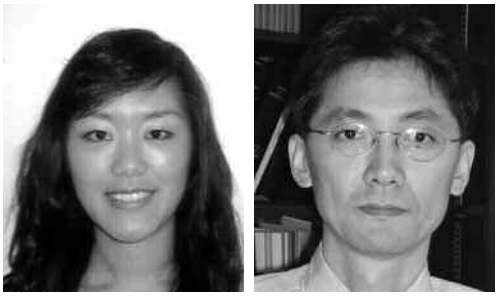
Editorial

Gout and Quality of Life



Gout is a common inflammatory arthritis triggered by the crystallization of uric acid within the joints[1]. Gout causes severe pain and suffering and is a substantial cause of morbidity. Further, emerging evidence suggests that gout is strongly associated with the metabolic syndrome[2] and may lead to myocardial infarction[3-5], diabetes[6], and premature death[7,8]. A number of epidemiological studies from a diverse range of countries suggest that gout has increased in prevalence and incidence in the past few decades. Using the NHANES III age/sex prevalence and the corresponding 2005 population estimates from the US Census Bureau, it is estimated that up to 6.1 million adults aged ≥ 20 years have ever had gout[9]. Consequently, gout has a significant economic impact in society due to both direct medical costs and indirect costs[9-12].

A substantial proportion of gout patients under the care of physicians fail to achieve adequate control of hyperuricemia or symptoms[13]. Recent studies indicate that the majority of gout patients under the care of physicians are not adequately managed with currently available anti-gout therapies[13-17]. These gout cases have been referred to as "treatment-failure gout" and have become the primary target for quality improvement of care, including new drug development[13,18-23]. Although recent treatment guidelines and increased educational efforts could improve the quality of gout care, even under the very best of conditions, between 100,000 and 300,000 in the US are expected to be classified as "treatment-failure gout" cases with currently available anti-gout therapies[13].

Being a painful arthritic disorder, gout, particularly "treatment-failure gout," affects quality of life. Recently, several papers assessed the influence of gout on health-related quality of life (HRQOL) among various study populations using different definitions of gout (Table 1)[24-32]. These studies often employed generic HRQOL instruments such as the Medical Outcome Study Short-Form 36-item health status survey (SF-36)[26-30,32] and/or the Health Assessment Questionnaire-Disability Index (HAQ-DI)[24-26,29] and only 2 previous studies evaluated the potential utility of a disease-specific HRQOL measure for gout called the Gout Assessment Questionnaire (GAQ)[27,28]. HAQ-DI scores from these studies suggested gout patients have mild disability (HAQ score range, 0.2 to 0.6)[24,25,29]. Similarly, SF-36 data showed that the physical component summary (PCS) score was worse (e.g., 1.1 standard deviation below the US general population norm)[29]. However, none of these previous studies addressed HRQOL data specifically in the "treatment-failure gout" population.

In this issue of *The Journal*, Becker and colleagues report on a multicenter, prospective observational study examining this issue[26]. The authors evaluated self-reported quality of life, disability, and disease severity among patients with "treatment-failure gout." Their definition of "treatment-failure gout" was (1) symptomatic, crystal-proven gout of at least 2 years' duration; and (2) intolerance or refractoriness to conventional urate-lowering therapy, as reflected by serum uric acid (SUA) > 6.0 mg/dl. The study enrolled 110 patients and collected SF-36 and HAQ-DI data and gout disease severity-related variables bimonthly. The followup rate by the first 4 months was acceptable (86%), but was low by the end of the 12 months (47%).

The cross-sectional analysis based on the baseline data (mean age 59 yrs) showed that the mean SF-36 physical functioning score was lower than that of the general population of similar age, and was in fact analogous to that of individuals aged ≥ 75 years. Similarly, the mean HAQ-DI score at baseline indicated a moderate level of physical disability in this treatment-failure gout population, which was worse than that observed in gout populations without treatment status specified[24,25,29]. These data support the empirical notions that the HRQOL impairment in patients with "treatment-failure gout" is substantial, and that this population is the right target for considerable improvement in the quality of care.

As anticipated, the number of painful joints, swollen joints, and flares at baseline were associated with worse scores on all the SF-36 subscales. Further, analyses based

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Table 1. Studies of health-related quality of life (HRQOL) in patients with gout.

Author	Location	Study Population	Mean Age, yrs	HRQOL Measures	Results
Picavet[30]	Netherlands	Self-reported gout (n = 138)	Not given	SF-36, EQ-5D	Gout patients had lower scores on all SF-36 (75.6 vs 87.8 for PF, 68.1 vs 85.8 for RP, 70.2 vs 84.1 for bodily pain, 64.7 vs 72.8 for GH, 60.8 vs 69.3 for vitality, and 73.2 vs 79.7 for MH), versus those without MSK disease. Similar results were noted for all EQ-5D dimensions
Alvarez-Nemegyei[25]	Mexico	Gout* with chronic renal failure (n = 90)	54	HAQ	47% of patients had MSK disability with average HAQ score 0.17
Colwell[27]	USA	Subjects in phase II trial of febuxostat (uric acid < 8.0 mg/dl; n = 126)	54	GAQ, SF-36	Assessment of reliability, validity, and responsiveness of GAQ 2.0 vs SF-36. Patient SF-36 data not presented
Alvarez-Hernandez[24]	Mexico	Gout* (n = 206)	56	HAQ-DI, SF-36	Mean HAQ-DI score was 0.59. Patient SF-36 score data not presented
Hirsch[28]	USA	Gout* (n = 308)	62	GAQ2.0, SF-36	Assessment of reliability, validity, and responsiveness of GAQ 2.0 vs SF-36. Patient SF-36 data not presented
Khanna[29]	USA	Chronic stable gout* (n = 80)	60	SF-36, HAQ-DI	Mean SF-36 PCS and MCS score was 38.9 and 48.6 (1.1 SD below and 0.1 SD below US general population mean)†. Mean HAQ-DI score was 0.6
Roddy[31]	UK	Gout* (n = 137)	64	WHO, QOL, BREF	Overall QOL, satisfaction with health, and physical health-related QOL were impaired in gout patients
Singh[32]	USA	ICD-9 code for gout in Veterans Affairs healthcare system (n = 1581)	68	SF-36V	Mean SF-36 PCS and MCS score was 34.4 and 46.8
Becker[26]	USA	Treatment-failure gout (n = 110)	59	SF-36, HAQ-DI	Mean scores for SF-36 PF, RP, and PCS were 46.8, 35.0, and 34.2. Subjects with CVD had significantly lower PF than those without CVD (32.7 vs 48.6; $p < 0.03$). Mean HAQ-DI score at baseline was 1.0

† Summary scores were normed to the US general population with mean of 50 and SD of 10; * defined by American Rheumatism Association classification. PF: physical functioning, RP: role physical, PCS: physical component summary, MCS: mental component summary, GH: general health; MH: mental health, EQ-5D: EuroQOL questionnaire, HAQ-DI: Health Assessment Questionnaire-Disability survey; WHO-QOL BREF: World Health Organization's BREF Quality of Life assessment; SF-36V: a modified, validated version of SF-36 for veterans, MSK: musculoskeletal, CVD: cardiovascular disease.

on the first 4-month followup data confirmed that the number of flares during the followup was associated with worse scores on several SF-36 subscales. Presence of tophi was also associated with lower scores on SF-36 subscales and PCS, which was consistent with a previous report of a more than 4-fold increased risk of musculoskeletal disability among those with tophi[25]. These data indicate that these disease severity measures are likely determinants of HRQOL in gout patients and thus are appropriate target outcomes in gout care.

An interesting null finding of the study was the lack of association between SUA levels and HRQOL. This observation was also reported in a previous study[27]. These findings support the notion that clinical disease outcomes, and not SUA levels, are meaningful for the quality of life in patients with gout. While the initial clinical trials for new urate-lowering agents employ SUA levels as endpoints for several logistic reasons[18-20,22,23], more direct evidence demonstrating that these new drugs lead to improved clinical measures (e.g., gout flares, HRQOL) should be sought in future research.

Another notable observation is the potential effect of common comorbidities on HRQOL of patients with "treatment-failure gout." As expected, the vast majority of the participants had comorbid conditions, typically cardiovascular and metabolic conditions, and those with comorbidities experienced greater disability compared to patients with gout only. Further, subjects with cardiovascular comorbidities had worse scores on the physical functioning subscale than those without cardiovascular comorbidities. While it is likely that these comorbidities explain at least part of the observed poor HRQOL in this population, no data accounting for such an effect is provided. Thus, whether gout or gout severity variables are independently associated with poor HRQOL in this population is yet to be confirmed.

HRQOL measurements in gout are challenging, as gout is often characterized as an intermittent, progressive chronic disease. Nevertheless, the Special Interest Group for gout outcomes at the Outcome Measures in Rheumatology Clinical Trials (OMERACT) 7 and 8 meetings recognized the importance of HRQOL measurement in gout and includ-

ed it as a core domain for clinical trials for chronic gout[23,33]. This proposal was also supported by the recent US Food and Drug Administration draft guidance for industry on how to use patient-reported outcome instruments as effectiveness endpoints in clinical trials (www.fda.gov/Cder/guidance/5460dft.pdf). As "treatment-failure gout" is a debilitating condition that affects patient functioning and well-being, accurate assessment of HRQOL, particularly in this population, is important in clinical care and research. So far, clinical trials of new urate-lowering drugs, such as febuxostat and pegloticase, for chronic gout have been reported, but HRQOL outcomes are yet to be adopted as an endpoint[18-23].

Future studies should refine both the optimal choices of HRQOL tools for gout and the way one should interpret these HRQOL scores in the clinical context of gout. The ability to effectively measure HRQOL is vital to describing the effects of disease, treatment, or other limitations, including normal aging, upon the patient. It is also important to determine the minimum clinically detectable difference specifically in patients with gout, as it helps both researchers and clinicians better understand the overall health burden of gout and, ultimately, the optimal approach to managing gout. With these advances, patient-reported HRQOL measurements in clinical trials of gout treatment will be able to provide more useful and practical information.

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