [16]	0.68–1.0	0.27–0.65.	NR	JFL: 23.75–66 Without JFL: 37.59–81.43	HAQ-DI ($r = -0.1$ to -0.5)	NR	NR	NR	>20% change: PF, SF, health perception, pain
AIMS [16]	0.66–0.96	0.11–0.70	NR	JFL: 3.05–6.62 Without JFL: 1.99–5.46	HAQ-DI ($r = 0.1$–0.6)	NR	NR	NR	>20% change: dexterity, daily activity, social development, pain, depression
HAQ II [18]	0.94	NR	Ceiling 25.8%	Excellent/very good health = 0.28, good = 0.44, fair/poor = 1.39	PF 10 ($r = -0.79$), SF-36 [−0.35 (MH) to 0.72 (RP)]	Yes	NR	NR	NR
PF 10 [18]	0.94	NR	NR	Excellent/very good health = 71.91, good = 74.27, fair/poor = 39.33	HAQ-DI ($r = -0.75$), SF-36 [0.30 (MH)–0.68 (RP)]	Yes	NR	NR	NR

SDC: smallest detectable change; GRR: Guyatt's responsiveness ratio; NR: not reported; JFL: joints with functional limitations; SF-36 subscales: RP, role physical; MH, mental health; SF, social function; RE, role emotional; freq.: frequency.

of poor HRQOL in gout. One cohort study of treatment-failure gout showed lower scores in all SF-36 domains (except mental health and MCS) compared with age- and sex-matched US normative distributions (PCS and MCS normative distributions have a mean of 50 and a standard deviation of 10 for the US population) [33]. One cohort [17] and two cross-sectional studies [21, 22] highlighted the greater impact of gout on physical HRQOL as measured by the SF-36 [17] and WHOQOL-BREF ($P < 0.001$) [21], with a lesser reduction seen in the MCS compared with US norms ($P < 0.001$) [22]. However, the impact on physical function was mild, as shown in two studies using the HAQ-DI, with a baseline HAQ-DI of 1 for those with treatment-failure gout [33] and 0.43 in chronic tophaceous gout [16]. (Consensus-based cut-off for mild disability as measured by the HAQ-DI is a score <1, moderate disability 1–2 and severe disability $\geqslant 2$ [36].) Similarly the average HAQ score (surrogate for musculoskeletal disability) in another study was 0.17 [28]. Two cross-sectional studies [27, 30] comparing the impact of gout with that of other rheumatic diseases showed substantially lower levels of disability (mean HAQ-DI 0.54) in patients with gout compared with those with RA (0.97) and OA (1.00) [27]. Those with severe gout (three or more flares in the previous year and confirmed tophi) had similar health utility (SF-6D) scores as patients with average RA or systemic lupus [36]. In two studies that utilized the GIS, participants' gout concern remained high despite their reporting that they found treatment helpful [19, 24], and in another cohort study using the generic BIPQ, the impact of gout was most severe on perceptions of chronicity [25]. Gout severity was also associated with an increased utilization of primary care clinics in a cross-sectional study of health care resources utilization ($P = 0.005$) [29].

Factors associated with poor HRQOL in gout

Two studies of physical functioning (measured by the SF-36 and HAQ-DI) as a surrogate marker of HRQOL and another study of health care utilization found that associated comorbidities contribute to poorer HRQOL (PCS, $r = -0.18$ to -0.43, $P < 0.01$ [22]; HAQ-DI, $P < 0.03$ [33]) and a greater number of primary care visits ($P = 0.006$) [29]. In one study of US veterans, comorbidities were solely responsible for poor HRQOL, with no difference in HRQOL between those with and without gout after comorbidities had been adjusted for [20]. However, in one cross-sectional study the association between gout and poor physical HRQOL of the WHOQOL-BREF remained significant after adjustment for medical (diabetes, hypertension and chronic kidney disease) and musculoskeletal comorbidities (WHOQOL-BREF, $P = 0.001$ [21]). Cross-sectional association of gout characteristics [presence of tophi (PCS, $P < 0.01$; MCS, $P < 0.05$), uncertainty about the presence of tophi (PCS, $P < 0.001$; MCS, $P < 0.01$) and four or more flares in the last 12 months (PCS, $P < 0.05$; MCS, $P < 0.05$)] with poor HRQOL and high activity impairment also remained significant even after adjustment for comorbidities [30]. In one cohort [25] and four cross-sectional studies [7, 22, 28, 30], gout-specific features, including increasing frequency of flares ($P = 0.002$ [22], $P = 0.044$ [25], $r = 0.51$ [7], $P < 0.05$ [30]), time with pain between attacks ($P < 0.001$ [22]), pain during a typical attack ($P = 0.023$ [22]), number of joints involved in a typical attack ($P = 0.004$ [22]) and presence of tophi {relative risk (RR) = 4.3, 95% confidence interval (CI) 1.2, 15.1 [28], $P < 0.05$ [30]} were reported to be associated with worse HRQOL (measured by the GIS, SF-36, SF-12v2, HAQ and BIPQ) even after adjustment for age, gender, gout features and comorbidities. Increased frequency of flares in the previous year (three or more) (PCS, $P < 0.05$) and confirmed tophi (severe gout) (PCS, $P < 0.01$; MCS, $P < 0.01$) led to worse HRQOL compared with asymptomatic patients [30]. The presence of tophi had a significant impact on activity impairment ($P < 0.05$ [30]) and led to an increased likelihood of consultation with a rheumatologist {odds ratio (OR) = 7.92, 95% CI 2.81, 22.34, $P < 0.0001$ [29]} in two cross-sectional studies [29, 30]. Other cross-sectional variables such as physician-rated severity (primary care OR = 1.46, 95% CI 1.02, 2.08, $P = 0.037$; rheumatologist OR = 1.52, 95% CI 1.08, 2.14, $P = 0.018$), time since last gout attack (primary care OR = 0.65, 95% CI 0.55, 0.76, $P < 0.0001$; rheumatologist OR = 0.78, 95% CI 0.67, 0.91, $P = 0.001$) and an attack within the last 3 months (primary care OR = 3.48, 95% CI 1.84, 6.58, $P < 0.0001$; rheumatologist OR = 2.11, 95% CI 1.22, 3.65, $P = 0.008$) were also associated with health care resources utilization [29]. While some studies support the association of tophi (GIS, $P = 0.029$ [24]; PCS, $P < 0.01$; MCS, $P < 0.05$ [30]) and serum uric acid (SUA) ($P = 0.002$) [25] with poor HRQOL, others do not (tophi: patient-severity rating, $r = 0.174$ [26]; SUA: WHOQOL-BREF, $P = 0.750$ [21]; GIS, $r < 0.29$ [24]; patient-severity rating, $r = 0.06$ [26]). There was a paucity of cross-sectional evidence for positive effects of allopurinol on HRQOL from a patient's perspective (WHOQOL-BREF, $P = 0.618$ [21]; HAQ, $P = 0.79$ [28]), whereas steroid and non-steroidal anti-inflammatory drugs were associated with greater musculoskeletal disability [28]. Although tophi, comorbidities, polyarticular disease and radiographic damage were associated with worse HRQOL at baseline, after multivariate analysis, a reduction in flares ($P = 0.001$–0.06) and baseline SUA ($P = 0.001$–0.04) were predictors of improvement in HRQOL in one cohort study [17].

Discussion

Although none of the identified instruments to measure HRQOL in gout in this review were satisfactory in all domains of the assessed clinimetric properties, generic instruments (HAQ-DI, SF-36) received the highest ratings. Correlations with clinical characteristics, other instruments and change in scores coupled with clinical change strengthened their construct and concurrent validity as well as responsiveness. The SF-36 and HAQ-DI have been endorsed by the OMERACT group as validated tools to measure HRQOL and functional disability in gout [37, 38]. While the generic instruments allow

comparison between the impact of different diseases, their treatments and cost-effectiveness analyses, they may lack the sensitivity to capture the true impact of gout, especially in those with less severe disease [39]. The disease-specific GIS may focus on HRQOL domains more relevant in gout (hence a better correlation with patient-reported factors) and be more responsive to small changes in health status [40]. However, it may miss any unexpected adverse outcomes and does not allow comparison between disease states. Furthermore, the OMERACT group has not yet unreservedly endorsed the Gout Assessment Questionnaire 2.0 and its GIS subscale as fully validated HRQOL measures in chronic gout [38].

A consistent finding of all the instruments reviewed is that people with gout had lower physical HRQOL compared with the normative distribution [20, 22] as well as study controls [21], even after adjusting for comorbidities [7, 22, 24]. This may be due to the strong emphasis on physical functioning as a surrogate measure for HRQOL in the generic instruments. The impact of SUA and tophi were variable, with some studies reporting an adverse effect on HRQOL [17, 24] but others showing no effect [21, 26]. SUA may have an indirect relationship with HRQOL in gout, as it is positively correlated with the frequency of flares in the last 12 months as well development of tophi [28, 30, 41]. Although allopurinol is not perceived by patients to improve HRQOL [21, 28], its use in primary care is often suboptimal [42] and it has been shown to reduce the number of flares as well as tophi [43, 44]. Patients may be unaware of the rationale behind ULT, with many discontinuing treatment at the onset of flares when ULT is initiated [32].

The robustness of the findings of this review is supported by data extraction and quality assessment using validated tools by two independent reviewers. Our search strategy included a filter that is 90–97% sensitive in retrieving clinimetric articles [12], therefore it is unlikely that we would have missed any such articles. Nevertheless, the findings of the review need to be interpreted in the context of the limitations of the study design as well as those of the literature identified. A limitation is that the articles included in the review were restricted to English (due to a lack of translation facilities) as well as not searching for grey literature (presumed low yield). The generalizability of the results may be limited by the highly selective populations studied (treatment failure or chronic tophaceous gout in the intercritical stage, mainly Caucasian males), study settings (private or specialist clinics) and variable response rates.

Existing studies of HRQOL in gout are limited by their paucity of longitudinal data, recruitment from highly selective secondary care populations and use of mostly generic instruments to measure HRQOL. Hence there is a need for a primary care–based prospective cohort study using both gout-specific and generic questionnaires to determine how HRQOL changes over time in the clinical setting, where most patients with gout are treated, identify which factors (such as disease characteristics, treatment, comorbidities including anxiety and depression) predict changes in HRQOL and also identify those at risk of deterioration to better target their treatment.

Rheumatology key messages

- Existing studies of gout most commonly use generic measures of HRQOL.
- Gout is associated with poorer physical HRQOL.
- Poor HRQOL in gout is associated with both disease-specific characteristics and comorbidity.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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