Leg Ulcers

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ABSTRACT

Leg ulcers are common in older adults and a serious problem. Underlying conditions that increase risk include age-related increases in chronic venous insufficiency, peripheral artery disease, connective tissue and autoimmune conditions, reduced mobility, and diabetes mellitus. Geriatric patients have a higher risk of wound-related complications including infection, cellulitis, ischemia and gangrene, with possible need for amputation, negatively impacting quality of life and function. Understanding and early identification of the underlying conditions and wound features are crucial for effective ulcer healing and complication mitigation. This chapter provides a focus on three major types of leg ulcers, venous, arterial, and neuropathic, including evaluation and potential new treatments.

KEY WORDS

Leg ulcers, Venous ulcers, Arterial Ulcers, Arterial-Ischemic ulcers, Diabetic Ulcers, Neuropathic ulcers, evaluation of ulcers, management of leg ulcers

Introduction

Leg ulcers are a significant worldwide healthcare burden occurring more frequently in persons over the age of 65 who, in at least one study, were also classified as being frail (1). It has been stated that the incidence of venous leg ulcers in persons 65 and older is as great as 4% with about 85% of leg ulcers being of venous in origin (2), and overall having a significant cost burden (3-6). Quality of life of those living with leg ulcers is demonstrably downgraded (7, 8). Early diagnosis and targeted treatment are important to minimize the totality of the leg ulcer burden on the patient (9-13) . In this chapter the major types of leg ulcers that are the main focus are those of venous, arterial, and neuropathic origin with the later type often diabetes related that carries with it significant patient risks of amputation and even mortality (14-16). General and specific aspects of these are considered followed by more detailed discussions and relevancy to the geriatric population in subsequent sections.

History and Examination

Although the most common causes of leg ulcers are due to venous insufficiency, arterial insufficiency, or neuropathy there are a large number of less common causes. These include those caused by injury, infection (17, 18), vasculitis or microvascular dysfunction (19-22), malignancy (23-25) and drug related (26, 27). Thus, a thorough evaluation of patients with leg ulcers is necessary in order to plan for appropriate targeted treatment. Since the most prevalent leg ulcers are venous, arterial, and neuropathic, the presence of the following underlying conditions are suggested to be investigated first (28). History of deep vein thrombosis, stroke, miscarriage, obesity, multiple pregnancies, and pain after standing for long periods of time would raise suspicion for venous ulcers, while history of smoking tobacco, Type

2 diabetes, elevated cholesterol or lipids, and intermittent claudication would be more likely present in ulcers of arterial nature. Another important factor to inquire about is the presence of pain as venous ulcers often present as moderately painful, arterial present as severely painful and neuropathic present as painless. Venous ulcers often present with other signs of venous insufficiencies including varicose veins and peripheral edema, whereas arterial ulcers often present with severely diminished or absent peripheral pulses, increased capillary refilling time, and neuropathic ulcers present with decreased sensation. Malignancy should always be investigated. Other less common causes of leg ulcers such as those listed above should be considered if findings are not consistent with arterial, venous, or neuropathic ulcers. Inquiring about medication use, history of disease, and development course can also help recognize the less common causes that also include, pyoderma gangrenosum (29), panniculitis (30, 31) and spider bites (32). Approaches toward improvements in differential diagnosis among leg ulcers is an ongoing effort (9, 33-35).

Venous ulcers

Venous ulcers are the most common chronic lower extremity skin wounds among adults aged 65 years and older, with a reported annual prevalence of 1.7% in developed countries (36, 37). As the population increases, the prevalence of venous leg ulcers increases as well (38). Women are more likely to develop venous leg ulcers than men (39). Settings where individuals are more likely to develop venous leg ulcers include nursing homes and hospitals, as well as individuals who with obesity, sedentary lifestyles, or a history of deep vein thrombosis and phlebitis (39). Venous ulcers pose both an economic and clinical burden to healthcare systems

globally, estimating around $10.73 billion (USD) per year in direct medical costs for patients managed in Australia, France, Germany, Italy, Spain, the UK and the US combined (6). Venous disease tends to increase with age, and accordingly, venous ulcers represent an increased challenge in the geriatric population (40). Factors involved in the development of venous ulcers include venous reflux and venous hypertension due to incompetence of deep and communicating vein valves and thrombosis of deep vein segments (41). In addition, chronic venous insufficiency is associated with obstruction of venous drainage and increases in venous pressure and reflux due to the formation of arteriovenous fistulas. The exact pathophysiology of venous leg ulcers remains unclear; however, many theories and hypothetical models have been described (42-44). For example, the "white cell trapping" theory describes a release of free radicals that result in tissue death as a consequence of hypertension (45). Increased activation of platelets, monocytes and neutrophils leading to microvascular aggregation and microvascular entrapment of neutrophils has been reported (46).

Although the evolution of skin ulcers from venous hypertension is not fully understood; contributory factors include inflammatory processes, intercellular and vascular adhesion molecule upregulation, protein rich edema, leukocyte trapping, oxygen deprivation, and microcirculatory deficits (46). Venous hypertension-induced microangiopathy may be associated with abnormally dilated and tortuous capillaries, loss of some functional capillaries, microvascular thrombosis, increased capillary permeability and transcapillary fluid efflux, tissue edema and altered function of lymphatics (44).

Arterial-Ischemic ulcers

Arterial- Ischemic ulcers compose 10-20% of all non-healing lower extremity leg ulcers (47). Its most common predisposing condition is advanced peripheral vascular disease affecting lower extremity arteries that supply the leg and foot (48). Other risk factors include atherosclerosis, hypertension, diabetes, and atrial fibrillation, all of which are more prevalent in the geriatric population(49).

Arterial ulceration is caused by insufficient vascular perfusion to the lower limbs, leading to ischemia and hypoxia of subcutaneous tissue (50). These ulcers will often occur in areas subject to pressure or trauma, typically at the toes, between toes and the shin at pressure points (51). Given the impact of aging on changes in lower extremity blood flow, such ulcers are likely to be more prevalent in the geriatric population, not because of their age, but because the prevalence of vascular disease is far more likely in this age group (52). These ulcers are difficult to heal in the absence of an adequate restoration of blood flow, which itself may be difficult to accomplish due to the presence of comorbid conditions, especially in the absence of surgical correction (53).

Diabetes-related neuropathic ulcers

Diabetes-related skin ulcers in persons with diabetes are generally at increased risk of developing skin ulcerations due to multiple predisposing factors, predominantly from the presence of neuropathy, ischemia, and poor glycemic control (54). The higher likelihood of peripheral arterial disease and the presence of microvascular deficits in diabetes (55) increase the likelihood for vascular ischemia, tissue to breakdown, and ulcer formation. These causative factors may be more likely present in the geriatric population (56). Risk factors for developing

foot ulcers in patients with diabetes, based on a recent meta-analysis, include; older age, increased BMI, duration of diabetes, and comorbid neuropathy, nephropathy, or retinopathy (57)

Ulcers in diabetic patients are also more difficult to heal due to the reduced blood flow and wound oxygenation (58, 59), deficits in wound cell (60), and the possible additional presence of infection. Healing time is also reported dependent on the ulcer location, with ulcers on the heel taking the longest time to heal (61). In some patients with diabetes, it takes less local pressure to reduce skin blood flow in regions of bony prominence thereby laying the groundwork for ulcerations at these sites. When sensory neuropathy is present, normal pressure/pain signals are diminished or absent, removing warning signs or symptoms of tissue injury. The presence of visual impairment in many patients with diabetes makes it difficult to recognize the presence of foot ulcers, as they are also often painless due to co-existing neuropathy. Most ulcers develop on the sole of the foot, with plantar ulcers often associated with neuropathy with considerable variability is shape and area (62). In these cases, elimination of foot pressures combined with standard wound care are indicated. Statistics suggest that about 15-25% of persons with diabetes will get a foot ulcer (63) with an annual incidence rate of 2- 4% (64). Diabetic-related non-healing ulcers account for 140,000 extremity amputations per year in the US (65), and an annual amputation incidence rate between 0.5-- 0.8% amputations per patient-year. In a 10-year population-based cohort study, the incidence of unilateral lower limb amputation for diabetic women was 195 per 100 000 person per year and 197 for diabetic men (63). The incidence of amputations due to non-healing wounds specifically in the geriatric population has not been systematically studied.

Disease burden of neuropathic ulcers disproportionately affects racial and ethnic minority groups (66). Native Americans, African Americans (AA) and Hispanics all experience greater rates of Diabetes Mellitus and its complications compared to whites. Minority groups are also less likely to undergo limb salvage than their white counterparts, highlighting that health disparity goes beyond difference in access. (67) Other social determinants of health that greatly impact glycemic control and ultimately health outcomes include food insecurity, neighborhood safety, perceived stress, depression, self-efficacy as well as perceived discrimination. (66) People living in more rural areas of the U.S., as well as people who live in the South also experience higher rates of lower limb amputation compared to those who live in the Northeast (68). It is important to better understand and inquire about factors that contribute to health disparities to deliver fair and equitable care.

FACTORS RELEVANT TO THE GERIATRIC POPULATION

Venous Ulcers

Previous leg injuries, deep vein thrombosis, phlebitis, obesity, and older age are all risk factors for the development of venous ulcers. (69, 70) About 1.5% of Americans have venous ulcers with a female to male ratio of about 1.6 to 1. About 20% of persons who develop venous ulcers do so prior to the age of 40, and the rest (a majority) develop venous ulcers after the age of 40. About 85% of venous ulcers occur in adults over 65 years of age (71). Further, 40% of patients who develop venous ulcers have a history of deep vein thrombosis and a diagnosis of chronic venous insufficiency. One in five patients with venous disease also have some arterial disease. Risk of venous ulcers increases with age – affecting 20/1000 people aged over 80 years

old (72) with a reported prevalence as high as 5% in persons over 65 years of age (73). Age specific risk factors that contribute to this prevalence in older adults are endothelial dysfunction, frailty and immobility. (74) In older adults, endothelial dysfunction presents as reduced vasodilation and an increased prothrombotic environment due to changes in the muscle fibers of the venous wall and decreased anticoagulant properties. These changes increase the risk of deep vein thrombosis in older adults and subsequently its dermatological manifestation of venous ulcers. Similarly, immobility also increases the risk of venous ulcers by increasing blood viscosity and stasis. Since the geriatric population is most at risk of experiencing long-term immobility, they are at a greater risk of developing venous ulcers.

About 80% of lower extremity wounds are venous ulcers with nearly 95% of them located in the gaiter area, referring to the area between the knee and the ankle with variable areas and shapes (75). An example of a venous ulcer located in the gaiter area is shown in **figure 1.** This figure demonstrates some of its more common features, typically a shallow ulcer with irregular margins, often with surrounding hyperpigmentation. The recurrence rate of venous ulcers once healed is near 70%.

Factors that impact the development of chronic venous insufficiency (CVI) a condition that is most often associated with venous hypertension that itself increases with age, include (1) dysfunction of valves in superficial and/or communicating veins, (2) dysfunction of valves located in the deep venous system, (3) obstruction to outflow from the deep venous system and (4) dysfunction or failure of the calf muscle pump. The progression to venous ulceration is most often precipitated by the reverse flow in medial calf perforating veins that gives rise to pressure-induced venous injury, tissue damage and skin breakdown. The blood flow path

process is schematically illustrated in **figure 2** in which the normally low-pressure superficial veins become exposed to the high pressures induced by the reverse flow pathways associated with incompetent valves. Concomitant with the tissue injury are inflammatory processes, increased vascular permeability and edema and or lymphedema. In **figure 3** an example of a venous ulcer is shown in which skin blood perfusion is being measured in the peri-ulcer region using laser Doppler. The initial perfusion measurement is made at a skin temperature of 35^{o}C and then the tissue is locally heated to 44^{o}C with typical responses as shown in **figure 4.** The responses shown in figure 4 demonstrates a common finding for ulcers of venous origin; an elevated peri-ulcer basal resting flow with little if any vascular reserve when stimulated with heat as shown in part B, but with normal responses in healthy control skin as shown in part A.

Arterial Ischemic Ulcers

Arterial ulcers represent about 5% of all leg ulcers and are commonly located on the leg or foot area but have features quite distinct from venous ulcers. Some of these differences are summarized in **table 1** with an illustration of an arterial ischemic ulcer shown in **figure 5**.

Arterial ulcers are associated with conditions in which arterial blood flow to a tissue region is chronically less than needed for adequate tissue nourishment and metabolic needs. These ulcers are difficult to heal especially in the absence of procedures to augment blood flow to the region. They are often painful and cause sleep disturbances, more frequent among the aged (11). A common etiology for limitation in blood flow is the presence of lower extremity peripheral arterial disease due to numerous risk factors, most increasing with age, including atherosclerosis, diabetes, bed bound status and length of bedfast period (76). Bedfast refers to the inability to leave bed or being bedbound due to illness or disability. In addition to the

higher likelihood of being bedfast with age, there is also an age-related higher risk of developing both atherosclerosis and diabetes, making the geriatric population at higher risk for the development of ischemic ulcers, (77, 78).

Diabetes-Related Ulcers

The pooled global prevalence of diabetic foot ulcers has been reported as 6.3% with the greatest prevalence in North America at 13.0% (79). Persons with Type 2 diabetes mellitus (T2D) who had a foot ulcer tended to be older and had more co-present conditions including smoking history and hypertension than those without foot ulcers. Peripheral arterial disease, peripheral neuropathy, inability for foot self-examination, poor glycemic control and anemia are all significant risk factors for diabetic foot ulceration. (80) An early study investigated the possible relationship between foot ulcer healing outcomes and other parameters including initial ulcer size and age in 194 patients with foot ulcers (81). In their study group, about 2/3 of the ulcers were of neuropathic origin, with most present on the forefoot. Although healing time correlated with the initial ulcer area, there was no detectible dependence on age in their study group of patients that had a mean age of 56.6 ± 12.6 years. A more recent study evaluated the impact of older age (≥ 75 years) on healing rates of 1008 patients with diabetes and foot ulcers (82) . They report that despite the presence of significant comorbidities, including 93% with neuropathy, healing was achieved in 84% of surviving patients without the need for major amputations. In another age comparison study, healing rates of foot ulcers of 684 Chinese patients with T2D were found to be similar between patients < 65 years vs. those ≥ 65 years (83). In a study of 435 patients with diabetic foot ulcers, no essential age-related differences in ulcer presentation above and below age 65 were found (84). Thus, although age may be a risk

factor for developing diabetes-related ulcers attributable to factors such as cardiovascular and neuropathic comorbidities, age itself may not fully determine the healing potential of the ulcers. This perspective highlights the importance of prioritizing risk reduction in older people to prevent negative outcomes of diabetes-related ulcers such as amputation.(82)

Other potential geriatric-related ulcers

Although venous, arterial, and neuropathic ulcers comprise the bulk of lower extremity ulcers, other skin ulcerations to be considered include those related to vasculitis, infection, and malignancy. Ulcers attributed to vasculitis are most frequently found in the lower leg in part because of the relatively reduced blood perfusion and temperature in this area and the greater likelihood of this area experiencing trauma. Vascular inflammatory processes, including those caused by arteritis, contribute to leg ulcer development by causing insufficient local blood flow and tissue oxygenation. These leg ulcers are generally difficult to heal and tend to recur (85). Diagnostic and treatment guidelines are available (86). Because there is an age-dependent factor in the different forms of arteritis (87-89), consideration for an underlying causative arteritis for some ulcers is relevant in the geriatric population. Once formed, ulcer healing is delayed or prevented due to the presence of cellulitis or osteomyelitis, which are common causes of nonhealing ulcers (90). It is not clear if the incidence of these infections is more prevalent in the geriatric population but should also be considered in all nonhealing ulcers. In addition, a nonhealing ulcer may raise the concern of the presence of a cutaneous malignancy that might be mistaken for a different form of leg ulcer (91-93). A case in point was the misdiagnosis in a 70-year-old with Acral Amelanotic Melanoma, which highlighted the importance of considering malignancy in the presence of non-healing ulcers (94) Given the age

dependent incidence of the various skin cancers, the malignant leg ulcer possibility is important to consider (95-97).

TREATMENT APPROACHES AND OUTCOMES FOR GERIATRIC PATIENTS

Leg ulcers that develop in geriatric patients may eventually progress to a chronic or non-healing state (98). Furthermore, complications such as cellulitis, infection, malignancy, musculoskeletal changes, erythema and pain may lead to mortality (99). Factors such as aging skin, lack of mobility, functional states as determined by activities of daily living (ADL), nutritional and social support, and multiple pathologic co-morbidities common in the geriatric population all play a significant role in the development and persistence of non-healing ulcers (100). Life- style modifications such as a well-balanced diet, cessation of smoking, and consistent physical activity is also recommended to prevent recurrence (101). Therefore, treating non-healing leg ulcers in the geriatric population requires a holistic, comprehensive and multidisciplinary approach (102). The goal of treatment should be to control symptoms, prevent complications, and improve patients' quality of life (102, 103).

The presence of multiple co-morbidities in the geriatric population warrants the need for a thorough physical examination and risk assessment before devising a treatment plan (104). The importance of early detection and diagnosis cannot be overstated, as a delay in treatment may lead to progression of the disease (45). Imaging techniques such as color duplex ultrasonography or triggered angiography non-contrast-enhanced magnetic resonance imaging are valuable and objective diagnostic tools that recognize the presence of valvular insufficiency and occlusion (45, 105).

In the geriatric population, the current standard of treatment for chronic venous leg ulcers consists of compression, elevation of the legs and exercise (104, 106). Compression therapy with zinc paste double-wrapped bandages or stockings with multilayer inelastic 30-40 mmHg high-compression bandages, re-dressed once a week, is thought to promote healing, reduce venous reflux, and minimize edema (45, 100, 104, 106). To prevent recurrences, compression therapy must be continued for the rest of a patient's life (104). Other techniques may include topical negative pressure, therapeutic ultrasound, and laser treatment (38). Several studies have supported the use of oral pentoxifylline in conjunction with compression therapy (107, 108). Although there have not been sufficient studies on the use of pentoxifylline in the treatment of non-healing wounds in the geriatric population specifically, clinical use of the drug is indicated with close monitoring of blood pressure and glucose (109-111). A majority of reported adverse effects, if any, were gastrointestinal in origin (72-74).

In addition, perforator ligation, amputations, skin grafting and superficial vein surgery to the non-healing wound may be options, however, a majority of geriatric patients generally opt for non-invasive interventions (104, 112). Most importantly, physicians should focus on addressing and treating the patients' underlying pathologies and co-morbidities, such as diabetes or heart failure (99). In contrast, arterial ulcers do not respond well to pharmaceutical intervention and instead, mainstay treatment focuses on reestablishing perfusion to the affected area, minimizing further tissue loss, and applying compression (113, 114).

EMERGING AND DEVELOPING CONCEPTS OR TREATMENTS

Standard of care treatment of ulcers comprises of pressure off loading and surgical debridement as well as lifestyle and dietary management (115). In attempts to decrease the rate of failure in healing of wounds, especially in patient with microvascular dysfunction, new treatments have emerged. (116) These treatments include skin substitutes (e.g. flowable bovine collagen), recombinant human epidermal growth factor to manipulate wound environment, antibiotics to prevent infection and neuropathic drugs for symptomatic relief. (116) Since immunomodulators have the potential to improve cutaneous homeostasis and decrease inflammation, these medications have been suggested to help wound healing in a patient with impaired endothelial function. Becaplermin (Regranex) is a growth factor medication in gel form that is approved by the FDA for treatment of diabetic neuropathic foot ulcers of stage III and IV, although it has not been successful for every patient. (116) For the care of nonhealing wounds, bioengineered skin substitutes have been proposed. Unfortunately, these therapies are expensive, have variable success rates and carry a high risk of infection. (116) A combination of treatments that fits the individual presentation of each patient should be considered for the treatment of ulcers. Other possible treatments that are currently being investigated include cell-based therapies and gene therapies to aid in synthesis of growth factors necessary for wound healing. (117) Targeting of Protein Tyrosine Phosphatase 1B which is involved in the regulation of wound healing through the regulation of growth factors and vascular remodeling after injury, also has therapeutic potential in patients with endothelial dysfunctions (117). Nevertheless, these therapies are still in the preliminary stages of research and investigation still is required to evaluate effectiveness and safety. (117)

CONCLUSION

Leg ulcers are a highly prevalent and concerning problem in the geriatric population. They are often caused by underlying conditions such as venous insufficiency, peripheral artery disease, connective tissue diseases, autoimmune conditions, and diabetes, which are more prevalent in older adults. Furthermore, geriatric patients are at a higher risk of developing complications such as infection, cellulitis, and amputation, significantly impacting their quality of life and ability to function. The importance of routine examination of the lower extremities periodically in all older adults, especially those with diabetes mellitus, is emphasized. Early identification and proper management of these underlying conditions are crucial for the healing of leg ulcers and the prevention of said complications. Treatment must be made on a case-by-case basis, considering the patient's underlying condition, comorbidities, and overall health status. It is best achieved by a multidisciplinary approach that involves not only the patient's primary care physician but also specialists such as wound care doctors, physical therapists, and vascular surgeons to properly address the unique challenges faced by geriatric patients.

KEY POINTS

- The three major types of leg ulcers in older adults are venous, arterial, and neuropathic in origin.
- Venous ulcers are the most common chronic lower leg ulcer in the geriatric population, and due to inflammatory processes secondary to venous reflux and hypertension.
- Arterial-ischemic ulcers are due to lower extremity vascular disease which itself tends to increase with increasing age setting the stage for an age-related increase in leg ulcers.
- Persons with diabetes are at increased risk of developing foot ulcers in part due to neuropathy and ischemia, both of which tend to increase with advancing age.
- Increased incidence of venous, arterial and microvascular deficits predisposes older adults to a greater incidence of leg ulcer development.
- Leg ulcers with vasculitis or malignant causes should be ruled out in geriatric patients.
- Early identification of the ulcer and prompt management is crucial for effective treatment.
- Treatment is best made on a case-by-case basis, considering the patient's underlying condition, comorbidities, overall health status and life expectancy.
- Geriatric patients benefit from a multidisciplinary approach that addresses their comorbidity and unique needs.

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FIGURES AND LEGENDS

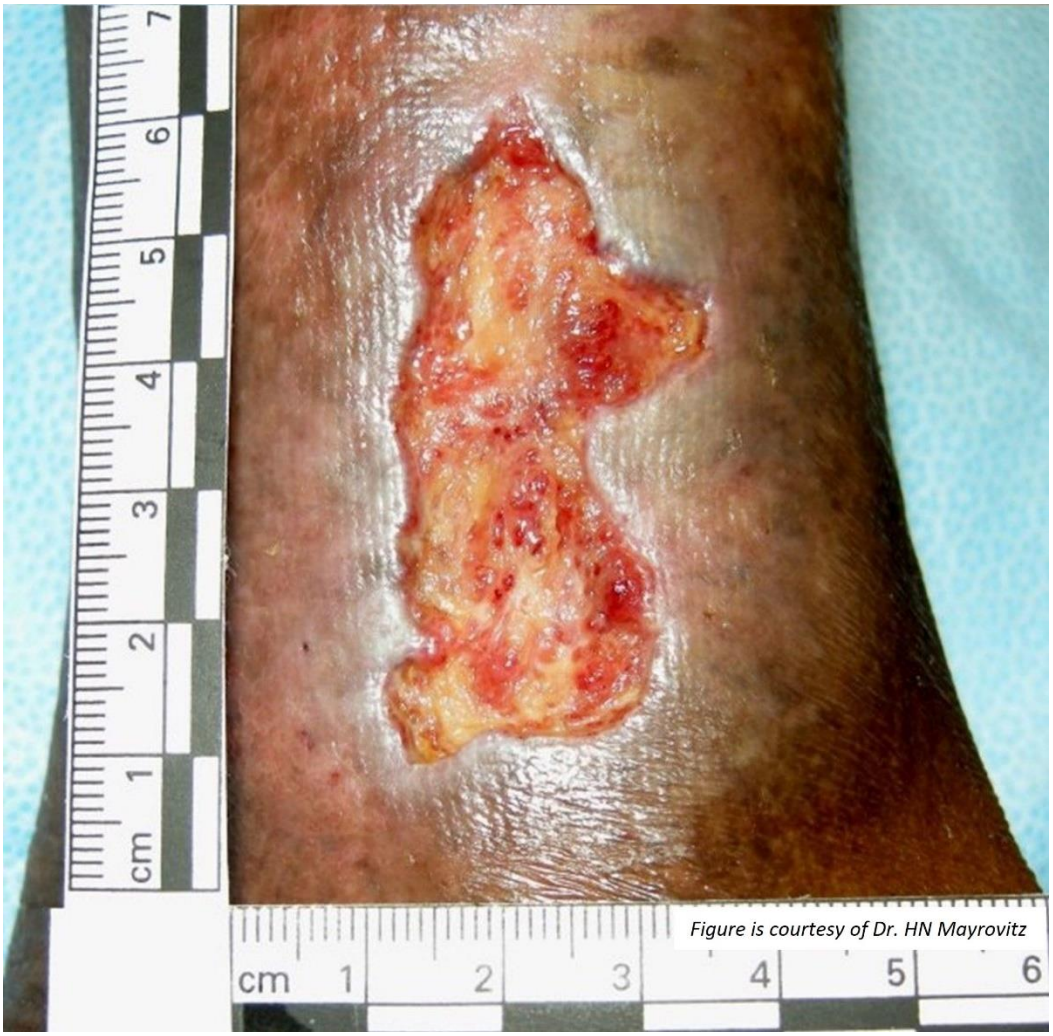

Figure 1. <u>Venous ulcer located on the lateral gaiter area.</u>

These ulcers typically have an irregular shape and characteristic wound bed granulation tissue and surrounding tissue hyperpigmentation. Figure is provided as a courtesy of Dr. HN Mayrovitz

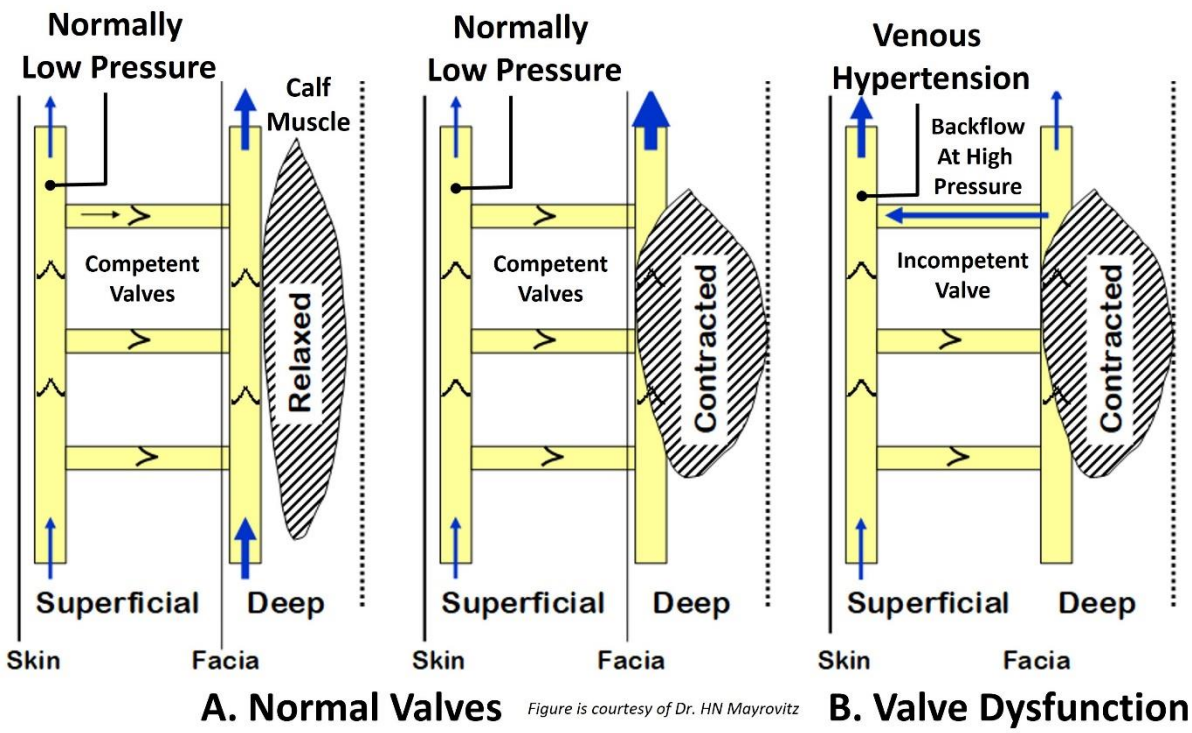

Figure 2. Schematic of the impact and hemodynamics of incompetent venous valves.
The normally low pressure experienced by the superficial veins is subject to high pressures in the presence of the valve incompetency as shown in part B. This elevated pressure is not well tolerated and causes venous injury that triggers a sequence of events that may lead to the development of a venous ulcer. Figure is provided as a courtesy of Dr. HN Mayrovitz

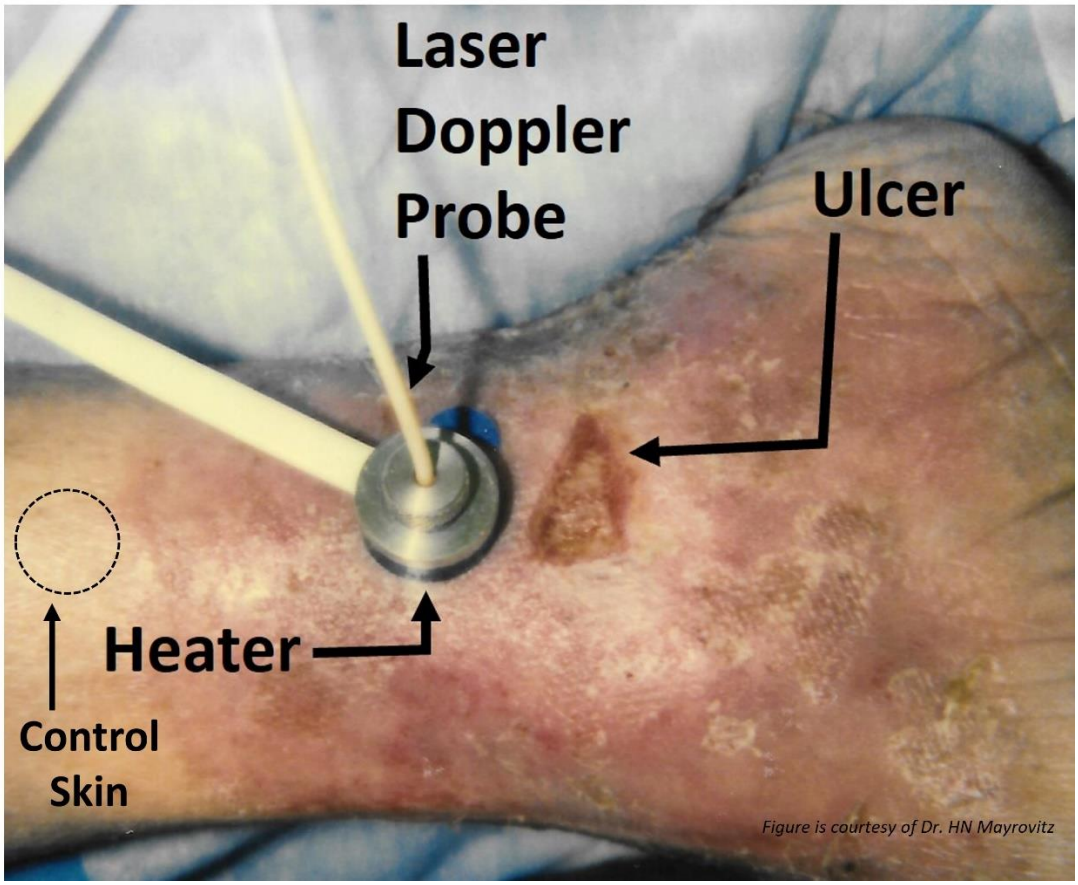

Figure 3. A laser Doppler probe is fitted through a concentric hole in the heater that is in contact with skin. Localized heating produces an increase in microvascular perfusion in healthy skin but with a differ pattern in peri-wound skin as shown in figure 4. Figure is provided as a courtesy of Dr. HN Mayrovitz

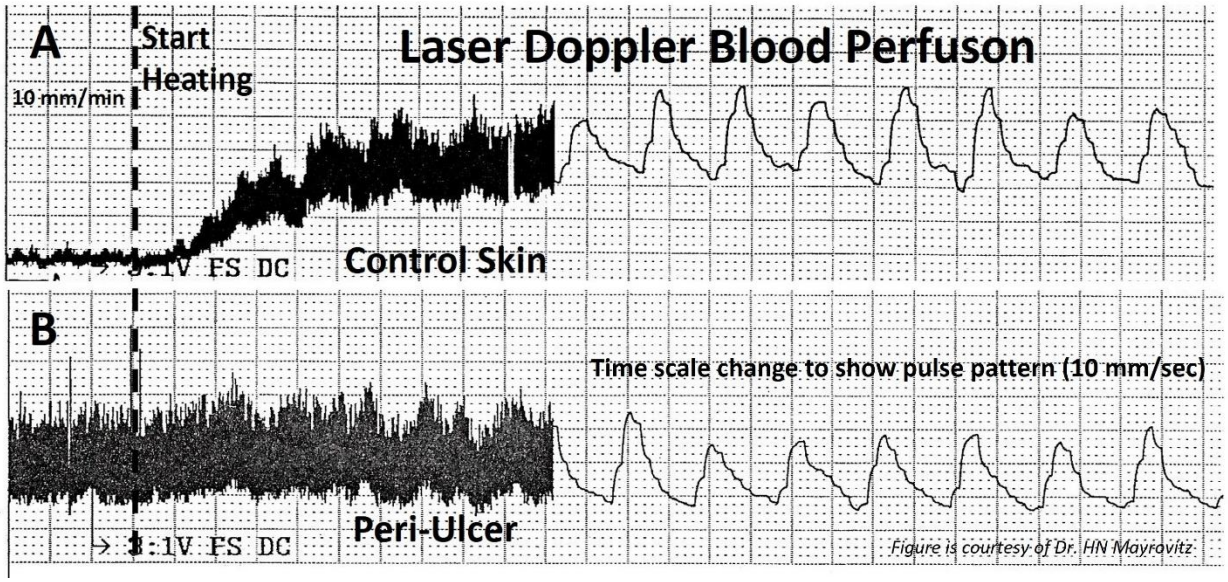

Figure 4. Skin blood perfusion responses to heating in healthy vs. peri-ulcer skin.

The responses show a normal response to localized heating (A) and a common finding associated with venous ulcers (B). In B, an elevated peri-ulcer basal resting perfusion is noted with little if any microvascular reserve when stimulated with heat. Contrastingly, in control skin as shown in part (A) a normal active hyperemia is noted in response to the heating. Figure is provided as a courtesy of Dr. HN Mayrovitz

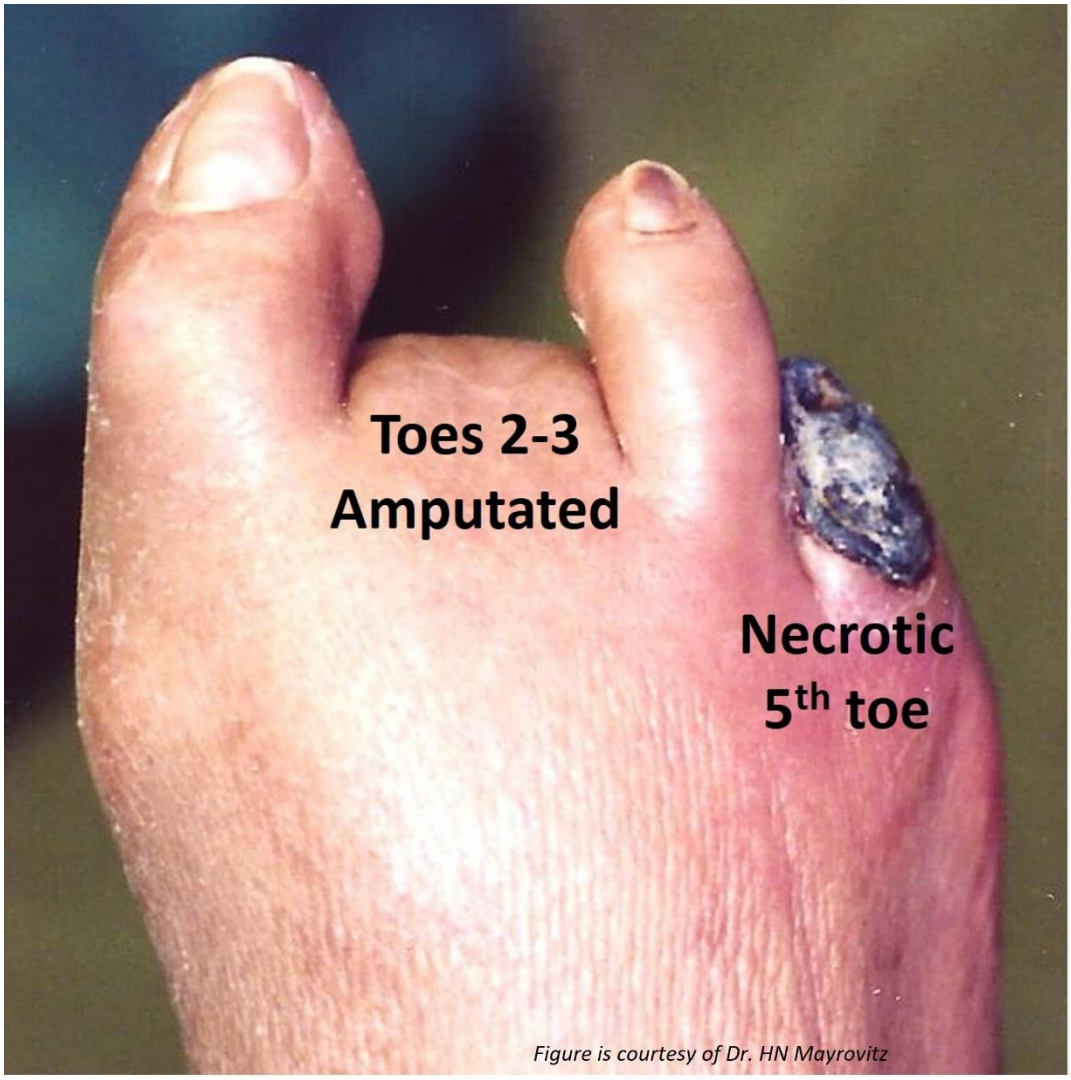

Figure 5. Illustrating some aspects of an arterial ulcer.

A patient with critical ischemia due to significant PAD in whom toes 2-3 were previously amputated and toe 5 is necrotic. Figure is provided as a courtesy of Dr. HN Mayrovitz

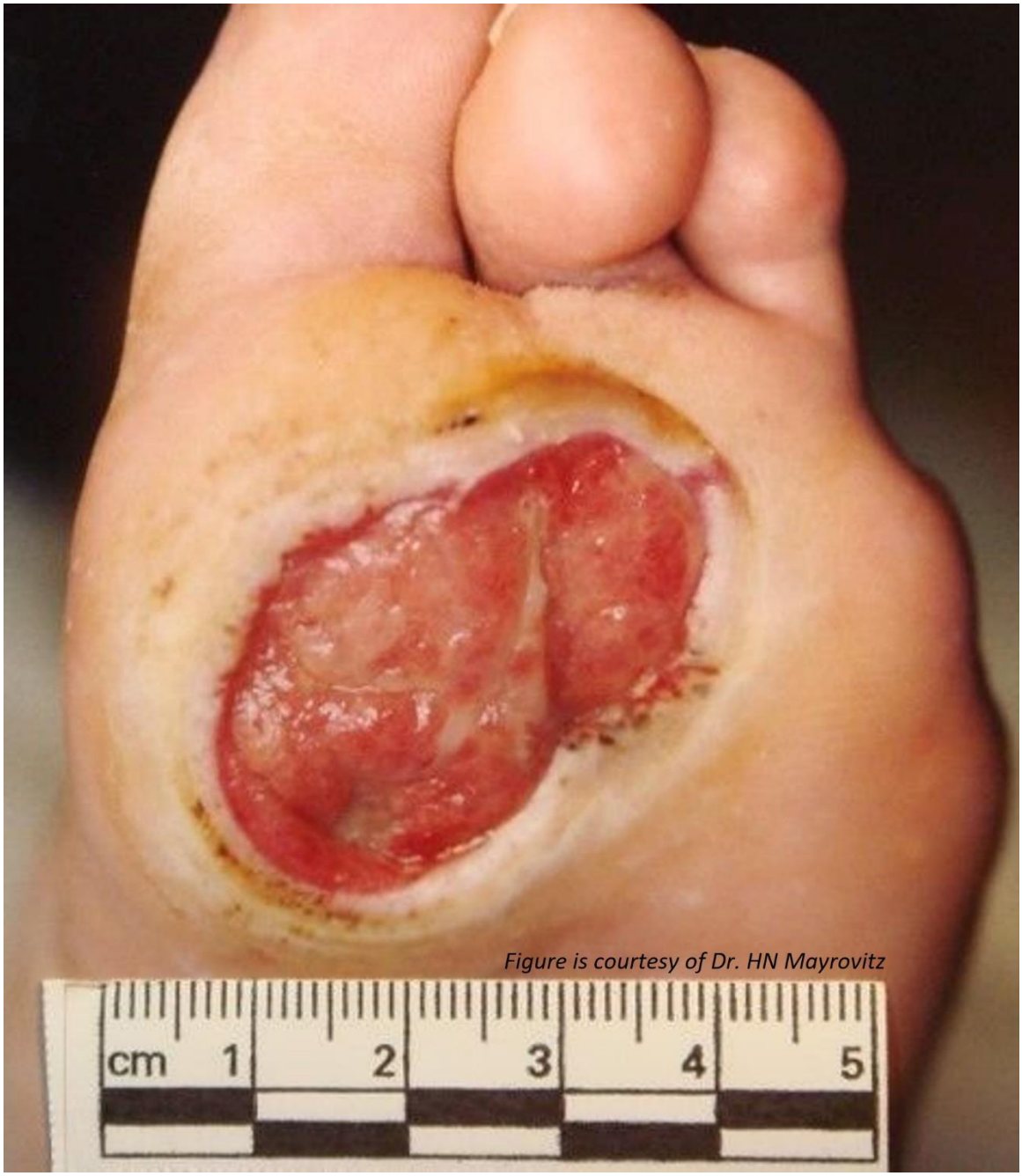

Figure 6. A common site of a plantar diabetic neuropathic ulcer

Figure is provided as a courtesy of Dr. HN Mayrovitz

Tables

	Venous Ulcer	Arterial Ischemic Ulcer	Diabetic / Neuropathic
Location	Gaiter Below knee Malleolar Area	Distal leg sites Pressure Sites Toes	Toe Mid-Foot Heel
Size	Variable	Small	Variable
Borders	Irregular	Round	Variable
Wound Base	Granulation	Eschar or Bone Necrotic	Ulcer stage dependent
Peri-Ulcer Skin	Pigmented Hemosiderin Lipodermatosclerosis	Pale Shiny Hair loss	Pale to normal to Erythemic depending on stage
Symptoms	Foul Drainage	Rest Pain Pain with activity Pain relieved by rest Claudication	Painless
Common Other Findings	Leg Edema Leg Lymphedema	Weak pulses Slow capillary refill Blanching on leg elevation	Neuropathy Nephropathy Retinopathy Obesity

Table 1. Comparison of some features of venous, arterial, and neuropathic ulcers