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Gender-related differences in systemic sclerosis

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ABSTRACT

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disease which is characterised by autoimmunity, widespread tissue fibrosis of the skin and internal organs, and vasculopathic alterations. SSc is more common in women but has a more severe expression of disease including internal organ-based complications and higher mortality in men. The extant literature shows that although important pathophysiological sex differences are present in SSc, behavioural differences (e.g. higher smoking rates in men) and occupational exposures may contribute to poorer outcomes in men with SSc. The higher death male death rate in the general population and greater prevalence of lung fibrosis are likely the key factors responsible for excess mortality found in men. Other important factors include (but are not limited to) a greater prevalence of the disease subset, delayed time to diagnosis, and higher disease activity in early disease in men. SSc carries a significant burden of disease-related morbidity; however, no qualitative studies to date have focussed on gender differences in SSc. The purpose of this review is to provide a comprehensive overview of gender differences in SSc including (but not limited to) epidemiology, pathophysiology, clinical expression of disease, mortality, SSc in transgender individuals, and psychosocial aspects of disease.

1. Introduction

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disease which is characterised by autoimmunity, widespread tissue fibrosis of the skin and internal organs, and vasculopathic alterations [1–3]. Although significant advancements have been made in understanding pathogenesis and the availability of a number of treatments for many of the organ-based complications, SSc still carries a significant burden of disease-associated morbidity and mortality. In general, men with SSc have significantly reduced survival rates than women and report more severe disease. The purpose of this review is to examine aspects of sex and gender differences in SSc relating to epidemiology, pathogenesis, diagnosis, health behaviours and occupational exposures, clinical expression of disease including early disease and organ-based complications, mortality, SSc in transgender individuals, and psychosocial aspects of disease.

2. Review strategy

The breadth of this comprehensive review was not amenable to a formal systematic literature review procedure due to the need to both identify and appraise a broad range of sources including cross-sectional studies, registry analyses, and qualitative research methods. The following standardised search criteria were applied within the National Institutes of Health's National Library of Medicine (PubMed) to facilitate the identification of manuscripts relevant to pathogenesis, epidemiology and clinical features (2356 citations on 26th May 2019):

((gender) OR (sex) OR (men)) AND ((systemic sclerosis) OR (CREST) OR (Scleroderma)) AND ((pathogenesis) OR (assessment) OR (classification) OR (clinical trial) OR (impact) OR (burden) OR (treatment) OR (clinical) OR (management) OR (features) OR (therapy) OR (work) OR (qualitative) OR (experience) OR (social) OR (function) OR (distress) OR (disability) OR (symptoms) OR (pain) OR (distress) OR

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(social) OR (quality of life))

In parallel, a specific search was performed to identify manuscripts which were relevant to the psychosocial aspects:

((gender) OR (masculinity) OR (masculine) OR (masculinities) OR (masc*) OR (men's health) OR (hegemonic)) AND ((systemic sclerosis) OR (scleroderma) OR (SSc) OR (lcSSc) OR (dcSSc)) AND ((Coping) OR (Cope) OR (self-manage*) OR (self management) OR (impact) OR(depress*) OR (low mood) OR (emotion) OR (quality of life) OR (QOL) OR (helplessness) OR (wellbeing) OR (adjustment) OR (adaptation) OR (identity) OR (self care) OR (self-care) OR (self belief) OR (self-belief) OR (self efficacy) OR (self-efficacy) OR (support) OR (psych*)).

The titles and abstracts of journal articles identified from this search strategy formed the main basis of identifying the relevant works. We also performed grey searches of the manuscripts that were cited within these articles. We excluded articles relating to erectile dysfunction as the focus of this review was on gender-related differences in SSc.

3. Epidemiology of SSc

SSc is more common in females compared to males; although the exact ratio between the sexes has varied widely in the reported literature. In general, the ratio between female and males SSc patients is considered to be approximately 3:1 and as high as 7–8:1 [4–12]. Tamaki et al. [13] reported in their study, which included 629 patients that examined applicants for free medical care in Tokyo, that the male: female ratio was as high as 14.5:1. There is also evidence of variation within individual countries. For example, within the United Kingdom, Silman et al. [14] reported that the male: female ratio was 3.92:1 in the West Midlands, whereas, Allocock et al. [15] found that the ratio was 4.7:1 in the North East of England. In a recent study that used data from the Clinical Practice Research Datalink between 1994 and 2013, of the 1327 incident cases, the crude and adjusted rate ratio between females and males was 4.9 and 4.7, respectively [16].

3.1. Ethnicity

SSc is more common in African-American (compared to Caucasian) patients, who also exhibit a more severe expression of the disease. This is potentially related to the higher prevalence of the diffuse subset of the disease, including a lower prevalence of anticentromere antibodies [17] and greater positivity of the anti-Scl-70 antibody [4,17,18]. Mayes et al. [17] investigated the epidemiology, including survival, in a large cohort of patients (n = 706, 106 black) based on the census of SSc cases during the period of 1989 to 1991 in the Detroit area. The disease was more frequently observed in black women compared to black men with a reported prevalence of 433.5 and 103.9 per million, respectively [17]. In a retrospective study of black patients (n = 63) with SSc who attended a tertiary hospital in South Africa, the male to female ratio was 4.6:1 [16]. The authors further reported that calcinosis more frequently occurred in men, whereas, arthralgia's/arthritis were more common in women [16]. Nitert and Silver [19] examined the patterns of hospital admissions and emergency room visits among patients (n = 785) with SSc over 5 years in South Carolina. The authors found that the number of visits/admissions was greater in black compared with white males, and also for older women aged between 50 and 64 years, and > 65 years [19].

4. Pathogenesis

The preponderance of SSc in females provides the clearest signal for the existence of important sex-related aetiopathogenic drivers in SSc. Putative factors that may account for differences in both prevalence and observed outcomes include the influence of female reproductive hormones, fetal microchimerism, X-linked genetic factors (including skewed inactivation, X-linked non-coding RNA and X-linked nucleotide polymorphisms) and also environmental/occupational exposures [20].

The potential role of sex hormones on the pathogenesis of SSc has also received research attention. A recent systematic literature of the sex hormones and sex hormone-targeting therapies literature concluded that oestrogens (particularly oestradiol) may have important pro-fibrotic but vasculoprotective properties in SSc [21]. Apparent differences in clinical phenotype in females presenting before and after the menopause [22,23] also suggests a link between sex hormone levels and clinical phenotype (with lower fibrosis but higher rates of PAH associated with hypo-oestrogenic states [21]. These findings have been challenged by recent work suggesting an anti-fibrotic role of oestrogens in pre-clinical models of SSc [24], which is consistent with the more severe clinical phenotype in males (see below). These contrasting findings have important implications for medications such tamoxifen and their potential effects in SSc. Studies examining androgen levels have yielded conflicting results, but high levels of oestradiol in older men are reported to be associated with heart involvement, skin progression, and death [25]. Androgens may also be important in SSc pathogenesis and one study has identified higher levels of androgens in post-menopausal female patients with SSc carrying anti-topoisomerase antibodies [26].

The preponderance of women with SSc (and high prevalence of autoimmunity in Klinefelter's diseases) has also led to interest in X-linked genes [20,27]. Methylation of a number of candidate X-chromosome genes may contribute to increased susceptibility to SSc (and discordance in twin studies) [28]. Skewed X-chromosomal inactivation also appears to increase susceptibility to SSc and the suppressive capacity of Tregs [29]. An IRAK1 haplotype containing the 196Phe functional variant (rs1059702), located on Xq28, has been shown to confer susceptibility to SSc with strong associations with the diffuse subset, the presence of anti-topoisomerase I antibodies, and SSc-ILD [30] . A study of patients with early SSc (< 3 years since first non-RP symptom) enrolled onto the EUSTAR registry, suggested men were more likely to carry anti-Scl-70 (54% vs. 7%) compared to females [31] and the genetic contribution to these observations may relate to genes on the X chromosome. The strong signal within the Xq28 region is also related to overexpression of MECP2 gene (related to diffuse cutaneous SSc) in SSc [32]. A recent study reported reduced expression levels of IRAK1 messenger RNA (inter-related to MEP2) in peripheral blood mononuclear cells (PBMCs) in SSc patients compared to controls, but also lower in male patients compared to females and appears to be associated with severe skin involvement [33]. PBMC expression of miR-146a (which downregulates IRAK1) is also reduced in SSc patients; particularly in males and those with severe skin involvement [33]. Other genes such as IL13RA2 have been shown to be associated with SSc in female populations [34]. Recent high-resolution global transcriptome analyses has identified a VGLL3-regulated pro-inflammatory network that promotes female-biased autoimmunity, highlighting the value of studying genetic risk separately in females and males [35]. Such studies may help to establish genetic signatures (and potential therapeutic targets) that shed light on sex-related differences in aetiopathogenesis and clinical phenotype in SSc. Pregnancy-related microchimerism may be an additional factor resulting in sex-related differences in SSc. It has been reported that female patients who had more children prior to their diagnosis of SSc, were more likely to have limited SSc and pulmonary fibrosis [36]. The interval between the birth of the first child and onset of SSc has also been noted to be shorter when the child was female [36].

Several studies have reported that men are more likely to carry anti-Scl-70 or anti-RNA polymerase III antibodies than anticentromere antibodies [31,37–41]. One study has found nucleolar antibodies targeting U3-RNP and Th/To are more common in females (in both Caucasian and African-American population) [39]. However, men have also been reported to have a higher probability of being antinuclear antibody negative [41,42]. A prospective study from the Spanish Systemic Sclerosis Study Group RESCLE (Registro de ESCLErodermia) register which included 1506 patients with SSc, men were significantly less

likely to be antinuclear antibody positive compared to women (85% vs. 93%, respectively) [41].

5. Time to diagnosis

Overall, the literature suggests that women tend to experience a longer time to diagnosis compared to men [41] after the onset of Raynaud's phenomenon (RP) [43,44], and the first non-RP symptom [44]. However, in the previously described study from the Spanish Systemic Sclerosis Study Group, men were reported to have a shorter duration from SSc onset to diagnosis (odds ratio of 0.98) [41]. In a study from the Scleroderma Canadian Group registry which included 1129 patients with SSc, the median time to diagnosis was significantly longer for women with diffuse cutaneous SSc compared to men (1.1 vs. 0.8 years, respectively), following the onset of RP [44]. Similarly, in another study of 408 patients with dcSSc, the time to diagnosis after the onset for RP was significantly longer in women compared to men [43]. This could potentially be explained (in part) by the overrepresentation of the limited subset of the disease in females, which is often characterised by a long duration of RP (potentially even decades). In addition, as described later, there is evidence to suggest that males have more severe vasculopathy, including digital vascular disease, than females.

6. Health behaviours and occupational exposures

Smoking has been reported to be more frequent in males with SSc [41,45]. For example, the authors of the previously described study from the RESCLE registry reported that smoking was significantly more common in men compared to women (odds ratio of 2.57) [41]. Whereas, in a study which included 231 patients of Greek origin with SSc between 1995 and 2011, there was no significant difference observed in smoking between men and women [46]. It is likely that there are important cultural influences in relation to smoking prevalence/gender differences. Important occupational exposures have been implicated in the aetiopathogenesis of SSc [47]. In a case control study examining occupational exposure to heavy metals in 100 patients with SSc, the authors found a marked association between antimony and platinum in males, and antimony, cadmium, lead, mercury, palladium and zinc in females [48].

7. Disease expression

7.1. Early SSc

In the previously described cross-sectional study of EUSTAR patients, in early disease (< 3 years from first non-Raynaud's symptom), men had more active disease (as assessed by the European Scleroderma Study Group SSc activity score), diffuse disease, anti-Scl-70 antibody positivity, elevated acute phase reactants, and pulmonary and muscular involvement [31]. These differences between the sexes were confirmed in patients with the limited, but not diffuse subset of the disease [31]. Furthermore, these findings were also similar when patients (n = 650) with < 3 years from the first SSc symptom, including RP, were also analysed [31].

7.2. Clinical phenotype

7.2.1. Disease subset

The diffuse subset of the disease is more commonly observed in men compared to women [31]. A cross-sectional study analysis which included 1027 patients enrolled in the European Scleroderma Trials and Research group (EUSTAR) database, in patients with early disease (< 3 years), men were more likely compared to women to have diffuse (61% vs. 34%) compared to limited (35% vs. 57%) cutaneous SSc [31].

7.2.2. Digital vasculopathy

In general, digital vasculopathy has been reported to be more severe in men, including digital ulcer (DU) disease [46,49–53]. However, some investigators have either found no difference in DU disease between the sexes [54] or being more common in females [55]. In the previously described Turkish study, DUs developed within the first three years in 54% of men compared to 31% of women [46]. Although RP is more common in women [56], men report a lower median daily frequency of attacks of RP compared to women (0.82 vs. 1.93, respectively) [57]. In a study which included 4642 patients with complete information on their digital gangrene status, the odds ratio of females (compared to males) developing gangrene was 0.73 (95% CI = 0.53–1.01, P = .055) during the observation period between April 2008 and November 2014 [58].

7.2.3. Cardiac

There is an emerging evidence to suggest that men may have a greater risk of scleroderma heart disease/cardiomyopathy [41,45,59–62]. For example, in a prospective observational study which included 9182 patients with at least two years follow-up data, extracted from the EUSTAR database, male sex was independently associated with heart failure (odds ratio of 2.22) [60]. Furthermore, in another case-control study of patients (n = 7073) from the EUSTAR database, multiple regression revealed that male sex was independently associated (odds ratio of 3.48) with left ventricular dysfunction [59].

7.2.4. Respiratory

Respiratory involvement: pulmonary artery hypertension (PAH) and interstitial lung disease (ILD) are now the leading causes of disease-related mortality in patients with SSc. The extant literature strongly indicates that ILD is more common in men [41,45,63]. For example, in the Spanish RESCLE study, male sex was independently associated with ILD (odds ratio of 1.58) [41]. Male sex has also been reported to be associated with progression of ILD [64,65].

Previous studies have reported a preponderance of pulmonary hypertension in both males [45,60,63] and females [41,66]. For example, in the previously described EUSTAR study examining cardiac dysfunction in SSc, male sex was independently predictive of new onset PAH (odds ratio of 2.66) [60]. In a study that included patients with SSc-PAH enrolled in the DETECT cohort study for up to three years, univariate logistic regression revealed that male sex was associated (odds ratio of 4.1) with disease progression [67]. Whereas, in the Spanish RESCLE cohort study, the investigators reported a clear predominance of pulmonary hypertension in females, in particular, in the absence of interstitial lung disease [41]. Of mechanistic interest, Scorza et al. [22] conducted a retrospective cohort study of female (n = 189) patients with SSc and observed that the postmenopausal condition was significantly associated (odds ratio of 5.2) with the development of isolated PAH. The authors also found evidence of a significant association between the postmenopausal condition and HLA-B35 (odds ratio of 15.2) [22]. Furthermore, in a small retrospective cohort study of 61 patients with SSc, in those 20 patients who received hormone replacement therapy (for a mean duration of 6.7 years), none of the patients developed isolated pulmonary hypertension, compared to 8 (out of 41) who did and were studied for a similar time period [68]. Pasarikovski et al. [69] reported significant sex disparities in their cohort study of 378 patients with SSc-PAH. Compared to female patients, males had a shorter time from SSc diagnosis to PAH diagnosis (1.7 vs. 5.5 years) and shorter PAH duration (3.5 vs. 4.7 years) [69].

7.2.5. Renal

Scleroderma renal crisis is a potentially life-threatening complication in SSc and is strongly associated with recent steroid exposure [70,71]. Male sex has been reported to be associated with an increased risk of scleroderma renal crisis [41,46,69,72]. For example, in the previously described study by Panopoulos et al., during the first three

years from disease onset, the scleroderma renal crisis developed in 17% of men and 3% of women [46]. Similarly, Pasarikovski et al. [69] examined sex disparities in SSc, and observed an increased frequency of renal crisis in males compared to females (19% vs. 8%, respectively).

7.2.6. Gastrointestinal/genitourinary

There is no clear evidence for significant sex differences relating to gastrointestinal (GI) involvement in SSc [41,73]. However, it is important to highlight that GI involvement is highly heterogeneous and often multifactorial within the SSc population. In an international multicentre study, which assessed urinary incontinence and quality of life of patients with SSc (n = 334) as assessed by self-administered questionnaires, the prevalence of incontinence was 63%, and this was significantly associated with female sex (odds ratio of 10.8) [74].

7.2.7. Bone health

A higher prevalence of osteoporosis has been reported in patients with SSc compared to the general population. However, this remains a contested issue, including whether there is any difference observed between the sexes [75–78]. In a recent cohort study using the Taiwan National Insurance database, compared to age- and sex matched controls, patients with SSc (n = 1712) had a significantly high incidence rate ratio of vertebral (1.78) and hip (1.89) fractures [79]. Multivariable cox regression analysis revealed that female sex was a significant risk factor (hazard ratio of 4.88) for osteoporotic fractures [79].

8. Mortality

Men with SSc have been consistently reported worldwide to be have a higher rate of premature death than their female counterparts [41,45,66,80,81]. In the previously described study from Detroit, male sex negatively affected survival (odds ratio of 1.81) [17]. In another large single-center cohort study from Pittsburgh, which included 2686 consecutive patients with SSc, males had significantly reduced survival at 5 and 10 years after the onset of SSc (73% and 45%, respectively) [45]. Similarly, In a study from the United Kingdom, during a mean duration of follow-up of 12.5 years, the standardised mortality ratio was higher in men compared to women (1.54 vs. 1.30, respectively) [82]. However, it is important to note that males have a higher death rate in the general population compared to females. Sex has been reported to be a very important (negative) determinant of SSc-PAH survival [83,84], including in the modern era [84]. In a systematic review and meta-analysis, which included 22 studies, male sex was associated with a hazard ratio for survival of 1.57 [83].

9. Transgender individuals

Only one study that has considered SSc in transgender individuals was identified. Campochiaro et al. [85] reported a case series of three patients who developed SSc after they had initiated hormonal therapy as part of their transition (male to female). The authors highlight in their cases (and another two additional cases from the literature) the very heterogeneous clinical and antibody profile of the patients, and the absence of any evidence-base to guide the continuation or cessation of hormonal therapies. In their detailed review of the literature, they highlight the different mechanisms by which hormonal modification, as part of gender transition, could be relevant in the acquired development of SSc [85].

10. Psychosocial aspects

Five papers were identified that focused on psychosocial aspects of SSc. All were quantitative and had insufficient male participants in their study samples to enable definitive conclusions on sex differences to be drawn. No qualitative studies were identified that have considered the influence of gender (i.e. the socially constructed characteristics of women and men, rather than biological ones) on issues such as work disability; psychosocial impact of sexual functioning, intimacy and relationships; nor self-management and coping.

Two studies have considered sex differences in health-related quality of life (HRQoL). A French cross-sectional study found both male and female SSc patients (n = 379; 16% male) to have mean scores lower than 40 out of 100 on all eight domains of the SF-36 including both physical and mental components [63]. This indicates poor HRQoL when compared with normative SF-36 scores, which have been reported to range from 60.3–88.4 [86]. A Chinese cross-sectional study [87] reported there were no sex differences between SF-36 scores for patients with SSc. However, they did disaggregate and report male and female data, and only 13% (10/38) of the sample were male.

Nguyen et al. [63,88] have found anxiety slightly more common in female than male SSc patients (62.3% vs 43.5%) as measured by the Hospital Anxiety and Depression Scale (HADS) [89]. However, this finding did not reach statistical significance, and male and female patients did not differ according to levels of depression. A Serbian cross-sectional study [90] (n = 35, 23% male) did not contain sufficient male patients to statistically compare gender differences, but reported 78% of female patients experienced depression compared to 38% of male patients (three of eight men) according to the Beck Depression Inventory [91], whilst 78% of female patients experienced anxiety compared to 88% of male patients (seven of eight men) according to the Zung's anxiety self-assessment scale [92].

One study [93] has focused on body image with participants (n = 98; 12% male) completing Likert scales to rate body image dissatisfaction relating to typical features of SSc such as finger ulcers and hand contractures. The authors noted high levels of body image dissatisfaction in both men and women, but did not include sufficient male patients to compare sex differences.

11. Conclusion

This review has drawn together the current evidence on sex differences in SSc for the first time. Although SSc is less common in men compared to women, men have a more severe expression of the disease including internal organ-based complications and higher mortality. The higher death male death rate in the general population is probably the most important factor responsible for excess mortality together with a greater prevalence of lung fibrosis. The extant literature shows that although pathophysiological sex differences are present in SSc, behavioural differences (e.g. higher smoking rates in men) and occupational exposures may contribute to poorer outcomes in men with SSc. Other important factors include (but are not limited to) a greater prevalence of the disease subset, delayed time to diagnosis, and higher disease activity in early disease in men. SSc carries a significant burden of disease-related morbidity; however, to date, no qualitative studies to date have focussed on gender differences in SSc. Future research is required to understand gender differences in SSc including to understand the experiences and support preferences of men to inform clinical practice and contribute to the development of appropriate and effective care tailored to men with SSc.

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