CONCISE REPORT

Impact of age and comorbidities on the criteria for remission and response in rheumatoid arthritis

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Objective: To determine to what extent health status impairment in rheumatoid arthritis (RA) measured by self report of pain, global assessment, and functional disability is attributable to age and other comorbid conditions as opposed to the disease itself.

Methods: Pain, global assessment, and Health Assessment Questionnaire Disability Index (HAQ-DI) were measured in a random sample of 1530 adults in the Central Finland District, Finland. Median regressions were used for multivariable analyses.

Results: The mean age was 55.4 years and 72% were women. A large majority of the population reported some pain (76%) and less than perfect general health (83%). The overall mean values of pain, HAQ-DI, and general health were 20 mm, 0.25 units, and 21 mm, respectively. The most common self reported musculoskeletal comorbidities were osteoarthritis (24%) and chronic back pain (25%). Age and number of comorbidities were the only statistically significant correlates of pain and general health in multivariable analyses.

Conclusions: Self reported disability, pain, and poor health were widely prevalent in the general population and are related to age and comorbid conditions. This needs to be taken into account when interpreting remission and response rates using current criteria and for future development of definitions for these end points in RA and other rheumatic diseases.

Remission is unusual among patients with rheumatoid arthritis (RA), regardless of the definition used. Self report of pain, global assessment of disease activity, and functional disability are important health related quality of life (HRQoL) components of remission as well as clinical response in randomised controlled trials of RA.[1] These measures have also been proposed as potential tools to define low disease activity in RA. However, their population characteristics and correlates are unknown. Understanding the general population characteristics will help us to design better clinical trials and cohort studies while lending a practical perspective to the data from these studies. This study reports the population characteristics of these measures and assesses the implication on interpreting criteria for remission, response, and low disease activity.

PATIENTS AND METHODS

Subjects and sampling

A stratified random sample of 2000 people who were aged at least 30 years and living in the Central Finland District was drawn from the Finnish Population Registry in June 2000. Details of sampling have been published.[2]

Outcomes measured

The wording of global assessment of disease activity (such as the one by the American College of Rheumatology (ACR)) is not applicable to general population. We therefore used global assessment of general health as the corresponding measure in our group taken from the general population. The pain and global assessment scale consists of a doubly anchored, horizontal visual analogue scale scored from 0 (best) to 100 (worst). The Health Assessment Questionnaire Disability Index (HAQ-DI) is a measure of functional disability commonly used in the ACR response criteria.[3 4] By convention, the disability index is expressed on a scale from 0 (no disability) to 3 (maximum functional disability) units, representing an average score (see http://aramis.stanford.edu/, accessed 26 June 2005). Data on date of birth, height, and weight for calculating the body mass index (weight in kilograms divided by the square of height in metres), years of education, and self reported comorbidities were also collected in the questionnaire.

Statistical methods

Differences in mean measures between groups were tested using Student's *t* test. Relationships between HAQ-DI, pain, and global health were measured using Pearson's product moment correlation coefficient (*r*). We defined values greater than the 95th centile values of pain (72 mm), HAQ-DI (1.5 units), and global health assessment (66 mm) as abnormal/severe and calculated the proportions of subjects with one or more abnormal value.

To visualise the non-linear relationship between HAQ-DI and comorbidities, we used fractional polynomial modification

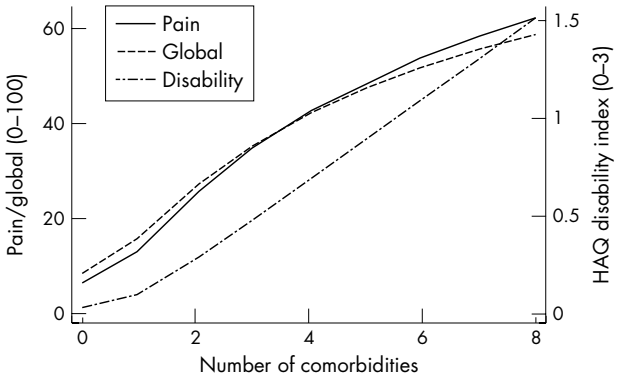

Figure 1 Relationship between pain, global assessment, and functional disability with increasing number of disease conditions.

Abbreviations: ACR, American College of Rheumatology; HAQ-DI, Health Assessment Questionnaire Disability Index; HRQoL, health related quality of life; RA, rheumatoid arthritis

Table 1 Percentage of general population with abnormal values (≥95th centile) for the self reported ACR response measures (pain, global assessment, and HAQ-DI)

Number of comorbid conditions	Number of abnormal measures			
	0	1	2	3
0	89.7	3.9	2.3	4.1
1	90.9	3.8	4.3	1.0
2	82.3	9.5	6.5	1.7
3	69.2	10.1	11.2	9.5
≥4	54.9	23.1	13.9	8.1
Overall	82.2	7.9	6.0	3.8

ordinary least squares regression.[5] Median regression was used to examine the relationship between pain and global general health, on the one hand, and age, sex, body mass index, and number of comorbidities, on the other. This regression is similar to ordinary least squares regression but differs from it in that the median of the dependent variable is the modelled measure and the sum of deviations as opposed to the sum of the squares is the minimised entity when the regression line is fitted, minimising the effect of outliers.

RESULTS

Descriptive characteristics of the sample

Of the 2000 subjects, 1530 returned the completed questionnaire, representing a 77% response rate. Women comprised 72% of the responders. The mean (SD) age of the sample was 55.4 (14.9) years and the mean (SD) education level was 10.8 (4.1) years. All respondents were white and residents of the Central Finland District. The mean (SD) number of comorbidities in our sample was 1.6 (1.6) (range 0–8).

Normative data

Overall, the estimated average population pain level was 20 mm (95% confidence interval 19 to 21). Overall, 76% (n = 1038) of the respondents reported some pain (pain score >0). Not all subjects replied to this question. The estimated population means (95% confidence interval) pain for men and women were similar at 19(16 to 21) and 20 (19 to 22), respectively. Table W1 shows the percentile normative data on pain (available at http://www.annrheumdis.com/supplemental).

A large majority (83%) of the population rated their health as less than perfect (that is, >0). The overall mean (95% confidence interval) global general health score was 21 mm (20 to 23). There was no significant difference between mean scores for men (20 (18 to 22)) and women (22 (20 to 23)). Table W2 (http://www.annrheumdis.com/supplemental) shows the centile values of global health on a visual analogue scale.

Table W3 (http://www.annrheumdis.com/supplemental) shows the normative data on HAQ-DI in this population.[6]

HRQoL and comorbidities

Seventy two per cent of the survey respondents admitted to at least one medical condition. The most common were hypertension (30%), back pain (25%), osteoarthritis (24%), and post-traumatic injuries (12%). Four per cent of the responders reported fibromyalgia. As expected the outcomes worsened steadily with increasing number of comorbidities (fig 1). The three HRQoL measures correlated with each other and had correlation coefficients of 0.82 (pain and global assessment), 0.59 (pain and HAQ-DI), and 0.62 (HAQ-DI and global assessment) (web fig W1 (http://www.annrheumdis.com/supplemental))

Table 1 shows that as the number of comorbidities increase, the number of subjects with high levels of pain, global health assessment, and HAQ-DI increase. When there are three or more comorbidities, one in five (20%) of the general population has two or more clearly abnormal measurements. In median regressions, the only independent predictors of pain and global general health were age and comorbidities (table 2).

DISCUSSION

Our study has demonstrated the prevalence of ACR HRQoL deficits in the general population. These were prominent in older age groups and those with multiple comorbidities. Thus, in research studies such as clinical trials where these data are formally collected (using tools such as the Health Assessment Questionnaire as well as pain and global general health visual analogue scales), interpreting HRQoL data poses several problems:

Firstly, an HRQoL indicator such as pain or disability not only reflects the disease in question but also other comorbidities.[7 8] The interpretation of self reported HRQoL data is relatively easy in clinical practice where the physician can examine them in the context of the rheumatological and non-rheumatological comorbidities, age, and psychosocial background. In research studies, asking the patient for pain or disability *attributable* to a specific disease (such as RA), is

Table 2 Independent predictors of self reports of pain and global assessment in the general population by median regression

Covariate	Coefficient	95% Confidence interval	p Value
Pain			
Age (for each year)	0.083	0.034 to 0.132	0.001
Female sex	−0.310	−1.541 to 0.922	0.622
Education (for each year)	−0.177	−0.331 to −0.024	0.024
Body mass			
Index (for each unit)	−0.003	−0.132 to 0.126	0.963
Comorbidity (per each condition)	7.509	7.097 to 7.922	<0.001
Global assessment			
Age (for each year)	0.208	0.130 to 0.287	<0.001
Female sex	−0.556	−2.508 to 1.396	0.576
Education (for each year)	−0.171	−0.422 to 0.081	0.184
Body mass			
Index (per unit)	0.078	−0.126 to 0.282	0.454
Comorbidity (for each condition)	6.834	6.174 to 7.493	<0.001

unlikely to solve the problem. For example, rewording the question to ask about pain attributable to RA will not help because pain from knee and hand osteoarthritis, an important concurrent source of pain, is indistinguishable from the pain due to RA. A global self assessment question can be reworded to ask how well the RA is doing, but this approach assumes that the patient can apportion symptoms between the arthritis and other comorbidities according to the underlying disease—a sweeping and unvalidated assumption.

Secondly, changes of the HRQoL measure in longitudinal observational studies and randomised controlled trials are not entirely due to the disease/drug in question. The longer the study lasts, the greater will be the impact of age.

Thirdly, simple statistical adjustments for comorbid conditions, especially musculoskeletal ones, are not available. The interactions of these comorbid conditions with RA may be unique and a summary count of these may not be valid.[9]

Definitions of RA remission and low disease activity state based on arbitrarily fixed numeric cut off values for pain and other self reports of HRQoL are likely to be unreliable. An alternative might be to use cut off values (if at all) based on population normative values such as ours.

Our study has implications on the sample size calculation in clinical studies as well. Typically, a priori calculation of study size takes into account baseline prevalence of the outcome measure in question among controls and the expected effect size/risk difference of the intervention. Because the prevalence of worse HRQoL indicators increases with age, one would need to have a larger population to have the power to demonstrate the same effect size in older patients. In such situations, consideration may be given to using the distribution of the measure in question in the comparison group (such as control arm in a clinical trial) to arrive at a more realistic sample size estimation.

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Tables W1-W3 and fig W1 can be seen at http://www.annrheumdis.com/supplemental

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