Disability and quality-of-life are not influenced by the prevalence of autoantibodies in early rheumatoid arthritis patients – results of the Brasília Cohort

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ABSTRACT

Introduction: Although many studies have suggested that the presence of autoantibodies, such as rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) in rheumatoid arthritis (RA) are predictors of joint damage, the association with disability and quality of life questionnaires are not known. **Objectives:** To evaluate the correlation between the Health Assessment Questionnaire (HAQ) and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) scores with serological markers, such as RF, anti-CCP, and anti-citrullinated vimentin (anti-Sa). **Patients and methods:** Sixty five patients with early RA (ERA) from the Brasília Cohort of ERA were evaluated. Serology tests (ELISA) for RF (IgM, IgG, and IgA), anti-CCP (CCP2, CCP3, and CCP3.1), and anti-Sa were performed, with the application of the HAQ and SF-36 questionnaires in the initial evaluation. **Results:** The mean age was 45 years, with a female predominance (86%). At the initial evaluation, RF was positive in 32 individuals (49.23%), anti-CCP in 34 (52.3%), and anti-Sa in nine (13.8%). The initial HAQ score was 1.8. The SF-36 scores were as follow: role-emotional, 19.3; social functioning, 43.1; bodily pain, 25.43; general health, 57.6; mental health, 48.1; vitality, 49.5; role-physical, 4.6; and physical functioning, 24.7. The HAQ and SF-36 scores did not vary with autoantibody levels. **Conclusion:** In many patients, ERA has a major impact on physical ability and health-related quality of life. Although RF and anti-CCP tests have been related with joint destruction and worse clinical prognosis, there is no correlation with the results of questionnaires of quality of life and disability.

Keywords: rheumatoid arthritis, quality of life, rheumatoid factor, citrulline, cohort studies.

INTRODUCTION

Rheumatoid arthritis (RA), even in its early stage, can cause a considerable impact on health-related quality of life (HRQoL).[1] HRQoL is a very broad concept, which can be simplified as the impact of health on the functional ability of an individual and on the well-being perceived in their physical, mental, and social life.[2]

Several tools have been proposed to evaluate the physical capacity and quality of life in patients with RA, to detect changes in health status over time, and to assess the prognosis and the risks and benefits of a particular therapeutic intervention,[3]

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including both generic tools, such as the Medical Outcomes Study 36-Item Short-Form Health Survey (MOS 36-SF), and specific tools, such as the Health Assessment Questionnaire (HAQ).[5] Few studies have evaluated tools for measuring quality of life, both generic and specific, in patients with early RA (ERA).[6,7]

Although recent evidence confirms that the presence of autoantibodies in patients with RA is associated with more aggressive disease, greater joint damage and poor prognosis, the possible association between these tools and the presence of serological markers, such as rheumatoid factor (RF), anti-cyclic citrullinated peptides (anti-CCP), and anti-citrullinated vimentin (anti-Sa), is not known.[8–10]

The aim of this study was to assess the possible association between the scores of certain quality of life questionnaires (HAQ and SF-36) and some serological markers (RF, anti-CCP, and anti-Sa) in a group of RA patients with less than 12 months of symptoms at the initial evaluation.

PATIENTS AND METHODS

An incident prospective cohort study was performed (part of the Brasília Cohort Early Rheumatoid Arthritis), where consecutive patients diagnosed with ERA were assessed with regular follow-up for 36 months after diagnosis. Patients were evaluated at the Rheumatoid Arthritis Clinic of the Hospital Universitário de Brasília, Brazil. The data presented refer to the initial assessment (time of diagnosis) of 65 patients.

ERA was defined as the occurrence of joint symptoms compatible with the disease (inflammatory pattern of pain and joint swelling with or without morning stiffness or other manifestations suggestive of inflammatory joint disease, as assessed by a single observer), lasting more than six weeks and less than 12 months, regardless of fulfillment of the American College of Rheumatology classification criteria.[11]

To analyze the impact on the quality of life related to health in patients with ERA, the questionnaires used in the study were the HAQ (a specific tool) and the SF-36 (a generic tool).

The RF study (IgG, IgM and IgA) was performed using Quanta Lite™ RF IgA ELISA, Quanta Lite™ RF IgG ELISA, and Quanta Lite™ RF IgM ELISA tests (INOVA Diagnostics, CA, USA), according to the manufacturers protocol. Values greater than 15 IU/mL (RF IgM and IgA) and 20 IU/mL (RF IgG) were considered as the positive cutoff points.

Anti-CCP was studied using Quanta Lite™ CCP IgG ELISA, Quanta Lite™ CCP3 IgG ELISA and Quanta Lite™ CCP3.1 IgG/IgA ELISA (INOVA Diagnostics, CA, USA) tests, according to the manufacturer's protocol. The serum from each patient was initially diluted 1:100 in sample diluent. If the sample result was above an optical density of 2.5, it was re-tested with dilutions of 1:500 and 1:2,500, and the resulting unit value was multiplied by the dilution factor. The results were calculated and expressed in units, with < 20 U being negative, 20–39 U being weakly positive, 40–59 U being moderately positive, and ≥ 60 U being strongly positive, for all tests.

The anti-Sa detection test was performed on the original plates developed by the McGill University Autoimmune Research Laboratory – myelin basic protein bovine ELISA assay.[12] The results were calculated and expressed in units, with < 20 U being negative, 21–79 U being doubtful and ≥ 80 U being positive.

To detect differences between two means, the Student *t* test or paired *t* test were used for samples exhibiting a normal distribution, considering the mean values and standard deviation. For cases where normality was rejected, the nonparametric Wilcoxon or Mann-Whitney test was applied, taking into account the value of the median and interquartile range. A significance level of 5% was considered.

Sample size calculation used a pilot sample of 10 patients. Considering a significance level of 5%, a test power of 80% and the information obtained from the pilot sample, the minimum sample size was calculated to be 40 patients.

The study was approved by the research Ethics Committee of the Faculdade de Medicina, Universidade de Brasília, Brazil.

RESULTS

Characteristics of the population studied

Of the 65 patients initially diagnosed with RA (from the Brasília Cohort of Early Rheumatoid Arthritis), the mean age was 45.64 ± 14.51 years, ranging between 26–71 years of age. Female individuals (56 patients, 86.15%) and white ethnicity (31 patients, 47.69%) predominated. According to data from the clinical history, the average duration of joint symptoms at diagnosis was 32 ± 15.4 weeks, and 23 patients (35.3%) had less than 12 weeks of symptoms at initial diagnosis, indicating very early arthritis.

Demographic and clinical characteristics of the cohort were previously published.[13]

Autoantibodies

In the first evaluation of the 65 patients, 32 individuals (49.23%) were positive for at least one RF isotype, 28 patients (43.07%) for RF IgA, 19 (29.23%) for RF IgG and 32 (49.23%) for RF IgM.

Regarding the anti-CCP antibodies, 34 patients (52.30% of the total) were positive for at least one of the techniques used in the screening (CCP2, CCP3 or CCP3.1).

Using the ELISA2 (CCP2) technique, 33 patients (50.77% of the total population tested) were negative, five (7.69%) were weakly positive and 27 (41.54%) were strongly positive. When using the ELISA3 technique (CCP3), 30 patients (46.15%) were negative, five (7.69%) were weakly positive, two (3.08%) were moderately positive and 28 (43.08%) were strongly positive. Using the ELISA3.1 (CCP3.1) technique, 31 patients (47.69%) were negative, two (3.08%) were weakly positive, three (4.62%) were moderately positive and 29 (44.62%) were strongly positive.

In the initial evaluation of the 65 patients analyzed, 52 (80%) were negative for anti-Sa, four (6.15%) presented an ambiguous result and nine (13.85%) were positive.

The laboratory characteristics of patients enrolled in this Brazilian cohort were previously published.[14]

Quality of life and capacity evaluation questionnaires

The scores obtained from the HAQ and SF-36 quality of life questionnaires in the initial evaluation of the 65 patients are shown in Table 1. Pattern of responses to questionnaires addressing quality of life in the Brasília Cohort of Early Rheumatoid Arthritis were previously published.[15]

Quality of life questionnaires and its association with serum markers in ERA

Rheumatoid factor

There was no difference in the HAQ score or any of the SF-36 domains between patients who were positive or not for RF IgA, IgG, and IgM, as illustrated in Table 2.

Anti-CCP

As illustrated in Tables 3, 4, and 5, there was no difference in the HAQ score and any of the SF-36 domains between patients who were positive or negative for anti-CCP using the

Table 1
Patients with RA diagnosis according to HAQ and SF-36 questionnaire scores (initial evaluation, n = 65)

Questionnaire	Score*
HAQ	1.87 (0.81)
SF-36 (domains)	
Role-emotional (RE)	19.37 (37.04)
Social functioning (SF)	43.16 (34.78)
Bodily pain (BP)	25.43 (19.76)
General health (GH)	57.68 (26.30)
Mental health (MH)	48.18 (15.89)
Vitality (VT)	49.59 (15.44)
Role-physical (RP)	4.68 (15.98)
Physical functioning (PF)	24.76 (27.05)

*Mean (SD).

Table 2
HAQ and SF-36 questionnaire scores for ERA patients positive or negative for IgG, IgA, and IgM RF at baseline evaluation

Questionnaire	IgA RF*		Mann-Whitney	P	IgG RF*		Mann-Whitney	P	IgM RF*		Mann-Whitney	P
	Negative	Positive			Negative	Positive			Negative	Positive		
HAQ	1.75 (1.50)	2.00 (1.13)	0.68	0.40	2.13 (1.25)	1.88 (1.14)	0.45	0.50	2.38 (1.25)	1.75 (1.13)	1.40	0.23
SF-36 (domains)												
Role-emotional	0.00 (33.33)	0.00 (0.00)	0.01	0.99	0.00 (33.33)	0.00 (0.00)	0.78	0.37	0.00 (0.00)	0.00 (33.33)	0.01	0.93
Social functioning	25.00 (50.00)	37.50 (62.50)	0.18	0.66	25.00 (50.00)	37.50 (37.50)	0.04	0.83	25.00 (37.5)	37.5 (62.5)	2.47	0.11
Bodily pain	22.00 (31.00)	22.00 (20.00)	0.02	0.96	22.00 (31.00)	22.00 (29.00)	0.05	0.94	22.00 (22.00)	22.00 (29.00)	0.26	0.60
General health	67.00 (45.00)	52.00 (42.00)	1.67	0.19	65.00 (50.00)	60.00 (40.00)	0.78	0.37	67.00 (45.00)	55.00 (45.00)	0.54	0.46
Mental health	52.00 (24.00)	52.00 (16.00)	0.01	0.90	52.00 (20.00)	52.00 (16.00)	0.27	0.59	52.00 (24.00)	52.00 (20.00)	0.42	0.51
Vitality	50.00 (20.00)	50.00 (10.00)	0.93	0.33	50.00 (20.00)	55.00 (10.00)	2.48	0.11	50.00 (15.00)	50.00 (10.00)	2.13	0.14
Role-physical	0.00 (0.00)	0.00 (0.00)	0.45	0.50	0.00 (0.00)	0.00 (0.00)	0.10	0.74	0.00 (0.00)	0.00 (0.00)	0.12	0.72
Physical functioning	20.00 (40.00)	10.00 (45.00)	0.42	0.51	15.00 (40.00)	10.00 (40.00)	0.05	0.82	5.00 (40.00)	25.00 (40.00)	0.91	0.33

* Median (interquartile range).

Table 3
HAQ and SF-36 questionnaire scores for ERA patients positive or negative for anti-CCP2 at baseline evaluation

Questionnaire	CCP2 Media (standard deviation)		Paired *t* test	P
	Negative	Positive		
HAQ	1.99 (0.81)	1.81 (0.78)	0.92	0.36
Questionnaire	**CCP2 Median (interquartile range)**		**Mann-Whitney test**	**P**
	Negative	**Positive**		
SF-36 (domains)				
Role-emotional	0.00 (0.00)	0.00 (33.33)	1.05	0.30
Social functioning	25.00 (37.50)	43.75 (62.50)	3.17	0.07
Bodily pain	22.00 (26.00)	26.50 (24.50)	3.68	0.05
General health	62.50 (44.50)	52.00 (14.00)	0.04	0.82
Mental health	52.00 (24.00)	50.12 (14.58)	0.29	0.58
Vitality	50.00 (15.50)	50.00 (17.50)	0.05	0.80
Role-physical	0.00 (0.00)	0.00 (0.00)	0.10	0.74
Physical functioning	5.00 (40.00)	25.00 (47.50)	2.27	0.13

Table 4
HAQ and SF-36 questionnaire scores for ERA patients positive or negative for anti-CCP3 at baseline evaluation

Questionnaire	CCP3 Median (interquartile range)		Mann-Whitney test	P
	Negative	Positive		
HAQ	2.00 (1.50)	1.88 (1.38)	0.01	0.91
SF-36 (domains)				
Role-emotional	0.00 (0.00)	0.00 (33.33)	1.86	0.17
Social functioning	25.00 (37.50)	50.00 (62.50)	4.67	0.02
Bodily pain	21.50 (21.00)	26.50 (29.00)	3.17	0.07
Mental health	52.00 (20.00)	52.00 (16.00)	1.30	0.25
Vitality	50.00 (20.00)	50.00 (15.00)	0.02	0.87
Role-physical	0.00 (0.00)	0.00 (0.00)	0.02	0.88
Physical functioning	5.00 (40.00)	22.50 (45.00)	1.48	0.22
SF-36 (domain)	**CCP3 Media (SD)**		**Paired *t* -test**	**P**
	Negative	**Positive**		
General health	59.27 (25.41)	56.29 (27.38)	0.45	0.65

CCP2 technique. Regarding CCP3 and CCP3.1, there was a statistically significant difference for the social functioning domain, which was significantly better for those with positive serology for anti-CCP by these two techniques (P = 0.02 for both).

Anti-Sa

As illustrated in Table 6, there was no difference in the HAQ score and any of the SF-36 domains between patients who were positive or negative for anti-Sa.

Table 5
HAQ and SF-36 questionnaire scores for ERA patients positive or negative for anti-CCP3.1 at baseline evaluation

Questionnaire	CCP3.1 Median (interquartile range)		Mann-Whitney test	P
	Negative	Positive		
HAQ	2.00 (1.50)	1.88 (1.38)	0.01	0.91
SF-36 (domains)				
Role-emotional	0.00 (0.00)	0.00 (33.33)	0.80	0.37
Social functioning	25.00 (37.50)	50.00 (62.50)	4.67	0.02
Mental health	52.00 (20.00)	52.00 (16.00)	0.83	0.36
Vitality	50.00 (16.00)	50.00 (20.00)	0.02	0.87
Role-physical	0.00 (0.00)	0.00 (0.00)	0.02	0.88
Physical functioning	5.00 (40.00)	22.5 (45.00)	1.48	0.22
SF-36 (domain)	**CCP3.1 Media (standard deviation)**		**Paired *t*-test**	**P**
	Negative	**Positive**		
Bodily pain	21.50 (18.09)	28.91 (20.77)	−1.51	0.13
General health	57.37 (25.78)	57.97 (27.14)	−0.09	0.92

Table 6
HAQ and SF-36 questionnaire scores for ERA patients positive or negative for anti-Sa at baseline evaluation

Questionnaire	Anti-Sa Median (interquartile range)		Mann-Whitney test	P
	Negative	Positive		
HAQ	1.88 (1.63)	2.13 (0.50)	0.18	0.66
SF-36 (domains)				
Role-emotional	17.12 (35.58)	28.20 (42.70)	0.96	0.33
Social functioning	25.00 (50.00)	37.50 (50.00)	0.10	0.74
Bodily pain	22.00 (31.00)	31.00 (20.00)	1.60	0.20
General health	65.00 (47.00)	52.00 (45.00)	0.33	0.56
Mental health	52.00 (20.00)	48.00 (12.00)	0.10	0.74
Vitality	50.00 (20.00)	50.00 (16.00)	0.01	0.89
Role-physical	0.00 (0.00)	0.00 (0.00)	0.21	0.64
Physical functioning	15.00 (45.00)	10.00 (40.00)	0.16	0.68

DISCUSSION

Our study confirms a big impact on the quality of life and physical capacity of patients with ERA. The previously published cohorts demonstrate wide variation in the HAQ average at the initial evaluation,[16] but the mean scores found in most of them were around 1 (0.8–1.3),[16–20] which is lower than that found in our population. With regards to the SF-36 questionnaire, the low scores of the domains at initial evaluation, particularly in the domains of 'role-limitation due to physical and emotional' quality of life, demonstrate that, in the patients of our cohort, these were the quality of life aspects that were most affected in the initial evaluation. The domains 'mental health' and 'vitality' were the least impaired at the time of diagnosis.

In our cohort, there was no difference in the HAQ scores or any SF-36 domain between patients positive or negative for RF IgA, IgG, IgM RF, anti-CCP-2, or anti-Sa. For CCP3 and CCP3.1, there was statistically significant difference only for the social functioning domain, which was significantly better for those with positive serology for anti-CCP antibodies using third generation techniques. The analysis of our data suggests that disability and quality of life assessment tools, such as the HAQ and the SF-36, may reflect the damage caused by RA activity but behave independently of autoantibodies. The isolated association of anti-CCP, by the techniques CCP3 and CCP3.1, with the social functioning domain, which evaluates the integration of individuals in social activities, appears to have been by chance.

Silva et al.[21] published that the HAQ score did not correlate with RA activity, duration of the disease and positive RF (RF IgM), although it was significantly associated with positive anti-CCP (CCP 2).

In the Swedish STRIP study,[22] it was observed that the evolution of the HAQ score was not different between patients serologically positive or negative for anti-CCP, although the HAQ had correlated with activity markers, such as ESR, CRP, and DAS-28.

Evaluating 52 patients with an average of three years of RA diagnosis, Mohd Shahrir et al.[23] reported that there was a correlation between the HAQ score and anti-CCP levels (CCP2).

There are no studies on the correlation of the SF-36 questionnaire and the occurrence of autoantibodies in RA. Furthermore, the possible association between the HAQ and the SF-36 scores and the presence of anti-Sa has not been evaluated.

CONCLUSIONS

The population evaluated in our cohort (Brasília Cohort of Early Rheumatoid Arthritis) demonstrated a large impact on the quality of life due to RA, as measured by the HAQ and SF-36 questionnaires at diagnosis, where this was more established than in other cohorts previously evaluated.

There was no difference in the HAQ score and any of the SF-36 domains between patients positive or negative for RF IgA, IgG, IgM, and anti-CCP or anti-Sa. Tools for assessing disability and quality of life, such as the HAQ and SF-36, may reflect the damage caused by the activity of RA but behave independently of autoantibody levels.

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