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Original Research Article

A STUDY ON ULTRATHIN SKIN GRAFT IN EARLY HEALING OF DIABETIC FOOT ULCERS

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Abstract

Diabetic foot ulcerations are historically difficult to treat despite advanced therapeutic modalities. There are numerous modalities described in the literature ranging from noninvasive topical wound care to more invasive surgical procedures such as primary closure, skin flaps, and skin grafting. While skin grafting provides faster time to closure with a single treatment compared to traditional topical wound treatments, the potential risks of donor site morbidity and poor wound healing unique to the diabetic state have been cited as a contraindication to its widespread use. In order to garner clarity on this issue, a literature review was undertaken on the use of split-thickness skin grafts on diabetic foot ulcers

Material and methods: The study was carried out in the Department of General Surgery, Vels medical college and hospital

Results: The interval between skin graft and complete wound healing in the seven successful cases ranged from 2 to 3 weeks. No recurrence of the ulcer was noted in those patients during the follow- up period, which ranged from 2 to 19 months.

Conclusions: On burn patients, split-thickness skin grafts have upwards of 100% success rates. There is minimal research available studying STSGs on diabetic patients

Key Words: Degenerating wounds, skin cancer, marjolin ulcer, chronic wounds

Introduction

There are many means of treating diabetic ulcerations. A conservative approach may entail regular debridement and dressing changes. Topical solutions such as saline, iodine, antimicrobial absorbent fiber sheets, and collagenase ointments may be included. For wounds with macerated edges it may be adventitious to apply gauze with diluted iodine to prevent further maceration. In hyperkeratotic, fibrotic, or dry necrotic tissue borders, it is preferred to apply hydrogels to hydrate the surrounding area. It is important to debride fibrotic wounds. This can be done mechanically by applying saline wet to dry dressings, and then after the dressing is changed, it removes fibrotic tissue with it. Some institutions employ the use of negative pressure wound therapy (NPWT) to stimulate granulation tissue and help remove fibrotic tissue formation [1]. Also, NPWT is good for draining wounds, along with calcium alginates which help absorption. Collagenases can be used to chemically debride wounds, and sharp debridement is a time tested method to remove non-viable tissue. There are also several bioengineered products that may facilitate wound closure once the wound is infection-free and has a primarily granular base. These materials help deliver fibroblasts to wounds and help serve as a scaffold for new tissue growth. Sometimes chronic wounds remain or the

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wound is deep with an irregular contour, and plastic surgery techniques must be employed such as skin grafts and flaps. More advanced flaps are ideal for plantar or weight-bearing wounds because they have more substance and contain their own blood or nerve supply which increases graft take. These are also indicated in wounds with avascular bases such as directly over tendons, or bone without periosteum. Advanced techniques are challenging at times and create a new wound or leave a large donor site deficit. This, on a diabetic patient with diminished healing properties and increased susceptibility to infection, is not ideal. Thus, if a flap is not possible, split-thickness skin grafts may be the better treatment option to close challenging wounds once a granular base is achieved. Split-thickness skin grafting (STSG) is a plastic surgery technique with documented use dating back to 3000 B.C. in India for traumatic facial wounds [2]. In a recent study with 17 ulcers of various etiology, we have shown that a skin grafting was improved by a combination of single-donor allogeneic platelet gel and fibrin glue [3]. However, as patients may express safety concerns on the use of allogeneic blood products, the current study evaluates for the first time to our knowledge the safety and efficacy of using autologous platelet gel, without fibrin glue, to enhance skin graft take for nonhealing diabetic lower extremity ulcers. The ultrathin graft was macroscopically identified by its transparent nature and punctuated minor bleed at the donor site . The graft was applied over the wound and fixed with multiple staples to ensure contact between the graft and the wound bed. The wound was dressed with petrolatum gauze, followed by applying a nonadherent soft pad with a soft cloth backing. An 8-layer plaster of Paris slab was used to immobilize the ankle joint. The donor site was covered with petrolatum gauze, and a tight compression dressing was applied. The wound dressing was first opened on postoperative day 5 and subsequently as required (usually every third day). Staples were removed after 10 to 14 days.Epidermal grafting for wound healing is not a new concept. Several case reports have indicated good wound healing outcomes; however, it is unknown whether the healing rate is comparable to that of STSG, a mainstay of treatment for wounds that cannot be closed primarily

Materials and Methods

Study Design:

The study was carried from Oct 2021 to July 2022 at Department of General Surgery, Vels medical college and hospital .Detailed history and complete physical examination was recorded. Informed written consent was taken from all the study subjects.

Results

This study included a total of 545 patients with DM, 137 patients with DFU, and 408 patients with DM without DFU with a response rate of 100%. Patients with DFU were older than patients without DFU with the mean (SD) age of 51.67 (1.11) years and 40.51 (0.59) years (P = 0.003), respectively. Slightly more than half of the cases and controls were men 71 (51.8%) and 213 (52.2%), respectively. The proportion of cases and controls who completed at least a secondary education was 63 (46.0%) and 233 (57.1%), respectively. A large proportion of the cases and controls lived in urban areas, 95 (69.3%) and 271 (66.4%), respectively. There were significantly more patients with DFU who belonged to the lower wealth index group than among the controls with DM 83 (60.6%) versus 99 (24.3%), respectively, with a P value of 0.000.Fibrinogen presents in the PRP polymerized into a fibrin gel, leading to the formation of platelet gel that adhered to the wound bed (Figure 1). No treatment associated adverse reactions were observed during the study. Most (8/9) of the skin grafts took well apart from one . The interval between skin graft and complete wound healing in the seven successful cases ranged from 2 to 3 weeks. No recurrence of the ulcer was noted in those patients during the follow- up period, which ranged from 2 to 19 months. Eight of nine ulcers

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had complete healing corresponding to a healing rate of 88%, the time to healing ranging from 2 to 3 weeks. A 65-year-old male, diabetic for 6 years, suffered from two non healing ulcers of left lower leg, measuring 15 × 10 cm2 and 5 × 7 cm2, respectively, due to stasis dermatitis for 6 months. The surrounding tissue was severely scarred (Figure 2(a)). Debridement was performed twice to remove the necrotic tissue. One week after the second debridement the wound bed was sprayed with autologous platelet gel (Figure 2(b)). A thin split-thickness skin graft was put on gel-covered bed (Figure 2(c)). Compression stocking (30– 40 mmHg at the ankle) was used once the wound healed. The postoperative course was uneventful, and the patient has durable wound coverage 10 months after skin graft (Figures 2(d) and 2(e)).

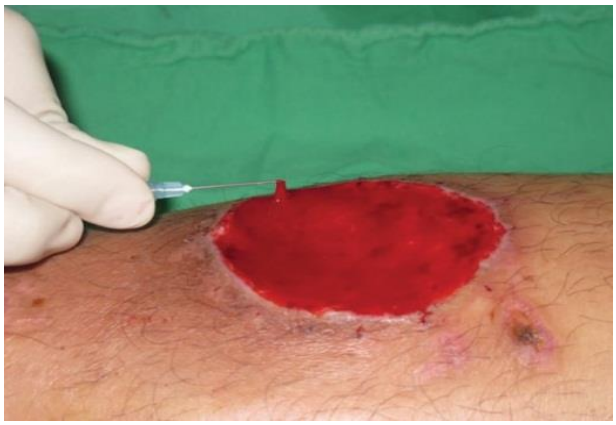
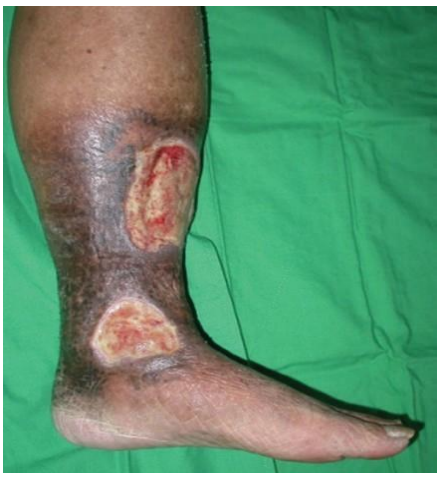
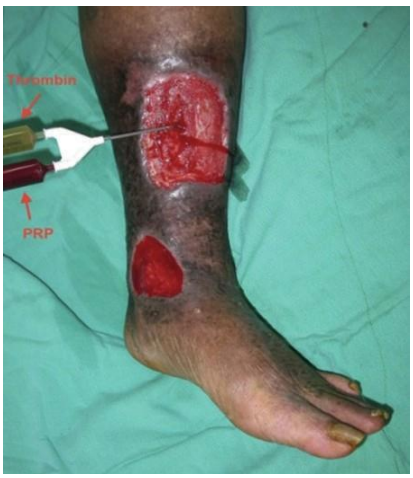


FIGURE 1: Platelet gel formed on the wound by conversion of fibrinogen into fibrin.



(a)



(b)

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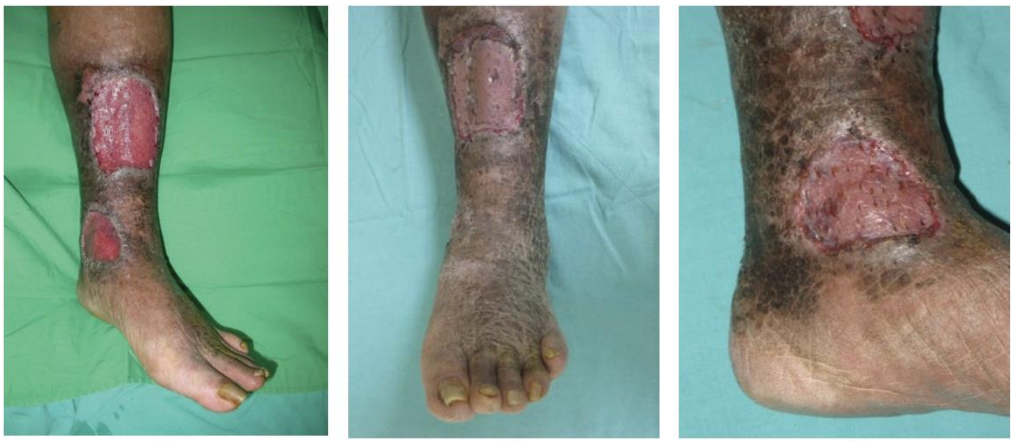

(c) (d) (e)

FIGURE 2: Two chronic ulcers (15 × 10 cm^2 and 5 × 7 cm^2) with surrounding scar tissues (a). After adequate debridement, the wound was sprayed with PRP and thrombin (b). Skin graft was applied on gel-covered wound bed (c). Durable wound coverage 10 months after skin graft (d, e).

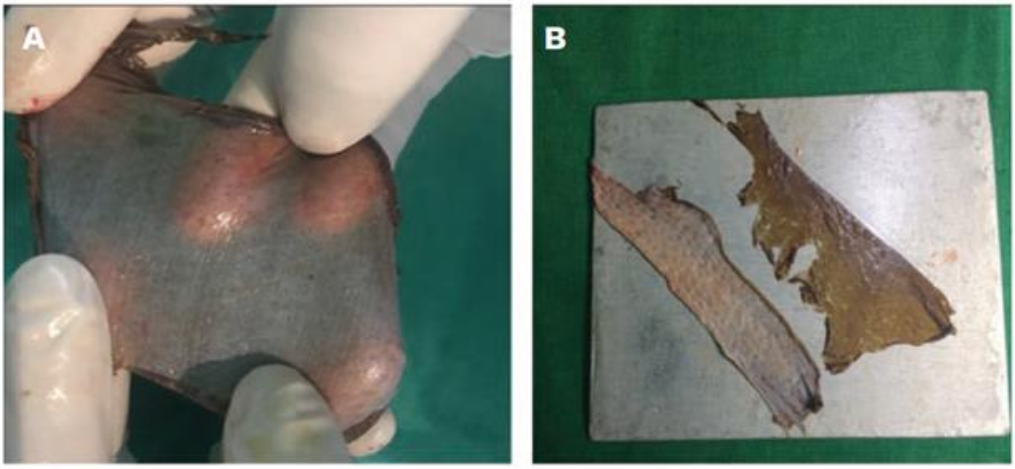

Figure 2 (A) Ultrathin skin graft, demonstrating its transparency. (B) Split-thickness skin graft.

Only a split-thickness skin graft was performed.Wet-to-dry compressive dressing was administered until the graft skin had taken . After the graft skin had taken, ointment and foam dressing were applied daily.

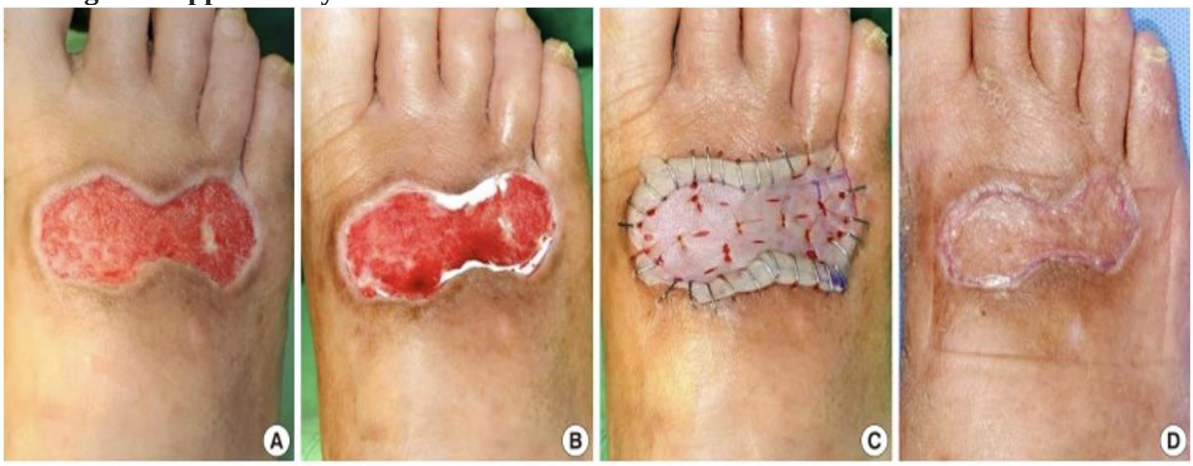

Figure 3: The patient stayed in the hospital for five weeks, and had healed completely at six weeks postoperation. The elasticity ratio was 0.75. (A) After debridement, the fascia was exposed. (B) Matriderm was applied to the fascia. (C) A split-thickness skin graft was performed. Immediate postoperative image. (D) Image of completely healed state at six weeks postoperation.

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Table 1: Sociodemographic characteristics of adult patients with diabetes mellitus.

Variable	Category	Cases* (n = 137)	Controls* (n = 408)	*P* value
Age, y	18–27	7 (5.1)	51 (12.5)	0.007
	28–37	28 (20.4)	113 (27.7)	
	38–47	33 (24.1)	97 (23.8)	
	>47	69 (50.4)	147 (36.0)	
Sex	Male	71 (51.8)	213 (52.2)	0.451
	Female	66 (48.2)	195 (47.8)	
Marital status	Married	82 (61.3)	237 (58.1)	0.269
	Single	53 (38.7)	171 (41.9)	
Educational status	No education	25 (18.2)	58 (14.2)	0.162
	Primary education	49 (37.8)	117 (28.7)	
	Secondary education	33 (24.1)	120 (29.4)	
	Tertiary and above	30 (21.9)	113 (27.7)	
Occupational status	Unemployed	53 (38.7)	163 (40)	0.266
	Employed	84 (61.3)	245 (60)	
Residence	Urban	95 (69.3)	271 (66.4)	0.301
	Rural	42 (30.7)	137 (33.6)	
Wealth index	High	28 (20.4)	225 (55.1)	0.000
	Medium	26 (19.0)	84 (20.6)	
	Low	83 (60.6)	99 (24.3)	

* Values are presented as n (%).

Table 2: Clinical characteristics of patients with diabetes mellitus (DM).

Variable	Category	Cases* (n = 137)	Controls* (n = 408)	*P* value
Regular follow-up	Yes	120 (87.6)	368 (90.2)	0.353
	No	17 (12.4)	40 (9.8)	
Diabetes medication currently	Oral anti-DM medication only	47 (34.3)	145 (35.5)	0.421
	Insulin only	53 (38.7)	118 (29.0)	
	Both insulin and oral anti-DM medication	37 (27.0)	145 (35.5)	
Ever had a diabetic foot ulcer	Yes	26 (19.0)	66 (16.2)	0.351
	No	111 (81.0)	342 (83.8)	
Duration of first-time diagnosis of DM	≤10	36 (26.3)	248 (60.8)	0.000
	>10	101 (73.7)	160 (39.2)	
Blood glucose	Well controlled	54 (39.4)	266 (65.2)	0.052
	Poor controlled	83 (60.6)	142 (34.8)	
Type of DM	Type 1	43 (31.4)	241 (59.1)	0.031
	Type 2	94 (68.6)	167 (40.9)	
Comorbidities and complications	Hypertension	64 (46.7)	83 (20.3)	0.004
	Renal problem	5 (3.6)	13 (3.2)	0.721
	Asthma	10 (7.3)	24 (5.9)	0.291
	Heart disease	3 (2.2)	5 (1.2)	0.421
	Peripheral vascular	30 (21.9)	84 (20.6)	0.398

	disease			
	Retinopathy	13 (9.5)	27 (6.6)	0.276
	Peripheral neuropathy	64 (46.7)	28 (6.9)	0.000
	Callus of the feet	52 (38.0)	132 (32.4)	0.251
	Foot deformity	24 (17.5)	60 (14.7)	0.342
Body mass index	Normal	19 (13.9)	191 (46.8)	0.000
	Overweight	41 (29.9)	154 (37.8)	
	Obese	77 (56.2)	63 (15.4)	
Foot skin texture	Smooth and moist	108 (78.8)	334 (81.9)	0.390
	Dry skin and/or cracked	39 (21.3)	74 (18.1)	
Specially prescribed diet	Yes	121 (88.3)	368 (90.2)	0.461
	No	16 (11.7)	40 (9.8)	

* Values are presented as n (%).

Table 3: Behavior characteristics of patients with diabetes mellitus (DM).

Variable	Category	Cases* (n = 137)	Controls* (n = 408)	*P* value
Adherence to medication	Yes	129 (94.9)	395 (96.8)	0.300
	No	7 (5.1)	13 (3.2)	
Adherence to meal	Yes	47 (34.3)	150 (36.8)	0.681
	No	90 (65.7)	258 (63.2)	
Adherence to physical exercise	Yes	27 (19.7)	98 (24.0)	0.348
	No	105 (76.6)	311 (76.2)	
Adherence to blood glucose measurement at home	Yes	49 (21.2)	124 (30.4)	0.243
	No	108 (78.8)	284 (69.6)	
Previous history of alcohol	Yes	38 (27.7)	105 (25.7)	0.431
	No	99 (62.3)	303 (74.3)	
Current history of alcohol	Yes	39 (28.5)	118 (28.9)	0.973
	No	98 ((71.5)	270 (71.1)	
Previous history of smoking	Yes	21 (15.3)	55 (13.5)	0.641
	No	116 (84.7)	353 (86.5)	
Current history of smoking	Yes	16 (11.7)	15 (9.7)	0.562
	No	121 (88.3)	140 (90.3)	
Previous history of khat chewing	Yes	21 (15.3)	50 (12.3)	0.356
	No	116 (84.7)	358 (87.7)	
Current history of khat chewing	Yes	6 (4.4)	42 (10.3)	0.040
	No	131 (95.6)	366 (89.7)	
Knowledge about DM	Good knowledge	71 (51.8)	211 (51.7)	0.264
	Poor knowledge	66 (48.2)	197 (48.3)	
Diabetic foot self-care practice	Good practice	22 (16.1)	253 (62.0)	0.000
	Poor practice	115 (83.9)	155 (38.0)	

* Values are presented as n (%).

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Discussion

Chronic non healing diabetic ulcers of lower extremity develop as a result of peripheral neuropathy, ischemia, and trauma [4]. The goal of treatment is to obtain expeditious wound closure. The standard treatments include adequate debridement, control of infection, re-vascularization of ischemic tissue, and avoidance of undue pressure on the wound. Live skin equivalents show some efficacy but have short shelf-life and are expensive [5]. GAM501 was found to help the treatment of non healing diabetic foot ulcer in 15 patients [6]. However, the ulcer size at base-line was small (1.2 to 4,86 cm^2), thereby questioning the clinical relevance for the cure of serious ulcer cases [7]. In a more recent study, complete closure incidence observed in GAM501 (ulcer size: 3.1 ± 1.7 cm^2) and formulated collagen alone (ulcer size: 2.9 ±1.1cm^2) was not statistically significant [7]. *In vivo* cellular-therapy-based PRP or growth factors can serve as an adjunct to those treatments. There is increasing evidence of the efficacy of PRP-based materials to enhance wound healing [8]. In the most common size of diabetic foot ulcers (<7.0 cm^2 in area and <2.0 cm^3 in volume), PRP gel-treated wounds are more likely to heal than control wounds [9]. The effect of split- thickness skin grafts versus a conservative wound dressing on the healing times of diabetic foot ulcers has also been studied. The results showed that a 100% skin graft take was recorded in 84% of the patients on the fifth postoperative day and in 62% on weeks 3 and 8, but 8% had ulcer recurrence and 4% a superficial infection within the following year [10]. Comparing to these previous studies, our results suggest that combining PRP and skin graft enhances the efficacy of treating chronic diabetic wounds by enhancing healing rate and decreasing recurrence rate. In conclusion, although the clinical safety and effective- ness data is derived from a pilot study rather than from a randomized controlled trial, it provides, together with our previous series [11], a confirmation of the advantages of platelet materials in skin graft procedure to treat large non healing diabetic ulcers of lower extremity. Patients with DM with DFU usually have a long past history of DM[12-18] Consistent with prior studies, the current study found that the duration of DM was a strongly associated with the presence of DFU. Patients who had been diagnosed with DM for more than 10 years were 2.3 times more likely to develop DFU than patients who have been diagnosed with DM for 10 years or less. The current study revealed that those with peripheral neuropathy were 3.9 times more likely to de- velop DFU than did patients with DM without neuropathy. An- other case-control study conducted in Addis Ababa, Ethiopia, also reported that patients with DM with peripheral neuropathy were more likely to experience. According to the Center for Disease Control's national report, approximately 34.2 million (1 in 10) Americans are affected by diabetes as of 2020. Along with the constant maintenance of glucose levels, diabetics with uncontrolled and high glucose levels can develop complications including major cardiovascular diseases, neuropathy, nephropathy, and lower extremity wounds. In 2016, there were 130,000 reported cases of lower extremity amputations by hospitals [19]. These lower extremity amputations are a result of foot ulcers which costs patients a total of $38.6 billion in the United States annually [20]. Diabetics with persistently high levels of blood glucose levels typically develop wound healing complications. Microcirculatory deficiencies in diabetics include a smaller capillary size, larger basement membrane, thickening of arterial vessel wall. These microcirculatory deficiencies described can result in improper circulation in the extremities of body. Nutrients, oxygen, and immune cells have difficulty passing through the membrane and vessel walls for exchange with surrounding cells. Neuropathy is also linked with microcirculatory defects in motor, sensory, and autonomic neurons. These can lead to an increased risk for trauma as well as infections due to high compressive forces from motor neuro deformation [21]. Diabetic foot ulcers are

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the most common form of chronic wounds found in diabetic patients with uncontrolled blood glucose levels. These ulcers typically have an increased secretion of matrix metallo proteinases (MMPs) and decrease in tissue inhibitors of metallo proteinases (TIMPs) which results in delayed healing. A large reduction in transforming growth factor (TGF-β1) – an important cytokine needed for immune cell activation – can also be observed in diabetic foot ulcers with increased infections [22]. Chronic foot ulcers are at a higher risk of infection and eventual amputation. Fish skin cellular/tissue based therapy (CTP) presents a portion of a solution to diabetic wound care for the lower extremity. These CTPs, like other tissue based therapies, can transition chronic wounds stalled at the inflammatory stage to the proliferation and remodeling stage for faster wound healing. Acellular fish skin CTPs, and other products high in collagen type I, have been reported to balance the enzymatic activities of MMPs by acting as an attachment site for breakdown of scaffold rather than developing host tissue and ECM components [23].

Conclusions

On burn patients, split-thickness skin grafts have upwards of 100% success rates. There is minimal research available studying STSGs on diabetic patients. The majority of litera- ture available on diabetic patients is retrospective reviews or case studies, which further limits this literature review. Also, the accessible articles do not mention the vascular status of the patients, which is often diminished in diabetics; this is an important factor in wound healing. Infection control, nutritional status, and pressure off -loading are pertinent to treating diabetic wounds and optimizing the recipient wound bed for STSG survival. Another aspect that was limited in the revises is the location of the wounds and graft application.

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