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REVIEW

Comorbidity burden in systemic sclerosis: beyond disease-specific complications

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Abstract

Systemic sclerosis (SSc) is a chronic, systemic disease characterized by fibrosis of the skin and internal organs, vasculopathy, and auto-immune activation. On the top of severe organ involvement such as interstitial lung and myocardial fibrosis, pulmonary hypertension, and renal crisis, individuals diagnosed with SSc may suffer from a number of comorbidities. This is a narrative review according to published recommendations and we searched the online databases MEDLINE and EMBASE using as key words the following terms: systemic sclerosis, scleroderma, myocardial fibrosis in combination with micro- and macro-vascular disease, cardiac involvement, atherosclerosis, cardiovascular disease and coronary arteries, infections, cancer, depression, osteoporosis, and dyslipidemia. Although data are usually inconclusive it appears that comorbidities with significant impact on life expectancy, namely cardiovascular disease, infections, and cancer as well as phycological disorders affecting emotional and mental health are highly prevalent in SSc population. Thereafter, the aim of this review is to summarize the occurrence and the clinical significance of such comorbidities in SSc population and to discuss how rheumatologists can incorporate the management of these conditions in daily clinical practice.

Keywords Systemic Sclerosis · Scleroderma · Cancer · Infections · Depression · Comorbidities

Introduction

Systemic sclerosis (SSc) is a rare systemic disease characterized by profound fibrosis of the skin and the internal organs, endothelial injury leading to microagiopathy and dysregulation of auto-immunity. SSc is a devastating auto-immune disease with a standardized mortality ratio of 3.5 [1] predominantly due to accumulation of inappropriately produced extracellular matrix in visceral organs such as lungs, cardiac tissue, and bowel. In parallel with fibrotic process, pulmonary and

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coronary microvascular involvement resulting in pulmonary hypertension and myocardial impairment, respectively, represents important vascular guises of the disease, all of which account for the premature morbidity and mortality in SSc patients compared to general population [2–4]. Subsequently, the focus has been posed over the management of severe internal organ involvement and less attention has been paid on the impact of other comorbidities on disease course and prognosis.

For instance, infections, cancer, and cardiovascular (CV) disease are important causes of death in SSc patients [5]; however, their contribution to the adverse outcomes is usually overlooked and underestimated in daily clinical setting. In contrast to other systemic inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus, the data regarding the prevalence and influence of comorbidities in SSc are limited. The clinical complexity and heterogeneity of SSc makes the evaluation of comorbid conditions even more difficult as the bidirectional influence between disease itself and comorbidities may promote tissue damage culminating in worse outcomes and prognosis. Despite the better understanding of SSc pathophysiology and the implementation of more disease-specific treatments [6, 7], the overall management of the disease remains suboptimal. The identification of SSc patients with comorbidities remains problematic, and only recently comparative studies between SSc and other auto-immune disease have addressed the question whether such conditions are more prevalent in one or the other disease [8]. The aim of this review is to illustrate the current knowledge about comorbid conditions in SSc (Fig. 1) and to discuss how these conditions could be efficiently managed in daily clinical practice. The presentation of SSc-related complications is beyond the scope of the current review which will focus only on comorbidities presented in SSc subjects.

Search strategy

The online databases MEDLINE and EMBASE were searched until December 2018 for either research papers or review articles concerning the micro- and macro-vascular involvement in

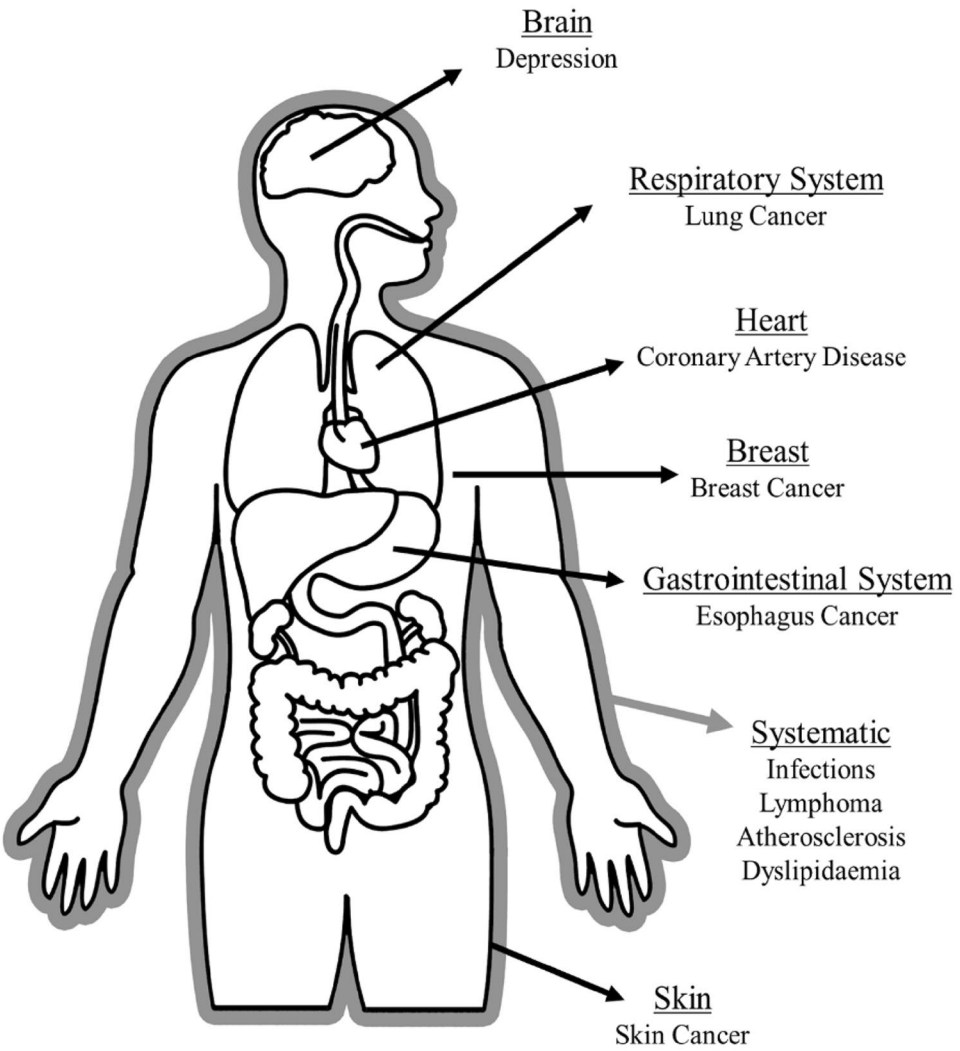

Fig. 1 The spectrum of comorbidities in SSc. Apart from disease-specific fibrotic complications of internal organs namely pulmonary, myocardial, bowel, and upper gastrointestinal system involvement, cancer and infections could affect almost any organ and tissue in SSc patients. Macro-vascular atherosclerotic vasculopathy may exacerbate the deleterious effects of obliterative microvasculopathy contributing to increase cardiovascular morbidity

SSc. The following terms were used as keywords to search for relevant publications: systemic sclerosis, scleroderma, myocardial fibrosis in combination with micro- and macro-vascular disease, cardiac involvement, atherosclerosis, cardiovascular disease and coronary arteries, infections, cancer, depression, osteoporosis, and dyslipidemia. Articles that had been published as full journal articles in English were included in our review. Poster presentations, conference proceedings, not accessible abstracts, and data from ongoing pharmaceutical research and not translated in English reports were excluded [9].

Atherosclerosis and coronary artery disease

The association between premature atherosclerosis, CV disease, and chronic inflammation has been well established in patients with rheumatoid arthritis [10] and systemic lupus erythematosus [11]. Given that macro-vascular complications were not originally considered as a feature of SSc, research has been focused primarily on microvascular injury rather atherosclerosis [12, 13]. However, an increasing amount of epidemiological data suggest that macro-vascular atherosclerotic disease might affect CV morbidity and mortality in SSc (Table 1) accounting for approximately 20–40% of mortality in SSc [14–18]. Recent evidence from the Danish Registry renders SSc as significant CV risk factor for the composite endpoints of stroke, myocardial infarction, and overall cardiovascular death [19]. In line with such observations, national registries and observational studies have demonstrated higher rates of coronary artery disease and increased rates of CV mortality in SSc patients compared to healthy controls [20–26].

A qualitative systematic review about the prevalence of coronary artery disease in SSc concluded that the

Table 1 Summary of the studies assessing the prevalence of coronary artery disease and the risk for cardiovascular events in systemic sclerosis

First author	Year	Type of study	Study population	Definition of CAD	Outcome
D'Angelo [25]	1969	Retrospective	58 SSc autopsy cases/58 controls	Small coronary arteriosclerosis on autopsy	17.2% vs. 1.7% $p<0.01$
Bulkley [24]	1976	Retrospective	52 SSc cases	Coronary atherosclerosis on autopsy	7.7%
Youssef [4]	1995	Retrospective	31 SSc cases/31 controls	AMI/Angina	32.7% vs. 22.6% RR 1.7 95% CI (0.8–3.7)
Jacobsen [8]	1998	Retrospective	344 SSc cases—160 deaths	CVD mortality (AMI, HF, cerebral palsy, PE)	41% of non-SSc-related causes of death
Hesselstrand [7]	1998	Retrospective	249 SSc patients—49 deaths	CVD mortality (no clarification)	20.5% of all deaths
Akram [117]	2006	Cross-sectional	172 SSc cases	Positive coronary angiography	22.1% similar to the general population
Tarek [28]	2006	Cross-sectional	14 SSc cases	Positive coronary angiography	21.4%
Khurma [15]	2008	Retrospective	17 SSc cases/17 controls	Coronary artery calcification on CT	52.9% vs. 17.6%, $p=0.03$
Komosci [27]	2010	Cross-sectional	120 SSc cases	Positive coronary angiography	12.5%
Tyndall [9]	2010	Retrospective	5860 SSc cases—234 deaths	CVD mortality (AMI, HF, stroke, arrythmia, PE, pericarditis)	26% of SSc-related causes and 29% of non-SSc-related causes of death
Mok [16]	2011	Retrospective	23 SSc cases/23 controls	CT coronary artery calcium score ≥ 101	56.5% vs. 45.5%, OR 10.9 95% CI (2.2–53.8)
Ngian [13]	2012	Cross-sectional	850 SSc cases/8802 Australian controls	Previous PCI, CABG, angina or MI	10.4% vs. 7.3% OR 3.2 95% CI (2.3–4.5)
Man [12]	2012	Retrospective	865 SSc cases/8643 controls	AMI	Incidence rate 4.4% vs. 2.5% HR 1.8 95% CI (1.1–3.1)
Nordin [17]	2013	Retrospective	111 SSc cases/105 controls	AMI, angina	11.7% vs. 3.8% OR 3.3 (1.1–10.6)
Chu [14]	2013	Retrospective	1344 SSc cases/134 controls	AMI	Incidence rate 5.4 vs. 3.1 HR 2.5 95% CI (1.6–3.8)
Dave [6]	2014	Retrospective	308,452 SSc hospitalizations	CAD, mortality	5.4% of hospitalizations
Avipa-Zubieta [11]	2016	Retrospective	1239 SSc cases/12,390 controls	AMI	Incidence rate 13 vs. 3.1 HR 3.49 95% CI (2.52–4.83)
Hesselvig [10]	2017	Retrospective	1962 SSc cases/5,428,380 controls	Composite of CVD death, AMI, stroke	Incident rate 23.1 vs. 8 HR 2.2 95% CI (1.99–2.48), $p<0.001$

majority of case–control studies reported increased prevalence (10–56%) or incidence (2.3%) of CV disease in SSc patients compared to controls (prevalence 2–44%; incidence 1.5%), while SSc itself was found to be an independent predictor for coronary atherosclerosis [27]. A meta-analysis of four observational studies confirmed the association between SSc and coronary artery disease demonstrating an overall 1.82-fold (95% CI 1.40–2.36) increased risk amongst SSc subjects compared with non-SSc participants [28]. The same group reported a significant association between SSc and cerebrovascular disease with an overall 1.68-fold (95% CI 1.26–2.24) increased risk for ischemic stroke in SSc subjects compared with non-SSc participants [29]. With regards traditional CV risk factors, the data are conflicting with no robust evidence supporting higher prevalence of hypertension, smoking, obesity, and abnormal lipid metabolism in SSc compared to controls [27].

The pathophysiology of cardiovascular disease in SSc has not been clearly understood, yet. Chronic inflammation, auto-immune dysregulation, and endothelial dysfunction could result in accelerated atherosclerosis, vasospasm, and thrombosis, and thus in macro-vascular disease in patients with SSc [10, 12, 30]. On one hand, chronic inflammation promotes atherosclerosis by altering endothelial function via inflammatory mediators and activated inflammatory cells [31], while on the other hand, it triggers the coagulation cascade, resulting in a hypercoagulable state [32]. This inflammation-mediated process, in conjunction with the vasculopathy of SSc, may serve as a background for the development of premature coronary artery and peripheral arterial disease [33, 34]. Several studies have revealed an increased subclinical macro-vascular coronary atherosclerotic burden in SSc [24, 25, 35–37]. Furthermore, there is also evidence, although contradictory in several studies, about an accelerated subclinical atherosclerosis in peripheral arteries of patients with SSc, too [38]. Ozen et al. demonstrated that subclinical atherosclerosis in SSc, as assessed by carotid intima-media thickness (CIMT) was as frequent as in rheumatoid arthritis and could not be identified with cardiovascular risk scores for the general population [39]. Another study revealed SSc to be an independent risk factor for coronary calcification, in addition to the conventional risk factors for coronary atherosclerosis, such as age and hypertension [25]. In addition, a meta-analysis of observational studies assessing CIMT and flow-mediated dilation in SSc confirmed the high prevalence of atherosclerosis compared to healthy controls [40].

In general, current data demonstrate a tendency to support the hypothesis about the increased risk for major CV events associated with SSc, as well as the presence of subclinical atherosclerosis. However, the prevalence of coronary artery disease varies among different studies, mainly due to the heterogeneity, regarding the methodology, the definition of CV events, the cohort size, and the outcome. Consequently, there is a need for large epidemiological studies with prespecified CV definitions and outcomes, to have robust evidence regarding the association of SSc with CVD and its complications.

Dyslipidaemia

Dyslipidaemia is a strong contributor to vascular disease and, therefore, to endothelial dysfunction, which is present increased in patients with SSc [41].

Some authors have reported only a significant increase in the levels of the triglycerides [42, 43], possibly mediated through reduced LPL activity as a consequence of the formation of anti-LPL antibodies [43]. Other pathogenic factors involved in SSc-associated vascular damage include increased LDL [44]. In a case–control study, the lipoprotein profile of 24 female SSc patients and 24 healthy age- and sex-matched controls was determined and was concluded that significantly lower levels of high-density lipoprotein (HDL) cholesterol and total cholesterol were observed in SSc patients than in controls [45]. On the contrary, results from the Australian Scleroderma Cohort Study including 850 SSc patients, as well as 15,787 and 8802 individuals as controls from the National Health Survey (NHS) and the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) respectively, showed that hypercholesterolemia was significantly less prevalent in SSc patients than in controls [22].

Infections

Infections are highly prevalent in patients with SSc, especially in those with esophageal and pulmonary involvement, severe Raynaud's phenomenon, calcinosis, and treated with specific drugs [46]. Patients with esophageal involvement are at high risk of aspiration pneumonia, due to the dysfunction of the esophageal sphincter [47–50]. Pulmonary complications have been reported as a cause of death in 17–24% of scleroderma patients [51, 52]. Pulmonary infections are more prevalent in patients with pulmonary fibrosis, especially those with interstitial lung disease [16]. Severe Raynaud's phenomenon complicated with digital ulcers set scleroderma patients at high risk of localized infections [49], as well as severe calcinosis [53]. Vice versa in patients with refractory skin ulceration underlying infections contribute to the severity of the digital ischemia and should be managed effectively [54].

Several types of infection have been reported in patients with SSc, including bacterial, viral, and fungal infections.

For example, case reports reporting bacterial infections include streptococcus pyomyositis [55], soft tissue S aureus [53], bacterial peritonitis [56], mycobacterium avium intracellulare as a cause of septic arthritis [57], and mycobacterium kansasii as a cause of tenosynovitis [58]. In a case–control study including 124 patients with SSc and 50 controls, it was shown that Helicobacter pylori infection is more prevalent in patients with scleroderma than in general population [59]. Regarding opportunistic infections, pneumocystis carinii has also been reported in SSc patients [60].

The prevalence of tuberculosis (TB) has been investigated in a nationwide study using the Taiwan National Health Insurance Research Database including 838 patients with SSc and 8380 randomly selected age-, sex-, and comorbidity-matched controls. In this study, the risk of tuberculosis was higher in SSc patients than controls ($p=0.004$) and for pulmonary TB in particular ($p=0.022$). Age ≥ 60 years [hazard ratio (HR) 3.52, 95% CI 1.10–11.33; $p=0.035$] and pulmonary hypertension (HR 6.06, 95% CI 1.59–23.17; $p=0.008$) [61] were established as independent risk factors for the occurrence of tuberculosis in this study highlighting the need for close surveillance in this subgroup of SSc subjects.

Although large population-based studies have not been conducted yet, reported cases show a correlation between infection and specific treatments. Aggressive use of immunosuppression and autologous stem cell transplantation in a neutropenic scleroderma patient resulted in a lethal infection [62] although the rates of severe infections in patients undergoing autologous stem cell transplantation appear to improve in recent studies Patients receiving cyclophosphamide and low-dose prednisone have been reported with pneumonia [63] and local infections occurred in 10% of SSc patients receiving subcutaneous relaxin [64]. Collectively, infections represent a neglected and underrecognized comorbidity in SSc patients and the awareness of this increased risk amongst clinicians dealing with this specific population is of outmost importance.

For instance, the implementation of prevention strategies with immunization against common bacterial and viral pathogens can reduce the burden of serious and/or mild infections in SSc population [65, 66]. The vaccination status should be assessed in the course of the disease for patients with auto-immune inflammatory rheumatic diseases including SSc individuals [67]. Although there are many pending issues regarding the duration of protection, the need for booster doses, the safety of live vaccines, the timing between vaccination and biologic disease-modifying anti-rheumatic drugs' (bDMARDs) administration, and the impact of novel biologic agents on vaccine immunogenicity vaccines against influenza and pneumococcus are strongly recommended, while live vaccines should be assessed on individual basis [68, 69]. The EULAR recommends avoiding the use of live vaccines whenever possible with the possible exceptions of herpes zoster and MMR or the temporary discontinuation of the immunosuppressive medication [67]. In conclusion, a vaccine strategy should be implemented in the everyday practice regarding to all the restrictions mentioned above, to reduce as possible infections in patients with SSc.

Cancer

Malignancies in patients with SSc occur in a percentage of 3.6–10.7% with male gender, older age, diffuse type of the disease, and presence of auto-Abs against polymerase I/III [70] represent the main risk factors [71]. However, the incidence of cancer largely varies amongst studies reflecting the heterogeneity of SSc as well as the epidemiologic variations of the disease across different countries. It is worth noting that malignancies tend to occur at organs affected by fibrosis such as lungs, esophagus, breast, and skin, with a standardized incidence ratio (SIR, the observed cancer cases to the expected cancer cases for a particular population) ranging from 1.5 to 5.1 compared to general population [72]; similarly to what occurs with other systemic auto-immune disease lymphoproliferative disorders are also common in SSc individuals [71, 73]. On the other hand in a pooled analysis of clinical trials, SSc patients were at higher risk of developing cancer, but the absolute risk was relatively low as the SIR for the incidence of cancer overall was 1.41 [74].

Even though the most common disease-specific auto-antibodies such as anti-centromere (ACA) or anti-topoisomerase I (anti-Scl70) are not associated with malignancy, a subgroup of patients with auto-Abs against polymerase I/III exhibit a striking temporal relationship between the onset of cancer and scleroderma [70]. Further research in this field has provided intriguing evidence that the immunologic response against cancer may be the trigger for the development of SSc. Molecular analysis of cancer tissue obtained from these patients revealed mutations in the gene-encoding polymerase III. Experimental evidence indicates that these mutations may trigger cellular and humoral immune responses that eventually lead to production of auto-antibodies against the mutated polymerase III. These auto-Abs may cross react with the native polymerase III and trigger the development of SSc by undetermined mechanisms [75, 76]. On the other hand, the presence of antinuclear antibodies (ANA) and SSc patients with cancer is associated with better outcomes compared to ANA-negative SSc persons diagnosed with neoplastic disease [77].

The etiology for increased malignancy rates in this population remains unclear, but chronic immunologic activation, fibrotic process, and immunosuppressive agents mediated by environmental and genetic influence are the main contributing factors to the development of neoplasms [78]. For

example, excessive inflammation and fibrosis of the lung parenchyma are considered to initiate a precancerous cascade with the most common mechanism to be the atypical epithelial regenerative changes [79]. In this respect, lung cancer is the most common malignancy [73]. In a large cohort study including 441 patients with scleroderma from the South Australian Scleroderma Registry, the SIR for lung cancer was 5.9; 95% CI 3.05 to 10.31) [79, 80]. As expected, smoking carries a sevenfold increased incidence rate for the presence of lung cancer ($p=0.008$) among SSc individuals [81].

Following in frequency among solid tumors in SSc patients stands breast cancer [82]. David Launay et al. noted a close relationship between the onset of scleroderma and breast cancer suggesting a pathophysiological relation between these two conditions [83]. The authors note as possible links paraneoplastic syndrome, endothelial cell activation, and altered immune response. Tim et al. in a study of 21 patient with both systemic sclerosis and breast cancer suggested an association between human leukocyte antigen (HLA) haplotype and the BRCA gene mutation [84]. Both the above studies showed an association between limited scleroderma and ACA positivity [83, 84].

Results from reports studying the correlation between scleroderma and the development of lymphoma are inconclusive with Rosental et al. reporting high SIRs for non-Hodgkin's lymphoma (SIR = 9–6; 95% CI l.l–34.5) in a population-based study of 233 patients in Sweden [85],whereas such observations were not confirmed in a large case–control study of 262 patients conducted by Roumm and Medsger [86]. A retrospective study including 218 SSc patients reported that lymphoma has a 1.9–2.5-fold increased incidence in patients with scleroderma than in general population [73]. Besides immunosuppressive treatment, the higher frequency of chromosomal abnormalities observed in SSc persons compared with healthy controls may provide an alternative explanation for the predisposition to hematologic cancer demonstrated in this condition [87].

In conclusion, cancer is more common in SSc compared to general population and confers an additional unfavorable impact on prognosis and survival in this population. Currently, there are no specific guidelines for SSc patients and clinicians should implement strategies suggested for general population. For example, screening for breast and colon cancer accompanied by high index of suspicion based on age, gender, and type of disease as well as effective management of risk factors such as smoking may reduce cancer risk and contribute to better long-term outcomes.

Psychological burden

Functional disability is a well-established entity and SSc patients have poor health-related quality of life (HRQoL) [88–90]. Disease-specific disability and pain appear to be the main determinants of such poor outcomes, whereas disability due to musculoskeletal discomfort is predominantly associated with male gender [91]. The burden of disease is mostly measured with disability-adjusted life years (DALYs) and is equal with one lost year of healthy life. In 2011 a study conducted in Spain aiming to estimate the scleroderma-based burden of disease according to the Global Burden of Disease study, systemic sclerosis generated 1732 DALYs with higher prevalence in the population aged 15–54 years [92].

Depression is found to be frequent among patients with scleroderma in rates ranging from 51 to 65% with at least mild-to-moderate symptoms [93]. Depression is strongly connected with pain in these patients, component that affects the quality of life. In a study of 142 SSc patients recruited through the Johns Hopkins and University of Maryland Scleroderma Center, it was reported that pain and depressive symptoms, even at mild levels, were significantly associated with physical functioning and social adjustment [94]. Many psychiatric symptoms can be associated with SSc. In a case–control study conducted in Greece including 30 female patients and 33 female controls, Angelopoulos et al. found a high prevalence of anxiety, depression, and somatization among patients with scleroderma [95]. The correlation between depression and systemic sclerosis is well established and many studies conducted have not found yet an association between the clinical symptoms of systemic sclerosis and depressive symptoms. In a study of 54 patients who completed the Beck Depression Inventory (BDI) questionnaire, no direct relationship between the severity of the illness and the depressive symptoms was established [96]. In addition, another study including 42 patients and using the Montgomery-Abserg Depression Rating Scale concluded that the scores were not associated with the extent of skin or organ involvement, but were significantly higher in patients with pulmonary restrictive disease ($p=0.009$) [97]. Another study evaluating 50 patients showed that BDI scores are not associated with disease severity variables, such as skin score and internal organ involvement [97]. Depression is a symptom that has to be taken under serious consideration by doctors and be evaluated with the appropriate criteria. Although studies until now have conflicting results on whether depressive symptoms are related to the severity of systemic sclerosis, it is clear that it has an impact on social adaptation and daily functioning. On the other hand, the psychologist and psychotherapist would be very helpful in all these cases. Above all, in terms of social adaptation and day-to-day functioning outside of the drug component, it would add another dimension to the solution of the feeling of depression.

Fibromyalgia (FM) is strongly related with depression, generalized pain, and low HRQoL. A study in 2017 tested three (FM) tools [a screening tool (FiRST), diagnostic

criteria (ACR 1990 and revised 2010)] to compare the prevalence between FM and SSc patients. 122 SSc consecutive patients were enrolled and FiRST detected FM in 27.8% of them with confirmation in 30.3% (ACR1990) and 23.7% (ACR2010), showing a high prevalence of FM in SSc [98]. On the contrary, a recent study in 2018 enrolled 30 SSc patients and the frequency of fibromyalgia in this population was only 2 (6.67%) [99].

Sleeping disorders appear to have a high prevalence in patients with scleroderma, which plays an important role in daily functioning. A Canadian National Survey confirmed the importance of core symptoms such as pain in SSc patients and showed that, in a total of 464 patients, 76% had sleeping difficulties and this symptom had a moderate-to-severe impact on daily activities in a 67% [100]. A case–control study of 48 SSc patients assessed sleep disturbances using the Pittsburgh Sleep Quality Index (PSQI), and concluded that SSc patients had poorer subjective sleep quality and higher scores in sleep latency, habitual sleep efficiency, sleep disturbance, and daytime dysfunction domains compared to the control group [101]. In 2002, Prado et al., using an all-night polysomnogram and a clinical interview blinded to sleep status, examined 27 consecutive SSc patients and found that sleep disorders have a high prevalence among the SSc population and esophageal dyskinesia and dyspnea are associated with indices of sleep disruption [102]. Reinforcing these results, in 2011 in a large observational study participating 180 SSc patients, sleep disturbances were examined and concluded that sleep disorders are common in SSc and are associated with worsening dyspnea, depressed mood, and severity of reflux symptoms [103]. Sleep is crucial for the well-being and its disorders can lead to increased morbidity [104].

Taking all together, physiological consequences and poor quality of life in SSc patients constitute an important but usually unrecognized aspect of the disease. To lend more support a recent study conducted in Asian population with systemic auto-immune disorders reported poorer HRQoL in SSc subjects compared to patients with rheumatoid arthritis and lupus highlighting the unmet need for better management, psychological support, and education in this population [105].

Osteoporosis

Osteoporosis is a common comorbidity between SSc patients with a prevalence of 6.7–51.1 [106–108]. Many different factors contribute in this pathophysiology, such as chronic inflammation, malnutrition, malabsorption, decreased activation of Vitamin D, and medical treatments, such as glucocorticoids [109]. In a large cohort of 106 consecutive patients, a strong correlation was found between whole-body Z score with BMI ($p < 0.001$) and lung involvement in multivariate analysis ($p = 0.037$) [110]. Fractures are commonly seen in SSc patients [111, 112]. Regarding postmenopausal women with scleroderma, a case–control study demonstrated a prevalence of 22% of osteoporosis and vertebral fractures in this group compared to controls, with no difference between the lcSSc and dcSSc [112].To further reinforce the connection between osteoporosis and systemic sclerosis, a population-based case–control study including 1712 Taiwanese SSc patients and 10,272 controls showed a high risk of osteoporotic fracture (vertebral and hip) and furthermore that medication with glucocorticoids plays an important role in their occurrence [113]. Interestingly, no difference in the prevalence of osteoporosis or osteoporotic fractures between SSc and rheumatoid arthritis subjects was reported in a recent comparative study [24% vs 22%, $p = 0.619$; OR 1.08 ([95% CI 0.78–1.49) and 6.1% vs 6.7%, $p = 0.665$; OR 1.13 (95% CI 0.64–2.0), respectively] [8]. The latter actually confirms that similarly to what occurs in rheumatoid arthritis and other systemic diseases [114, 115], SSc population requires special care regarding prevention and management of osteoporosis, especially individuals with risk factors such as older age and female gender, exhibiting bowel dysmotility and receiving a high dose of steroids [113]. Prompt and sufficient osteoporosis risk assessment accompanied by targeted therapeutic interventions and efforts to improve bowel motility and nutritional status, including Vitamin-D supplementation [116], may result in better management and improve metabolic bone disease incidence in SSc patients.

Conclusions

Systemic sclerosis is a rare auto-immune disorder affecting many organs, and consequently causing comorbid conditions in the course of the disease. On the top of disease-related visceral organ involvement, malignancies, atherosclerotic vascular disease, infections, and depression have an important—usually underappreciated and neglected—unfavorable impact on prognosis and quality of life of SSc patients. The absence of large prospective studies clearly reflects this unmet need and underscores the necessity for better acknowledgment amongst physicians of comorbidities in this population. The latter will hopefully culminate in improved overall management and better outcomes including both SSc-related complications and comorbidities.

Authors contribution Conceived research idea and designed study: AG, GK, and THD; acquired data: EP, AA, and DD; analyzed and interpreted data: EP, AA, DD, and THD; provided supervision or mentorship: AG, GK, and THD. Each author contributed important intellectual content during manuscript drafting or revision and accepts

accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest All authors disclose that they do not have any financial or other relationships, which might lead to a conflict of interest regarding this paper.

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