Human keratin matrix in addition to standard of care accelerates healing of venous ulcers: a case series

Objective: Venous leg ulcers (VLUs) are often large and complicated wounds that, despite combinations of advanced wound care techniques and systemic treatment of underlying vascular issues, take many months to heal and have high rates of recurrence. In this study, we investigated the efficacy of a novel wound care solution—human keratin matrix (HKM).

Method: A case series of VLUs were treated with HKM in conjunction with indicated vascular intervention and standard of care (SoC) procedures. For analysis, these wounds were divided into very large (>200cm^2) and smaller (<35cm^2) wounds.

Results: The cohort comprised 16 VLUs (very large=7; smaller=9). Very large VLUs were reduced in size by an average of 71% within 10 weeks, and showed a 50% size reduction within four applications of HKM. Smaller VLUs reduced by 50% in size within the first three weeks of treatment, and 88.9% of these wounds healed completely with an average of 4.5 HKM applications over an average of 6.5 weeks.

Conclusion: The results of this series highlight the potential of HKM, in combination with indicated systemic interventions and SoC, as an effective treatment for hard-to-heal (chronic) VLUs, even in very large wounds.

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Venous leg ulcers (VLUs) are hard-to-heal (chronic) lower extremity wounds with high prevalence, affecting 1–3% of the US population.[1] Insight into the pathogenesis of VLUs has increased significantly in the last two decades. VLUs are primarily caused by venous hypertension, in patients with genetic predisposition and coexistence of other risk factors, such as obesity, ageing and low levels of physical activity.[2] These lead to chronic inflammation, causing red and white blood cell extravasation into the dermis and secretion of numerous proinflammatory cytokines. Skin break and ulceration at these areas soon follows.[3] VLUs are often large with an irregular shape, and are characterised by multiple episodes of infection, drainage and cellulitis.[2–4] Many patients with VLUs also have coexisting diabetes, obesity and other comorbidities. Often these VLUs are mixed aetiology ulcerations of primarily venous origin.

Therapies for VLUs are broadly divided into topical ulcer treatments and interventional treatments targeting venous hypertension. Surgical and medical therapies are primarily directed at eliminating venous hypertension, thereby promoting VLU healing. These mainly consist of compression application and endovenous interventions.[2,4,5]

Topical VLU therapies are used as adjuncts to systemic interventional measures, and a large variety of products have been studied and approved in the last two decades. These products often aim to reduce inflammation, promote fibroblast and keratinocyte migration and proliferation, or both. The majority of these products are either alginate constructs, acellular matrices or cellular constructs, with either live or non-living cells.[6]

Despite these advances in both topical and systemic forms of VLU healing, VLUs take an average of six months to heal, and ulcer recurrence rates at five years are >50–55%.[7] This highlights the necessity for further innovation in the treatment of VLUs.

Keratins are a very diverse and large family of abundant proteins that can be found intracellularly as intermediate filaments, or extracellularly as part of the hair and nails. These structural proteins are mechanically and chemically robust, and can resist enzymatic degradation in biological conditions due to their insolubility, and the high degree of covalent and non-covalent crosslinking that stabilises their structure.[8] Hair and nails are built from a somewhat separate subfamily of 'hard' or 'trichocytic' keratins, commonly designated as 'hair keratins'. Humans have 17 slightly different hair keratins.[9] Keratins are extracted from an abundant and sustainable keratin source—human hair—making it a unique and economical material for the creation of biomaterials for multiple applications.

Wound healing is one such application, given the significant role of keratin in the skin and wound biology. The ability of keratinocytes to migrate is critical for

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wound re-epithelialisation.[10] Keratins are the major protein in keratinocytes and are essential for keratinocyte migration.[11,12] Upregulation of keratin expression has been observed in response to wound formation in the acute phase.[12,13] The importance of keratin in wound healing has been demonstrated,[13] and additionally downregulation of keratins has been associated with ulcer chronicity. Animal keratin-based dressings have been approved for use in several regions of the world, including for use as a topical agent for wound care, and the use of wool-derived oxidised keratin has been associated with positive responses in hard-to-heal wounds.[14,15] Keratin products, as with other advanced wound care products, are often indicated for a variety of acute and hard-to-heal wound types, including VLUs, which were the focus of this work.

In this case series, we retrospectively evaluated the efficacy of a human keratin matrix (HKM), (ProgenaMatrix, ProgenaCare Global LLC, US) as a topical mode of treatment to promote wound closure in a diverse group of VLUs, including a subgroup of very large VLUs, in addition to noninvasive venous function interrogation, compression and other systemic measures.

Methods

Ethical statement and patient consent

All research reported in this manuscript complies with the guidelines of the Declaration of Helsinki. Approval for this work was obtained from the Stony Brook University Institutional Review Board (approval #IRB2022-00584). All patients provided written informed consent to participate in the study.

Venous ulcer groups

The VLUs were divided into two distinctive groups: very large ulcers (>200cm^2) and smaller ulcers (<35cm^2).

All patients selected for this study were being treated at the Stony Brook Southampton wound care centre during a six-month time period. Patients in the very large hard-to-heal VLU group (>200cm^2) were included because all other available treatment methods had failed up to that point. These ulcers had not made any clinically meaningful progress before their inclusion into the study group. No exclusion criteria were applied to any patient.

Prior to initiation of the HKM treatment, all wounds had received ongoing wound care following standard practice for VLU treatment—compression, surgical debridement and application of various products, including other advanced wound care products.

Human keratin matrix application technique

All VLUs of both groups received venous duplex ultrasound for detection of deep vein thrombosis and venous reflux. Based on the results, patients received endovenous ablations, microphlebectomies, or both, to treat superficial venous insufficiency. All patients received standard of care (SoC) in addition to the application of HKM—surgical debridement after application of local anaesthesia with a disposable dermal curette (Integra Miltrex, Integra Lifesciences, US). Following debridement, the VLUs were treated for one minute with a hypochlorous acid solution-soaked gauze (Vashe, URGO Medical, US), followed by irrigation with normal saline. HKM was then fenestrated with a scalpel blade and applied directly to the VLU bed. The periwound area was treated with a protective barrier (Cavilon, 3M, US) and the HKM was then secured with a fenestrated, one-sided adhesive silicon contact layer (Versatel One, Medline, US). In VLUs with no drainage, hydrogel was also applied and covered with a moist gauze and foam dressing as a form of moisture balance. Highly exudative VLUs were covered with a hydroconductive wound dressing (Drawtex, Urgo Medical, US). Compression was applied from behind the toes to just below the kneecap with either Unna boots or application of a three-layer compression wrap.

Patients were seen weekly for routine care, as described above, and the HKM was inspected. If it was found structurally and visually intact, it was left in place and not replaced with a fresh piece. If the HKM was not intact, it was removed and a new HKM was applied. In this way, all wounds received keratin treatment every week. Whether a new HKM was applied or the same piece was left in place, wounds were given the same SoC including debridement and irrigation, and overlying dressing layers were changed weekly. Ulcers were cultured and treated with antibiotics if they were found to have recurrent tenderness, erythema or increased drainage.

Statistics

Statistics were analysed using Prism 10.1.2 (GraphPad Software, US). Significance was determined using α=0.05, with the following statistical tests: patient history data and comorbidities were compared using Fisher's exact test; initial would size was compared using a Mann–Whitey U test; and average wound size after each treatment was evaluated by a Kruskal–Wallis test.

Results

A total of 16 VLUs from 13 patients were included in this series; seven VLUs in the very large group, and nine in the smaller group.

The very large VLUs had been previously treated for a significant amount of time (mean: 14.52 months) and had a mean ulcer area of 333cm^2. The remaining, smaller VLUs (mean ulcer area: 17.55cm^2) had appeared more recently (mean: 3.43 months). The two VLU groups had significant differences in size ($p<0.0002$) and a notable difference in wound duration. The very large VLU group had a higher incidence of a history of deep vein thrombosis and popliteal vein reflux than the smaller VLU group (Table 1), though neither of these differences reached significance given the population sizes. The groups had no significant difference in general medical comorbidities, as well as the presence of varicosities around the ulcer (Table 1), and none of these conditions were used to exclude patients from this series.

Table 1. Demographic and patient history comparison of the two patient groups

Total number of VLUs (n=16)	Very large VLUs (n=7)	Smaller VLUs (n=9)	Fisher's Exact Test p-value
Males/Females	5/2	5/4	0.6329
VLU surface area (cm^2)	333	17.55	0.0002
Ipsilateral Iliac vein obstruction, n	2	0	0.1750
History of DVT, n (%)	4 (57.14)	2 (22.00)	0.3024
Popliteal vein reflux, n (%)	6 (85.71)	3 (33.33)	0.0601
Above the knee LSV reflux, n (%)	6 (85.71)	6 (66.66)	0.5846
Below knee LSV reflux, n (%)	5 (71.42)	5 (55.55)	0.6329
Present varicose veins on treatment initiation, n (%)	6 (85.71)	7 (77.77)	0.9999
Periulcer phlebectomy, n (%)	3 (42.85)	4 (44.44)	0.9999
LSV ablation, n (%)	5 (71.42)	5 (55.55)	0.6329

DVT—deep vein thrombosis; LSV—long saphenous vein; VLU—venous leg ulcer

Very large VLU group

VLUs (n=7) were measured during each follow-up visit, and surface area was calculated and plotted over the course of the treatment (Fig 1). As mentioned above, not all patients were treated weekly, for several reasons. First, some patients missed visits at the wound care centre and, second, on follow-up visits, the HKM was inspected, was found to be structurally intact and was not replaced.

The most notable reduction in wound size was observed in the first five weeks of treatment. By week 3, the mean surface area of the group was reduced by >50%. From week 3 to week 5 the rate of size reduction decreased, with a further reduction in size of only 10%. Overall, in five weeks of HKM treatment, a 66.5% size reduction was observed (Fig 2). During the entire treatment period, an average of six HKM applications was used. A 50% size reduction was achieved with ≤4-applications of HKM.

Smaller VLU group

Small and medium size VLUs (n=9) were also measured during each follow-up visit, and wound sizes plotted over time (Fig 3). As with the very large VLU group, not all patients were treated weekly for the reasons mentioned above. In this group, a rapid size reduction of the mean surface area by 50% in the first three weeks of treatment was observed, with an average of 75% reduction in wound size by week 5 (Fig 2). By week 8, 7/9 (77.8%) VLUs were healed. Overall, 8/9 (88.9%) of the ulcers in this group healed completely, with an average of 4.5 HKM applications over an average of 6.5 weeks.

Discussion

VLUs continue to have high incidence (0.17%) and prevalence (0.32%) in the US, and which is higher still in many parts of the world.[1] In the US, VLUs are the second or third most common form of ulceration overall, and the most common leg ulcer, with a very large social and financial burden.[16] VLUs are not associated with increased amputation rates, but are associated with significant chronicity and decrease in all quality of life (QoL) metrics.[17] Despite many recent improvements in treatment, VLUs are still associated with prolonged healing times. Even with appropriate treatment, the average time for healing VLUs varies from 6–12 months, and one-fifth of VLU cases do not heal within 24 months, with a very high five-year recurrence rate.[7]

A wide variety of systemic and local treatments have been applied to VLUs over the last two decades. However, clinical results and contemporary perception still show that because of the resistance to heal and the significant recurrence rates, overall treatment efficacy is low.[7,18,19]

Several advanced wound care products have shown increased healing rates when combined with SoC in VLUs.[20–23] These products are designed and marketed to address specific pathogenetic features of VLUs depending on the clinical phase of the VLU. In VLUs that appear to be in an arrested and dysfunctional or dysregulated inflammatory phase, products target biofilm reformation and contribute to metalloproteinase quenching in order to change the ulcer environment to a more anti-inflammatory and proliferative profile.[22,23] At this point, cellular and acellular products are indicated to accelerate the VLU proliferative phase of healing by providing anti-inflammatory and regenerative growth factors, or by acting as healing scaffolds or signal transducers for regenerating fibroblasts and keratinocytes.[20–22] These products are usually applied when previous treatment modalities do not help ulcers heal by 40% in four weeks.

In this case series, we evaluated the effects of HKM on the healing of VLUs of different sizes. Keratin is one of the most abundant proteins found in the skin and, accordingly, plays an important role in skin biology and the various stages of wound healing. In the inflammatory phase of healing, keratin is shown to modulate the inflammatory wound environment. Wound chronicity is attributed, at least in part, to a prolonged inflammatory environment that does not transition to the proliferative and remodelling phases of healing. Naive macrophages plated on hair keratin-coated surfaces are shown to polarise towards proregenerative M2 phenotypes,[11] more so on keratin than on other biopolymer surfaces.[24]

Additionally, keratin has been shown to affect other cell types crucial to wound healing. Keratinocytes that grow in the vicinity of keratin demonstrate increased gene expression of keratinocyte activation factors and molecules involved in inflammatory wound modulation.[10,12,13,25] In the literature, keratinocyte activation is also linked to keratin,[12] which primarily involves the migratory phenotype of keratinocytes that is crucial to the process of wound re-epithelialisation.[26] Activated keratinocytes also interact with dermal cells to promote wound closure,[27] and keratin also plays a role in the responses of these cells by stimulating fibroblast proliferation and remodelling of granulation tissue.[28]

Fig 1. Wound surface area reduction of seven very large venous leg ulcers (VLUs) treated with human keratin matrices

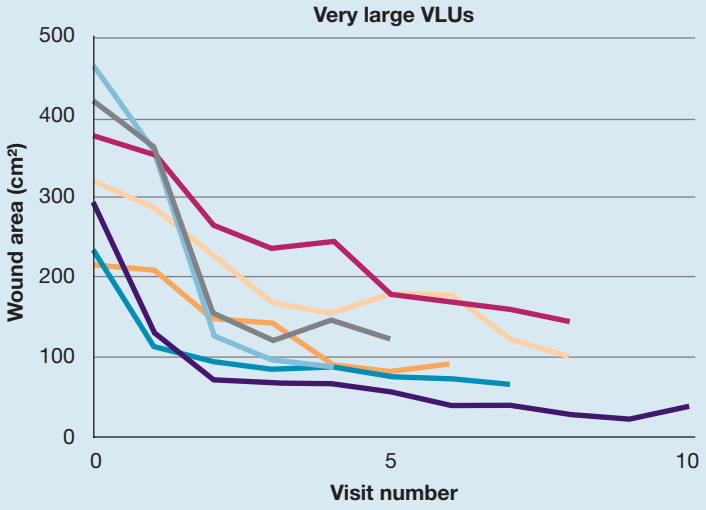
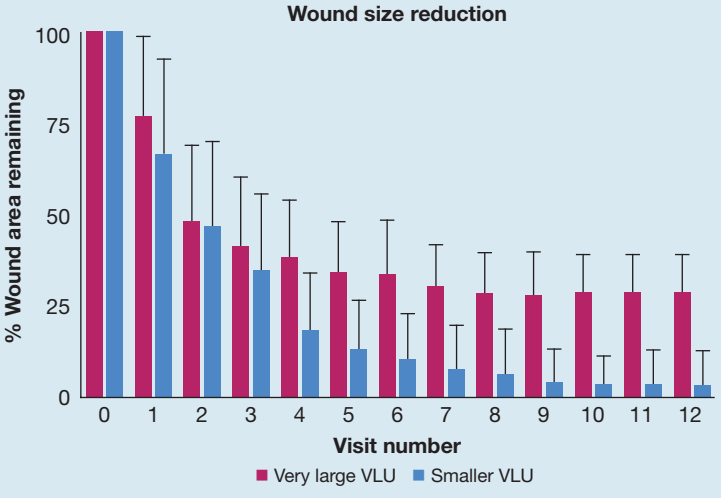


Fig 2. Wound area reduction of both venous leg ulcer (VLU) groups over time, calculated as the percentage of the original wound area remaining. Bars show mean±standard deviation, with last observation carried forward for all patients to 12 weeks



These in vitro effects could be involved in the clinical responses observed in this case series, and future investigation into the cellular and molecular responses to HKM is needed.

The ulcers treated with HKM in this case series showed a profound positive response during treatment, producing an overall 66.5% surface area reduction by week 5. After that, the size of these ulcers did not decrease significantly with continued HKM applications. A possible explanation of this effect is that these VLUs were more hard-to-heal compared to those in the smaller sized VLU group, and had a much higher incidence (85.71%) of popliteal vein reflux, a well-established and largely incurable factor for ongoing venous ulceration. Another factor that may have contributed to this finding could be the exhaustion of local tissue resources, such as skin progenitor cells.[25,29] While epithelial stem cell exhaustion has been previously studied in pulmonary diseases,[30] similar concepts such as local cell senescence due to proliferative stresses are only just beginning to be studied in hard-to-heal wound healing.[31]

Despite the cessation of further size reduction, the initial effect of 66.5% surface area reduction is clinically significant. These very large VLUs usually do not respond despite the use of multiple treatment modalities, and the wound product armamentarium is notably deficient in large size products with reasonable pricing. Due to the cost-effectiveness of keratin and its sustainable sourcing, it is able to be offered at price levels which allow the treatment of these larger wounds, unlike many other products in this class. These very large VLUs had been present and treated for an average of 14.5 months, representing a significant cost in terms of both treatment and clinical time with no progress toward closure. By quickly reducing VLUs to a size where additional interventions may be indicated, HKM has a high potential clinical and economic value.

The effect of HKM application on the smaller sized VLU group (mean surface area 17.55cm^2) that were more recent was significant. While smaller than those in the very large VLU group, these ulcers were still relatively large compared to those reported by other investigators.[5,32] As with those VLUs in the very large group, these ulcers closed rapidly in the initial weeks of HKM treatment, but continued to complete closure with a very high healing rate (88.9%) at eight weeks. These wounds had previously been treated with no appreciable progress toward closure for an average of 3.4 months, yet achieved a high rate of complete healing with HKM treatment in less time. This demonstrates the potential value of HKM in reducing overall treatment time of VLUs. Furthermore, due to the durability of keratin matrices in the wound environment, fewer applications of the product may be necessary over the same time period as compared to other advanced wound care products, which can quickly dissolve into the wound and require weekly reapplication to maintain efficacy. This may further reduce the cost of treatment.

Confirmation of wound closure at various timepoints after treatment was not assessed in this initial investigative case series of HKM. Recurrence is a concern in the treatment of hard-to-heal wounds, and is often an assessment of the quality and efficacy of the treatment modality used. VLUs are particularly complex in this regard, as the wound aetiology involves pathophysiological factors, such as deep venous insufficiency. Patients that have not had or cannot have these factors treated are at risk of recurrence regardless of the wound care employed, and the evaluation of these factors was outside the scope of this study. However, one recent study evaluating the efficacy of HKM in hard-to-heal wounds included a 'healing confirmation visit' in which the patient returned for evaluation several weeks after wound closure. No

incidence of recurrence was reported, suggesting wound healing with HKM was durable at least in the short-term,[33] though further study is needed.

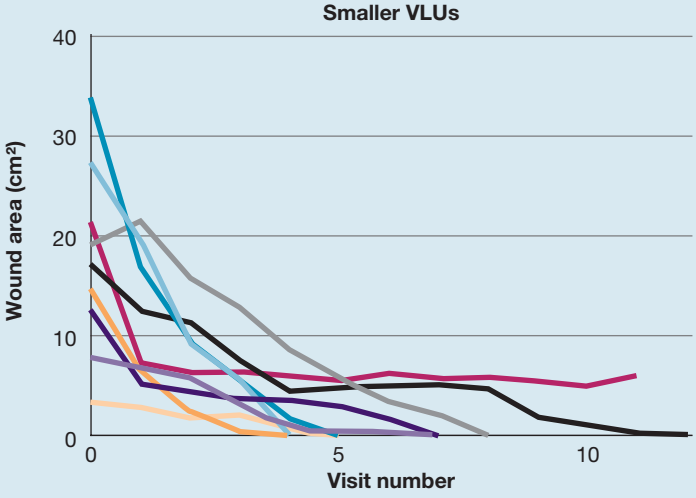
HKM produced an important and clinically beneficial effect by reducing the size of the VLUs and making them eligible for other treatments and wound care products, as well as split-thickness skin grafting applications, that would not be practical on a very large wound.

Though not directly quantified, it is possible HKM treatment improved patient QoL through wound size reduction by reducing wound maintenance complexity and offering evidence that the wound was able to reduce in size. Changes to patient QoL would be an interesting metric to quantify in future clinical studies. Another limitation of this case series is the lack of a control group for wounds not treated with HKM. The SoC treatment for VLUs is compression therapy plus endovenous treatment without an advanced wound care product or skin substitute. A retrospective analysis of 777 patients with VLUs treated with compression therapy observed that 42.2% of wounds with an average initial size of 9.8±22.1cm^2 healed in 12 weeks.[19] In the present work, 50% of wounds healed in this timeframe, with an average initial size of 155.6±172.2cm^2, showing a similar healing rate in much larger and more varied ulcers. This supports future study with greater controls, suggesting HKM is as effective or more effective than standard compression therapy.

The study of HKM in VLUs with a surface area >75cm^2 is being expanded by the authors, and will include a greater number of patients, to better understand its benefit in these larger wounds. This is important for future studies in order to collect real-world evidence relating to the treatment of these very large wounds. Many randomised controlled trials for advanced wound care products have strict inclusion criteria relating to target ulcer size—as small as 2–12cm^2 in one study [34]—and even single case studies of large wounds[35] are much smaller than the very large wounds reported here. This demonstrates a lack of evidence in the real-world scenarios of very large VLUs. Therefore, it is important that future randomised, controlled trials include these very large wounds to fully understand the efficacy of HKM in the closure of VLUs.

Finally, HKM may be effective in the treatment of other hard-to-heal wound types beyond VLUs. A recent case series showed up to 185% increase in healing rate in diabetic foot ulcers (DFUs) treated with HKM over the healing rate of those same wounds treated with SoC and collagen-based wound dressings.[36] Additionally, a recent clinical trial has also demonstrated high rates of wound healing in DFUs that was independent of whether HKM was reapplied weekly or left on for two weeks at a time.[33] That protocol reflects the methods used in this case series and is possible due to the durability of the crosslinked keratin protein found in HKM. Wounds were evaluated weekly and if the HKM was found to be intact, the same piece was left in place for another week. This sustained efficacy of a single application of the material represents clinical flexibility for the physician and patient, and further addresses the high cost of treating very large wounds with advanced wound care products.

Fig 3. Wound surface area reduction of nine smaller venous leg ulcers (VLUs) treated with human keratin matrix



Limitations

All patients were treated with HKM. As such, there was no randomisation applied to this study, nor was a control arm evaluated, which are limitations of this work. Although a real-world, all-comer patient population may be clinically relevant, the use of inclusion criteria and wound size limitations would have made it easier to compare the effects of HKM to other published data from more defined trials. Additionally, the comparison of the two groups may be limited because of the significant difference in the wound sizes. These are areas of consideration for future work to further elucidate the potential role of HKM in the treatment of VLUs.

Conclusion

In summary, we evaluated the effect of a novel HKM, in addition to SoC, on a group of very large hard-to-heal VLUs and a second group of smaller and more recent VLUs. There was significant size reduction in the very large VLU group in 4–5 weeks, and in the second VLU group by week 8, suggesting that HKM has a beneficial effect on VLU healing rates. Further investigation is warranted to address the small sample size of the present study, and a control arm may be included in future work to further demonstrate the effect of HKM. Furthermore, additional endpoints could be included in larger future studies, such as QoL assessment and incidence of recurrence, to further understand the clinical benefits of HKM. The results of this study show that HKM should be considered as an adjunct to SoC of hard-to-heal VLUs, and that HKM should also be investigated in other types of lower extremity wounds. JWC

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Reflective questions

- When would you consider using human keratin matrix (HKM) in the treatment of venous leg ulcers (VLUs)?
- What treatment options are currently available for large to very large VLUs?
- What is the potential role of keratin products in advanced wound care?
- What is the advantage of having a successful means of reducing large venous ulcer size?