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Sex, Symptom Severity, and Quality of Life in Rheumatology

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Abstract Inflammatory rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) show a striking female predominance ranging from 3:1 in RA up to 9:1 in SLE. The background for those gender bias is not fully understood yet, but seems to be the result of a complex interaction between sex hormones, (epi-)genetics, and possibly even the composition of gut microbiota. Moreover, time of disease onset, the clinical phenotype including co-morbidities as well as the course of the diseases during life differ between genders. The patient's sex therefore plays an emerging role for individual therapy decisions and co-morbidity screening in rheumatologic care. Male lupus patients, for example, tend to show more severe features such as renal involvement, pleurisy, and serositis, when being compared to female patients. Among RA patients, women are more likely to acquire conditions like thyroid dysfunctions, fibromyalgia, and depression than their male counterparts. These examples emphasize the importance of the patient's gender for the clinical routine and the resulting implications for prevention and therapy. The present article is going to review potential causes for the female predominance of rheumatic diseases and will examine the gender's impact on the disease phenotype, symptom severity, co-morbidities, and quality of life. For reasons of scope, the focus will be on RA and SLE as two of the most important rheumatic diseases with a large socioeconomic impact on society due to their incidence as well as mortality.

Keywords Gender-specific differences · Rheumatoid arthritis · Systemic lupus erythematosus · Quality of life · Symptom severity · Microbiome · Genetics

Introduction

Autoimmune diseases (AID) affect up to 6% of the western population [1] with a prevalence of 0.5–1% alone for rheumatoid arthritis (RA) [2]. Overall, there is a great variability in prevalence and incidence among different countries [3], probably reflecting the importance of environmental as well as genetic factors in the pathogenesis of AID.

Epidemiological studies exhibit a remarkable predominance of females being affected by AIDs. This is particularly true for a lot of rheumatic conditions such as RA, systemic lupus erythematosus (SLE), and systemic sclerosis (SSc). The potential causes at hand include sex hormones and genetic factors, but new research fields such as the microbiome are emerging and might be related to this gender bias.

This article is going to review potential reasons for the female predominance of rheumatic diseases and will examine the gender's impact on symptom severity, co-morbidities, and quality of life. The focus will be on RA and SLE as two of the most important rheumatic diseases with a large impact on the population due to their incidence as well as mortality.

Gender-Specific Differences in Immunity

As a matter of fact, gender-specific differences in epidemiology and severity of autoimmune disorders are well known. Most systemic rheumatic diseases predominantly occur in women (Table 1). Overall, the female immune system shows an increased reactivity with providing an enhanced antibody

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Table 1 Epidemiology and gender preferences of selected rheumatic diseases in adults, sorted by incidence

Disease	Incidence[a]	Female/male ratio	References
Polymyalgia rheumatica	70	1.5–3:1	[4–7]
Rheumatoid arthritis	53	2.4–4:1	[6, 8]
Systemic lupus erythematosus	5.6	4.3–9:1	[6, 8]
Antiphospholipid syndrome	5	9:1	[8–10]
Systemic sclerosis	1.1–4.3	3–9.7:1	[8, 11, 12]
Sjögren's syndrome	3.9	4–20:1	[6, 8]
Mixed connective tissue disease	1.9	8:1	[8, 9, 13]

Ranges in incidence and prevalence mainly result from a different geographical distribution, probably reflecting environmental and genetic influences on the distinct disease

[a] Per 100.000

production [14], a stronger type 1 Interferon (IFN) response [15], an increased antigen presenting activity by monocytes, and a higher homograft rejection rate [16]. Men though are more prone to infections with an increased inflammatory response to infectious pathogens [17]. The potential causes of these differences, however, have been elucidated in recent years only.

Two main factors seem to be responsible and might have further influence on other contributors such as microbiome differences:

- *Sex hormones* and
- *(Epi-)Genetics*.

Sex Hormones

Besides the striking female predominance of many rheumatic diseases, the assumption, that sex hormones might be pathogenically involved is emphasized by the presence of distinct hormone receptors on or within immune cells [18–20].

Estradiol acts in a dose-dependent manner. In general, lower doses seem to stimulate pro-inflammatory cytokines such as tumor necrosis factor (TNF) or interleukin (IL-) 1 beta [21]. Higher doses though, as during pregnancy, lead to anti-inflammatory effects by suppressing the signaling of pro-inflammatory cytokines, by inducing expression of anti-inflammatory cytokines (Th2 phenotype shift), and by activating regulatory T cells (Tregs), respectively [21, 22]. The named phenotype shift towards Th2/Treg responses is physiologically important to maintain maternofetal immune tolerance during pregnancy [23]. Very important in this respect, SLE, unlike RA, is meant to be a Th2 cytokine-driven disease [24]. Of note, estradiol is able to increase IFN production and consequently enhances type 1 IFN responses in particular for SLE [15]. Chronic activation of the IFN pathway is thought to be involved in the pathogenesis of SLE [15].

Progesterone on the opposite, rather counteracts the estradiol effects. Similar findings have been made for *testosterone*, which seems to inhibit pro-inflammatory cytokine and immunoglobulin production [25].

Details of sex hormone effects on both SLE and RA can be taken from Fig. 1.

Systemic Lupus Erythematosus

The incidence of SLE in women is the highest between menarche and menopause, when female sex hormones are at their peak. This observation is in accordance with the findings that nulliparity [26] and early menarche [27] are risk factors for SLE development. The duration of female sex hormone exposure therefore seems to be important for the risk of SLE. Besides, SLE shows a late onset in men further supporting the assumption of hormone involvement in disease risk.

As we know from clinical observations, physiological changes in hormone concentrations, e.g., during pregnancy, influence SLE severity and even induce disease flares. Nevertheless, findings from clinical trials are less obvious, despite efforts to use standardized disease activity assessment tools such as the SLE Disease Activity Index (SLEDAI) [28–30]. However, scientific consensus is that SLE does flare during pregnancy indeed [31, 32]. Up to half of the pregnancies show a measurable disease activity [33] with lupus nephritis, arthritis, cutaneous disease, and thrombocytopenia being the most common manifestations. Overall flare risk seems to be elevated in women who had an active disease within 6 months prior to conception [34]. The risk is highest during the third trimester and the first postpartum months [35].

Moreover, more pregnancy complications (e.g., preterm birth) are seen in women with SLE [32], in particular, in the presence of lupus nephritis [36]. As mentioned before, SLE is a Th2-driven disease. Since the Th2 phenotype is important for maternofetal immune tolerance, there might be a causative connection between the pathogenesis of SLE and the increased disease severity during pregnancy. This thesis is emphasized by the finding that estradiol increases IgG production by enhancing B cell activity and IL-10 production [37] (see

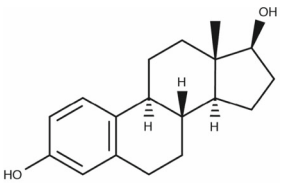
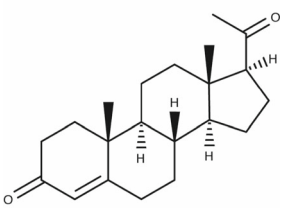
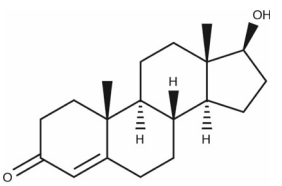
	Impact on SLE	Impact on RA
 Estradiol	loss of tolerance to nuclear antigen by type 1 IFN response promotion [15] , survival of self-reactive B cells and enhanced IgG autoantibody (lupus nephritis) production by B cells [37] ; increased SLE risk and severity [15, 21, 37]	suppression of synovial inflammation by inhibition of cytokine (e.g. TNF) signaling in pregnancy (high estradiol levels), induction of immune tolerance; reduced severity during pregnancy [15, 21]
 Progesterone	potentially reduces SLE risk by counteracting estradiol effects, e.g. through suppression of type 1 IFN responses [15, 52]	potentially reduces RA severity during pregnancy by Treg induction and suppression of Th17 differentiation, therefore promoting anti-inflammatory cytokines such as IL-10 [15, 20]
 Testosterone	seems to limit autoantibody production and therefore lupus nephritis [15, 25, 38] [1]	might be protective against autoantibody production, arthritis and lung disease [51][1]

Fig. 1 Distinct sex hormones and their impact on SLE and RA. [1]Limited data available, partly from animal models. *IFN* interferon, *IgG* immunoglobulin G, *IL-10* interleukin-10, *Treg* regulatory T cells

Fig. 1). In this respect, IL-10 as a pleiotropic cytokine has opposite effects in SLE compared to RA.

Progesterone might provide positive effects in SLE patients by counteracting estradiol effects, e.g., by negatively interfering with type I IFN responses [15] (see Fig. 1).

Limited data is available on the impact of testosterone on SLE. Besides its general anti-inflammatory properties, testosterone seems to suppress double-stranded DNA (dsDNA) antibody production [38]. Intriguingly, in SLE patients, peripheral androgen levels are reduced due to increased aromatase activity [39]. This abnormal aromatase regulation seems to be caused by inflammatory cytokine production [39]. Aromatase physiologically converts androgen precursors to estradiol. An increased activity not only leads to lower androgen levels but also to higher estradiol levels, which has been observed in female SLE patients in comparison to healthy subjects [40].

Rheumatoid Arthritis

The incidence and gender preference of RA varies with age: while it is generally more common in women (approx. 2.4–4:1, see Table 1), this female predominance diminishes with rising age and vanishes in people aged 75 years and above [23]. Moreover, contrary to SLE prevalence, RA prevalence increases with age and generally affects post-menopausal women more often than premenopausal ones [41]. Interestingly, women with RA show another incidence peak in their early 30s [42]. While pregnancy might cause a reduction of RA risk, nulliparity seems to increase RA risk [15]. As a matter of fact, female RA patients often get better or even reach remission during pregnancy [43]. One study even suggests that a resulting positive effect might be sustainable, since pregnancy after RA onset was associated with lower HAQ scores in general—over a 15-year period [44]. In this context, estradiol and progesterone both might have a protective effect in RA, see Fig. 1.

Broadly accepted risks for RA development include genetic factors, various environmental agents such as smoking, and even aging itself (premature immunosenescence) [45–47] rather than gender differences. Nevertheless, the mentioned age-dependent differences in prevalence point towards hormonal influences on RA risk. Large cohort studies though

did not find any relationship between either oral contraception and RA risk [48]. As for disease activity, results are conflicting with beneficial as well as adverse effects deriving from female sex hormones [23]. Synovial fluid analyses showed increased estrogen concentration in RA patients for both sexes [39]. Again, this is thought to be the result of an increased aromatase activity caused by inflammatory cytokines such as TNF, which are found to be elevated in RA synovitis [39]. A case-control study demonstrated that low testosterone levels in men are predictive for RA [49]. In this regard, the use of androgen replacement therapy resulted in positive effects in male patients [50].

As for SLE, detailed data on testosterone is limited. Results from animal models with experimental arthritis suggest a protection against lung disease, arthritis, and autoantibody production [51].

(Epi-)Genetics

General Aspects

A normal karyotype consists of two sex chromosomes, one derived from each parent. The female karyotype comprises two X chromosomes, the male though one maternal X and one paternal Y chromosome. In females, one of the X chromosomes is silenced early in embryogenesis. This silencing includes mechanisms such as DNA methylation. As we know today, silencing though is not complete with approx. 15% of the genes escaping inactivation. This finally leads to an overexpression of some X-linked genes in women [53]. While the X chromosome contains about 1000 genes, the Y chromosome only holds a small number with the gene for the sex determining region y (SRY) being the most important one. SRY is a DNA-binding protein responsible for initiation of male sex determination in human beings [54].

A lot of genes encoding for proteins involved in immunity (e.g., CD40 ligand [CD40L], IL-1 receptor-associated kinase [IRAK1], Toll-like receptor 7 [TLR 7]) are mapped on the X chromosome. The higher prevalence of AID in females has therefore been attributed to a potential gene dosage effect provided by the reactivation, inactivation, or aneuploidy of an X chromosome. Nevertheless, the genetic causes of the clinical observed sexual dimorphism have not yet been fully discovered. Hereditary monosomies of the X chromosome (as in *Turner's syndrome*—45, X) and X chromosomal structural abnormalities emphasize the importance of the X chromosome further, since they can lead to autoimmune diseases and even cholestasis in some cases [55]. Investigations on otherwise healthy women with primary biliary cirrhosis (PBC) showed an increased frequency of X monosomy in peripheral white blood cells [56]. Similar findings have been made in women with systemic sclerosis [57]. For both RA and SLE, potentially causative X-linked genes have been found in association studies [58–60]. Table 2 gives an overview of X chromosome genes probably being involved in the female preference of RA and SLE.

Systemic Lupus Erythematosus

Interestingly, men with the *Klinefelter syndrome* (47, XXY) seem to have the same SLE risk as women [61]. Concordantly, the prevalence of Klinefelter syndrome is 10 times higher in male SLE patients compared to the general population [62].

Different X-linked genes (Table 2), such as TLR7, have been associated with the sex bias in SLE [60]. TLR7 seems to be responsible for anti-ribonucleoprotein (anti-RNP) antibody production. Its activation also triggers enhanced IFN expression [63]. Recently, TLR8 has been shown to increase autoantibody production and IFN levels by inducing neutrophils in females due to inefficient inactivation of one gene [64].

Another X-linked gene, IRAK1, has been identified as a susceptibility locus for SLE [65]. IRAK1 is involved in IFN production and TLR signaling. In close proximity to IRAK1, the gene for methyl-CpG-binding protein 2 (MECP2) is located on the X chromosome. MECP2 is crucial for DNA methylation, and, furthermore, silencing has been associated with SLE [66]. In this context, CD40L has been shown to be overexpressed on T helper cells in SLE women, but not men with the disease [67]. This observation seems to be a result of DNA demethylation of CD40L on the silenced X chromosome [67]. CD40L encodes for a co-stimulatory B cell molecule, and its overexpression in female SLE patients potentially contributes to autoantibody production during disease flares [68]. Post-translational DNA modifications, termed epigenetics, also contribute to the sexual dimorphism in SLE. Methylation of T cell DNA has been positively correlated with disease severity in both genders. Remarkably, men require a greater genetic risk/DNA methylation ratio to reach a disease severity comparable to women [69].

When it comes to post-translational DNA modification, micro(mi)RNAs are of utmost importance. miRNAs are short, non-coding RNAs regulating gene expression at a post-translational level. In particular, miRNAs located on the X

Table 2 X-linked genes potentially involved in the female predominance of rheumatic diseases

Disease	Genes	Reference(s)
Rheumatoid arthritis	TIMP1, IL9R	[58]
Systemic lupus erythematodes	CD40L, IRAK1, TLR7/8	[59, 60]

See text for details

TIMP1 tissue inhibitor of metalloproteinase-1, *CD40L* Cluster of Differentiation 40 Ligand, *IL9R* interleukin-9 receptor, *IRAK1* interleukin-1 receptor-associated kinase 1, *TLR7/8* Toll-like receptor 7/8

chromosome have been attributed a role in gender specific immunity [70] since a different gene expression between both sexes has been reported [71]. Expression levels of miRNAs could be affected by the presence of a second X chromosome in women [23]. Furthermore, some miRNAs have been found to be overexpressed in SLE patients in general [72–75] which is even more pronounced in female patients [68]. Very interesting in this regard is the fact that estradiol is able to regulate miRNA expression on different levels [76].

Some X-linked miRNAs have been further studied, especially relevant for SLE—among others—seems to be miR148a, for example. It is upregulated in T cells from SLE patients and directly affects DNA methyltransferase 1 (DNMT1) negatively, resulting in DNA hypomethylation [73]. This in turn leads to overexpression of autoimmune-associated methylation-sensitive genes like CD70 and lymphocyte function-associated antigen 1 (LFA1) [73].

DNA hypomethylation is known to be involved in SLE pathogenesis as has been outlined above in regard to CD40L. Furthermore, drugs that are able to induce a lupus-like disease (e.g., hydralazine) also inhibit T cell DNA methylation and therefore induce autoreactivity [77]. These findings emphasize the importance of DNA (de-)methylation in SLE gender bias.

An extensive sex-specific genetic association study on autosomal genes (5932 female and 1495 male samples) revealed that men most likely require a higher cumulative genetic load than women to develop an SLE [78].

Rheumatoid Arthritis

Contrary to SLE, RA has been described only rarely in men with the Klinefelter syndrome, suggesting that the surplus X chromosome does not provide an additional RA risk [23]. Nevertheless, two X-linked genes with a possible impact on gender bias in RA have been identified (Table 2): tissue inhibitor of metalloproteinase-1 (TIMP1) and interleukin-9 receptor (IL9R). Single-nucleotide polymorphisms (SNPs) of both genes showed an association either with RA in general (TIMP1) or anti-cyclic citrullinated peptide (anti-CCP) antibody-positive RA (IL9R) [58]. IL9R exhibited even a male-specific association with an increased male/female RA risk ratio [58].

With the knowledge that decreased androgen levels might be connected to RA risk, Stark et al. investigated the CYB5A gene, which encodes for cytochrome b5 being an important co-factor in the androgen synthesis. CYB5A was then identified as a susceptibility gene for RA, since polymorphisms of this gene were associated with an RA risk reduction in women only by increasing the androgen synthesis capacity [79].

X-linked miRNAs, which have been discussed earlier in this paper with regard to SLE, have also been studied in RA patients. A recent case-control study comparing RA patients with sex- and age-matched controls not only revealed a higher expression of different miRNAs in patients compared to controls but also a higher expression of miRNAs in male compared to female RA patients [80]. Among the investigated miRNAs being overexpressed in male RA patients was miR98, which might have a cartilage-protective effect by reduction of TNF production [81]. Further investigations on miRNA and sexual dimorphism are needed to make final conclusions on the impact on RA pathogenesis.

Gut Microbiota

Very recent research not only even found striking evidence for a connection between the gut microbiota and the AID but also for a contribution to gender bias. An elegant study on type 1 diabetes (T1D) in non-obese diabetic (NOD) mice showed that testosterone levels are connected to the constitution of the gut microbiota. “Removing” of the microbiota in male mice decreased testosterone levels while they increased in female mice. Furthermore, male mice lost their intrinsic T1D protection with the removal of the commensal microbiota. The most remarkable finding though was the fact that a transfer of microbiota from adult male mice to immature female mice lead to elevated testosterone levels, reduced autoantibody production, and provided a T1D protection among the receiving female mice [82].

To date, studies on the relevance of gut microbiota in rheumatic diseases with regard to gender bias are rather limited though. The most important findings are shortly reviewed in this section.

Systemic Lupus Erythematosus

There are a growing number of studies on the impact of (altered) gut microbiota on SLE. A study with germ-free (GF) MRL-lpr mice did not find any effect on SLE prevalence or severity when comparing them to conventional MRL-lpr mice [83]. MRL-lpr mice have a distinct mutation and spontaneously develop a lupus-like autoimmune syndrome including massive lymphoproliferation, autoantibody production (very similar to those in human SLE patients), and immune complex nephritis. Both the GF and the conventional mice developed autoantibodies and histological verified nephritis, even when being on an antigen-free diet in an additional experiment. The authors therefore concluded that (exogenous) infectious agents are not involved in lymphoproliferation and B cell autoimmunity. They draw the hypothesis that the immunomodulatory mechanisms failing in humans with SLE rather have to be genetic [83]. However, another study dating back to 1975 had contradictory findings in a comparable lupus mouse model, showing not only a significant decrease in

incidence and severity of renal disease but also lower gammaglobulin levels [84].

Newer investigations found a lower *Firmicutes*/*Bacteroidetes* ratio in the gut microbiota of SLE patients compared to controls [85, 86]. Another study found a significantly reduced species diversity of the microbiome in SLE patients compared to controls, independent of treatment. Surprisingly, as in RA (see the following section), *Prevotella copri* was more abundant in the SLE group as well [87].

Just recently, Lopez et al. reported that microbiota from the stool of SLE patients promote lymphocyte activation as well as Th17 differentiation from naive lymphocytes to a greater extent than microbiota from healthy controls [88]. They also showed that two *Clostridia* strains reduced the Th17/Th1 balance, while supplementation of *Bifidobacterium bifidum* prevented lymphocyte overreaction [88]. Moreover, *Synergistetes*, a phylum of anaerobic bacteria, has been negatively correlated with IL-6 serum levels and was reduced in patients when anti-dsDNA titers were increased [88].

While there is some evidence that the gut microbiota might play a role in SLE, investigations related to a potential gender bias are missing to date. Further research is needed to characterize the connection between the gut microbiota and the SLE in detail; the striking female predominance of the disease should be considered.

Rheumatoid Arthritis

Besides a strong genetic predisposition (e.g., "shared epitope," HLA DRB1*0401), environmental factors (e.g., smoking) are major players in the pathogenesis of RA. Since not all patients harbor genetic risk factors for RA and smoking is just one environmental risk factor, other influences had to be considered. Findings of gut microbial DNA in the synovial fluid of RA patients [89] and the high prevalence of periodontal inflammatory disease caused by Porphyromonas gingivalis among patients [90] support the idea of a commensal microbiota involvement. Other investigators even showed a strong correlation between distinct bacterial species in stool samples (*Prevotella copri*) and recently onset RA (compared to the controls) [91]. In this context, arthritis-susceptible (DRB1*0401) transgenic mice were found to have an increased gut permeability, providing a way for the bacteria to translocate extra-intestinal [92]. Furthermore, arthritis-susceptible mice lost age-related changes in the gut microbiota composition while arthritis-resistant mice (DRB1*0402) retained those changes [92]. In the same extensive study, the investigators were able to show that the gut microbiota of arthritis-susceptible mice is dominated by the *Clostridium*-like bacteria *Clostridiales* (males over females) in contrast to arthritis-resistant mice, which are enriched by *Bifidobacteria* (females over males). This finding is of particular importance, since the expansion of *Clostridiales* is significantly correlated with a simultaneous upregulation of pro-inflammatory cytokines and downregulation of regulatory cytokines in female compared to male arthritis-susceptible mice [92]. *Clostridiales* have also been isolated from the synovia of RA patients which might be the consequence of a translocation through a potentially disturbed gut barrier [92, 93].

In line with these results, other animal models even showed that germ-free mice did not develop joint inflammation whereas monocolonization with one germ drove Th17-dependent arthritis [94].

Summing up those findings, there is evidence that changes in gut microbiota might contribute to inflammatory arthritis such as RA, in particular, in individuals with a genetic predisposition such as the shared epitope. The distinct HLA genotype (DRB1*0401) might even be involved in altering the gut microbiota composition in females which in turn leads to an upregulation of pro-inflammatory cytokines on one hand and a bacterial translocation on the other hand [92]. Nevertheless, more research on that topic is imminent to find further proof for the impact of the gut microbiota on the gender bias in RA and elucidate the distinct mechanisms behind it in detail.

Symptom Severity and Quality of Life

When comparing the impact of either RA or SLE on patients, RA seems to have the more negative effect on quality of life, than SLE [95]. Both physical and mental domains of the used Short Form 36 (SF-36) questionnaire have been affected. This difference most likely is a result of the more pronounced physical limitations (including the inability to run, climbing stairs, or lifting heavy objects) RA patients tend to suffer from [95]. These results have been confirmed at least partly by another recent investigation: while the physical domains have been lower in RA patients compared to SLE patients, the mental domains have been worse in SLE patients [96].

Nevertheless, symptom severity differs between genders, as epidemiology of the same rheumatic disease does. The difficulty lies in the distinction between true differences in severity and virtual ones resulting from measurement methods or gender-specific symptom perception. Important in this regard is the erythrocyte sedimentation rate (ESR), for example. This value is part of the Disease Activity Score 28 joints (DAS-28), which is widely used for RA disease activity measurement. Unfortunately, ESR is elevated in women compared to men [97, 98], therefore potentially overestimating the disease activity when being used for scoring. For this reason, C-reactive protein (CRP) might be preferably used, an inflammatory marker not being elevated in women compared to men [98, 99].

Furthermore, women are known to report more symptoms [100] and even poorer scores than men when answering questionnaires [101]. Potential explanations vary from gender

differences in pain perception [102, 103] to sex-related distinctions in musculoskeletal performance and strength [104]. On the other hand, men generally seek less frequently medical help than women [105].

Systemic Lupus Erythematosus

SLE disease activity and symptom severity are different between genders. Male patients have been shown to be at higher risk of a severe disease activity already at the time of diagnosis (OR 3.11) [106]. Severe disease activity was defined as a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score ≥12. In accordance with this finding, a recent meta-analysis investigating studies with a total of 11.934 SLE patients found renal involvement, serositis, and pleurisy to be predominant in male patients [107], see Table 3. Renal involvement alone can score for up to 16 points in the SLEDAI. Another large meta-analysis added an increased ratio of seizures in male patients as a result of neuropsychiatric involvement and showed that men with SLE even have a higher risk to die from the disease (OR 2.0) [108]. Male sex was also identified as a predictor for a reduced 10-year survival [109].

Summing up these results, men seem to have more severe organ involvement, than women. "Less severe" features such as alopecia, photosensitivity, mucosal ulcers, and malar rash though were significantly more often found in women. In addition, arthritis was more common in female SLE patients [107]. As for laboratory findings, thrombocytopenia and anti-dsDNA antibodies are more frequent in male patients, while leukopenia, lupus anticoagulant, low-level C3, and ANAs are more common in women [107].

Interestingly, depression and signs of anxiety, which are both more frequent in female SLE patients [110, 111], seem to have the same negative impact on quality of life (as measured using the SF-36) in men and women [110]. Other factors associated with a poor quality of life are disease activity itself and fibromyalgia [112–114].

Table 3 SLE features with a significant sex variety; given are female/male ratios

Disease feature	Female/male ratio	Reference(s)
Alopecia	2.5–3.3	[107, 108]
Mucosal ulcers	1.4–2.5	[107, 108]
Photosensitivity	1.4–2	[107, 108]
Malar rash	1.4–1.7	[107, 108]
Arthritis	1.3–1.4	[107, 108]
Pleurisy	0.8	[107]
Serositis	0.7	[107]
Renal involvement[a]	0.5–0.7	[107, 108]
Seizures[b]	0.4	[108]

[a] Including hematuria, proteinuria, nephrotic syndrome, renal insufficiency, renal failure, and requirement of a renal biopsy

[b] Only seizures requiring a therapy for at least 6 months

Rheumatoid Arthritis

Intriguingly, the disease phenotype of RA seems do differ between genders in terms of erosive disease and extra-articular manifestations [42], which are both more common in male patients [115]. These findings seem rather contradictory, since disease activity has been reported repeatedly to be increased in female patients; this is particularly true for the advanced disease [101, 116–119]. In this respect, the measured disease activity in women was even higher despite similar radiographic joint destruction [118]. Furthermore, female RA patients report poorer quality of life than their male counterparts—which is attributed to co-morbidities such as depression and osteoporosis by the authors of the respective studies [120, 121].

In line with this finding, male RA patients being asked by questionnaires for therapy success in a large Swedish survey report better outcomes for pain and physical function (as measured by using Visual Analogue Scale [VAS], Health Assessment Questionnaire [HAQ], and SF-36), despite similar treatment [103]. The findings of this study being undertaken from 1997 to 2009 are also congruous with earlier observations about poorer scoring in questionnaires by women. Interestingly, a recent study on the effects of biologic disease-modifying anti-rheumatic drugs (bDMARDs) found that depressive symptoms improved significantly in women compared to men under such a therapy [122]. Contrary to the self-reported symptom severity, early RA shows an accelerated course and more (severe) extra-articular manifestations in men [42].

Moreover, various clinical trials on RA therapy, mainly using anti-TNF agents, revealed a better and faster therapy response in men [116, 117, 123–125], which is also observed in early RA [119]. Recent investigations on rituximab showed no gender difference with regard to the European League Against Rheumatism (EULAR) therapy response, but remission rates were significantly higher in male patients after 12 months. Furthermore, remission rates were increased in men after anti-TNF therapy failure [126]. A large four-arm treatment trial (sequential monotherapy, step-up combination therapy, initial combination with prednisone, or initial combination with infliximab) in recent-onset RA patients found that male patients were also more likely to achieve drug-free remission than female patients [127].

Co-Morbidities

Systemic Lupus Erythematosus

Lupus is a complex systemic disease with a great variety of symptoms. Moreover, SLE patients are at an increased risk of developing different co-morbidities with further impact on quality of life and even life expectancy itself [128, 129]. The most recent data on the frequency of co-morbidities in SLE is derived from a large UK study also providing sex-specific results [130]. Details can be obtained from Table 4.

End-Stage Renal Disease

Unfortunately, in up to 30% of the patients, lupus nephritis leads to ESRD within 10 years of diagnosis [132, 133]. Renal involvement is a common feature of SLE, occurring in 40–70% of the patients [132] with a male predominance [107, 108], in particular, for chronic renal failure [111]. Recent findings suggest that ESRD might be slightly more frequent among male patients, but confidence intervals (CI) were wide and the authors concluded there was no significant difference between genders [130]. Nevertheless, ESRD showed a decreasing incidence with age and the risk seems to be highest below the age of 40 [130].

Osteoporosis

Osteoporosis is a common co-morbidity and is generally attributable to three different causes: the disease itself, steroid medication and—in women—menopausal status [134]. Due to higher prevalence of osteoporosis in women in the general population and the high amount of female SLE patients, osteoporosis in SLE has been mostly investigated in female patients [135, 136]. While current data shows a higher risk for female compared to male SLE patients, male SLE patients are at a particular increased risk when being compared to healthy men [130]. The attending rheumatologist has to be vigilant in both genders bearing diagnosis and therapy in mind, especially in patients under supplementary glucocorticoid therapy.

Table 4 SLE co-morbidities in female compared to male patients, sorted from the highest to the lowest female/male ratio

Co-morbidity	Female/male ratio	Reference(s)
Osteoporosis	2:1	[130]
Depression	1.7:1	[111]
Infections	1.3:1	[130]
Malignancies	0.5–0.7:1	[111, 130]
ESRD[a]	1:1	[130]
Stroke	0.6–1:1	[130, 139]
CVD	0.6:1	[111, 130]

Data mainly taken from [111, 130] and amended by other literature as indicated

CVD cardiovascular disease, *ESRD* end-stage renal disease

[a] Confidence intervals were wide, so the authors concluded there was no difference

Depression

Depression is common among SLE patients, and the risk is similar to that in patients with RA [137]. While signs of depression are more frequent in female SLE patients compared to healthy women, there is no such difference for male SLE patients when being compared to healthy men [110]. Moreover, women with SLE are at higher risk, than male patients [111]. Depression is associated with anxiety and poor sleeping quality which has a negative impact on quality of life, in particular, in women [110, 138]. Unfortunately, SLE patients with depression also show a strong risk of developing fibromyalgia [114], which further impairs quality of life [113].

Cardiovascular Diseases and Stroke

Lupus patients have an increased risk for cardiovascular diseases, which was estimated to be doubled, at least [139]. The term cardiovascular diseases (CVD) summarizes different diseases such as myocardial infarction and coronary heart disease, for example. As for strokes, the risk is increased by up to 2.5-fold with a higher risk for a hemorrhagic than an ischemic stroke [130, 131]. While the relative risk for CVD increases with age also in SLE patients, the absolute risk is highest among young patients [130, 139].

The background for an increased cardiovascular risk seems to be the combination of "traditional" risk factors such as hypertension and diabetes on one hand and SLE-specific risk factors like chronic inflammation, secondary antiphospholipid syndrome (APS, Hughes syndrome), hypercoagulability due to nephrotic syndrome, and long-term glucocorticoid use on the other hand. Male SLE patients are at higher risk of CVD, but this might only reflect the comparable higher risk (male > female) in the general population [130]. Nevertheless, SLE seems to be closely associated with cardiovascular events. Female SLE patients have an increased risk for myocardial infarction (MI) when being compared to healthy controls [140], but men with SLE have an even higher MI risk [108, 111]. A large meta-analysis was able to show that the risk for a venous thromboembolism (VT) is increased at least five times in comparison to the general population [141]. For pulmonary embolism (PE), the risk seems to be comparably increased [142] and was further increased in a cohort in Taiwan [143]. Interestingly, the authors concluded that this result was not only attributable to secondary APS alone but also to the risks

already mentioned previously. Indeed, most studies on thromboembolism in SLE do not differentiate between positive and negative APS status [141], so that the events are at least partly result of an APS. The study from Taiwan also found the risk to be increased in female SLE patients for both VT and PE [143]. CI in this study were wide though and multiple other investigations came to contrary results with men being much more likely to incur a thromboembolic event, than women (OR of up to 2.9) [108, 111]. This is kind of contradictory, since female SLE patients are more likely to develop a secondary APS than men [144], which could serve as a proper explanation for increased thromboembolic events.

Infections

Infections of any kind are increased in SLE patients, by up to 30% [130]. This finding is not surprising and most likely attributable to the systemic inflammation of the disease as well as the immunosuppressive therapy. Infections are a leading cause of SLE morbidity and mortality being accountable for 15% of the hospitalizations [145]. The proportion of deaths in SLE patients caused by infections ranges from 17 up to over 30% [145]. Infections as co-morbidity are therefore of utmost importance for the attending rheumatologist who has to give particular attention to clinical signs of infections. Since women with SLE are more likely to develop infections [130], this is especially true for female patients.

Malignancies

SLE patients have a small increased risk across all kind of cancers [130, 146, 147]. It seems to be particularly increased not only for hematological malignancies such as non-Hodgkin's lymphoma (NHL) and leukemia but also for cancers of vulva, lung, thyroid, and liver [130, 146]. On the other hand, the risk might be decreased for cancers of breast, endometrium, and ovaries [146, 147], even if that reduced risk was not found in the latest investigation [130].

The higher risk for male patients found in the study of Rees et al. [130] could not be attributed to a certain malignancy but was also found in another investigation [111]. Other investigators found the risk for NHL being increased 4-fold in male compared to female patients [111].

While female SLE patients have a higher incidence for osteoporosis and infections, male SLE patients have a higher rate of CVD, stroke, and malignancies with a dominance of hematological cancers. The reasons for these differences have not been fully elucidated yet. Clinicians can only use the epidemiological data to stratify the individual risk for certain co-morbidities to ensure proper diagnostics and therapy.

Rheumatoid Arthritis

Co-morbidities can precede the actual disease, can occur with the disease, or can be caused iatrogenic. On average, the patient with an established RA has two or more co-morbidities [148]. Since co-morbidities are directly related to quality of life [148], they are of utmost importance for the RA patient himself and the attending physician. The most frequent co-morbidities according to a large cross-sectional study of 3920 patients (Comorbidities in RA, COMORA [149]) can be obtained from Table 5. Unfortunately, no gender-specific evaluations have been made in this study and clinically important co-morbidities such as osteoarthritis (OA), osteoporosis, and fibromyalgia are missing. OA, for example, seems to be particularly important in early RA and might confound radiographic and clinical assessment [150]. A very recent study also found higher frequencies of peptic ulcers and diabetes mellitus in male RA patients compared to female patients, but data is limited [121].

Despite seemingly higher disease activity in women on one hand and better therapy response to anti-TNF agents in men on the other hand, male patients seem to carry a higher burden with regard to co-morbidities. A study conducted by Weyand et al. in the late 1990s not only showed a higher frequency of erosive disease but also rheumatoid nodules and lung disease being more likely in men [42]. In this respect, cardiovascular events are much more common in men suffering from RA [151]. Recent data shows that other co-morbidities such as fibromyalgia, thyroid disease, depression, and osteoporosis are more present in female RA patients (see Table 6) and might contribute to higher disease activity scores.

Fibromyalgia

Fibromyalgia (FM) is an important co-morbidity with a prevalence of 1–2% [152] in the general population and an increased prevalence of up to 17% among RA patients [153,

Table 5 Most frequent co-morbidities in RA patients, gender independent

Co-morbidity	Prevalence
Depression	15%
Asthma	6.6%
Cardiovascular events[a]	6%
Solid malignancies[b]	4.5%
COPD	3.5%

Data taken from the results of the COMORA study [149]

COPD chronic obstructive pulmonary disease

[a] Including myocardial infarction and stroke

[b] Without basal cell carcinoma

154]. Either way, women are significantly more affected in both groups with a comparable female/male ratio (4–6:1 in general, 3–6.5:1 in RA patients, see Table 6). FM in RA patients impairs health status, functional capacity, and quality of life, which is reflected by worse scores in common RA questionnaires such as DAS28, HAQ, and SF-36 [153]. Furthermore, it is associated with other co-morbidities, in particular, depression [154].

Thyroid Disease

In RA patients, thyroid diseases (including hormonal dysfunction and autoimmune thyroid disease [ATD]) are present in up to 34% with a higher frequency in women [155]. ATD is more prevalent in female RA patients than in females without RA [155].

The prevalence of clinical hypothyroidism is three times higher in female RA patients than in females in the general population [156]. Importantly, it is associated with a 4-fold increased risk for cardiovascular diseases such as coronary, cerebral, and peripheral arterial disease when being compared to euthyroid female RA patients [156]. Therefore, hypothyroidism alone has an important impact on the overall RA mortality. A screening for subclinical hypothyroidism, in particular, in female RA patients, is therefore reasonable.

Table 6 RA co-morbidities in female compared to male patients, sorted from the highest to the lowest female/male ratio

Co-morbidity	Female/male ratio	Reference(s)
Fibromyalgia[a]	3–6.5:1	[153, 158]
Thyroid disease	2.5–3:1	[158]
Depression	2:1	[157, 158]
Osteoporosis	1.4–2.7:1	[158, 162]
Malignancies[b]	0.75–2.2:1	[158]
Stroke	0.5–1.34:1	[151, 158, 168, 169]
COPD	0.4–0.7:1	[158, 169, 175]
Melanoma[c]	0.4:1	[158, 167]
Coronary heart disease	0.3–0.8:1	[158, 169]
Myocardial infarction	0.25:1	[151]

Data mainly taken from a publication upon the results of the *Course and Prognosis of Early Arthritis* (CAPEA) cohort and the German biologic register *Rheumatoid Arthritis Observation of Biologic Therapy* (RABBIT) [158]. The RABBIT register alone contains data of more than 15,000 RA patients in Germany. Findings of international studies have been amended

COPD chronic obstructive pulmonary disease

[a] Rate varies with different definitions of fibromyalgia

[b] Rate varies depending on disease stage and seems to be higher in males after a longer disease duration

[c] Under anti-TNF therapy

Depression

Depression is a common RA co-morbidity and probably the most frequent one [149] with a prevalence of up to 20% which is two to three times higher than in the general population [157]. It occurs twice as often in female compared to male RA patients [157, 158]. Regular screening using tools such as the Beck Depression Inventory II (BDI-II) or the Patient Health Questionnaire (PHQ-9) [159] therefore seem advisable.

Osteoporosis

Being a systemic inflammatory disease, RA itself is an independent risk factor for developing osteoporosis [160]. This is most likely a result of elevated cytokine levels (in particular of TNF) in serum and synovial fluid, since TNF is able to activate osteoclasts and therefore enhances bone resorption [161]. Moreover, osteoporosis can also be a consequence of glucocorticoid therapy [161]. British data reveals a prevalence for osteoporosis in RA patients of almost 27% [162]. In female RA patients, it occurs up to 2.7 times more often, than in male patients and prevalence rises with age [121, 158, 162]. Female RA patients also have a higher risk for fractures, when being compared to healthy women [163]. Interestingly, two studies [164, 165] found comparable rates of osteoporosis in female and male RA patients; one of these studies showed that osteoporosis in men (50.5%) and post-menopausal women (55.7%) are more frequent compared to premenopausal women (18%) [164]. An important reason might be the influence of the menopausal state. In this regard, male patients seem to be undertreated—in terms of prophylaxis as well as definite osteoporosis therapy [165]. This is most likely caused by a missing awareness of osteoporosis in men in general.

Malignancies and Melanomas

Patients with RA have an increased risk of almost 30% for specific malignancies such as lymphomas and lung cancer—even without ever receiving a bDMARD [166]. The risk for lung cancer is higher in male, than in female RA patients [158]. If treated with a bDMARD though, skin cancer risk for both non-melanomas (OR 1.5) and melanomas (OR 2.3) is increased [148]. This is particularly true for melanomas and anti-TNF users as data from a large Swedish register shows [167]. Furthermore, male RA patients are at a much higher risk of developing a melanoma under anti-TNF therapy (hazard ratio (HR) 2.7 in male, HR 1.2 in female patients) [167]. The broad range of the female/male ratios given in Table 6 most likely results probably from disease duration. Data was taken—among others—from the German early arthritis cohort *Course and Prognosis of Early Arthritis* (CAPEA) where women showed a higher risk for malignancies, than men

[158]. A long disease course and a continuing therapy with (b)DMARDs might shift that ratio to the disadvantage of male patients.

Stroke

In comparison to the general population, the risk of an ischaemic stroke is increased in RA patients (HR 1.3) for both sexes [168]. The risk rises significantly with disease duration of 10 years and more (HR 2.3) but not as much as the risk of ischaemic heart disease [168]. While the German register data and the results of the Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis study (QUEST-RA) suggest that stroke is more frequent in male patients [151, 158], other investigations found an equal risk for both sexes [168] or even quite the opposite [169]. Therefore, further investigations with regard to the gender-dependent stroke risk in RA are needed.

Coronary Heart Disease

Probably due to the systemic inflammation, atherosclerosis is accelerated in RA. There is emerging evidence that RA itself as well as RA disease activity is associated with the expression of pro-inflammatory cytokines by endothelial cells [170]. RA patients exhibit a 60% increase in risk of overall cardiovascular mortality [171]. In the absence of a sufficient RA therapy using either TNF inhibitors or methotrexate, RA is associated with a 50% increased risk of repeat revascularisation after the need of a first percutaneous coronary intervention (PCI) [172]. Coronary [ischaemic] heart disease is more frequent in men than in women with RA [121, 158, 169], see Table 6.

Myocardial Infarction

The risk of a myocardial infarction is—consistent with ischaemic heart disease—increased in RA patients with risk ratios ranging from 1.6 to 3.2 [154, 173]. When only comparing the female sex, the risk of myocardial infarction in female RA patients is increased 2-fold compared to women without RA. It rises up to 3.1 with a disease duration of more than 10 years [174]. Among RA patients, myocardial infarction seems to be more prevalent in male patients [151], but more studies on that topic are required.

Chronic Obstructive Pulmonary Disease

Besides the interstitial lung disease (ILD) as an extra-articular RA manifestation, obstructive lung diseases (OLD) like COPD are common in RA patients with a HR of 1.5 [175]. When being adjusted for sex, the COPD risk is increased in male and decreased in female patients compared to the general population [169, 175].

As recommended by the ACR and the EULAR, rheumatologists and other clinicians should be aware of the systemic character of RA and have to consider the gender-specific differences in co-morbidities when assessing the individual patient to not overlook important conditions related to RA. Co-morbidities contribute largely to the overall mortality of RA, which is particularly true for cardiovascular diseases and therefore affected males.

Concluding Remarks

Rheumatic diseases, in particular SLE and RA, show a striking female predominance. Recent research efforts lead to a much better understanding of the potential reasons behind this phenomenon which also causes a different clinical presentation between genders. Important advances have been made to decipher sex-related genetic alterations and the impact of sex hormones on the different prevalence and severity of those diseases. Female sex hormones like estradiol not only take influence on the course of SLE but also increase the disease risk itself.

Susceptibility genes, many of them mapped to the X chromosome, have been identified for SLE as well as for RA. There are also clear indications that epigenetic modifications, mediated by microRNAs, might contribute to the gender bias. However, there is much more research necessary to substantiate these hypotheses.

A whole new research field emerged with the “discovery” of the microbiome. Recent studies suggest that the gut microbiota influences the pathogenesis of RA and SLE; as for RA, even gender-related differences in composition of the commensal microbiota have been reported.

Further insight in the differences of disease activity and co-morbidities between female and male patients came from epidemiological studies and extensive register data, providing important knowledge for the clinician.

As any other specialty, rheumatology and immunology are advancing fields and there still lies much work ahead of us to fully understand the obvious differences between women and men in autoimmune diseases.

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