Full title of manuscript:

Prevalence of comorbidities and risk factors of for comorbidities in patients with spondyloarthritis in Latin America: a comparative study with the general population and data from the multinational ASAS-COMOSPA study

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Abstract:

Objectives Increased risk of comorbidities has been reported in spondyloarthritis (SpA). The objective of this study was to determine the prevalence and risk of developing comorbidities in SpA-patients in three Latin America (LA) countries, and to compare that prevalence with the general-population.

Methods Data from 390 SpA-patients enrolled in the ASAS-COMOSPA study from Argentina, Colombia and Mexico were analyzed. Age and gender standardized-prevalence (95%CI) was estimated for arterial-hypertension (AHT), tuberculosis (TB), and malignancies. Age-and gender-specific data from general-population were obtained from CARMELA-study for AHT, Global TB-report and GLOBOCAN-project for malignancies. Data analyzed for AHT was confined to Colombia and Mexico. The prevalence in SpA-patients was compared with the prevalence in

general-population per age- and gender-specific stratum resulting in standardized risk ratios (SRR).

Results In total, 64% of the SpA patients were male with a mean age of 45(SD 14.7) years. The most common comorbidities in the three LA-countries were, AHT (25.3%, 95%CI 21.2-30.0), hypercholesterolemia (21.5%, 95%CI 17.6-26.0) and osteoporosis (9.4%, 95%CI 6.8-12.9). AHT-prevalence in Colombia and Mexico was 21.4% (95%CI 15.4-28.9) and was increased compared to general-population (12.5%, 95%CI 11.4-13.7) resulting in an SRR of 1.5. TB-prevalence in the three LA-countries was 3.3% (95%CI 1.8-5.7), which was importantly higher than expected from general-population (0.32%), leading to an SRR of 10.3. The prevalence of malignancies was not increased.

Conclusions Patients with SpA in Latin-America are at increased risk of AHT and TB in comparison to the general-population. While this sample of patients may not be entirely representative of the patient population in each country, a systematic evaluation of these comorbidities in all patients with SpA still may help to monitor these conditions better.

Key indexing terms: Spondyloarthritis; risk factors, prevalence

INTRODUCTION

Comorbidities are frequently associated with inflammatory rheumatic diseases such as ankylosing spondylitis (AS), psoriatic arthritis (PsA) and rheumatoid arthritis (RA). In addition to the musculoskeletal manifestations for SpA and SpA-related extra-articular features (psoriasis, uveitis, inflammatory bowel disease (IBD)), patients may also have an increased risk of cardiovascular (CV) events, metabolic syndrome, malignancies and infections[1, 2, 3]. These comorbidities may result in premature-death[4].

The risk of developing comorbid conditions seems to be higher in patients with SpA than in the general population[5], and these co-morbidities may manifest already shortly after the onset of initial symptoms[6]. CV events occur more frequently in AS patients, likely due to an increased prevalence of traditional risk factors (e.g. metabolic syndrome, arterial hypertension (AHT))[7,8,9] and to the medications used for the treatment of SpA (e.g. non-steroidal anti-inflammatory drugs (NSAIDS). The increased risk of tuberculosis (TB) may be due to immune disturbances by the disease itself and by pharmacological immunosuppression[10]. Additionally, the risk of developing malignancies may be related to chronic inflammation and autoimmunity, although epidemiological evidence that AS is associated with the development of malignancy is lacking[11].

The Assessment of SpondyloArthritis international Society of COMOrbidities in SpA (ASAS-COMOSPA) study[12] is a cross-sectional observational study to assess comorbidities and their risk factors in SpA. This initiative included three Latin American (LA) countries, and provides an opportunity to explore the association of these comorbidities with SpA. While there are data in the literature on comorbid conditions in SpA in other regions, this information is limited in LA countries.

The objective of this study was (1) to determine the prevalence of and the risks to present comorbidities as assessed in the ASAS-COMOSPA-study used as a reference group in patients with SpA in three LA countries; and (2) to compare the prevalence of these with the information in the general population, in order to find out if the prevalence of -and the risk on - comorbidities is increased.

METHODS

Study design and patient recruitment

This was a cross-sectional study that used data from the worldwide ASAS-COMOSPA-study [12]. Briefly, the ASAS-COMOSPA-study was an observational, multicenter and international study (22 countries from four continents) that included consecutive adult patients who fulfilled the ASAS SpA-criteria (axial or peripheral). The patients in the ASAS-COMOSPA-study enrolled from Argentina, Colombia and Mexico (one academic center in each country) were selected and analyzed for the present study. Additionally, 47 Colombian patients with data that made them eligible to ASAS-COMPOSPA but that were offered after the electronic database for the international study had been locked, were also included in this analysis. The results in which the Global ASAS-COMOSPA study data are reported in this study include the data from the LA countries. The study was approved by the Ethics and Research Committee of the Hospital Militar (No.C-2014-027) and was conducted according to the guidelines for good clinical-practice. All patients sign the informed-consent.

Data collection

Details of the data collection methods have been published previously[12]. A case report form was used in the study to collect the data including patient's demographics, SpA disease characteristics and extra-articular manifestations (uveitis, psoriasis, IBD). Information about past and current medications (NSAIDs, corticosteroids, conventional-synthetic and biologic-DMARDs) were also collected.

The following comorbidities and risk factors for comorbidities were collected. AHT was defined as a history of AHT or use of anti-hypertensive therapy or a blood pressure at the study visit >140/90. TB was defined as a history or current active TB. Cancer was defined as a history of neoplasia in the colon, skin (melanoma and basocellular-carcinoma), lymphoma (Hodgkin's and Non-Hodgkin's disease), breast and cervix (for women) and prostate (for men). All data were collected by a study investigator by interview and were completed by reviewing medical records. The information was collected and registered in a centralized electronic-case report form.

Data from the general population

Total and gender- and age-group specific prevalence data for AHT of general population were obtained from the Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA-study). This is a population-based observational study (n=11,550)[13, 14] assessing the prevalence of cardiovascular risk-factors in seven Latin American cities including Buenos Aires, Bogotá and México City. The analyses of data of the general population for AHT was confined to Colombia and Mexico. We found a huge inter-country variability with regard to the AHT prevalence in the region, especially the data reported in Argentina. Whereas the AHT prevalence in

the general-population in Colombia and Mexico was comparable (13 and 11% respectively), in Argentina the reported prevalence was 29%. Because of this discrepancy, which can be explained by genetic, ethnic and demographic differences between the countries in the region, the analyses for AHT was limited only to these two countries with respect to comparison with general-population.

Prevalence data obtained from the general population of Argentina, Colombia and México were standardized for TB and malignancies. Specific prevalence data for TB stratified for gender and age categories have been obtained for the three countries using the 2015 Global Tuberculosis-report[15]. This report is an initiative of the World Health Organization that provides comprehensive information on the status of the disease at global and country levels. Regarding malignancies, gender- and age-group specific prevalence data have been obtained for the three countries using the 2012 GLOBOCAN-project[16, 17]. This initiative provides prevalence estimates for the major types of cancer worldwide.

Statistical analyses

Descriptive statistics were used for the demographic data, disease characteristics, disease activity, risk factors and the comorbidities of the patients included in the analyses. Data are presented as numbers (%) for qualitative variables and as the mean (SD) for continuous variables. The data were stratified for age categories and for males and females separately by comparing expected (general-population) versus observed (Latin America) frequencies. Data from the Global ASAS-COMOSPA-study was included for comparison with LA countries. In addition 95%CIs were estimated using the method described by Wilson[18], which is considered

an accurate and precise method for calculating CIs[19]. Standardised risk-ratios (SRR) were determined to compare event rates (in this study, comorbidities and risk factors) in SpA patients vs. the general-population. SPSS Statistics 22 was used to perform the statistical analyses.

RESULTS

In total, all 390 patients from the three countries Argentina (n=236), Colombia (n=85) and México (n=69) participating in the ASAS-COMOSPA-study were included in the analysis. Patient characteristics including demographic and disease characteristics by country, for the LA countries combined and the global study population -which includes information for the LA countries- are presented in table-1. In the LA countries, sixty-four percent were male, with a mean age of 45 (15) years and a mean disease duration since symptom onset of 7.0 (8.1) years. The proportion of patients with arthritis, enthesitis and dactylitis was higher in the three LA countries (74%, 62% and 24%, respectively) as compared with all patients (n=3,984) in the ASAS-COMOSPA-study (56%, 38% and 16%, respectively). The usage of NSAIDS and DMARDS (particularly methotrexate) was higher in LA countries than in the entire ASAS-COMOSPA-study (72% and 48% respectively for NSAIDS, and 68% and 33% respectively for DMARDS), whereas biological therapy was less frequently used (34% vs 44% respectively). The most common comorbidities and risk factors in all three LA countries were: AHT (25.3%)(95%CI 21.2 to 30.0), hypercholesterolemia (21.5%)(95%CI 17.6 to 26.0), osteoporosis (9.4%)(95%CI 6.8 to 12.9) and gastrointestinal ulcer (7.7%)(95%CI 5.3 to 10.9).

Prevalence of comorbidities and risk factors

The prevalence of AHT limited to SpA patients in Colombia and Mexico was higher (21.4%, 95%CI 15.4 to 28.9) as compared to the general-population (12.5%, 95%CI 11.4 to 13.7) in these two countries. The prevalence of AHT was higher in men than in women, especially in the stratum of 55-64 years (57% vs 11%, respectively) and also in patients ≥65 years (70% vs 25%, respectively), in whom cardiovascular risk is expected to be more similar in both genders. Additionally, in young patients (25-44 years) the prevalence of AHT was consistently increased in both genders compared to the general-population. All of these findings were consistent with the prevalence data of the global ASAS-COMOSPA-study. The total AHT risk of patients with SpA in Colombia and Mexico between 24 and 64 years was increased (SRR: 1.5) compared to the general-population. This risk was increased in women and in men (1.5 and 1.4 respectively) and consistent across different age groups, except in the stratum of 55-64 years in which the risk in women was lower. Detailed data on the prevalence of AHT compared to the general-population are shown in table-2.

The distribution of TB prevalence and risk is presented in table-3. Overall, the observed prevalence of TB infection in LA patients with SpA in the three countries was 3.3% (95%CI 1.8 to 5.7), which was much higher than expected from the general population (0.32%) in these three LA countries and also higher than the prevalence data of the global ASAS-COMOSPA-study (2.5%) (95%CI 2.0 to 3.0). TB prevalence in LA was lower in men than in women (2.8 vs. 4.2% respectively); in contrast to the global study in which the prevalence was higher in men (3.0 vs. 1.6% respectively). Cases of TB in LA were observed after the age of 35 and homogeneously distributed among all age groups regardless of gender (in total: 7 cases of TB in males and 6 cases in females). Seven of these cases were reported in Argentina and six in

Colombia. In contrast in the ASAS-COMOSPA-study, TB cases were reported as early as at an age of 25 years and were more frequent in men (78 male and 23 female cases). The average risk of TB was 10.3 times higher in SpA patients than in the general-population. The risk was more increased in women than in men (18.2 vs. 6.8 respectively) and was found in all age categories except in patients ≥65 years in whom the risk declined in both genders.

The malignancies found in SpA patients in men were: prostate-cancer (n=2), skin-cancer (n=2), colon-cancer (n=1); and in women: cervix-cancer (n=2), breast-cancer (n=2) and skin-cancer (n=2). The majority of cases had been reported in patients ≥50 years of both genders, (7 cases in Argentina, 3 cases in Colombia and one case in Mexico). The overall prevalence of malignancies observed in the three LA countries was 2.8% (95%CI 1.4 to 5.1), which was slightly lower than the prevalence in the global ASAS-COMOSPA-study (3.2%, 95%CI 2.6 to 3.8) and not significantly increased in comparison to the general-population (2.6%) (p=0.5). The SRR for malignancies was 1.0. There was not a significant increase in the prevalence and the risk to develop malignancies in patients with SpA compared with the general-population (Table-4).

DISCUSSION

The results of this study show that the prevalence and the risk of ATH and TB is increased in patients with SpA if compared to the age- and gender-adjusted general-population in LA. Of note, the prevalence and the risk to develop malignancies were not significantly increased in SpA patients in comparison to the reference population.

Studies assessing the prevalence of AHT in AS patients have yielded different results. These discrepancies could be explained by the heterogeneity of study populations investigated[20]. A cross-sectional US analysis [21] of the risk factors of CV disease showed an increased prevalence ratio of AHT in AS (1.3 [95%CI 1.1-1.4]) compared with control subjects (27% vs. 22%). Similar rates were observed in patients with PsA in this study. In a recent Dutch study a higher prevalence of AHT, stratified by age and gender, was observed in AS patients (41%) than in the general population (31%)[22]. Furthermore, a Canadian study has shown that AHT was more common in AS patients (23%) than in matched controls without AS (18%)[23]. Our results are consistent with these studies, reporting a higher AHT prevalence in patients with SpA as compared to a reference population of non-SpA individuals. In contrast, a Swedish study did not find a substantial difference between AS patients and controls regarding AHT (32% vs 29%, respectively) [24]. While chronic inflammation may have had a detrimental effect on endothelial function and may have accelerated the progression of atherosclerosis, the common use of NSAIDS that we found in the current study (72%) is a more likely explanation for the increased prevalence of AHT.

A significantly higher prevalence and risk of developing TB in patients with SpA was found. Genetic factors favouring disease reactivation from latent TB or progression of the infection in addition to conventional risk factors for TB (e.g., age, gender, socioeconomic status, and occupation) may explain this finding. Additionally, it is also challenging to relate the increased prevalence of TB to the immune disturbances caused by the disease itself, which may also contribute to the risk of developing TB. This increased rate of TB has been observed previously in the early stages of disease in patients with SpA[6] and was expected to be present also in

patients with longer disease duration (and longer exposure to inflammation), as in the current study (mean disease duration of 7.0 years). Previous studies in anti-TNF naïve RA patients have shown an increased risk of developing TB (ranging from a 4-fold to a 7-fold increase) compared with the general population[10], suggesting that uncontrolled and chronic inflammation predisposes to TB.

Although some studies have reported that the overall prevalence of TB is lower in women, plausible reasons to explain such a differential effect remain obscure. Factors such as differences in the progression from infection to clinically manifest disease, differences in immune system responsivity and biological differences in disease presentation may be part of the explanation[25]. Although the incidence of TB in LA has declined in the last two decades, the region is still considered an endemic area for TB, mainly due to the presence of social factors that predispose to the disease[26]. In general, these factors increase the exposure to TB-bacilli.

The risk of developing a malignancy was not significantly increased in SpA patients in comparison to the general population. This finding is consistent with previous studies reporting that the overall risk of malignancies was not significantly higher in AS and PsA patients, including those treated with DMARDs or TNF-inhibitors[27]. While malignancies are not rare in patients with AS, there is not a biologically plausible reason to expect a higher risk of cancer in these patients[12].

Previous studies in LA have assessed the prevalence rates of comorbid conditions, especially in RA. A systematic literature review evaluating CV risk factors in RA patients[28] found that AHT

was the most common finding in almost all studies performed in the region, with an overall prevalence of 28% (range 11.2% to 80.6%). In our study, we found a prevalence of AHT in SpA patients of 25.3%, in the three LA countries, which was higher than expected from the general population but still lower than the prevalence reported in RA. This finding is consistent with the data observed in AS patients, in whom CV risk factors are less manifest than in RA[8]. Regarding TB data in LA, a recent prospective Brazilian study of patients with chronic inflammatory arthritis including AS, RA and PsA has suggested that patients who start TNF blockers have a significantly higher rate of active TB than healthy-controls (87 vs 36/100,000 person-years) [29].

This study has limitations. First, the sample of patients may not be generalizable to the patient population in each country or the whole region. This cohort may not have been fully representative of all SpA patients in the participating countries; moreover, the sample was rather small (especially for Colombia and Mexico) and limited to those patients that had access to specialized rheumatology care in academic centers. In particular the higher educational status in Mexico and Colombia gives rise to the suggestion that the sample that was investigated may not be entirely representative of the population of SpA patients in these countries. This should be taken into account when interpreting the results.

In addition, the patients in this study were from only three LA countries, namely those that participated in the international ASAS-COMOSPA-study. Moreover, data of Argentina with regard to AHT was not included in the analyses for comparison to general population and calculation of SRR. It was mainly due to a high inter-country variability of data in the general population as a result of ethnic and demographic differences; therefore, the AHT data was

analysed only for two countries. This limits the ability to extrapolate findings to the whole region. Second, the prevalence of some comorbidities might have been underestimated, because patients may have been unable to participate due to clinically relevant conditions. On the other hand, comorbidities might have been overestimated because of investigation bias: SpA patients with comorbidities that are known to be associated with the disease may be overrepresented in this sample. Finally, it is important to mention an additional source of potential bias in relation to TB-case-ascertainment: While the global TB report had been based on comprehensive data reported at the national level according to guidelines by the World Health Organization, in the COMOSPA study cases of TB had been ascertained by the patients and subsequent medical record review. These data do not necessarily yield the same results.

In conclusion, LA patients with SpA have an increased risk of developing AHT and TB compared with the general-population. These findings illustrate the need for optimal detection and monitoring of these conditions in SpA patients, and have implications for rheumatologist's health assessments, prevention and treatment planning in LA countries.

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