Review

SCLERODERMA SYNDROME AND MUSCLE: A NARRATIVE REVIEW

P.F. Carls[1] and L. Zucchinelli[2]

[1]Consultant, Oral-Maxillofacial Surgeon, Oxford, UK
[2]Private Practice, Bergamo, Italy

Correspondence to:
Peter F. Carls, MD
Consultant, Oral-Maxillofacial Surgeon,
69 Banbury Road, Oxford, UK
e-mail: carls@doctors.org.uk

ABSTRACT

Skeletal and smooth muscles are both affected by complicated muscle involvement in scleroderma, also known as systemic sclerosis (SSC). The understanding of the cellular and molecular processes underlying the diverse participation of the smooth muscle has significantly increased in recent years. A better knowledge of the clinical features has been made possible by the new techniques for studying smooth muscle cells from the gastrointestinal tract or the vascular wall. In cases of myopathy that are inflammatory in character, it is advised to utilize glucocorticoids, modifying antirheumatic drugs, and calcium channel blockers such as nifedipine and amlodipine. Patients typically do not receive treatment when there is no discernible inflammatory component. The prognosis for SSC is greatly improved by early diagnosis and novel therapeutic options, but it continues to have a severe course and a high chance of premature death. This review summarizes the epidemiology, histopathological factors, and muscle involvement related to SSC and provides insight into ongoing treatment.

KEYWORDS: *scleroderma syndrome, systemic sclerosis, myopathies, non-inflammatory myopathy*

INTRODUCTION

Scleroderma, also known as systemic sclerosis (SSC), is a rare disorder that can cause parts of the skin to become hard and thickened, and it can also cause difficulties with the body's internal blood vessels and organs. The immune system's attack on the connective tissue that lies beneath the skin and that which surrounds internal organs and blood vessels is the root cause of scleroderma. SSC can lead the tissues surrounding joints to become more rigid, limiting the possible range of motion in those joints. In addition, it might cause swelling and pain around the joints that are afflicted. SSC might also present itself with a weakness in the muscles on occasion (1).

If the disease has also affected their muscles, people with scleroderma may experience more severe symptoms, including those involving their heart, lungs, and digestive system. SSC affects the muscles, one of the disease's most critical symptoms; around one-third of all patients report muscle weakness. 15% of these individuals have signs of muscle atrophy, also known as muscle wasting, and 10% have high blood levels of creatine kinase, which is a biomarker of myopathy, also known as muscle sickness. In persons with scleroderma, myopathy has been related to a worse prognosis (likely disease course), but few researchers have studied the associated clinical aspects of this condition (2). The involvement of the muscle in scleroderma is complicated and can affect both smooth muscle and skeletal muscle (3).

Received: 10 January 2022
Accepted: 03 February 2022

Smooth muscle can be found in the vascular system and the digestive tract. In recent years, there has been a significant increase in understanding of the molecular and cellular mechanisms responsible for the diverse participation of the smooth muscle (4, 5).

A better knowledge of the clinical features has been made possible due to the newly developed techniques for studying smooth muscle cells taken from the vasculature or the gastrointestinal tract. Myositis and non-inflammatory myopathy are two forms of skeletal muscle involvement that are important factors in the debilitation of SSC patients (6). It has been demonstrated that skeletal muscle involvement in SSC can be represented by myositis or non-inflammatory myopathy. Compared to other types of organ involvement, muscle intervention in scleroderma has received comparatively less research attention in terms of its pathophysiology and implications (7). Therefore, this study has been designed to explore the involvement of muscles in scleroderma syndrome.

MATERIALS AND METHODS

We utilize a wide array of search strategies to identify papers that are relevant to their work. When researching and looking for information, we used websites as data collection tools such as Scopus, MEDLINE, PUBMED, and Google Scholar, from 2010-2021. The terms “scleroderma syndrome” and “systemic sclerosis” are examples of key phrases that were employed in the study as well as “muscle”, “myositis”, “myopathy”, “scleroderma syndrome” and “systemic sclerosis”.

RESULTS AND DISCUSSION

Epidemiology

The prevalence of myopathy in scleroderma varies significantly due to the absence of classification criteria that may parse out the variability of muscle disease in scleroderma. This results in a lack of standardization. In earlier research, the presence of muscle disease was determined by the availability of muscle weakness or a mixture of weakness and impaired motor enzymes, aberrant electromyography, or muscle biopsy (8). This definition of muscle disease was based on the assumption that muscle disease could only be diagnosed through biopsy. The lack of diagnostic agreement criteria results in estimates of 5 to 96 percent frequency of SSC-associated muscle participation (9). There is a possibility that SSC is present in as much as 42 percent of myositis patients who also have overlap connective tissue disease (2). Therefore, in addition to obvious cases of overlap myositis, which occur when patients meet assessment criteria for SSC and myositis, there is additional pathogenesis for myopathy and/or weakness in SSC, such as inactivity, malnutrition, or other neurologic diseases. This is in addition to clear cases of overlap myositis.

The diffuse cutaneous SSC subtype, being of African American descent, male, and having a shorter duration of SSC disease are all variables that are considered to be risk factors for SSC-associated myopathy. Muscle histology has contributed significantly to our understanding of myopathy and how it is caused by SSC (10). More recent research has estimated the incidence of muscular weakness in a large scleroderma cohort to be over 25% (11). However, a meta-analysis indicated that the prevalence of proximal muscle weakness was 16%, while the prevalence of myositis was 13% (2). Although the prevalence of myopathy continues to vary depending on the definition used for each study, it is becoming more apparent that SSC patients with concomitant muscle disease have poorer outcomes, including disability and death. This is the case even though the definition of myopathy continues to vary (12).

Histopathologic feature

The basic clinical characteristics are primarily cutaneous symptoms; nevertheless, the involvement of internal organs is what decides the fate of the condition. As the process advances through its many stages, the skin becomes increasingly tauter and thicker. Initial symptoms include swelling of the hands and fingers as well as edema and swelling of the skin more generally. The initial complaint is frequently described as morning stiffness and pain in the joints of the hands. Other symptoms may also be present. The early skin changes of scleroderma might last for several months before the usual skin induration that results from the excessive deposition of collagen and other connective tissue components (13). This induration arises due to an abnormally high level of collagen deposition. Changes in skin pigmentation are one of the most prevalent manifestations of scleroderma. Patients may develop localized hypo- or hyperpigmentation that is frequently follicular rather than the widespread hyperpigmentation that is characteristic of Addison's disease. Skin involvement near the metacarpophalangeal joints is the major criterion for diagnosing systemic sclerosis as the condition in question. The vast majority of these individuals will almost surely be affected by Raynaud's phenomenon. Involvement of the esophagus, most often in the form of esophageal dysmotility, is a hallmark of all types of scleroderma (11).

The muscle histology of patients with weak scleroderma has been the subject of previous research, showing that it is diverse. Histopathologic diagnoses in a single study of 42 scleroderma patients with muscle biopsies ranged from overlapping polymyositis, necrotizing myopathy, dermato-myositis, and fibrosis (14). Other studies have primarily characterized the predominant attributes of patients with weak scleroderma muscle biopsies as necrosis and inflammation (15, 16). This finding supports the conclusion that in the spectrum of overlap myositis, SSC is the most prevalent connective tissue condition associated with idiopathic inflammatory muscular dystrophy, accounting for 42.6% of overlap myositis patients (17).

In scleroderma, fibrosis of the muscles can be a hallmark of the disease's early stages rather than its later stages. In scleroderma muscle apathy, vascular involvement in the muscle histology is more common than in inflammatory myopathies. Scleroderma is a disease that affects the muscles, and a specific histopathologic subtype of the condition called fibrosing myopathy may indicate a more dire prognosis (2).

Muscle involvement

In patients with SSC, a broad vasculopathy is present before the development of tissue fibrosis (18). It is one of the primary pathogenic characteristics that contribute to the development of Raynaud's phenomenon, oral ulcers, pulmonary hypertension, and scleroderma kidney crises (19, 20). When the local vascular injury is not treated correctly, the result is a disorganized accumulation of extracellular matrix (21). The development of profibrotic myofibroblasts is a hallmark of progressive tissue fibrosis (20), precipitated by the disruption of microvascular circulation. The involvement of the esophagus in SSC patients often results in symptoms such as dysphagia and gastroesophageal reflux disease (22). These are two of the most common clinical manifestations of the disease.

Approximately 90 percent of SSC patients may experience some form of esophageal dysfunction (23). Although there may not be any clinical signs in the very early stage, there may be evidence of esophageal involvement on a histological level (24). The development of esophageal dysmotility is significantly influenced by the wasting away of smooth muscle and the formation of fibrosis. Skeletal involvement in SSC might range from general muscle involvement without inflammatory muscle changes to a true inflammatory form of myositis in the affected muscles. There is, however, a “grey area” with individuals who are difficult to categorize as having either one or the other of these conditions. Patients may develop non-progressive, non-inflammatory myopathy due to digestive disturbances, malnutrition, inactivity, or contractures of fibrotic skin. This condition is not progressive and does not cause inflammation. In some instances, it manifests itself as an overlapping condition with inflammatory myopathy in patients who fit the criteria for classification of both disorders (2, 25).

Ongoing therapies

The necessity of inhibiting the autoimmune process as well as inflammation and managing SSC in an organ-specific manner contributes to the complexity of the treatment. Disease-modifying medications and therapies that target specific organs are the mainstays of treatment for SSC, which has a poorly understood etiology. After an accurate assessment of symptoms, the length of the disease, its activity, and any complications, therapeutic recommendations should be made. There is currently no treatment that is specifically indicated for patients suffering from SSC-associated myopathy. Glucocorticosteroids are recommended for use in cases of myopathy that are inflammatory. Patients frequently do not receive treatment if no inflammatory component is detected (2). Treatment for arthritis and muscle pain caused by SSC typically involves either disease-modifying antirheumatic medications or glucocorticoids. Calcium channel blockers, such as nifedipine and amlodipine, are usually prescribed for treating peripheral vasculopathy and digital ulcers. If the patient only shows a moderate reaction, phosphodiesterase type 5 antagonists should be used.

Prostanoids given intravenously are shown to considerably improve the microcirculation and the recovery period of digital ulcers. Even though SSC prognosis can be greatly improved with early detection and the availability of novel therapy options, the disease is nevertheless defined by a harsh course and a high risk of passing away at an early age (2, 26).

CONCLUSIONS

Systemic sclerosis is a connective tissue disease characterized by vascular damage, immune system dysfunction, and muscle and organ fibrosis. SSC treatment requires inhibiting the autoimmune process, inflammation, and organ-specific management. SSC is treated using disease-modifying and organ-specific medicines because its pathophysiology is complex. Symptoms, disease duration, activity, and consequences should inform therapeutic decisions. The prognosis

for SSC is greatly improved by early diagnosis and novel therapeutic options, but it continues to have a severe course and a high chance of premature death.

REFERENCES

1. Arada Rojana-Udomsart, Fabian V, Hollingsworth PN, Walters SE, Zilko PJ, Mastaglia FL. Paraspinal and Scapular Myopathy Associated With Scleroderma. *Journal of Clinical Neuromuscular Disease*. 2010;11(4):213-222. doi:https://doi.org/10.1097/cnd.0b013e3181c139f6
2. Paik JJ. Muscle disease in scleroderma. *Current Opinion in Rheumatology*. 2018;30(6):576-580. doi:https://doi.org/10.1097/bor.0000000000000552
3. Romano E, Rosa I, Fioretto BS, Matucci-Cerinic M, Manetti M. New Insights into Profibrotic Myofibroblast Formation in Systemic Sclerosis: When the Vascular Wall Becomes the Enemy. *Life*. 2021;11(7):610-610. doi:https://doi.org/10.3390/life11070610
4. Trojanowska M. Cellular and molecular aspects of vascular dysfunction in systemic sclerosis. *Nature Reviews Rheumatology*. 2010;6(8):453-460. doi:https://doi.org/10.1038/nrrheum.2010.102
5. Romano E. The Role of Pro-fibrotic Myofibroblasts in Systemic Sclerosis: From Origin to Therapeutic Targeting. *Current Molecular Medicine*. 2021;22(3):209-239. doi:https://doi.org/10.2174/18755666mte18mdu4x
6. Lóránd V, Czirják L, Minier T. Musculoskeletal involvement in systemic sclerosis. *La Presse Médicale*. 2014;43(10):e315-e328. doi:https://doi.org/10.1016/j.lpm.2014.03.027
7. Corallo C, Cutolo M, Volpi N, et al. Histopathological findings in systemic sclerosis-related myopathy: fibrosis and microangiopathy with lack of cellular inflammation. *Therapeutic Advances in Musculoskeletal Disease*. 2017;9(1):3-10. doi:https://doi.org/10.1177/1759720x16671928
8. Zhou M, Jiang L, Nie L, et al. Myopathy is a Risk Factor for Poor Prognosis of Patients with Systemic Sclerosis. *Medicine*. 2020;99(33):e21734. doi:https://doi.org/10.1097/MD.0000000000021734
9. Bhansing KJ, Lammens M, Knaapen HK, van Riel PL, van Engelen BG, Vonk MC. Scleroderma-polymyositis overlap syndrome versus idiopathic polymyositis and systemic sclerosis: a descriptive study on clinical features and myopathology. *Arthritis Res Ther*. 2014;16(3):R111. Published 2014 May 13. doi:10.1186/ar4562
10. Hughes M, Pauling JD, Armstrong-James L, Denton CP, Galdas P, Flurey C. Gender-related differences in systemic sclerosis. *Autoimmunity Reviews*. 2020;19(4):102494. doi:https://doi.org/10.1016/j.autrev.2020.102494
11. Raymond J, Oskarsson B, Mehta P, Horton K. Clinical characteristics of a large cohort of US participants enrolled in the National Amyotrophic Lateral Sclerosis (ALS) Registry, 2010–2015. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*. 2019;20(5-6):413-420. doi:https://doi.org/10.1080/21678421.2019.1612435
12. Chaigne B, Simao Rodeia, Nouria Benmostefa, et al. Corticosteroid-sparing benefit of intravenous immunoglobulin in systemic sclerosis-associated myopathy: A comparative study in 52 patients. *Autoimmunity Reviews*. 2020;19(1):102431-102431. doi:https://doi.org/10.1016/j.autrev.2019.102431
13. Ibrahim RA, Abdalla NEHH, Shabaan EAH, Mostafa NBH. An Unusual Presentation of a Rare Scleroderma Mimic: What is Behind the Scenes? *Current Rheumatology Reviews*. 2019;15(2):172-175. doi:https://doi.org/10.2174/1573397114666180808091621
14. Paik JJ, Wigley FM, Lloyd TE, et al. Spectrum of Muscle Histopathologic Findings in Forty-Two Scleroderma Patients With Weakness. *Arthritis Care and Research*. 2015;67(10):1416-1425. doi:https://doi.org/10.1002/acr.22620
15. Bhansing KJ, Lammens M, Knaapen HK, van Riel PL, van Engelen BG, Vonk MC. Scleroderma-polymyositis overlap syndrome versus idiopathic polymyositis and systemic sclerosis: a descriptive study on clinical features and myopathology. *Arthritis Research & Therapy*. 2014;16(3):R111. doi:https://doi.org/10.1186/ar4562
16. Bhansing KJ, Riel van, Engelen van, Fransen J, Vonk MC. Patients with Systemic Sclerosis/polymyositis Overlap Have a Worse Survival Rate Than Patients Without It. *The Journal of Rheumatology*. 2016;43(10):1838-1843. doi:https://doi.org/10.3899/jrheum.151425
17. Aguila LA, Remião M, Zon Pretti F, et al. Clinical and laboratory features of overlap syndromes of idiopathic inflammatory myopathies associated with systemic lupus erythematosus, systemic sclerosis, or rheumatoid arthritis. *Clinical rheumatology*. 2014;33(8):1093-1098. doi:https://doi.org/10.1007/s10067-014-2730-z
18. Cutolo M, Soldano S, Smith V. Pathophysiology of systemic sclerosis: current understanding and new insights. *Expert Review of Clinical Immunology*. 2019;15(7):753-764. doi:https://doi.org/10.1080/1744666x.2019.1614915
19. Bruni C, Cuomo G, Rossi FW, Praino E, Bellando-Randone S. Kidney involvement in systemic sclerosis: From pathogenesis to treatment. *Journal of Scleroderma and Related Disorders*. 2018;3(1):43-52. doi:https://doi.org/10.1177/2397198318758607
20. Bellando-Randone S, Galdo FD, Lepri G, et al. Progression of patients with Raynaud's phenomenon to systemic sclerosis: a five-year analysis of the European Scleroderma Trial and Research group multicentre, longitudinal registry study for Very Early Diagnosis of Systemic Sclerosis (VEDOSS). *The Lancet Rheumatology*. 2021;3(12):e834-e843. doi:https://doi.org/10.1016/S2665-9913(21)00244-7
21. van Caam A, Vonk M, van den Hoogen F, van Lent P, van der Kraan P. Unraveling SSc Pathophysiology; The

Myofibroblast. *Frontiers in Immunology*. 2018;9(9). doi:https://doi.org/10.3389/fimmu.2018.02452

22. Petcu A, Ghib L, Grad S, et al. Upper gastrointestinal involvement in systemic sclerosis: Findings in a real-life setting. *Experimental and Therapeutic Medicine*. 2019;18(6). doi:https://doi.org/10.3892/etm.2019.8125
23. Voulgaris T, Karamanolis G. Esophageal manifestation in patients with scleroderma. *World J Clin Cases*. 2021;9(20):5408-5419. doi:https://doi.org/10.12998/wjcc.v9.i20.5408
24. Denaxas K. Evaluation and management of esophageal manifestations in systemic sclerosis. *Annals of Gastroenterology*. 2018;31(2). doi:https://doi.org/10.20524/aog.2018.0228
25. Pettersson H, Boström C, Bringby F, et al. Muscle endurance, strength, and active range of motion in patients with different subphenotypes in systemic sclerosis: a cross-sectional cohort study. *Scandinavian Journal of Rheumatology*. 2018;48(2):141-148. doi:https://doi.org/10.1080/03009742.2018.1477990
26. Sobolewski P, Maślińska M, Wieczorek M, et al. Systemic sclerosis – multidisciplinary disease: clinical features and treatment. *Reumatologia/Rheumatology*. 2019;57(4):221-233. doi:https://doi.org/10.5114/reum.2019.87619