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ORIGINAL ARTICLE

Skin grafting for the treatment of chronic leg ulcers – a systematic review in evidence-based medicine

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Abstract

Skin grafting is one of the most common surgical procedures in the area of non-healing wounds by which skin or a skin substitute is placed over a wound to replace and regenerate the damaged skin. Chronic leg ulcers are an important problem and a major source of expense for Western countries and for which many different forms of treatment have been used. Skin grafting is a method of treatment that decreases the area of chronic leg ulcers or heals them completely, thus improving a patient's quality of life. Skin grafting is an old technique, rediscovered during the first and second world wars as the main treatment for wound closure. Nowadays, skin grafting has a pivotal role in the context of modern wound healing and tissue regeneration. The aim of this review was to track and to analyse the specific outcomes this technique achieved, especially in the last decade, in relation to venous, arterial, diabetic, rheumatoid and traumatic leg ulcers. Our main findings indicate that autologous split-thickness skin grafting still remains the gold standard in terms of safety and efficacy for chronic leg ulcers; skin grafting procedures have greater success rates in chronic venous leg ulcers compared to other types of chronic leg ulcers; skin tissue engineering, also supported by genetic manipulation, is quickly expanding and, in the near future, may provide even better outcomes in the area of treatments for long-lasting chronic wounds.

Introduction

Skin grafting is one of the most used techniques in plastic-reconstructive surgery and dermatology (1), and its birth is lost in the mists of time. More than 3000 years ago, the earliest use of skin grafting took place in India, where skin grafts from the gluteal region were harvested to reconstruct noses that had been amputated as punishment (2). However, only in 1823, almost 5000 years later, Buenger, a German physician, documented the first successful skin graft, transferring skin from buttock to the nose (3). After Reverdin's first autotransplantation in 1869 (4), other pioneers tried to improve the techniques and results of grafting. In the next few years, techniques of skin grafting progressed through countless attempts, and at the beginning of 20th century, they saw an

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Key Messages

- skin grafting is one of the most used techniques in plastic-reconstructive surgery and dermatology
- skin grafting offers an important therapeutic option in the treatment of chronic leg ulcers (CLUs), such as chronic venous leg ulcers (CVLUs) and arterial leg ulcers (ALUs), diabetic ulcers (DUs), rheumatoid ulcers and traumatic ulcers such as those deriving from savage amputation stumps

- in the field of CLUs, skin grafts represent a second line strategy when standard treatments fail
- autologous split-thickness skin grafts (STSGs) remain the gold standard in terms of safety and efficacy especially for CVLUs

accelerated growth in use. During these years, Padget and Hood invented the dermatome, an essential device used even today to harvest large portions of skin. In 1929, Brown established his technique of split-thickness skin grafting, differentiating between full-thickness, intermediate-thickness and epidermal grafts (5). In World War II, techniques were refined, and many others were invented to treat injuries suffered by many soldiers, with prominent advances especially in burn injury treatment. Nowadays, skin grafting is no longer considered an option of last resort but is preferred to other techniques and treatments during soft tissue reconstruction, considering that grafts act not only as a skin replacement but also as a stimulus for healing (1).

Skin grafting offers an important therapeutic option in the treatment of chronic leg ulcers (CLUs) (6), which generally include vascular ulcers, such as chronic venous leg ulcers (CVLUs) and arterial leg ulcers (ALUs), diabetic ulcers (DUs), rheumatoid ulcers and traumatic ulcers such as those stemming from savage amputation stumps (7).

CLUs affect 1% of the adult population in Western countries and are associated with decreased quality of life, representing an important economic problem because of their recurrent nature and long-term care with subsequent large socioeconomic costs. These ulcers may resist medical treatment and require skin grafting for healing (7).

The aim of this review article is to provide evidence of specific outcomes of skin grafting in the field of CLU treatment.

Materials and methods

Search strategy

We searched for publications addressing technical aspects and outcomes of skin grafts in the area of CLUs, consulting Medline and Scopus databases. Any retrospective or prospective study design or systematic review focusing on the aforementioned topic and written in the English language was accepted (see full search strategy in Figure 1).

Study selection and quality assessment

Two reviewers judged titles and abstracts of studies for eligibility independently. Suitable articles that matched the predefined selection criteria were then obtained in full.

Results

Study descriptions and inclusion

Our search rendered 605 hits (411 from Medline and 194 from Scopus). After removing the duplicates, there were 476 studies. After progressive screening, 87 full texts were assessed for eligibility, and 52 studies were included in qualitative synthesis as showed in Figure 1.

Basic consideration and indication for grafting

Wounds with skin loss close through two main mechanisms: epithelial migration and wound contraction. Both processes occur from the edges of the wound and aim to fill the lesion and to shrink the wound edges. When these natural mechanisms are insufficient, skin grafts or flaps can be considered a suitable solution, especially after 6 weeks of non-healing wounds despite appropriate treatment (7,8). Skin grafts are commonly and frequently used in a variety of clinical situations, such as traumatic wounds, CLUs (i.e. venous, arterial, diabetic, rheumatoid), burn reconstruction, scar contracture release, defects after oncological resection, congenital skin deficiencies, hair restoration, vitiligo and nipple-areola reconstruction (1,8). Obviously, different types of wounds require different treatments and different typologies of grafts that must be selected individually for each defect in order to restore the functional integrity of the skin with the best possible cosmetic outcome (6).

Classification of skin grafts

Skin grafts can be classified according to the thickness of the graft, geometry and source. According to the thickness of the grafts, split-thickness skin grafts (STSGs) and full-thickness skin grafts (FTSGs) are distinguished.

Split-thickness skin grafts consist of epidermis and some layers of dermis. In the context of STSGs, different types of skin grafts can be identified: thin STSG (0·2 mm), middle STSG (0·4 mm) and thick STSG (0·6 mm).

Full-thickness skin grafts are composed of epidermis, dermis and various layers of subcutaneous tissue.

The amount of dermis has a central role in determining mechanical, functional, aesthetical properties and trophism of the graft. Indeed, a thicker graft has better mechanical, functional and aesthetical properties, but neovascularisation and revascularisation occur with some difficulties and take at least 5 days (9,10).

STSGs are characterised by a poor cosmetic outcome, so they are frequently used only for functional repair. From this perspective, if the cosmetic outcome represents the main goal, STSGs can also be implanted temporarily until the risk of wound recurrence is diminished; then, the graft can be excised, and a definitive cosmetic reconstruction can be performed (1,11). Moreover, STSGs contain less tissue requiring revascularisation after implantation, so thin grafts can be used to treat wounds with a reduced blood supply, such as venous or arterial insufficiency ulcers (1,12). If the most important goal is the aesthetic outcome, then FTSG represents the best choice. FTSGs are most commonly used to treat facial defects, caused by the removal of a skin cancer, and are harvested from the skin surrounding the defects, with the same colour and texture (13,14).

According to the geometry of skin grafts, these can be classified as sheet grafts, mesh grafts, meek grafts and punch grafts.

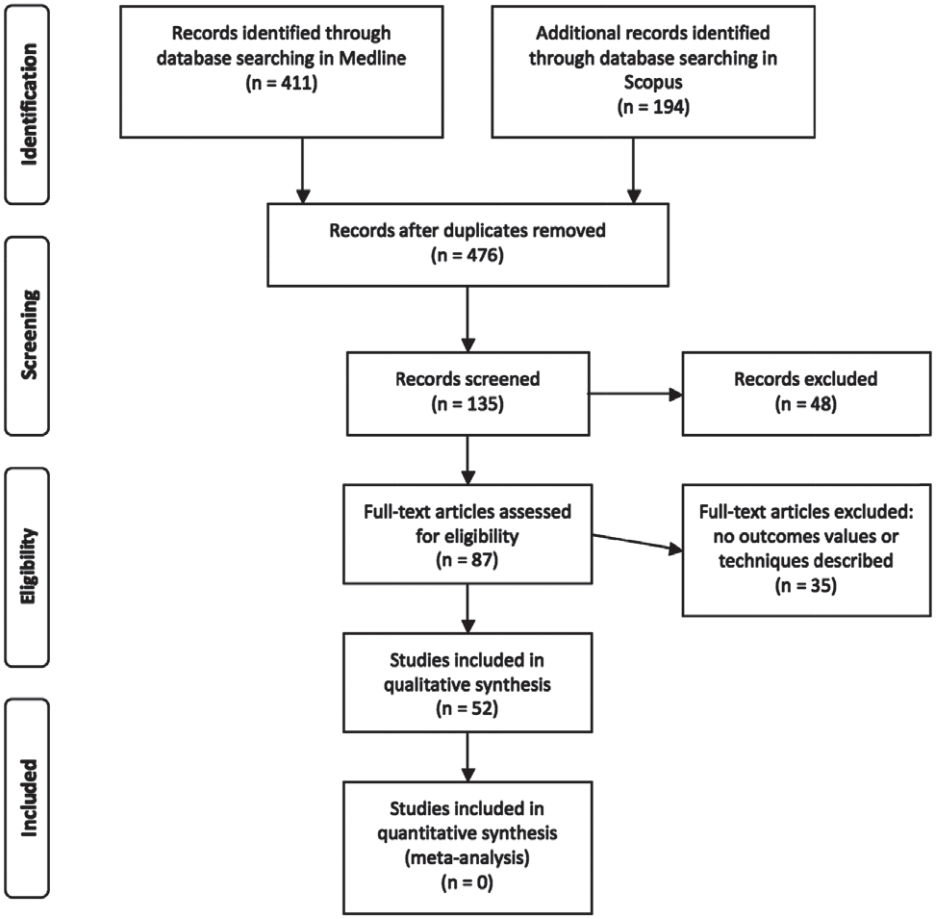

Figure 1 Search strategy flow diagram.

If the graft is directly placed on the wound without additional treatment, the graft is defined as a sheet graft. This technique is commonly used when the graft has to be implanted in aesthetically demanding regions such as the face and hands. Disadvantages of sheet grafts are poor elasticity and the need for harvesting a large donor site. Moreover, this technique does not allow blood and fluid under the graft to be drained outside, an unpleasant event that requires perforation of the graft in order to not impair neovascularisation and revascularisation (15).

If an STSG is passed through a mesher, a mesh graft can be obtained. A mesh graft, characterised by multiple rows of small cuts, has many advantages. This technique allows the graft to better achieve the edges of the recipient site, minimising the donor site and maximising the area covered by a graft. Moreover, mashing helps to drain fluid, and this can reduce the risk of a haematoma or seroma. Mashing has disadvantages such as visible marks of meshing even after healing and the tendency to contract. For these reasons, it is better to avoid meshing the grafts when these have to be implanted in areas like the face, arms or joints (16).

If an STSG is passed through a dermatome, which makes multiple squares, a Meek graft can be created (17). A $4 \times 4\,cm^2$ graft is placed on a piece of cork of the same size and cut into $3 \times 3\,mm^2$ squares by a special dermatome. The squares are applied to a prefolded nylon sheet that is then expanded, whereby the distance between the squares is doubled. The Meek graft has the same advantages as the mesh graft; however, it has slightly better aesthetic results. The biggest disadvantage is the management of the graft, which is very time consuming.

If an STSG is harvested with a punch or a tangential cut with a scalpel, a punch graft will be created. This technique is used to implant areas of epithelialisation in a small chronic wound and can be performed with local anaesthesia (9).

Skin grafts can also be classified, according to the source of donor tissue, as autografts when taken from the patient, allografts when donated from another person (from alive or dead donor) and xenografts if a non-human donor is used (e.g. porcine xenografts act similar to human cadaveric skin) (1).

In many countries, skin banks have been established from the 1970s in order to ensure a sufficient amount of grafts required for grafting. The cadaveric skin represents almost the only source of banked skin allograft and, in most cases, is used just as a temporary dressing for complicated wounds, which, for some reason, cannot be closed immediately, in order to obtain a better preparation of the wound bed prior to autograft transplantation (18). The allograft from a cadaver can be preserved and stored with two different techniques: cryopreservation and glycerol preservation. Cryopreserved allografts (CPA), introduced in 1979, carry the putative benefit of viability. Glycerol-preserved allografts (GPA), in use since the 1980s,

are non-viable but have antimicrobial and antiviral properties and appear to be less immunogenic. Cinamon *et al.* (19) studied rejection processes by comparing fresh, cryopreserved and glycerol-preserved allografts. Histological examination showed better outcomes for fresh and cryopreserved grafts, but no significant clinical differences were observed on days 4 and 7 after surgery.

Moreover, since the early 1990s, biological products simulating the structure and the function of the skin have been developed. These materials can be classified into those consisting mainly of epidermal components (epidermal skin substitutes), those containing dermal components (dermal skin substitutes) and composite products containing epidermal and dermal components (combined epidermal and dermal skin substitutes) (1,20).

Basic surgical procedure

Grafting is a multistep operation that takes place in several stages. The exact plan of action depends on the sites chosen, wound type, coverage needed, infection, patient's medical condition and other factors. Only when the plan is coordinated will the operations begin.

The surgeon will choose an area considering availability of healthy skin, visibility of a scar and patient requests (21), and the donor site should be similar to the recipient site in terms of consistency, thickness, colour and texture (22). Donor sites are also chosen according to the typology of grafts needed. The body sites that are commonly suited for STSGs include the anteromedial thigh, the buttock, the abdomen, the inner and outer upper arm and the inner aspect of the forearm (1). While harvesting, the primary importance of FTSGs is to match the characteristics of the donor skin to the surrounding recipient area. Usually, FTSGs are harvested from preauricular skin, postauricular skin, supraclavicular and clavicular areas, neck, upper eyelid, nasolabial folds and inner upper arm areas (1).

The donor sites are marked, prepared, draped and then injected with a tumescent saline solution. Harvesting is usually performed under local anaesthesia. Epinephrine is also used to induce local vasoconstriction and decrease bleeding. The skin graft is harvested with a knife or a dermatome, depending mostly on type of grafts and size. If a dermatome is used, some mineral oil is applied on the selected area, and the dermatome is used to harvest the skin. For FTSGs, it is necessary to remove all the fat remaining on the undersurface of the graft in order to help the graft take. Obtained grafts can be mashed in order to allow the graft to better achieve the edges of the recipient site, minimising the donor site and maximising the area covered by a graft. Moreover, mashing helps to drain fluid, and this can reduce the risk of a haematoma or seroma. Mashing has disadvantages such as visible marks of meshing even after the healing and the tendency to contract. For these reasons, it is better to avoid meshing the grafts when these have to be implanted in areas like the face, arms or joints (1).

The graft is placed over the recipient bed and, kept under traction, is fixed to the edges of the recipient bed with stitches placed diagonally to each other. The graft is then sutured using the halving method. Tie-over dressing can also be performed as an alternative option of graft fixation, especially in concave surfaces (9).

Donor site care

Donor site management is necessary to avoid or minimise postoperative problems.

While full-thickness skin grafts, donor sites can be closed primarily, split-thickness full graft donor sites are at first covered with wet gauze or strewed with vasoconstrictor agents in order to control initial bleeding. The next step of management depends on the typology of the harvested graft.

Generally, after thin or middle STSGs have been harvested, the donor sites heal by re-epithelialisation. This process can be aided by the application of a fat gauze or special dressing, such as polyurethane films, that are able to contain the exudate, decrease postoperative pain and speed epithelialisation.

In case of thick STSGs in regions with thin skin or in case of large full-thickness skin grafts, skin grafting of the donor site using a thick STSG might be necessary. (1,9)

Recipient site care and frequent complications

Recipient site management represents the hardest phase on which depends the result of what has been previously described. First, wound debridement is an essential step to prepare the wound bed to receive the graft and involves the removal of torn, devitalised or contaminated tissue, which helps to reduce microbe toxins and other substances that inhibit healing, so as to improve graft take rate/survival (23,24). Wound debridement can be accomplished through five main methods: surgical, autolytic, enzymatic, mechanical and biosurgery (myiasis). The choice of debridement method depends mostly upon wound features such as size, position and type, and in some cases, it might be proper to use more than one method of debridement (25). Autolytic and enzymatic debridement are highly selective methods by which endogenous and exogenous proteolytic enzymes respectively decompose necrotic tissue. However, autolytic and enzymatic debridement might not be fast enough to achieve a rapid wound bed preparation, while surgical debridement represents the fastest quite selective method to remove necrotic tissue (23). Surgical debridement may be carried out by the use of the Versajet™, Smith & Nephew, London, UK hydrosurgery system, which has shown to be an effective device for wound debridement. The fluidjet equipment consists of a power console that is controlled by a foot pedal, a disposable handpiece, a bag of saline (the fluid irrigant) that is connected to the power console with pressure tubing and a waste container for effluent. The power console propels the highly pressurised saline through the tip of the handpiece; the saline is collected by the collector device and creates a localized vacuum – the Venturi effect. The fluidjet tip excises the unwanted tissues, while the vacuum aspirates the debris at the suction point. The ability to quite selectively excise necrotic tissue while sparing the healthy tissue is a remarkable feature that makes this tool suitable for better wound bed preparation and especially for the preparation of advanced wound-healing techniques, such as skin grafting (25).

Postoperative immobilisation is essential during a period of 5–10 days in the position of maximal graft stretching. This will help to improve graft take and minimise graft shrinkage. After 7 or 10 days of immobilisation, physiotherapy can be started, with care taken to avoid shear forces. It is also important to prevent the drying of the skin graft by applying fat cream and lotion for 6–12 weeks. Scar treatment with massage or silicon sheets might be necessary in order to prevent the formation of hypertrophic scar (1,9).

Poor or inadequate management of the recipient site can lead to a number of complications that can be divided into early complications and late complications.

Early complications are responsible for failure of graft take. Haematoma, seroma and infections are the most frequent early complications leading to graft failure. Infections can be prevented by the use of preoperative and perioperative antibiotics and leg elevation (1,6).

Late complications can be aesthetic or functional. Colour and texture mismatch of the graft with the surrounding skin, hypopigmentation and hyperpigmentation and prolonged erythema are common long-term cosmetic complications. Because of the absence of adnexal structures, STSGs are predisposed to xerosis and the build-up of keratinous debris. Functional considerations are of paramount concern, especially because STSGs contract more than FTSGs. The amount of contraction increases as the thickness of the graft decreases and can lead to significant cosmetic deformities. Hypertrophic scarring in the graft and donor site may also occur as well as graft fragility and breakdown in areas of trauma. Postoperative early and long-term complications after placement of FTSGs are similar to those of STSGs, although wound contraction in the recipient site is less expected (1,26).

Associated adjuvant treatments

We can associate either systemic or topical adjuvant treatments to improve skin graft take and, thus, speed up wound-healing rates. Serra and coworkers (27) showed that low molecular weight heparin (LMWH) administered both in the preoperative period (4 hours before intervention) and in the postoperative period at the same dosage of 2850 IU/0·3 ml given by subcutaneous injection once a day and continued for 12 months was able to improve both early and late results of patients who underwent skin graft procedures for CVLUs. Moreover, the same group (8) also showed the efficacy of the topical application of platelet gel in several types of CLUs (venous, arterial and diabetic).

Romano *et al.* (27) reported encouraging outcomes obtained from the use of growth factors, $CD34^+$ cells and fibrin for the management of CVLUs. This treatment appears to stimulate fibroblasts, macrophages and mesenchymal cells, inducing re-epithelialisation and neovascularisation, postulating its efficacy as sole treatment, without skin grafting or other surgical procedures.

Further interesting applications in the area of topical support for skin grafts are the local application of devices based on physical forces. One of this is a vacuum-assisted closure (VAC) device, also known as topical negative pressure (TNP), a relatively new technology primarily designed for the treatment of difficult-to-manage acute and chronic wounds (28). It consists of the application of open-cell foam, suitably cut to fit the selected wound that will be subsequently covered with an adhesive drape with an additional 3–5 cm border of intact skin and connected to a vacuum pump and a container for effluent liquids. A sub-atmospheric pressure is then applied in a controlled way (29). Many studies reported encouraging results in terms of healing rate, and the VAC device is nowadays largely used for the treatment of a variety of wounds such as acute or chronic lower-limbs ulcerations, amputation sites, burns, abdominal wounds, sternotomy wounds and, as mentioned before, skin grafts (24). Even though the application of the VAC device to increase graft take rates/survival is controversial, there is much evidence suggesting that TNP increases the quantity and quality of STSGs take compared to traditional bolster dressings, as measured by a reduction in the number of repeated STSGs. (30,31).

Outcomes in chronic venous leg ulcers

CVLUs amount to 70% of all CLUs and consist of excavation located in lower leg skin because of the loss of inflammatory necrotic tissue as a result of insufficient venous blood circulation because of structural abnormalities of the vein draining the legs. These abnormalities can be detected in the superficial veins, the communicating veins or the deep veins and mostly consist of faulty valves unable to ensure forward progression of blood. This alteration leads to an increased venous pressure with progressive dilation of the veins and egress of proteins, such as fibrinogen. The resulting fibrin complexes compromise the microcirculation and cause the phlogosis onset. Finally, cell death and necrotic tissue evolve into venous ulcerations. CVLUs consist of irregular, shallow and painful lesions usually located over bony prominences such as medial malleolus, with granulation tissue and fibrin present in the ulcer base. Other important findings may be oedema, varicosities, hyperpigmentation and lipodermatosclerosis with thickening and fibrosis of the adipose layer under the skin (32).

CVLUs can be treated in many ways according to the severity of the lesion. Suitable options include conservative management such as compression therapy and leg elevation, mechanical treatment by VAC, medications including non-steroidal anti-inflammatory drug (NSAID), antibiotics and hyperbaric oxygen therapy and surgical treatment that should be considered in patients with venous ulcers that do not heal with conservative therapies. The pivotal surgical procedure for the treatment of CVLUs is skin grafting, especially when lesions are large and refractory to standard treatments (7). Autografts, allografts or human skin equivalents can be used, with a resulting healing rate of 73% (33). Overall, all patients suffering with CVLUs and being considered for skin graft should undergo surgery for venous insufficiency in order to correct the underlying venous abnormalities causing the ulcerations and avoid surgical breakdown (34–37). Skin grafting for CVLUs can also be followed by additional treatment to try to speed up the healing. Serra *et al.* (26,33) described how long-term LMWHtherapy and the use of platelet gel after skin grafting appear to be effective and safe tools in order to increase the healing rate of difficult-to-treat ulcers, reaching a healing rate up to 90% at 5 years.

Jones *et al.* (38) reviewed and compared the specific outcomes of several trials using different types of grafts for the treatment of CVLUs: dressing with autograft, frozen allografts with dressings, fresh allografts with dressings, autografts with frozen allograft, pinch graft (autograft) with porcine dermis (xenograft), growth-arrested human keratinocytes and fibroblasts with placebo, autograft delivered on porcine pads with an autograft delivered on porcine gelatin microbeads, meshed graft with a cultured keratinocyte autograft and frozen keratinocyte allograft with a lyophilised (freeze-dried) keratinocyte allografts. The study concluded that significantly more ulcers were healed when treated with bilayer artificial skin than with dressings.

Furthermore, Salomè *et al.* (12) showed how split-thickness skin grafting resulted in better health-related quality of life and self-esteem in patients with venous leg ulcers than did different treatments.

Outcomes in arterial leg ulcers

ALUs, also known as ischaemic ulcers, are the second most common with a percentage of 10–30% of lower extremity ulcers caused by reduced arterial blood supply to the lower limbs (39). The skin and the overlying tissues are then deprived of oxygen and nutrients with consequent tissue damage and formation of an open wound. The main cause of ALUs is atherosclerotic disease of the medium- and large-sized arteries such as iliac and femoropopliteal. This pathological condition, known as peripheral arterial disease (PAD), is also characterised by an increased endothelial and platelet activation because of a proinflammatory and prothrombotic state, leading to thrombotic or thromboembolic episodes that contribute to tissue damage and ulcer formation. Other common causes of ALUs are arteriosclerosis, diabetes, high blood pressure, thromboangiitis, vasculitis and thalassaemia (40,41).

Arterial ulceration typically occurs over the toes, the outer ankle or bony prominences of the foot. The ulcer appears punched out and round-shaped with well-demarcated edges, characteristically deep and not bleeding, with a non-granulating and often necrotic base. The surrounding skin may exhibit dusky erythema and may be cool to touch, hairless, thin and brittle, with a shiny texture (42).

The use of skin grafts in this field is poorly described in the literature, where we can find only small clinical trials with promising results (8).

Outcomes in diabetic ulcers

Diabetic ulcers (DUs) represent a common complication of diabetes and are responsible for more hospitalisations than any other complication of diabetes; in fact, about 15% of diabetic patients develop DUs, and from 12 to 24% of individuals diagnosed with such ulcers will require amputation (43).

The use of skin grafting for chronic lower-limb ulcerations has been controversial for a long time and has been considered not suitable for such ulcers because of the concrete risk of failure, especially in patients with plantar diabetic foot wounds. However, a study by Rose *et al.* has shown that the application of STSGs to chronic lower-limb ulcerations is an effective method for the promotion of wound healing regardless of wound location and presence of diabetes (44).

Nowadays, the management of DUs includes several procedures and grafting may be considered for difficult-to-treat ulcerations. For diabetic foot ulcerations, grafting can be performed with engineered substitutes or STSGs. Autologous STSGs represent a gold standard for the reconstruction of DUs. These grafts require a well-perfused granular wound, preferably not located at weight-bearing sites of the foot. STSGs for the diabetic foot usually have a thickness of 0·018 inches and are harvested with an electric dermatome from the thigh or the lower extremity of leg or foot. STSGs can be used for the treatment of different types of DUs, such as acute, chronic, traumatic and post-amputation wounds. However, this typology of grafts should be avoided for the treatment of wounds with bone or joints exposed because these wounds are devoid of the vascularisation required for STSGs engraftment (45,46). Unfortunately, despite some promising observational studies (8), the articles examined do not report sufficient data concerning the healing rate of DUs treated with skin grafting.

Outcomes in rheumatoid ulcers

CLUs are frequent in patients suffering from rheumatoid arthritis (RA), with an approximate prevalence of 9% (47,48). The aetiology of chronic ulcerations in such patients is multifactorial but is often associated with venous insufficiency, systemic rheumatoid vasculitis or both. Rheumatoid ulcerations (RUs) particularly caused by systemic vasculitis are noted to be more painful and more resistant to treatment if compared to the other types of ulcers.

Öien *et al.* (49) described the effect of pinch grafting on pain and healing of RUs caused by both venous insufficiency and systemic vasculitis as an alternative to conservative treatment. They found a remarkable reduction in pain and an increased healing rate of RUs after pinch grafting. However, grafting success and then ulcer healing mostly depends on two primary predictive factors, ulcer size and ulcer duration. So, the best outcomes have been observed in smaller and recent ulcerations.

Although pinch grafting is found to be an excellent tool to treat RUs, in the last few years, many studies established the effectiveness of pharmacological therapies in the treatment of such ulcers. With respect of this, Hellmann *et al.* (50) reported the successful treatment of rheumatoid vasculitis-associated cutaneous ulcers using rituximab in two patients with RA. Even in the case of RUs, the literature is poor in results concerning the healing rate of such ulcers.

Outcomes in salvage amputation stumps

Skin grafting has shown a substantial effectiveness as a tool to salvage amputation stumps. Above all, amputation represents a common outcome in lower-limb trauma. In this case, the main target is to save the knee joint – of below-knee amputations – in order to allow the amputee to preserve, with the aid of prosthesis, a quite normal ambulation in terms of energy expended and speed of walking (51,52). Skin grafting for amputation stumps should be considered when the stump

results extensively degloved, with insufficient viable skin to achieve primary stump closure. In a case report (53), Anderson *et al.* described satisfying results about the use of STSGs and FTSGs to treat below-knee amputation. They treated six patients who required an average of five surgery procedures to have their stumps healed. STSGs were used in four patients, while in two patients, FTSGs were harvested from the amputee part and used for stump cover. Regardless of the typology of the grafts, all patients have had minor stump problems necessitating periods of time off their prosthesis; three of the five patients returned to full-time employment; three patients required minor stump revision surgery. Even if the outcomes concerning the healing rate of amputation stumps treated with skin grafts are exiguous, skin grafting represents an effective tool to salvage below-knee amputation stumps.

Discussion

As the aging population is dramatically increasing in size, as a direct consequence of improved life expectancy, CLUs will become an increasing burden for health care expenditures because of the important patient morbidity that is associated with this disease (7,54).

Depending on the size of the ulcer and its duration, complete healing rates of CLUs may sometimes be difficult to achieve with standard treatments, and, in this case, skin grafting may be a useful and effective aid (7,8).

Skin grating is one of the most commonly used reconstructive techniques among plastic surgeons (21) and is one of the most effective treatments for non-healing ulcers (7,8). It has been also demonstrated that the use of skin grafts significantly determines an improvement in the quality of life and in the reduction of pain (12).

From a technical point of view, the autologous STSG remains the gold standard. In fact, as blood supply in the first phase of graft take is maintained only by osmosis, the thinner the graft, the easier it is to feed the graft. However, depending on the patient's conditions, sometimes, donor site may not be available, and other solutions may be used instead, such as allogeneic grafts from cadavers or skin substitutes. The latter consists of wound dressings and wound closure materials (21).

The better results for autologous skin grafts might be because of a more natural and physiological healing and a better interaction with the extracellular matrix (ECM) that is pivotal during wound healing (55).

In fact, non-healing wounds do not generally progress from the tissue replacement phase to a competent resolving phase and thus remain in an immature state of cellular proliferation and matrix deposition/remodelling (55), and, in this context, some soluble mediators of ECM, such as matrix metalloproteinases (MMPs), appear to play an important role in difficult-to-heal chronic wounds of different origins (56–59).

Furthermore, improving the microenvironment of ECM with adjuvant systems, through the use of systemic administrations of drugs (e.g. LMWH) (33) or through the local application of substances or forces (e.g. platelet gel, VAC) (8,28–31), appears to speed up the healing and the take of autologous STSG, with positive outcomes of up to 90% success rate at 5 years (8,28–31,33).

Tissue-engineered dermo-epidermal skin substitutes have been recently proposed as an alternative to autologous STSG, but unfortunately, they are characterised by an insufficient initial vascularisation, resulting in some kind of nutritional crisis in the early phase of graft take. A promising strategy to enhance the vascularisation of such kind of grafts is represented by the pre-vascularisation with adipose-derived cells (60).

Laboratory investigations have revealed that living skin equivalents (LSEs) constructed using human amnions as a matrix resembles human skin both morphologically and ultrastructurally, with good mechanical properties in which fibroblasts show good adherence and proliferation, and in the near future, LSEs may probably be useful as valid skin substitutes (61).

While tissue engineering represents a promising approach to generate replacement skin, one of the most important obstacles in the development of valid and fully functional skin is controlling cellular behaviour during wound healing and graft take; hence, some studies focused on the role of control of cell activity by MicroRNA (miRNA) regulation (62). Klingerberg *et al.* (63) compared gene expression in healed engineered skin after in vivo grafting and normal human skin healing, and different patterns of expression were highlighted. So, it is conceivable that the delivery of miRNA is able to push the gene expression profile of grafted bioengineered skin equivalents to better emulate normal skin, mimicking physiological wound healing as that of autologous skin grafts (62).

Considering the outcomes among the different types of CLUs, we can say that skin grafting is a safe and effective procedure especially for CVLUs, and this is supported by the results of several clinical trials (8,27,33,38), but there is little evidence of this in the other types of CLUs, such as arterial, diabetic and traumatic wounds, except for some encouraging observational studies (8).

The most common outcome parameters, such as graft take and time to wound healing, are not only influenced by the techniques or the type of wounds but also by the recipient site care; in fact, Hierner *et al.* stated that the success of skin grafting depends entirely on the quality of the recipient bed, which is guaranteed by a correct wound bed preparation (9), and the Versajet™ hydrosurgery system has shown to be an effective device for wound debridement in order to prepare the wound bed for skin grafts (25,64).

In the field of CLUs, skin grafts represent a second-line strategy when standard treatments fail. Autologous STGSs remain the gold standard in terms of safety and efficacy, especially for CVLUs. In the near future, the control of skin cells behaviour by means of genetic manipulations may expand the field of skin tissue engineering with better outcomes in this area.

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