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Impact of Comorbidity on Physical Function in Patients with Ankylosing Spondylitis and Psoriatic Arthritis Attending Rheumatology Clinics. Results from the CARdiovascular in rheuMAtology (CARMA) study.

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Comorbidity Impact on Physical function in Spondyloarthritis

ABSTRACT

Objective: To evaluate the impact of comorbidities on the physical function in patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Methods: Cross-sectional analysis of the baseline visit from the CARMA study. Multivariate models with physical function as the dependent variable (BASFI and HAQ for AS and PsA, respectively) were performed. Independent variables: A proxy for the Charlson Comorbidity Index (CCIp) (range: 0-27); sociodemographic data; disease activity (ESR and BASDAI in AS; DAS28-ESR in PsA); disease duration; radiographic damage and treatments. Results were reported as β-coefficients, 95% confidence intervals [95%CI] and p-values.

Results: We included 738 patients with AS and 721 with PsA; 21% of them had more than one comorbidity. Comorbidity burden (CCIp) was independently associated with worse adjusted physical function in patients with PsA (β: 0.11). Also, female sex (β: 0.14), disease duration (β: 0.01), disease activity (DAS28-ESR, β: 0.19), NSAIDs (β: 0.09), glucocorticoids (β: 0.11) and biologics (β: 0.15) were associated with worse function in patients with PsA. A higher educational level was associated with less disability (β: -0.14). In patients with AS, age (β: 0.03), disease activity (BASDAI; β: 0.81), radiographic damage (β: 0.61) and the use of biologics (β: 0.51) were independently associated with worse function on multivariate analyses, but CCIp was not.

Conclusion: The presence of comorbidities in patients with PsA is independently associated with worse physical function. The detection and control of the comorbidities may yield an integral management of the disease.

Significance and Innovations:

- A large number of comorbidities has been identified in a nation-wide cohort of patients with SpA.
- Comorbidity burden was independently associated with physical function in patients with PsA.
- Associations between female gender and worse physical function and between higher educational level and better function were identified in patients with PsA.
- Associations between physical function and some well-known related factor, such as age, disease activity and radiographic damage, were confirmed in Spanish patients with SpA.

Physical function (PhF) is a crucial aspect in patients with Spondyloarthritis (SpA) and, along with health-related quality of life, is considered a major outcome in patients with Ankylosing Spondylitis (AS) and Psoriatic Arthritis (PsA). Furthermore, functional improvement is one of the ultimate goals of therapy for patients with AS and PsA. Patients with AS have increased comorbidity when compared to the general population, particularly with regard to some specific disorders, such as cardiovascular (CV) disease and osteoporosis (1). It is also known that patients with PsA have increased comorbidities, such as CV disease, diabetes, metabolic syndrome and depression, and over 50% of them have more than one comorbidity (2).

Although both conditions have an impact over the PhF, which is directly related to disease activity and structural damage (3,4), other factors may also deteriorate PhF in patients with chronic inflammatory rheumatic diseases (CIRD). For example, comorbidity has been found to be relevant in patients with rheumatoid arthritis (RA), where functional status becomes worse with increasing levels of comorbidity, independently of disease activity (5). However, less studies have focused on the impact of comorbidity on PhF in patients with AS and PsA, even though the PhF impairment and the quality of life limitations of such patients are similar to those with RA (6).

Taken together all these considerations, the main purpose of the present study was to analyze the impact of comorbidities on PhF in Spanish patients with AS and PsA.

Patients and Methods

Study design

Cross-sectional study drawing upon baseline data from the CARdiovascular in rheuMAtology (CARMA) project, an ongoing multicentric 10-year prospective national study of a cohort of patients with CIRD. It included patients with RA, AS and PsA, and age- and sex-matched subjects without CIRD from 67 randomly selected Spanish outpatient rheumatology clinics (recruited from July 2010 to January 2012). The patient's recruitment criteria have previously been published (7).

Patients

For this study 738 patients with AS (modified New York Criteria) and 721 with PsA (Moll and Wright Criteria) were analyzed. It was performed following the principles outlined in the Helsinki Declaration, and written informed consent was obtained from all subjects before their inclusion into the CARMA project. The study protocol was approved by the Ethics Committee for Clinical Research of Lugo, Galicia, Spain (protocol number: 2009/077).

Variables and operative definitions

Dependent variable

The main outcome was PhF, measured through the Spanish validated versions of the Bath AS Functional Index (BASFI) in patients with AS, and the Health Assessment Questionnaire (HAQ) in patients with PsA, respectively.

Independent variables

1) Demographic data: age, sex and educational level; 2) Disease activity: assessed in patients with AS by persistently raised erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and by the Bath AS Disease Activity Index (BASDAI) Spanish validated version; in patients with PsA, DAS28-ESR (Disease Activity Score using 28 joints and ESR) was used; 3) Disease duration; 4) Radiographic damage, defined in this study as "spinal radiographic changes" for AS and "presence of erosions" for PsA patients, observed in standard radiographs; 5) The treatments for the rheumatic disease and the comorbidities were also registered; 6) Comorbidities were recorded as dichotomic variables and also quantitatively by using a proxy of the Charlson Comorbidity Index (CCI), which is a well-known validated index to measure comorbidity disease status (8). It is a weighted score of 19 different comorbidities, selected according to their potential influence on mortality. The sum of the weights of each condition can range from 0 to 33 and the CCI score is an indicator of disease burden. The proxy we used (CCIp) consisted of a minor modification of the original CCI, made by pooling all the tumors (solid, leukemia and lymphoma) into a single item, named Cancer. The rest of comorbidities were collected and rated as in the original CCI. Consequently, the sum of the possible scores in our proxy ranged between 0 and 27.

Statistical analysis

Descriptive analyses were performed for the demographic and clinical variables. Then, bivariate analyses were conducted to investigate the associations between the independent variables and PhF. Numerical variables were assessed using the Student t test or the Mann–Whitney U test. Qualitative variables were assessed by Chi-square, Yates correction or Fisher exact tests in 2 x 2 tables. To study the association between single comorbidities or CCIp scores and PhF, two different multivariate linear models were performed, with PhF as the dependent variable (BASFI and HAQ, respectively), adjusted for potentially confounding factors.

The selection of the independent variables in the multivariate models was based on those found to be statistically significant in the bivariate analyses and also on clinical judgement. Estimates for these associations are shown as beta (β) coefficients, 95% confidence intervals (95%CI) and p-values. All analyses were performed using the SPSS 22.0 program (IBM SPSS Statistics for Windows. IBM Corp. Armonk, NY, USA). Statistical significance was assumed at $p<0.05$.

Results

Clinical and demographic features of the patients and comorbidities

We analyzed 1459 patients (738 AS and 721 PsA) whose demographic and clinical features are summarized in the **supplementary table 1 (see supplementary material)**. Briefly, patients with AS had an earlier disease onset and were younger at the time of study inclusion than those with PsA. Also, the AS cohort had a higher percentage of men than that of patients with PsA. A similar percentage of patients in both groups were receiving biologic therapies but more patients with AS received non-steroidal anti-inflammatory drugs (NSAIDs) whereas a higher number of patients with PsA used conventional synthetic

disease-modifying anti-rheumatic drugs (DMARDs), combined (synthetic plus biologic DMARDs) therapies and glucocorticoids.

The comorbidities and CCIp percentages of the two groups are summarized in **table 1**. Regarding traditional CV risk factors, patients with PsA had higher body mass index (BMI) and hypercholesterolemia prevalence. In contrast, we found more current smokers among AS patients. Apart from a higher prevalence of chronic obstructive pulmonary disease (COPD) among patients with AS and a non-significant increase of mild liver disease in patients with PsA, no other differences in the prevalence of the different comorbidities between the two groups were identified. Regarding comorbidity burden, 21% of the patients had more than one comorbidity (CCIp>1) in both groups and, more specifically, AS patients had a mean (SD) CCIp of 1.32 (0.73) whereas those with PsA had a CCIp of 1.30 (0.66).

Physical function and comorbidity

When we analyzed PhF distribution (using BASFI in the AS group and HAQ for patients with PsA) across different levels of comorbidity, we did not detect differences in AS patients (median [IQR] BASFI 3.3 [1.6-5.6] for patients with CCIp>1 vs 3.0 [1.2-5.1] for those with CCIp=1; p=0.353). However, we observed that patients with PsA and more comorbidities had worse PhF (HAQ 0.75 [0.25-1.25]; for CCIp>1) than patients with just one comorbidity (HAQ 0.25 [0.0-0.75]; p<0.001).

Independent variables associated with physical function

AS cohort

On bivariate analyses **(table 2)**, PhF was associated with age, female sex, disease duration, disease activity (BASDAI and ESR) and spinal radiographic damage. Also, treatment with NSAIDs and glucocorticoids was associated with PhF. In contrast, a higher educational level was associated with less disability. We also identified association between PhF and some individual comorbidities (obesity, hypertension, hiatal hernia and thyroid disease; or the

increase in triglycerides) or the use of statins, on bivariate analyses. However, we did not identify an association between PhF and comorbidity burden (CCIp).

In the multivariate model **(table 3)**, no association between PhF and comorbidity burden (CCIp) was found. Besides, age, disease activity (measured by BASDAI and ESR) and spinal radiographic damage were associated with higher disability. Also, treatment with biologic DMARDs was associated with PhF. At this point, no significant associations with gender or educational level were identified in patients with AS.

PsA cohort

In patients with PsA, an independent association between comorbidity burden and PhF was observed **(table 2)**. In this regard, the increase in CCIp was significantly associated with higher disability (β: 0.11 [0.05-0.17]) on the adjusted multivariate model **(table 3)**. In addition, we identified association between PhF and age, female sex, disease duration, disease activity (DAS28-ESR), use of NSAIDs, biologic DMARDs and glucocorticoids, on bivariate analyses. Apart from age, all of the above-mentioned associations were confirmed in the multivariate model. Also, some comorbidities, such as obesity, hypertension or the increase in triglycerides, were associated with PhF on bivariate analysis. Interestingly, a higher educational level was associated with less disability in these patients.

Discussion

The present multicenter national survey indicates that the presence of comorbidities may decrease the reported PhF of the patients with SpA. Comorbidity burden was independently associated with PhF in patients with PsA. Moreover, the study confirmed that comorbidity is common among patients with SpA. However, some differences between AS and PsA were observed. In this regard, some CV risk factors such as high BMI and hypercholesterolemia

were more prevalent in patients with PsA. In addition, obesity was associated with worse function on bivariate analysis in such patients. Obesity negatively influences not only CV risk but also other disease outcomes. In this regard, obesity and overweight reduce the chances to achieve minimal disease activity in patients with PsA receiving traditional or biologic DMARD therapy (9).

Smoking is known to be a harmful factor in patients with AS, leading to worse outcomes, including radiographic damage (10). In keeping with that, in our survey we disclosed that smoking habit and COPD were more common in patients with AS. Therefore, AS patients should be encouraged to refrain from smoking as soon as a diagnosis of the disease is made.

Interestingly, we identified a relationship between comorbidity burden and PhF in patients with PsA. The most commonly reported factors affecting PhF in patients with PsA are disease activity and radiographic damage (4). However, we believe that comorbidity may also exert some negative influence in the PhF of PsA patients and our results support this view. In this case, the measurement of PhF would reflect not only the disease process but also other factors related to the patients' general health. In this way, a recent study from the ASAS-COMOSPA cohort identified a relationship between comorbidity and functional status in patients with axial and peripheral SpA (11). The understanding of the different causes that impact on the functional disability becomes more relevant now that remission-inducing therapies are available. However, the disability related to causes different from the disease itself may not be improved if they are not properly detected. Therefore, it is important to recognize the comorbid conditions that overshadow the outcome of SpA patients. In fact, recommendations for their identification and management have been recently published (12). However, to ascertain the impact of the comorbidity control on long-term outcomes such as function, longitudinal studies are needed.

A recent study showed an association between comorbidity burden and PhF in patients with SpA (11). However, we could not confirm this association in our patients with AS. Methodological differences, such as different populations and the use of different indexes to measure comorbidity burden, may explain such a discrepancy. Moreover, since comorbidity has been reported to be a major contributor to functional limitation in late AS (13), it is possible that this association may be more evident in longstanding AS patients, due to the increase of comorbidities with aging.

Our study also revealed an association between female gender and worse function in patients with PsA. This is in agreement with previous reports that showed an association of female gender with worse function and quality of life (14). In patients with AS we identified an association between female gender and worse function, however, it was not confirmed on the adjusted multivariate model. In this sense, the gender impact on function is still unclear in patients with AS, with some cross-sectional studies reporting worse function among women with AS whereas a prospective study did not identify gender-differences in disease activity or PhF over time in AS (15). In our study, although the bivariate analysis showed worse function in women with AS, it was not confirmed by the multivariate model.

The association between higher educational level and lower reported disability identified in our patients with PsA has already been reported in patients with SpA (11). The fact that the educational level can influence the way in which the patients handle, or report, their disease process cannot be dismissed.

Finally, other well recognized factors with impact on PhF, such as age, disease activity and radiographic damage in patients with AS (3), as well as disease duration and disease activity in patients with PsA (4), were also associated with worse function in our study. Likewise, the

association between the use of biologics in AS, and that of NSAIDs, GC and biologics in PsA with worse PhF, would probably indicate a more severe disease.

Among the strengths of our study, we highlight the large nation-wide sample of patients from daily clinical practice that, unlike patients included in clinical trials, had different levels of comorbidity and disability. Thus, the results are representative of the Spanish SpA (AS and PsA) patients attending rheumatology outpatient clinics.

Nevertheless, this study has several limitations. First, its cross-sectional nature, which precludes causal inferences. Second, the use of a proxy of the Charlson index (CCI). However, we judged this proxy as a useful estimate of the comorbidity burden in our cohort, as the information collected was not complete to apply the original CCI. Since there is no standard comorbidity index currently utilized in rheumatology research, variations of the CCI are used because they have been extensively validated throughout different medical and research contexts. However, the CCI was primarily developed to predict mortality and not functional disability. Furthermore, our proxy was not able to overcome the fact that the CCI does not include osteoporosis or depression, highly prevalent comorbidities in patients with AS and PsA, which may also be relevant to physical disability. Third, although definitions for radiographic damage in both diseases were used in the CARMA study protocol, quantification of radiographic damage by using validated scores was not performed. This fact may explain the lack of association between function and radiographic damage in PsA patients. Nevertheless, since several studies have shown a close relationship between radiographic progression and disease duration, the multivariate models performed in our study were also adjusted for the effects of disease duration.

In conclusion, as shown in our large series of SpA patients followed-up at outpatient rheumatology units, the presence of comorbidities may decrease the reported PhF of patients with SpA. In this setting, a high prevalence of comorbidities has been disclosed. More importantly, as the comorbidity

burden increases the reported PhF of the patients with PsA decreases. The detection and control of the comorbidities may yield an integral management of the disease.

Table 1. Comorbidities of the patients with ankylosing spondylitis and psoriatic arthritis.

Variable	***Ankylosing Spondylitis*** *(n=738)*	***Psoriatic Arthritis*** *(n=721)*	***p-value***
BMI, kg/m^2, mean (SD)	27.4 (4.4)	28.2 (4.7)	**<0.001**
Hypertension	190 (25.7)	213 (29.5)	0.105
Hypercholesterolemia	199 (27)	257 (35.6)	**<0.001**
Obesity (BMI ≥30)	186 (25.2)	209 (29.1)	0.097
Current smokers	254 (34.4)	157 (21.8)	**<0.001**
Past smokers	240 (32.5)	227 (31.5)	
Never smokers	244 (33.1)	337 (46.7)	
Myocardial infarct	21 (2.9)	11 (1.5)	0.085
Congestive heart failure	4 (0.5)	7 (1.0)	0.344
Peripheral vascular disease	8 (1.1)	7 (1.0)	0.830
Dementia	1 (0.1)	0 (0.0)	0.323
Chronic obstructive pulmonary disease	20 (2.71)	9 (1.3)	**0.045**
Ulcer disease	32 (4.3)	26 (3.6)	0.476
Diabetes mellitus	52 (7.1)	61 (8.5)	0.312
Cerebrovascular disease	3 (0.4)	0 (0.0)	0.087
Mild liver disease	20 (2.7)	33 (4.6)	0.057
Hemiplegia	0 (0.0)	0 (0.0)	-
Moderate or severe renal disease	18 (2.4)	14 (1.9)	0.517
Diabetes with end organ damage	3 (0.4)	5 (0.7)	0.458
Cancer*	17 (2.3)	16 (2.2)	0.914
Moderate or severe liver disease	4 (0.5)	2 (0.3)	0.430
Metastatic Cancer	1 (0.1)	0 (0.0)	0.323
CCIp, median [IQR]	1 [1-1]	1 [1-1]	0.912
CCIp=1	585 (79.3)	567 (78.6)	
CCIp>1	153 (20.7)	154 (21.4)	0.769

Data expressed as number (n) and percentages (%) unless specified. SD: standard deviation; IQR: interquartile range (IQR=p25–p75). BMI: body mass index; *Solid tumors, leukemia and lymphoma pooled; CCIp: proxy of the Charlson Comorbidity Index.

Table 2. Comorbidity and physical function: variables associated with BASFI in patients with AS and with HAQ in patients with PsA. Unadjusted estimates.

Variables	***Ankylosing Spondylitis***			***Psoriatic Arthritis***		
	β	***95% CI***	***p-value***	**β**	***95% CI***	***p-value***
Age at inclusion	0.04	(0.03, 0.06)	**<0.001**	0.01	(0.00, 0.01)	**<0.001**
Sex (reference, male)	0.74	(0.34, 1.14)	**<0.001**	0.36	(0.27, 0.44)	**<0.001**
Disease duration	0.02	(0.01, 0.04)	**<0.001**	0.01	(0.01, 0.02)	**<0.001**
Educational level (ref, Primary)						
Basic	1.07	(0.08, 2.05)	**0.03**	0.23	(0.04, 0.24)	**0.02**
Secondary	-0.16	(-0.59, -0.26)	0.45	-0.17	(-0.28, -0.06)	**<0.01**
University	-1.01	(-1.46, -0.56)	**<0.001**	-0.24	(-0.35, -0.13)	**<0.001**
CCIp	0.17	(-0.08, 0.41)	0.19	0.21	(0.14, 0.27)	**<0.001**
Obesity	0.77	(0.36, 1.19)	**<0.001**	0.19	(0.09, 0.29)	**<0.001**
Statins	0.66	(0.17, 1.15)	**0.01**	0.08	(-0.02, 0.19)	0.13
Hypertension	0.74	(0.33, 1.15)	**<0.001**	0.20	(0.11, 0.30)	**<0.001**
Triglycerides*	0.40	(0.15, 0.65)	**<0.001**	0.11	(0.05, 0.17)	**<0.001**
GI bleeding	0.51	(-0.69, 1.71)	0.403	0.49	(-0.20, 1.19)	0.16
Hiatal hernia	1.39	(0.71, 2.07)	**<0.001**	0.17	(-0.02, 0.36)	0.07
Thyroid disease	1.60	(0.44, 2.76)	**0.01**	0.18	(-0.01, 0.37)	0.06
NSAID	0.78	(0.41, 1.14)	**<0.001**	0.12	(0.03, 0.21)	**0.01**
Biologic DMARD	0.21	(-0.14, 0.58)	0.240	0.12	(0.03, 0.21)	**0.01**
GC	0.99	(0.33, 1.65)	**<0.001**	0.25	(0.13, 0.36)	**<0.001**
DAS28-ESR		NA		0.24	(0.21, 0.27)	**<0.001**
BASDAI	0.82	(0.77, 0.88)	**<0.001**		NA	
ESR	0.03	(0.01, 0.04)	**<0.001**	0.01	(0.00,0.01)	**<0.001**
Radiographic damage[§]	0.82	(0.31, 1.34)	**<0.001**	0.03	(-0.07, 0.14)	0.499

The dependent variable for patients with AS was BASFI (0-10) and for patients with PsA was HAQ (0-3); BASFI: Bath AS Functional Index; HAQ: Health Assessment Questionnaire. Data are expressed as β coefficients (95%CI) and p-values. CCIp: proxy of the Charlson Comorbidity Index; * Triglycerides analyzed per 100 mg/dl increase; GI: gastrointestinal; NSAID: non-steroidal anti-inflammatory drugs; DMARD: disease-modifying anti-rheumatic drugs; GC: glucocorticoids; DAS28-ESR: Disease Activity Score using 28 joints and ESR; ESR: erythrocyte sedimentation rate; BASDAI: Bath AS Disease Activity Index; § defined as "spinal radiographic damage" in patients with AS and "presence of erosions" in patients with PsA; NA: not applicable.

Table 3. Comorbidity and physical function: variables associated with BASFI in patients with AS and with HAQ in patients with PsA. Adjusted multivariate model.

Variables	*Ankylosing Spondylitis*			*Psoriatic Arthritis*		
	β	***95% CI***	***p-value***	**β**	***95% CI***	***p-value***
Age at inclusion	0.03	(0.02, 0.05)	**<0.001**	0.00	(-0.00, 0.00)	0.906
Sex (reference, male)	-0.11	(-0.38, 0.16)	0.430	0.14	(0.06, 0.22)	**<0.001**
Disease duration	0.01	(-0.00, 0.02)	0.095	0.01	(0.00, 0.01)	**0.015**
Educational level (ref, Primary)						
Basic	0.21	(-0.45, 0.86)	0.532	0.14	(-0.03, 0.31)	0.096
Secondary	0.01	(-0.26, -0.29)	0.925	-0.08	(-0.17, -0.01)	0.093
University	-0.22	(-0.52, 0.08)	0.154	-0.14	(-0.24, -0.04)	**0.004**
CCIp	0.03	(-0.13, 0.20)	0.701	0.11	(0.05, 0.17)	**<0.001**
NSAID	0.11	(-0.14, 0.37)	0.390	0.09	(0.02, 0.17)	**0.017**
Biologic DMARD	0.51	(0.27, 0.76)	**<0.001**	0.15	(0.07, 0.23)	**<0.001**
GC	0.03	(-0.40, 0.46)	0.899	0.11	(0.01, 0.21)	**0.026**
DAS28-ESR		NA		0.19	(0.16, 0.22)	**<0.001**
BASDAI	0.81	(0.75, 0.86)	**<0.001**		NA	
ESR	0.01	(0.00, 0.02)	**0.013**		NI	
Radiographic damage[§]	0.61	(0.28, 0.95)	**<0.001**		NI	

The dependent variable for patients with AS was BASFI (0-10) and for patients with PsA was HAQ (0-3); BASFI: Bath AS Functional Index; HAQ: Health Assessment Questionnaire. Data are expressed as β coefficients (95%CI) and p-values. AS: ankylosing spondylitis; PsA: psoriatic arthritis; CCIp: proxy of the Charlson Comorbidity Index; NSAID: non-steroidal anti-inflammatory drugs; DMARD: disease-modifying anti-rheumatic drugs; GC: glucocorticoids; DAS28-ESR: Disease Activity Score using 28 joints and ESR; ESR: erythrocyte sedimentation rate; BASDAI: Bath AS Disease Activity Index; § defined as "spinal radiographic damage" in patients with AS and "presence of erosions" in patients with PsA; NA: not applicable; NI: not included in the multivariate model.

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