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## **Comorbidities in spondyloarthritis including psoriatic arthritis**

**Anna Moltó<sup>1,2</sup>, Maxime Dougados<sup>1,2</sup>**

<sup>1</sup>Paris Descartes University

Department of Rheumatology - Hôpital Cochin. Assistance Publique - Hôpitaux de Paris

<sup>2</sup>INSERM (U1153): Clinical epidemiology and biostatistics, PRES Sorbonne Paris-Cité. Paris, France

- Anna Moltó : [anna.molto@aphp.fr](mailto:anna.molto@aphp.fr)  
Service de Rhumatologie B – hôpital Cochin – 27 rue du fg Saint-Jacques – 75014 Paris
- Maxime Dougados : [maxime.dougados@aphp.fr](mailto:maxime.dougados@aphp.fr)  
Service de Rhumatologie B – hôpital Cochin – 27 rue du fg Saint-Jacques – 75014 Paris

Corresponding author : Anna MOLTÓ

Service de Rhumatologie B – hôpital Cochin – 27 rue du fg Saint-Jacques – 75014 Paris

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## **Abstract**

Comorbidities in spondyloarthritis including psoriatic arthritis have to be differentiated to the concept of clinical features of spondyloarthritis (e.g. uveitis, psoriasis, inflammatory bowel disease,...). Apart from the atherosclerosis related cardiovascular diseases, the most frequent comorbidities in spondyloarthritis are osteoporosis, fibromyalgia and depression.

Moreover, the current available drug therapies (e.g. NSAIDs, corticosteroids, biologics) might increase the risk of some comorbidities such as infections and gastro-intestinal disorders. The awareness of these comorbidities is crucial in order to improve their screening and management. For this purpose any systematic periodical review should integrate a program (ideally internationally standardized) focused on comorbidities.

## I. Spondyloarthritis *versus* psoriatic arthritis

There is an ongoing (endless) debate whether we should consider psoriatic arthritis as part of spondyloarthritis or as a distinct entity. Based on the observed data, there is a huge overlap of the clinical rheumatological manifestations (axial symptoms, peripheral articular arthritis, enthesitis, dactylitis) with probably peripheral rheumatological manifestations more frequently observed in case of concomitant skin psoriasis [1,2].

In the context of comorbidities, two notions have to be kept in mind:

- Psoriasis is associated with a metabolic syndrome which can explain at least partially the higher frequency of metabolic disorders even in patients suffering from a recent onset pure axial disease [3,4].
- The past history of-and/or the current presence of peripheral arthritis might have been or might indicate a corticotherapy which might be responsible for some comorbidities (e.g. infections, osteoporosis, cardiovascular diseases,...).

These notions are important to consider when proposing a management plan to the patients and, in particular, the frequency of a systematic periodical review which should be more frequent in case of concomitant psoriasis and/or corticotherapy.

## II. Clinical features *versus* comorbidities

Spondyloarthritis is a chronic inflammatory rheumatic disease which might have different clinical presentations. The most common is the axial disease with inflammatory back pain and buttock pain. The extra-spinal manifestations include enthesitis, dactylitis and peripheral synovitis. There is also the possibility to observe extra-rheumatological manifestations, the most common ones being acute anterior uveitis, psoriasis and inflammatory bowel disease. Occasionally, other extra-rheumatological manifestations can occur such as vasculitis [5], aortic deficiency [6], cardiac conduction disturbances [7] and rarely nowadays renal impairment due to amyloidosis. These extra-rheumatological manifestations are directly related to spondyloarthritis and are considered as clinical features of spondyloarthritis. Apart from these clinical features which are directly related to spondyloarthritis, patients may suffer from other distinct additional disorders, classically referred to as "comorbidities". A comorbidity can be defined as a condition that co-exists with the disease of interest. However, we have to recognize that the distinction between clinical feature and comorbidity might sometimes be challenging. For example, at the heart level, the most commonly observed manifestations are related to an accelerated atherosclerosis responsible for myocardial infarction; heart failure and premature death [8]. However aortic deficiency and/or conduction defects are considered as, even rare, clinical features. Therefore, in case of heart failure and/or sudden death, it might be difficult to attribute this clinical event to a comorbidity or a clinical feature [9].

## III. Multimorbidity *versus* comorbidity, hyper- *versus* iso- *versus* hypo-comorbidity

Some authors define comorbidity as the simultaneous presence of two or more diseases which are associated with each other through pathogenic mechanisms and more frequently than it could be expected by chance in contrast to multimorbidity which refers to the simultaneous presence of two or more diseases which appear randomly, not having any connection to each other through

pathogenic mechanisms [10]. This approach might appear attractive but difficult to apply in practice since the pathogenic mechanisms of diseases are not so well established.

There is also an interesting suggestion to the term comorbidity for the co-occurrence of two or more diseases but by explicating the term “hypercomorbidity” for the association of two or more diseases that appear at a higher rate than expected by chance, the term “hypocomorbidity” for diseases that appear together at a lower rate than expected and, finally, the term “isocomorbidity” for diseases that appear at a similar rate than expected [11].

This distinction might be of importance in the context of spondyloarthritis for at least 3 reasons:

- For the researcher in order to make specific efforts to understand the underlying pathological pathway existing between spondyloarthritis and a specific comorbidity (e.g. osteoporosis)
- For the rheumatological team in order to clearly list the comorbidities to be specifically checked in patients with spondyloarthritis
- For the patients suffering from spondyloarthritis in order to prevent any fear, anxiety when discussing the different comorbidities to be evaluated via either an initiative led by the rheumatological team or via a self-administered questionnaire.

#### **IV. Impact of comorbidities on the rheumatic disease**

The co-existence of different disorders in spondyloarthritis might have several impacts at different levels:

- The increased risk of mortality observed in spondyloarthritis is largely explained by the high prevalence of comorbidities and in particular cardiovascular diseases
- The presence of comorbidities might influence the outcome measures evaluating the activity and/or the severity of spondyloarthritis. For example, a concomitant fibromyalgia or depression might hugely influence the value of the BASDAI or ASDAS.
- Spondyloarthritis patients with more comorbidities experience greater functional impairment
- The presence of comorbidities might influence the treatment decision. For example, TNF-blockers are not recommended in case of a recent (<5 years) history of cancer
- The presence of comorbidity might influence the tolerability of the anti-rheumatic treatment (e.g. bronchiectasis and the risk of infection due to glucocorticosteroids and/or biologics).

In the field of spondyloarthritis, evidence is increasing on the prevalence of several comorbid conditions [12] and their added burden on excess disease activity, functional disability, poor work-related outcomes [13] and mortality [14].

#### **V. Main comorbidities in Spondyloarthritis**

Four key comorbidity areas have been observed in SpA patients, mainly in the axial forms of the disease but also, for some, in the peripheral forms of SpA (e.g. peripheral SpA or psoriatic arthritis

(PsA)): osteoporosis, cancer, infections and fibromyalgia. In this review, cardiovascular disease will not be included, since another extensive review included in this Supplement will focus specifically in this topic.

#### **a. Osteoporosis**

Bone formation, the cornerstone lesion in axSpA, leads to ankylosis and permanent disability of patients; paradoxically, osteoporosis or low bone density has been found to be the most prevalent comorbidity in these patients. [12] Osteoporosis in other rheumatic inflammatory diseases (i.e. RA) has been largely documented, both related to the phenotype of patients (post-menopausal women), and treatment (e.g. glucocorticoids, very frequently used in RA) but also related to inflammation. [2,15,16] Osteoporosis in SpA patients can be hardly explained by the phenotypic characteristics such as age and gender, or systemic treatments, since usually the disease occurs in young males[17] and glucocorticoids are barely used, particularly in axial forms, unless they present with concomitant IBD. [18]

Osteoporosis in axSpA can be related to ankylosis and immobilization: indeed, prevalence of osteoporosis in radiographic-axSpA (r-axSpA) patients has been reported to range between 19%-50% [19,20] and disease duration and ankylosis of the spine (e.g. measured by the modified Stokes Ankylosing Spondylitis Spine Score, mSASSS) have been classically found to be predisposing factors[20]

However, osteoporosis has also been reported in early forms, with prevalence as high as 13.0% ; in these early forms, factors associated with osteoporosis were mainly inflammation, systemic (e.g. increased CRP) or local, defined by bone marrow oedema (inflammatory lesions) on MRI. [21,22]

The prevalence of vertebral fractures (VFs) in SpA patients is controversial: it has been classically reported a prevalence of VF as high as 30-40% in patients with axSpA [23] with a greater risk of VFs (ranging from three to seven-fold) when compared to the general population. [24,25] It is worth noticing however that definition of VFs varies greatly across studies. Semi-automated methods of morphometry are often used to assess VFs in large studies, and these methods might also capture these vertebral deformities, overestimating the prevalence of osteoporotic VFs in this population, since not all vertebral deformities are VFs. [26,27] A very recently analysis of the early axSpA DESIR cohort revealed (based on expert assessment and no semi-automated method) a very low incidence of VF over 5 years of follow-up, i.e. a 5-year incidence of VFs of 1.6%.[28]

Spinal fractures should be distinguished from VFs, since they are not related to osteoporosis or low bone mineral density (BMD) and are the consequence of trauma in patients with an ankylosed spine. This event is a major complication in SpA, but is not considered a comorbidity, and thus its prevalence and mechanisms will not be detailed in this review.

Regarding the impact of treatment of axSpA on osteoporosis and vertebral fractures, anti-inflammatory drugs are expected, through both the increased mobility related to pain relief and the increased activity, to have an effect on BMD in axSpA patients. Indeed this protective effect for BMD has been reported in a prospective study of early axSpA [29] ; regarding the potential protective effect of NSAIDs on VF, data are conflicting. [30,31]

The positive effect of TNF inhibitors (TNFi) on BMD in SpA patients has been reported in several prospective studies both in early and long-standing forms.[29,32] No clinical data is available yet regarding the potential positive effects on bone of IL-17 blockade with IL-17 inhibitors used in SpA treatment, but animal models seem to confirm their protective effect. [33]

Although no specific guidelines for the management of osteoporosis in SpA exist, some national scientific societies have proposed to perform a BMD evaluation at least once in the course of the disease in patients with SpA. [12] However, in patients with severe osteoporosis, prevalent fractures or several risk factors, available guidelines for osteoporosis management (e.g. male osteoporosis) should be used.[15]

## **b. Cancer**

While an increased risk of malignancy (i.e. lymphoma) has been reported in patients with RA[34], no increased risk of cancer has been reported in patients with SpA [35,36]. Several registers have consistently reported reassuring data: Swedish registers reported a standardized incidence ratio (SIR) of malignancy of 1.05 (95% CI 0.94 to 1.17), for the 1965-1995 period in patients with axial SpA [37]; a recent collaborative analysis of two Scandinavian registers confirmed this findings for the 2001-2011 period, with a RR for malignancy of 1.1 (1.0 to 1.2) in SpA patients compared to the general population, and very similar results for the r-axSpA and PsA forms (RR = 1.1 (95% CI 1.0 to 1.3) and RR=1.0 (0.9 to 1.1), respectively).[38] A Canadian prospective cohort of PsA also confirmed these findings, reporting a non-significant malignancy SIR of 0.98 (95% CI 0.77 to 1.24)[39]

The risk of developing a colorectal cancer (CRC) is increased in patients with IBD, which often coexists with SpA: this risk is estimated to be two-fold increased in this population, particularly in males (RR =1.6, 95% CI, 1.2 to 2.2 and RR= 1.9, 95% CI =1.5-2.4 for males and females, respectively). [40] However, prospective observational data from SpA registers and cohorts have not reported an increased risk of CRC: indeed, in the Swedish register, no increased risk for colon cancer was observed (SIR 0.95, 95% CI 0.58 to 1.47) and the risk of rectal cancer was found to be significantly less frequent (SIR=0.41, 95% CI 0.15 to 0.89).[41] This latter finding for rectal cancer has not been confirmed in other registers, but no increased risk has been reported either. [39]

Screening recommendations for the most common type of cancer are available for the general population and some others are specific depending on the treatment (e.g. Dermatologist consult in patients receiving TNFi treatment), but their implementation has been reported to be far from optimal: a cross sectional international study[12] revealed that only 32.7% (CRC) to 44.0% (breast cancer) of SpA patients were in agreement with general population recommendations for cancer prevention; and that only 10.7% of patients with TNFi treatment were optimally screened for skin cancer.

Regarding the impact of SpA treatment on cancer, historically, an increase in malignancy risk and mortality was reported in patients with SpA (particularly in axial forms) due to the historic treatment for SpA, which was based on radiotherapy of the spine: an increased mortality risk up to 28% was reported in these patients, compared to the general population, and a particular three-fold increase in mortality due to leukaemia in these patients. [42] Fortunately, with the arrival of novel and effective therapeutic options, radiotherapy courses have been abandoned for the treatment of SpA.

Oral 8-methoxypsoralen-UV-A (PUVA) and narrowband UV-B (NB-UVB) are phototherapies used in skin psoriasis. An increased risk of skin cancer (squamous cell carcinoma (SCC) mainly, among the non-melanoma cancers) has been reported in patients undergoing PUVA therapy, with a dose-ranging effect: the risk of SCC was significantly higher for patients exposed to >200 PUVA, compared to low-dose exposed patients (<100 sessions), while results for melanoma were conflicting, with most of the US studies suggesting an increased risk of melanoma in exposed patients, while European studies did not find any association. [43]

The potential beneficial effect of NSAIDs in recurrent CRC has been reported in several systematic reviews. In particular COX-2 inhibitors (celecoxib and rofecoxib) were reported to be highly effective in reducing the incidence of recurrent colorectal adenomas: [44,45] in a recent meta-analysis, the incidence of recurrent adenomas and advanced adenomas over a 3-year follow-up was significantly reduced (pooled RR =0.66 , 95% CI 0.59 to 0.72 for celecoxib and RR= 0.76 [0.69 to 0.83] for rofecoxib). However, the increased risk for gastro-intestinal events and the relative contra-indication in patients with IBD (the main risk population) represents a crucial drawback to the use of these drugs as prevention therapy in populations at risk. In any case, no data suggest that NSAIDs may increase the risk of CRC.

Compared to the literature on cancer in RA patients, treated with TNFi, data on cancer risk in SpA patients exposed to TNFi is limited, and most of the available studies only include RCTs (and thus, with rather short follow-up)[46-48]; nevertheless none of them reported an increased risk for malignancy in this population. A recent collaborative analysis including 8703 patients with SpA initiating a first TNFi between 2001 and 2011 reported no increased cancer risk in TNFi exposed SpA patients (compared to TNFi-naïve SpA patients, RR=0.8 (95% CI 0.7 to 1.0)). Similar results were found for r-axSpA and PsA, when analysed separately (RR= 0.8 (95% CI 0.6 to 1.1) and RR= 0.9 (95% CI 0.7 to 1.1), for r-axSpA and PsA, respectively).[38] Data on the increased risk of a second neoplasm in patients with history of cancer and treated with TNFi is controversial with some studies suggesting a greater risk in TNFi SpA treated patients compared to the general population[49], while larger studies focusing in RA have not found any significant increased risk. [50,51] Due to the small number of studies evaluating this subgroup of patients with previous history of cancer, these treatments should be used with caution, and always in agreement with the oncological team.

### **c. Infection**

In contrast to RA, data on infectious risk in SpA patients are poor and derive mainly from randomized controlled trials and are therefore issued from selected populations and with a short-follow-up. A 2008 systematic review and meta-analysis including 14 RCTs reported only two serious infections in 2202 r-axSpA patients not exposed to immunosuppressive drugs (0.09%, i.e., 0.4 per 100 person years [pyrs]).[52] Conversely, data from observational trials yield slightly higher severe infection rates: a recently published analysis of 440 SpA patients followed for a total of 1712 patient-years (pys) revealed 23 serious infections, i.e., a serious infection rate of 1.3 (95% CI 0.9 to 2.0)/100 pys. [53] Interestingly, in this study, the use of DMARDs, was associated with infection.

Indeed, in most studies, infection rates are higher in the group of patients exposed to TNFi compared to placebo or any other csDMARD: in a systematic review [52], 14 serious infections were found in the TNFi exposed group (14/996, 0.7% 95% CI 0.3% to 1.4%), i.e., 1.9/100 pyrs), but the meta-analysis of the RCTs showed that the increase in serious infections with TNF blockers compared with placebo



was not significant: risk difference=0.4% (-8% to 1.6%). However, another meta-analysis of etanercept trials including 1323 subjects (>1500 subject-years of treatment)[48] reported a serious infections rate of 2.19 (95% CI 0.22 to 107.79) for the TNFi exposed compared to sulfasalazine-exposed or placebo.

Based on this increased risk, specific recommendations for vaccination have been published for patients exposed to biologics and regardless of age, seasonal flu and pneumococcal vaccination are strongly recommended in these patients. [54] Despite this, vaccination rates are far from optimal in this population: a cross sectional study of 1911 patients at risk among the 3989 SpA included patients, only 332 (17.3%) had received a pneumococcal vaccination within the past 5 years and 726 (38.0%) had received an influenza vaccination within the past 12 months.[12] These results suggest that there remains an unmet need for improving infection prevention in SpA, particularly in high-risk cases such as patients exposed to biologics.

#### **d. Fibromyalgia**

Fibromyalgia is a complex chronic condition of unknown aetiology being considered as a pain amplification syndrome associated with a central nervous system sensitization mechanism[55] ; Its hallmark symptoms are chronic widespread musculoskeletal pain and generalized tender points, but other symptoms can be present, such as fatigue, sleep alteration and stiffness leading to significant physical disability and reduce quality of life [56,57]. Its prevalence has been estimated around 2-7% of the general global population and predominantly in women [55]. Fibromyalgia can frequently be associated with other rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus and Sjögren Syndrome [58]. In spondyloarthritis, this association has been reported in 15-25%. [59-61]

In spondyloarthritis and in particular in axial spondyloarthritis, this association may present diagnostic and treatment dilemmas since some clinical features of spondyloarthritis (e.g. pain at entheses) can be also found in fibromyalgia patients.

Nowadays, fibromyalgia is based on the ACR criteria of fibromyalgia and the modified 2010 preliminary ACR criteria) in the absence of specific biomarkers[56,62] . However, these criteria were developed for research and classification purposes and are difficult to apply in daily practice because they are time consuming and require some training to be implemented [63]. Moreover, these criteria (i.e. ACR 1990) integrate tender points at physical exam that might reflect in patient with spondyloarthritis, enthesitis.

Therefore, there is an ongoing debate to select the best tool in order to identify fibromyalgia in clinical practice and search.

For this purpose, the self-reported Fibromyalgia Rapid Screening Tool (FiRST) was developed and has been shown to be a valid tool in axial spondyloarthritis [64]. Other possibilities exist to suspect the co-existence of fibromyalgia in spondyloarthritis such as extreme scores in Patient Reported Outcomes (for example a score of  $\geq 7$  in at least 3 questions of the BASDAI) and/or concomitant intake of antidepressants and/or myorelaxants [65].

This is of particular interest in patients presenting with axial symptoms suggestive of spondyloarthritis but without objective sign of inflammation at the MRI, Sacroiliac Joint level and/or structured damage of the sacroiliac joints at either X-Rays, MRI or CT scan.

This is important since, if the diagnosis of spondyloarthritis is made, the co-existence of fibromyalgia might be responsible of high score in BASDAI and ASDAS. This level of symptoms together with a status refractory to multiple NSAIDs might result in the initiation of biologics. [66]

Therefore, there is the current debate whether fibromyalgia is responsible of a misdiagnosis of spondyloarthritis or fibromyalgia co-exist with true spondyloarthritis but might have an impact on the treatment response [66].

## **VI. Management of comorbidities in spondyloarthritis**

### **a. Concept**

The question of the management of comorbidities in spondyloarthritis can be raised at different levels: the reporting of comorbidities (e.g. history of cancer), the screening for comorbidities (e.g. mammography for breast cancer) and/or screening for risk factors of comorbidities (e.g. vaccination status, blood pressure, lipids metabolism,...), the prevention of comorbidities (e.g. vaccination, treatment of hypertension, treatment of dyslipidemia,...), the treatment of comorbidities (e.g. treatment of a cancer, a myocardial infarction).

It is clear that the treatment of a comorbidity has to be managed by the appropriate health care provider (usually a specialist of a specific disease such as an oncologist or a cardiologist). The prevention of comorbidities has also to be managed by the appropriate health care provider. However, in this area, because of some so-called “hypercomorbidities” and in particular infections, cardiovascular disease and osteoporosis, international scientific societies have provided some specific recommendations (e.g. EULAR recommendations for vaccination [67], for screening for cardiovascular disease [68], for the use of high and low dose corticosteroids [69]). Because these specific recommendations are not well known by the general practitioner, a specific task for the rheumatologist is to liaise with the appropriate health care provider to be sure that the prevention of specific frequent comorbidities is adequately implemented.

The question of the screening for risk factors of comorbidities is even complicated by the fact that there is a gap between the ideal situation explained in the recommendations and the reality observed in daily practice. This is notably the case in terms of vaccination of patients with spondyloarthritis taking biologics [12]. This gap raises the question of the role of the rheumatological team not only by checking the vaccination status of the patients but also by performing the vaccination.

Finally, the reporting of comorbidities has to be managed by the rheumatological team in order to facilitate the choice of anti-rheumatic therapies and to appropriately evaluate the tolerability of a specific treatment.

### **b. Practical implications**

Comorbidities can be collected in 2 ways: either collecting each comorbidity separately (e.g. diabetes, heart failure,...) or summarizing the comorbidity information into a single score that provides a single score that provides a single parameter for measuring multiple comorbidities. The advantage of comorbidity indices is that by reducing all co-existing disorders into a single numerical score the evaluation of the impact of the comorbidities on the burden of the disease is facilitated. This is the reason why these indices are mainly used in clinical trials and/or epidemiological studies.

At variance, the preference is given to a program specific to each frequent comorbidity in terms of reporting, screening and treatment in daily practice. Moreover, in both conditions (e.g. comorbidity indices and programs for daily practice), self-administered questionnaire might be of interest.

#### **V.B1. Comorbidity indices**

The most frequently used indices are the Charlson comorbidity index [70] and the Elixhauser comorbidity measure [71].

- The Charlson comorbidity index has been elaborated based on the mortality rates of 607 patients. Sixteen diseases have been included in this index with different weights (see table).
- The Elixhauser's comorbidity measure is including 30 different diseases (the sixteen from the Charlson's index and fourteen additional). In their indices, there is no weighting system and the calculation of the score is only based on the number of observed medical conditions.

#### **V. B2. Comorbidity programs for daily practice**

EULAR has provided recommendations (points to consider) in order to standardize the way of collecting the information related to the reporting, screening and preventing of the most frequently observed comorbidities in chronic inflammatory rheumatic disorders.[72] Several initiatives are ongoing in order to evaluate the impact of programs led by rheumatologists or nurses.

For example, a recent clinical trial (COMEDSPA , NCT02374749) has recently been conducted in 500 spondyloarthritis patients in order to evaluate a nurse led program. As an example, the percentage of patients who have received an influenza or a pneumococcal vaccination during the 12 months follow-up of the study was 28.6% vs. 9.9% (influenza) and 40.0% vs. 21.1% (pneumococcal) in the group of patients who have visited a nurse at baseline checking for comorbidities *versus* the group of patients who have visited a nurse without specific attention to comorbidities [73].

These data are strongly in favor of a systematic periodical review of any patient with spondyloarthritis (even at disease onset) optimally performed by a nurse according to a standardized program.

#### **V. B3. Comorbidity self-administered questionnaire**

Several self-administered questionnaires have been proposed that self-administered questionnaire might be used by "themselves" (considering the collected data as real data and therefore used in clinical trials and/or observational studies) or (and probably better) these questionnaires might be of

benefit to prepare and to facilitate the work of the health care provider (e.g. the nurse or the rheumatologist) [74]

## **VII. Summary**

There is an increasing body of evidence suggesting the importance of checking for comorbidities in patients with spondyloarthritis.

The content of the list of conditions to check and the frequency of this check might be related to the clinical features of spondyloarthritis (in particular a specific more frequent attention has to be done in case of concomitant skin psoriasis).

Based on the observed data, it seems that at least osteoporosis, atherosclerosis related cardiovascular disease, fibromyalgia and depression should be considered as hypercomorbidities in spondyloarthritis. On the other hand, the current available therapies (e.g. NSAIDs, corticosteroids, biologics) might be responsible for some comorbidities (e.g. gastro-intestinal disorders, renal failure,...).

Systematic periodical review of spondyloarthritis should integrate a standardized program focused on comorbidities.

Key words: spondyloarthritis, comorbidities, systematic review

### Practice points:

- Extra-rheumatological clinical features of spondyloarthritis (e.g. uveitis, psoriasis, IBD,...) have to be distinguished from comorbidities (e.g. osteoporosis).
- The presence of skin psoriasis and/or the intake of corticosteroids increase the risk of atherosclerosis related cardiovascular diseases
- Each single spondyloarthritis patient should be systematically screened for potential concomitant fibromyalgia
- Any systematic periodical review program of spondyloarthritis should integrate a section on comorbidities

### Research agenda

- Clinical studies should further evaluate the best way to discriminate fibromyalgia from spondyloarthritis
- The risk of clinically relevant vertebral fracture in axial spondyloarthritis should be further evaluated
- A standardized program permitting to collect, detect the most frequent comorbidities and/or risk factors of comorbidities should be elaborated and implemented in daily practice.
- The frequency of a systematic assessment of comorbidities should be individualized based on the risk factors such as skin psoriasis and/or specific treatments

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**Table 1: Charlson Comorbidity Index**

| <b>Disease</b>                     | <b>Points</b>  |
|------------------------------------|--|
| <b>Myocardial Infarction</b>       | 1  |
| <b>Congestive Heart Failure</b>    | 1  |
| <b>Peripheral Vascular Disease</b> | 1  |
| <b>Cerebrovascular Disease</b>     | 1  |
| <b>Dementia</b>                    | 1  |
| <b>COPD</b>                        | 1  |
| <b>Connective Tissue Disease</b>   | 1  |
| <b>Peptic Ulcer Disease</b>        | 1  |
| <b>Diabetes Mellitus</b>           | 1 point if uncomplicated<br>2 points if end-organ damage |
| <b>Moderate to Severe CKD</b>      | 2  |
| <b>Hemiplegia</b>                  | 2  |
| <b>Leukemia</b>                    | 2  |
| <b>Malignant Lymphoma</b>          | 2  |
| <b>Solid Tumor</b>                 | 2 points<br>6 points if metastatic                       |
| <b>Liver Disease</b>               | 1point if mild<br>3 points if moderate to severe         |
| <b>AIDS</b>                        | 6 points   |

**Adapted from:** Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.*1987;40:373-83.

**Footnote:**

- *Calculation:* Add all items of the Comorbidity score: The total score is the Charlson Comorbidity Index.
- *Abbreviations:* COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease