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REVIEW ARTICLE

Role of comorbidities in spondyloarthritis including psoriatic arthritis

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Abstract

Spondyloartrhitis (SpA) are a group of diseases characterized by inflammation at articular and entheseal sites. Moreover, patients with SpA suffer from impaired articular function and reduced quality of life. Beyond the articular involvement, SpA and in particular psoriatic arthritis (PsA) are associated with extra-articular manifestations and comorbidities that might increase the burden of the disease. The aim of this article was to review the available evidences on the presence of comorbidities in SpA, including PsA, focusing the attention on the cardiovascular, metabolic aspects, as well as other comorbidities, and their possible management in an integrated manner. Comorbidities in SpA should be carefully evaluated because of their important impact.

Keywords Ankylosing spondylitis · Comorbidities · Outcome · Psoriatic arthritis · Spondyloarthritis · Treatment

Background

Spondyloarthritis (SpA) are a group of inflammatory diseases that affect axial and peripheral joints with the possible association of extra-articular manifestations (psoriasis, uveitis, inflammatory bowel diseases). Inflammation at joints and entheseal sites leads to bone and articular damage, impaired articular function, disability, and reduction in quality of life [1]. The Assessment of SpondyloArthritis International Society (ASAS) developed the classification criteria for patients with axial and peripheral SpA [2, 3]. Axial SpA is divided in two subsets: non-radiographic axial SpA (nr-axSpA) and ankylosing spondylitis (AS). Patients with nr-axSpA and those with AS have comparable, but not identical, clinical manifestations and burden of disease, with differences in the progression of radiographic new bone formation and some other clinical features [4]. The group of peripheral SpA includes diseases with a prevalent peripheral joint involvement, more often associated with peripheral enthesitis, psoriasis, and dactylitis. Psoriatic arthritis (PsA) represents the prototype of peripheral SpA, with an increasing incidence in general population [5]. With the introduction of biologic and targeted synthetic drugs, the treatment and outcome of SpA has radically changed [6–11]. Despite the available possibility to achieve disease remission, in recent years, clinical research in the field of SpA focused the attention on the possible association of these diseases with some comorbidities and, in particular, with cardiovascular and metabolic manifestations, which may affect the outcome. In fact, there are some evidences that patients with AS and PsA have an increased mortality, higher incidence of cardiovascular events, and cardiometabolic diseases in respect to general population [12]. Moreover, the concept of psoriatic disease was proposed in recent years to describe a condition that is beyond the involvement of skin and joints, encompassing some comorbidities, in particular metabolic syndrome (MetS), obesity, hypertension, and type II diabetes [13]. The complex pathogenesis of PsA is in fact characterized by the production of several pro-inflammatory cytokines with the development of not only entheseal and synovial inflammation, but also with the involvement of metabolic activities and effects on adipose tissue and lipid profile. These could lead to the presence of MetS, type II diabetes, hyperlipidemia, hypertension, and obesity with a profound impact on the management of PsA patients [13]. Beyond the well-known association with uveitis,

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psoriasis and inflammatory bowel diseases that might be considered as extra-articular manifestations of the disease, with a common immune pathogenesis, the aim of this article was to review the available evidence on the presence of comorbidities in SpA (including PsA), focusing the attention on the cardiovascular and metabolic aspects, as well as other comorbidities, and their possible management in an integrated manner.

Main text

Comorbidities in axial SpA: inflammation and cardiometabolic diseases

AS represents the prototype of axial SpA and most of available evidences for the possible presence of comorbidities have been shown in AS patients, while further studies on the non-radiographic form are needed. In the past decade, some studies showed an increased mortality and morbidity, due to cardiovascular diseases, among AS patients. In fact, it has been reported a greater mortality rate, in terms of standardized mortality ratio (SMR), ranging from 1.32 to 2.62, compared to the general population, with cardiovascular disease as a leading cause in most of the studies [14]. This could be related not only to chronic inflammation but even to treatment and mainly to the use of non-steroidal anti-inflammatory drugs (NSAIDs), which are known to increase cardiovascular risk. However, Backland et al. demonstrated that mortality ratio was related to infrequent use of NSAIDs rather than a continuous one [14]. Therefore, the increased cardiovascular risk appears to be mainly due to atherosclerotic-related diseases (such as myocardial and cerebral infarction), and, only in a low percentage of patients, to the so-called AS-specific cardiac manifestations. Different studies have assessed preclinical atherosclerosis in AS [15, 16], and most of them revealed morphological and/or functional disturbances in vessel morphology and function (in particular an increased intima-media thickness and/or impaired flow mediated dilatation), demonstrating correlations with the presence/duration of AS, various measures of disease activity, function or metrology, and a range of laboratory parameters. The presence of inflammation, and in particular, the expression of pro-inflammatory cytokines, plays a crucial role in all phases of atherosclerotic process that could be enhanced in AS patients, promoting not only the development of arterial plaque but also its rupture. Traditional cardiovascular risk factors, as well as the underlying chronic inflammatory process, are important for the increased atherosclerotic risk in AS. However, in terms of clinical assessment, the most prevalent comorbidities in patients with AS were hypertension (16.4%), peptic ulcers (13.9%), and headache (10.2%) [17, 18]. These could be obviously attributed to treatment, while fewer studies assessed the presence of type II diabetes and other traditional cardiovascular risk such as hyperlipidemia or obesity in AS patients. In particular, the prevalence of type II diabetes seems to be higher than in general population: in a study on Chinese AS patients, the authors showed that the incidence of type II diabetes was higher in the AS cohort, with an adjusted hazard ratio of 1.16 (95% CI = 1.05–1.29). Furthermore, authors reported that the adjusted ratio of the disease was higher in young AS patients (≤ 50 years of age) than older ones [19]. On the other hand, in AS patients, there was a significant decrease in triglycerides, total cholesterol, and high-density lipoprotein cholesterol, mainly related to disease activity [20]. Data on the presence of obesity and body composition in patients with AS are sparse, controversial, and involve few participants. Lower fat mass assessed by bioelectrical impedance was described in AS patients; however, other studies did not find a difference in the fat mass component between AS and controls [21].

In conclusion, the chronic inflammation in AS is known to contribute as an independent risk factor, but the presence of some comorbidities should be taken into account. The assessment of the potential role of new and old treatment in reducing this persistent inflammatory status is one of the unmet need in AS, and further studies are needed in this challenging topic.

Comorbidities in axial SpA: osteoporosis

Osteoporosis of the spine frequently occurs in AS and can lead to vertebral fractures at a young age. Because of the stiffness of the ankylosed spine, minor trauma can also cause vertebral fractures and should be considered if the pattern of pain and mobility changes after minor or major trauma. The use of computed tomography scan can help to detect these fractures, which may be missed with conventional radiography. Decreased bone mineral density (BMD) is a common feature in AS, with prevalence ranging from 19 to 62%. Many studies have shown decreased BMD in AS with long disease duration and, from a pathogenetic point of view, it could be related not only with reduced mobility, but even with the presence of systemic inflammation [22]. In a more recent work, the prevalence of osteoporosis and fractures in a cohort of early axial SpA was found to be quite high, with 15% of patients showing at least one vertebral fracture. Furthermore, alcohol intake, steroid use, and low levels of 25-OH-vitamin D were present in these patients and should be carefully evaluated as potential risk factors. Vertebral fractures are often asymptomatic and could be present even in patients with early disease [23, 24]. In other studies, male sex, disease duration, new bone formation at x-ray of the spine, and low BMD at the hip and distal forearm were associated with the risk of vertebral fractures in patients with AS. Despite the higher prevalence of vertebral fractures, the risk of hip fractures in AS was not statistically significant [OR (95% CI) 1.17 (0.71–1.92)] as reported in a

recent paper [25]. However, current evidence on the risk of hip fractures in patients with AS are inconsistent. These aspects are of crucial importance in the management of axial SpA patients since the presence of fracture may have an important impact on the quality of life and function.

Comorbidities in axial SpA: fibromyalgia

Fibromyalgia (FM) is one of the most common causes of generalized pain and can coexist with other diseases. FM-like symptoms are also commonly associated with rheumatic diseases. It might also be a confounding factor in patients with low back pain, especially in women. Different studies assessed the presence of concomitant FM in patients with a diagnosis of AS or axial SpA and, overall, the presence of FM has been reported in 4–25% of patients with axial SpA, mainly in women. Furthermore, it has been showed that measure of disease activity, such as pain and patient global assessment, are significantly higher in patients with concomitant FM and do not improve as much with treatment. This should be taken into account when assessing a patient with axial SpA and concomitant FM [26, 27]. Interestingly, in the SpA subgroups, FM was more common in the non-radiographic form than in AS patients (23.9 and 6.4%, by 1990 American College of Rheumatology (ACR) criteria; 37.3 and 7.2% if classified by expert opinion), raising questions about the specificity of the ASAS criteria [28]. However, more recent data suggest that FM patients only rarely fulfill classification criteria for axial SpA and the presence of FM was more frequent in patients with AS [29].

Comorbidities in axial SpA: anxiety and depression

Increasing amounts of data suggest that inflammatory responses and, more in general, inflammation linked to chronic inflammatory conditions, have an important role in the pathophysiology of depression and in the determination of depressive symptoms. In fact, high levels of C reactive protein (CRP) or other inflammatory cytokines and pathways were linked to the presence of depression in SpA [30].

In axial SpA, the anxiety and depression have been frequently reported and these disorders, and their treatment, affect significantly the quality of life. On the other hand, the presence of functional impairment, reduced motility, and reduced quality of life has an important role on the development of depression. The prevalence of current major depressive disorder and anxiety disorder were 10.6 and 15.6%, respectively, in a recent study on Chinese patients using specific instruments [31]. Furthermore, the rate of doctor-diagnosed depression is increased about 80% in female and 50% in male AS patients evaluated in a large population-based cohort study performed in Sweden [32]. However, other reports showed an even higher prevalence of anxiety and depression [33]. Interestingly, there are some reports that showed the effectiveness of biologic drugs in the improvement of mood in AS patients, probably acting by suppress inflammation and pain and by improving quality of life and function [33].

Comorbidities in axial SpA: malignancy

Cancer is a multifactorial disease; however, the role of an imbalance of immune system in the development and growth of tumor mass is well recognized. Several chronic inflammatory conditions and autoimmune diseases have been found at risk of progression to cancer; furthermore, there is a proved link between chronic tissue inflammation and progression to dysplasia [34]. There are few studies that assessed the presence and prevalence of cancer in axial SpA and the possible risk to develop malignancy. It seems that chronic inflammation could increase the risk, as demonstrated in a large population-based study performed in Taiwan, in which the overall risk of cancer was significantly higher in the patients with AS than in the patients without AS (incidence rate of 1.15, 95% CI 1.03–1.27). In this study, bone cancer, colon cancer, prostate cancer or a hematological malignancy were found in a higher rate of AS patients in respect to those without AS. Interestingly, female patients with AS was found to be at higher risk of developing colon cancer [35]. Recently, a meta-analysis of 23 studies showed that AS is associated with a 14% increase in the overall risk for malignancy. On subgroup analysis, evidence from high-quality cohort studies indicated that AS patients from Asia are at highest risk for malignancy overall [36]. The introduction of biologic treatment for axial SpA raised the question if the risk of cancer might be increased by using immune-modulators agents; however, evidence coming from trials and meta-analysis lacks to show a significant association of anti-TNF and anti-IL-17 agents with malignancy in patients with axial SpA [37, 38] but further studies with a long follow-up are needed.

Comorbidities in psoriatic arthritis: inflammation and cardiometabolic disease

PsA is associated with increased mortality compared with general population. Increased cardiovascular mortality is particularly prominent in observational cohort studies, and it seems to be associated with disease severity. A higher inflammatory burden, proved by a high erythrosedimentation rate and/or the presence of more severe radiological damage, was in fact associated with increased all-cause mortality [39]. PsA also showed to be associated with a higher prevalence of classical risk factors for cardiovascular disease, even when compared to patients with rheumatoid arthritis (RA) and psoriasis (PsO), as reported in a large study recently published: the prevalence for RA, PsO, and PsA cohorts for hypertension was 18.6%, 16.6%, and 19.9%, respectively; for diabetes

mellitus 6.2%, 6.3%, and 7.8%; for hyperlipidemia 9.9%, 10.4%, and 11.6%; and for obesity 4.4%, 3.8%, and 6.0%. These are the main features present in patients with MetS, which has been observed frequently in PsA [40].

In the development of MetS, an important role is played by the chronic low-grade inflammatory state. PsA is a chronic inflammatory condition, with the presence of inflammation in different structures and with the presence of inflammatory mediators that was responsible for the interaction with adipose tissue.

A central role in the pathogenesis of MetS is in fact performed by white adipose tissue (WAT), which represents not only a tissue devoted to energy storage, but has also the essential role of endocrine organ able to secrete numerous pro- and anti-inflammatory molecules, regulating both inflammation and metabolic state [41]. An increase in visceral fat deposits could bring to the development of high values of waist circumference, visceral obesity, and insulin resistance. Excess presence of WAT may lead to a persistent production of some important cytokines and adipocytokines such as TNF, IL-6, IL-1β, leptin, and adiponectin. These molecules may contribute to the development of a pro-inflammatory state and may promote a subclinical inflammation at the level of vessel intima, which results in enhanced atherosclerotic processes [42]. The role of Th17-derived cytokines in the pathogenesis of obesity and related inflammatory diseases is also important. In fact, obesity has been shown to promote expansion of IL-17 producing T cells in adipose tissue (especially visceral fat) and peripheral tissues [43], linking the presence of obesity with a key cytokine in the pathogenesis of PsA. Moreover, a recent Italian study evaluated the decrease of serum levels of adipokines in a group of 28 PsA patients after treatment with Secukinumab (an anti-IL-17A monoclonal antibody): resistin and chemerin level resulted significantly decrease (interestingly only in man) after 6 months of this treatment. Further studies with greater numbers of patients are needed to determine whether these preliminary results have clinical relevance [44]. The evidence of an increased prevalence of MetS in PsA was investigated in different studies. Mok et al. reported a higher prevalence of MetS in PsA (38%) than in RA (20%) and in AS (11%) [45]. Eder et al. evaluated the prevalence of MetS in PsA patients compared to those with psoriasis without arthritis, observing a higher prevalence of MetS in the first group but not statistically significant [46]. In addition, in another study, a higher prevalence of MetS in PsA patients was also reported in comparison to patients with non- inflammatory articular conditions (osteoarthritis, fibromyalgia, regional musculoskeletal pain, and osteoporosis) (44 vs 29%, $p = 0.009$). Among the components of MetS, increased waist circumference and hypertension were significantly more common among PsA patients [47]. Furthermore, type II diabetes, which in other inflammatory autoimmune diseases (RA, Systemic Lupus Erythematosus etc) could be related to steroid treatment, seems to be an important health problem in PsA, not always correlated to treatment strategies. In a large population-based study, in fact, PsA patients were found to be at risk for the development of diabetes compared with the general population. In this report, 1065 patients were included in the analysis, and, of this, 73 patients developed diabetes during follow-up. Based on multivariate analyses, tender joint count (HR 1.53) and ESR predicted the development of diabetes. The evidences coming from these and other studies showed that the prevalence of diabetes seems to be higher in PsA patients in respect to general population. Furthermore, the disease activity plays an important role because patients with more inflammatory burden are at higher risk of developing diabetes [48].

The role of immune-modulating treatments on the comorbidities and on the potential cardiovascular risk in PsA patients is also confirmed in some studies. PsA patients using DMARDs have been reported to have a lower cardiovascular risk than those not using them. Furthermore, TNF inhibitors may be associated with reduced risk of adverse cardiovascular events in preliminary epidemiologic studies; however, large randomized controlled trials and epidemiologic studies with well-characterized populations will be necessary to elucidate their exact effects. The short-term data regarding the safety of IL-12/23 inhibitors showed that, to date, there are no increased cardiovascular events compared to the general population [49].

Comorbidities in psoriatic arthritis: osteoporosis

The magnitude of the problem of osteoporosis in PsA seems to be mild: in a study performed on Spanish PsA patients, the authors found no differences in BMD status between the patients and the general population, neither in the whole series nor in the disease subgroups. Frequency of osteoporosis was found to be of 16% and obviously higher in postmenopausal women (28%) than in men (9%) or premenopausal women (4%). Frequency of clinical fractures was 13%, and it accounted mainly in postmenopausal women [50]. These data were confirmed in a recent study in which BMD was found to be higher in patients with PsA compared with controls at lumbar spine (1.213 vs 1.147 g/cm2, $p = 0.003$) and femoral neck (0.960 vs 0.926 g/cm2, $p = 0.02$), but not at total hip (1.013 vs 0.982 g/cm2, $p = 0.11$) [51].

Comorbidities in psoriatic arthritis: fibromyalgia

FM is often diagnosed in patients with PsA and its prevalence ranging from 9 to 17% of patients [52]. Furthermore, FM could be confused with the presence of polyenthesitis in patients with PsA, because the involvement of different entheseal sites may present as widespread pain, indistinguishable from FM, or may emerge as the dominant feature after successful biological therapy. A recent study showed the presence of higher mean tender points and enthesitis scores, as

well as more somatic symptoms and less response to NSAIDs, in patients with FM in respect to PsA. In this study, Marchesoni and colleagues showed that the presence of ≥ 6 FM-associated symptoms and ≥ 8 tender points was the best predictor of FM [53] and could help to differentiate symptoms derived from the two conditions. The shared clinical features of PsA and FM that had the greatest discriminating power for FM were the number of FM-associated symptoms and tender point count [54]. Moreover, the assessment of FM or widespread pain in PsA patients is obviously of great importance because FM is able to influence disease activity measurements in PsA. Its influence should be taken into consideration in the treatment algorithm to avoid unnecessary upgrading of treatment [55].

Comorbidities in psoriatic arthritis: anxiety and depression

Anxiety and depression are common clinical features in PsA. The presence of these conditions had a profound impact on quality of life of PsA patients. Furthermore, the impact of psoriasis is more than cosmetic or pain centered, with suicidal ideation being reported in approximately 10% of patients aged 18–34 years. In a recent review, it was showed that patients with psoriasis had an increased risk of suicide attempts and suicide ideation, especially in those with severe skin involvement. Furthermore, studies suggested that patients with PsA are at particular risk of psychiatric comorbidities. Patients with PsA also commonly suffer from sleep disorders, fatigue, and low-level stress, which have a considerable impact on quality of life. In an individual with pain, such as that experienced in PsA, this condition can contribute to physical and emotional suffering through inactivity/deconditioning and social isolation. Also, patients with PsA have a high risk for depression, which appears to be greater than for patients with psoriasis.

The prevalence of both anxiety and depression was higher in patients with PsA (36.6 and 22.2%, respectively) compared to those with only PsO (24.4 and 9.6%). The presence of depression and/or anxiety was associated with difficulties in finding and keeping a job, female sex, and higher actively inflamed joint count as well as fatigue and pain. Moreover, depression or anxiety has an impact on disability. In the multivariate reduced model, employment was protective for depression (OR 0.36), while the severity of fatigue was associated with an increased risk of depression (OR 1.5). [56–58]. There are rising evidences that depression may be linked with systemic inflammation and, in particular, with the presence of IL-6 that could drive a depressive effect on mood. Levels of CRP and TNF are also elevated in the blood of individuals with depression. Additionally, various anti-cytokine therapies

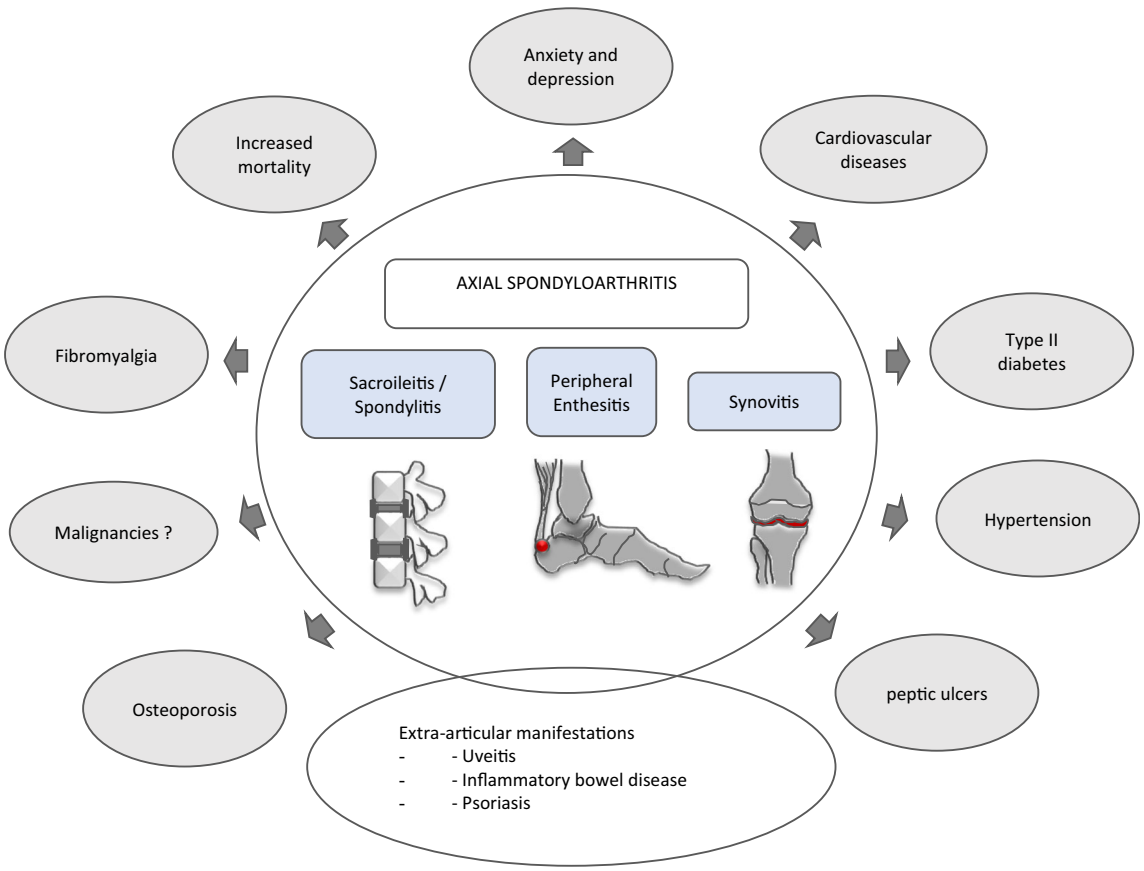

Fig. 1 Axial spondyloarthritis associated manifestations

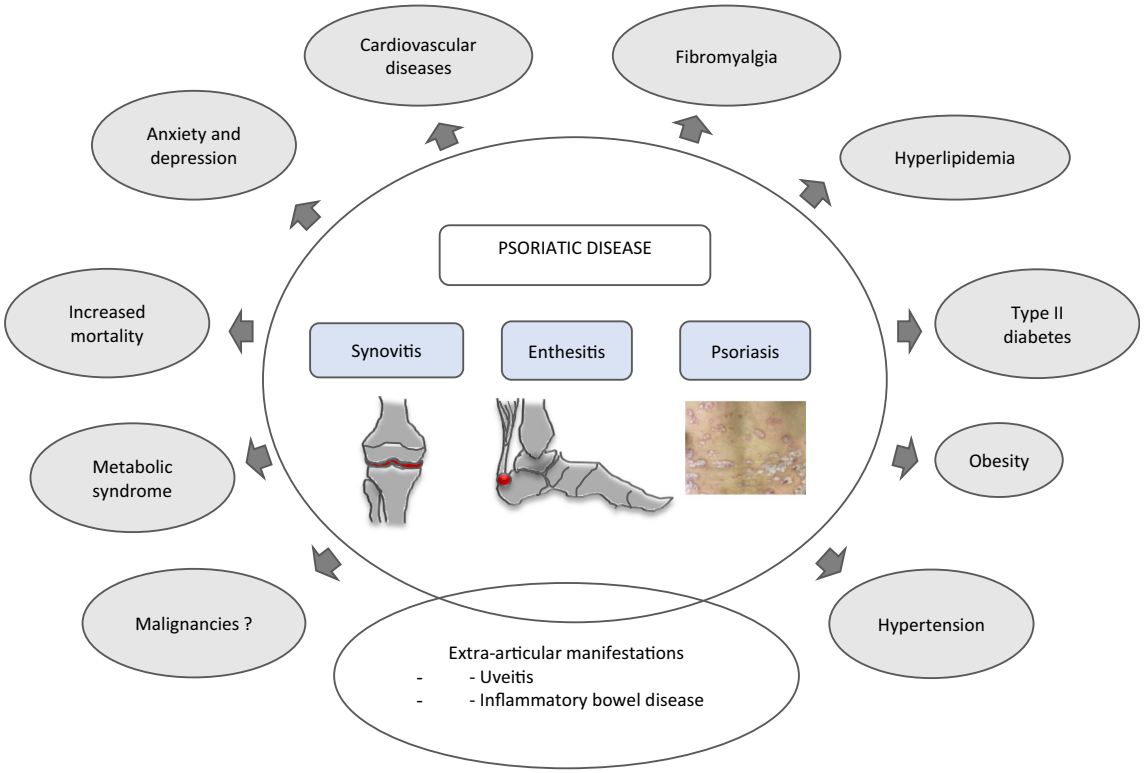

Fig. 2 Psoriatic disease associated manifestations

have been reported to improve depression symptoms in individuals with inflammatory conditions [58].

Comorbidities in psoriatic arthritis: malignancy

Some studies showed that patients with psoriasis have an increased risk of non-melanoma skin cancers and T cell lymphomas [59, 60]. The risk of malignancy in the related PsA is understudied, and knowledge of this risk is important because malignancy is a prominent comorbidity and cause of death in PsA.

A recent retrospective study performed in the Olmested County showed that cumulative incidence of malignancy at 10 years was 12.3% (±2.5%) in the PsA cohort (diagnosis performed between 1970 and 2008) and 8.6 (± 1.5) in the non-PsA cohort with a Hazard ratio of 1.41. In particular, breast cancer had a higher 10-year incidence, with a hazard ratio of 3.59 [61]. However, the study had some limitations and data in literature are not exhaustive, with different studies showed no increase in the risks of cancer in patients treated with anti-TNF or traditional DMARDs [37] and data from registries showed no increase in the risk of malignancies for the inhibitors of IL-12/23 [62], while further studies are needed for the more recent approved anti-IL-17 drugs and inhibitors of phosphodiesterase 4 (PDE4). However, being malignancies may manifest as a long-term sequelae and becoming detectable with long-term post-marketing surveillance, the detection of an association using post-approval available databases is an essential approach to further investigate this topic.

Conclusion

SpA and, in particular PsA, are multifaceted diseases with the involvement of different domains and potentially associated with comorbidities that have to be taken into account in the management of patients (see Figs. 1 and 2).

A management strategy has to be performed when these patients are evaluated, in a way to assess all domains of the disease and identifying the treatment strategy, sometimes as target to treat more than treat-to target [63]. Indeed, comorbidities are some of the potential targets to be assessed and treated.

Compliance with ethical standards

Disclosures None.

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