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Update on the epidemiology, risk factors, and disease outcomes of axial spondyloarthritis

Clementina López-Medina [a, b, c, *], Anna Moltó [a, b]

[a] Rheumatology Department, Cochin Hospital, Paris, France
[b] Inserm (U1153), Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France
[c] Rheumatology Department, Reina Sofía University Hospital, Maimonides Institute for Biomedical Research of Cordoba (IMIBIC), University of Cordoba, Cordoba, Spain

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A B S T R A C T

Axial spondyloarthritis (axSpA) is the prototype of a class of a rheumatic chronic inflammatory disease named spondyloarthritis (SpA). The prevalence of axSpA ranges between 0.1% and 1.4% globally, hence showing geographic differences that can be explained mostly by the prevalence of the HLA-B27 antigen. However, not many studies have evaluated the incidence of this disease.

Inflammation may be initiated in the enthesis as a consequence of the action of IL-23, which can activate resident T cells. The elevated expression of IL-23 has been explained by three hypotheses: the presence of HLA-B27, variations in the gut microbiome and the biomechanical stress at the enthesis. However, the role of IL-23 in this whole context is still unclear.

In axSpA, the presence of syndesmophytes at baseline, systemic inflammation, and smoking may promote the spinal radiographic damage in these patients. The most frequent comorbidity in these patients is osteoporosis, which is directly associated with ankylosis and inflammation.

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Introduction

Spondyloarthritis (SpA) is a chronic inflammatory disease that affects the axial skeleton (spine and sacroiliac joints (SIJs), producing inflammation of the vertebrae leading to bone growth and fusion), peripheral joints, and enthesis (insertion sites of tendons and ligaments to the bone surface) [1].

* Corresponding author.
E-mail address: clementinalopezmedina@gmail.com (C. López-Medina).

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Moll and colleagues [2] were, in 1974, the first authors to coin the SpA "concept," thus highlighting a number of signs and symptoms that clustered in diseases that were, at the time, separated entities: psoriatic arthritis, arthritis related to inflammatory bowel disease (IBD), reactive arthritis, undifferentiated SpA, and ankylosing spondylitis (AS – the prototype of axial SpA (axSpA)). Indeed, the shared characteristics can appear in the same individual (simultaneously or at different timepoints) and also in a family member (e.g., a patient can be diagnosed with psoriasis and his father with Crohn's disease). Additionally, different clinical manifestations (e.g., psoriasis and eye involvement) are identical regardless of the diagnosis.

Diagnosis and classification of spondyloarthritis

No validated diagnostic criteria are available for SpA, but several classification criteria have been proposed.

In the 1930s, with the emergence of plain radiography, it was confirmed that structural damage in AS started in the SIJs [2], being the structural damage at this site (i.e., called "sacroiliitis") the cornerstone of its diagnosis. In 1963, interpretation of sacroiliac radiographs was standardized through the use of a score agreed by the "Atlas of Standard Radiographs of Arthritis" and the "New York Conference for Population Studies" (Table 1) [3,4]. This grading scale is still used currently and allows for the classification for radiographic axSpA (r-axSpA).

In the 1970s, the first set of criteria was proposed to classify patients with AS, which was subsequently updated in 1984 (Table 2): the modified New York criteria [5]. However, to fulfill these criteria, patients had to present with structural damage (i.e., radiographic sacroiliitis) of the SIJs, which very often appears only several years after disease onset, thereby resulting in a mean diagnostic delay of 9 years [6] in patients with clinical symptoms but without such structural damage. Furthermore, these criteria included only axial symptoms, and patients presenting with peripheral manifestations could not be classified as suffering from AS in the absence of structural damage. To prevent this diagnostic delay, as well as to incorporate the different clinical presentations of SpA (e.g., peripheral arthritis, uveitis, and enthesitis), other sets of classification criteria were proposed. In the early 1990s, Amor and colleagues presented the Amor criteria [7] that included for the first time peripheral features, good response to nonsteroidal anti-inflammatory drugs (NSAIDs), and excluded mandatory radiographic sacroiliitis for the first time, although kept it weighted to a great extent (Table 3).

In the late 90s, a new imaging modality such as magnetic resonance imaging (MRI) allowed for the first time to assess the presence of inflammation in the SIJs and spine. This inflammation could be seen in patients with structural damage (i.e., radiographic sacroiliitis and syndesmophytes) and also in

Table 1
Grading of radiographic sacroiliitis.

Grade 0	Normal
Grade 1	Suspicious changes
Grade 2	Minimal abnormality – small localized areas with erosions or sclerosis, without alteration of the joint width
Grade 3	Unequivocal abnormality – moderate or advanced sacroiliitis with one or more erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis
Grade 4	Severe abnormality – total ankylosing

Adapted from Bennett PH, et al. [4].

Table 2
The modified New York Criteria for Ankylosing Spondylitis.

Clinical criteria	Low back pain and stiffness for more than 3 months, which improves with exercise but is not relieved by rest
	Limitation of motion of the lumbar spine bot in the sagittal and frontal planes
	Limitation of chest expansion relative to normal values correlated for age and sex
Radiological criteria	Sacroiliitis grade $\geq$2 bilaterally or grade 3 or 4 unilaterally
Definite Ankylosing Spondylitis: if the radiological criterion is associated with at least 1 clinical criterion.	

Adapted from van der Linden S, et al. [5].

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Table 3
Amor classification criteria for Spondyloarthritis.

A. Clinical symptoms/history	Score
1. Pain at night (spine) or morning stiffness	1
2. Asymmetrical oligoarthritis	2
3. Gluteal (buttock) pain (any) OR	1
alternating gluteal pain	2
4. Sausage-like digit or toe (dactylitis)	2
5. Enthesitis (heel)	2
6. Uveitis	2
7. Urethritis/Cervicitis within 1 month before the onset of arthritis	1
8. Diarrhea within 1 month before the onset of arthritis	1
9. Psoriasis, balanitis, or inflammatory bowel disease	2
B. X-RAY	
10. Sacroiliitis (grade 2 bilaterally or grade 3 unilaterally)	3
C. GENETIC BACKGROUND	
11. HLA-B27 positive or positive family history for AS, ReA, uveitis, psoriasis, or inflammatory bowel disease.	2
D. GOOD RESPONSE TO NSAIDs	
12. NSAIDs show a good response within 48 hours, or relapse within 48 hours after NSAIDs are stopped	2

Adapted from Amor B, et al. [7].

patients without such damage. These findings led to the idea that inflammation could be the first step in the sequence that would eventually lead to radiographic progression and definitive AS.

In 2004, an international group of experts, the Assessment of SpondyloArthritis international Society (ASAS), decided to revise the classification criteria for SpA, to allow an earlier recognition of the disease, by including MRI findings and an abnormal C-reactive protein (CRP) level in a set of criteria for the first time. This approach led to the publication in 2009 of the ASAS classification for SpA [8,9], both for axial and peripheral presentations [10]. If we focus on the axial forms, one patient can fulfill the criteria either by the presence of imaging abnormalities for the SIJ, e.g., radiographic or MRI sacroiliitis and the presence of at least another SpA feature (i.e., this patient would fulfill the "imaging arm" of the ASAS criteria), or by the presence of the HLAB27 antigen along with at least two other SpA features (i.e., one this patient would fulfill the "clinical arm" of the ASAS).

In parallel to these new criteria, and reflecting the widespread use of MRI, the concepts of radiographic and non radiographic axSpA forms emerged; former AS was currently referred to as r-axSpA (e.g., patients fulfilling the "imaging arm" by the presence of radiographic sacroiliitis), whereas all other patients fulfilling the ASAS criteria ("MRI-imaging arm" and "clinical arm") were defined as having non-radiographic axSpA. This nomenclature appeared when nonradiographic forms were believed to correspond to (very) early forms of axSpA that would eventually progress to radiographic forms, thus leading to the concept that nonradiographic forms were less severe and had a lower burden of disease for patients. However, several studies are starting to report that not all patients with nonradiographic axSpA will progress to r-axSpA even after several years [11], thus suggesting that maybe the nonradiographic and radiographic states are not part of a continuum but only different presentations of a single disease as it is the case for rheumatoid arthritis (RA), where patients may present erosive or nonerosive forms. Furthermore, some studies have also reported that the burden of the disease (in terms of quality of life and function) is comparable in patients with r-axSpA and nonradiographic axSpA [12].

The ASAS criteria are currently most commonly used; their performance has been extensively evaluated [13–15] and is currently widely accepted.

Epidemiology of spondyloarthritis

Prevalence

It is believed that the prevalence of SpA ranges between 0.1% and 1.4% globally, thus showing geographic differences that can be explained mostly by the prevalence of the HLA-B27 antigen [16],

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which is strongly associated with the development of the disease. The highest prevalence of the HLA-B27 antigen (53%) is found in the Pawaia tribe in Papua New Guinea [17], followed by that in the Haida indigenous Americans in Western Canada (50%) [18]. In contrast, the lowest prevalence of HLA-B27 positivity has been described in Japan (approximately 1%) and Arab populations (3%) [19,20].

These frequencies are in agreement with the prevalence of SpA, which is most prevalent in Haida indigenous Americans (with a prevalence rate between 6% and 10%) [18] and less prevalent in the Japanese population (0.0065%) [19].

There are also important differences in the prevalence of the disease across continents. Recently, a systematic review estimated the AS prevalence in each continent. In Europe, the mean prevalence rate of SpA has been reported as 23.8 per 10,000 individuals for the entire continent [21]. In Asia, the prevalence rate was 16.7 per 10,000 individuals, whereas in North America, South America, and Africa, the prevalence rate was estimated between 13.1 and 31.9, 2.6 and 19.0, and 7.4 per 10,000 individuals, respectively. In this study, the authors also evaluated the prevalence of AS grouped by country and continent. The higher prevalence of SpA in Europe has been reported in a population survey in Northern Norway, which revealed a prevalence of AS according to the New York criteria of 1.8% [22], followed by Germany, with 0.86% [23]. In contrast, Greece has shown the lowest prevalence of AS in Europe, i.e., of 0.24% [24], which can be explained by the lower prevalence of the HLA-B27 antigen in these populations.

Incidence

Not many studies have evaluated the incidence of SpA. The countries where the incidence of the disease has been evaluated are the US, Finland, and Norway. One of the most important studies was conducted in Rochester (Minnesota), which concluded that the overall annual incidence rate, adjusted for age and sex, was 6.6 per 100,000 individuals in the white general population (between 1935 and 1973) [25]; however, in that study, HLA-B27 determination was not yet available for clinical use. In a subsequent study carried out in a different period (1935–1989), an annual incidence rate of 7.3 per 100,000 individuals in the white population of Rochester was reported by using the modified New York criteria; however, the incidence rate was similar to that reported in the previous study adjusted by age and sex [26].

A study from Finland was performed using a nationwide health insurance proposal covering a population of approximately 1 million adults, which estimated an average annual incidence rate of 6.9 per 100,000 individuals. A second study performed in Kuopio, a city in Central Finland, showed an average annual incidence rate of 5.8 per 100,000 individuals [27].

In Norway, a study published in 2005 showed an annual incidence rate of SpA of 7.26 per 100,000 individuals, which showed a significantly higher incidence in towns than in surrounding rural regions [28].

This incidence rate of SpA has been reported to be lower in Japan, perhaps because of the lower prevalence of HLA-B27 in this population [19].

Ethnic distribution

Studies on the ethnic distribution of the aforementioned diseases are focused on the prevalence of HLA-B27 among different races. In 2012, J.D. Reveille and collaborators carried out the first large-scale population study of the prevalence of HLA-B27 in the US [29]. They observed that the overall age-adjusted HLA-B27 prevalence in non-Hispanic white adults was estimated at 7.5%, whereas in all other US ethnicities combined, the age-adjusted HLA-B27 prevalence estimate was 3.5%. Specifically, Mexican Americans showed an estimated age-adjusted HLA-B27 prevalence rate of 4.6%. Subsequently, another study was performed to evaluate disease severity of SpA in three ethnic groups in the US [30]; it seemed that black patients had greater disease activity either by subjective measures (Bath Ankylosing Spondylitis Disease Activity Index – BASDAI) [31] and by objective measures (either the erythrocyte sedimentation rate (ESR) or CRP) than Caucasians or Latinos. They also found different percentages regarding the occurrence of HLA-B27: 62.5% among blacks, 85.3% among Caucasians, and 86.7% among Latinos.

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Gender distribution

The gender distribution of SpA seems to differ depending on the clinical form, with an historical sex ratio of male prevalence of 2-3:1 but with more balanced proportions in earlier (or milder) forms [32].

In the OASIS cohort, which included patients with r-axSpA from the Netherlands, Belgium, and France and with a mean disease duration of 20 years, the percentage of males was 70% [33]; in the DESIR cohort [32], a national multicenter French cohort that included patients with early inflammatory back pain (<3 years but >3 months) suggestive of axSpA, 58.8% of males fulfilled the mNY criteria (i.e., they could be diagnosed with AS or r-axSpA).

Risk factors for the development of spondyloarthritis

To date, it remains difficult to evaluate the influence of factors such as genetic or environmental factors on the development of the disease. Several studies have suggested that musculoskeletal inflammation in SpA, in particular in axSpA, may be initiated in the enthesis [34] as a consequence of the action of IL-23, which can activate resident T cells within this anatomical interface [35].

The elevated expression of IL-23 in these patients has been explained by three hypotheses, which can be considered as risk factors for the initiation of the disease processes. These three hypotheses are the presence of HLA-B27, variations in the gut microbiome, and the biomechanical stress at the enthesis.

Genetics and HLA-B27

Several studies of familial aggregation of r-axSpA estimate that genetic factors account for between 80% and 90% of the susceptibility to develop the disease [36]. In particular, the presence of the HLA-B27 antigen (a major histocompatibility complex molecule (MHC) type I discovered in 1973 [37,38]), contributes to 30% of the heritability of the disease. This gene is present in 8–10% of the general population as opposed to in 80–90% of patients with r-axSpA [16].

This association was further confirmed by Hammer et al. [39] who demonstrated that HLA-B27 transgenic rats spontaneously developed inflammatory disease involving the gastrointestinal tract, peripheral and vertebral joints, male genital tract, skin, nails, and heart, strikingly similar to the clinical manifestations seen in humans with SpA. The exact role of HLA-B27 in SpA pathogenesis has not been clearly established yet; however, there are three hypotheses that might explain it.

The "*arthritogenic peptide*" *hypothesis* proposes that the MHC-I (HLA-B27) might be involved in the presentation of peptides from microbial antigens or self-antigens to CD8+T cells, which can be reactivated in the joints [40]. However, this hypothesis was questioned because HLA-B27-transgenic rats that lack $CD8^+$ also developed a SpA-like disease [41]. Under physiological conditions, the HLA-B27 antigen is generated as a free heavy chain joined to β2-microglobulin (β2m) and an antigenic peptide, thereby forming a trimolecular complex, which interacts with $CD8^+$ T cells. However, the "*free heavy chain homodimers*" *hypothesis* proposes that, in patients with SpA, HLA-B27 is prone to form heavy chain homodimers on the cell surface without β2m [42]. Consequently, $CD8^+$ T cells are not activated; instead, a direct and peptide-independent activation of natural killer (NK) cells and $CD4^+$ T cells through killer cell immunoglobulin-like receptors (KIRs) occurs. Finally, the "*misfolding*" *hypothesis* proposes that intracellular misfolding of HLA-B27 can lead to an "unfolded protein response" (UPR) [43] or endoplasmic stress, thereby inducing the production of high levels of IL-23 by myeloid cells by activating the "receptor recognition patterns" (RRPs) [44].

Infectious agents and the gut microbiome

For years, the clinical association between SpA and bowel inflammation has been known, considering that approximately 5–10% of patients with SpA develop IBD and up to 70% might have subclinical bowel inflammation [45]. In 2010, Danoy et al. demonstrated the genetic overlap between SpA (in particular r-axSpA) and IBD by identifying new genes and loci common to both diseases [46]. Prominent genes among them are IL-23R, IL-12B, and STAT3, which suggest an important role of the IL-23

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pathway. Considering all these factors, increasingly clear is the role of the gut microbiome in the development of the acquired immune response, and the impression that it can predispose to the appearance of SpA.

In contrast to reactive arthritis (ReA), which is known to be triggered by the intestinal presence of specific pathogens (*Salmonella*, *Shigella*, or *Yersinia*), for axSpA, an evident infectious trigger has not been identified. Instead, small variations in the gut microbiome diversity (such as the presence of Lachnospiraceae and Bacteroidaceae, and the decrease in the number of Ruminococcaceae and Rikenellaceae) could play a key role in the pathogenesis of axSpA [47].

On this basis, it seems that the gut microbiome alteration triggers an increase in the production of IL-23 from the terminal Ileum epithelium. Consequently, IL-23 interacts with the IL-23R located on T cells residing in the enthesis, thereby causing local inflammation and bone remodeling through the production of IL-22 and IL-17 cytokines by T cells [35]. Nevertheless, the role of IL-23 in this whole context is still unclear.

Biomechanical stress

In 2001, McGonagle et al. proposed that interactions between biomechanical factors and the innate immune response may lead to the development of enthesitis in AS [48]. This hypothesis was recently confirmed through the observation that enthesitis development is dependent upon biomechanical strain in a murine model [26]. In this study, hind limb unloading prevented the onset of Achilles enthesitis in $TNF^{\Delta ARE}$ mice, which showed similar arthritis severity as that of weight-bearing controls. This tissue stress may alter the threshold for entheseal $CD3^{+}CD4^{-}CD8^{-}IL\text{-}23R + ROR^{+}$ T cells in the entheses of mice and provoke inflammation [49].

To date, there are no human studies validating this theory.

Main outcomes

SpA has a variable disease course, characterized by periods of remission and flares. However, disease duration is an important negative factor in the development of structural damage, comorbidities, days of sick leave, and functional deterioration. To date, some factors have been widely investigated owing to their impact on the long-term outcome of these patients, in terms of quality of life, sick leave, economic considerations, and health expenditures: structural damage and comorbidities.

Structural damage

The pathogenesis of structural remodeling and new bone formation in AS, which leads to ankylosis of the spine and SIJ. One hypothesis holds that osteoproliferation and structural remodeling are related to endochondral bone formation pathways. In experiments performed in TNF-alpha transgenic mice models, activation of the Wnt pathway through the blockade of its inhibitor (Dickkopf-related protein 1 (DKK1)), reversed the bone destruction process and induced fusion of the SIJs [50,51]. A second hypothesis proposes that osteoproliferation is independent of inflammation because, despite clinical efficacy, TNF alpha blockers have not been demonstrated to halt radiographic progression in r-axSpA [52].

As we have previously exposed, axSpA can be divided into two subgroups depending on the presence of structural changes in the SIJs: r-axSpA and nonradiographic axSpA. Because some patients with SpA never develop structural damage, a few studies aimed to evaluate the natural history of the disease to determine the rate of radiographic progression and the predisposing factors from switching from nonradiographic axSpA to r-axSpA.

Regarding radiographic progression in SIJ, Dougados and collaborators [53] proposed, in 2006, three definitions through the evaluation of each SIJ by two readers in the DESIR cohort: a) a change of at least one grade in at least one SIJ after 2 years of follow-up; b) a change of at least one grade in at least one SIJ after 2 years of follow-up and an absolute score of the "worsened" joint at year 2 of at least two grades (i.e., at least minimal abnormality); c) a change other than 0 in the total score of the two SIJs (mean of the two readers). Among the total patients who did not fulfill the modified New York criteria at baseline, 4.9% became positive after 2 years of follow-up. According to the first definition, 11.1% of

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patients were defined as "progressors" (i.e., change of at least one grade in at least one SIJ after 2 years of follow-up). Considering the "true" percentage of progression as the percentage of patients who experienced worsening minus the percentage of patients who experienced improvement, the progression was always higher in the subgroup of patients with baseline radiographic structural damage. In addition, the mean change in the total SI joint score (range 0–8) was small but significant (0.1 ± 0.8). In addition, three predisposing factors for progression were identified: smoking status, HLA-B27 positivity, and MRI inflammation of the SIJ.

A similar analysis was conducted subsequently in the same cohort to evaluate radiographic progression for 5 years of follow-up [11]. 5.1% of patients switched from non-radiographic axSpA to modified New York criteria, 13% progressed in at least one grade in at least one SIJ, and 10.3% changed of at least one grade but ignoring a change from 0 to 1. In this study, baseline MRI inflammation on SIJ was associated with radiographic damage after 5 years in HLA-B27-positive and also in HLA-B27-negative patients, although to a lesser extent [OR 5.39 (95% CI 3.25 to 8.94) vs. OR 2.16 (95% CI 1.04 to 4.51), respectively].

The most important radiographic changes in the spine are squaring of vertebral bodies due to the anterior longitudinal ligament ossification; shiny corners (Romanus lesions) because of sclerosis, and the annulus fibrosus ossification, which develop on the appearance of syndesmophytes, which can lead to the image of "bamboo spine." Such abnormalities can be evaluated through a score system named mSASSS (Modified Stoke Ankylosing Spondylitis Spine Score) [54].

Currently, it is well known that there are some risk factors for spinal radiographic damage in axSpA, such as the presence of syndesmophytes at baseline, elevated levels of markers of systemic inflammation (ESR and CRP), and cigarette smoking [55].

Indeed, a study published by Ramiro et al. demonstrated that disease activity measured by ASDAS is longitudinally associated with radiographic progression in the spine in patients with r-axSpA [33]. Although disease activity seems to be related to radiographic progression, most of the studies with TNF alpha blockers have not yet shown an inhibition of this radiographic progression. Three open-label extensions of randomized controlled trials of TNF alpha blockers in AS for 2 years, published between 2008 and 2009, did not demonstrate inhibition of radiographic progression [56–58]. This hypothesis on the lack of effectiveness of these drugs on structural damage has been refuted recently by a longitudinal analysis of up to 10 years of follow-up, which demonstrated an association between TNF alpha blocker use and reduced risk of spinal structural damage, both in terms of mSASSS and new syndesmophyte formation [59]. A new human anti-IL-17A monoclonal antibody (secukinumab) has demonstrated significantly improved signs and symptoms in r-axSpA [60]. Regarding structural damage, the mean change in mSASSS during 2 years of secukinumab therapy was 0.30 (SD 2.53) overall. However, comparisons between these results and those reported in studies with TNF alpha blockers and historical cohorts cannot be made because of differences in study designs and populations. For this reason, the effect of secukinumab on radiographic progression in r-axSpA is still unclear.

A dose-dependent relationship between tobacco smoking and the development of structural damage in the spine in patients with axSpA has been reported. Absolute mSASSS worsening by 2.20 ± 4.62 units for 2 years was reported in heavy smokers (>10 cigarettes a day), while in moderate smokers (≤10 cigarettes a day) mSASSS worsening was 0.48 ± 1.48. These differences among the different smoking doses are clearer in the AS group, whereas in nonradiographic axSpA, no clear difference was observed [61].

Another factor that can induce radiographic progression is long-term physically demanding jobs, which seem to amplify the effects of inflammation on bone (syndesmophyte) formation in AS. This relationship, however, can be mediated by smoking and confounded by socioeconomic factors, which may have separate effects on bone formation [62].

Comorbidities

Comorbidities are deemed as clinical manifestations that appear as a consequence of persistent inflammatory activity and/or treatment; that is, they are not etiopathogenically related to the rheumatic disease [63]. This is unlike extra-articular manifestations that may occur during the course of the disease and belong to the spectrum of SpA and thus do not, by definition, fulfill the criteria for comorbidity.

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In 2016, the EULAR group [64] expressed the importance of the evaluation of comorbidities in rheumatic disease because of three reasons: first, because the prevalence of some comorbidities is increased in patients with rheumatic inflammatory diseases compared to the general population (i.e., due to the chronic inflammatory status and/or treatments used chronically) [65]. Second, because for several comorbidities, there are specific recommendations to be applied in patients with rheumatic inflammatory diseases [66,67]. Finally, because quite often, these patients (particularly when patients are treated with biologics), they are not followed up by general practitioners and do not receive the screening programs that should be applied to the general population (including them).

In 2016, we reported the first study to evaluate the prevalence of comorbidities in patients with SpA worldwide [68]. In these patients, the most frequent comorbidities are osteoporosis (13.4%) and gastroduodenal ulcer (11%). While the prevalence of cardiovascular (CV) disease was not higher than that in general population, the prevalence of specific CV risk factors (such as hypertension, dyslipidemia, and smoking) is higher than that in healthy people [69]. This higher prevalence of CV risk factors could be explained by the chronic inflammatory status, by the use of NSAIDs (which can induce hypertension), and by the presence of metabolic syndrome, particularly in patients with psoriasis. However, the lower prevalence of CV disease in patients with SpA, specifically in the COMOSPA cohort, could be explained by the low mean age of this population (44 years old) [68].

Osteoporosis

There are different studies regarding the factors associated with osteoporosis in patients with SpA, with different results and conclusions. Some studies have reported that low bone mineral density (BMD) and vertebral fractures (VFs) are directly associated with the mSASSS [70,71], that is, these comorbidities are reportedly more frequent in patients with ankylosis, which depend on the disease duration. However, there are other factors associated with low BMD, such as ESR, CRP, and BASDAI, which can lead to the appearance of osteoporosis in young patients or those with recent disease onset [71]. This was confirmed by Briot et al. [72] who analyzed in the DESIR cohort 332 patients with a mean age of 33.8 years and a mean of 1.6 years of axial symptom duration. As much as 13% of patients had low BMD (while the expected prevalence in this population was 2.2%) [73], and the main risk factors associated with this low BMD were bone and systemic inflammation (assessed by MRI) and biological parameters. This observation confirmed the link between low BMD and inflammation in patients with SpA, even in early forms.

Cardiovascular disease

The high prevalence of CV disease and CV risk factors in patients with RA is a proven fact for more than 15 years; however, data about their incidence and prevalence in SpA are still scarce and even heterogeneous [74]. Most of the studies conclude that in patients with AS, CV risk factors are also increased compared with those among the general population in almost all age ranges but to a lesser extent than that in RA [75,76].

Increased mortality has been described in patients with AS compared with that in the general population, which can be explained by the higher prevalence of CV disease, such as ischemic heart disease, stroke, and peripheral vascular disease in these patients [77,78]. In 2016, Eriksson et al. conducted a study on a Swedish national cohort of patients with AS, in which they observed a relative risk of 1.3 for the appearance of acute coronary syndrome compared with that in the general population. Similarly, the relative risk for stroke was 1.5, thus indicating that these patients have a moderately increased risk (30%–50%) of developing CV disease compared to that in the general population [74]. Another important study was conducted by Peters et al. on a German cohort of patients with AS in which they suggested that these patients had between two to three times higher risk of acute myocardial infarction than that in the general population [79].

In general, it is accepted that this increased risk in the development of CV disease can be explained by three factors: chronic systemic inflammation, higher prevalence of classic CV risk factors [80], and different modalities of treatment, particularly the continued use of NSAIDs. Further, environmental and sociodemographic factors and habits (such as smoking, psychological stress, and socioeconomic status) can influence the development of certain CV risk factors, just as occurs in the rest of the population.

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Accelerated atherosclerosis is considered one of the most important causes for the increase in mortality in SpA, and it seems that inflammation plays a key role as an accelerating mechanism of atherogenesis. The presence of a chronic inflammatory process in these patients can contribute to the development of atherosclerotic plaques with consequent vascular events. In many cases, these plaques can be subclinical, and they can be detected in people without clinically evident CV events. In 2009, González-Juanetey et al. [81] corroborated these data, observing that, in patients with AS without CV disease, there was a high prevalence of subclinical macrovascular atherosclerotic disease. In addition, they observed that longer disease duration and high levels of ESR (i.e., greater inflammatory response) predicted subclinical atherosclerotic severity.

Another important cause that can explain the mortality associated with CV disease in these patients is the higher incidence and prevalence of CV risk factors. Recently, Papagoras et al. [82] analyzed the CV risk profile in Greek patients with SpA and compared them with a control group. They observed that the prevalence of smoking was 68.7%, much higher than that observed in the general population, where the frequency of smoking was 40%. Regarding obesity, they did not find significant differences between patients with SpA and the control group. However, HDL levels but not LDL were decreased in patients with SpA, thus showing an atherogenic index (total cholesterol/HDL) significantly higher in these patients than that in the general population.

The treatment used in these patients may also influence the development of CV disease [81]. NSAIDs are the cornerstone in the management of these patients; however, their use implies some risks because they inhibit COX enzymes, thus inducing adverse effects derived from the inhibition of prostaglandins. However, in patients with SpA, increase in this risk is not clear. Some studies have reported a reduction in CV disease rates in these patients treated with NSAIDs [83,84], which can be explained by the reduction of inflammation, which may greatly contribute to the development of CV disease in these patients. However, a study conducted on rheumatic patients followed up periodically showed that despite a low inflammatory activity, the prevalence of CV disease was higher than that in the general population [83]. This observation explains why the chronic inflammatory status may be considered as an independent risk factor in the development of CV diseases [85].

Summary

SpA prevalence ranges between 0.1% and 1.4% globally, depending on the prevalence of the HLA-B27 antigen, which differs among the different geographical areas. Despite SpA being studied in detail, there are still many unanswered questions, and most of them concerns the physiopathology and the role of IL-23.

In axSpA, the presence of syndesmophytes at baseline, systemic inflammation, and smoking may promote the spinal radiographic damage in these patients. However, we do not know whether non-radiographic and radiographic states are not part of a continuum but different manifestations of a single disease.

The most frequent comorbidity in these patients is osteoporosis, which is directly associated with ankylosis and inflammation. Increased risk in the development of CV disease in these patients can be explained by chronic systemic inflammation, higher prevalence of classic CV risk factors and the use of NSAIDs, which leads to an increased mortality in patients with AS compared with that in the general population.

Practice points

- Axial spondyloarthritis is not a rare disease: its prevalence could be up to 1% in some geographical areas, depending on the prevalence of the HLA-B27 antigen. However, this antigen is not imperative for the diagnosis.
- Because inflammation seems to influence radiographic progression, disease activity should be evaluated in each medical visit.
- Annual screening of comorbidities is needed in these patients, especially regarding cardiovascular disease and osteoporosis.

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Research agenda

- There are yet no human studies validating the theory that biomechanical stress may lead to the development of enthesitis.
- The role of diet and the microbiome in the pathogenesis of the disease remains unclear.
- It remains unclear why not all patients with nonradiographic axSpA will progress to radiographic axSpA even after several years.
- The pathogenesis of inflammation leading to structural remodeling and new bone formation in axSpA is still unclear.

Conflicts of interest

The authors have no conflicts of interest related to this work.

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