

# Systemic sclerosis presents its cutaneous manifestations with innovative triple therapeutic regime

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**Abstract** *Objective* To record and evaluate the different cutaneous manifestations of all patients with an established diagnosis of systemic sclerosis and to have a new therapeutic trial.

*Methods* This is a cross-sectional descriptive clinical study with a therapeutic trial that was conducted during the period from 2014 to 2023. All patients with a well-established diagnosis of systemic sclerosis were evaluated for various skin manifestations. A triple therapeutic trial was carried out using oral zinc sulfate, sildenafil, and prednisolone.

*Results* The main early presenting symptoms were the sensation of coldness usually cold hands and feet seen in 25 (100%) cases, followed by dusky blue red hands and feet observed in 23(92%) cases, followed by difficult hands movement and stiffness together with loss of facial expression in 21 (84%) of patients. Later on, patients mentioned hardening of the face and hands skin with the enhanced shininess of the face. Also pitting scarring of pulps and tips of fingers and sometimes toes could be considered as early symptoms of the disease, seen in 25 (100%) of patients. While the most striking findings on examination were shiny hardening of skin which was most prominent on the face and hands. Difficulty in opening the mouth and protruding the tongue was also a common finding that was detected in 19 (76%) cases. Angiomatous macules and papules of the face were rarely seen as observed only in 3 (12%) female patients. Pitting the pulps and tips of fingers were very early striking findings and very helpful diagnostic signs for diagnosis. Calcinosis cutis commonly affecting elbows were observed as late findings that commonly associated with necrosis of tissue and infections and only observed in 2 (8%) cases.

*Conclusion* Systemic sclerosis usually manifests in cold weather and patients complain of coldness especially on hands and feet with hardening of the skin. Pitting and scarring of the tips of fingers are significant diagnostic findings that are often followed by ischemic changes. While facial angiomatous macules and papules, calcinosis cutis, and rippling pigmentation with leukoderma were detected lately. Triple therapy showed its effectiveness in improving the complaints of patients.

**Key words**

Systemic sclerosis, Zinc sulfate, Shiny skin, Calcinosis cutis, Rippling pigmentation, Triple therapy.

## Introduction

Scleroderma is an idiopathic disease, characterized by loss of cutaneous elasticity, and hardening and thickening of the skin, resulting from vasculopathy of small vessels and fibrotic changes as mentioned by Gintrac in 1847.<sup>1</sup>

Clinically, patients complain of skin ulcers, digital pitting scars, subungual hyperkeratosis, telangiectasias, fissures, and dermal calcinosis.<sup>2</sup> Much later, the disease called systemic sclerosis SSc is characterized by variable fibrosis of major organs such as the gastrointestinal tract, heart, lungs, and kidneys.<sup>3-4</sup>

The two principal subsets typically used for classification are limited SSc (lcSSc) variant that so called CREST syndrome, and diffuse SSc (dcSSc).<sup>5-7</sup> A slower and more insidious disease progression is observed in lcSSc and manifestations are confined to the extremities and face.<sup>6-7</sup> A rapid disease onset and more extensive thickening are observed dcSSc.<sup>6</sup> Typical facial features of SSc include microstomia, telangiectasia and a mask-like facial stiffness. Other typical dermatological manifestations include hypo-/hyper-pigmentation or the loss of hair follicles and sebaceous glands.<sup>6-8</sup>

Abnormalities in the homeostasis of key immune cells and related cytokines have been heavily implicated in the pathogenesis of systemic sclerosis (SSc).<sup>9</sup> A prominent feature of SSc is fibrosis, and many studies have indicated that some cytokines such as IL-4, TGF- $\beta$  and IL-6, which are elevated in SSC, are fibrogenic and are therefore potentially major contributors to its development.<sup>10-11</sup> The most heavily implicated cytokine is IL-6, a pro-inflammatory cytokine. This is because elevated levels are observed in the sera and skin of SSc patients and IL-6 levels have been shown to correlate with disease severity.<sup>11-12</sup> IL-6 has also been implicated in skin thickening, lung fibrosis and vasculopathy in SSc, which is key in early abnormal immune responses.<sup>10-11</sup> This suggests that IL-6 plays a significant role in early development. IL-4 and TGF $\beta$  are thought to

promote or induce fibrosis respectively. Cytokines such as IL-4 and TGF- $\beta$  have been implicated in the development of the disease. This is because IL-4 and TGF- $\beta$  levels are frequently elevated in the skin, lungs and blood of SSC patients. Mouse models show the deletion of IL-4 and TGF- $\beta$  or the production of antibodies against the cytokines can prevent skin/dermal fibrosis.<sup>11</sup> Many immune cell types from both the adaptive and innate immune responses are implicated in the pathogenesis of SSc. For example, imbalances in regulatory T cell (Treg) and Th17 cell levels have been reported in SSc studies. The reduction of Treg cells in the skin lesions of SSc patients suggests a reduced capacity for immune response regulation in SSc.<sup>11-12</sup> Macrophages have also been implicated in the initiation and progression of fibrosis in SSc.<sup>11,13</sup> Vast numbers of strongly activated circulating macrophages have been found in the skin of SSc patients. Additionally, macrophages produce TGF- $\beta$ , and studies suggest M2 macrophage activation may be mediated by IL-6.<sup>11</sup>

While B cells are heavily implicated in the immunopathogenesis of SSc, as they are well-known fibrosis inducers and SSc patients have abnormal b-cell homeostasis in the blood.<sup>14-15</sup> B-cell activating factor (BAFF) is a B-cell cytokine also implicated in SSc pathogenesis as BAFF levels are higher in SSC patients and their levels correlate with disease severity.<sup>14</sup> Increased levels of IL-6-producing B-effector cells and reduced levels of regulatory B cells, which negatively regulate inflammation and autoimmunity, have also been observed in the blood of SSc patients.<sup>11,15</sup> Further, B-cells are implicated in the development of autoantibodies, as in mouse models, increased levels of CD19, a positive regulator of B-cells, increased levels of autoantibodies.<sup>14,16</sup>

The epidemiology of SSc is not certainly

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recognized owing to the relative infrequency of the disease, variable clinical presentations, and difficulty in diagnosis. In Iraq, SSc is a rare disease, still infrequent cases were reported at ages ranging between 20-40 years.<sup>17</sup>

There are many therapeutic regimes that have used in treatment of the cutaneous manifestations of systemic sclerosis Including, calcium channel blocker, phosphodiesterase-5 inhibitor, prostaglandin, endothelin receptor antagonist, glyceryl trinitrate patches. Combination therapy often advocated and most effective.<sup>18</sup>

Zinc is an essential micronutrient for humans and its importance can be highlighted from the fact that it is an essential component of more than 300 metalloenzymes.<sup>19-20</sup> Sharquie has tried oral zinc sulfate in treatment of systemic sclerosis and morphea for the last 30 years,<sup>21</sup> in addition to other drugs and proved its effectiveness as zinc sulfate has many pharmacological and therapeutic actions like it has immunomodulator, antioxidants, antimicrobial and cytotoxic actions. Hence oral zinc sulfate through its different actions has been used effectively in treatment many diseases like Bechet's disease,<sup>22</sup> acute cutaneous leishmaniasis,<sup>23</sup> recalcitrant viral wart,<sup>24</sup> recurrent aphthous stomatitis,<sup>25</sup> alopecia areata,<sup>26</sup> premalignant and malignant disorder,<sup>27</sup> xeroderma pigmentosa,<sup>27</sup> rosacea,<sup>28</sup> acne vulgaris, ulcers and wound healing, psoriasis, eczema, leprosy, and many other skin diseases.<sup>18-19,29-30</sup>

To our knowledge, there is no previous research about the prevalence of skin manifestations in Iraqi patients with SSc. In this article, different cutaneous manifestations of the SSc were evaluated, which could be very helpful as a marker of disease activity, early diagnosis and management. In addition, a therapeutic regime

was tried using oral zinc sulfate, sildenafil, prednisolone plus topical mometasone ointment.

## **Patients and methods**

This is a cross-sectional descriptive clinical study with a therapeutic trial that was conducted during the period extended from January 2014 till February 2023, where all patients with a well-established diagnosis of systemic sclerosis relative to 2013 American Academy of Rheumatology/ European Group Against Rheumatism for the organization of SSc.<sup>15</sup> All patients were fully investigated including antinuclear antibody (ANA), and anti-scleroderma 70 (AntiSc170) before referral to dermatologists. All participants were evaluated for different skin manifestations, age, gender, disease duration, and seasonal variation. Informed consent was attained from each subject included in this report. Scleroderma-like cutaneous changes happen in diabetes mellitus and hypothyroidism, and patients with end-stage renal disease were excluded from this work. Besides that, the other overlapped connective tissue diseases or inflammatory arthritis were omitted.

Laboratory investigation was carried out, including complete blood count, fasting blood sugar, and renal function test.

A triple therapeutic trial with close monitoring of this stubborn disease was carried out using oral zinc sulfate 100mg twice a day, sildenafil tab 4mg/day, prednisolone tab 10mg/day plus topical mometasone ointment, with adjusting the dose for patients below 18 years old. The duration of therapy ranged from 3months to many years.

## **Results**

Over 10 years, a total of twenty-five patients

**Table 1** Frequency of skin manifestations (n=25).

Data	n (%)
Early skin manifestations	
Sensation of coldness of hands and feet	25 (100%)
Pitting scarring of pulps and tips of fingers and sometimes toes	25 (100%)
Dusky blue red hands and feet	23 (92%)
Difficult hands movement and stiffness together with loss of face expression.	23 (92%)
Hardening of face and hands skin with enhanced shininess of the face	21 (84%)
Difficulty to open the mouth and to protrude the tongue	19 (76%)
Angiomatous (telangiectasia-like) macules and papules of the face	3 (12%)
Late skin manifestations	
Curving of nails and gangrenous changes	11 (44%)
Rippling pigmentation associated with leukoderma of neck, chest, upper back, and around shoulders	2 (8%)
Calcinosis cutis affecting elbows	2 (8%)

n → number; % → percentage



**Figure 1** Twenty-five years' male patient with SSc showing (A, B), rippling pigmentation associated with leukoderma of neck, chest, around shoulders, and upper back (C), pitting scarring of pulps and tips of fingers.

with SSc were included, their ages ranged from 6 to 40 years with a mean of 27 years, with 19(76%) females and 6(24%) males, with a female to male ratio was 3:1.

The mean duration of disease at the time of the patient's presentation was 5 (3-14) months, and 19 (76%) of cases complained of cutaneous symptoms during the cold months that usually started from November- April. All participants reported early skin manifestations and presenting symptoms (**Table 1**), including coldness sensation and usually cold hands and feet, followed by pitting scarring of pulps and tips of fingers and sometimes toes, which were very early striking findings and very helpful diagnostic signs, especially in doubtful cases (**Figure 1C,2B**).

## Methods

Other early complaints were dusky blue-red hands and feet, difficult hands movement and stiffness together with loss of facial expression in 23 (92%) of cases. Later on, 21 (84%) patients revealed the most prominent finding on examination was a shiny hardening of skin with enhanced shininess of the face and hands. Also, 19 (76%) individuals had difficulty opening the mouth and protruding the tongue. Another striking rare finding was angiomatous (telangiectasia-like) macules and papules of the face that was observed only in 3 (12%) female cases (**Figure 3,4**).

Later on, with disease progression and patients self-neglect, the late skin manifestations might be seen, these were curving of nails and gangrenous changes and seen in 11(44%) patients. Calcinosis cutis commonly affecting elbows was observed as a late finding that was



**Figure 2** Six years' female patient with SSc showing (A) pitting scarring of pulps and tips of fingers (B), pitting scarring of pulps and tips of toes (C), calcinosis cutis affecting elbows.



**Figure 3** Thirty-six years' female patient with SSc showing (A) dusky blue red hand with enhanced shininess of the face (B), red hands and feet (C), dusky blue red planter surface of feet.

commonly associated with necrosis of tissue and infections and only observed in 2(8%) cases. Rippling pigmentation that might be associated with leukoderma was an important diagnostic finding that was commonly seen on the neck, upper back and around shoulders, but rarely observed as seen in two (8%) patients (**Figure 1,2C**).

The last delayed complaints of all patients were esophageal involvement with the difficulty of swallowing hard objects followed by fluid. While Raynaud's phenomenon (RP) was

affecting 14 (56%) of cases. The full criteria of the CREST variant could be only seen in late cases.

The therapeutic trial showed two beneficial findings, the first improvement in both symptoms and signs of the disease and detected in the first month of therapy and this recovery continued over time. The 2<sup>nd</sup> beneficial action of therapy was stabilization in the activity and slowing of the progression of the disease. The dose the drugs could be tapered in hot months while increased in cold months of year.



**Figure 4** Showing 3 female patients with SSc (A, B), angiomatous macules and papules with enhanced shininess of the face (C), angiomatous macules and papules of the face and hands.

## Discussion

Systemic sclerosis is a disabling illness that shortens life expectancy and most published literature focused on internal organ involvement. Ongoing clinical research at this time is arranged to evaluate the skin manifestations. The disease could present early with cutaneous manifestations that are usually missed or neglected by the patient or their doctor, and avert early diagnosis and management. SSc is a disease of women with females to males ratio is 3:1, and this finding was comparable with previous work.<sup>29</sup>

The noninflammatory obliterative vasculopathy without vasculitis in SSc may be responsible for the reported coldness sensation and cold hands and feet, also the pitting scarring and ulceration of pulps and tips of fingers and sometimes toes, these were seen in all participants of the current report. They are very early prominent features and actual supportive diagnostic signs, particularly in doubtful cases, and these findings were not defined and recognized and published before the present work. Later on, curving of nails and gangrenous complications are seen in up to 44% of patients, which lead to extensive hand disability. Meanwhile, RP reported in the present research up to 56% of cases as late cutaneous findings, characterized by paroxysmal attack of digital discoloration, together with pain, affect the hands and feet after contact with cold temperatures or emotional stress. The various previous clinical research, only reported the initial skin manifestations including very painful digital pulps ulcers that occurred in up to 50% of patients, and RP affected up to 95% of subjects. SSc can disturb the micro- and macro vasculature disease resulting in complications such as ischemic digital sores and gangrene.<sup>16,30,31</sup>

In the current study, we reported for the first

time, the early cases of SSc that complained of dusky blue-red hands and feet before the beginning of RP, and difficult hands movement and stiffness together with loss of facial expression that seen in 92% of cases. Later on, 84% of patients revealed shiny hardening of skin with enhanced smoothness of face and hands and this is considered the most prominent finding.

Other preceding studies documented that the earliest skin manifestation of SSc typically comprises non-pitting edema of the digits and extremities. The skin gradually thickens, resulting in joint contractures, and restricting sclerodactyly. While in the late stages of the illness, the affected skin becomes thin and atrophic.<sup>9,32</sup>

Up to 76% of participants in the present had difficulty to open the mouth and protruding the tongue and this induced by collagen fibers deposition that led to fibrosis in the perioral area. This fibrosis will lead into a reduced range of mandible motion, preventing mastication, talking, and bad mouth hygiene. This agrees with other earlier work that reported microstomia, which is characterized by reduced oral opening and thinning, with limiting jaw movement.<sup>33</sup>

The current study mentioned another striking uncommon finding which was angiomatous (telangiectasia-like) macules and papules of the face that was observed only in up to 12% of female cases. The role of vasculogenesis in SSc is indistinct, and there are incompatible reports about the role of circulating endothelial progenitor cells in SSc disease, which lead to capillaries dropout as well as atypical capillary architecture.<sup>34</sup> Koenig *et al.* presented microvascular changes to be successive.<sup>35</sup> Capillary expansion is followed by capillary injury followed by capillary telangiectasias.

While another study displayed telangiectasias in up to 69% of cases.<sup>36</sup>

The previous study showed that the calcinosis cutis is a frequent outcome of systemic sclerosis and occurring in approximately 25% of patients. characterized by abnormal deposition of calcium in soft tissues of the fingers, elbows, and knees independent of the serum levels of calcium and phosphorous.<sup>37</sup> On the other hand, the present research showed rare late presentations of calcinosis cutis affecting only elbows commonly associated with necrosis of tissue and infections and only observed in 8% of cases.

The current work showed that rippling pigmentation with leukoderma, as an important diagnostic finding that is commonly seen on the neck, upper back and around shoulders and affecting only 8% of cases. While other prior reports referred to cutaneous hyper-melanosis which was existing in up to 31% of cases.<sup>32,36</sup>

The ideal treatment of SSc is a challenge, owing to the pathogenesis of SSc being blurred and rare disease. However, concerning hand impairment in SSc, minimal evidence is existing on patient therapy and outcomes. Individuals must keep their fingers warm and covered, mainly in cold environments. While in the current work, a therapeutic trial was carried out using triple agents like oral zinc sulfate 100mg twice a day, sildenafil tab 4mg/day, prednisolone tab 10mg/day. This drug combination gave a synergistic effect and showed an improvement in both symptoms and signs of the disease and was detected during the first month and this recovery continued over time. In the meantime, patients get stabilization in the activity and slowing the progression of the disease, and it seems to have promising outcomes in the management. The systemic and topical steroid plus oral zinc sulfate had the specific aim as to abort and/ or modulate the

activation in the immune system, and reduce the production of extracellular matrix by fibroblast.<sup>16</sup>

Many preceding studies in which the sildenafil and tadalafil have been revealed to decline digital pain and ulcers and improve the frequency and duration of attacks of RP. They are phosphodiesterase-5 inhibitors that have been shown to increase capillary blood flow in resistant cases.<sup>38</sup> Shenoy *et al.* observed the effectiveness of adding tadalafil, but with incomplete relief of symptoms.<sup>39</sup>

A single limitation is the small number of participants, because SSc is a rare disease, besides that there is no dermatological consultation and referring of SSc cases from a Rheumatologist or GIT specialist. So this paper does not represent the definite incidence.

## Conclusion

Systemic sclerosis manifests usually in cold weather and patients complain of coldness particularly in hands and feet with hardening of the skin. Pitting and scarring of the tips of fingers are significant diagnostic findings that are often followed by ischemic changes. Another prominent uncommon finding was facial angiomatous macules and papules. Rarely, calcinosis cutis, and rippling pigmentation with leukoderma were detected. The criteria of CREST syndrome could never be seen as complete criteria and often confusing and are not helpful for diagnosis, especially in early cases and some of them might never appear. The triple therapy that had been used for the first time showed its effectiveness mainly improving and stabilizing the complaints of the disease.

## References

1. Gintrac M. Note sur la sclerodermie. Rev Med Chir Paris. 1847;2(1847):2

2. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, *et al.* Classification criteria for systemic sclerosis: an ACR-EULAR collaborative initiative. *Arthritis and rheumatism.* 2013;65(11):2737
3. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *New England Journal of Medicine.* 2009;360(19):1989-2003
4. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. *The Journal of clinical investigation.* 2007;117(3):557-67
5. Wollheim F. Classification of systemic sclerosis. Visions and reality. *Rheumatology.* 2005;44(10):1212-6
6. Sobolewski P, Maślińska M, Wieczorek M, Łagun Z, Malewska A, Roszkiewicz M, *et al.* Systemic sclerosis–multidisciplinary disease: clinical features and treatment. *Reumatologia/Rheumatology.* 2019;57(4):221-33
7. Krieg T, Takehara K. Skin disease: a cardinal feature of systemic sclerosis. *Rheumatology.* 2006;48(suppl\_3):iii14-iii18
8. Sampaio AL, Bressan AL, Vasconcelos BN, Gripp AC. Skin manifestations associated with systemic diseases–Part I. *Anais Brasileiros de Dermatologia.* 2022;96:655-71
9. von Kobyletzki G, Uhle A, Pieck C, Hoffmann K, Altmeyer P. Acrosclerosis in patients with systemic sclerosis responds to low-dose UV-A1 phototherapy. *Archives of dermatology.* 2000;136(2):275-6
10. Pattanaik D, Brown M, Postlethwaite BC, Postlethwaite AE. Pathogenesis of systemic sclerosis. *Frontiers in immunology.* 2015;6:272
11. Brown M, O'Reilly S. The immunopathogenesis of fibrosis in systemic sclerosis. *Clinical & Experimental Immunology.* 2019;195(3):310-21
12. Rosendahl AH, Schönborn K, Krieg T. Pathophysiology of systemic sclerosis (scleroderma). *The Kaohsiung Journal of Medical Sciences.* 2022;38(3):187-95
13. Truchetet ME, Brembilla NC, Chizzolini C. Current concepts on the pathogenesis of systemic sclerosis. *Clinical reviews in allergy & immunology.* 2021:1-22
14. Viswanath V, Phiske MM, Gopalani VV. Systemic sclerosis: current concepts in pathogenesis and therapeutic aspects of dermatological manifestations. *Indian journal of dermatology.* 2013;58(4):255
15. Asano Y. The pathogenesis of systemic sclerosis: an understanding based on a common pathologic cascade across multiple organs and additional organ-specific pathologies. *Journal of clinical medicine.* 2020;9(9):2687
16. Bournia VKK, Vlachoyiannopoulos PG, Selmi C, Moutsopoulos HM, Gershwin ME. Recent advances in the treatment of systemic sclerosis. *Clinical reviews in allergy & immunology.* 2009;36:176-200
17. Al-Adhadh RN, Al-Sayed TA. Clinical features of systemic sclerosis. *Saudi medical journal.* 2001;22(4):333-6
18. Vitiello M, Abuchar A, Santana N, Dehesa L, Kerdel FA. An update on the treatment of the cutaneous manifestations of systemic sclerosis: The dermatologist's point of view. *The Journal of clinical and aesthetic dermatology.* 2012;5(7):33
19. Bibi Nitzan Y, Cohen AD. Zinc in skin pathology and care. *Journal of dermatological treatment.* 2006;17(4):205-10
20. Sharquie IK, Sharquie KE, Al-bassam WW. Zinc as an essential element for normal immune reactions and as a therapeutic agent for autoimmune diseases. *Journal of Pakistan Association of Dermatologists.* 2022;32(4):719-25
21. Sharquie KE, Al-Jaralla FA, Sharquie IK. Intralesional Injection of Hyaluronic Acid as a Long Lasting Therapy of Morphea Sclerosis. *American Journal of Dermatology and Venereology.* 2019;8(3):45-8
22. Sharquie KE, Najim RA, AL-DORI WS, AL-HAYANI RK. Oral zinc sulfate in the treatment of Behcet's disease: A double blind cross-over study. *The Journal of dermatology.* 2006;33(8):541-6
23. Sharquie K, Najim R, Farjou I, Al-Timimi D. Oral zinc sulphate in the treatment of acute cutaneous leishmaniasis. *Clinical and experimental dermatology.* 2001;26(1):21-6
24. Al-Gurairi F, Al-Waiz M, Sharquie K. Oral zinc sulphate in the treatment of recalcitrant viral warts: randomized placebo-controlled clinical trial. *British Journal of Dermatology.* 2002;146(3):423-31
25. Sharquie KE, Najim RA, Al-Hayani RK, Al-Nuaimy AA, Maroof DM. The therapeutic and prophylactic role of oral zinc sulfate in management of recurrent aphthous stomatitis (ras) in comparison with dapsone. *Saudi medical journal.* 2008;29(5):734-8

26. Sharquie KE, Noaimi A, Shwail E. Oral zinc sulphate in treatment of alopecia areata (double blind; crossover study). *J Clin Exp Dermatol Res*. 2012;3(150):1000150
27. Sharquie KE, Noaimi AA, Kadir NO. Topical therapy of xeroderma pigmentosa with 20% zinc sulfate solution. *The Iraqi Postgraduate Medical Journal*. 2008;7:231-6
28. Sharquie KE, Najim RA, Al-Salman HN. Oral zinc sulfate in the treatment of rosacea: a double-blind, placebo-controlled study. *International journal of dermatology*. 2006;45(7):857-61
29. Gorial FI, Swady RN. Prevalence of Depression in Iraqi Patients with Systemic Sclerosis and Its Relationship with Disease Severity. *International Journal of Medical Research & Health Sciences*. 2018;7(4):69-74
30. Chung L, Fiorentino D. Digital ulcers in patients with systemic sclerosis. *Autoimmunity reviews*. 2006;5(2):125-8
31. Fox P, Chung L, Chang J. Management of the hand in systemic sclerosis. *Journal of Hand Surgery*. 2013;38(5):1012-6
32. Zhu JL, Black SM, Chen HW, Jacobe HT. Emerging treatments for scleroderma/systemic sclerosis. *Faculty Reviews*. 2021;10
33. Starnoni M, Pappalardo M, Spinella A, Testoni S, Lattanzi M, Femino R, *et al*. Systemic sclerosis cutaneous expression: Management of skin fibrosis and digital ulcers. *Annals of Medicine and Surgery*. 2021;71:102984
34. Distler JH, Allanore Y, Avouac J, Giacomelli R, Guiducci S, Moritz F, *et al*. EULAR Scleroderma Trials and Research group statement and recommendations on endothelial precursor cells. *Annals of the rheumatic diseases*. 2009;68(2):163-8
35. Koenig M, Joyal F, Fritzler MJ, Roussin A, Abrahamowicz M, Boire G, *et al*. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*. 2008;58(12):3902-12
36. Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G, *et al*. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine*. 2002;81(2):139-53
37. Robertson L, Marshall R, Hickling P. Treatment of cutaneous calcinosis in limited systemic sclerosis with minocycline. *Annals of the rheumatic diseases*. 2003;62(3):267-9
38. Fries R, Shariat K, von Wilmowsky H, Böhm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation*. 2005;112(19):2980-5
39. Shenoy PD, Kumar S, Jha LK, Choudhary SK, Singh U, Misra R, *et al*. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. *Rheumatology*. 2010;49(12):2420-8.