Chapter 11
Lower Limb Ulcers

Jelena Blagojevic and Silvia Bellando-Randone

Background

Prevalence of lower limb ulcers in SSc has not been investigated, but our unpublished data suggest that around 10% of patients develop leg ulcers. It seems that patients with long-lasting limited cutaneous form of SSc are at highest risk.

Their etiopathogenesis is often multifactorial. Microangiopathy is one of the disease hallmarks [1] and may be the primary cause of leg ulcers. Concomitant arterial and/or venous macrovascular disease can overlap. Lymphedema may contribute to fluid stasis and facilitate ulcer formation. In addition, cutaneous traction over the bone prominences and repetitive trauma, calcinosis, hyperkeratosis, often related to articular deformities, loss of the fat pad and altered posture, may be involved [2].

Clinical case: You are called to evaluate a patient with SSc and lower limb ulcers referred to the Wound Clinic.

J. Blagojevic (✉) · S. Bellando-Randone
Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

Department of Geriatric Medicine, Division of Rheumatology and Scleroderma Unit, AOUC, Florence, Italy
e-mail: blagojevicj@aou-careggi.toscana.it

M. Matucci-Cerinic, C. P. Denton (eds.), *Practical Management of Systemic Sclerosis in Clinical Practice*, In Clinical Practice,
https://doi.org/10.1007/978-3-030-53736-4_11

70-years old female with limited cutaneous form of systemic sclerosis diagnosed 30 years before was referred to the Wound Clinic for lower limb ulcers evaluation. She has a long-standing history of recurrent digital ulcers and hand calcinosis. Current medications: calcium channel blockers, proton pomp inhibitors, cholecalciferol. On clinical examination there are sclerodactyly and digital pitting scars on the fingertips. There are two leg cutaneous lesions: right pretibial ulcer and left perimalleolar medial ulcer. There is hard whitish material in the bed of the pretibial lesion and perilesional skin is very inflamed. She has leg edema, more evident on the left, varicose veins on both legs and there is cutaneous dyschromia in the gaiter region of the left leg.

1. **Describe clinical assessment of these lesions?**
2. **How would you classify the limb ulcers described above?**
3. **How should these ulcers be managed?**

Clinical Assessment of the Lower Limb Lesions

Diagnostic work-up of leg ulcers should always include:

- *Clinical history*: Thorough clinical history including medications must be collected. History of hand DU, ulcers in other sites and calcinosis should be investigated.
- *The elements suggestive of macrovascular arterial involvement* are intermittent claudication, pain that worsens following leg elevation, cardiovascular risk factors, previous cardiovascular events
- *The elements suggestive of venous disease* are previous venous thrombo-embolism, varicose veins or their treatment, multiple pregnancies, obesity, occupation that require prolonged standing or sitting. The ulcer-related pain is usually relieved by elevation of the leg and is more intense in the evening.
- *Clinical examination*: In addition to general examination, assessment of peripheral pulses and auscultation of the bruits, evaluation of venous insufficiency, search of calci-

nosis, hyperkeratosis and foot deformities should be performed. Asymmetrical/abolished pulses and arterial bruits are suggestive of macrovascular arterial peripheral diseases. Oedema, varicosities, skin hyperpigmentation and/or discoloration, inverted "champagne bottle" aspect of the leg, atrophie blanche and lipodermatosclerosis are indicative of venous pathology.

- *Ulcer assessment*: The following characteristics should be registered: localization, dimensions, borders, features of the bed of the lesion and of the perilesional skin, depth of the ulcer. Ulcer related pain should be registered, using VAS scale. Signs of infection ought to be searched.
- *Examinations*: All patients with lower limb ulcers should perform arterial and venous colour Doppler ultrasound (US) examination and ABI (ankle-brachial index) assessment. Patients with hemodynamically significant peripheral arterial disease on arterial colour Doppler US, with distribution consistent with the ulcer site, should undergo digital subtraction angiography (arteriography), if endovascular intervention is feasible and planned. Not-invasive CT/MR angiography should be performed if conventional angiography is contraindicated or in selected cases in order to assess localization and severity of arterial lesions and guide interventional strategies. The advantages of MR over CT angiography are no exposure to radiation and iodine contrast and higher soft tissue resolution [3]. However, it has higher motion artefacts and underestimates arterial calcifications [3]. Clinical utility of complementary exams, such as toe systolic blood pressure, toe-brachial index and transcutaneous oxygen pressure measurement, that may be useful in patients with medial calcinosis and incompressible arteries in other clinical setting [3, 4] has not been investigated in SSc.
- In patients with arterial macrovasular disease, the involvement of upper limb arteries ought to be assess. Carotid and coronary vessel disease should be also investigated especially in patients with traditional cardio-vascular risk factors.

- Supplementary investigations of the venous circulation, such as intravenous ultrasound and venography may be indicated in the selected cases. Angiologist/vascular surgeon must be actively involved in the decision making about the invasive procedures.
- Podiatric evaluation should be performed in patients with altered posture and foot deformities.
- If infection is suspected wound swab has to performed and if there is a suspicion of osteomyelitis, bone X-ray and subsequently MRI and CT ought to be done.
- If clinically indicated, additional examination (as Echocardiogram, Holter electrocardiogram, etc) should be performed for differential diagnosis with distal embolization, hematological disorders and overlap syndromes. Concurrent diabetes mellitus should be ruled out.
- All patients with lower limb ulcer ought to have the reassessment of disease activity and of internal organ involvement.

How Would you Classify the Limb Ulcers Described Above?

In SSc, the lower limb ulcers can be classified according to their origin and clinical features into:

1. **Ulcers associated with hyperkeratosis** (Fig. 11.1): Hyperkeratosis is represented by hypertrophy of the stratum corneum (eg callus and corn), located mainly in areas submitted to increased friction or pressure and fostered by foot deformities, loss of the fat pad, altered posture and microtrauma [2]. Hyperkeratosis promote an ulcer formation by pressing underneath tissues and causing their maceration, haematoma and autolysis, as occur in diabetic foot [5]. Ulcers associated with hyperkeratosis are usually hidden below the hyperkeratotic tissue and may be suspected when there is inflammation and oedema of perilesional skin. The final diagnosis can be made only after debridement, which is also mandatory for ulcer heling [2].

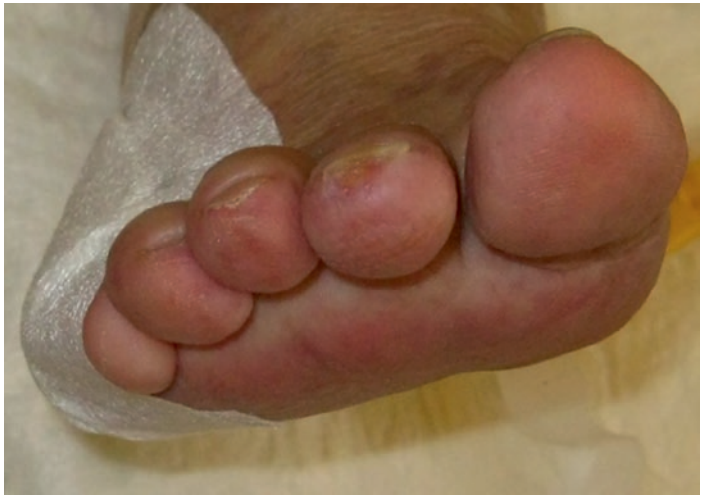

FIGURE 11.1 Ulcer associated with hyperkeratosis (reprinted with permission from Springer Nature)

2. **Ulcers secondary to calcinosis** (Fig. 11.2): These ulcers are directly caused by a mechanical action of calcinosis erupting through the skin. They are localised most frequently on pretibial area, have irregular borders and inflamed perilesional skin and calcinotic material erupting through the skin is often visible [2].
3. **Pure ulcers:** They can be defined as loss of epidermal covering with a break in the basement membrane not occurring in association with hyperkeratosis or with calcinosis. These lesions may be additionally classified into arterial, venous, mixed arterial-venous and pure microvascular ulcers, according to their origin.

   (a) **Venous ulcers** (Fig. 11.3)**:** Venous insufficiency seems to be the most frequent cause of lower limb ulcers in SSc. It has been estimated that 35–50% of ulcers have venous aetiology [2, 6]. Risk factors for venous disease have not been investigated is SSc, but traditional risk factors as previous thrombo-embolic events, vari-

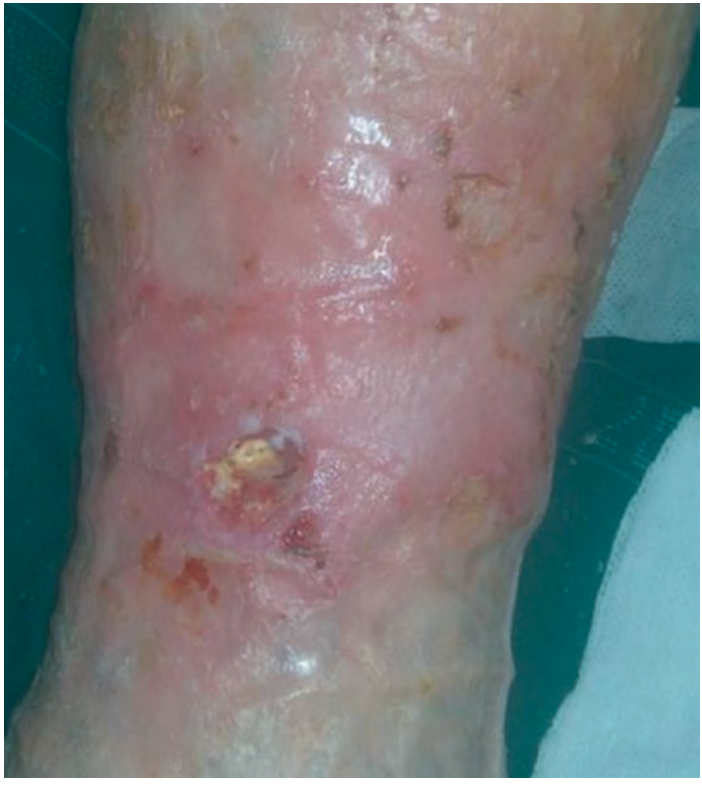

Figure 11.2 Ulcers secondary to calcinosis (reprinted with permission from Springer Nature)

cosities, pregnancies and obesity are probably involved. Venous ulcers are usually localized around the gaiter region, in SSc patients most frequently in the perimalleolar medial area [2]. They are typically shallow, have irregular shape, bed of the lesions is often covered by granulation tissue [4, 7, 8] and surrounding skin presents signs of venous insufficiency as described above [7, 8, 9].

(b) **Arterial ulcers** (Fig. 11.4): In the lower limbs, arterial disease may be the result of SSc-related macrovascular involvement and/or accelerated atherosclerosis [10–

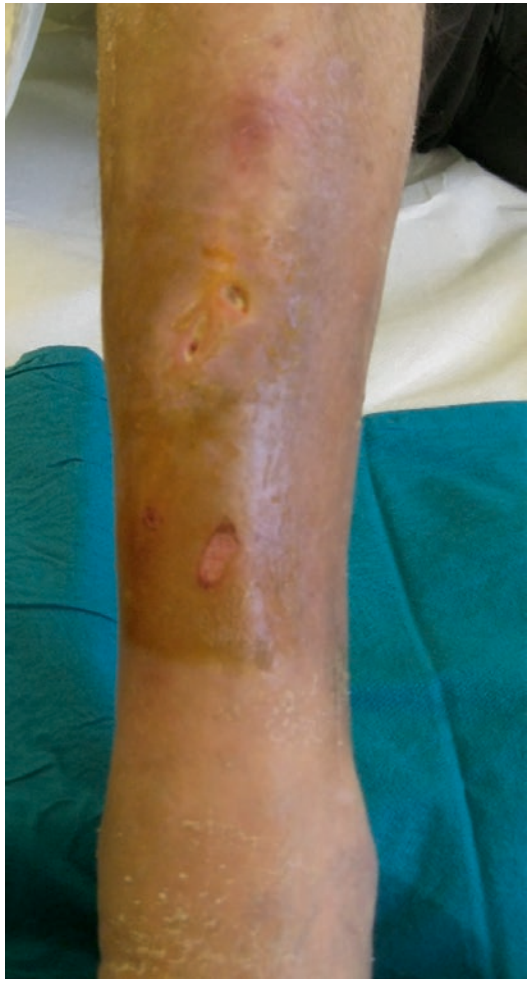

FIGURE 11.3 Venous ulcer (reprinted with permission from Springer Nature)

14]. Severe arterial involvement leading to lower limb ulcers has been described in 10–15% of SSc patients [2, 6]. Importantly, not all patients with significant arterial macrovascular involvement present leg ulcers. It seems that arterial involvement is more frequent in long

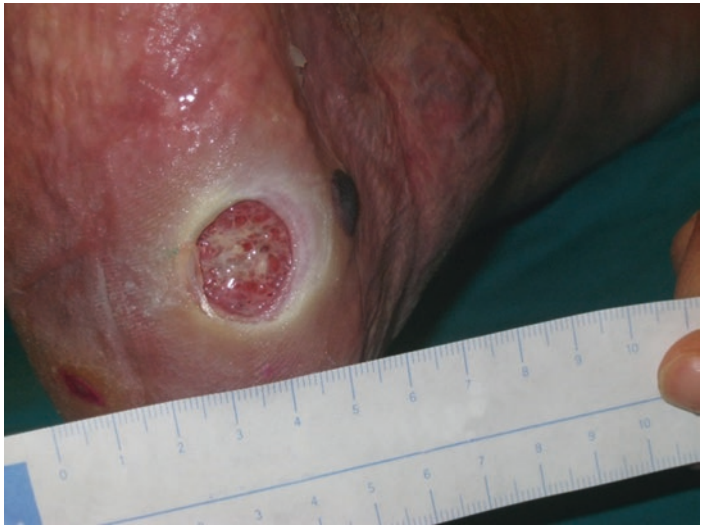

FIGURE 11.4 Arterial ulcer (reprinted with permission from Springer Nature)

standing limited cutaneous form of disease (**10,** personal observation), but risk factors/predictors for macrovascular arterial involvement in SSc has still to be determined.

Arterial ulcers have distinct borders, punched out appearance and cold surrounding skin [4, 7–9]. In SSc patients, they are localized more frequently on toes and heels and are the more painful than other types of leg ulcers [2].

(c) **Mixed arterial-venous ulcers:** Arterial macrovascular involvement and venous disease may overlap and contribute to the ulcer formation, as described in other clinical settings [4]. They have characteristics of both arterial and venous lesions, most frequently features of a venous ulcer in combination with signs of arterial impairment, such as absent or abolished pulses [7, 8].

(d) **Pure microvascular ulcers** (Fig. 11.5): These ischemic lesions are a consequence of SSc-related microangi-

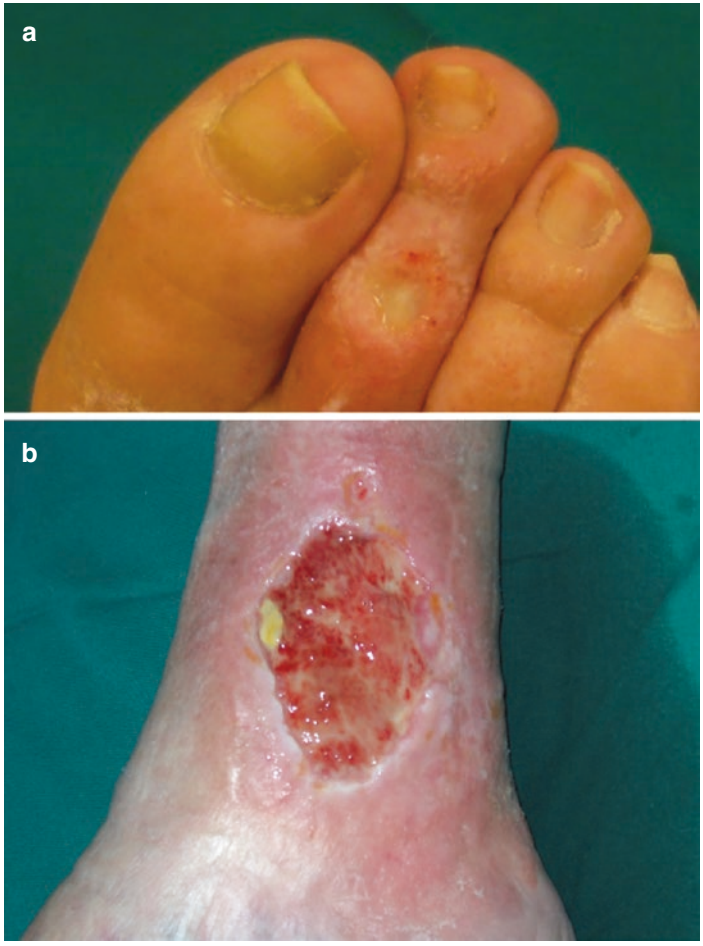

FIGURE 11.5 Pure microvascular ulcers (**a**) digital ulcer. (**b**) medial malleolus ulcer (reprinted with permission from Springer Nature)

opathy as digital ulcers in the upper limbs, although factors as tight skin and traction over the bony prominences (e.g malleolus) may contribute to the ulcer formation. Our personal observations suggest that longstanding limited cutaneous form of SSc, history of

digital ulcers and ulcers in other locations may represent risk factors for these lesions. Pure microvascular ulcers have morphological characteristics of arterial ulcers in the absence of signs of macrovascular impairment (such as absent or diminished peripheral pulses) and are most frequently found on toes and on perimalleolar lateral area [2].

How Should These Ulcers Be Managed?

The general management of the lower limb ulcers is based on few fundamental steps:

1. *Removing/avoiding factors that may contribute to the ulcer formation*: adequate footwear, insoles and foot orthotics when indicated, avoiding trauma, smoking cessation, treatment of cardiovascular risk factors, elastic compression for venous insufficiency and lymphedema, lymph drainage for lymphedema
2. *Supportive measures*: prompt analgesia, maintenance of adequate nutritional status
3. *Local treatment based on wound care principles*. To ensure ulcer healing, lesions must be vascularized, free of necrotic and nonviable tissue, without infection, and kept moist. One of the pivotal steps of the local treatment is debridement which consists in removal of necrotic, nonviable and infected tissue and is fundamental for the healing. Sharp debridement is the main treatment for ulcers associated with hyperkeratosis and ulcers secondary to calcinosis. Simple hyperkeratosis should be promptly debrided in order to prevent ulcer formation.
4. *Pharmacological treatment*: optimization of vasodilating/vasoactive treatment, consideration/increase of immunosuppression/immunomodulation, treatment of cardiovascular risk factors. Statins and anti-platelet medications may be useful, especially in patients with macrovascular arterial disease
5. *Additional treatments*: topical vitamin E, hyperbaric oxygen for severe and persistent ulcers [15].

Patients with critical arterial macrovascular disease with distribution consistent with the ulcer site and lesions suitable for endovascular treatment should be referred for digital subtraction angiography and endovascular procedures. The role of surgical revascularisation for SSc-related leg ulcers have not been established, but limited data suggest that its long-term outcome is significantly worse than those in non-scleroderma patients [16, 17]. For arterial ulcers intravenous prostanoids, statins and anti-platelet agents should be prescribed. Cardiovascular risk factors should be treated aggressively.

Treatment *pure microvascular ulcers* is based on optimizing vasodilating/vasoactive treatment and increasing of immunosuppression/immunomodulation, taking into account other disease manifestations. Anti-platelet agents and statins should be considered.

Treatment of *venous ulcers* is based on elastic compression (at least 18–24-mmHg pressure) [9]. Medications that that may aggravate peripheral oedema, as calcium channel blockers, should be avoided if possible. Role of endovascular venous ablation and/or radiofrequency ablation or laser therapy have not been established in SSc but might be discussed in selected cases.

Mixed arterial-venous ulcers should be managed closely with angiologist/vascular surgeon. Venous insufficiency should be treated with compression therapy and in selected cases superficial venous ablation may be considered. Indication for arterial revascularization in mixed ulcers is based on clinical presentation and ABI (generally <0, 7) [4].

Regarding compressive therapy for venous and mixed arterial-venous ulcers, there is a potential concern that the excessive compression might worsen arterial insufficiency; therefore, reduced compression is usually advised. However, it has been reported that even anelastic compression up to 40 mmHg does not obstruct arterial perfusion in patients with mixed arterial-venous ulcers with ABI >0, 5 and ankle pressure >60 mmHg [18].

Wound swab should be performed, and antibiotic treatment should be started if clinical signs of infection are present (purulent exudate, inflammation of perilesional skin).

Diagnostic and treatment algorithm is shown in Fig. 11.6.

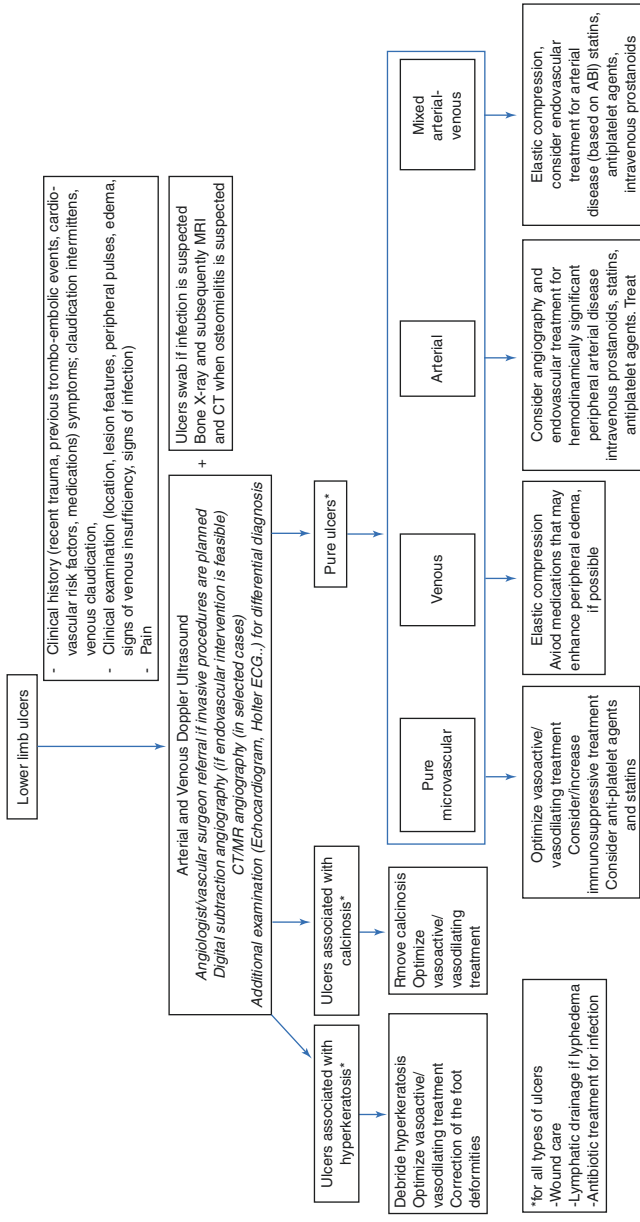

FIGURE 11.6 Leg ulcers: diagnostic and therapetic algorythm

Comments to the Questions Regarding Clinical Case

Left ulcer is likely of venous origin. Varicose veins, peripheral oedema and dyschromia in the gaiter region of the left leg are indicative of venous insufficiency. However, significant macrovascular arterial involvement should be always ruled out. The treatment is based on wound care and elastic compression. Topical vitamin E may be helpful. Substitution of calcium channel blockers with other vasoactive/vasodilating that cause les peripheral oedema should be considered.

Right ulcer is probably secondary to calcinosis (hard whitish material in the bed of the lesion is suggestive for stone calcinosis). The treatment is based on calcinosis removal and wound care. For calcinosis a number of different treatments, such as vasoactive/vasodilating drugs, bisphosphonates, colchicine, minocycline, warfarin, intravenous immunoglobulins and Rituximab have been proposed, with unsatisfactory results [19].

Take home points. Lower limb ulcers are often multifactorial in SSc and more than one type of ulcer may occur in the same patient. Macrovascular arterial and/or venous involvement must be always investigated. Local factors that may predispose to the ulcer formation should be removed. Topical wound management and optimising pharmacological therapy are mandatory for ulcer healing. Elastic compression is the main therapy for venous ulcers. Endovascular treatment should be considered for arterial macrovascular ulcers.

References

1. Varga J, Trojanowska M, Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. J Scleroderma Relat Disord. 2017;2:137–52.
2. Blagojevic J, Piemonte G, Benelli L, Braschi F, Fiori G, Bartoli F, et al. Assessment, definition and classification of lower limb ulcers in systemic sclerosis: a challenge for the rheumatologist. J Rheumatol. 2016;43(3):592–8.

3. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Röther J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I, ESC Scientific Document Group. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries endorsed by: the European stroke organization (ESO)the task force for the diagnosis and treatment of peripheral arterial diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39(9):763–816.
4. Hedayati N, Carson JG, Chi YW, Link D. Management of mixed arterial venous lower extremity ulceration: a review. Vasc Med. 2015;20(5):479–86.
5. Edmonds ME, Foster AV. Diabetic foot ulcers. BMJ. 2006;18(332):407–10.
6. Bohelay G, Blaise S, Levy P, Claeys A, Baudot N, Cuny JF, et al. Lower-limb ulcers in systemic sclerosis: a multicentre retrospective case-control study. Acta Derm Venereol. 2018;98(7):677–82.
7. Mekkes JR, Loots MA, Van Der Wal AC, Bos JD. Causes, investigation and treatment of leg ulceration. Br J Dermatol. 2003;148:388–401.
8. Wound and Skin Care Clinical Guidelines 2007, VIHA.www.viha.ca
9. Grey JE, Harding KG, Enoch S. Venous and arterial leg ulcers. BMJ. 2006;332:347–50.
10. Youssef P, Brama T, Englert H, Bertouch J. Limited scleroderma is associated with increased prevalence of macrovascular disease. J Rheumatol. 1995;22:469–72.
11. Ho M, Veale D, Eastmond C, Nuki G, Belch J. Macrovascular disease and systemic sclerosis. Ann Rheum Dis. 2000;59:39–43.
12. Blagojevic J, Matucci CM. Macrovascular involvement in systemic sclerosis: comorbidity or accelerated atherosclerosis? Curr Rheumatol Rep. 2007;9(3):181–2.
13. Hettema ME. Bootsma H, Kallenberg CG macrovascular disease and atherosclerosis in SSc. Rheumatology (Oxford). 2008;47:578–83.
14. Nordin A, Jensen-Urstad K, Björnådal L, Pettersson S, Larsson A, Svenungsson E. Ischemic arterial events and atherosclerosis

in patients with systemic sclerosis: a population-based case-control study. Arthritis Res Ther. 2013;15(4):R87. https://doi.org/10.1186/ar4267.
15. Mirasoglu B, Bagli BS, Aktas S. Hyperbaric oxygen therapy for chronic ulcers in systemic sclerosis - case series. Int J Dermatol. 2017;56(6):636–40.
16. Deguchi J, Shigematsu K, Ota S, Kimura H, Fukayama M, Miyata T. Surgical result of critical limb ischemia due to tibial arterial occlusion in patients with systemic scleroderma. J Vasc Surg. 2009;49:918–23.
17. Arhuidese I, Malas M, Obeid T, Massada K, Khaled A, Alzahrani A, Samaha G, Reifsnyder T. Outcomes after open infrainguinal bypass in patients with scleroderma. J Vasc Surg. 2016;64(1):117–23.
18. Valenzuela A, Chung L. Calcinosis: pathophysiology and management. Curr Opin Rheumatol. 2015;27(6):542–8.
19. Mosti G, Iabichella ML, Partsch H. Compression therapy in mixed ulcers increases venous output and arterial perfusion. J Vasc Surg. 2012;55:122–8.