

Original research article**Prospective evaluation of survival of split skin grafting in diabetic ulcers****¹Dr. Greeshma K Masthi, ²Dr. Arunkumar Bheemanna Bhavikatti, ³Dr. Bharath G R**¹Assistant Professor, ESIC MC & PGIMSR & Model Hospital, Rajajinagar, Bengaluru²Associate professor, ESIC MC & PGIMSR & Model Hospital, Rajajinagar, Bengaluru³Assistant professor, ESIC MC & PGIMSR & Model Hospital, Rajajinagar, Bengaluru**Corresponding Author:**

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Abstract

Background and Objectives: Diabetes mellitus is a metabolic disorder with profound impact on health and economy of the patient, their families and also the nation. Very few patients adhere to proper treatment protocols leading to several complications like retinopathy, renal disease, atherosclerosis, cardiomyopathy, intestinal paresis, vasculopathy, neuropathy etc., among which diabetic foot is most debilitating to the patient ^(1, 2). India is the diabetes capital of the world with as many as 50 million people suffering from type-2 diabetes. The WHO estimates that in India the increase in diabetics would be 58%, from 51 million people in 2010 to 87 million in 2030 ^(3, 4). The lifetime risk of a person with diabetes developing foot ulceration is reported to be as high as 25% ^(5, 6). The risk of lower extremity amputation is 15 to 46 times higher in diabetics than in others. The long term outcome for a diabetic patient after a major limb amputation is grave, with 50% of these patients deceased at 5 years ^(7, 8, 9). Diabetic ulcer is one of the leading causes of hospitalization in our hospital. These patients occupy the maximum number of inpatient beds leading to enormous economic burden. Moreover, these patients have a prolonged stay, hence decreasing the number of beds to be occupied by patients with other surgical disorders. Early treatment with split thickness skin grafting (STSG) in diabetic ulcers by reducing the healing time and hospital stay improves the quality of life for the patient and also reduces the economic burden of the patient and family by increasing the work days ^(9,10). STSG in diabetic ulcers also reduces the morbidity and disability resulting from amputations, by decreasing its progression to gangrene and other complications ^(12, 13, 14). The objective of the study is to determine the factors affecting the success of STSG in diabetic ulcers.

Methods: In this study, total of 100 patients with diabetic foot ulcers who fulfilled the criteria were selected and included in our study. Surgical technique of STSG and prospective care was standardized. Factors affecting graft uptake as considered in our study were- age, size of ulcer, haemoglobin level, Albumin level, FBS, PPBS, HbA1c, arterial doppler findings. Outcome measures considered were percentage of graft uptake on 5th post op day and 15th post op day. 90% or more uptake of skin graft on postoperative day 15 was considered as successful grafting. Individual factors were correlated with successful grafting and significance of each factor was statistically analysed.

Results: Total of 100 diabetic patient underwent STSG in our Hospital. The mean age of patient was 53.13+/-12.83. Male patients contributed to 81%, and females constituted 19% of the study population. It was observed that as the age of patient increases, the chances of graft failure also increases. Our study demonstrated that as the haemoglobin levels decrease the chances of graft failure increases. 57.1% of the patients with haemoglobin level < 10g/dl had graft failure with statistical analysis showing suggestive significance.

Fasting and post prandial blood sugars, if under specified limits had significant positive association with successful graft uptake with P value of <0.001 and 0.002 for FBS and PPBS respectively.

HbA1c levels which reflect the blood sugar levels of 3 months had strong correlation with successful graft uptake with p value <0.001.

Our study also showed serum albumin to be strong significant factor deciding successful grafting.

Conclusion: Success of split thickness skin grafting in diabetic patients with ulcers depends on age, haemoglobin, FBS, PPBS, HbA1c and serum albumin levels.

Keywords: Diabetes, ulcers, split thickness skin grafting, graft uptake, graft failure

Introduction

Diabetes Mellitus is a metabolic disorder with profound impact on health and economy of the patient. The Diabetic Foot ulcer is a debilitating long-term complication of diabetes mellitus and may be defined as an array of foot abnormalities, resulting from peripheral neuropathy, microangiopathy,

immunodeficiency and other consequences of metabolic disturbances [15, 16, 17]. These different factors may be present alone or occur in combination in patients with diabetes mellitus. Neuropathy, particularly symmetrical distal polyneuropathy, is the major causative factor, and is present in 85% of the patients with diabetic foot problems [18, 19].

Diabetic patients have always suffered from foot ulceration, cellulitis and other associated complications. The lifetime risk of a person with diabetes developing foot ulceration is reported to be as high as 25%. This complication has become more prevalent since advances in the general medical care of diabetes, particularly the discovery of insulin, have prolonged the life expectancy of diabetic patients [20, 21, 22]. The risk of lower extremity amputation is 15 to 46 times higher in diabetics than in others and the long term outcome for a diabetic patient after a major limb amputation is grave, with 50% of these patients deceased by 5 years [22, 23, 24]. Hence despite progress in the treatment of ulcers, prevention and achieving healing of established ulcers remains a considerable challenge. Diabetic foot ulcers have important effects on the quality of life of affected individuals as well as pose important demands on the health care system in terms of manpower and costs [24, 25]. Limitation of walking, special footwear, frequent hospital visits or admissions, and the eventual consequences of an amputation all pose a major burden to the patient. Every year, more than 1 million people with diabetes lose a leg as a consequence of this disease. This means that every 30 second, a lower limb is lost to diabetes somewhere in the world [24, 25, 26].

Biomechanical off-loading, vascular surgery, aggressive treatment of infection and meticulous wound care are presently seen as essential elements in the treatment of diabetic foot disease and a multidisciplinary approach is essential. Due to lack of evidence, the treatment is frequently empiric and is determined by personal preference, availability of local expertise and resources [23, 27].

Diabetic foot ulcer usually takes several months to heal and in this period there is always the risk of foot infection or progressive gangrene with amputation as the final outcome [25, 26, 28].

Split-thickness skin grafts (STSG) have withstood the test of time as a method for soft tissue coverage in open wounds of many etiologies [29]. For diabetic foot and ankle wounds, which are notoriously difficult to heal and tend to reopen after initial closure, STSG has become a common option. STSG is a relatively simple and minimally invasive procedure for the management of diabetic wounds [30, 31, 32]. Despite its popularity, there is little objective information available in the literature regarding the application of an STSG as treatment of choice for wounds in diabetic patients [31, 32]. Only a few small studies have been published to date regarding STSG in diabetic ulcers: Mahmoud *et al.* [33] reported on 50 patients, Puttirutvong [34] reported on 42 patients, and Younes *et al.* [35] reported on 16 patients. The purpose of our study was to study a large group of diabetic patients treated with STSG, providing information regarding outcomes and factors leading to complications.

Aim and Objective of Study

Aim and Objective: To determine the factors affecting the success of split thickness skin grafting in diabetic foot and leg ulcers.

The variables that are being considered are:

Age of the patient, Haemoglobin (HB), Fasting blood sugar (FBS), Post prandial blood sugar (PPBS), Glycosylated haemoglobin (HBA1C) and Albumin (ALB).

Materials and Methodology

Source of Data

The study conducted on patients admitted in ESIC MEDICAL COLLEGE & HOSPITAL.

Methods

Study Period: 18 months.

Study Area: ESIC Medical College and Hospital.

Study Design: Prospective cohort Study.

Study Population: Admitted patients with diabetic foot ulcer in department of General surgery undergoing STSG.

Inclusion Criteria

All diabetic ulcers fit for STSG.

Exclusion Criteria

1. Arterial ulcers with Diabetes mellitus.
2. Varicose venous ulcers with Diabetes mellitus.
3. Diabetic ulcers that are unfit for STSG such as:
 - Active infection.
 - Bone exposure.
 - Tendon exposure.
 - Pressure bearing area.

Study Methods**Data Collection**

- a) Clinical history along with patient's proforma is collected.
- b) Informed written consent from the patient is obtained.

Study Methods

Patients and relatives were explained about the split skin grafting procedure and study and necessary approval was obtained from them prior to intervention. Patients admitted underwent thorough debridement and dressing, treated with sensitive antibiotics and supportive measures. After satisfactory granulation tissue formation patient was posted for Split Skin Grafting. Patient evaluated for the take of graft on 5th and 15th post-operative day.

Data regarding the name, age, sex, education, occupation, address, chief complaint, history regarding the mode of onset of disease, past medical and surgical history, personal history was collected from patient and accompanying relatives. Survival of graft in terms of percentage of take noted.

Study variables

- 1) Percentage of graft uptake after STSG at 5 days and 15 days.
- 2) Factors affecting graft uptake.

Statistical Analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean \pm SD (Min-Max) and results on categorical measurements are presented in Number (%).

Significance is assessed at 5% level of significance. The following assumptions on data is made, Assumptions:

1. Dependent variables should be normally distributed.
 2. Samples drawn from the population should be random, cases of the samples should be independent.
- Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven's test for homogeneity of variance has been performed to assess the homogeneity of variance.
- Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small.

Significant figures

+Suggestive significance (P value: $0.05 < p < 0.10$).

*Moderately significant (P value: $0.01 < p < 0.05$).

** Strongly significant (P value: $p < 0.01$).

Statistical Software

The Statistical software namely SPSS 23.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Ethical Clearance

Ethical clearance has been obtained from "Ethical clearance committee" of the Institution.

Results

Study Design: A prospective cohort study consisting of 100 patients with diabetic ulcers undergoing STSG. Factors affecting the success of STSG in diabetic patients is studied. More than or equal to 90% uptake on POD 15 is considered successful grafting.

Table 1: Age Distribution of Patients Studied

Age in years	No. of patients	%
31-40	21	21.0
41-50	27	27.0
51-60	24	24.0
61-70	17	17.0
71-80	11	11.0
Total	100	100.0

Mean \pm SD: 53.13 \pm 12.83.

The highest number of patients were in the age group 41-50, followed by age group 51-60.

Table 2: Gender Distribution of Patients Studied

Gender	No. of patients	%
Female	19	19.0
Male	81	81.0
Total	100	100.0

Male patients contributed to 81% of study population.

Table 3: Hemoglobin (g/dl) distribution of patients studied

Hemoglobin (g/dl)	No. of patients	%
<10	7	7.0
10-12	53	53.0
12-14	36	36.0
>14	4	4.0
Total	100	100.0

More than half of the patients had Haemoglobin levels between 10-12 g/dl, 36% of the patients had levels of 12-14g/dl. 7% of the patients had haemoglobin less than 10g/dl, and only 4% of the patients had haemoglobin more than 14g/dl.

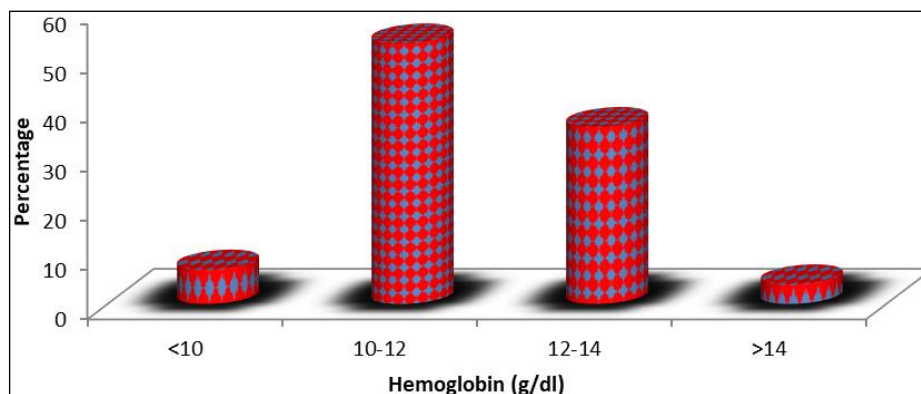


Chart 1

Table 3: Blood sugar distribution of patients studied

Variables	No. of patients (n=100)	%
FBS (mg/dl)		
• <100	0	0.0
• 100-126	25	25.0
• >126	75	75.0
PPBS (mg/dl)		
• <140	9	9.0
• 140-200	79	79.0
• >200	12	12.0

75% of the patients had FBS >126mg/dl, 25% of the patients had FBS between 100-126 mg/dl. 79% of the patients had PPBS between 140-200 mg/dl, 12% of them had PPBS >200mg/dl and only 9% of them had PPBS <140mg/dl.

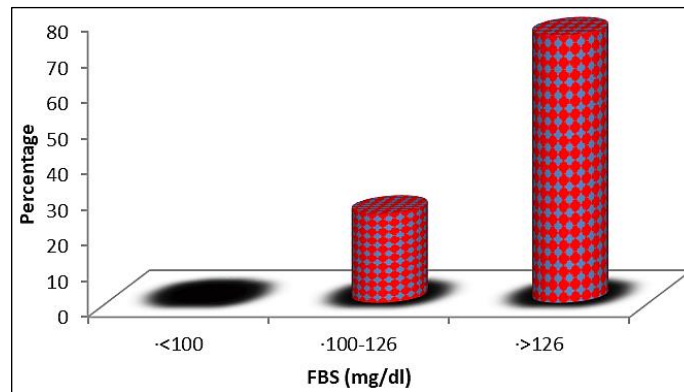


Chart 2

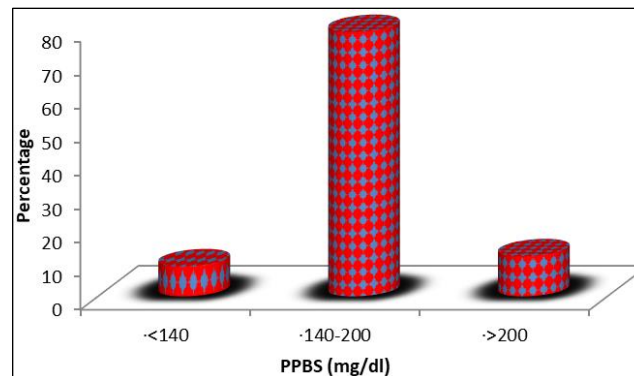


Chart 3

Table 4: HbA1c% distribution of patients studied

HbA1c%	No. of patients	%
<6	2	2.0
6-9	81	81.0
>9	17	17.0
Total	100	100.0

81% of the patients had HbA1c between 6-9, 17% of them > 9 and 2% of them had HbA1c less than 6.

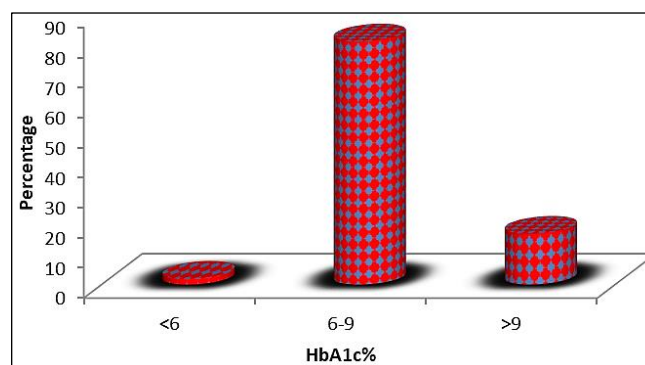


Chart 4

Table 5: Serum Albumin level (ALB) distribution of patients studied

ALB (g/dl)	No. of patients	%
<2	0	0.0
2-3	22	22.0
3.1-4	69	69.0
>4	9	9.0
Total	100	100.0

69% of the patients had Serum Albumin between 3.1-4g/dl, 22% of the patients between 2-3 g/dl and 9% of them more than 4g/dl.

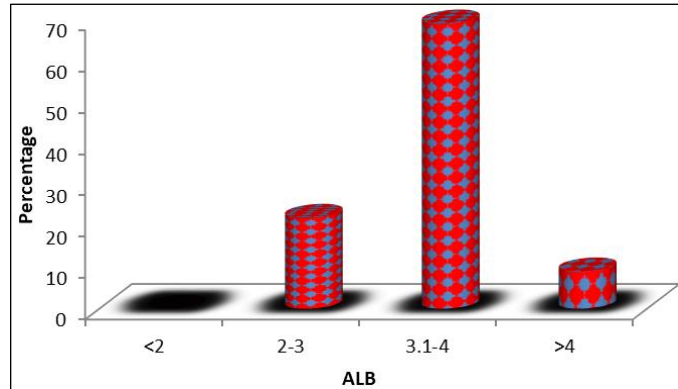


Chart 5

Table 6: Arterial Doppler distribution of patients studied

Arterial Doppler	No. of patients	%
Atherosclerosis	31	31.0
Normal	69	69.0
Total	100	100.0

69% of the patients had normal arterial doppler study, 31% of them had atherosclerosis.

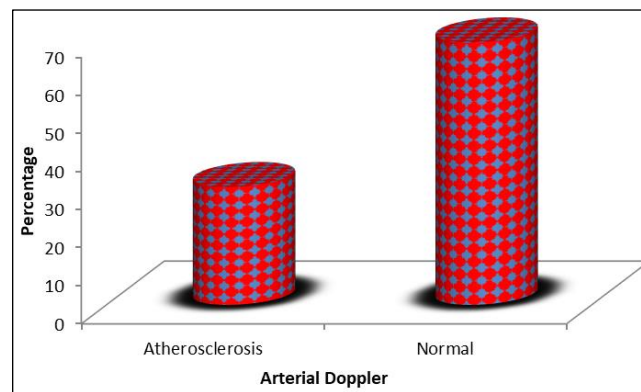


Chart 6

Table 7: % Uptake 5th POD distribution of patients studied

Uptake 5 th POD	No. of patients	%
0-10	1	1.0
10-20	1	1.0
20-30	3	3.0
30-40	5	5.0
40-50	8	8.0
50-60	16	16.0
60-70	33	33.0
70-80	20	20.0
80-90	4	4.0
90-100	9	9.0
Total	100	100.0

33% of the patients had skin graft uptake of 60-70% on POD 5, followed by 20% of them having uptake of 70-80% and 9% of the patients had uptake of 90-100%.

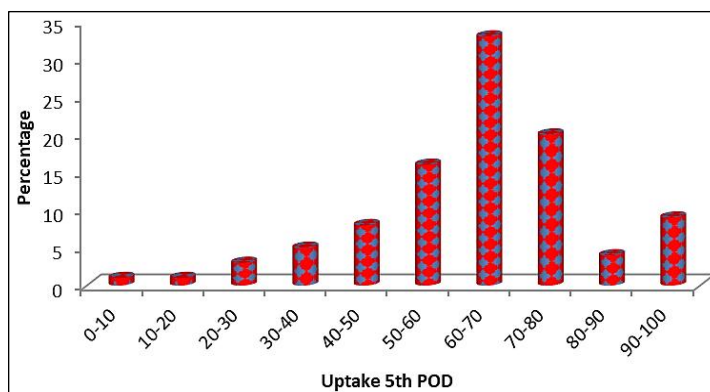


Chart 7

Table 8: % Uptake 15th POD distribution of patients studied

Uptake 15 th POD	No. of patients	%
0-10	1	1.0
10-20	0	0.0
20-30	0	0.0
30-40	1	1.0
40-50	2	2.0
50-60	6	6.0
60-70	8	8.0
70-80	8	8.0
80-90	3	3.0
90-100	71	71.0
Total	100	100.0

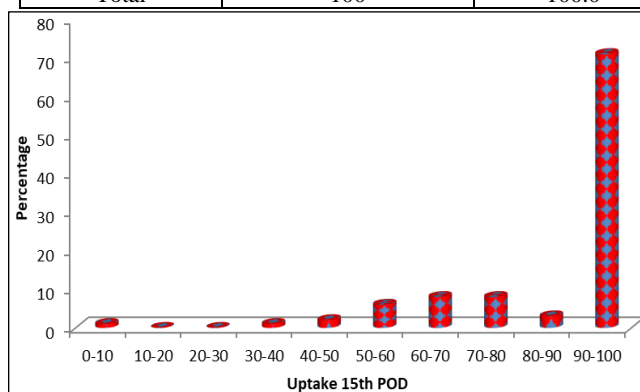


Chart 8

71% of the patients had 90-100% of graft uptake.

Table 9: Outcome distribution of patients studied

Outcome	No. of patients	%
Failure	29	29.0
Successful	71	71.0
Total	100	100.0

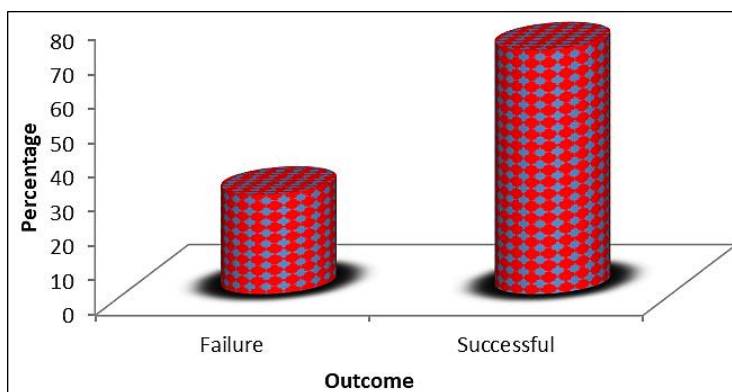


Chart 9

Uptake of skin graft more than or equal to 90% on POD 15 is considered successful grafting in our study. 71% of patients had successful graft uptake.

Table 10: Association of basic demographic variables in relation to outcome of patients studied

Variables	Outcome		Total (n=100)	P value
	Failure (n=29)	Successful (n=71)		
Age in years				
• 31-40	2(6.9%)	19(26.8%)	21(21%)	0.010**
• 41-50	5(17.2%)	22(31%)	27(27%)	
• 51-60	8(27.6%)	16(22.5%)	24(24%)	
• 61-70	7(24.1%)	10(14.1%)	17(17%)	
• 71-80	7(24.1%)	4(5.6%)	11(11%)	
Gender				
• Female	5(17.2%)	14(19.7%)	19(19%)	0.774
• Male	24(82.8%)	57(80.3%)	81(81%)	

Chi-Square/Fisher Exact Test.

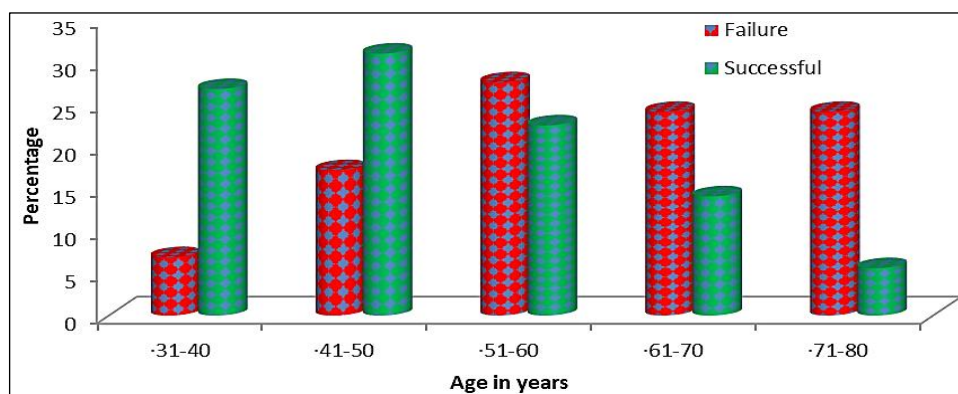


Chart 10

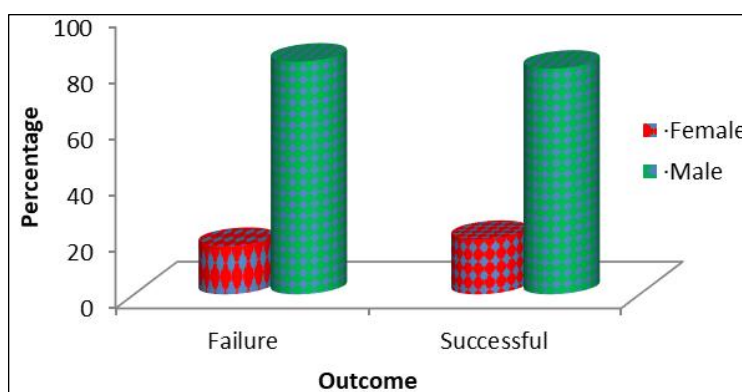
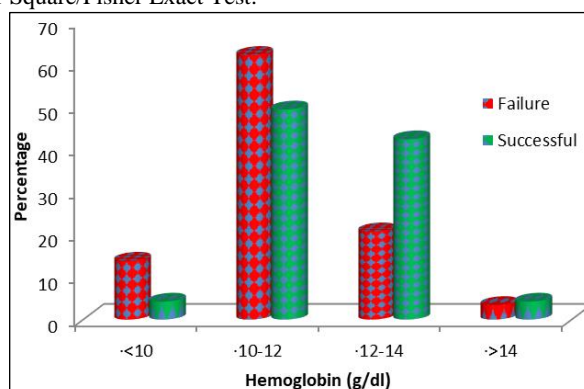
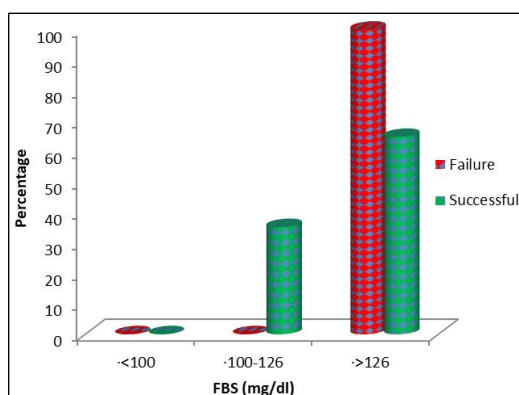


Chart 11

Table 11: Association of Clinical variables in relation to outcome of patients studied

Variables	Outcome		Total (n=100)	P value
	Failure (n=29)	Successful (n=71)		
Hemoglobin (g/dl)				
• <10	4(13.8%)	3(4.2%)	7(7%)	0.087+
• 10-12	18(62.1%)	35(49.3%)	53(53%)	
• 12-14	6(20.7%)	30(42.3%)	36(36%)	
• >14	1(3.4%)	3(4.2%)	4(4%)	
FBS (mg/dl)				
• <100	0(0%)	0(0%)	0(0%)	<0.001**
• 100-126	0(0%)	25(35.2%)	25(25%)	
• >126	29(100%)	46(64.8%)	75(75%)	
PPBS (mg/dl)				
• <140	0(0%)	9(12.7%)	9(9%)	0.002**
• 140-200	21(72.4%)	58(81.7%)	79(79%)	
• >200	8(27.6%)	4(5.6%)	12(12%)	
HbA1c%				
• <6.0	0(0%)	2(2.8%)	2(2%)	<0.001**
• 6.0-8.0	10(34.5%)	49(69%)	59(59%)	
• 8.0-10.0	13(44.8%)	18(25.4%)	31(31%)	
• >10.0	6(20.7%)	2(2.8%)	8(8%)	
ALB				
• <2.0	0(0%)	0(0%)	0(0%)	<0.001**
• 2.0-3.0	17(58.6%)	5(7%)	22(22%)	
• 3.1-4.0	12(41.4%)	57(80.3%)	69(69%)	
• >4.0	0(0%)	9(12.7%)	9(9%)	

Chi-Square/Fisher Exact Test.

**Chart 12****Chart 13**

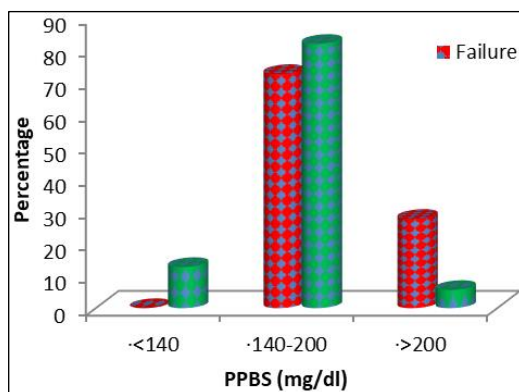


Chart 14

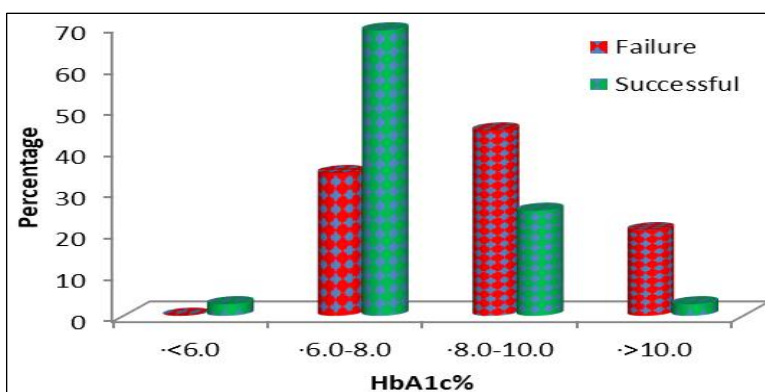


Chart 15

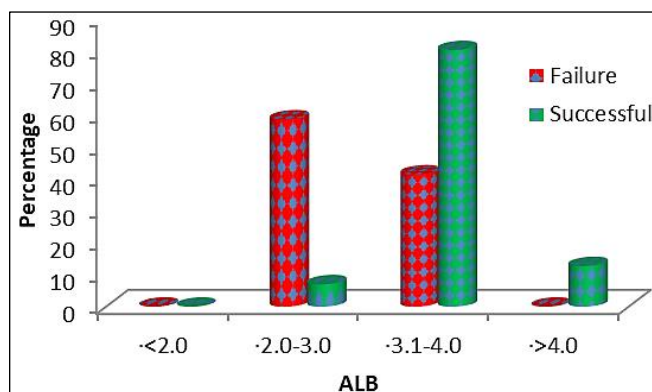


Chart 16

Table 12: Arterial Doppler in relation to outcome of patients studied

Arterial Doppler	Outcome		Total
	Failure	Successful	
Atherosclerosis	18(62.1%)	13(18.3%)	31(31%)
Normal	11(37.9%)	58(81.7%)	69(69%)
Total	29(100%)	71(100%)	100(100%)

P<0.001**, Significant, Chi-Square Test.

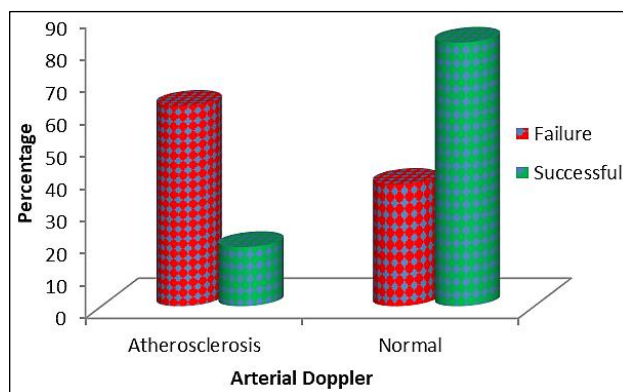


Chart 17

Table 13: % Uptake at 5th POD and 15th POD in relation to outcome of patients studied

% Uptake	Outcome		Total (n=100)	P value
	Failure (n=29)	Successful (n=71)		
%Uptake 5 th POD				
• 0-10	1(3.4%)	0(0%)	1(1%)	<0.001 **
• 11-20	4(13.8%)	0(0%)	4(4%)	
• 21-50	22(75.9%)	7(9.9%)	29(29%)	
• 51-80	2(6.9%)	54(76.1%)	56(56%)	
• 81-100	0(0%)	10(14.1%)	10(10%)	
%Uptake 15 th POD				
• 0-10	1(3.4%)	0(0%)	1(1%)	<0.001 **
• 11-20	0(0%)	0(0%)	0(0%)	
• 21-50	9(31%)	0(0%)	9(9%)	
• 51-80	18(62.1%)	0(0%)	18(18%)	
• 81-100	1(3.4%)	71(100%)	72(72%)	

Chi-Square/Fisher Exact Test

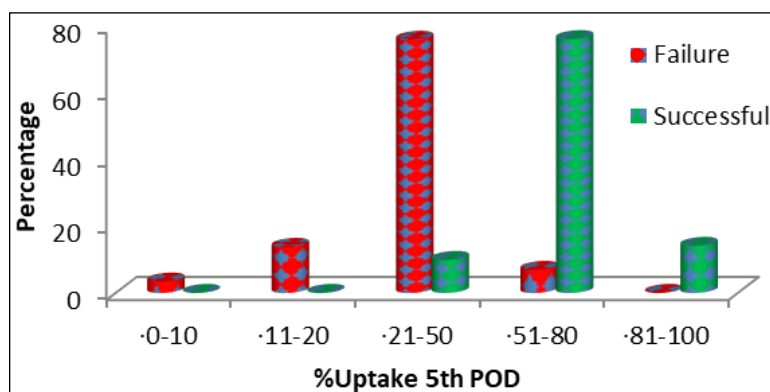


Chart 18

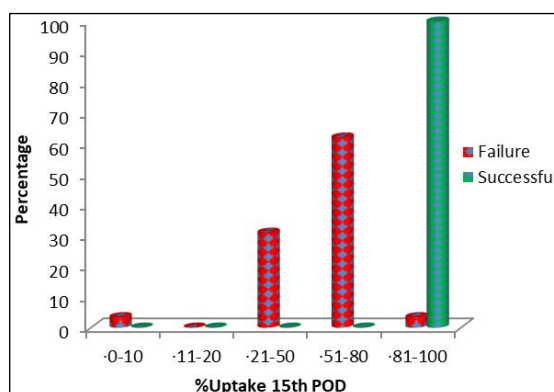


Chart 19

Table 14: A Comparison of clinical variables in relation to outcome of patients studied

Variables	Outcome		P value
	Failure	Successful	
Age in years	60.55±12.72	50.10±11.67	<0.001**
Hemoglobin (g/dl)	11.36±1.33	12.07±1.25	0.012*
FBS (mg/dl)	151.00±17.86	134.86±18.03	<0.001**
PPBS (mg/dl)	187.59±27.45	161.82±20.92	<0.001**
HbA1c%	8.98±1.44	7.73±1.16	<0.001**
ALB	3.06±0.37	3.66±0.45	<0.001**
Uptake 5 th POD	38.62±14.57	67.61±13.78	<0.001**
Uptake 15 th POD	58.1±16.61	93.94±4.30	<0.001**

Discussion

There is abundant information in the literature regarding the successful use of STSG for wound coverage, yet most previous studies have focused on wounds in non-diabetic populations and included wounds throughout the body. Prior studies for STSG on diabetic foot and ankle wounds are limited.

Of note, although the literature in this area is sparse, McCartan and Dinh ^[33] performed a meta-analysis of the few available publications on STSG placement for diabetic wounds. They computed a graft take rate of more than 90% in 78% of patients by 8 weeks, and therefore recommended it as a viable option in wound care.

Mahmoud *et al.* ^[34] prospectively studied patients treated with STSG versus conservative wound dressings for diabetic foot wounds. They reported a significant reduction in healing time and duration of hospital stay for those patients treated with STSG compared with using paraffin gauze and diluted povidone-iodine soaked gauze, yet they did not elaborate on possible indicators for complications encountered.

Puttirutvong ^[35] compared the use of meshed skin grafts to normal STSG in a randomized study for diabetic foot wounds and found no statistically significant difference between the techniques for healing time.

A small study by Younes *et al.* ^[36] reported only on the outcomes for the use of phenytoin for wound preparation on large STSG treated diabetic foot wounds.

All patients in our study had type 2 diabetes mellitus and percentage of graft uptake on post op day 15 was looked into.

A study by Mahmoud *et al.* ^[34] showed 62% of 50 skin-grafted foot wounds in diabetic patients healed by postoperative week 8. This outcome was also found in a study by Younes *et al.* on 16 patients treated with STSG for diabetic foot wounds. Most studies on STSG in nondiabetic populations demonstrate healing times of 2 to 4 weeks. Longer healing times in diabetic patients can be attributed to several factors, including impaired microcirculation, infection and endothelial dysfunction.

A study by Marston found a direct relationship between hyperglycemia and wound healing. Further modification of the way the patients were divided into groups for analysis based on glycosylated hemoglobin levels-particularly if we classified them into 2 groups (those with a HbA1c greater than 7.0 and those less than or equal to 7.0)-could have affected the statistical significance.

Previous studies have shown prolonged wound healing and decreased graft uptake with increasing age, our study re-emphasizes this. Aging produces intrinsic physiologic changes that results in delayed or impaired wound healing. Likewise, we did not find correlation between graft uptake and gender.

In our study, we found that as the haemoglobin levels decrease the chances of graft failure also increases. 57.1% of the patients with haemoglobin level < 10g/dl had graft failure, however statistical analysis noted suggestive significance only.

Well controlled fasting and post prandial blood sugars had significant positive association with successful graft uptake with P value of <0.001 and 0.002 for FBS and PPBS respectively.

HbA1c levels which reflect the blood sugar control levels of 3 months had strong correlation with successful graft uptake with p value <0.001.

Nutritional status is an important factor in wound healing. Serum albumin is an important nutritional marker. In our study we noticed that patients with lower serum albumin levels had higher failure rates. The statistical analysis showed it to be a strongly significant factor for successful grafting. It is imperative to maintain serum albumin levels more than 3.5g/dl for successful grafting.

In a retrospective review of 200 patients undergoing STSG placement for foot wounds, Ramanujam *et al.* found that comorbidities associated with diabetes, such as peripheral vascular disease, retinopathy, nephropathy, and cardiovascular disease, conferred more risk of graft failure than the diabetes itself. In the present study, we did not thoroughly evaluate patient comorbidities; however, the graft failures we observed were more in patients with peripheral vascular disease. We found that peripheral vascular disease significantly affected the graft uptake with P value <0.001. Therefore, we also believe that, when choosing a closure method for diabetic foot wounds, it may be prudent to consider other important comorbidities and not just the presence or absence of diabetes.

Although mechanical barriers, such as seroma formation, between the STSG and the recipient wound bed

are common causes of graft failure in other studies, none of the grafts in our patients experienced this complication. Contrary to other studies, there were no donor site complications in our patients. Mahmoud et al found donor site morbidity in 4% of their grafted patients, which responded to conservative care. Furthermore, duration of the initial wound, peripheral neuropathy, duration of diabetes were not addressed in our study. These factors have been shown to affect wound healing, and their inclusion in the analysis may have provided additional important findings.

Conclusion

The findings of our study confirm that success of split thickness grafting in diabetic wounds depends on various factors. Age, haemoglobin, FBS, PPBS, HbA1C, serum albumin and presence of peripheral vascular disease having significant association. We also observed that split thickness grafting reduced the length of hospital stay thereby reducing the morbidity, mortality and also expenses spent on treating these ulcers.

It is important to maintain haemoglobin levels >10g/dl, FBS <126mg/dl, PPBS <140mg/dl HbA1c <9, serum albumin > 3.5g/dl, and to optimise vascular supply for successful grafting.

We conclude that split thickness skin grafting is an effective way to promote wound healing in diabetic patients with success rate of 71% as observed in our study and above mentioned factors significantly affects the uptake. Hence these factors have to be optimized prior to surgery for successful uptake of skin graft.

References

1. International Diabetes Federation, IDF Diabetes Atlas, 7th edition; 2015
2. Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. *World J Diabetes*. 2012;3:110–117.
3. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;87:4–14.
4. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract*. 2011;94:311–321.
5. Aalaa M, Malazy OT, Sanjari M, Peimani M, Mohajeri-Tehrani M. Nurses' role in diabetic foot prevention and care; a review. *J Diabetes Metab Disord*. 2012;11:24.
6. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. *Diabetes Metab Res Rev*. 2012;28:574–600.
7. Nather A, Bee CS, Huak CY, Chew JL, Lin CB, Neo S, Sim EY. Epidemiology of diabetic foot problems and predictive factors for limb loss. *J Diabetes Complications*. 2008;22:77–82.
8. Malone JM, Snyder M, Anderson G, Bernhard VM, Holloway GA, Bunt TJ. Prevention of amputation by diabetic education. *Am J Surg*. 1989;158:520–523.
9. Bakri FG, Allan AH, Khader YS, Younes NA, Ajlouni KM. Prevalence of Diabetic Foot Ulcer and its Associated Risk Factors among Diabetic Patients in Jordan. *J Med J*. 2012;46:118–125.
10. Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. *Am J Surg*. 1998;176:5–10.
11. Shahbazian H, Yazdanpanah L, Latifi SM. Risk assessment of patients with diabetes for foot ulcers according to risk classification consensus of International Working Group on Diabetic Foot (IWGDF) *Pak J Med Sci*. 2013;29:730–734.
12. Dhanaram B, Arunachalam J, Muthukumaraswamy B. Split skin graft for diabetic ulcers: an analysis. *Int Surg J* 2016;3:2160-2.
13. Anderson JJ. Split thickness skin grafts for the treatment of non-healing foot and leg ulcers in patients with diabetes: a retrospective review. *Diabet Foot Ankle*. 2012;3:10204.
14. Maramreddy Revanth et al., Survival of Split Thickness Skin Graft in Diabetic and Non-diabetic Wound Management *International Journal of Anatomy, Radiology and Surgery*, 2016 Jan, Vol 5(1) 20-24
15. Jeffcoate WJ, Harding KG: Diabetic foot ulcers. *Lancet* 2003, 361: 1545-1551
16. Bakker K, Schaper NC. The development of global consensus guidelines on the management and prevention of the diabetic foot 2011. Wiley online library(wileyonlinelibrary.com): *Diabetes/Metabolism Research and Reviews*; 2012; 28(sup I): 116-118
17. Alvin C Powers. Diabetes mellitus. Chapter 323. In: Harrison's Principles of Internal Medicine. 16th edition. McGraw-Hill Publications 2005; 2:2152-2154.
18. Walters DP et al. The distribution and severity of diabetic foot disease: A community study with comparison to a non-diabetic group. *Diabetic med* 1992; 9: 354-358
19. Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, Armstrong DG, Woo K, Boeni T, Ayello EA, Kirsner RS. Diabetic foot ulcers: Part II. Management. *J Am Acad Dermatol*. 2014;70:21.e1–2124; quiz 21.e1-2124.

20. American diabetic association. From diabetes care. 2002; 25(Suppl 1):S5-S20.
21. Bortoletto MS, de Andrade SM, Matsuo T, Haddad Mdo C, González AD, Silva AM. Risk factors for foot ulcers--a cross sectional survey from a primary care setting in Brazil. *Prim Care Diabetes*. 2014;8:71–76.
22. Marston WA. Risk factors associated with healing chronic diabetic foot ulcers: the importance of hyperglycemia. *Ostomy Wound Manage*. 2006;52:26-28.
23. Naves CCLM. The Diabetic Foot: A Historical Overview and Gaps in Current Treatment. *Adv Wound Care*. 2016 May;5(5):191–7..
24. Vileikyte L. Diabetic foot ulcers: a quality of life issue. *Diabetes Metab Res Rev*. 2001;17:246–249.
25. Ragnarson Tennvall G, Apelqvist J. Health-economic consequences of diabetic foot lesions. *Clin Infect Dis*. 2004;39 Suppl 2:S132–S139.
26. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet*. 2005;366:1719–1724.
27. Frykberg RG, Zgonis T, Armstrong DG, Driver VR, Giurini JM, Kravitz SR, Landsman AS, Lavery LA, Moore JC, Schuberth JM, et al. Diabetic foot disorders. A clinical practice guideline (2006 revision) *J Foot Ankle Surg*. 2006;45:S1–66.
28. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJG, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2012 Jun;54(12):e132-173.
29. Liu ZJ, Velazquez OC. Hyperoxia, endothelial progenitor cell mobilization, and diabetic wound healing. *Antioxid Redox Signal*. 2008;10:1869-1882.
30. Davis JS. The story of plastic surgery. *AnnSurg*. 1941;113:641-656. Chick LR. Brief history and biology of skin grafting. *Ann Plast Surg*. 1988;21:358-365.
31. Rose JF, Giovinco N, Mills JL, Najafi B, Pappalardo J, Armstrong DG . Split-thickness skin grafting the high-risk diabetic foot. *J Vasc Surg*. 2014;59(6):1657-63
32. Donegan RJ, Schmidt BM, Blume PA. An overview of factors maximizing successful split-thickness skin grafting in diabetic wounds. *Diabet Foot Ankle*. 2014 Jan;5(1):247-69.
33. McCartan B, Dinh T. The Use of Split-Thickness Skin Grafts on Diabetic Foot Ulcerations: A Literature Review. *Plast Surg Int*. 2012;2012:1–6
34. Mahmoud SM, Mohamed AA, Mahdi SE, et al. Split-skin graft management of diabetic foot ulcers. *J Wound Care*. 2008;17:303-306.
35. Puttirutvong P. Meshed skin graft versus split thickness skin graft in diabetic ulcer coverage. *J Med Assoc Thai*. 2004;87:66-72.
36. Younes N, Albsoul A, Badran D, Obedi S. Wound bed preparation with 10-percent phenytoin ointment increases the take of split-thickness skin graft in large diabetic ulcers. *Dermatol Online J*. 2006;12:5.