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Impact of Gender in the Quality of Life of Patients with Rheumatoid Arthritis

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Abstract

Objective: To evaluate the impact of gender in the quality of life (QOL) of rheumatoid arthritis (RA) patients and the factors associated with such effect.

Methods: Seventy RA patients of each gender were cross-sectionally evaluated as per pre-established protocol: medical history review, standardized disease severity measurements, and comprehensive psychological and disease-related behaviors and coping strategies assessment. QOL was assessed with the SF-36 questionnaire. Univariable and multivariable analyses were performed to examine the contribution of gender and other variables to QOL.

Results: Both groups were comparable regarding age at diagnosis, disease duration, disease activity, and radiological damage. Women showed higher functional impairment (mHAQ: 0.89 ± 2.6 vs. 0.22±0.9, p=0.04), higher prevalence of depression and of osteoporosis, as well as higher scores in the Beck scale (10.7 ± 7.52 vs. 7.8 ± 6.8, p=0.016) but not in other psychological and behavioral variables. In the SF-36, women also showed a greater impairment than men in physical functioning (PF) (57.7 ± 22.1 vs. 67.3 ± 22.7; p=0.01), general health (GH) (41.3 ± 21.7 vs. 50.0 ± 24.3, p=0.02), mental health (MH) (63.7 ± 22.0 vs. 71.8 ± 21.1, p=0.02) and physical component summary score (PCS) (39.3 ± 8.9 vs. 42.4 ± 9.3, p=0.04). Female gender remained significantly associated with poorer PF in multivariable analysis even after adjusting for the Beck Scale (p=0.08), and osteoporosis (p=0.09).

Conclusions: Female RA patients have lower QOL levels than their male counterparts. Depression and osteoporosis may play an important role in this effect. These data should be taken into account in the management of these patients.

Main findings

-Gender medicine is a new paradigm of studying chronic diseases.

-RA patients of both genders present similar biological and immunological features but women experience poorer QOL.

-This is the first study on gender differences in RA examining two sets of RA patients evaluated comprehensively using a standardized protocol inclusive of clinical, ancillary, functional, QOL and psychosocial variables.

Keywords: Quality of life (QOL); Rheumatoid arthritis; Gender disparities

Abbreviations: ACR: American College of Rheumatology; Anti-CCP: Anti-Citrullinated Peptide Antibody; BDI: Beck Depression Inventory; BP: Bodily Pain; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; GH: General Health; IBQ: Illness Behaviour Questionnaire; ISEL: Interpersonal Support Evaluation List; JE: Joint Erosion; JSN: Joint Space Narrowing; MD-GA: Physicians Global Assessment; mHAQ: modified Health Assessment Questionnaire; MH: Mental Health; mSVH: Modified Sharp by Der Heidje Method; PCS: Physical Component Summary Score; PF: Physical Functioning; PGA: Patient Global Assessment; PROs: Patient Reported Outcomes; QOL: Quality of life; RA: Rheumatoid Arthritis; RAI: Rheumatology Attitudes Index; RE: Role Emotional; RF: Rheumatoid Factor; RP: Role Physical; SE: Perceived Self-Efficacy; SF-36: Medical Outcome Survey Short Form; SF: Social Functioning; SJC28: Joint Count for 28 Swollen Joints and Tender joints (TJC28); VAS: Visual Analog Scale; VT: Vitality

Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory disease characterized by pain, stiffness, swelling and tenderness of synovial joints that may ultimately lead to joint destruction, permanent disability and reduced quality of life (QOL).

RA is the most common form of inflammatory arthritis and it has a prevalence ranging between 0.5 and 1% with an annual incidence of 3 per 10,000 adults [1]. Although the disease occurs in both genders, whether it is expressed differently in women and men has been scarcely studied; moreover the published studies have been primarily focused

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on the biological aspects of the disease including immunological characteristics, inflammatory markers and/or radiographic damage.

It is important to point out the difference between sex and gender. Sex denotes biologically–determined characteristics whereas gender also indicates culturally and socially shaped variations between men and women. Gender relates to how women and men are perceived, are expected to think and to act and function in society not only because of their biological differences [2].

Gender-based differences may emanate either from biomedical (genetic, hormonal, anatomical, physiological), psychosocial (personality, coping, symptom reporting), or epidemiological (population-based risk factors) characteristics. In fact, rarely biology acts alone to determine these differences. Moreover, psycho-social variables interact with each other and may exacerbate biological vulnerabilities.

Gender medicine is a new paradigm focused on the differences between men and women in both health and disease. Over the past decade, gender has been shown to affect the clinical presentation, natural history and response to medications in several rheumatic diseases [3-5]. Thus, it has been reported that women have a more pronounced pain perception than men [6], and that they experience more limitations in daily physical functioning although the latter not always correlates with specific biomarkers of disease activity or damage [4]. Applying this model to RA may allow the identification of gender-based outcomes beyond classical objective parameters (e.g. activity indices, radiographic damage). To achieve this goal, it is important to evaluate differences in several psychosocial variables which can influence the course of the disease as well as to assess the distinct emotional impact of the disease as a function of gender. This approach is consonant with the use of QOL assessments or patient reported outcomes (PROs) and with the bio psychosocial model of medicine as described by Engel in 1977 [7-9].

For all the afore mentioned reasons, we have now examined the impact of gender in the outcome of RA from a global perspective using as primary outcome a global PRO which reflects the quality of life perceived by the patient. Our hypothesis is that gender, independently of disease activity, may have a differential impact in the outcome of RA, particularly in terms of quality of life (QOL).

Patients and Methods

Design, setting and patient selection

This is a cross-sectional study performed in Hospital Sierrallana, a teaching University Hospital located in Torrelavega in Northern Spain and covering a health area close to a 200.000 population. This is the only center providing specialized rheumatology care in the entire area.

Patients satisfied the 1987 American College of Rheumatology (ACR) RA classification criteria. Two subsets of patients (70 women and 70 men) were recruited consecutively from the outpatient clinic of our Rheumatology Division. All patients provided written informed consent prior to being enrolled in the study according to the declaration of Helsinki. The study was carried out in agreement with Local Internal Review Boards and conducted in accordance with good clinical practice.

The primary objective of this study was to identify possible differences in the outcome of RA (measured as QOL as assessed by the SF-36 questionnaire) and the biological and/or psychosocial factors associated with this outcome. Secondary objectives were to compare the levels of disease activity, radiographic damage, and disability between women and men as well as to examine potential psychosocial differences by gender.

Patient evaluation

All patients were seen at the clinic and assessed according to an *ad hoc* protocol. The following procedures were performed:

- Medical history review and patient evaluation: Demographic data, including marital status, education status (years of attendance to school), work status (full time, part time, not working outside home, disabled, retired), drug utilization and relevant clinical information (date of diagnosis, extra articular manifestations (nodulosis, Sjögren Syndrome, vasculitides, pulmonary interstitial disease and escleritis), number of surgeries due to RA, comorbidities smoking status (current, former, never smoker), hypertension, diabetes, dyslipemia, depression, solid or haematologicalneoplasia, cardiac failure, ischemic heart disease, chronic obstructive pulmonary disease, cardiovascular events, peptic ulcer, osteoporosis were obtained from the medical history review and patient interview.

- Clinical assessment: Physical examination including joint count for 28 swollen joints (SJC28) and tender joints (TJC28), patient global assessment (PGA) on a visual analog scale (VAS) where 0 mm is "no disease activity" (0 mm.) and 100 mm is the "highest disease activity". Physicians completed a similar VAS, (MD-GA) to evaluate his rating of disease activity the day of the visit [10-12].

- Laboratory tests obtained at the time of the evaluation included hemoglobin (mg/dl), acute phase reactants [erythrocyte sedimentation rate (ESR) in mm/h and C-Reactive Protein (CRP) in mg/L], Rheumatoid Factor (RF) (IgM anti IgG) assessed by nephelometry, anti-citrullinated peptide antibody (Anti-CCP) assessed by ELISA against CCP-2,(cutoff point:50 U/ml, maximum value:3,200 U/ml) and antinuclear antibody (ANA) by indirect immunofluorescence using a Hep-2 cell line.

Disease activity was assessed with the DAS 28, based on the ESR, swollen and tender 28 joint counts and the PGA-VAS [13-16]. A DAS 28 between 2.6 and ≤3.2 was considered as low disease activity, between >3.2 and ≤5.1as moderate activity and above 5.1 as high activity.

- Radiographic assessment: Anatomical damage was evaluated by two previously trained readers using the modified Sharp by der Heidje (mSVH) method [17-22]. The total mSVH radiographic score ranges from 0 to 448, being the total score the sum of the joint erosion (JE) score (0-280) and the joint space narrowing (JSN) score (0-168). These two trained readers examined a set of 20 radiographs reaching an intra-class correlation coefficient greater than 0.9 with a 95% confidence interval of (0.86-0.92). All radiographs were obtained following a predefined protocol.

-Bone density: Osteoporosis was defined by bone densitometry (Hologic) (T value of -2.5 on total lumbar score and/or femoral neck)

Quality of life, psychosocial and behavioral evaluation

All questionnaires were completed in the waiting room before the clinical assessment; questions were resolved by the investigator or the specialized unit's nurse.

- Quality of life and functional status: The SF-36 (Medical Outcome Survey Short Form) was used to assess the patients' QOL. The SF-36 is a self-administered measure of health and well-being status, assessing eight domains: physical functioning (PF), role limitation due to

physical health problems (role physical (RP)), vitality (VT), general health (GH), bodily pain (BP), social functioning (SF), role limitation due to emotional problems (role emotional (RE)) and mental health (MH). These subscales are summarized into two measures representing physical (PCS) and mental (MCS) components of health that are often interrelated [23-26]. These summary components are generated by a factor analysis that has been validated in Spain [25].

- Psychosocial and behavioral variables:

The Beck depression inventory (BDI) was used to measure depressive symptoms and their severity (not to diagnose depression). BDI is a Likert-type, self-reported 21 items-questionnaire, ranging from 0 ("not at all") to 3 ("extreme form of each symptom") so the maximal score is 63 (0-9, no symptoms; 10-18 mild; 19-29 moderate and 30-63 severe). A BDI score of ≥ 13 was chosen as the cut-off point for mild to moderate depressive symptoms [27-29].

Social support was assessed with the ISEL (Interpersonal Support Evaluation List), a questionnaire designed to measure the perceived availability of four separate specific functions of social resources tangible, appraisal, self-esteem and belonging support. The questionnaire contains 40 statements .The overall score was chosen for these analyses [30,31].

The Illness Behaviour 52-items questionnaire delineates the patient´s relation to illness and identifies physical complaints that are manifestations of a psychiatric disorder. It consists of seven factors: general hypochondriasis, disease conviction, and psychological perception of illness, inhibition of affect, affective disturbance, denial and irritability. All questions are in a yes/no format, with a score ranging from 0 to 35, higher values indicating the patient's greater inadequacy in dealing with the disease [32-34].

Perceived Self-Efficacy (SE) or the belief that one can perform a specific behavior or task in the future or a state of mind, refers to personal judgments of performance capabilities in a given activity domain [35]. We used the Self-Efficacy for Managing Chronic Disease 6 Item-Scale to measure this construct; scores range from 10 (not at all confident) to 100 (totally confident). Higher scores indicate greater confidence or self-efficacy [36].

The Arthritis Helplessness Index or the Rheumatology Attitudes Index (RAI) measures patient´ perception of their abilities (9 items) or inabilities (6 items) to control their arthritis and the associated pain. Patients rate these 15 items using a 5 point Likert format scale ("strongly disagree", "disagree", "do not agree or disagree" agree" and "strongly agree"). The total score ranges from 15 to 60 with higher scores indicating greater helplessness [37,38].

In all cases, validated Spanish versions of these questionnaires were used [39,40]. In order to avoid any misunderstanding due to regional language peculiarities, all questionnaires were reviewed and suitable changes were made as needed. The study investigator was specifically trained in the administration of these questionnaires.

Statistical analyses

Standard descriptive tests were used. Chi square was used to compare categorical variables and Students t test for continuous ones. In order to clarify the factors responsible for differences found between both genders, successive multivariable linear regression models were built using the SF-36 scores as outcome and gender as regressor, adjusting for those variables found to be significant in the univariable analyses. All the analyses were performed with the Stata 12/SE package (Stata Corp., College Station, TX).

Results

Baseline demographic and clinical features

Seventy women and 70 men of comparable age (±SD) at diagnosis (49.9 ± 13.4 and 52.9 ± 13.6 years, respectively p=0.18)) and disease duration (82.4 ± 74.5 and 81.3 ± 74 months, respectively, p=0.93) were studied. Their main clinical and immunological characteristics were also comparable and so were the main inflammatory markers including hemoglobin, ESR and CRP (Table 1).

Disease activity and radiographic damage

The DAS-28 (3.8 ± 1.4 for women and 3.5 ± 1.4 for men; p=0.21) and its components were comparable in both genders (Table 2). Likewise, the MD-GA was comparable in both groups of patients (32.1 ± 24.7 vs 27.4 ± 25.5 mm respectively; p=0.26).

Radiographic damage including the total mSVH score as well as the JE and JSN scores were comparable in both genders. These data are depicted in Table 2.

Comorbidities and unhealthy behaviors

Table 3 depicts the comorbidity profile of both subsets of RA patients. There were no differences in the proportion of current smokers but men were more likely to have been smokers in the past. Also a higher proportion of men had diabetes mellitus (22.8 vs. 8.5%, p=0.02), peptic ulcer disease (18.5 vs. 5.7%; p=0.02), ischemic cardiovascular disease (10.0 vs. 1.4%; p=0.02) and chronic obstructive pulmonary disease (17.1 vs. 2.8%; p<0.01). Women presented depression (28.5 vs. 2.8%; p=0.00) and osteoporosis (18.5 vs. 5.7%; p=0.02) more frequently than men.

	Women,mean(SD) N=70	Men,mean(SD) N=70	p value
Age at diagnosis, years	49.9 ± 13.4	52.9 ± 13.6	0.18
Disease duration, months	82.4 ± 74.5	81.3 ± 74.0	0.93
Extra articular disease (%)	16.0	24.0	0.31
Hemoglobin, g/dL	13.0 ± 1.3	14.5 ± 3.7	0.00
CRP, mg/L	8.4 ± 13.6	10.2 ± 13.4	0.43
ESR, mm/h	31.3 ± 19.3	34.0 ± 26.4	0.48
RF positivity (%)	58.5	61.4	0.58
Anti-CCP positivity (%)	67.1	68.5	0.71
ANA positivity (%)	32.8	25.7	0.35

RF: Rheumatoid Factor positive; Anti-CCP: Anti-Citrullinated Peptide Antibodies; CRP: C Reactive Protein; ESR: Erythrocyte Sedimentation Rate; ANA+: Antinuclear Antibodies

Table 1: Demographical and clinical data.

Variable	Women (mean ± SD)	Men (mean ± SD)	p value
TJC28	4.2 ± 6.6	3.2 ± 5.3	0.32
SJC28	2.3 ± 3.5	1.7 ± 3.6	0.32
PGA	39.8 ± 23.8	36.2 ± 26.9	0.40
MD-GA	32.1 ± 24.7	27.4 ± 25.5	0.26
DAS28	3.8 ± 1.4	3.5 ± 1.4	0.21
mSVH			
-JSN	13.8 ± 23.8	11.9 ± 14.6	0.58
-JE	10.9 ± 26.3	10.4 ± 14.9	0.90
-Total	24.6 ± 48.4	22.1 ± 27.7	0.71

TJC28: 28 tender joint count; SJC28: 28 swollen joint count. PGA: Patient´ Global Assessment; MD-GA: Physicians´ Global Assessment; DAS28:28 Joint Disease Activity Score; JSN: Joint Space Narrowing

Table 2: RA related variables.

	Women % n=70	Men % n=70	P value
Current smoker	30.0	27.1	0.70
Former smoker	18.5	40.0	<0.01
Hypertension	32.8	25.7	0.35
Diabetes	8.5	22.8	0.02
Dyslipidemia	27.1	30.0	0.70
RA-related Surgeries	11.4	22.8	0.07
Depression	28.5	2.8	0.00
Depression, Treatment	15.7	0.0	<0.01
Solid Neoplasia	1.4	5.7	0.17
HaematologicalNeoplasia	0.0	1.4	0.31
Cardiac Failure	0.0	0.0	
Ischemic Heart Disease	1.4	10.0	0.02
COPD	2.8	17.1	<0.01
Cardiovascular Events	5.7	7.1	0.73
Peptic Ulcer Disease	5.71	18.5	0.02
Osteoporosis	18.5	5.7	0.02
Osteoporosis Treatment	15.7	5.7	0.05
Other Comorbidities	34.2	25.7	0.26

COPD: Chronic obstructive pulmonary disease

Table 3: Comorbities.

	Women (mean ± SD)	Men (mean ± SD)	p value
BDI	10.7 ± 7.5	7.8 ± 6.8	0.01
SELF EFFICACY	63.5 ± 19.2	61.5 ± 21.9	0.55
IBQ score	11.9 ± 6.0	10.5 ± 5.8	0.18
ISEL total	8.0 ± 1.3	8.0 ± 1.2	0.89
RAI	42.3 ± 6.6	41.4 ± 6.9	0.40
SF-36 (PF)	57.7 ± 22.1	67.3 ± 22.7	0.01

BDI: Beck Depression Inventory; SELF-EFFICACY: Self Efficacy test; IBQ: Illness Behaviour Questionnaire; ISEL total: Interpersonal Support List, total value; RAI (LH score): Arthritis Helplessness Index, LH score; SF-36(PF): Physical functioning of the Medical Outcome Survey Short Form

Table 4: Psychosocial parameters and health related quality of life.

Psychological and behavioral variables

Table 4 depicts these data; the only differences noted were on the BDI where higher scores were seen in women than in men (10.7 ± 7.5 vs 7.8 ± 6.8, p=0.01). All other questionnaires gave comparable results in both genders except for the IBQ in which numerically higher scores were observed in women (11.9 ± 6.0 vs. 10.5 ± 5.8, p=0.18).

Quality of life analysis

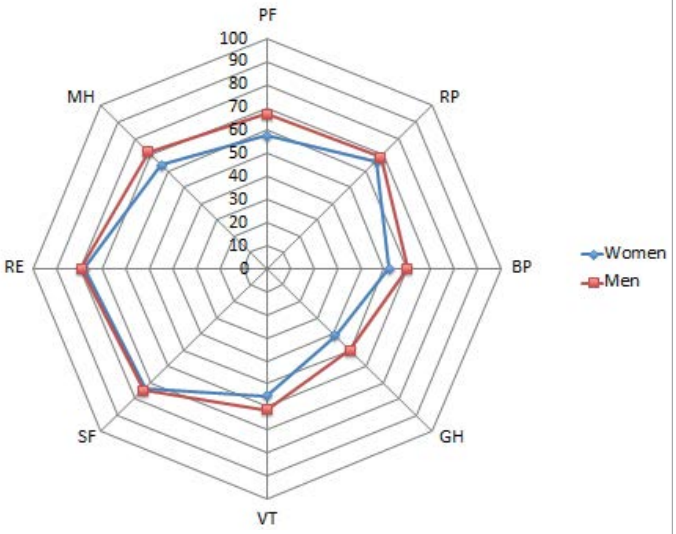
As shown in Figure 1 women had lower scores in MH (63.7 ± 22.0 vs. 71.8 ± 21.1; p=0.02), GH (41.3 ± 21.7 vs. 50.0 ± 24.3; p=0.02), PF (57.7 ± 22.1 vs. 67.3 ± 22.7; p=0.01 as well as in the PSC (39.3 ± 8.9 vs. 42.4 ± 9.3, p=0.04) indicating greater functional impairment.

Multivariable analyses

A series of multivariable linear regression models were performed to further clarify the factors responsible for between gender differences in the SF-36 domains were gender differences were noted, namely physical functioning (SF36-PF), mental (MH) and general heath (GH); age and variables either significant (or approaching significance) in the descriptive analyses were included in these regressions. The results are displayed in Table 5. Women scored 9.5 points lower than men in the SF36-PF (Table 5A) after adjusting for age at diagnosis, (Model 1). Additional adjustments for BDI (Model 2) or osteoporosis (Model 4) decreased the mean advantage to 6.45 points, while adjusting for IBQ did not substantially change the gender differences observed (Model 3). When adjusting simultaneously for the BDI and osteoporosis (model 5), the differences in physical functioning between men and women were no longer significant. Women also scored lower in the SF-36 MH (Table 5B) and GH (Table 5C) domains. In both cases a negative association with older age was also noted. However when the BDI was entered into the models (Models 2 and 5) the associations of MH or GH with gender were no longer evident. For these two SF-36 domains no statistical association with osteoporosis was noted (Models 4) but this was not the case for IBQ (Models 3), underscoring the relationship between this psychological domain and the emotional impact of the disease. Finally, similar models were built with the PSC as the dependent variable obtaining similar results than with PF. However, no significant association were observed when the BDI and osteoporosis were entered which most probably relates to the inclusive nature of this summary measure (Data not shown).

Discussion

We have shown that women with RA as compared to men



MH: Mental Health; RE: Role Emotional; SF: Social Functioning; VT: Vitality; GH: General Health; BP: Bodily Pain; RP: Role Physical; PF: Physical Functioning.

Figure 1: Short Form-36 (SF-36) health domain scores in 70 female and 70 male Rheumatoid Arthritis patients.

Physical Functioning (PF): 5A

Model	Variables	Coefficient	95% C.I		P value
1	GENDER AGE	-9.4 -0.0	-1.8 0.2	-17.0 -0.2	0.01 0.89
2	GENDER AGE BDI	-6.4 0.05 1.0	0.8 0.3 1.5	- 13.7 -0.2 0.5	0.08 0.68 0.00
3	GENDER AGE IBQ	-8.5 0.05 0.8	-1.0 0.3 1.4	-15.9 -0.2 0.2	0.02 0.71 <0.01
4	GENDER AGE OP	-6.2 -0.1 -22.6	1.1 0.1 -11.2	-13.6 -0.3 -34.0	0.09 0.35 0.00
5	GENDER AGE BDI OP	-0.1 -0.05 1.09 -22.7	3.8 0.2 1.5 -12.1	-10.1 -0.3 0.6 -33.4	0.37 0.68 0.00 0.00

Mental Health (MH): 5B

Model	Variables	Coefficient	95% C.I	P value
1	GENDER AGE	-7.2 -0.3	-0.06 -14.4 -0.04 - 0.57	0.05 0.03
2	GENDER AGE BDI	-1.9 -0.1 2.0	3.7 -7.4 0.03 -0.3 2.3 1.6	0.51 0.10 <0.01
3	GENDER AGE IBQ	-4.7 -0.1 2.2	0.9 -10.4 0.1 -0.3 2.7 1.7	0.10 0.28 <0.01
4	GENDER AGE OP	-7.2 -0.3 -0.1	0.2 -14.6 -0.03 -0.5 11.2 -11.5	0.06 0.03 0.98
5	GENDER AGE BDI IBQ	-2.3 -0.1 1.3 1.2	2.9 -7.5 0.08 -0.3 1.8 0.8 1.8 0.7	0.38 0.25 <0.01 <0.01

General Health (GH): 5C

Model	Variables	Coefficient	95% C.I	P value
1	GENDER AGE	-7.6 -0.39	-0.0 -15.2 -0.11 - 0.67	0.05 <0.01
2	GENDER AGE BDI	-3.4 -0.29 1.5	3.4 -10.3 -0.04 -0.54 2.0 1.0	0.32 0.02 <0.01
3	GENDER AGE IBQ	-5.4 -0.23 2.0	1.2 -12.0 0.02 -0.47 2.5 1.4	0.11 0.07 <0.01
4	GENDER AGE OP	-7.6 -0.39 0.45	0.2 -15.4 -0.10 - 0.68 12.5 -11.6	0.06 <0.01 0.94
5	GENDER AGE BDI IBQ	-3.9 -0.23 0.8 1.3	2.6 -10.5 0.02 -0.47 1.4 0.2 2.1 0.6	0.24 0.07 <0.01 <0.01

BDI: Beck depression inventory; OP: Osteoporosis; IBQ: Illness Behaviourquestionnaire.C.I. Confidence Interval

Table 5: Linear regression between physical functioning (PF), mental health (MH) and general health (GH) (dependent variable) and gender (regressor) adjusting for age at diagnosis, BDI, IBQ, and osteoporosis. Men are used as reference, negative values mean than female gender score lower than men. The other coefficients are each year in age and BDI and IBQ one point.

experience poorer QOL specifically in terms of perceived functional impairment and emotional impact. This does not seem to be explained by overt disease-related biological differences rather by differences in the patients' comorbidity profile (osteoporosis) as well as by the presence of depressive symptoms as assessed by the BDI. As far as we know, this is the first study on gender differences in RA examining two sets of RA patients evaluated comprehensively using a standardized protocol inclusive of clinical, ancillary, functional, QOL and psychosocial variables.

Both groups of patients were comparable in terms of their demographic, clinical, laboratory and radiological features. Despite the cross sectional nature of these data our study strongly suggest that biological features do not explain the differences observed in terms of physical functioning and overall QOL. In fact, most authors when comparing disease features in men and women with RA have found no differences with some exceptions in which women have been described as having higher disease activity than men [41-44].

Supporting the notion that there are no major differences in the biological course of the disease are the data from Ahlen et al showing no differences in radiographic damage as a function of gender [44]. Having similar mSVH radiographic scores confirms that no differences in disease severity between genders exist.

On the other hand, it is important to point out that patients with RA suffer important comorbidities which may play a major role on the outcome of the disease [45]. In fact, we found important differences in the comorbidity profile of our patients as a function of gender. Men presented higher prevalence of cardiovascular risk factors as diabetes, dyslipemia, cardiovascular events (ischemic cardiovascular disease) and obstructive pulmonary disease (COPD). Conversely, women showed higher rates of osteoporosis and depression [46,47]. During the last few years, it has been largely acknowledged that RA is an independent risk factor for Cardiovascular (CV) disease; in fact CV disease is one of the leading causes of mortality in RA [48,49]. It is very likely that the higher prevalence of CV disease among men plus that of COPD and DM might have an important impact on these patients' survival, but this could not been examined in this cross-sectional study. However, the higher prevalence of these comorbidities in men does not seem to have a major impact in their perceived QOL. Quite to the contrary, we observed that osteoporosis has a deleterous impact in this outcome. Women are more prone to develop osteoporosis and RA certainly is an additional risk factor for it. Our results indicate that both osteoporosis and depression may partially explain the disability burden observed in RA. These findings underscore the importance of osteoporosis and depression prevention and detection in all RA patients but particularly in women.

RA, as others chronic disorders, may have a great impact in the patients' mood, auto-esteem and other psychosocial constructs. Among these constructs which have been previously shown to be relevant in the prognosis of chronic and rheumatic conditions we found that either depression or the intensity of depressive symptoms (as assessed by the BDI) were higher in women and affected these patients' QOL independent of other factors as noted in the multivariable analyses. Whether depression or depressive symptoms represent a primary psychiatric illness (true comorbidity) or a reactive response to a chronic disease or both could not be determined. Nevertheless it has been reported that RA increases the probability of having a psychiatric disorder and it has been estimated that the prevalence of depression in these patients is two to three-fold higher than in the general population (between 13-20% vs. 2-4%) [50]. Furthermore, it has been reported that depression rates in RA women are twice higher than in men across all age groups. Explanations for such difference are elusive and may include psychological, neurochemical, anatomic, hormonal, and genetic and personality factors. Our results reinforce the idea that depression and depressive symptoms occur frequently in RA patients and specifically among women and that they may have negative prognostic consequences.

No other clear differences in the different psycho-social and behavior domains that we have explored were observed. However, IBQ showed a clear association with the mental related domains of SF36 and general well-being where gender differences were found. Nevertheless, IBQ gender differences were only numerical and did not reach statistical significance and, on the other hand, multivariable models suggest that depressive symptoms explain the observed gender differences in MH and GH. However we cannot rule out that sample size limitations might have precluded identifying a role for IBQ in these gender differences in the emotional impact of RA.

Our study has some limitations, which deserve to be discussed. First, the cross-sectional study design makes it impossible to determine the causality of the observed associations. Second, differential social roles in gender may also influence the attitude and response in confronting a disease like RA but this issue could not be suitably studied. Third, some areas of uncertainty remain about the true validity of the different

instruments used in the assessment of the psychosocial variables; furthermore some of them have redundant information which may difficult the interpretation of the statistical analyses. However, all the instruments used for these assessments have been previously validated and used in RA or in other chronic rheumatic disorders. Finally, our results may not be entirely applicable to patients in other geographic areas or socioeconomic-demographic settings.

In conclusion, RA patients of both genders present similar biological and immunological features. However, women report poorer QOL than men, specifically in terms of the physical functioning and mental health domains of the SF-36. A higher prevalence of osteoporosis and greater frequency and severity of depressive symptoms seem to explain these differences. Preventing and/or treating these comorbidities may have a beneficial impact on this subset of RA patients.

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