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Review

Identifying and Diagnosing Inflammatory Arthritis: A Narrative Literature Review of Sex-Related Differences

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Abstract

Living with inflammatory arthritis can have a significant impact; early identification, diagnosis and treatment has been shown to improve outcomes. The clinician working in settings where people with undiagnosed inflammatory arthritis may present for assessment has a crucial role in early identification and onwards referral. Inflammatory arthritis varies in its presentation with respect to gender. Rheumatoid arthritis tends to affect females more than males; historically, Axial Spondyloarthropathy was felt to predominately affect males but the distribution is now known to be equal between men and women. Psoriatic arthritis also affects males and females without obvious sex prevalence. Objectives: To investigate, through a narrative literature review, the early clinical manifestations of inflammatory arthritis, focusing on sex differences and key signs which primary care clinicians should recognise. Methods: A narrative literature review was undertaken with regards to presentation of three commonly seen inflammatory arthritis conditions: Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis. Studies describing differences in presentation of these conditions between the sexes were selected for this descriptive analysis. Results: Overall, when compared to males, females endure a longer time to diagnosis, and experience increased disease activity, elevated levels of pain and poorer response to medication. Conclusions: Understanding the difference in presentation of inflammatory arthritis between sexes can accelerate diagnosis and improve treatment.

Keywords: gender medicine; inflammatory arthritis; time to diagnosis; musculoskeletal

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1. Introduction

Working in the musculoskeletal (MSK) field in primary care requires a combination of diagnostic and rehabilitation skills. For this review, the aim is to consider the vital role MSK clinicians have in identification and onward referral in supporting the early identification of inflammatory arthritis, and to better support this role by considering differences between the sexes in presentations across the more commonly seen patients who present with inflammatory pathology. For the purposes of this article, with respect to gender, the terms 'male'/'male sex' and 'female'/'female sex' refer to individuals assigned male at birth and those assigned female at birth, respectively.

Too often, those living with undiagnosed inflammatory conditions experience unnecessary extended delays to both diagnosis and treatment [1]; these protracted timeframes increase the burden of the disease and can have both short- and long-term consequences [2].

It has been shown consistently that females experience longer time to diagnosis in the commonly seen inflammatory arthritis conditions. Well-informed, thorough and inquisitive Primary Care clinicians can and will lead to a reduction in potential diagnostic lag despite gender differences seen in presentation. This manuscript outlines current delay intervals before diagnosis, the variations between males and females, and the factors that underpin these discrepancies. It also highlights strategies for the MSK clinician to support appropriate screening and early diagnosis.

2. Background

Females present as the majority of cases in many autoimmune diseases [3]. This overrepresentation of females is observed in autoimmune diseases such as multiple sclerosis, thyroid pathology, rheumatological, systemic or immune diseases such as systemic lupus and Sjögren's syndrome [4]. The reason for this female bias is not entirely clear but genetic (X-linked) factors and hormonal effects are thought to be involved [5].

Assignation of male/female sex at birth (AMAB/AFAB) and its relation to health is a relatively novel field of study wherein differences between males and females with respect to their baseline health and manifestation of disease are investigated [6]. Male or female sex has been shown to directly affect the course of disease, the presentation of symptoms and the patient's response to pharmaceutical treatment; this can be as a result of hormonal, genetic, functional, social and environmental influences [7].

The influence of sex and gender in the likelihood of susceptibility to disease probably involves differences in male and female endocrinology and differences in physical characteristics beyond the reproductive system, which is rarely seen in childhood diseases due to the fact that at this stage of life, differences between male and female sex hormones are minimal [8]. An outlier to this is juvenile idiopathic arthritis (JIA)—which is rare amongst childhood disorders—due to the existence of a female predominance, suggested to be of a ratio of between three and six to one [9].

There is a burgeoning body of evidence which indicates that a significant difference in the presentation of certain rheumatological conditions exists as a result of gender [9]. This paper will review the literature regarding how gender can alter the presentation, disease course and response to treatment of certain inflammatory conditions—namely, Psoriatic Arthritis (PsA), Axial Spondyloarthritis (AxSpA) and Rheumatoid Arthritis (RA).

Working in the field of rheumatology or being able to diagnose rheumatological conditions that may present in consultations outside of a specific rheumatology clinic requires a high level of skill and expertise. The presentation of such conditions can be subtle and does not always subscribe to the exact or 'classic' signs and symptoms outlined in the literature. This is compounded by the fact that some of the standard blood tests used to assist in diagnosing rheumatological conditions are not always reliable [10] and in early presentation of rheumatological conditions, radiographs can lack sensitivity [11].

Despite an increasing body of evidence regarding sex-specific medicine, it is said to remain neglected, with findings of a disregard for information concerning gender-related biomedical aspects [12] rendering this an area where development of knowledge is required for Health Care Professionals.

The objective of this literature review (Appendix A) is to explore and outline the early clinical manifestations of inflammatory arthritis, with emphasis on how these conditions can present different clinical pictures between the sexes and also key signs which Primary Care clinicians should have the ability to recognize.

3. Review

3.1. Gender Differences in Psoriatic Arthritis

3.1.1. An Introduction to Psoriatic Arthritis

Psoriatic Arthritis is an inflammatory, immune-mediated disease associated with skin psoriasis (PsO). Its prevalence in males and females is equal. There exist diverse effects of PsA on organ systems and the peripheral and axial joints, skin, entheses and nails. Up to 30% of PsO patients develop psoriatic arthritis [12,13]. PsA has coexisting conditions such as anterior uveitis, cardiovascular disease, inflammatory disease of the bowel and, in more established cases, osteoporosis. Given the heterogeneity of its manifestation, it is appreciable that the diagnosis of PsA can be challenging.

3.1.2. Presenting Signs and Symptoms in Psoriatic Arthritis

In a study which analysed data from the Dutch Early Psoriatic Arthritis Register, 620 PsA patients homogenous for ethnicity and smoking status (307 men and 313 women) showed no differences in age of onset of PsA between genders [7]; however, females reported a significantly longer duration of symptoms prior to diagnosis of PsA (11 vs. 7.4 months). Passia et al., 2022 [7] also observed that a single joint oligoarthritis was the predominant pattern of PsA in both sexes but there existed a higher prevalence in men (45.9% in men vs. 34.2% in women, $p < 0.05$). At baseline, women were found to demonstrate more severe limitations in function and worse quality of life compared with men, based on all patient-reported outcomes: disease activity measured with Composite Psoriatic Disease Activity Index (CPDAI), GRAPPA Composite Score (GRACE), Psoriatic Arthritis Disease Activity Score (PASDAS) and Disease Activity Score for Psoriatic Arthritis (DAPSA at baseline and 1-year follow-up). The mean DAPSA was statistically significantly higher in females, as were total joint count (TJC) and swollen joint count (SJC), as well as Patient Global Assessment (PtGA). Females, compared with males, reported higher mean pain (5 (+2.78) vs. 4 (+2.60), $p = 0.003$) and worse mean PtGA (5.01 (+2.51) vs. 3.99 (+2.45), $p < 0.001$).

In a 2023 literature review, Lubrano et al. [14] investigated similarities and differences between 141 males and 131 females living with PsA; they found no significant differences between genders with respect to a variety of factors and symptoms including age, disease duration, age of onset of psoriasis, C-reactive protein (CRP) levels, dactylitis, PsA patterns of presentation, enthesitis and Physician Global Assessment of disease activity (PGA). There were also no significant differences in the current pharmacological therapy between genders, though more women had been prescribed conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and tumour necrosis factor inhibitors (TNFi) whilst male patients were more likely to have been prescribed anti-interleukin 12 and 23 (IL-12/23) inhibitors [14]. Lubrano et al., 2022 [14], found that there was a greater prevalence of multi-joint arthritis in females (25.4% in women vs. 19.6% in men) though this did not reach the level of the study's significance parameters. There was a significantly higher prevalence of enthesitis in females than males (14.3% vs. 5.9%, $p < 0.05$). These investigators state that there was anecdotal evidence of higher rates of axial skeleton involvement at initial presentation. Swollen joint count (SJC) was equal between sexes but females presented at baseline with a greater tender joint count (TJC) than males. PsO skin lesions were more common in males; however, females had a higher likelihood of PsO reported in family members and a worse disease burden if PsO was present. In females, there was a higher frequency in presentation of anxiety, fatigue and coexisting medical conditions such as chronic inflammatory diseases.

Coates et al., 2023 [15] undertook a systematic review of the literature to investigate gender-specific differences in clinical presentation, disease activity and patient-reported

outcomes (PROs) in PsA. Thirty-one publications were included. Their review found that there was greater axial joint involvement and skin disease in males. Females displayed higher rates of peripheral joint disease and higher tender joint count scores. There were found to be no differences in BMI between genders, whether mean or median average, which tended towards the overweight or obese categories. Across the patient-related outcomes, females displayed worse scores for pain and fatigue. Women also experienced a poorer response to treatment with a variety of drugs measured by outcome measures such as American College of Rheumatology (ACR) responses and disease activity.

In a retrospective cross-sectional study by Queiro et al., 2001 [16], one hundred PsA patients (63 men and 37 women) were investigated for any gender differences in PsA presentation. Twenty-three patients presented with axial involvement in isolation (with a male to female ratio of 3.6:1), 41 patients presented with an oligo-axial pattern (with a male to female ratio of 1.7:1). Thirty-six of these patients presented with a poly-axial disease (with no differences between males and females, with a male to female ratio of 1:1). The frequency of the genetic marker HLA-B27 showed correlation with isolated axial disease ($p = 0.016$). Furthermore, female gender was associated with reduced compliment titrations ($p < 0.05$), joint erosions and severe, progressive disease ($p = 0.05$), a greater number of swollen joints ($p = 0.002$), greater functional deterioration, and greater numerical scores on the health assessment questionnaire (HAQ) specifically for inflammatory spondyloarthritis, with a p value less than 0.05.

Eder et al., 2013 [17] undertook a cross-sectional analysis of 590 PsA patients (345 males and 245 females) and found that spinal involvement was more common among males (42.9% versus 31%, statistically significant at $p = 0.003$). In addition to this, males presented with an increased chance of developing rapidly progressive PSA disease with radiographic damage affecting the peripheral articulations [17]. In contrast to this, females reported reduced functional outcomes plus lower quality of life [17].

Other investigators, in a multi-centre cross-sectional study, assessed a group of 1038 PsA patients (678 females and 360 males) [18]. These researchers reported that females demonstrated higher Disease Activity Score-28 (DAS28) and Clinical Disease Activity index for Psoriatic Arthritis (cDAPSA). In this study, males were found to have a greater frequency of remission measured using Minimal Disease Activity (MDA). The incidence rates of insertional pathology, inflammatory digital swelling (dactylitis), tenosynovitis and inflammatory disease of the bowel (IBD) were comparable between genders, with the exception of axial involvement which was found to be more prevalent amongst males [18]. In addition to this, females presented with higher BMI and reported later onset of disease as well as higher scores on both the Health Assessment Questionnaire (HAQ) and Fibromyalgia Rapid Screening Tool (FIRST). Short form 36 (SF-36) scores were lower for females than for males [18].

3.1.3. Time to Diagnosis in Psoriatic Arthritis

Delayed PsA diagnosis has been shown to be associated with worse physical function; even as little as a 6-month delay from onset of symptoms to the initial consultation with a rheumatologist caused worse outcomes for patients with PsA, with more erosive disease affecting the sacro-iliac joints, peripheral joints, and lower HAQ scores [13]. A shorter time to PsA diagnosis is associated with a greater probability of achieving MDA and DAPSA remission over time, suggesting the presence of a key therapeutic phase in PsA. This is a key discovery because currently, approximately 50% of patients presenting with PsA have a diagnostic delay of more than one year. Female patients and those presenting with enthesopathy, longstanding back pain or normal C-reactive protein (CRP) levels endured an even longer delay to diagnosis [19].

3.1.4. Blood Tests in Psoriatic Arthritis Between Genders

Whilst the HLA-B27 gene is said to be more prevalent in northern latitudes and is said to be present in 6% of healthy individuals in the USA [20], the presence of this allele is not imperative for the development of spondyloarthropathy, but it is highly associated with the development of the disease. PsA patients expressing this allele tend to present with a reduced interval between the onset of skin disease and disease affecting the joints; they are also more prone to developing uveitis, enthesitis and dactylitis, and are more likely to develop both axial and peripheral joint disease [16].

A study by Gladman et al., 1992 [21], which was thought to be the first of its kind, could not discern any sex-specific difference in terms of HLA-B27 in a sample of 194 patients with psoriatic arthritis (82 females, 112 males). By contrast, a study by Queiro et al., 2001 [16] elucidated that the frequency of HLA-B27 was higher among male patients with psoriatic spondyloarthritis compared to their female counterparts (48% versus 11%, statistically significant $p = 0.002$). These differences are said to be possibly explicable by taking into account the heterogeneity of the countries involved in this investigation and potential influential ethnic factors, differing samples, and inconsistencies in assay collection and analysis [12]. However, this is in contrast to Queiro et al., 2016 [16] who found that the frequency of HLA-B27 was greater among male patients with psoriatic arthritis, compared to females with disease onset <40 years old (42% vs. 30%—statistically significant at $p < 0.002$). A declining effect of HLA B27 was seen with advancing age at disease onset.

The correlation of erythrocyte sedimentation rate (ESR) and/or CRP to disease activity is frequently disappointing in PsA, since they are both elevated in only half of the patients with active PsA [22]. The absence of a reliable CRP signal in PsO and PsA is considered to be due to the fact that interleukin (IL)-6, the progenitor of CRP, has no influence on these diseases [23]. These researchers investigated the serum of 210 subjects (105 healthy controls and 105 patients with psoriatic disease) with either homogenous skin (S), enthesis (E) or joint (A) involvement and a variety of combinations thereof (EA, SA, SE, SEA), testing whether TNFi or IL-17 inhibitor therapy normalised these markers. CRP was found to be 'not elevated' or was 'rarely elevated' in the subgroups (S 0%, E 0%, A 20%, SE 7%, SA 33%, EA 27%, SEA 33%) despite the presence of active psoriatic disease [23].

3.2. Gender Differences in Rheumatoid Arthritis

3.2.1. An Introduction to Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory, symmetric small joint arthropathy mainly affecting the hands, wrists, and feet and is associated with progressive joint damage and extra-articular manifestations [20]. Women, smokers, and those with a family history of the disease are more often affected [24].

Whilst joint disease is a classic characteristic of RA, there is also a significant morbidity as a consequence of extra-articular comorbidities associated with systemic inflammation [1]. RA can be characterised immunologically by the presence of autoantibodies against immunoglobulin G (IgG), known as rheumatoid factor; also, the inflammatory process of the amino acid arginine being converted to citrulline (citrullination) creates anti-citrullinated or anti-CCP protein antibodies which can be measured to assist in RA diagnosis [9]. The female to male ratio of RA prevalence is said to be 3:1 and has been said to be on the increase in females in recent decades [25].

Some cytokines play a role in promoting inflammation and inducing cartilage degradation in RA. Conversely, other cytokines mediate an anti-inflammatory role [26]. Yu et al., 2020 [2] undertook genetic studies to assess for gender differences in presentations and manifestations of RA. The expression of interleukin-4 (IL-4) was found to be lower in an RA group (based on the ACR 1987 revised classification criteria) compared to a non-RA group

and the expression of IL-4 was lower in a group of female RA patients when compared to IL-4 levels in male RA patients. These researchers felt that this confirmed that there was a significant gender difference in the expression of IL-4 only in people living with RA and that the imbalance between pro-inflammatory and anti-inflammatory cytokines is thought to be the main cause of chronic joint damage. IL-4 is considered to be an anti-inflammatory, chondroprotective cytokine and its absence, or paucity, is postulated to lead to the development of RA through the pathways of cytokine receptor interaction [27].

3.2.2. Presenting Signs and Symptoms in Rheumatoid Arthritis

A large cross-sectional, international cohort of RA patients demonstrated higher levels of disease activity and worse function in female patients with RA compared with males as measured by the disease activity score (DAS28) [28]. It is notable, in this study, that inclusion criteria required diagnosis of RA by the treating rheumatologist, rather than just using ACR criteria.

Favalli et al., 2018 [29] undertook a review of patient sex and the management of rheumatoid arthritis. These investigators found males were slightly more likely to have arthritis in large joints, to develop early radiographic damage and to present with a different pattern of extra-articular manifestations (more nodules, lung and pericardial disease) but less keratoconjunctivitis sicca when compared to females [29]. Male patients also showed a significantly later onset of RA and have significantly higher titers of anti-cyclic citrullinated peptide antibodies (ACPA) when compared to female patients [25].

Fibromyalgia syndrome is characterized by widespread musculoskeletal pain, fatigue and poor sleep. Fibromyalgia is much more common in women than men [30] and may be diagnosed in 21.7% of RA patients compared to 2.5% in the general population [31]. In terms of RA comorbidities, Favalli et al., 2018 [29] found that fibromyalgia was much more common in women with RA than in men with RA, with a female/male ratio ranging between three and 6.8 to one. Shin et al., 2021 [25] found that fibromyalgia, depression and osteoporosis rates were higher in women with RA than men. These researchers stated that cardiovascular disease risk is known to be higher in men than women in the general population, but male and female patients with RA have similar risk levels [25]. Favalli et al., 2018 [29] found that there was a similar risk in both male and female patients in the development of RA risk factors such as stroke, coronary artery disease and cardiovascular complications.

In a prospective study on onset and outcome after two years [32], a total of 844 consecutive patients (538 women) with RA, as per ACR 1987 criteria, of duration less than 12 months were studied. Standardized clinical and radiographic assessments were undertaken at study entry and after 2 years. The association of several variables at study entry with the outcome variables DAS28, functional disability measured by the HAQ, and, in 390 patients, Larsen score at the 2-year follow-up, were analysed in men and women separately. These researchers found that, at study entry, the women were younger compared to the men and the sexes showed different age distributions. The women had higher DAS28 and HAQ scores. However, women below 50 years of age at study entry had milder disease than older women and close to that of men. At 2-year follow-up the women still had higher DAS28 and HAQ scores compared to men, more of whom had achieved remission. Larsen score showed no sex difference either at study entry or after 2 years. Presence of rheumatoid factor (RF) was associated with lower age at study entry, and higher DAS28 at follow-up, in men only. Higher DAS28 and HAQ scores at entry were more strongly correlated with severe disease at follow-up in women than in men. Presence of the 'shared epitope' was not associated with age or the outcome variables DAS28 and Larsen score in either sex.

Shin et al., 2021 [25] studied a large group consisting of 5376 Korean patients living with RA (women = 4574) as per ACR/EULAR 2010 classification criteria. These investigators pointed out that most of the research to date into gender differences in RA had been conducted on Western or Latin American patients. Their findings were, however, harmonious with the existing literature which indicates that female RA patients presented with more erosive disease and longer disease duration than men with higher scores in DAS28, HAQ and patient-related outcome measures (PROMs). The prevalence of interstitial lung disease, cardiovascular disease and diabetes in men was higher than that in women [25]. The longitudinal change in disease activity and the rate of achieving clinical remission were found to be worse in women with RA [25].

3.2.3. Blood Tests in Rheumatoid Arthritis Between Genders

Rheumatoid factor (RF), anti-CCP, ESR and CRP are considered reliable blood tests to assess for rheumatoid arthritis [24]. There is a paucity of work undertaken in this area, however. Favalli et al., 2018 [29] undertook a review of gender and the management of rheumatoid arthritis. These investigators found males living with RA were slightly more likely to be positive for rheumatoid factor than females living with RA. However, females were found to have similar disease activity at baseline, swollen joint counts (SJC), radiographic changes and RF seropositivity to males [33]. Sokka et al., 2009 [28] also noted no differences between males and females in rheumatoid factor positivity.

A positive anti-CCP result predicts joint erosion in RA (odds ratio 4.4; 95% CI 3.6 to 5.3) [34] and is present in 23% of patients with early stage RA, in 50% at diagnosis and in approximately 53–70% of patients 24 months post-diagnosis [34]. In a group of 324 RA patients, as per ACR 1987 criteria, the range of anti-CCP titers in RA was 0.2–133.4 U/mL and showed no significant difference in the prevalence or mean value between males and females ($p = 0.761$) [35].

In an analysis of 589 RA patients, as per ACR 1987 criteria, which investigated differences between ESR and CRP levels between men and women at baseline [36], both the ESR and CRP were associated with age, sex, and body mass index (BMI), although the association with BMI disappeared in multivariate analyses. ESR and CRP levels significantly increased with age (β-ESR = 0.017, $p < 0.001$ and β-CRP = 0.009, $p = 0.006$), independent of the number of tender and swollen joints, general health, and sex. For every decade of aging, ESR and CRP levels became 1.19 and 1.09 times higher, respectively. Moreover, females presented with average ESR levels that were 1.22 times higher than those of males ($\beta = 0.198$, $p = 0.007$); conversely, men presented with CRP levels 1.20 times higher than women ($\beta = -0.182$, $p = 0.048$). Effects were strongest on the ESR. BMI became significantly associated with both inflammatory markers after 1 year, showing higher levels with increasing weight. Age continued to be significantly associated, whereas sex remained only associated with the ESR level [36].

3.3. Gender Differences in Axial Spondyloarthritis

3.3.1. An Introduction to Axial Spondyloarthritis

Axial spondyloarthropathy is a disorder which is inflammatory, chronic and primarily affects the axial skeleton and sacroiliac joints; peripheral and non-articular manifestations can also present which will affect the degree of symptomatology [37]. It has been stated that many physicians view AxSpA as mainly a male disease with some estimates ranging up to a male/female ratio of 10:1; however, there is said to exist a lack of appreciation of the differing disease manifestations in women [38]. Recent research has indicated little difference in gender prevalence and the male preponderance has been attributed to misdiagnosis of female AxSpA sufferers due to differing clinical presentations [37].

Rusman et al., 2018 [39] undertook a systematic review aggregating the existing findings in gender differences in axial spondyloarthropathy; they found that male and female AxSpa patients expressed differing levels of TNF and of interleukins IL-6, IL-17 and IL-18. Male AxSpa patients showed significantly elevated levels of TNFα and IL-17 compared to female patients. In addition, in AxSpA patients with syndesmophytes, men had significantly higher IL-18 levels, whereas women showed significantly elevated IL-6 [39].

3.3.2. Presenting Signs and Symptoms in Axial Spondyloarthritis

Several studies noted a higher frequency of extra-articular manifestations (EAM) in female AxSpA patients such as enthesitis, psoriatic skin disease and inflammatory disease of the bowel (IBD) [40,41]. Anterior uveitis was found to be more prevalent in males [41]. In another study, males presented with more advanced radiological damage as measured with the Bath Ankylosing Spondylitis Radiology Index (BASRI) and modified Stoke Ankylosing Spondylitis Spine Scores (mSASSS); however, disease activity measured with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and quality of life scores as measured with AsQol scores were significantly greater in women and there was a longer diagnostic delay in females [37]. With respect to this delay, one set of researchers noted a lag of 10 years in women in comparison to 3 years in men [42]. A later pooled analysis comprising a total of 42 studies which collectively included 23,889 patients (32.3% women) observed a significantly greater time from symptom onset to diagnosis in female patients [43].

3.3.3. Time to Diagnosis in Axial Spondyloarthritis

A number of hypotheses have been proposed which could clarify the reasons as to why a protracted time to diagnosis exists among females with AxSpA. These include female patients presenting with a reduced frequency of typical signs of axial spondyloarthropathy pain as an initial presenting symptom but more prominent upper thoracic and neck pain; widespread pain being misdiagnosed as fibromyalgia due this condition's ability to masquerade as entheseal pain; and also due to an overlap of symptoms of widespread pain with AxSpA [39]. These authors also cited less severe radiographic change and progression in females as an issue. Furthermore, evidence exists that suggests that an increased prevalence of non-radiographic AxSpA (nr-AxSpA) is present in women when compared to men, which also creates diagnostic uncertainty [44].

3.3.4. The Impact of Gender Differences in Axial Spondyloarthritis

Whilst AxSpA affects both males and females, radiological AxSpA (r-AxSpA) is reported to have a male to female ratio of three to one, by the mNY (modified New York) criteria, but a one-to-one ratio for nr-AxSpA [45]. It is also notable that female patients are said to lack representation in clinical trials in AxSpA, leading to a bias towards men in diagnosis, classification, management and treatment [37]. The increased rate of occurrence of r-AxSpA in males compared to females has underpinned some of the research into sex differences in this particular disease. In chronic r-AxSpA, male patients tend to present with more advanced joint pathology on X-ray than females and often more signs of inflammation [46,47]. Some investigators have observed that female r-AxSpA patients are more likely to present with involvement affecting the cervical spine, pain in the peripheral articulations, and poorer patient-reported outcomes (PROMs) [47,48]. A greater duration of time from onset of symptoms (based on patient history) to diagnosis has been commonly reported in studies investigating female patients with r-AxSpA [49].

In a study entitled Spondyloarthritis Caught Early (SPACE) [50], 719 patients with chronic back pain (CBP) (n = 444; 62% females) underwent subjective and objective clinical assessment including CRP, ESR and HLA-B27 blood tests plus pelvic X-ray and MRI to

assess for AxSpA. In this investigation, 301 of 719 CBP patients (42%) received a diagnosis of AxSpA (146 male, 155 female). Although symptom duration was similar between sexes, pathognomic findings on imaging, such as pathological ossification forming within spinal ligaments (syndesmophytes), was more likely to be observed in female patients [50]. These authors concluded that male patients have an increased likelihood of being diagnosed with AxSpA [50]; they did not, however, assert that separate diagnostic strategies were necessary for males and females. The role of sex hormones might also play a role in the development and progression of AxSpA; oestrogen is said to suppress TNF alpha production, therefore dampening the inflammatory response in AxSpa and its comorbidities [39]. In a small, dated study, an oral dose of oestrogen was prescribed for 17 female patients; the researchers observed a reduction in the activity of the arthritic process in these subjects [51]. These investigators also demonstrated that in premenopausal female patients with active AxSpA, oestrogen levels were lower compared to females with inactive disease, and significantly lower compared to controls [51]. Moreover, in post-menopausal AxSpA patients, oestrogen levels were lower when compared to matched controls. This is contentious, however, as other investigators failed to observe any differences in both symptom onset and severity in 571 females with AxSpa; in this investigation, 448 women had been administered oral oestrogen treatment when compared with 123 women who did not receive hormonal treatment [52].

A study design comprising both a case-control study and a review was undertaken in 50 male and 10 female AxSpA patients [53]. These investigators observed that serological testosterone levels were not found to be raised in AxSpA patients compared to controls and did not appear to exert any mediating influence over disease progression. As a caveat, the same authors proposed that the precursor of both testosterone and estradiol, dehydroepian-drosterone (DHEAS) might initiate the onset and potentiate the severity of this disease. These studies which have investigated sex differences in sex hormones, genetic connections and immune response have produced findings which have elucidated biological mechanisms which might contribute to different disease manifestations, clinical findings and therapeutic responses in males and females with AxSpA [39].

3.3.5. Blood Tests in Axial Spondyloarthritis Between Genders

The most important genetic marker test for AxSpA is HLA-B27: several studies have found that 74–89% of people eventually diagnosed with AxSpA test positive for HLA-B27 [44]. It also appears that patients who test positive for HLA-B27 have a greater likelihood of experiencing more severe symptoms with more rapid onset than those who test negative [54]. At time of diagnosis of AxSpA, male patients were found to be younger and had an increased likelihood to present with positive tests for the genetic marker HLA-B27 [44]. Recurrence of AxSpA was found to be high amongst the offspring of HLA-B27-positive parents but rare in HLA-B27-negative families [45]. However, testing positive for HLA-B27 does not guarantee the development of axial spondyloarthritis. About 6% of people in the United States are positive for HLA-B27, whereas only 1% have AxSpA [55]; this percentage is even lower in minorities, such as Hispanic and Black populations. Furthermore, HLA-B27 positivity does not have to be present in patients diagnosed with AxSpA.

CRP is said to be raised in around 50% of AxSpA patients [47]. Studies of sex differences in CRP level in AxSpA patients show significantly elevated baseline levels in men with AxSpa compared to female counterparts [14,46]. However, another group of researchers found that in a group of 181 patients with AxSpA (124 men and 57 women) there was no difference in CRP levels between males and females [56].

The CRP level in AxSpA patients is a key indicator of inflammation and is also considered to be a predictor of clinical response to anti-TNF treatment [39]. In a number of multi-centre, randomised, double-blind studies, patients with elevated CRP at baseline have demonstrated significantly greater responses to anti-TNFs compared with patients with low CRP levels, as well as those receiving placebo treatment [57].

3.3.6. Response to Treatment

In patients with AxSpa, the overall treatment effectiveness of TNF inhibitors (TNFi) is significantly reduced in women compared to men [40] and female patients have a significantly reduced adherence to pharmaceutical treatment in most randomised controlled trials (RCTs). These differences between male and female patients were not shown in most RCTs, which can be ascribed to the relatively low numbers of women included and because most of the studies were designed to investigate the effectiveness of the drug, rather than to provide an analysis to elucidate differences in gender response.

Obesity increases the incidence of RA and PsA, with a weight–dose effect [58]. In general, women have an elevated body fat percentage in comparison to males, as well as differing sex-related endocrinology; both of these could affect drug clearance [39].

With reference to the predictors which have been found to be associated with an enhanced treatment response to TNFi, these include HLA-B27 positivity, the absence of enthesopathy, shorter disease chronicity, and naivety to TNFi [59]. Interestingly, these predictors of treatment response are juxtaposed to the symptoms observed in female AxSpA patients: women with AxSpA have a higher prevalence of entheseal pain, and an increased time to diagnosis. These factors may play a role in the gender differences observed in TNFi adherence and also in therapeutic response [59].

At present, gender differences in treatment response to pharmaceuticals are not completely transparent because almost no studies specifically investigating gender and sex differences have been performed. A re-investigation of randomised clinical trials, which are focused on drug effectiveness and side effects with comparisons being between the studied drug and a placebo, rather than on sex-related differences, has only been undertaken in three TNFi studies which investigated the drugs Etanercept, Adalimumab, and Infliximab; we are not aware of any studies on the other TNF inhibitors nor the IL-17 blockers [39].

4. Discussion

Many autoimmune conditions display a notable imbalance between the sexes, with females representing the majority of cases [4]. The reasons for this overrepresentation of women are not clear but genetic factors and hormonal aspects are highly likely to be involved, with the possibility of environmental and occupational factors also.

There is a well-documented prevalence of female over male RA patients at a ratio of three to one [25]; however, even in rheumatological conditions such as PsA where there is an equivalence of gender presentation between the ages of 40–50 [13] and AxSpA where there is no gender prevalence, females still appear to be disadvantaged in terms of time to diagnosis and in treatment due to gender-specific differences in presentation, radiological findings and treatment response [2,39]. This increased time to diagnosis in females sits juxtaposed to the finding that men are known to be generally more reluctant to consult a doctor [60].

Women also experience increased disability and greater disease activity scores and indices in PsA [18], RA [28] and AxSpA [37]. However, this is said to be possibly attributable to the fact that greater muscle strength and bone mineral density in males allows them to compensate for functional deficits, and not necessarily because there is an absolute gender difference in the RA disease process per se [4]. It should be stated that oestrogen can

promote lower perception of pain in females whilst sudden fluctuations can cause increased pain and contribute to fibromyalgic symptoms, as has already been stated; fibromyalgia is more common in women and can complicate RA [61]. It has also been stated that differing occupational demands between genders can have a bearing on these disability scores in rheumatological patients [15].

The current literature suggests that testosterone may possess anti-inflammatory effects in vivo [62]. This is derived mainly from two observations: firstly, that testosterone deficiency is associated with increased levels of inflammatory cytokines, and secondly that testosterone supplementation decreases inflammatory cytokine levels. Testosterone may also modulate the secretion of cytokines from adipose tissue and immune cells to achieve its anti-inflammatory effects [62]. Dated research has suggested that sex hormone metabolism in the synovium of RA patients may be unfavourable for females, and TNF inhibitors may change the metabolism of sex hormone metabolism at the site of the synovial tissues [63].

As is widely accepted, sex and gender may alter drug efficacy and safety in adults as a result of pharmacokinetic and pharmacodynamic responses differing between males and females. Because of their tendency towards a smaller build, women are exposed to greater blood drug concentrations and more protracted drug clearance times than males, resulting in potential drug overdose and female-biased adverse drug reactions. The common practice of prescribing equal drug doses to men and women is to neglect sex differences in pharmacokinetics and exposes the majority of females to a higher drug dose and longer drug clearance [64].

Though women may generally be of a smaller build than men, for the same BMI females typically present with approximately 10% higher body fat than males [65]. Factors that are secreted by adipose tissue are collectively referred to as adipokines and excess adipose mass (as occurs in individuals with higher body fat) is associated with increased levels of CRP. Conversely, interventions aimed at causing weight loss lead to reductions in the levels of pro-inflammatory proteins, including CRP and IL-6 [66]. Coates et al., 2023 [15] found that BMI tended towards overweight and obesity categories in those living with PsA. It is possible that the altered clinical manifestations, higher disability scores and tender joint counts (TJCs) seen in females in various studies of rheumatoid diseases could be as a result of a synergistic effect of adipokines causing systemic inflammation as they combine with cytokines which are produced as part of the disease process.

Between 16% and 25% of women in a UK cohort study of 140 female patients experienced a spontaneous remission of their rheumatoid arthritis symptoms during pregnancy [67]. It has been noted that cessation of RA symptoms seen during pregnancy can have long-lasting effects; this was noted in a study from the Norfolk arthritis register which recorded lower HAQ scores in RA women who had experienced one or more pregnancies after the onset of RA, suggesting that even a short period of disease improvement could result in overall reduced disability in later years [68].

5. Conclusions

The issue of gender differences in rheumatic disease deserves to be closely investigated. These gender differences could be hormonal, related to gene expression, related to differences in pain perception, female menstrual cycle, physiology, anatomy, occupational and environmental factors or indeed combinations of these.

In summary, gender contributes to several pathogenic and epidemiological aspects of rheumatic disease. This creates important differences in how affected males and females present in terms of clinical manifestations, age, serology and radiological investigations. Moreover, there are signs of differences in the way in which females respond to standard pharmacotherapy regimens compared to males. Women often have an increased disease

burden as a result of an increased diagnostic delay, an elevated level of disease activity and a reduced effectiveness of treatment. There appears to be a persisting lack of knowledge regarding this gender difference.

Health care professionals should be aware of and expect different patterns of disease onset and presentation, disease activity, response to treatments, disability, radiographic progression and extra-articular manifestation/comorbidities according to gender (Table 1). More frequent comorbidities in females such as fibromyalgia, depression and osteoporosis may impact on treatment choice and outcomes. All these aspects suggest that gender should be very carefully considered in the assessment and bespoke treatment of rheumatological conditions over the whole course of the disease.

Table 1. Gender differences in presentation characteristics, blood test results and co-morbidities.

Characteristic	Psoriatic Arthritis	Rheumatoid Arthritis	Axial Spondyloarthritis
Prevalence (M/F)	1:1 [16]	1:3 [25]	1:1 [37]
Disease Activity	Increased in females [7,18]	Increased in females [25,28,32]	Increased in females [47,48]
Radiographic Damage	More in males [16,17]	Earlier in males [29]	Earlier in males [46,47]
Function/Quality of Life	Worse in females [7,16,17]	Worse in females [28]	Increased in females [47,48]
Time to Diagnosis	Longer in females [7,19]	no data	Longer in females [39,42–44,49]
Diagnostic Blood Tests	More B27 +ve in males [16]	Anti-CCP/RF same [25,35]	More B27 +ve in males [45]
Inflammatory Blood Tests	CRP equal [14,23] ESR equal [23]	ESR higher in females [36] CRP higher in males [36]	CRP higher in males [45]
Cardiovascular Disease	no data	Equal [29], higher in males [25]	no data
Osteoporosis	no data	More likely in females [25]	no data
Fibromyalgia	More likely in females [18]	More likely in females [25,29]	no data
Depression	no data	More likely in females [25]	no data
Psoriasis	Greater in males [15]	no data	Greater prevalence in females [40,41]
Inflammatory Bowel Disease	Equal male to female [18]	no data	Greater prevalence in females [40,41]
Enthesitis	Equal male to female [18]	no data	Greater prevalence in females [40,41]
Anterior Uveitis	no data	no data	Greater prevalence in males [41]
Peripheral Joint Disease	More in females [15]	no data	no data

Abbreviations: RF = Rheumatoid Factor; +ve = positive; ESR = Erythrocyte Sedimentation Rate; CRP = C-Reactive Protein; Notes: no data relates to the lack of finding in this particular literature search.

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Appendix A

The following search strategy was used to identify source materials/references for this manuscript:

Peer-reviewed literature on the early presentation of inflammatory arthritis, with a focus on sex-based differences and diagnostic approaches in primary care was identified. Databases searched comprised PubMed, Scopus, Web of Science, MEDLINE and Google Scholar (for grey literature). The following keywords and Boolean operators were used:

("inflammatory arthritis" OR "early arthritis") AND

("early symptoms" OR "early signs" OR "initial presentation") AND

("sex differences" OR "gender differences") AND

("primary care" OR "general practice" OR "family medicine") AND

("diagnosis" OR "clinical assessment" OR "recognition")

Inclusion criteria were (i) articles published in English, (ii) initially studies from the last 10 years, except where there were no data, or older articles were considered essential and still relevant to this area, (iii) human studies, (iv) focus on clinical early-stage inflammatory arthritis, (v) discussion of sex/gender differences, (vi) relevance to primary care settings.
Exclusion criteria were (i) studies focusing solely on post-diagnostic treatment of inflammatory arthritis, (ii) non-human studies, (iii) articles not peer-reviewed, including abstracts.

Reference lists of included articles were also scanned for additional sources.

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