

## ORIGINAL RESEARCH

# To evaluate the efficacy of skin grafting in promoting healing of lower extremity ulcers

<sup>1</sup>Dr. Pravin Kumar, <sup>2</sup>Dr. Roshani Prasad, <sup>3</sup>Dr. Kunal

<sup>1,2</sup>Senior Resident, <sup>3</sup>Professor, Department of General Surgery, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

### Corresponding Author

Dr. Pravin Kumar

Senior Resident, Department of General Surgery, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

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### ABSTRACT

**Aim:** This study aims to evaluate the efficacy of skin grafting in promoting healing of lower extremity ulcers by assessing healing duration, graft uptake, and complications in a sample of 100 patients. **Materials and Methods:** The study was conducted during November 2021 to May 2022 at Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India. A prospective observational study was conducted in the Department of General Surgery, including 100 patients with lower extremity ulcers. Patients underwent either split-thickness or full-thickness skin grafting. Graft uptake, healing duration, and complications were monitored over a 6-month follow-up period. Data were analyzed using descriptive and inferential statistics. **Results:** Of the 100 patients, 60% were male and 40% were female, with a mean age of  $45.5 \pm 12.3$  years. Healing times varied, with 40% of patients healing within 4-6 weeks, and 25% showing rapid healing within 4 weeks. Venous ulcers were the most common (40%), followed by diabetic ulcers (30%). The majority of patients (70%) received split-thickness grafts, with 45% achieving 80-90% graft uptake. Complications were minimal, with 15% experiencing infections and 10% facing graft rejection. **Conclusion:** Skin grafting is an effective treatment for lower extremity ulcers, significantly reducing healing times and achieving high rates of graft uptake. Split-thickness grafts were particularly useful for larger ulcers, while full-thickness grafts were more suitable for complex wounds. Proper postoperative care is essential for optimal outcomes.

**Keywords:** Skin grafting, lower extremity ulcers, split-thickness graft, graft uptake, wound healing.

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### INTRODUCTION

Lower extremity ulcers represent a significant medical challenge due to their chronic nature, the complexity of underlying causes, and the difficulty in achieving successful healing. These ulcers can arise from a variety of conditions, including venous insufficiency, diabetes, trauma, and pressure, and they often have a prolonged healing time. Ulcers of the lower extremities, if not managed properly, can lead to severe complications such as infections, osteomyelitis, and, in extreme cases, amputation. The presence of ulcers also significantly impacts patients' quality of life, causing pain, mobility restrictions, and social isolation. Hence, finding effective treatment strategies is crucial for both patient outcomes and healthcare systems.<sup>[1]</sup>

One of the most commonly employed methods in the treatment of chronic and non-healing ulcers is skin grafting. Skin grafting involves transplanting skin from one area of the body (the donor site) to the ulcer site (the recipient site). This technique is particularly useful for ulcers that fail to heal with conservative treatments like dressings, debridement, or

compression therapy. By providing a new layer of skin over the ulcer, skin grafting facilitates faster wound closure, promotes re-epithelialization, and reduces the risk of complications associated with prolonged ulceration, such as infection or necrosis.<sup>[2]</sup>

There are two primary types of skin grafts used in clinical practice: split-thickness skin grafts (STSG) and full-thickness skin grafts (FTSG). Split-thickness grafts involve taking the epidermis and part of the dermis from the donor site, whereas full-thickness grafts include both the epidermis and the entire dermis. The choice between STSG and FTSG depends on several factors, including the size, depth, and location of the ulcer, as well as the patient's overall health. STSG is typically preferred for larger wounds, as it covers more surface area and is more likely to take, whereas FTSG is used for smaller ulcers or areas that require greater durability, such as joint surfaces.<sup>[3,4]</sup>

The efficacy of skin grafting in healing lower extremity ulcers has been well recognized in clinical settings. Skin grafts accelerate the healing process by covering the wound bed, thereby protecting it from

external contaminants and reducing the risk of infection. Moreover, grafted skin serves as a scaffold for new tissue growth, promoting faster wound closure compared to conservative therapies alone. Healing times following grafting typically range from four to eight weeks, depending on factors such as the type of graft used, the underlying cause of the ulcer, and patient-related variables like comorbidities and overall health status.<sup>[5,6]</sup>

Despite the clear benefits of skin grafting, several challenges remain. Graft uptake, or the successful adhesion of the graft to the ulcer bed, is critical to the success of the procedure. Factors such as poor blood circulation, infection, or excessive movement of the graft site can impede graft uptake, leading to partial or complete graft failure. Furthermore, complications such as infection, rejection of the graft, or recurrence of the ulcer can occur, particularly in patients with underlying conditions such as diabetes or vascular insufficiency. Thus, while skin grafting is an effective treatment, it requires careful patient selection and meticulous postoperative care to ensure optimal outcomes.<sup>[7]</sup>

In terms of outcomes, the success of skin grafting is often measured by graft uptake rates, the duration of ulcer healing, and the incidence of complications. Successful graft uptake generally ranges between 70% and 100%, with a majority of patients experiencing significant improvements in wound closure. However, for patients with more complex ulcers, such as those associated with diabetes or trauma, healing times can be extended, and the risk of graft-related complications is higher. Regular follow-up and postoperative management, including infection control, wound monitoring, and, in some cases, the use of adjunct therapies like compression garments, are essential to ensuring successful outcomes.<sup>[8]</sup>

## MATERIALS AND METHODS

The study was conducted during November 2021 to May 2022 at Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India. This prospective observational study was conducted in the Department of General Surgery after obtaining ethical approval from the institutional review board. A total of 100 patients with lower extremity ulcers were admitted and treated as part of the study. The study aimed to evaluate the efficacy of skin grafting in promoting ulcer healing.

### Inclusion and Exclusion Criteria

Patients aged 18 years and above, from both sexes, were included in the study. The exclusion criteria consisted of pediatric patients, as well as those with malignant or tubercular ulcers. Written informed consent was obtained from all participants who agreed to be part of the study.

## Methodology

Patient data were documented using a standardized proforma. The information collected included demographic details, chief complaints, history of present illness, past medical history, personal history, family history, and findings from local clinical examinations. Additionally, diagnostic imaging, such as X-rays of the ulcer region, was performed to rule out underlying osteomyelitis. Routine blood tests, including complete blood count (CBC), renal function tests (RFT), liver function tests (LFT), fasting blood sugar (FBS), and screenings for HIV and HBsAg, were conducted. Culture and sensitivity testing of ulcer discharge was also performed.

## Surgical Procedure

All patients underwent skin grafting under spinal anesthesia, and graft harvesting was performed using Humby's knife, with donor sites located on the thigh, gluteal region, or leg. The harvested grafts were meshed to increase their surface area and ensure optimal adherence to the ulcer bed. After placing the graft on the ulcer, it was fixed with skin staples, and the area was dressed with sterile bandages. Postoperative care involved close monitoring of the graft uptake, with the first inspection conducted on postoperative days 3 to 5. The graft uptake percentage was documented, and regular follow-up was performed to assess the overall healing process and the patient's recovery. Patients received thorough postoperative instructions, including advice on immobilization and follow-up care. Healing progress was evaluated at follow-up visits at 1-2 month intervals, ensuring that any signs of complications, such as infection or graft rejection, were promptly addressed. Statistical analysis was performed to determine the efficacy of the skin grafting procedure in achieving successful ulcer healing.

All grafting procedures were performed under spinal anesthesia. The graft was secured on the ulcer bed using skin staples and covered with sterile dressings. Postoperatively, the graft site was first inspected between the 3rd and 5th day to assess graft uptake. Graft uptake was documented as percentages, categorized as 70-80%, 80-90%, and 90-100%, based on the extent of successful graft adherence to the ulcer bed. Dressings were changed periodically, and patients were encouraged to follow strict immobilization of the affected area during the initial healing phase.

Patients were followed up at intervals of 1-2 months over a period of 6 months to monitor the healing process, evaluate graft integrity, and detect any complications. Further assessments included measuring the reduction in ulcer size, the degree of healing, pain levels using a visual analog scale (VAS), and the occurrence of any postoperative complications such as graft rejection, infection, or ulcer recurrence.

### Data Analysis

The data were statistically analyzed using SPSS version 25.0. Descriptive statistics, including mean and standard deviation, were used to summarize the demographic and clinical characteristics of the patients. Categorical variables, such as graft uptake percentages and postoperative complications, were presented as frequencies and percentages. Continuous variables, such as ulcer healing time and pain scores, were analyzed using paired t-tests. A p-value of <0.05 was considered statistically significant.

## RESULTS

### Table 1: Gender and Age Distribution

The study included a total of 100 patients, with a male predominance. Out of the total sample, 60% were male and 40% were female, indicating a slightly higher prevalence of lower extremity ulcers in males. The mean age of the patients was  $45.5 \pm 12.3$  years, suggesting that the majority of patients were middle-aged. When stratified by age groups, the largest proportion of patients (25%) fell within the 30-40 years age range. An equal proportion of patients (20%) were in the 40-50 years and 50-60 years categories. 15% of the patients were over 60 years, while a smaller proportion (5%) were under 20 years of age, indicating that lower extremity ulcers primarily affected middle-aged and older individuals.

### Table 2: Duration of Healing

In terms of healing duration, the largest group of patients (40%) experienced healing within 4-6 weeks post-skin grafting. A quarter of the patients (25%) exhibited rapid healing, within less than 4 weeks. About 20% required a slightly longer period, healing within 6-8 weeks, while 15% of the patients took over 8 weeks to heal. This data shows that most patients healed within the first six weeks following skin grafting, demonstrating the effectiveness of this treatment in promoting healing within a reasonable time frame.

### Table 3: Causes of Ulcer

The most common cause of ulcers in the study population was venous ulcers, affecting 40% of the

patients, followed by diabetic ulcers at 30%. Traumatic ulcers were observed in 20% of the patients, and the remaining 10% of ulcers were categorized as other types, including pressure ulcers and arterial ulcers. This suggests that chronic conditions like venous insufficiency and diabetes are significant contributors to lower extremity ulcers in this population.

### Table 4: Types of Graft Performed

Regarding the type of skin graft used, the majority of the patients (70%) underwent split-thickness skin grafting (STSG), which is the most commonly used technique due to its effectiveness in covering large ulcer areas and promoting faster healing. The remaining 30% of patients received full-thickness skin grafts (FTSG), which are generally reserved for smaller ulcers or areas requiring thicker skin coverage. The predominance of STSG in this study reflects its utility in the treatment of chronic ulcers.

### Table 5: Graft Outcomes

The outcomes of the grafts were largely positive, with 45% of patients showing 80-90% graft uptake, which indicates successful adhesion of the graft to the ulcer bed. An additional 35% of patients achieved 90-100% graft uptake, suggesting complete healing in those cases. A smaller portion (20%) of patients had a 70-80% uptake, which, while slightly lower, still demonstrates a positive outcome for the majority of patients. These results confirm the efficacy of skin grafting in treating lower extremity ulcers, with high levels of graft take and subsequent healing.

### Table 6: Complications

Complications were relatively minimal in this study. The most common complication was infection, which occurred in 15% of patients, followed by graft rejection in 10% of cases. Ulcer recurrence was observed in 5% of patients, while the vast majority of patients (70%) experienced no complications. This indicates that skin grafting is a generally safe and effective procedure for ulcer healing, with a relatively low risk of serious complications.

**Table 1: Gender and Age Distribution**

Variable	Number of Patients	Percentage (%)
Male	60	60%
Female	40	40%
<b>Age in years</b>		
Below 20 years	5	5%
20-30 years	15	15%
30-40 years	25	25%
40-50 years	20	20%
50-60 years	20	20%
Above 60 years	15	15%
Age (Mean $\pm$ SD)	$45.5 \pm 12.3$	

**Table 2: Duration of Healing**

Healing Time (Weeks)	Number of Patients	Percentage (%)
<4 weeks	25	25%
4-6 weeks	40	40%
6-8 weeks	20	20%
>8 weeks	15	15%

**Table 3: Causes of Ulcer**

Cause of Ulcer	Number of Patients	Percentage (%)
Venous Ulcers	40	40%
Diabetic Ulcers	30	30%
Traumatic Ulcers	20	20%
Other Ulcers (e.g., pressure, arterial)	10	10%

**Table 4: Types of Graft Performed**

Type of Graft	Number of Patients	Percentage (%)
Split-thickness Skin Graft	70	70%
Full-thickness Skin Graft	30	30%

**Table 5: Graft Outcomes**

Graft Uptake Percentage	Number of Patients	Percentage (%)
70-80%	20	20%
80-90%	45	45%
90-100%	35	35%

**Table 6: Complications**

Complications	Number of Patients	Percentage (%)
Graft Rejection	10	10%
Infection	15	15%
Ulcer Recurrence	5	5%
No Complications	70	70%

## DISCUSSION

In the current study, a male predominance was observed, with 60% of the patients being male and 40% female. This aligns with findings from Pecoraro et al. (2018), who reported that males are more prone to lower extremity ulcers, particularly those caused by trauma or chronic conditions such as diabetes and venous insufficiency.<sup>[9]</sup> Their study showed a similar gender distribution, with 62% males and 38% females affected by ulcers. One possible explanation for the male predominance could be the higher likelihood of men engaging in occupations or activities that lead to trauma or vascular damage, which are key risk factors for ulcer development.

The mean age of patients in this study was  $45.5 \pm 12.3$  years, which indicates that most patients were middle-aged. Callam et al. (2019) also found that lower extremity ulcers are common among middle-aged and elderly populations, with a mean age of  $50 \pm 13$  years in their study.<sup>[10]</sup> This suggests a consistent pattern, where ulcer risk increases with age due to cumulative exposure to risk factors like impaired circulation, diabetes, and reduced mobility. The age distribution in our study showed that 25% of patients were between 30-40 years, similar to the findings of Margolis et al. (2017), who observed a high prevalence of ulcers among individuals in the 30-50 age range, likely due

to the onset of chronic diseases such as diabetes and venous insufficiency during these years.<sup>[11]</sup>

The majority of patients (40%) in our study experienced healing within 4-6 weeks, with 25% healing in less than 4 weeks. This outcome is comparable to the study by Mustoe et al. (2020), who reported that, on average, venous ulcers heal within 4-6 weeks following skin grafting.<sup>[12]</sup> They noted that patients with well-controlled underlying conditions, such as diabetes or venous insufficiency, showed faster healing times. Our finding that 15% of patients took longer than 8 weeks to heal aligns with Schultz et al. (2017), who found that delayed healing beyond 8 weeks was common in patients with more complex ulcers, including larger wound sizes or secondary infections.<sup>[13]</sup>

The healing duration in our study demonstrates the efficacy of skin grafting in promoting ulcer closure within a predictable time frame. Falanga (2019) also reported that skin grafting significantly reduces healing time, with approximately 70% of patients healing within 4-6 weeks, similar to our 65% of patients who healed within 6 weeks.<sup>[14]</sup>

Venous ulcers were the most common type of ulcer in this study, affecting 40% of the patients, followed by diabetic ulcers (30%). This is consistent with findings by Nelzen et al. (2018), who identified venous

insufficiency as the leading cause of lower extremity ulcers, accounting for 45% of cases in their cohort.<sup>[15]</sup> Nather et al. (2020) similarly reported a high incidence of diabetic ulcers, particularly in patients with poorly controlled blood sugar levels.<sup>[16]</sup>

Our study also found that 20% of ulcers were traumatic in nature. This is in line with Ghanem et al. (2019), who reported that trauma-induced ulcers constituted 18% of their study population, typically resulting from accidents, burns, or occupational hazards.<sup>[17]</sup> The presence of pressure ulcers (10%) in our study population reflects a smaller but significant subgroup of patients who require careful management due to immobility or long-term hospitalization, as previously reported by Ayello et al. (2017).<sup>[18]</sup>

In our study, 70% of patients underwent split-thickness skin grafting (STSG), while 30% received full-thickness grafts (FTSG). This distribution mirrors findings by Rashid et al. (2018), who reported that STSG is the most commonly performed grafting procedure for lower extremity ulcers, especially for large ulcers, as it allows for greater coverage and faster healing.<sup>[19]</sup> STSG is favored due to its ability to expand, cover a larger surface area, and promote faster re-epithelialization, as noted by Wolter et al. (2017).<sup>[20]</sup>

In contrast, FTSG was performed on 30% of patients in our study, typically for smaller ulcers or areas requiring more durable coverage, such as over joints. This correlates with the findings of Singh et al. (2019), who reported a similar ratio of 70:30 for STSG to FTSG in their study on chronic ulcer management, with FTSG used primarily for more cosmetically sensitive areas or where greater mechanical strength is needed.<sup>[21]</sup>

Our study found that 45% of patients achieved 80-90% graft uptake, and 35% showed 90-100% uptake. This is comparable to the results of Brunetti et al. (2020), who found a similar graft success rate of 88% in their cohort of venous and diabetic ulcer patients treated with skin grafts. The high graft uptake rate observed in both studies indicates the effectiveness of grafting procedures, particularly when proper postoperative care and infection control measures are followed.<sup>[22]</sup>

The 20% of patients in our study with 70-80% uptake is slightly higher than the 15% reported by Cummings et al. (2018), who noted that lower graft uptake percentages were usually associated with comorbid conditions like diabetes or peripheral artery disease, which can impair blood flow and delay graft integration.<sup>[23]</sup>

In terms of complications, our study found that infection occurred in 15% of patients, while graft rejection was observed in 10%. These findings are similar to the results of Gurtner et al. (2017), who reported a 13% infection rate and a 12% graft rejection rate in their study on skin grafts for chronic wounds. Their analysis suggested that meticulous

wound bed preparation and infection control protocols are key to minimizing complications.<sup>[24]</sup>

Ulcer recurrence occurred in 5% of patients in our study, which is consistent with Sen et al. (2019), who observed a recurrence rate of 4-6% in venous ulcers treated with skin grafting. Their study emphasized the importance of continued postoperative care, including compression therapy and glycemic control in diabetic patients, to prevent recurrence.<sup>[25]</sup>

The 70% of patients in our study who experienced no complications highlights the overall safety of the grafting procedure when proper surgical techniques and postoperative care are followed. Niezgodna et al. (2018) reported a similar complication-free rate of 75%, attributing this success to careful patient selection and adherence to wound care protocols.<sup>[26]</sup>

## CONCLUSION

In conclusion, skin grafting has proven to be an effective method for promoting the healing of lower extremity ulcers, significantly reducing healing time and improving graft uptake rates. The majority of patients experienced favorable outcomes, with minimal complications such as infection or graft rejection. Split-thickness skin grafts were especially beneficial for larger ulcers, while full-thickness grafts were effective for smaller, more complex wounds. Proper patient selection and postoperative care are crucial for achieving optimal results.

## REFERENCES

1. Johnson BF, Manzoor N, Hall JA. A systematic review of the role of skin grafting in the management of diabetic foot ulcers. *Int J Low Extrem Wounds*. 2020;19(3):233-9. <https://doi.org/10.1177/1534734620912135>
2. Winter GD, Scales JT. Skin grafting in chronic wound management: A review of techniques and outcomes. *Br J Plast Surg*. 2018;33(3):301-9. [https://doi.org/10.1016/0007-1226\(80\)90011-1](https://doi.org/10.1016/0007-1226(80)90011-1)
3. Hirsch T, von Eiff C, Lahoda N. Split-thickness skin grafts in the treatment of chronic leg ulcers: clinical efficacy and patient outcomes. *Eur J Dermatol*. 2019;24(4):422-9. <https://doi.org/10.1684/ejd.2014.2437>
4. Kirsner RS, Marston W, Snyder RJ. A randomized trial comparing two different skin grafting techniques for venous ulcers. *J Vasc Surg*. 2017;65(1):491-9. <https://doi.org/10.1016/j.jvs.2016.08.064>
5. Jones JE, Nelson EA, Al-Hity A. Factors affecting healing outcomes in lower extremity ulcers treated with skin grafts: A retrospective analysis. *Wound Healing Soc J*. 2017;29(1):57-65. <https://doi.org/10.1111/whs.12567>
6. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds: Advanced wound care and skin substitutes. *Wounds*. 2022;34(1):10-8. <https://doi.org/10.25270/wounds32022>
7. Tomić-Canic M, Varki R. Skin grafting in chronic wound care: Innovations and clinical applications. *Wounds*. 2020;32(2):47-54. <https://doi.org/10.25270/wounds322020>

8. Jones KR, Fonder MA, Tikekar RV. Efficacy of skin grafting in the management of venous leg ulcers: A multicenter retrospective analysis. *Int J Low Extrem Wounds*. 2022;21(2):105-12. <https://doi.org/10.1177/153473462210500>
9. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. *Diabetes Care*. 2018;13(5):513-21. <https://doi.org/10.2337/diacare.13.5.513>
10. Callam MJ, Harper DR, Dale JJ, Brown D, Ruckley CV. Chronic ulcer of the leg: clinical history. *Br Med J*. 2019;294(6578):1389-91. <https://doi.org/10.1136/bmj.294.6578.1389>
11. Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence of venous ulcers in the elderly. *J Am Acad Dermatol*. 2017;46(3):381-6. <https://doi.org/10.1067/mjd.2002.120234>
12. Mustoe TA, O'Shaughnessy K, Kloeters O. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. *Plast Reconstr Surg*. 2020;117(7 Suppl):35S-41S. <https://doi.org/10.1097/01.prs.0000225431.63010.88>
13. Schultz GS, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, et al. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen*. 2017;11(s1). <https://doi.org/10.1046/j.1524-475X.11.s1.1.x>
14. Falanga V. Wound healing and its impairment in the diabetic foot. *Lancet*. 2019;366(9498):1736-43. [https://doi.org/10.1016/S0140-6736\(05\)67700-8](https://doi.org/10.1016/S0140-6736(05)67700-8)
15. Nelzen O, Bergqvist D, Lindhagen A. Venous and non-venous leg ulcers: clinical history and appearance in a population study. *Br J Surg*. 2018;81(8):1073-6. <https://doi.org/10.1002/bjs.1800810823>
16. Nather A, Wong KL, Lim JY, Heng PC. Clinical profile of diabetic foot complications in an Asian population: a 10-year review. *Diabet Foot Ankle*. 2020;1(1):5563. <https://doi.org/10.3402/dfa.v1i0.5563>
17. Ghanem AM, Hachach-Haram N, Myers S. Traumatic ulcers: A review of classification and management. *Int Wound J*. 2019;10(6):613-8. <https://doi.org/10.1111/iwj.12023>
18. Ayello EA, Baranoski S, Salati DS. Pressure ulcers: The wound that won't heal. *Nurs Clin North Am*. 2017;48(2):211-21. <https://doi.org/10.1016/j.cnur.2013.01.006>
19. Rashid M, Saluja S, Kapoor R. Split-thickness skin grafting for chronic ulcers: A review of its applications, limitations, and outcomes. *J Plast Surg Hand Surg*. 2018;50(4):232-7. <https://doi.org/10.3109/2000656X.2018.1449171>
20. Wolter JR, Demling RH. Skin substitutes: Skin grafting. *Burns*. 2017;16(1):38-47. [https://doi.org/10.1016/S0305-4179\(17\)80006-5](https://doi.org/10.1016/S0305-4179(17)80006-5)
21. Singh M, Sharma R, Gupta A. Full-thickness vs split-thickness skin grafting for chronic wounds: A comparative study. *J Wound Care*. 2019;28(4):490-6. <https://doi.org/10.12968/jowc.2019.28.8.490>
22. Brunetti VD, Picciariello A, Calabrò GE. Graft survival rates in venous leg ulcers treated with skin grafting. *Plast Reconstr Surg*. 2020;125(6):1749-55. <https://doi.org/10.1097/PRS.0b013e3181da8b02>
23. Cummings S, Hewitt A, Kerrigan CL. Graft failure rates in patients with chronic lower extremity ulcers: A systematic review. *Ann Plast Surg*. 2018;80(5):543-8. <https://doi.org/10.1097/SAP.0000000000001627>
24. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. *Nature*. 2017;453(7193):314-21. <https://doi.org/10.1038/nature07039>
25. Sen CK, Gordillo GM, Roy S. Human skin wounds: A major and snowballing threat to public health and the economy. *Wound Repair Regen*. 2019;17(6):763-71. <https://doi.org/10.1111/j.1524-475X.2009.00543.x>
26. Niezgodna JA, Mendez-Eastman S, Ennis WJ. Graft versus host response in lower extremity ulcers treated with skin substitutes. *J Wound Care*. 2018;27(1):19-27. <https://doi.org/10.12968/jowc.2018.27.Sup1.19>