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A Clinicopathological Study on Split Thickness Skin Graft Uptake in Diabetics and Factors Affecting Graft Uptake

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Abstract

Introduction: Split thickness skin grafting is a preferred treatment for ulcers. Studies have shown the graft uptake and outcome to be poor in patients with diabetes and other comorbidities as compared to non-diabetics and diabetics without comorbidities.

Aim: This study aimed to assess the outcomes of STSG in diabetic patients in terms of the prevalence of comorbidities among diabetics undergoing Split Thickness Skin Graft and factors affecting graft uptake with incidence of graft failure on patient follow up to predict the outcome of STSG and aid in proper patient selection.

Methodology: This prospective descriptive study was conducted in 40 patients with >18 years of age with ulcers having healthy granulation tissue and no contraindication for split thickness skin grafting. All the patients underwent STSG for the management of ulcer after following standard criteria. Donor site in all patients was the thigh. Patients were followed up after 1 month and graft status noted and any residual ulcer size was measured. Eighty percent take of the skin graft was considered to be successful graft uptake.

Results: The mean graft uptake percentage in this study was 81.14 ± 30.434. In the average percentage uptake was 95.47 ± 5.615 and 31.76 ± 29.3 respectively in successful graft uptake group and graft failure group, average graft uptake percentage was. Among the graft success group 20 (64.5%) out of 31 patients had a positive swab culture while among the graft failure group 8 out of 9 patients had a positive swab culture with the most common organism being *Pseudomonas* species (50% and 55.6% respectively). There was statistically significant association of hypoalbuminemia with poor graft uptake.

Conclusion: The rate of graft failure in diabetics undergoing split thickness skin graft was 18.86% with hypoalbuminemia as a significant factor affecting graft uptake and *Pseudomonas* species being most common infection affecting graft uptake.

Keywords: Split thickness skin graft; Diabetes mellitus; Ulcers; Graft uptake

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Introduction

India is home to the second largest number (77 million) of adults with diabetes worldwide with adults aged 50 to 70 years having the highest diabetes prevalence among all age groups [1].

Diabetes mellitus is quite rampant in India with very few patients adhering to proper treatment and maintaining good glycemic control. Such patients with uncontrolled diabetes are more prone for diabetic complications among which the most common is diabetic foot. The lifetime risk of a person with diabetes developing foot ulceration is reported to be as high as 25% [2,3]. Leg and foot ulcers are a leading cause of hospital admission in diabetic patients and precedes about 70% to 80% of all diabetic associated amputations [4,5].

It is not only a difficult condition to treat but is a major cause of morbidity thereby posing a big economic and social burden to the entire family. Mean annual expenditure per person with diabetes in India was 92 USD [1].

The most common method of management of diabetic ulcer is ulcer debridement and follow-up with appropriate dressing. Once ulcers are healthy; split skin grafting has been proven to hasten the complete healing of ulcers. Reducing the need for prolonged conventional daily dressings

and thereby improving the quality of life of patients and decreasing the financial burden of the disease. Currently Split Thickness Skin Grafting (STSG) has been proved to be the most effective and rapid method for reconstruction of large skin defects [6,7]. STSG has been used to successfully treat chronic diabetic foot ulcer [8-10].

Various factors affect the success of skin grafts including age, nutritional status, serum albumin levels, presence of diabetes, positive swab culture prior to grafting, HbA1c levels, duration of diabetes, cardiovascular disease, nephropathy and chronic kidney disease, peripheral artery disease, etc.

Studies have shown the graft uptake and outcome to be poor in patients with diabetes and other comorbidities as compared to non-diabetics and diabetics without comorbidities [11]. Diabetic patients are at a higher risk for delayed healing time from split thickness skin graft compared to non-diabetics [11].

Therefore, this study aims to assess the outcomes of STSG in diabetic patients in terms of the prevalence of comorbidities among diabetics undergoing split thickness skin graft and factors affecting graft uptake with incidence of graft failure on patient follow up to predict the outcome of STSG and aid in proper patient selection.

Methodology

This prospective descriptive study was conducted after approval from Institutional Ethics Committee among diabetic patients with healing ulcers admitted in surgical wards of Goa Medical College. Patients with >18 years of age with ulcers having healthy granulation tissue and no contraindication for split thickness skin grafting were selected for the study. Patients having HIV infection, tuberculosis or proven malignancy were excluded from the study. All the necessary information regarding the study was explained to the patients and/or their valid guardian and written informed consent was obtained.

Detailed history and physical examination were done in each case and noted as per the proforma. Ulcer size was assessed on the day prior to surgery by tracing on opsite and then subsequently on graph paper. Patients were subjected for a pre-operative anesthetic evaluation. All the patients underwent STSG for the management of ulcer after following standard criteria. Donor site in all patients was the thigh. Patients were followed up after 1 month and graft status noted and any residual ulcer size was measured. 80% take of the skin graft was considered to be successful graft uptake. Following data collection, data was entered into Microsoft excel worksheet (Microsoft, USA). Data analysis was done using IBM Statistical Package for Social Sciences (Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) Categorical data was described in terms of frequencies and percentages. Continuous data was presented by mean and Standard Deviation (SD).

Results

The study was done on 40 patients between October 2018 and March 2020. The data was collected and analyzed as follows. For this study >80% of graft uptake in terms of surface area (in cm^2) was considered as Successful graft outcome. While <80% graft uptake was considered as the Failure group.

Table 1 shows the mean age of study participants in both the groups was 53 ± 11 years. There were 19 (61.3%) males and 12 (38.7%) females in graft success group as compared to 8 (88.9%) males and 1 (11.1%) female in graft failure group with no significant difference between the groups. The mean duration of diabetes mellitus was 6.93 ± 5.70 years in graft success group as compared to 6.66 ± 3.08 years in graft failure group with no significant difference between the groups.

Table 2 shows culture characteristics of pre-op wound swab of study participants. Cultures were found to be positive in 20 (64.5%) and sterile in 11 (35.4%) participants out of total 31 (100%) participants in graft success group whereas 8 (88.9%) were positive and 1 (11.1%) negative out of 9 (100%) participants in graft failure group. The further subdivision of positive culture swab showed infection by *Pseudomonas* species, *Klebsiella* species, *Staphylococcal* species, *Acinetobacter* species and *Citrobacter* species but the distribution between two groups showed no significant difference. As the majority of the culture showed infection by *Pseudomonas* species, analysis was performed to compare it with sterile cultures. The difference between infection by *Pseudomonas* species and sterile culture did not show significant difference between the groups.

Table 1: Comparison of demographic characteristics of study participants in graft success group and graft failure group.

Parameter		Graft success group (n=31)	Graft failure group (n=9)	p-value
Age in years (Mean ± SD)		53 ± 11	53 ± 11	1.000 NS
Gender (n, %)	Male	19 (61.3%)	8 (88.9%)	0.119 NS
	Female	12 (38.7%)	1 (11.1%)	
Duration of diabetes mellitus (Mean ± SD)		6.93 ± 5.70	6.66 ± 3.08	0.446 NS

Table 2: Comparison of culture characteristics of pre-op wound swab of study participants in graft success group and graft failure group.

Parameter		Graft success group (n=31)	Graft failure group (n=9)	p-value
Pre-op wound swab (n, %)	Positive culture	20 (64.5%)	8 (88.9%)	0.160 NS
	Sterile	11 (35.4%)	1 (11.1%)	
Wound swab-Positive culture	*Pseudomonas* species	10 (50%)	5 (62.5%)	0.641 NS
	Klebsiella species	3 (15%)	2 (25%)	
	Staphylococcal species	2 (10%)	1 (12.5%)	
	Acinetobacter species	4 (20%)	0	
	Citrobacter species	1 (5%)	0	
Wound swab-Positive Pseudomonas culture	*Pseudomonas*	10	5	0.120 NS
	Sterile	11	1	

Table 3: Comparison of laboratory parameters of study participants in graft success group and graft failure group.

Parameter	Graft success group (n=31)	Graft failure group (n=9)	p-value
HbA1c (Mean ± SD)	8.37 ± 1.95	8.41 ± 2.17	0.479 NS
Serum Albumin (Mean ± SD)	3.24 ± 0.53	2.81 ± 0.35	0.013*
Hemoglobin (Mean ± SD)	10.7 ± 1.62	11.1 ± 1.07	0.666 NS

Table 3 shows comparison of laboratory parameters among study participants. The mean HbA1c values were 8.37 ± 1.95 and 8.41 ± 2.17 respectively with no significant difference between the groups. Similarly, the mean Hemoglobin values were 10.7 ± 1.62 and 11.1 ± 1.07 respectively with no significant difference between the groups. The mean serum albumin levels were 3.24 ± 0.53 in graft success group whereas it was 2.81 ± 0.35 in graft failure group with statistically significant difference between the groups. Figure 1 shows distribution of comorbidities across the two groups and the difference was statistically not significant on comparison.

Table 4 depicts the distribution of study participants based on percentage of graft uptake. The mean graft uptake percentage in this study is 81.14 ± 30.434. In the graft success group the average percentage of uptake was 95.47 ± 5.615, while in the graft failure group, average graft uptake percentage was 31.76 ± 29.3. Five patients (12.5%) had a graft uptake of less than 20% and sixteen patients (40%) had a graft uptake of 100%. The proportion of patients with successful graft uptake was 77.5% (31 out of 40).

There were 17 (42.5%) study participants without any comorbidities. Out of the remaining 23 patients 16 had hypertension, 5 patients had ischemic heart disease and 5 patients had peripheral artery disease. One patient had varicose veins and one had Parkinson's disease. Two patients were cigarette smokers and 6 gave history of chronic alcohol use. Figure 1 depicts the group wise distribution of comorbidities.

Discussion

Diabetes mellitus is characterized by hyperglycemia due to defective action of insulin on cells, improper secretion of insulin or both. India is home to the second largest number of adults with diabetes worldwide with a prevalence of 77 million. Adults aged 50 to 70 years have the highest diabetes prevalence among all age groups. Leg and foot ulcers are a leading cause of hospital admission in diabetic patients and precedes about 70% to 80% of all diabetic associated amputations [4,5]. Split thickness skin grafts are a widely accepted method for soft tissue cover of open ulcers and wounds [12]. STSG has been used to successfully treat chronic diabetic foot ulcer [8-10].

Various factors affect the success of skin grafts including age, nutritional status, serum albumin levels, presence of diabetes, positive swab culture prior to grafting, HbA1c levels, duration of diabetes, cardiovascular disease, nephropathy and chronic kidney disease, peripheral artery disease, etc. Studies have shown that healing time and rate of uptake of skin grafts in diabetics with comorbidities is worse as compared to non-diabetics and diabetics without comorbidities [11].

This study was carried out on 40 diabetic patients who underwent split thickness skin grafting under the Department of General Surgery, Goa Medical College between the period of October 2018 and March 2020.

Table 4: Distribution of study participants based on percentage of graft uptake.

Graft Uptake	No. of Patients
1-10%	4
11-20%	1
21-30%	0
31-40%	1
41-50%	0
51-60%	0
61-70%	2
71-80%	1
81-90%	9
91-99%	6
100%	16
Total	**40**

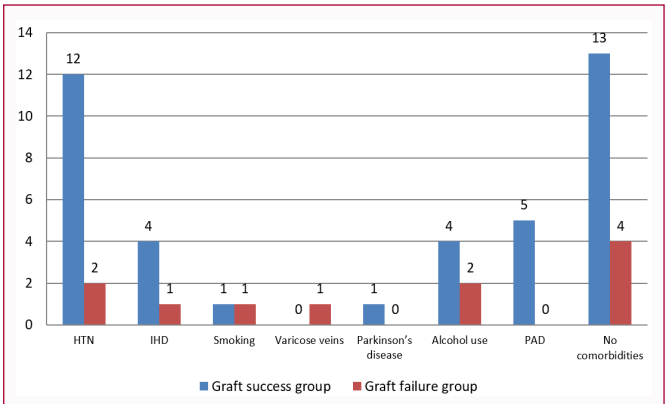

Figure 1: Distribution of comorbidities in graft success group and graft failure group.

The mean graft uptake percentage in this study was 81.14 ± 30.434. This is comparable to a study done by Thourani et al. [12]. where the mean graft success among patients with diabetes mellitus was 81 ± 29. In study done by Revanth et al. [13] the mean graft uptake was 55.94% which is less than in our study. Mowlavi et al. [14] in their study found the incidence of skin graft take to be 60% among diabetics. Studies done by Mahmoud et al. [15] and Reddy RST and Muneendra Kumar [16] had a success rate of around 86%. Similarly, a study by Jewell et al. [17] on burns patients undergoing STSG reported slightly higher healing times in diabetic patients.

In the successful graft uptake group the average percentage uptake was 95.47 ± 5.615. In the graft failure group, average graft uptake percentage was 31.76 ± 29.3. Five patients (12.5%) had a graft uptake of less than 20%. And sixteen patients (40%) had a graft uptake of 100%. The proportion of patients with successful graft uptake was 77.5% in this study. McCartan and Dinh [18] on performing a meta-analysis of publications on STSG on diabetic wounds calculated a graft uptake rate of ≥ 90% in 78% of patients by 8 weeks. The study done

by Turissini et al. [19], Reddy et al. [20] and Sanniec et al. [21] had a successful graft outcome of 66.66%, 61.11% and 65.85% respectively among diabetic patients which is relatively lesser as compared to our study.

In this study the mean age in the success and failure groups both were coincidently the same 53 ± 11 years. In a study done by Sanniec et al. [21] the mean age of the study population was 48.6 ± 9.8 years. Mean age of the success group was 49.2 ± 8.7 years and of the failure group was 47.8 ± 11.3 years; but was not found to be statistically significant.

Age when grouped into <55 years and >55 years groups, 76.19% and 78.94% were successful in respective age groups with no statistically significant difference between the groups. Thourani et al. [12] in their study got a mean success rate for patients <55 years as 92 ± 19% versus those older than >55 years as 79 ± 32% and was found to be statistically significant. Studies by Thourani et al. [12] and Mowlavi et al. [14] have demonstrated decreased wound tensile strength and prolonged wound healing with increasing age of the patients. With increasing age, the prevalence of diabetes in the population increases [22]. Diabetic patients are more likely to develop complications of diabetes with increasing age like microangiopathy, neuropathy, cardiovascular disease, etc. [12,14,22].

In this study the mean duration of diabetes of the patients in this study was 6.85 ± 5.199 years. The mean DM age in the graft success group was 6.93 ± 5.709 while it was 6.66 ± 3.082 in graft failure group with no statistically significant difference. In a study done by Ramanujam et al. [11] mean duration of DM in the study was 7.2 ± 4.9 years and found statistically significant association with unsuccessful split thickness skin grafting outcome. In our study, 57.5% of the patients had comorbidities. Due to the small sample size and low incidence of each comorbidity, the data could not be analyzed for association. Wattanakit et al. [23] have shown a strong association between chronic kidney disease and peripheral vascular disease and increased risk of foot complications. Ramanujam et al. [11] showed that the healing time for STSG was same for non-diabetics and diabetics without comorbidities. However healing time for STSG was prolonged in diabetic patients with comorbidities [11]. Reddy et al. [20] showed significant association between peripheral vascular disease and BMI on graft outcome. Turissini et al. [19] found association between presence of congestive heart failure, transplant suppression and hepatitis C infection with skin graft outcome.

In our study, the mean HbA1c value in the success group was 8.37% with a SD of 1.951 while it was 8.41% with a SD of 2.177 with no significant difference between the groups.

The mean HbA1c value for the success and failure groups of 6.8 ± 1.8% and 7.3 ± 2.4% respectively with no significant for effect on graft outcome in the study by Turissini et al. [19]. Similarly, Sanniec et al. [21] obtained a mean HbA1c of 8.7 ± 2.8% and 8.4 ± 3.1% in the success and failure groups with no significant difference. Ramanujam et al. [11] also did not find a statistically significant difference in preoperative HbA1c levels and healing time for STSG. On the contrary one study by Marston [24] found a correlation between hyperglycemia and wound healing.

The mean of serum albumin values of the patients in this study was 3.15 gm/dL with a SD of ± 0.526. The mean serum albumin levels were 3.24 ± 0.53 in graft success group whereas it was 2.81 ± 0.35 in graft failure group with statistically significant difference between the groups thus proving that serum albumin levels affect skin graft take. Serum albumin level is a useful indicator to assess the nutritional status of the patient [25]. Legendre et al. [26] in their study showed that protein deficiency in patients with leg ulcers is significantly associated with poor healing prognosis. Serum albumin levels are one of the best predictors of wound related complications [27]. Engelman et al. [28] reported that low Serum albumin (<2.5 g/dL) and abnormal BMI (<20 or >30 kg/m^2) was associated with increased post operative complications. Joshi et al. [29] observed that postoperative mortality was higher when serum albumin levels was less than 3.2 g/dL and BMI<20 kg/m^2. Beghetto et al. [30] observed that serum albumin was an independent variable related to infections in hospital set up, and was useful in predicting adverse hospital outcomes. Contrary to the above studies and our study Gherini et al. [31] showed that serum albumin levels could not predict postoperative complications. Ryan and Taft observed that there was no relation to serum albumin and wound infection rates [32].

The mean Hemoglobin value in the success group was 10.7 ± 1.62 gm% while in failure group it was 11.1 ± 1.07 gm% with no significant association with graft outcome. A retrospective study by Kale et al. [33] on STSG in patients with anemia (Hb<10 gm%) found that as long as perfusion and circulatory volume is maintained, mild to moderate anemia does not negatively affect split thickness skin graft uptake. Similarly, a study by Agarwal et al. [34] found no statistically significant difference between the mean graft uptake in those with Hb<10 gm% and those with Hb>10 gm%.

Wound swabs were taken 2 to 3 days prior to surgery for split thickness skin grafting. Infection is reported as one of the most common causes of skin graft failure [35-40]. Among the graft success group 20 (64.5%) out of 31 patients had a positive swab culture. The most common organism being *Pseudomonas* species (50%). Among the graft failure group 8 out of 9 patients had a positive swab culture. Again, the most common organism being *Pseudomonas* species (55.6%).

In this study, among the infected graft wounds the graft failure rate was 28.57% and among the swab negatives the failure rate was 9.09%. This is comparable with Nsaful et al. [40] and Unal et al. [41] who reported graft failure rate of 24.6% and 23.5% respectively in the positive culture group. Nsaful et al. [40] reported failure rate in the swab negative group of 6.7%. Henderson et al. [42] reported a lower graft failure rate due to infection of 15%. Aerden et al. [7] found no improvement in graft take among those with sterile cultures compared to infected (87% *vs.* 90%).

In this study *Pseudomonas* was the most common organism isolated (37.5%). Among those with <80% graft uptake *Pseudomonas* growth was noted in 50% patients and *Staphylococcus* was noted in 12.5% of patients. Matsumura et al. [43] showed that the culture from melting graft wound syndrome grows mainly *Staphylococcus aureus*. Skin graft failure due to *P. aeruginosa* was proposed in the year 1951 [44]. Graft loss in *Pseudomonas* infections is dramatic. This is due to high virulence of the organism; which includes a number of mechanisms to evade uptake by host phagocytes, to develop antibiotic resistance and biofilms [45-47], and production of toxins: Pyocyanin and endotoxin A, that are also responsible for total lysis of skin grafts [45,48,49].

Gilliland et al. [48] proved that isolation of *Pseudomonas* species and *Staphylococcus aureus* from the wounds prior to skin grafting impaired graft uptake significantly. McGregor [50] claimed that

infection with *P. aeruginosa* may reduce graft take by 5% to 10%: And this was less than the reduction in graft takes of *S. pyogenes* in their study.

Many studies reported that growth of *Pseudomonas* from the wounds prior to skin grafting significantly affected graft take [41,44,51-53]. Ratre et al. [51] found that only 4.7% of ulcers with *Pseudomonas* growth had a graft take of more than 80%; whereas among those with no growth 95.6% had a graft take of more than 80%. Hogsberg et al. [52] observed that wounds once infected with *Pseudomonas aeruginosa* even weeks to months prior to skin grafting showed reduced success of graft uptake. Hogsberg et al. [52] and Gilliland et al. [54] showed that *Pseudomonas aeruginosa and Staphylococcus aureus* has a negative effect on skin graft outcome. Gilliland et al. [54] calculated the median graft take reduction due to *Staphylococcus aureus* and *Pseudomonas* to be 15% and 40% respectively. Geethabanu et al. [53] calculated the mean graft uptake in wounds infected with *Pseudomonas aeruginosa* was 68.88% and for *Staphylococcus aureus* was 75.55%.

Conclusion

In this study the rate of split thickness skin graft uptake in diabetics was found to be 81.14%. Out of all the variables affecting skin graft outcome compared in this study Age, Sex, Duration of diabetes, Positive wound culture, presence of *Pseudomonas* growth, HbA1c and Hemoglobin levels were found to be not statistically significant in terms of affecting the rate of skin graft uptake. Among those with <80% graft uptake *Pseudomonas* growth was noted in 62.5% of patients. Accordingly, to this study there was statistically significant association of hypoalbuminemia with poor graft uptake. The rate of graft failure in diabetics undergoing split thickness skin graft was 18.86%. The main limitation of the study is that the sample size in this study is relatively smaller in comparison with previous studies with similar design. The data was collected from a single center. This study does not take into account possible interactions among the variables themselves which can influence the results.

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