KIEŁT, Weronika, KOZŁOWSKA, Julia, BRONIEC, Gabriela, WAJDOWICZ, Barbara, KUDŁA, Aleksandra, CZAPIEWSKA, Rozalia, DZIEWULSKA, Aleksandra, WRÓBEL, Aleksandra, PACEK, Laura and KOWALSKA, Klaudia. Composite skin substitutes, 3D skin bioprinting and the "BioMask" concept in regenerating skin defects - review. Journal of Education, Health and Sport. 2024;67:55096. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.67.55096
https://apcz.umk.pl/JEHS/article/view/55096

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 11.08.2024. Revised: 20.08.2024. Accepted: 12.09.2024. Published: 14.09.2024.

Composite skin substitutes, 3D skin bioprinting and the "BioMask" concept in regenerating skin defects - review

Weronika Kiełt (WK)
Medical University of Lublin, located at Aleje Racławickie 1, 20-059 Lublin, Poland
ORCID 0000-0002-1933-6271
https://orcid.org/0000-0002-1933-6271
E-mail: weronika.kielt@gmail.com

Julia Kozłowska (JK)
Medical University of Lublin, located at Aleje Racławickie 1, 20-059 Lublin, Poland
ORCID 0000-0002-6161-970X
https://orcid.org/0000-0002-6161-970X
E-mail: kozlowskajulia14@gmail.com

Gabriela Broniec (GB)
Non-public Healthcare Facility, Neodent Dental Clinic, located at 15 Wallenroda St., 20-607 Lublin, Poland
ORCID 0009-0006-6615-3677
https://orcid.org/0009-0006-6615-3677
E-mail: gaba9809@o2.pl

Barbara Wajdowicz (BW)
Non-public Healthcare Facility, Em-Dent Dental Clinic, located at 11 Weteranów St., 20-038 Lublin, Poland
ORCID 0009-0006-1754-6124
https://orcid.org/0009-0006-1754-6124
E-mail: baswaj2@gmail.com

Aleksandra Kudła (AK)
Medical University of Gdansk, located at 3a Marii Skłodowskiej-Curie St., 80-210 Gdańsk, Poland
ORCID 0009-0005-8734-8310
https://orcid.org/0009-0005-8734-8310
E-mail: k.aleksandra.xoxo@gmail.com

Rozalia Czapiewska (RC)
Medical University of Gdansk, located at 3a Marii Skłodowskiej-Curie St., 80-210 Gdańsk, Poland
ORCID 0009-0002-8198-471X
https://orcid.org/0009-0002-8198-471X
E-mail: rozalia.czapiewska@tlen.pl

Aleksandra Dziewulska (AD)
Non-public Healthcare Facility, Lekarze Specjalisci LLC, 7 Topolowa St., 20-352 Lublin, Poland
ORCID 0000-0001-6405-409X
https://orcid.org/0000-0001-6405-409X
E-mail: aleksandradziewulska01@wp.pl

Aleksandra Wróbel (AW)
Chair and Department of Public Health, Medical University of Lublin, 1 Chodźki St., 20-093 Lublin, Poland
ORCID 0009-0007-6104-3804
https://orcid.org/0009-0007-6104-3804
E-mail: aawrobel.98@gmail.com

Laura Pacek (LP)
Non-public Healthcare Facility, Lekarze Specjalisci LLC, 7 Topolowa St., 20-352 Lublin, Poland
ORCiD 0000-0001-6069-7653
https://orcid.org/0000-0001-6069-7653
E-mail: paceklaura@gmail.com

Klaudia Kowalska (KK)
Łukasz Bańczyk Specialist Dental Practice, 166 Jana Kilińskiego St., 42-218 Częstochowa, Poland
ORCID 0009-0001-5240-7983
https://orcid.org/0009-0001-5240-7983
E-mail: kowalska.dent@gmail.com

Abstract

The treatment of skin trauma, especially facial skin trauma, is a major challenge due to its complex structure, the presence of appendages, color, texture, and the large area to be reconstructed in extensive trauma. “The gold standard” for treating trauma is autologous intermediate thickness skin grafting. An alternative solution is the usage of bioengineered skin substitutes. Tissue engineering is intended to provide patients with better treatment options and more effective pain reduction. Unique skin lesions are those related to the face. To fulfill the need to improve the results of facial skin reconstruction, the “Biomask” concept was introduced for the treatment of facial wounds.

The purpose of this review is to analyze composite dermal-epidermal substitutes already on the market for clinical use, as well as briefly discussing materials in the testing phase, focusing on 3D skin bioprinting and facial trauma regeneration using “BioMask”.

PubMed and Google Scholar databases were searched for relevant sources. Search terms included “skin substitutes”, “synthetic skin substitutes”, “bioengineered skin”, “composite skin substitutes” and additionally each analyzed unit of composite skin substitutes was searched.

Bioengineered skin substitutes effectively fulfill the role of dressings during the reconstruction of skin injuries. The development of 3D skin bioprinting is enabling the

increasing and effective use of these materials. The high requirements in the treatment of facial skin injuries are the trigger for the development of new materials such as "BioMask". The synergy of new technologies makes it possible to create improved methods of wound dressing and reconstruction of skin defects.

Keywords: skin substitutes; bioengineered skin; composite skin substitutes; 3D skin substitute; BioMask

Introduction

The skin is the largest human organ that acts as a barrier between the body and the environment. It protects against external factors such as chemical, physical and biological agents, microorganisms, UV radiation. It participates in temperature regulation, gas exchange and prevents dehydration. It has mechanoreceptors, thermoreceptors and nociceptors. It consists of the epidermis, dermis and subcutaneous tissue.

Causes of skin loss include thermal injury, acute trauma, surgery, genetic diseases or chronic wounds. Wounds can be divided into epidermal, superficial partial-thickness, deep partial-thickness and full-thickness as the depth of injury increases.

Wound treatment with grafts includes autograft, allograft, xenograft (a transplant from an organism of another species, usually from porcine skin), and the use of amnion (1). "The gold standard" for treating trauma is autologous intermediate thickness skin grafting. It involves extracting the epidermis with the superficial part of the dermis from the donor site and then applying the graft to the wound. The graft donor site heals as a superficial wound due to migration of keratinocytes. The advantage of autografting is that there is no risk of rejection. However, a key drawback of autologous tissue grafting is donor site morbidity. An allograft is a human graft derived from a cadaver used to temporarily cover a wound. It can be fresh or frozen. It provides permanent coverage in patients with extensive burns for the first few weeks, when the immune response is pathologically suppressed. After vascularization of the allograft occurs, the highly immunogenic epithelial cells trigger a host immune response and are rejected, usually three to four weeks after transplantation (2). Allograft can be obtained from non-profit skin banks as well as commercially, such as Karoskin. The advantages are the natural porosity of the skin, an intact basement membrane and protection of the subcutaneous

tissue. On the other hand, it is associated with the risk of transmission of infectious diseases and the high cost of the procedure (3). Amnion has been used as a wound treatment for burns for about 100 years. It is rich in collagen and growth factors that promote healing, improve wound closure and reduce scar formation. It is characterized by the absence of immune markers, antimicrobial and pain-reducing properties (4). It is effective in treating burns, including facial burns (5,6).

An alternative solution is the usage of bioengineered skin substitutes. Tissue engineering is intended to provide patients with better treatment options and more effective pain reduction. Compared to traditional treatment methods, tissue engineering technology provides a new approach to treating skin injuries. There are many classifications of skin replacement products. They can be divided according to anatomical structure (epidermal, dermal, dermo-epidermal), the duration of coverage (temporary, semi-permanent, permanent), and type of biomaterial (biological: autologous, allogeneic, xenogeneic; synthetic: biodegradable, non-biodegradable) (2,7). Dermo-epidermal (composites) skin substitutes are composed of a layer of epidermis and dermis resembling normal skin in histological structure. They are the most advanced of all types of artificial grafts.

The basic requirements for bioengineered skin are safety, effectiveness and being convenient in application. Skin substitutes also share common characteristics. They are required to be a semi-permeable membrane that provides a barrier against pathogens as well as allowing gas exchange and drainage of excess secreted fluid. They should demonstrate free adhesion. It is crucial that they be non-toxic, exhibit a lack of immunogenicity, do not induce inflammation and do not cause allergic reactions. They should have appropriate mechanical qualities, such as biodegradability and elasticity (8). Despite remarkable advances in skin substitutes, commercially available materials have limitations such as abnormal scarring, lack of integration, poor mechanical integrity, fragility and immune rejection (9). Reduced and long vascularization increases the risk of graft failure, so a pre-vascularization process seems necessary to increase the effectiveness of the skin substitute (10). The presence of a capillary network in the skin substitute guarantees the formation of a functional anastomosis with the host vasculature within 4 days. In contrast, de novo vascularization of sterile constructs by the host vascular system requires at least 14 days, depending on the size of the implanted tissue (11).

Unique skin lesions are those related to the face. The face is the most important recognizable feature of a person. Disfigurement of the face because of trauma, tumor removal, congenital anomalies, or chronic diseases requires a complex approach due to functional restoration as well as the patient's aesthetic needs. Moreover, varying facial contours and constant facial movement limit the use of skin substitutes. To fulfill the need to improve the results of facial skin reconstruction, the “Biomask” concept was introduced for the treatment of facial wounds. (12).

The purpose of this review is to analyze composite dermal-epidermal substitutes already on the market for clinical use, as well as briefly discussing materials in the testing phase, focusing on 3D skin bioprinting and facial trauma regeneration using “BioMask”.

Material and methods

PubMed and Google Scholar databases were searched for relevant sources. Search terms included “skin substitutes”, “synthetic skin substitutes”, “bioengineered skin”, “composite skin substitutes”. Additionally, each unit was searched for relevant sources using the terms “Apligraf”, “OrCel”, “PolyActive”, “TissueTech Autograft System”, “StrataGraft”, “PermaDerm“, “3D skin”, “3D bioprinting”, “BioMask”. The most relevant published studies were selected and used in the current review.

Apligraf

Apligraf is a xenogeneic material composed of bovine type I collagen and human keratinocytes and fibroblasts from infant cells. It is available in the form of a 44cm^2 disk. It is the first allogeneic material approved by the FDA for the treatment of hard-to-heal venous ulcers and wounds in diabetic foot syndrome. Its effect is to transition from a chronic, non-healing ulcer to a healing state resembling an acute, healing wound (13). It is used as a temporary bioactive dressing due to its cell life of up to about 6 weeks (14). Sabolinski et al. conducted a comparative analysis of the effectiveness of wound treatment with bilayered living cellular construct (BLCC; Apligraf) and a fetal bovine collagen dressing (FBCD; PriMatrix) in pressure injuries based on the records of 1352 patients. Patients treated with BLCC were 66% more likely to heal, and healing time was about 2 months shorter compared to FBCD. Healing was more favorable with BLCC than FBCD at 4 weeks (13% vs. 7%), 8 (29% vs. 17%), 12 (42% vs. 27%), 24 (64% vs. 45%) and 36 (73% vs. 56%) (15). Eudy et al. presented a case of using Apligraf as a treatment for full-thickness skin injuries in a 3-year-

old girl (16). Kirsner et al. compared the effectiveness of Apligraf (BLCC) and EpiFix (dHACM) in treating diabetic foot ulcers. They evaluated the outcomes of 218 patients out of 226 treated for diabetic foot syndrome in 2014 at 99 centers. Inclusion criteria included ulcer size of 1-25cm^2, ulcer duration ≤52 weeks and ulcer area reduction of ≤20% in the 14 days prior to initial treatment with BLCC or dHACM. The percentage of healed wounds was higher for BLCC than dHACM at week 12 (48% vs. 28%) and week 24 (72% vs. 47%) (17). On the other hand, Glat et al. comparing AmnioBand (dHACA) and Apligraf showed greater efficacy of dHACA in the treatment of diabetic foot wounds on a group of 60 patients. The percentage of wounds healed at the end of the study (12 weeks) was 90% in the dHACA group compared to 40% after using Apligraf (18). Towler et al. compared a bioengineered skin graft substitute (Apligraf) with a living, cryopreserved, human skin allograft (TheraSkin). Higher healing rates were observed in the group treated with TheraSkin at both 12 weeks (93.3% vs. 75.0%) and 20 weeks (93.3% vs. 83.3%), but these differences in healing rates were not statistically significant (19).

OrCel

OrCel is a xenogeneic material based on bovine type I collagen enriched with cultured allogeneic keratinocytes and fibroblasts derived from the foreskin of a newborn. Its effect is comparable to Apligraf. It acts as a temporary dressing, absorbs within 7-14 days and 14-21 days after application no cellular DNA of the preparation is found in the wound (2). It is used to treat burns and also to cover wounds and donor sites created after surgical release of hand contractures (20).

PolyActiv

PolyActiv is a synthetic material consisting of soft PEO (polyethylene oxide terephthalate) and hard PBT (polybuthylene terephthalate), which form a porous matrix containing autologous cultured keratinocytes and fibroblasts. By using autologous rather than allogeneic cells, there is no risk of immune rejection or transmission of infectious agents. As a synthetic skin component, it is not biodegradable, which rules it out as a permanent skin substitute. Can be used as a biologically active dressing providing growth factors to accelerate wound healing (2). It is also used in bone and periosteum replacements (21) or dental implants (22). On the other hand, the material is increasingly being used to create membranes for separating CO2 emitted by industry. which is one way to combat climate change. (23–25).

TissueTech

The TissueTech Autograft System consists of two separate materials. The dermis substitute is Hyalograft 3D and the epidermis substitute is Laserskin. Autologous fibroblasts and keratinocytes grow on micro-perforated hyaluronic acid membranes. The material allows closure of wounds larger than $5cm^2$ in 85% of cases with a low recurrence rate (26). The material is used to treat ulcers, including diabetic foot ulcers (27). It is also effective in preventing depression or neck scars after parotid surgery (28).

StrataGraft

StrataGraft consists of allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat. It is a skin substitute produced in vitro by the organotypic culture of NIKS keratinocytes (29). Bioengineered NIKS-based skin substitutes have been compared with allografts from cadavers in a phase I/IIa clinical trial as a temporary dressing in full-thickness complex skin lesions prior to autografting. Host immune tolerance and the ability to prepare skin defects before transplantation were comparable in both materials (30). A similar study was conducted by Centanni et al. covering one half of patients' wounds with StrataGraft and the other half with an allograft from a bank cadaver. The morphology of the NIKS keratinocyte-based epidermis was indistinguishable from that of the prepared normal human epidermal keratinocytes tissue. There were also no statistically significant differences in immune response between StrataGraft and cadaveric allografts (31). StrataGraft is well tolerated and may be a safe alternative in patients with deep partial-thickness thermal burns (32). Gibson et al. conducted a phase 3, open-label, controlled, randomized, multicenter trial evaluating the efficacy and safety of StrataGraft construct in patients with deep partial-thickness thermal burns. They concluded that using this material after 3 months of treatment, permanent wound closure was achieved at the StrataGraft treatment site without the need for autografting in 83,1% of patients (33).

Permaderm

PermaDerm is a material based on the patient's own skin cells for the treatment of severe skin burns. It consists of autologous fibrocytes and keratinocytes cultured on collagen medium (34). A small patch of full-thickness skin is taken from the patient, the cells are isolated and then cultured in medium to multiply. Afterwards, they are combined with a substrate based on

biomedical polymer of collagen to form living skin substitute that contains both epidermal and dermal components. This technology makes it possible to transplant a hundred times more skin in 30 days. The aim of this material is to create permanent skin tissue that will not be rejected by the host immune system.

Bioprinting of 3D skin

To overcome imperfections in skin tissue engineering such as pigmentation, lack of skin appendages and scarring, attention has turned to 3D printing technology. It enables the fabrication of multi-layered complex structures of functionally active skin. The process begins by examining the depth, length and other information about the injury site via a digital device. Based on this data, the 3D printer's execution tip can produce artificial skin tissue tailored to the injury site. The 3D printer can directly deposit the bio-ink layer by layer in the wound, enabling in-situ printing. This method of producing skin substitutes aims to reduce material manufacturing time, automation and standardization. This advance is very promising, especially in military and first aid indications (35).

Cubo et al. published a study of the automation and in vitro production of printed human skin containing dermal and epidermal components based on human plasma and fibroblasts and keratinocytes obtained from skin biopsies. (36). Using 3D printing, Wanga et al. constructed a bilayer scaffold with hydrogel of sodium alginate as the dermis and polylactic acid-hydroxy glycolic acid copolymer (PLGA) as the epidermis. The skin structure showed good physical and chemical fidelity, maintained wound moisture, increased collagen deposition and neovascularization, and did not cause inflammation (37). Similar study conducted Lian et. al fabricate designed bilayer skin using an extrusion-based bioprinter and a gelatin/sodium alginate/gelatin methacrylate hydrogel. Bioprinted skin accelerated wound healing, reduced wound contraction and scarring, and facilitated wound skin epithelialization. Also microvascularization in the dermis and dense keratinocytes in the epidermis of the bioprinted skin were observed (38).

Baltazar et al. described the fabrication of an implantable multilayered vascularized bioengineered skin graft using 3D bioprinting. The graft was created using one bio-ink containing human foreskin fibroblasts (FB), human endothelial cells (EC) derived from human endothelial colony-forming cells (HECFC) of umbilical cord blood and human placental pericytes (PC) suspended in rat tail type I collagen to form the dermis, and then

printed with a second bio-ink containing human foreskin keratinocytes (KC) to form the epidermis. Completed graft was implanted into the back of the mouse and after 4 weeks vascularization was achieved (39). Levin et al. examined an in situ 3D printing method for treating full-thickness wounds in rat and pig models. In all animals, the injuries healed within 4 weeks - wound shrinkage, mature epithelial recovery and hair restoration could be observed without any signs of inflammation or rejection (40).

Biomask

Facial injuries have long-term consequences for an individual's physical, mental and social well-being. These injuries are emotionally difficult to accept. There may be functional limitations, patients may develop post-traumatic stress disorder, and the scars that remain bother patients (41). As a result of the frequency and complexity of facial injuries and the difficulty of matching available skin substitutes, the "BioMask" concept was developed. The basis of this concept is scanning the patient's injured face and using 3D bioprinting technology. A team led by Col. Robert Hale at the US Army Institute of Surgical Research has developed a mask consisting of a neodermal matrix with epithelium grafts using wound vacuum-assisted closure (VAC) technology (12). Seol et al. developed “BioMask” which is a customized bioengineered skin substitute combined with a wound dressing layer that snugly fits onto the facial wounds. The use of three-dimensional (3D) bioprinting allowed the skin substitute to adhere tightly to facial contours, which overcome limitations of traditional skin substitute products that are designed as simple flat sheets. It is bioenginereed skin substitute consists of three layers; a porous polyurethane (PU) layer, a keratinocyte-laden hydrogel layer, and a fibroblast-laden hydrogel layer. BioMask has great potential to offer effective and rapid restoration of aesthetic and functional facial skin. (42).

Conclusion

Bioengineered skin substitutes effectively fulfill the role of dressings during the reconstruction of skin injuries, especially in large area injuries with a deficit of autologous donor sites. The development of 3D skin bioprinting is enabling the increasing and effective use of these materials. The high requirements in the treatment of facial skin injuries are the trigger for the development of new materials such as "BioMask". The synergy of new technologies makes it possible to create improved methods of wound dressing and reconstruction of skin defects.

Author's contribution:

Conceptualization: Weronika Kiełt and Barbara Wajdowicz

Methodology: Julia Kozłowska and Klaudia Kowalska

Software: Gabriela Broniec and Aleksandra Dziewulska

Check: Aleksandra Kudła and Laura Pacek

Formal analysis: Aleksandra Wróbel and Rozalia Czapiewska

Investigation: Weronika Kiełt and Aleksandra Dziewulska

Resources: Barbara Wajdowicz and Laura Pacek

Data curation: Julia Kozłowska and Gabriela Broniec

Writing - rough preparation: Weronika Kiełt and Julia Kozłowska

Writing - review and editing: Barbara Wajdowicz and Rozalia Czapiewska

Supervision: Klaudia Kowalska and Aleksandra Wróbel

Project administration: Aleksandra Kudła

All authors have read and agreed with the published version of the manuscript.

Funding statement: The study did not receive funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: The authors declare no conflicts of interest.

Acknowledgements: Not applicable.

References

1. Vig K, Chaudhari A, Tripathi S, Dixit S, Sahu R, Pillai S, i in. Advances in Skin Regeneration Using Tissue Engineering. Int J Mol Sci. 2017;18(4):789. doi: 10.3390/ijms18040789
2. Shevchenko RV, James SL, James SE. A review of tissue-engineered skin bioconstructs available for skin reconstruction. J R Soc Interface. 2010;7(43):229–58. doi: 10.1098/rsif.2009.0403
3. Shahrokhi S, Arno A, Jeschke MG. The use of dermal substitutes in burn surgery: Acute phase. Wound Repair Regen. 2014;22(1):14–22. doi: 10.1111/wrr.12119
4. Fetterolf DE, Snyder RJ. Scientific and clinical support for the use of dehydrated amniotic membrane in wound management. Wounds Compend Clin Res Pract. 2012;24(10):299–

307.

5. Tenenhaus M. The Use of Dehydrated Human Amnion/Chorion Membranes in the Treatment of Burns and Complex Wounds: Current and Future Applications. Ann Plast Surg. 2017;78(2):S11–3. DOI: 10.1097/SAP.0000000000000983
6. Bujang-Safawi E, Halim AS, Khoo TL, Dorai AA. Dried irradiated human amniotic membrane as a biological dressing for facial burns—A 7-year case series. Burns. 2010;36(6):876–82. DOI: 10.1016/j.burns.2009.07.001
7. Kumar P. Classification of skin substitutes. Burns. 2008;34(1):148–9. DOI: 10.1016/j.burns.2007.04.016
8. Sopata M, Sopata M, Zaporowska-Stachowiak I. The latest achievements and future of skin substitutes in chronic wound management. Leczenie Ran. 2017;14(2):33–8. DOI: dx.doi.org/10.15374/LR2017008
9. Varkey M, Ding J, Tredget E. Advances in Skin Substitutes—Potential of Tissue Engineered Skin for Facilitating Anti-Fibrotic Healing. J Funct Biomater. 2015;6(3):547–63. DOI: 10.3390/jfb6030547
10. Mazio C, Casale C, Imparato G, Urciuolo F, Attanasio C, De Gregorio M, i in. Pre-vascularized dermis model for fast and functional anastomosis with host vasculature. Biomaterials. 2019;192:159–70. DOI: 10.1016/j.biomaterials.2018.11.018
11. Tremblay PL, Hudon V, Berthod F, Germain L, Auger FA. Inosculation of Tissue-Engineered Capillaries with the Host's Vasculature in a Reconstructed Skin Transplanted on Mice. Am J Transplant. 2005;5(5):1002–10. DOI: 10.1111/j.1600-6143.2005.00790.x
12. Cheng X, Yoo JJ, Hale RG. Biomask for Skin Regeneration. Regen Med. 2014;9(3):245–8. DOI: 10.2217/rme.14.22
13. Stone RC, Stojadinovic O, Rosa AM, Ramirez HA, Badiavas E, Blumenberg M, i in. A bioengineered living cell construct activates an acute wound healing response in venous leg ulcers. Sci Transl Med. 2017;9(371):eaaf8611. DOI: 10.1126/scitranslmed.aaf8611
14. Griffiths M, Ojeh N, Livingstone R, Price R, Navsaria H. Survival of Apligraf in Acute Human Wounds. Tissue Eng. 2004;10(7–8):1180–95. DOI: 10.1089/ten.2004.10.1180
15. Sabolinski ML, Archambault T. Real-world data analysis of bilayered living cellular construct and fetal bovine collagen dressing treatment for pressure injuries: a comparative effectiveness study. J Comp Eff Res. 2024;13(4):e230109. DOI: 10.57264/cer-2023-0109
16. Eudy M, Eudy CL, Roy S. Apligraf as an Alternative to Skin Grafting in the Pediatric Population. Cureus. 2021;13(7):e16226. DOI: 10.7759/cureus.16226

17. Kirsner RS, Sabolinski ML, Parsons NB, Skornicki M, Marston WA. Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting. Wound Repair Regen. 2015;23(5):737–44. DOI: 10.1111/wrr.12332
18. Glat P, Orgill DP, Galiano R, Armstrong D, Serena T, DiDomenico LA, i in. Placental Membrane Provides Improved Healing Efficacy and Lower Cost Versus a Tissue-Engineered Human Skin in the Treatment of Diabetic Foot Ulcerations. Plast Reconstr Surg - Glob Open. 2019;7(8):e2371. DOI: 10.1097/GOX.0000000000002371
19. Towler MA, Rush EW, Richardson MK, Williams CL. Randomized, Prospective, Blinded-Enrollment, Head-To-Head Venous Leg Ulcer Healing Trial Comparing Living, Bioengineered Skin Graft Substitute (Apligraf) with Living, Cryopreserved, Human Skin Allograft (TheraSkin). Clin Podiatr Med Surg. 2018;35(3):357–65. DOI: 10.1016/j.cpm.2018.02.006
20. Stojic M, López V, Montero A, Quílez C, De Aranda Izuzquiza G, Vojtova L, i in. Skin tissue engineering. W: Biomaterials for Skin Repair and Regeneration . Elsevier; 2019. s. 59–99. doi: 10.3389/fsurg.2021.640879
21. Shi R, Chen D, Liu Q, Wu Y, Xu X, Zhang L, i in. Recent Advances in Synthetic Bioelastomers. Int J Mol Sci. 2009;10(10):4223–56. doi: 10.3390/ijms10104223
22. Radder AM, Leenders H, Van Blitterswijk CA. Bone-bonding behaviour of poly(ethylene oxide)-polybutylene terephthalate copolymer coatings and bulk implants: a comparative study. Biomaterials. 1995;16(7):507–13. DOI: 10.1016/0142-9612(95)91122-f
23. Brennecke F, Clodt J, Brinkmann T, Abetz V. Numerical and experimental investigation of the unexpected thickening effect during PolyActive ™ coating of TFC membranes. J Adv Manuf Process. 2024;6(2):e10175. DOI: 10.1002/amp2.10175
24. Karunakaran M, Shevate R, Kumar M, Peinemann KV. CO_2 -selective PEO–PBT (PolyActive™)/graphene oxide composite membranes. Chem Commun. 2015;51(75):14187–90. DOI: 10.1039/C5CC04999G
25. Schuldt K, Lillepärg J, Pohlmann J, Brinkmann T, Shishatskiy S. Permeance of Condensable Gases in Rubbery Polymer Membranes at High Pressure. Membranes. 2024;14(3):66. DOI: 10.3390/membranes14030066
26. Nilforoushzadeh MA, Amirkhani MA, Khodaverdi E, Razzaghi Z, Afzali H, Izadpanah S, i in. Tissue engineering in dermatology - from lab to market. Tissue Cell. 2022;74:101717. DOI: 10.1016/j.tice.2021.101717

27. Uccioli L. A Clinical Investigation on the Characteristics and Outcomes of Treating Chronic Lower Extremity Wounds using the TissueTech Autograft System. Int J Low Extrem Wounds. 2003;2(3):140–51. DOI: 10.1177/1534734603258480
28. Bianchini C, Pelucchi S, Galassi G, Mandrioli G, Ciorba A, Pastore A. Use of autologous dermal graft in the treatment of parotid surgery wounds for prevention of neck scars: preliminary results. J Otolaryngol - Head Neck Surg J Oto-Rhino-Laryngol Chir Cervico-Faciale. 2008;37(2):174–8.
29. Steiglitz BM, Maher RJ, Gratz KR, Schlosser S, Foster J, Pradhan-Bhatt S, i in. The viable bioengineered allogeneic cellularized construct StrataGraft® synthesizes, deposits, and organizes human extracellular matrix proteins into tissue type-specific structures and secretes soluble factors associated with wound healing. Burns. 2024;50(2):424–32. DOI: 10.1016/j.burns.2023.06.001
30. Schurr MJ, Foster KN, Lokuta MA, Rasmussen CA, Thomas-Virnig CL, Faucher LD, i in. Clinical Evaluation of NIKS-Based Bioengineered Skin Substitute Tissue in Complex Skin Defects: Phase I/IIa Clinical Trial Results. Adv Wound Care. 2012;1(2):95–103. DOI: 10.1089/wound.2011.0343
31. Centanni JM, Straseski JA, Wicks A, Hank JA, Rasmussen CA, Lokuta MA, i in. StrataGraft Skin Substitute Is Well-tolerated and Is Not Acutely Immunogenic in Patients With Traumatic Wounds: Results From a Prospective, Randomized, Controlled Dose Escalation Trial. Ann Surg. 2011;253(4):672–83. DOI: 10.1097/SLA.0b013e318210f3bd
32. Holmes Iv JH, Cancio LC, Carter JE, Faucher LD, Foster K, Hahn HD, i in. Pooled safety analysis of STRATA2011 and STRATA2016 clinical trials evaluating the use of StrataGraft® in patients with deep partial-thickness thermal burns. Burns. 2022;48(8):1816–24. DOI: 10.1016/j.burns.2022.07.013
33. Gibson ALF, Holmes JH, Shupp JW, Smith D, Joe V, Carson J, i in. A phase 3, open-label, controlled, randomized, multicenter trial evaluating the efficacy and safety of StrataGraft® construct in patients with deep partial-thickness thermal burns. Burns. 2021;47(5):1024–37. DOI: 10.1016/j.burns.2021.04.021
34. Debels H, Hamdi M, Abberton K, Morrison W. Dermal Matrices and Bioengineered Skin Substitutes: A Critical Review of Current Options. Plast Reconstr Surg Glob Open. 2015;3(1):e284. DOI: 10.1097/GOX.0000000000000219
35. Wei Q, An Y, Zhao X, Li M, Zhang J. Three-dimensional bioprinting of tissue-engineered skin: Biomaterials, fabrication techniques, challenging difficulties, and future directions:

A review. Int J Biol Macromol. 2024;266:131281. DOI: 10.1016/j.ijbiomac.2024.131281

36. Cubo N, Garcia M, Del Cañizo JF, Velasco D, Jorcano JL. 3D bioprinting of functional human skin: production and *in vivo* analysis. Biofabrication. 2016;9(1):015006. DOI: 10.1088/1758-5090/9/1/015006
37. Wang S, Xiong Y, Chen J, Ghanem A, Wang Y, Yang J, i in. Three Dimensional Printing Bilayer Membrane Scaffold Promotes Wound Healing. Front Bioeng Biotechnol. 2019;7:348. DOI: 10.3389/fbioe.2019.00348
38. Lian Q, Jiao T, Zhao T, Wang H, Yang S, Li D. 3D Bioprinted Skin Substitutes for Accelerated Wound Healing and Reduced Scar. J Bionic Eng. 2021;18(4):900–14. DOI: 10.1007/s42235-021-0053-8
39. Baltazar T, Merola J, Catarino C, Xie CB, Kirkiles-Smith NC, Lee V, i in. Three Dimensional Bioprinting of a Vascularized and Perfusable Skin Graft Using Human Keratinocytes, Fibroblasts, Pericytes, and Endothelial Cells. Tissue Eng Part A. 2020;26(5–6):227–38. DOI: 10.1089/ten.TEA.2019.0201
40. A. Levin A, A. Karalkin P, V. Koudan E, S. Senatov F, A. Parfenov V, A. Lvov V, i in. Commercial articulated collaborative in situ 3D bioprinter for skin wound healing. Int J Bioprinting. 2023;9(2):675. DOI: 10.18063/ijb.v9i2.675
41. McCarty JC, Herrera-Escobar JP, Gadkaree SK, El Moheb M, Kaafarani HMA, Velmahos G, i in. Long-Term Functional Outcomes of Trauma Patients With Facial Injuries. J Craniofac Surg. 2021;32(8):2584–7. DOI: 10.1097/SCS.0000000000007818
42. Seol YJ, Lee H, Copus JS, Kang HW, Cho DW, Atala A, i in. 3D bioprinted biomask for facial skin reconstruction. Bioprinting. 2018;10:e00028. DOI: 10.1016/j.bprint.2018.e00028