

# PROGNOSTIC FACTORS FOR DELAYED HEALING OF VENOUS LEG ULCERS

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## ABSTRACT

Risk factors of poor healing of venous leg ulcers can be categorised into three main groups: those related to the ulcer, those related to the patient, and those related to the organisation of wound care. Identification of risk factors that predispose these patients to prolonged wound healing not only offers an opportunity to determine their clinical outcome, but can also be linked to the decision regarding alternative interventions or even reorganisation of the wound care. Factors related to the ulcer comprise large ulcer size and long ulcer duration. Also, some macroscopic features of venous leg ulcers are associated with delayed healing: fibrin covering more than 50% of the area of the wound and highly exuding ulcers. Coexisting non-venous vascular pathologies, such as arterial ischaemia or clinically relevant lymphedema, as well as history of deep vein thrombosis, can contribute to delayed healing. Additionally, pathological functioning of calf muscle pump can be associated with reduced healing. Some bacterium species seem to interfere with healing of venous leg ulcers, especially if the number of such microorganisms in the wound bed is high. Regarding patient characteristics, reduced mobility (patients being chair or bed-bound) is a risk factor, while it remains unclear whether the demographic characteristics of the patients or their non-vascular co-morbidities are really associated with impaired healing. In addition, a number of studies have shown that organisation of wound care of venous leg ulcer patients appeared to be important, and healing rates improved and the cost of care declined after the implementation of an evidence-based service.

**Key words:** venous insufficiency, leg ulcer, wound healing.

## REVIEW PAPER

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## INTRODUCTION

Despite developments in chronic wound care, there remains a small yet significant group of venous leg ulcer (VLU) patients with prolonged healing or lack of healing, even after the best available practice. Such ulcers may differ from others in their response to routine wound management. At least some of them may require non-standard procedures, such as skin grafting or tissue-engineered skin substitutes. Identification of risk factors that predispose ulcer patients to prolonged wound healing not only offers an opportunity to determine their clinical outcome, but can also be linked to the decision on alternative interventions or even reorganisation of the wound care. These risk factors of poor healing of VLUs can be categorised into three main groups: factors related to the ulcer, factors related to the patient, and factors related to the organisation of chronic wound care. In real life, however, these three groups are not separate, but rather interdependent. For example, long duration of VLU is a well-known risk factor of delayed healing. But in the majority of cases longstanding ulcer is not an outcome of unique biology but rather a consequence of suboptimally organised wound care in the community (limited access to healthcare professionals, improper leg bandaging, etc.) [1-4].

## RISK FACTORS RELATED TO THE ULCER

A number of clinical studies have looked for VLU parameters associated with delayed healing. Most of these studies gave a concise picture. Parameters predicting poor outcome comprise large ulcer size [5-17] and long ulcer duration [5, 6, 8-10, 12-16, 18, 19]. However, the cutoff values of the size and duration varied between the studies, probably because of different cohorts assessed (for example: all VLU patients in the community, only selected patients, those included into the clinical trials). Ulcer size was either defined in terms of its area – and the value predicting a delayed healing was either more than 10 cm<sup>2</sup> [6, 9, 10, 20] or more than 20 cm<sup>2</sup> [13], or in terms of the ulcer's diameter, with the cutoff predicting poor outcome: more than 10 cm [12, 15]. By contrast, very small ulcers (up to 1 cm in diameter) were more likely to heal within a short time [15]. Still, in some studies an association between initial VLU size and the time of healing could not be confirmed [19, 21]. All, except for one [21] of the published studies revealed a delayed healing of longstanding VLUs. However, the time predicting poor outcome was very different: more than 3 months [12], more than 6 months [6, 20], more than 12 months [9, 10, 13], more than 18 months [19], or more than 24 months [15]. Another reported prog-

nostic factor of unfavourable clinical outcome was lack of healing or small decrease of the ulcer area after dedicated time of standard management: 3 weeks [14], 4 weeks [12, 21-25], or 50 days [13]. Moreover, some authors reported delayed healing in cases of history of previous leg ulceration [17, 26], but such an association was not found by others [7, 15, 19]. Additional macroscopic features of VLU that were found to be associated with delayed healing are fibrin covering more than 50% of area of the ulceration [10, 13, 22] and highly exuding ulcers [17].

The severity and characteristics of chronic venous insufficiency also affected healing rates. A history of thrombophlebitis was associated with delayed healing [19]. Ulcers that developed secondarily to superficial venous reflux had a better healing prognosis, while history of DVT was associated with decreased healing rates [16, 19, 20]. Surgical elimination of superficial venous reflux during follow-up was associated with improved healing rates in a cohort study [22] but not in a randomised-controlled trial [27]. Nevertheless, a previous history of superficial venous surgery was associated with delayed healing [10], thus the role for venous surgery in improving healing rates of VLUs remains uncertain. Longstanding VLUs (a verified risk factor of poor healing) were more prevalent in patients with history of lower limb DVT and deep venous reflux [28]. The presence of lipodermatosclerosis, a sign of serious venous pathology, led to reduction of healing rates [10, 19, 26]. However, neither varicose eczema nor *atrophie blanche* were associated with delayed healing [19]. Conversely, coexisting non-venous vascular pathologies contributed to delayed healing. Ulcers of mixed arterio-venous aetiology [10, 11, 19, 28, 29] and those presenting with clinically relevant lymphedema [30] were less likely to heal. Also, a pathological functioning of the muscle pump resulted in decreased healing rates. Both poor ankle joint function (fixed ankle joint, or equinus foot deformity) [7, 13, 19, 20, 22] and calf muscle pump impairment revealed by means of air-plethysmography [31] were associated with reduced healing of VLUs.

Although no association was found between the presence of bacteria and delayed ulcer closure [1, 8, 16, 32], some bacterium species seemed to interfere with the healing, especially if the number of such microorganisms in the wound bed was high. A high number of bacteria ( $\geq 10^4$ ) in a standard punch tissue sample taken from an ulcer was associated with delayed healing [8]. However, such a delay was not seen in all infected ulcers, but only in wounds infected by some bacterial species:  $\beta$ -haemolytic Streptococci, *Pseudomonas* spp. [8] and some Gram-negative facultative anaerobes (*Morganella morganii*, *Enterococcus* spp., *Klebsiella* spp., *Enterobacter* spp. and *Escherichia coli*) [8, 33]. Furthermore, an infection with multiple bacterial genera significantly delayed the healing [21]. Other researchers also confirmed a deleterious role of several bacterial species resulting in poor healing: *Pseu-*

*domonas aeruginosa* [19, 34, 35], *Staphylococcus aureus* [19, 21, 33, 34], anaerobes [33], and  $\beta$ -haemolytic streptococci [33, 35]. However, in one study an infection with *Pseudomonas aeruginosa* was not associated with delayed healing even if the ulcers colonised by these bacteria were larger and of longer duration [33]. Of note, the results of already published bacteriological studies on VLUs should be interpreted with caution. Bacteria revealed by culture-based tests (smear or tissue sample) do not necessarily reflect an actual bioburden, since these diagnostic techniques cannot identify all of the bacteria present in the wound. On the contrary, a modern microbiological molecular-based diagnostics, such as PCR assay, can reveal different microbial species, including those affecting the wound healing process but difficult to detect by traditional tests [36]. Thus, it is likely that bacteriological studies on VLUs applying new technologies may challenge conclusions coming from the above-cited trials.

## RISK FACTORS RELATED TO THE PATIENT

Although there seems to be a genetic predisposition to the development of VLUs [37, 38], a role for genetic factors in healing prognosis remains elusive. Also, it remains unclear whether demographic characteristics of VLU patients or their co-morbidities are really associated with impaired healing. Some studies demonstrated a delayed healing in elderly patients [12, 16, 18, 26] while others found a better healing in this age group [19] or no association of the age with healing [8, 10, 13]. In one study the patients aged less than 40 years were more likely to have VLUs healed in a short time [15]. Except for two studies that reported more unhealed ulcers in male patients [17, 20], no association was found between gender and healing rates [8, 10, 13, 15, 19, 39]. Diabetes mellitus was not associated with delayed healing of VLUs [8, 10, 19, 26]. Obesity was a predictor of poor outcome revealed by some studies [12, 13, 17]. However, in one study obese patients were more likely to heal [8]. Other studies failed to detect an association between body mass index and healing of VLUs [16, 26]. Conversely, in one study protein deficiency was significantly associated with poor healing prognosis of VLUs [39]. Reduced patient mobility (patients being chair or bedbound) was found to be an independent risk factor of poor healing [6, 10, 13, 19, 20]. Moreover, it seems that some socioeconomic factors may play a role. In a study conducted about twenty years ago in London, UK low social class, lack of central heating, and being single were associated with delayed healing in a group of 168 VLU patients. However, when adjusted for such known risk factors as ulcer size, ulcer duration, and general mobility, only the lack of central heating remained significant [6]. The authors speculated that a lack of central heating might be a reflection of economic status that the other economic variables (such as personal income) failed to detect. Still, a possibility that this factor indeed played a physiologi-

cal role could not be ruled out. Although there was some evidence that a warmer temperature of the wound may contribute to improved healing [40], the results of clinical trials using warming therapies in chronic wound patients have not yet provided conclusive evidence of the effectiveness of such a management [41].

## FACTORS RELATED TO THE ORGANISATION OF WOUND CARE

A number of studies have shown that results of treatment of VLU did not depend exclusively on the ulcer or patient characteristics. Organisation of wound care appeared to be equally important. Most VLUs heal after standard management: exclusion of arterial ulcers by means of Doppler test (arterial ulcers may become worse after compression therapy), application of an appropriate dressing, and administering adequate compression with bandages or stockings. It was confirmed that patients who complied with such a treatment regimen had significantly faster healing and fewer recurrences when compared with less compliant subjects [22, 42]. Nevertheless, it is rather the healthcare providers and not the patients who are responsible for the adherence to guideline-recommended therapies. In a number of countries (Canada [2], the UK [3], Sweden [4], and Australia [29]) healing rates of VLUs improved and the cost of care declined after the implementation of an evidence-based service. Importantly, it was the organisation of care and not the setting where such care was delivered (in the patient's home or in a community nurse-led clinic) that influenced healing rates [43]. It is possible that the above-mentioned socioeconomic variables (low social class, being single, or lack of central heating) associated with delayed healing were rather a reflection of inadequate wound care provided by the healthcare system. In a study that evaluated frequency of VLUs in relation to socio-demographic pattern (a cohort of over 14,000 assessed patients) an increased prevalence of such ulcers was revealed among people living in areas of higher material deprivation (measured using census data linked to the area of residence), thus probably presenting with lower socio-economic status [44]. However, no relationship was observed between socio-economic deprivation and the healing or adverse outcomes in the clinical trials on VLUs [45]. Therefore, it was likely that VLU patients with low economic status simply received substandard care because of their area of residence. For example, it was found that patients living in areas of higher material deprivation were less likely to receive the recommended Doppler-aided assessment of peripheral vascular disease [44]. In this context, reimbursement of dressings and compression hosiery may also pose a problem, since the majority of VLUs occur among low-income people [46].

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