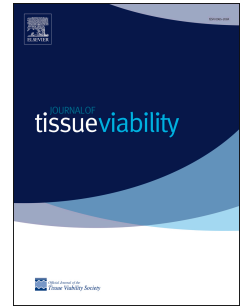


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Surrounding skin management in venous leg ulcers: a systematic review

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Keywords: chronic wound, venous leg ulcer, peri-ulcer skin, wound assessment, wound management

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Abstract

Objectives: Chronic venous insufficiency may lead to the development of venous leg ulcers, the most common form of chronic wounds in the lower extremity. Key to venous leg ulcer care is the maintenance of healthy skin surrounding the ulcer, as failure to maintain skin integrity may influence the healing outcome. We thus reviewed the scientific literature looking for assessment and management instruments regarding this common but often neglected issue.

Method: The search included all studies published between 2000 and May 2019. Keywords used were: “peri-wound skin care”, “surrounding skin venous ulcers”, “surrounding skin management leg ulcers”, and “peri-lesional skin management”.

Results: Management of moisture-balance with the selection of appropriate dressings is the most important target in surrounding-wound skin care. Moreover, contact dermatitis related to products and the dressings themselves is a neglected problem in patients with chronic leg ulcers which clinicians increasingly have to manage. The literature search revealed that there is an increasing interest in the use of noninvasive assessment tools in the field of wound care, and focusing on the surrounding-wound skin plays a role in assessing the potential of wound healing. Transepidermal water loss measurement (TEWL) and ultrasonography are two of the measurement techniques available.

Conclusion: The integrity of the surrounding skin is necessary for wound healing, and appropriate management is needed to address this aspect which is part of an overall approach to treating wounds.

Introduction

Venous leg ulcers (VLU) are the most common chronic wounds in the lower extremity and they involve a cycle of prolonged healing and recurrence [1].

Poor healing of chronic wounds is variously attributed to ambulatory venous hypertension, venous reflux, impaired tissue perfusion, and oxygen diffusion. Moreover, venous insufficiency after prolonged chronicity changes the skin and subcutaneous tissue of the lower leg with clinical aspects such as pigmentation and induration, described as chronic lipodermatosclerosis [2].

Wound care has historically focused on the wound bed, but the tissue environment surrounding the ulcer is also very important as this is the source of a secondary intention healing process to of the wound.

In addition, if the structure of the connective tissue of the surrounding dermis degenerates, it will be unable to withstand the everyday stresses and strains placed upon the skin, and thus the wound is likely to increase in size [3].

The skin surrounding wounds has a compromised barrier integrity due to underlying tissue inflammation, and is therefore highly susceptible to damage by chronic wound exudate, and prolonged exposure can irritate the skin and lead to maceration and loss of epithelium [4].

An optimal moisture balance at the wound interface is a key element in cutaneous tissue repair. The level of wound moisture is related above all to the type of wound, phase of wound healing, the absorptive capacity of local dressings, and the appropriate level of compression bandaging system.

The high level of exudate due to leg edema is a common feature in patients with VLU, often resulting in surrounding skin maceration with subsequent damage to the exposed tissue and enlargement of the wound [5, 6].

Another factor contributing to impaired wound healing is contact dermatitis, which is a very common problem in VLU patients, but often disregarded by clinicians. Two types of contact

dermatitis are frequently observed in patients with chronic leg ulcers; irritant contact dermatitis, caused by the wound exudate, and allergic contact dermatitis, caused by a contact allergen such as a specific type of wound dressing or other product [7].

Method

A review of the literature was performed by searching the PubMed database, Cochrane library and Scopus database for studies on the surrounding skin in venous leg ulcers (Table 1). The search included all studies published between 2000 and May 2019. Keywords used in the search were: “peri-wound skin care”, “surrounding skin venous ulcers”, “surrounding skin management leg ulcers”, and “peri-lesional skin management”.

Both prospective, observational and retrospective studies were included in the review. Case reports were excluded from this research. Only those journal articles published in English were eligible for inclusion.

Results

The evaluation of normal wound healing has historically been based on clinical observations.

From our review of the scientific literature, it is clear that the main problem in the surrounding skin management of venous leg ulcers is controlling the moisture balance at the wound bed interface.

According to the principles of wound bed preparation, exudate management is a fundamental aspect in chronic venous leg ulcers, as the exudate contains high levels of matrix metalloproteinases, which cause degradation of the extracellular matrix, resulting in the inhibition of growth factors, impaired cell migration and connective tissue deposition [8].

Having the right moisture balance reduces the risk of maceration and the drying out of the wound.

Although there are several instrumental assessment techniques reported in the literature, peri-wound skin damage is currently mainly evaluated by clinical inspection.

Characteristic manifestations of peri-wound skin damage include maceration (white or red), erosion, erythema, edema, blister formation, pruritus, edema, and pain. White maceration is when the skin appears white and swollen, which is due to inappropriate treatment such as bandage application or dressing selection. On the other hand, erythematous maceration is when the skin is reddened and inflamed mainly due to high level of different cytokines [9].

In the literature several attempts have been made to classify the skin lesions due to venous leg ulcer exudate, but we were unable to find a validated and standardized peri-ulcer skin assessment form. This is indicative of the underestimation of the problem.

Moisture balance

Although moisture is essential to promote wound healing, wound exudate contains endogenous protein-degrading enzymes that damage intact skin [10]. In addition, repetitive changes of adhesive dressings may strip away the periwound stratum corneum, precipitating further skin damage. The correlation between peri-wound maceration, pain during dressing changes, and delayed wound healing is acknowledged in the literature, however there are no exact incidence and/or prevalence data regarding this aspect [11].

The selection of the appropriate dressing is one of the key elements of moisture balance management. Although there are many products on the market, absorbent dressings are always made with the same materials: alginate, hydrofibers, polymers and foam. Choosing the appropriate one is influenced by the amount of wound fluid, as they have different capacities to lock in wound fluids. The absorption power of various dressings may also be affected by the polyurethane film backing and its ability to transfer moisture vapor out of the dressing and by the application of a compression bandage system [12].

In addition it is also very important to use an absorbent dressing that has an appropriate size for the wound bed, in order to reduce the risk of peri-wound damage due to lateral movement of fluids

inside the dressing over the skin and to correlate the dressing change frequency to wound exudation [6].

A matrix metalloproteinase modulator or a pH buffer can be used in order to reduce protease activity in wound fluids [13].

Repetitive changes of adhesive dressings may strip away the peri-wound stratum corneum, resulting in tissue damage such as erythema and edema up to blister formation. Dressings with a silicone layer on the wound side can prevent this kind of trauma, especially when frequent dressing changes are required, also with less discomfort and pain for the patient.

In contrast, excessive dryness of the peri-wound skin can be detrimental to the healing process. The loss of the physiological hydro-lipid skin barrier leads to scaling and fissurations, leading to inflammation due to irritant absorption into deep skin structures.

The application of moisturizing factors containing amino acids such as lactic acids, urea, glycerin or the use of ceramides and essential fatty acids, can be useful to maintain a functional skin barrier.

Skin cleansing

Just as cleansing is the first step in wound bed management, the same is true in peri-wound skin care. Mechanical cleansing of the surrounding wound skin removes scales, residues from previous dressings and reduces the number of microorganisms not only on the skin but also in the wound bed, thus helping to prevent secondary infections. We recommend removing the scales using forceps, after softening the hyperkeratotic skin with saline solution, almond oil or other emollients. In terms of cleansing agent, alkaline products should be avoided, as the pH of healthy skin is about 5 to 5.5 and a pH increase can promote bacterial growth [14].

Skin barrier products

Finding an effective barrier to protect healthy skin is the main goal in the management of surrounding venous wound skin. Many alternative treatments are available, and their advantages and disadvantages are detailed below [15].

Zinc oxide past is one of the most common barrier products. It has anti-inflammatory and antioxidant properties and protects from exudate damage. However it needs to be mixed with a small amount of white soft paraffin and liquid paraffin to make the application and removal easier, as it dries out and sticks to the skin [16]. It can also affect dressing adherence and absorption. Petrolatum-based ointments are very common and inexpensive and with their lubricating properties, they can be useful for dry skin care. On the other hand, these ointments can interfere with dressing adherence and can bind bacteria and dirt on the peri-wound skin [17].

Dimethicone or other silicone based ointments are easier to apply than zinc or petrolatum ointments. They are permeable to water vapor, thus allowing evaporation and perspiration but as with zinc and petrolatum based preparations, they can interfere with primary dressing adherence and absorption [18].

Polymer barrier preparations form a barrier film after evaporation of their solvents, thus protecting from maceration [14]. These films do not affect wound dressing adherence, in fact they make dressing changes easier and less traumatic. A transparent film also facilitates wound examination, unlike zinc ointment for example [19]. Allergic skin reactions and contact dermatitis have been reported after the application of film barrier products containing gum mastic. Alcohol, used as a solvent in many formulations of barrier films, may cause pain after application [20, 22].

Compression bandaging

Compression bandaging is a fundamental part of treatment in venous wound care [23]. A French survey by Dereure et al. found an interrelationship between peri-ulcer skin condition and

compression bandaging in venous leg ulcers. They conducted a prospective observational survey in general practice on 2842 patients, at the inclusion visit they scored the size and appearance of the ulcer and the peri-ulcer skin. Patients were asked about their concordance with compression and, if patients were seen at a three-week follow-up visit, ulcer and peri-ulcer characteristics and concordance were reassessed. The authors found that in patients who had been concordant with compression therapy, improvements were seen in edema, erythema and, to some degree, eczema at the three-week follow-up visit.

On the other hand concordance with compression was affected by peri-ulcer skin condition as the authors recorded the lowest concordance with the therapy in patients with the highest peri-ulcer skin severity score at baseline [24]. According to this data, the appropriate management of surrounding skin in venous leg ulcer may increase patients' concordance with compression therapy, which is in turn essential for healing.

Contact dermatitis

A very common problem in patients with leg ulcers is the onset of allergic contact dermatitis, particularly in the area of dressing application [25].

A wound that is deteriorating despite optimal treatment, requires further investigation, including a patch test and a biopsy if necessary for diagnostic purposes [26]. The risk of allergy is related to the duration of ulcerative disease rather than the duration of the current ulcer [27]. A genetic background combined with the disrupted skin barrier characterized by increased permeability and particularly with the long-term use of many topical devices lead first to sensitization and then to dermatitis [28]. Several studies have shown an incidence of a positive patch test among people with leg ulcers of between 45% and over 80% [29]. The most commonly-used sensitizers are Balsam of Peru, fragrances and wool alcohols, but also other excipients, topical antibiotics, antiseptics, topical anesthetic and topical corticosteroids are frequently reported [30].

Sensitization is also becoming common among advanced dressings, and hydrogels currently seem to be the most common sensitizers, followed by hydrocolloid and ionic silver-containing wound dressings [31, 32].

After the exclusion of strong sensitizers and highly irritant products from the pharmacopoeia of these patients, it may be useful and cost-effective to patch test all patients with long-lasting leg ulcers, especially when they have a present or recent history of contact dermatitis of surrounding skin, or non-healing wounds. Such patients should be tested not only for the European standard patch test series but also for the topical drugs and dressings commonly used in daily wound care [33, 30].

When a dermatitis occurs in peri-wound skin, in addition to the identification and removal of triggers, the application of local corticosteroids on the affected area at every dressing change could be useful until the inflammation has been reduced. However in patients with a positive patch test for corticosteroids, the administration of systemic treatments could be useful, choosing corticosteroids that are not cross-reactive with each other [25].

Skin measurement

Due to the increasing number of noninvasive measurement techniques available, the clinical assessment and the consequent management of chronic lesions can be optimized.

For example, the clinical diagnosis of chronic wound infection can be improved by using an infrared camera to measure wound bed temperature, as this is correlated with infection [34]. The values acquired from instrumental measurements are more sensitive, objective, reproducible, and comparable than clinical evaluation on its own. These noninvasive wound assessment techniques can differentiate in real time between mild, moderate, and severe levels of tissue damage thus resulting in a more suitable clinical management [35].

Maceration is frequently underestimated and one of the causes of delayed wound healing in chronic wounds. According to the instrumental TIME principles of wound assessment, the objective evaluation of the surrounding skin water content and water loss is also essential in order to promote wound healing [36].

Through the stratum corneum of the skin, there is a continuous passive diffusion of water from the deeper skin layers to the surface. This water flux is increased when the skin barrier is damaged, as in maceration

The measurement of trans-epidermal water loss (TEWL) could therefore be an indirect indicator of maceration on perilesional skin. The device used by Dini et al. to assess TEWL was hand-held and battery-operated, with a closed cylindrical chamber containing sensors for relative humidity and temperature. The results of their study demonstrated the correlation between TEWL values and intensity of maceration in venous leg ulcers [37].

For venous ulcers on the leg, ultrasonography (US) has been routinely used to evaluate the location and pattern of a limb's vessel disorders.

Using the same probes aimed at routine vascular investigations (10-14 MHz), Caggiati studied the morphology of cutaneous and subcutaneous layer in order to integrate the clinical evaluation of chronic venous disease [38].

Lipodermatosclerotic skin (C4B in the CEAP classification) can have two different ultrasound patterns, sclero-edematous or fibro-sclerotic, with focal subcutaneous layer rarefaction in lipodermatosclerotic areas during recrudescence of skin inflammation. Similar changes have been reported in other ulcerative conditions and, in Caggiati's study, subcutaneous layer rarefaction disappeared when compression was applied, whereas an ulcer opened in the patient who rejected compression therapy. This led to the hypothesis that subcutaneous layer rarefaction could be considered predictive of ulceration.

One of the main requirements in the healing process of chronic wounds is the oxygenation of the wound bed and surrounding tissue. Although some scientific reports have reported normal tissue oxygen levels using skin surface sensors, the occurrence of venous ulcers accompanied by hypoxia is indisputable in the literature. On the other hand, chronic wounds undergoing oxygen treatment heal more rapidly and effectively [39]. In fact, the thickness of the lipodermatosclerotic skin and increased intracapillary distance due to edema, interfere with blood perfusion and as well with oxygen diffusion [40].

Holmes proposed the investigation of the characteristics of blood capillaries in the peri-wound skin using Dynamic Optical Coherence Tomography (D-OCT) [41].

OCT is traditionally used by ophthalmologists, and the further development of “dynamic” OCT, means that the skin vasculature can be visualized via speckle variance detection [42].

D-OCT was used by Holmes to examine peri-wound skin, as enables capillaries of diameters as small as 20 μm to be imaged. Being able to evaluate the morphology and density of small blood vessels in high resolution opens up new possibilities in diagnosing wounds, in differentiating venous ulcers from other types, selecting therapies, and monitoring their effects. This is because angiogenesis plays a key role in the healing process, and a persistently low oxygen supply is the main reason for disturbed wound healing.

Another non-invasive assessment technique, proposed by Wolfgang, is peri-ulceral transcutaneous oxygen partial pressure measurement. Using a minimum of four electrodes placed as close to the wound margin as possible, he proposes a routine characterization of chronic wounds in terms of their oxygen status, and thus, their metabolic determining potential for healing and regeneration [43]. Wolfgang observed that in terms of oxygenation, chronic wounds are therefore nonhomogeneous within the wound itself (intra-individual wound nonhomogeneity) and between different wounds (inter-individual wound nonhomogeneity). Due to the extreme oxygen nonhomogeneity, single measurements are not diagnostically useful.

Wolfgang also studied oxygen distribution in the peri-wound skin during oxygen inhalation comparing it with healthy volunteers. In healthy individuals, the oxygen inhalation resulted in peri-ulcer oxygen partial pressure oscillations, which are not seen in non-healthy individuals. These oscillations can be interpreted as a sign of a functioning arterial vasomotor system and consequently predictive of the benefit of therapeutic oxygen inhalation.

We know that in the healing process there is an initial inflammatory response with an influx of neutrophils, which is followed by macrophages to clean up the resulting debris tissue. Wound-edge keratinocytes and fibroblasts then proliferate and migrate to close the wound, after filling the gap with granulation tissue and laying down a new extracellular matrix [44]. If the pro-inflammatory response is never fully attenuated for different reasons, and the wounds are thus constantly inflamed, the subsequent healing process will be incomplete [45].

Some authors have suggested that the percentage of senescent fibroblasts could be a marker of chronicity of a wound together with the composition of the extracellular matrix (reduced collagen and elastin) [46, 47].

Skin pathology

The evaluation of the histological and cytological composition of peri-ulcer skin requires a biopsy, especially in the case of a differential diagnosis with other atypical ulcers or when the diagnosis is not clear. Since skin biopsy is a minimally invasive technique, Sutcliffe et al. have proposed another approach [48].

They use a confocal multi-photon laser-scanning hand-held imaging device (based on second harmonic generation imaging) may be able to determine the extent of ECM degradation in order to plan a more precise surgical debridement procedure and, finally, to provide an indication of the progression or regression of healing in chronic wounds.

Conclusions

Perilesional skin care is an important step in venous leg ulcer management. The assessment and careful monitoring of the health status of the skin surrounding the wound are fundamental during treatment. In this review we found several useful non-invasive assessment techniques: some already consolidated in venous leg ulcer assessment protocols, others recently applied in perilesional skin monitoring.

The protocol for wound and skin management in venous patients always requires the appropriate care of the skin using barrier products and moisturizers, the appropriate wound dressing according to the level of exudate, and a careful decision-making regarding the frequency of dressing changes. The application of a bandaging system has shown to positively modify the compliance of patients and the level of control of the surrounding skin.

Future advances in technology will offer practitioners the opportunity to increase their knowledge in the management of this aspect and to remotely monitor their patients using biomedical sensors.

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Introduction

Venous leg ulcers (VLU) are the most common chronic wounds in the lower extremity and they often involve a cycle of prolonged healing and recurrence [1].

Poor healing of chronic wounds is variously attributed to ambulatory venous hypertension, venous reflux, impaired tissue perfusion, and oxygen diffusion [2]. Moreover, venous insufficiency after prolonged chronicity changes the skin and subcutaneous tissue of the lower leg with clinical aspects such as pigmentation and induration, described as chronic lipodermatosclerosis [3].

Wound care has historically focused on the wound bed, but the tissue environment surrounding the ulcer is also very important as this is the source of a secondary intention healing process to of the wound [4]

In addition, if the structure of the connective tissue of the surrounding dermis degenerates, it will be unable to withstand the everyday stresses and strains placed upon the skin, and thus the wound is likely to increase in size [5].

The skin surrounding wounds has a compromised barrier integrity due to underlying tissue inflammation, and is therefore highly susceptible to damage by chronic wound exudate, and prolonged exposure can irritate the skin and lead to maceration and loss of epithelium [4].

An optimal moisture balance at the wound interface is a key element in cutaneous tissue repair [4].

The level of wound moisture is related above all to the type of wound, phase of wound healing, the absorptive capacity of local dressings, and the appropriate level of compression bandaging system [4]. The high level of exudate due to leg edema is a common feature in patients with VLU, often resulting in surrounding skin maceration with subsequent damage to the exposed tissue and enlargement of the wound [5, 6].

Another factor contributing to impaired wound healing is contact dermatitis, which is a very common problem in VLU patients, but often disregarded by clinicians. Two types of contact dermatitis are frequently observed in patients with chronic leg ulcers; irritant contact dermatitis, caused by the wound exudate, and allergic contact dermatitis, caused by a contact allergen such as a specific type of wound dressing or other product [7]. They mainly differ from a diagnostic point of view because the allergic contact dermatitis is a delayed type of allergy and it is the only one where patch testing has to be performed.

Method

A systematic review of the literature was performed by searching the PubMed database, Cochrane library and Scopus database for studies on the surrounding skin in venous leg ulcers. The search included all studies published between 2000 and May 2019. Keywords used in the search have been chosen according to clinical terminology in wound care and were as follows: “peri-wound skin care”, “surrounding skin venous ulcers”, “surrounding skin management leg ulcers”, and “peri-lesional skin management”.

Both prospective, observational and retrospective studies were included in the review. Case reports were excluded from this research. Only those journal articles published in English were eligible for inclusion. We included only articles in English, with relevant information on the pathophysiology of venous leg ulcers and on surrounding skin management strategies.

Results

The PRISMA 2019 flow diagram shown in Figure 1 explains the search methodology used in the study. According to our review strategy we were able to include a total of 48 articles. Results from the systematic search are presented under several paragraphs according to each specific topic

selected and involved on surrounding skin clinical and instrumental observation and management. The literature searched is descriptive of papers and reviews on the topic selected and there is almost no data showing the influence of peri-ulcer skin care on wound healing.

Moisture balance

The correlation between peri-wound maceration, pain during dressing changes, and delayed wound healing is acknowledged in the literature [8], however there are no confirmed incidence and/or prevalence data regarding this aspect [4].

Although moisture is essential to promote wound healing, wound exudate contains endogenous protein-degrading enzymes that damage intact skin [9]. In addition, repetitive changes of adhesive dressings may strip away the periwound stratum corneum, precipitating further skin damage.

The selection of the appropriate dressing is one of the key elements of moisture balance management. Although there are many products on the market, absorbent dressings are always made with the same materials: alginate, hydrofibers, polymers and foam [10]. Choosing the appropriate one is influenced by the amount of wound fluid, as they have different capacities to lock in wound fluids [11]. The absorption power of various dressings may also be affected by the polyurethane film backing and its ability to transfer moisture vapor out of the dressing and by the application of a compression bandage system [10].

In addition it is also very important to use an absorbent dressing that has an appropriate size for the wound bed, as this can reduce the risk of peri-wound damage due to lateral movement of fluids inside the dressing over the skin and to correlate the dressing change frequency to wound exudation [6].

Repetitive changes of adhesive dressings may strip away the peri-wound stratum corneum, resulting in tissue damage such as erythema and edema up to blister formation [12]. Dressings with a silicone

layer on the wound side can prevent this kind of trauma, especially when frequent dressing changes are required, also with less discomfort and pain for the patient [12].

In contrast, excessive dryness of the peri-wound skin can be detrimental to the healing process. The loss of the physiological hydro-lipid skin barrier leads to scaling and fissurations, leading to inflammation due to irritant absorption into deep skin structures [12].

The application of moisturizing factors containing amino acids such as lactic acids, urea, glycerin or the use of ceramides and essential fatty acids, can be useful to maintain a functional skin barrier [12].

Skin measurement

The values acquired from instrumental measurements are more sensitive, objective, reproducible, and comparable than clinical evaluation on its own. These noninvasive wound assessment techniques can differentiate in real time between mild, moderate, and severe levels of tissue damage thus resulting in a more suitable clinical management [13]. Due to the increasing number of noninvasive measurement techniques available, the clinical assessment and the consequent management of chronic lesions can be optimized by evaluating skin and wound parameters in a more objective way.

For example, the clinical diagnosis of chronic wound infection can be improved by using an infrared camera to measure wound bed temperature, as this has been correlated with infection [14].

Maceration is frequently underestimated and one of the causes of delayed wound healing in chronic wounds. According to the instrumental TIME principles of wound assessment, the objective evaluation of the surrounding skin water content and water loss is also essential in order to promote wound healing [15].

Through the stratum corneum of the skin, there is a continuous passive diffusion of water from the deeper skin layers to the surface. This water flux is increased when the skin barrier is damaged, as

in maceration [13]. The measurement of trans-epidermal water loss (TEWL) could therefore be an indirect indicator of maceration on perilesional skin. The device used by Dini et al. [16] to assess TEWL was hand-held and battery-operated, with a closed cylindrical chamber containing sensors for relative humidity and temperature. The results of their study demonstrated the correlation between TEWL values and intensity of maceration in venous leg ulcers in 50 patients [16].

For venous ulcers on the leg, ultrasonography (US) has been routinely used to evaluate the location and pattern of a limb's vessel disorders which is correlating at the end with skin involvement [9]. Using the same probes aimed at routine vascular investigations (10-14 MHz), Caggiati [17] studied the morphology of cutaneous and subcutaneous layer in order to integrate the clinical evaluation of skin changes in chronic venous disease and to follow up with a specific treatment strategy.

Lipodermatosclerotic skin (C4B in the CEAP classification) can have two different ultrasound patterns, sclero-edematous or fibro-sclerotic, with focal subcutaneous layer rarefaction in lipodermatosclerotic areas during recrudescence of skin inflammation. Similar changes have been reported in other ulcerative conditions [3] and, in Caggiati's study, subcutaneous layer rarefaction disappeared when compression was applied, whereas an ulcer opened in the patient who rejected compression therapy because of poor compliance. This led to the hypothesis that subcutaneous layer rarefaction could be considered predictive of ulceration.

One of the main requirements in the healing process of chronic wounds is the oxygenation of the wound bed and surrounding tissue [2]. Although some scientific reports have reported normal tissue oxygen levels using skin surface sensors, the occurrence of venous ulcers accompanied by hypoxia is indisputable in the literature [4]. On the other hand, chronic wounds undergoing oxygen treatment heal more rapidly and effectively [18]. In fact, the thickness of the lipodermatosclerotic skin and increased intracapillary distance due to edema, interfere with blood perfusion and as well with oxygen diffusion [19].

Holmes proposed the investigation of the characteristics of blood capillaries in the peri-wound skin using Dynamic Optical Coherence Tomography (D-OCT) [20].

OCT is traditionally used by ophthalmologists, and the further development of “dynamic” OCT, means that the skin vasculature can be visualized via speckle variance detection by means of different color tone [21].

D-OCT was used by Holmes to examine peri-wound skin, as enables capillaries of diameters as small as 20 μm to be imaged. Being able to evaluate the morphology and density of small blood vessels in high resolution opens up new possibilities in diagnosing wounds, in differentiating venous ulcers from other types, selecting therapies, and monitoring their effects. This is because angiogenesis plays a key role in the healing process, and a persistently low oxygen supply is the main reason for disturbed wound healing [2].

Another non-invasive assessment technique, proposed by Barnikol et al., is peri-ulceral transcutaneous oxygen partial pressure measurement [22]. Using a minimum of four electrodes placed as close to the wound margin as possible, he proposes a routine characterization of chronic wounds in terms of their oxygen status, and thus, their metabolic determining potential for healing and regeneration [22]. Barnikol observed that in terms of oxygenation, chronic wounds are therefore nonhomogeneous within the wound itself (intra-individual wound nonhomogeneity) and between different wounds (inter-individual wound nonhomogeneity).

Barnikol also studied oxygen distribution in the peri-wound skin during oxygen inhalation comparing it with healthy volunteers. In healthy individuals, the oxygen inhalation resulted in peri-ulceral oxygen partial pressure oscillations, which are not seen in non-healthy individuals. These oscillations can be interpreted as a sign of a functioning arterial vasomotor system and consequently predictive of the benefit of therapeutic oxygen inhalation.

We know that in the healing process there is an initial inflammatory response with an influx of neutrophils, which is followed by macrophages to clean up the resulting debris tissue [4]. Wound-

edge keratinocytes and fibroblasts then proliferate and migrate to close the wound, after filling the gap with granulation tissue and laying down a new extracellular matrix [23]. If the pro-inflammatory response is never fully attenuated for different reasons, and the wounds are thus constantly inflamed, the subsequent healing process will be incomplete [24].

Some authors have suggested that the percentage of senescent fibroblasts could be a marker of chronicity of a wound together with the composition of the extracellular matrix (reduced collagen and elastin) [25,26].

Skin pathology

The evaluation of the histological and cytological composition of peri-ulcer skin requires a biopsy, especially in the case of a differential diagnosis with other atypical ulcers or when the diagnosis is not clear [4]. Since skin biopsy is a minimally invasive technique, Sutcliffe et al. have proposed another approach [27].

They use a confocal multi-photon laser-scanning hand-held imaging device (based on second harmonic generation imaging) may be able to determine the extent of ECM degradation in order to plan a more precise surgical debridement procedure and, finally, to provide an indication of the progression or regression of healing in chronic wounds.

Skin cleansing

Just as cleansing is the first step in wound bed management, the same is true in peri-wound skin care. Mechanical cleansing of the surrounding wound skin removes scales, residues from previous dressings and reduces the number of microorganisms not only on the skin but also in the wound bed, thus helping to prevent secondary infections [28]. We recommend removing the scales using forceps, after softening the hyperkeratotic skin with saline solution, almond oil or other emollients.

In terms of cleansing agent, alkaline products should be avoided, as the pH of healthy skin is about 5 to 5.5 and a pH increase can promote bacterial growth [28].

Skin barrier products

Finding an effective barrier to protect healthy skin is the main goal in the management of surrounding venous wound skin. Many alternative treatments are available, and their advantages and disadvantages are detailed below [29].

- Zinc oxide past is one of the most common barrier products. It has anti-inflammatory and antioxidant properties and protects from exudate damage [30]. However it needs to be mixed with a small amount of white soft paraffin and liquid paraffin to make the application and removal easier, as it dries out and sticks to the skin [30]. It can also affect dressing adherence and absorption.
- Petrolatum-based ointments are very common and inexpensive and with their lubricating properties, they can be useful for dry skin care. On the other hand, these ointments can interfere with dressing adherence and can bind bacteria and dirt on the peri-wound skin [31].
- Dimethicone or other silicone based ointments are easier to apply than zinc or petrolatum ointments. They are permeable to water vapor, thus allowing evaporation and perspiration but as with zinc and petrolatum based preparations, they can interfere with primary dressing adherence and absorption [32].
- Polymer barrier preparations form a barrier film after evaporation of their solvents, thus protecting from maceration [28]. These films do not affect wound dressing adherence, in fact they make dressing changes easier and less traumatic. A transparent film also facilitates wound examination, unlike zinc ointment for example [33]. Allergic skin reactions and contact dermatitis have been reported after the application of film barrier products containing gum mastic. Alcohol, used as a solvent in many formulations of barrier films, may cause pain after application [34,35].

Compression bandaging

Compression bandaging is a fundamental part of treatment in venous wound care with high quality of evidence [36,37]. A French survey by Dereure et al. found an interrelationship between peri-ulcer skin condition and compression bandaging in venous leg ulcers [38]. They conducted a prospective observational survey in general practice on 2842 patients, at the inclusion visit they scored the size and appearance of the ulcer and the peri-ulcer skin. Patients were asked about their concordance with compression and, if patients were seen at a three-week follow-up visit, ulcer and peri-ulcer characteristics and concordance were reassessed. The authors found that in patients who had been concordant with compression therapy, improvements were seen in edema, erythema and, to some degree, eczema at the three-week follow-up visit.

On the other hand concordance with compression was affected by peri-ulcer skin condition as the authors recorded the lowest concordance with the therapy in patients with the highest peri-ulcer skin severity score at baseline [38]. According to this data, the appropriate management of surrounding skin in venous leg ulcer may increase patients' concordance with compression therapy, which is in turn essential for healing.

Contact dermatitis

A very common problem in patients with leg ulcers is the onset of allergic contact dermatitis, particularly in the area of dressing application and mainly due to allergen found in topical treatment [39].

A wound that is deteriorating despite optimal treatment, requires further investigation, including a patch test and a biopsy if necessary for diagnostic purposes and to rule out several differential diagnosis including allergic contact dermatitis [40]. The risk of allergy is related to the duration of

ulcerative disease rather than the duration of the current ulcer [41]. A genetic background combined with the disrupted skin barrier characterized by increased permeability and particularly with the long-term use of many topical devices lead first to sensitization and then to dermatitis [42]. Several studies have shown an incidence of a positive patch test among people with leg ulcers of between 45% and over 80% [43,44,45,46]. The most commonly-used sensitizers are Balsam of Peru, fragrances and wool alcohols mainly found on skin moisturizers, but also other excipients, topical antibiotics, antiseptics, topical anesthetic and topical corticosteroids are frequently reported [44]. Sensitization is also becoming common among advanced dressings, and hydrogels currently seem to be the most common sensitizers, followed by hydrocolloid and ionic silver-containing wound dressings [45,46].

After the exclusion of strong sensitizers and highly irritant products from the pharmacopoeia of these patients, it may be useful and cost-effective to patch test all patients with long-lasting leg ulcers, especially when they have a present or recent history of contact dermatitis of surrounding skin, or non-healing wounds. Such patients should be tested not only for the European standard patch test series but also for the topical drugs and dressings commonly used in daily wound care [44,47].

When a dermatitis occurs in peri-wound skin, in addition to the identification and removal of triggers, the application of local corticosteroids on the affected area at every dressing change could be useful until the inflammation has been reduced. However in patients with a positive patch test for corticosteroids, the administration of systemic treatments could be useful, choosing corticosteroids that are not cross-reactive with each other [39].

Discussion

The evaluation of normal wound healing has historically been based on clinical observations.

From our systematic review of the scientific literature, it is clear that the most emphasized aspect in

the surrounding skin management of venous leg ulcers is controlling the moisture balance at the wound bed interface, but there are no data regarding its importance. According to the principles of wound bed preparation, exudate management is a fundamental aspect in chronic venous leg ulcers, as the exudate contains high levels of matrix metalloproteinases, which cause degradation of the extracellular matrix, resulting in the inhibition of growth factors, impaired cell migration and connective tissue deposition [9].

Having the right moisture balance reduces the risk of maceration and the drying out of the wound. Although there are several instrumental assessment techniques reported in the literature, peri-wound skin damage is currently mainly evaluated by clinical inspection.

Characteristic manifestations of peri-wound skin damage include maceration (white or red), erosion, erythema, edema, blister formation, pruritus, edema, and pain (Fig.2). White maceration is when the skin appears white and swollen, which is due to inappropriate treatment such as bandage application or dressing selection. On the other hand, erythematous maceration is when the skin is reddened and inflamed mainly due to high level of different cytokines [9].

In the literature several attempts have been made to classify the skin lesions due to venous leg ulcer exudate, but we were unable to find a validated and standardized peri-ulcer skin assessment form. This is indicative of the underestimation of the problem.

Conclusions

Perilesional skin care is an important step in venous leg ulcer management. The assessment and careful monitoring of the health status of the skin surrounding the wound are fundamental during treatment. In this review we found several useful non-invasive assessment techniques: some already consolidated in venous leg ulcer assessment protocols, others recently applied in perilesional skin monitoring.

The protocol for wound and skin management in venous patients always requires the appropriate care of the skin using barrier products and moisturizers, the appropriate wound dressing according to the level of exudate, and a careful decision-making regarding the frequency of dressing changes. The application of a bandaging system has shown to positively modify the compliance of patients and the level of control of the surrounding skin.

Future advances in technology will offer practitioners the opportunity to increase their knowledge in the management of this aspect and to remotely monitor their patients using biomedical sensors.

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Table 1. Surrounding skin management in venous leg ulcers: literature review from 2000 to 2019

Study	Year	Country	Type of article	Purpose of study	Findings
Okan D et al. [6]	2007	Canada	Continuing education activity	To provide information on wound moisture management	Importance of choosing correct dressings according wound moisture balance
Woo KY et al. [15]	2017	Canada	Scoping review	To update on the existing evidence related to the management and prevention of moisture-associated skin damage	They found 7 evidence-based strategies for the management of moisture-associated skin damage
Cameron J et al. [16]	2005	United Kingdom	Randomised controlled trial	To compare the efficacy and cost-effectiveness of Cavilon No Sting Barrier Film (NSBF) and zinc paste compound	Both were effective barrier products, but NSBF was easier to apply and transparent.
Hunter SM et al. [18]	2013	USA	Descriptive comparative study	To compare the effectiveness of two products on venous ulcer periwound skin.	The integrity of the periwound skin may be an important determinant in decreasing periwound and ulcer size.
Dini V et al. [19]	2008	Italy	Randomised controlled trial	To investigate the effects of Cavilon® No Sting Barrier Film (NSBF) on skin surrounding chronic wounds by monitoring transepidermal water loss (TEWL), compared to a control group using zinc oxide ointment	Statistical evaluation showed an overall reduction of 45% in TEWL values in both groups
Dereure O et al. [24]	2015	France	Prospective observational study	To evaluate concordance with compression therapy in ambulatory patients with VLU	Concordance with compression can be improved by a non-adherent primary dressing
D'Erme AM et al. [25]	2016	Italy	Review	To highlight the common but often neglected problem of contact dermatitis in patients with chronic leg ulcers	Contact allergies are very frequent and need a specific prevention and management
Valois A et al. [27]	2015	France	Prospective multicentre study	To determine the rate of sensitization (contact allergy) to modern dressings (MD) and substances present in dressings	Of 354 patients with VLU, 59.6% had at least one positive patch test reaction to an MD and 19% had at least one sensitization to an MD
Artüz F et al. [29]	2016	Turkey	Case-control study	To identify the allergens in patients with leg ulcers who have contact dermatitis in peri-ulcer skin and compare them with a control group of patients with lower extremity contact dermatitis	The number of patients who had positivity to at least one allergen was significantly higher in the patient group
Barbaud A et al. [30]	2009	France	Prospective multicentre study	To determine the frequency of contact sensitization in patients with chronic leg ulcers using a special series of patch tests and to determine whether the number of sensitizations was correlated with the duration of the chronic leg ulcers	Of the 423 patients with chronic leg ulcers, 73% had at least one positive patch test. The number of positive tests per patient was not correlated with the cause of ulcer but increased with the duration of the ulcer
Dini V et al. [37]	2014	Italy	Cohort study	To explore the use of TEWL measurement technique in the evaluation of surrounding skin maceration in VLU's patients	Statistics showed an increase in TEWL values as the maceration clinical score increased
Caggiati A [38]	2016	Italy	Cohort study	US comparative evaluation among wound bed, periwound skin and controlateral leg in	Sonography can improve knowledge of skin changes in chronic leg ulcers

				VLU	
Holmes J et al. [41]	2019	United Kingdom	Cohort study	To investigate D-OCT role in the evaluation of wound bed and periwound skin in VLU	Alterations in blood vessels morphology can be correlated to wound and periwound status
Barnikol WK et al. [43]	2012	Germany	Case-control study	Determination of the oxygenation status of VLU using peri-ulceral transcutaneous oxygen partial pressure measurements	Hypoxia was variously distributed in patient's leg itself and between patients and healthy volunteers, with important differences during oxygen inhalation
Sutcliffe JES et al. [48]	2017	United Kingdom	Cohort study	To understand the composition of dermis surrounding VLU using 2-photon imaging	The degradation of the extracellular matrix revealed by this technique may provide a new way of monitoring the progression of a chronic wound

Fig. 1: PRISMA flow diagram

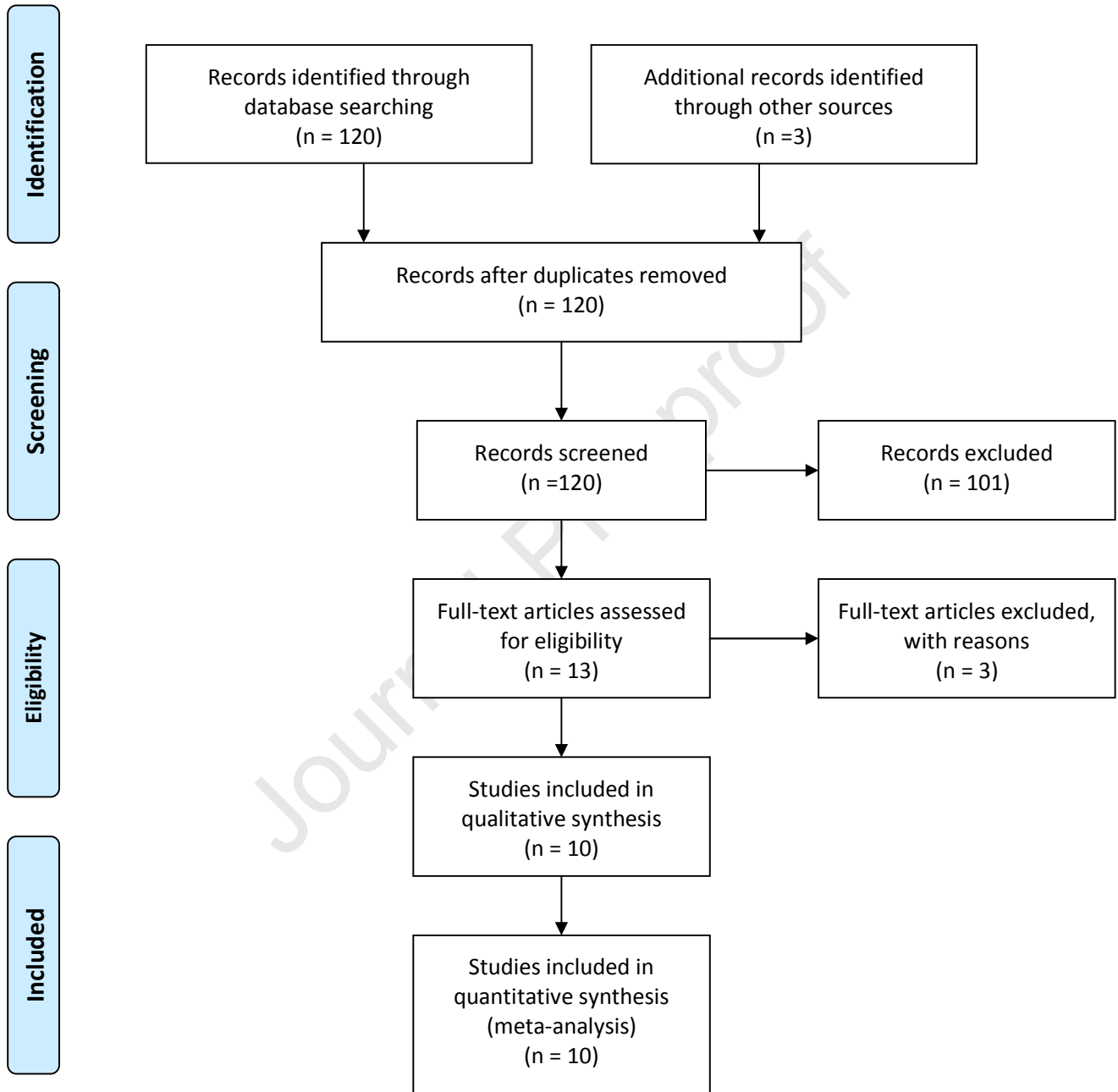






Table 2. Surrounding skin management in venous leg ulcers: clinical aspects

White maceration	Red maceration	<u>Xerosis</u>	Allergic contact dermatitis
			
Aim to control wound exudates with dressings, bandage and barrier products		Aim to remove scales and rehydrate dry skin	Aim to avoid allergens and to treat eczema

Journal Pre-proof

The authors declare no conflict of interest

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