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# Autonomic dysfunction in systemic sclerosis: A scoping review

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ABSTRACT

*Introduction:* Over the years several lines of evidence have implied a pathological involvement of autonomic nervous system (ANS) in systemic sclerosis (SSc). However, the relationship between autonomic dysfunction and SSc is not yet fully understood. The aims of this scoping review were to map the research done in this field and inform future research to investigate pathogenic hypotheses of ANS involvement.

*Methods:* We performed a scoping review of publications collected through a literature search of MEDLINE and Web of Science databases, looking for dysautonomia in SSc. We included original data from papers that addressed ANS involvement in SSc regarding pathogenesis, clinical presentation and diagnostic tools.

*Results:* 467 papers were identified, 109 studies were selected to be included in the present review, reporting data from a total of 2742 SSc patients. Cardiovascular system was the most extensively investigated, assessing heart rate variability with 24 h HolterECG or Ewing's autonomic tests. Important signs of dysautonomia were also found in digital vasculopathy, gastrointestinal system and SSc skin, assessed both with non-invasive techniques and histologically. Research hypotheses mainly regarding the relationship between sympathetic system – ischemia and the role of neurotrophins were then developed and discussed.

*Conclusion:* We described the currently available evidence on pathogenesis, clinical presentation and diagnostic assessment of dysautonomia in SSc patients. A strong influence of ANS deregulation on SSc clearly emerges from the literature. Future research is warranted to clarify the mechanisms and timing of autonomic dysfunction in SSc.

## Introduction

Systemic sclerosis (SSc) is a rare and chronic connective tissue disease characterized by a heterogeneous clinical profile that derives from a multifaceted pathogenesis. Vascular damage, initially presenting with endothelial dysregulation, and autoimmune derangement are thought to trigger an imbalanced extracellular matrix turnover, leading to fibrosis. This can occur in a number of tissue sites including skin, gastrointestinal tract, heart and lungs [1]. A concurrent pathogenic role of the autonomic nervous system (ANS) has been postulated since the early studies of the '80s that described autonomic neuropathy in SSc [2]. ANS is divided in three major branches: sympathetic system, parasympathetic system and enteric nervous system (ENS). Over time, several evidences were gathered regarding the involvement of each of those systems in SSc. ANS dysfunction was described in different organs using different methods, trying to provide pathogenic insights but some areas remain unclear. Therefore, we aimed to conduct a scoping review with the dual purpose of mapping the research done in this field so far and bringing out some pathogenetic hypotheses to inform future research efforts.

## Methods

This review was guided by the following research question: "Where to look for and how to assess ANS dysfunction in SSc?" and was performed according to PRISMA extension for scoping reviews [3]. We searched MEDLINE and Web of Science databases using a combination of MeSH terms and keywords: 'systemic sclerosis' and 'autonomic nervous system', 'dysautonomia', 'autonomic dysfunction', 'sympathetic', 'parasympathetic' or 'enteric nervous system'. We included only articles written in English and on human subjects, published up to 15th March

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2023. Papers that did not report original data (e.g. reviews) were excluded, while case reports were included. To avoid potential repetitions, meeting abstracts were not included. Sources were deemed eligible if they explicitly addressed ANS involvement in SSc regarding pathogenesis, clinical presentation and diagnostic tools, whereas treatment was out of the scope of this review. The same list of articles was screened twice and then data from eligible papers were charted in a standardized data abstraction tool designed for this study. These processes were carried out by two reviewers working in tandem. Any disagreement on study selection and data extraction was resolved by consensus and discussion among all the authors.

We abstracted data only on SSc patients (thus excluding overlapping forms, primary Raynaud's phenomenon, healthy controls, etc.) and, when easily evaluable, on mean age, sex and skin subset according to LeRoy [4]. For the descriptive purpose of this work, the age values reported in median or presented separately into subgroups were recalculated and included anyway, whereas cases of skin involvement not attributable to LeRoy classification were not considered. We extracted information on organ/system involvement, methods of assessment and main conclusions.

## Results

Out of 467 papers screened, 109 studies were included in the present review (Fig. 1). The vast majority (88 %) were observational studies, while there were no randomized controlled trials. Data from a total of 2742 SSc patients were examined. Although in some cases these entries could not be retrieved, the demographic description shows a predominantly female (85.2 %) population with a mean age of 50.5 ± 7.9 years. Out of 2012 patients assessed for skin subset, 55.6 % had a limited cutaneous form and 44.4 % a diffuse one (see Appendix A for further details). Table 1 and Fig. 2 summarize organ involvement and assessment methods reported to a larger extent.

**Table 1**
Most relevant organ involvement and assessment methods regarding autonomic dysfunction in SSc.

| ***Articles***, n (some with multiple entries) | |
|---|---|
| Cardiovascular involvement | 61 |
| • electrocardiogram | 39 |
| of which 24 h HolterECG | 26 |
| • Ewing's autonomic tests | 26 |
| Digital vasculopathy | 23 |
| • induction with cold test and/or lidocaine and/or postural changes | 12 |
| • laser doppler techniques | 9 |
| Gastrointestinal / Enteric nervous system | 18 |
| • manometry | 6 |
| • autoantibodies | 4 |
| • histology | 3 |
| Skin involvement | 13 |
| • sympathetic skin response | 6 |
| • histology | 5 |
| Eye involvement | 4 |
| • pupillometry | 4 |

### *Cardiovascular involvement*

Cardiovascular system is certainly the most investigated for ANS dysfunction in SSc. Heart rate variability (HRV), preferably assessed by 24 h Holter electrocardiogram, reflects the sympatho-vagal balance and proved to be a simple, non-invasive tool for evaluating the autonomic control of the heart [5–7]. Ewing's autonomic tests were the first to be used in the evaluation of the autonomic reflexes and still represent a valid method to obtain a general assessment of ANS status. They evaluate the heart rate responses to Valsalva maneuver, deep breathing and lying-to-standing, as well as the blood pressure responses during standing and sustained hand grip [8,9]. From the literature it clearly emerges a strong relationship between autonomic dysfunction and SSc cardiovascular system. In addition to the already mentioned rhythm disturbances [7], it was highlighted that dysautonomia can affect

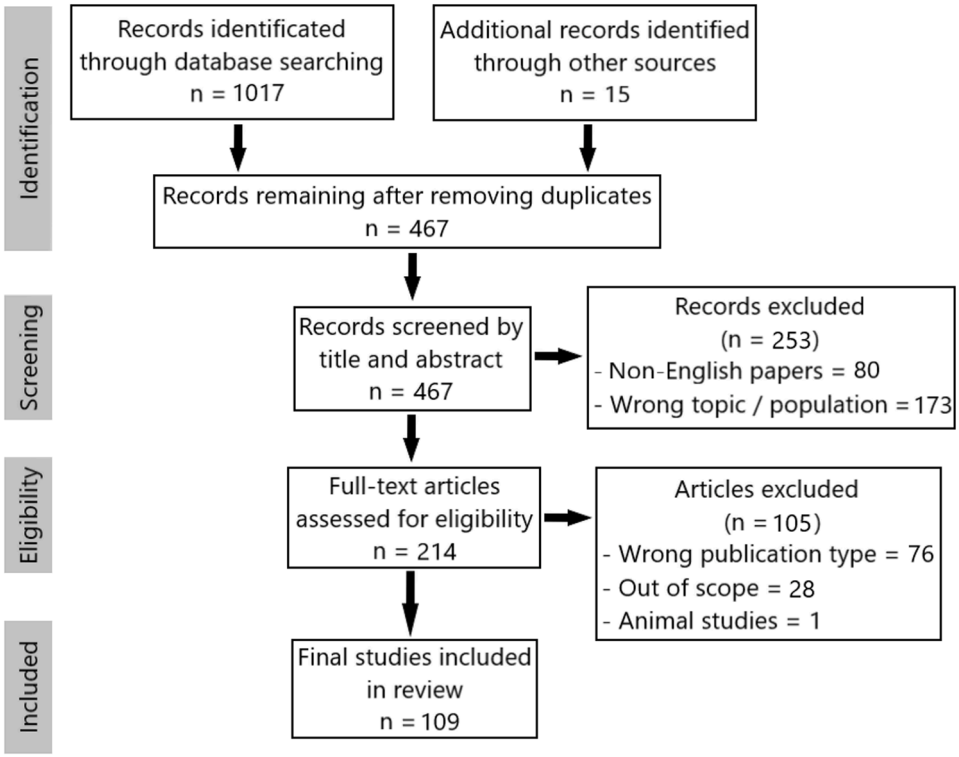


**Fig. 1.** PRISMA flow diagram for the scoping review.

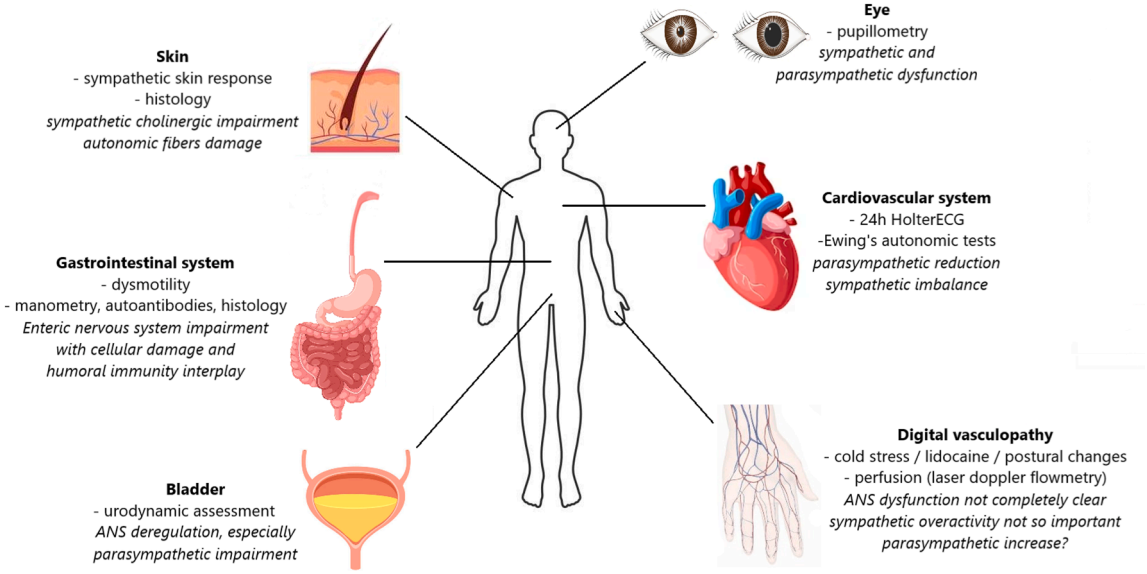


**Fig. 2.** Summary of autonomic nervous system dysfunction in SSc and assessment methods.

cardiac mechanics at all myocardial layers, particularly impairing both diastolic function and longitudinal strain, thus influencing biventricular remodeling [10,11]. It is worth to note that autonomic impairment in SSc heart was demonstrated to occur very early in the course of the disease, even in asymptomatic patients [9,12,13]. Such a preclinical heart involvement was strengthened by studies with $^{123}$I meta-iodobenzylguanidine scintigraphy that revealed inhomogeneous reduction of norepinephrine content in the hearts of asymptomatic SSc patients with no signs of myocardial ischemia and normal ventricular contractility, thus reflecting a very early sympathetic affection in SSc heart [14,15]. Altogether, the studies reviewed point towards a parasympathetic reduction and a sympathetic imbalance in SSc cardiovascular system. As recently suggested by a cohort study on 24 SSc patients, such affection seems to increase in step with skin involvement and to progress over time [16].

*Digital involvement*

Digital vasculopathy is another field extensively investigated over the years. Initially believed to be the main cause of digital vasospasm, autonomic response was frequently induced by a variable combination of cold stress tests, lidocaine injection and postural changes of the hands, evaluating subsequent perfusion responses usually by laser doppler flowmetry [17–19]. There is evidence from the literature of ANS involvement in SSc digital vasculopathy, especially in correlation with the progression of microangiopathic damage as assessed by nailfold videocapillaroscopy [20,21]. However, the exact direction of ANS branches dysregulation is not completely clear and sometimes seems to be in contrast with the findings from cardiovascular system. In fact, although sympathetic upregulation was initially believed to be pivotal in digital vasospasm [22], several articles have then indicated that sympathetic overactivity is not as important in SSc-associated Raynaud's phenomenon [17,23,24]. Conversely, a cross-sectional study on 27 SSc patients reported an increase in parasympathetic activity in correlation with microvascular damage expressed by the presence of digital ulcers, increased vascular endothelial growth factor and progression of the capillaroscopic pattern [25]. Finally, given their importance in maintaining sympathetic integrity, brain derived neurotrophic factor (BDNF) and other neurotrophins were intriguingly hypothesized to play a pivotal role in vascular and tissue sympathetic deregulation. In particular, BDNF is upregulated by ischemia and seemed to be crucial in the transition from sympathetic overactivity to inflammation [26].

*Gastrointestinal involvement*

Gastrointestinal involvement is one of the most frequent findings in SSc, thus its relationship with ENS dysfunction was a relevant field of research. The main manifestation of gastrointestinal dysautonomia is represented by dysmotility, which was usually diagnosed by manometry. Signs of dysautonomic dysmotility were found along the entire gastrointestinal tract, from the esophagus to the rectum [27–29]. From a pathogenic point of view, humoral immunity seems to play an important role in ENS impairment. Over the years we have gone from the initial descriptions of antimyenteric neuronal antibodies, to the well renowned muscarinic-3 acetylcholine (Ach) receptor autoantibodies, up to the more recent autoantibodies against nicotinic Ach receptor at autonomic ganglia [30–33]. Histologic studies confirmed the early involvement of ANS in SSc gastrointestinal tract, highlighting structural damages of ENS network with particular emphasis on the reduction of interstitial cells of Cajal [34–36].

*Cutaneous involvement*

The role of dysautonomia in SSc skin involvement was another research issue of great interest. Sympathetic skin response (SSR) is a non-invasive technique that records changes in skin conductance after the activation of sweat glands under the neural control of sympathetic cholinergic sudomotor fibers. SSR in response to peripheral nerve stimulation was the most common way to instrumentally assess cutaneous autonomic dysfunction. As a result, several papers have found that SSR is absent or significantly delayed in the skin of SSc patients [37–39]. Intriguing insights came from the histology of skin biopsies. The initial studies in the early '90s showed a decrease of the number of neuropeptides immunoreactive neurons (namely, calcitonin gene-related peptide and vasoactive intestinal polypeptide) in SSc skin [40,41]. However, those findings were not confirmed by a later study [42]. Finally, Provitera and colleagues demonstrated a nerve damage in SSc skin that seems to affect mainly both sensorial and autonomic unmyelinated fibers. Moreover, an interesting direct correlation between the expansion of dermal vascular bed and the increase of epidermal nerve fibers density was outlined, suggesting a role of local ischemia in inducing neuropathic processes [43,44].

*Other involvements*

Among other organ involvements, ANS dysfunction was found to occur in SSc eye and bladder, usually investigated by pupillometry and urodynamic evaluations, respectively [45–48]. It is worth to report that COMPASS-31 is a self-administered questionnaire specifically designed to quantify dysautonomic symptoms, investigating orthostatic intolerance and vasomotor, secretomotor, gastrointestinal, urinary and pupillomotor dysfunction. In the work from Adler and colleagues, COMPASS-31 revealed a strong impact of autonomic dysfunction on the quality of life of patients with SSc, particularly highlighting a greater burden in those with worse gastrointestinal involvement [49].

## Discussion

Our scoping review identified and summarized the findings of 109 studies addressing pathogenesis, clinical presentation and diagnostic assessment of autonomic dysfunction in SSc. Cardiovascular system was the most extensively investigated, especially because dysautonomia is correlated to evident cardiovascular manifestations that can be easily assessed in a non-invasive way. On the other hand, SSc skin represents the most accessible source for ANS histologic investigations. A strong influence of ANS dysfunction on SSc clearly emerges from the literature; however, the exact mechanisms of its occurrence are not yet fully understood.

On the basis of the results of this scoping review, some pathogenetic research hypotheses to be addressed in the future can be formulated. The relationship between sympathetic system and ischemia in SSc is certainly of interest, given the early preclinical involvement of the former and the central pathogenetic role of the latter. In fact, sympathetic system is very sensitive to ischemia/hypoxia, which causes an excessive increase of local noradrenaline concentrations by exocytotic release and a reduction of its presynaptic reuptake. This initially leads to noradrenaline overexpression in synapsis with post-synaptic downregulation of its receptors, and later to noradrenaline depletion [14,50]. Given these premises, the question that should be addressed in future researches is whether sympathetic deregulation in SSc is the trigger of endothelial/vascular derangement, or rather represents its earliest consequence.

Neurotrophins are essential for the development and maintenance of sympathetic neurons, thus the role of nerve growth factor (NGF) and BDNF in SSc dysautonomia is another interesting field of research. There are evidences that the blockade of NGF receptor leads to abnormalities in the morphology of sympathetic fibers [26]. Hence, a NGF pathway interference in SSc sympathetic system can be hypothesized. It is likely that this may be an inhibition rather than a downregulation, since a significant circulatory increase of NGF was revealed in SSc patients, which may therefore be interpreted as a compensatory mechanism [51]. BDNF proved to have all the attributes to be a pivotal molecule in the SSc pathogenesis. In fact, BDNF is upregulated by ischemia and has a central role in neuro-inflammatory events, acting also as a regulator in tissue fibrosis [52–54]. Animal models revealed that BDNF upregulates neuropeptide Y, a vasoconstrictive sympathetic co-transmitter, and controls the distribution of adrenergic fibers [55,56]. Moreover, the selective blockade of its receptor reduces sympathetic overactivity in rats [57]. Circulating levels of BDNF were found significantly reduced in SSc patients, negatively correlating with NGF levels and positively with forced vital capacity in limited cutaneous forms [58]. All these findings prompt to better elucidate the relationship between BDNF and autonomic dysfunction in SSc, both from a molecular and clinical point of view.

Finally, research efforts should also be addressed to Ach signaling, especially the anti-inflammatory pathway mediated via α7 nicotinic Ach receptor. This receptor is present not only in neurons, but also on vessels, where it mediates vasodilation, and on skin cells and fibroblasts, where it could reduce the response induced by transforming growth factor-β [59].

Our work has some limitations. The purpose of mapping the literature regarding ANS dysfunction in SSc limits this review to describe published data without quality assessment that one would expect in other systematic reviews. The choice to restrict the search only to articles in English and on human SSc subjects may have limited the information collected, especially regarding the pathogenesis which is mainly investigated in animal models.

## Conclusion

This scoping review aimed to describe the currently available evidence on pathogenesis, clinical presentation and diagnostic assessment of dysautonomia in SSc patients. Several sites and methods have been proposed for a broad investigation of ANS deregulation, thus highlighting an important role in SSc. However, the mechanisms and timing of autonomic dysfunction in SSc have not yet been clarified. Based on what emerged from the literature, we have proposed some research hypotheses to inform future research efforts.

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## Declaration of Competing Interest

None to declare.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152268.

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