International Surgery Journal
*Saroha R et al. Int Surg J. 2023 Feb;10(2):268-274*
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20230266

**Case Series**

# Fat grafting: an adjunct in management of chronic leg ulcers

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**Received:** 16 November 2022
**Accepted:** 20 January 2023

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## ABSTRACT

Chronic leg ulcers (CLU's) are one of the most challenging medical conditions, mostly resistant to conventional therapy. Several treatment modalities are present but none have become standard of care. Autologous fat contains adipose derived stem cells (ADSC's) which is believed to have abundant growth factors (GF's) required for its regenerative and reparative properties. Our observational study was conducted to see the feasibility and efficacy of fat grafting in management of CLUs with complete wound healing as final outcome. 14 patients with CLUs (any etiology, >3 months and multiple ulcers were counted as individual cases if >3 cm apart) were included with coagulopathies, uncontrolled diabetes mellitus (Hba1c>9 mmol/mol) being the exclusions. Fat was harvested using standard Coleman's technique. Study was conducted from December 2015 to December 2017 in tertiary care hospital and patients were followed up for next 24 months. All cases were evaluated clinically. Average age of wounds before intervention was 33.34 months, average wound size 16.46 $cm^2$ and 4.9 cc of average fat was transferred underneath the ulcer. 11 out of 14 wounds healed completely within average 27.4 days and final outcome was not achieved in 3. Pain assessed using visual analogue scale (VAS) in immediate post operative period till 48 hours (telephonically). Patients were evaluated at 1 week, 1 month, 3 months and 6 months after procedure for pattern of wound healing and related complications. Fat grafting is easy, safe, effective and a minimally invasive OPD procedure with short recovery time for managing CLUs.

**Keywords:** CLU, ADSC, GF, VAS

## INTRODUCTION

Wounds which have not healed (not attained anatomical and functional integrity) in 3 months with standard of care are termed as chronic wounds. With constantly improving life expectancy, co-morbidities are seen commonly in ageing population (out of which 1-2%) which are associated with CLU's leading to socioeconomic burden.[1-3] Four overlapping phases seen in normal wound healing. Most ulcers usually respond to the standard care and management of the primary cause. But in some prolonged inflammatory stage results in non healing. Venous insufficiency or arterial ischemia due to diabetes most common cause of CLU ultimately resulting in NHU, but at times etiology is not established. For treating physician they are a difficult nut to crack with conventional methods and leading to reduced quality of life with the length of treatment.[4-8] Wound environment is irregular and dynamic in chronic wounds making them resistant to conventional modalities specially if used alone so it is mandatory to use them in combinations for expected results.[9] Podiatry care is lengthy, expensive and with guarded efficacy. Reconstruction with grafts and flaps has shown little success due to high infection rates. In quest of new cost effective therapies for an enhanced healing of NHU's, fat grafting has emerged as a safe, easy to harvest, autologous and in adequate quantity tool in reconstructive surgery. Regenerative properties of fat are due to ADSC's which can be easily harvested and grafted without requiring culture or expansion. GF and

cytokines in fat cells promotes cell migration, reduced inflammation and angiogenesis resulting improved wound healing.[10-12] As described recently by Piccolo et al that refractory wounds are benefitted by autologous fat grafting.[13] Various other documents are suggestive of enhanced healing in chronic ulcers in animal studies with ADSC's.[14] Major limitation of fat grafting is the unpredictable survival after grafting with 80% reported resorption due to inadequate perfusion and vascularisation and anoikis.[15-16] In first 24 hours ischemia is hypothesized as most common cause of non viability of fat cells and resulting in their death.[17] Systematic review of multiple in vivo studies (~10) suggested only 15-58% survival over a period of 1-12 months and this low rate resulted in limited use so far.[18] 3-D imaging of fat grafting volume was done in one study as objective with 18% survival and survival was found to be related with the layer of grafting (81% in supra-muscular layer; 37% submuscular layer; 41% in subcutaneous tissue).[19-20] Our observational study was conducted to see the feasibility and efficacy of fat grafting in management of CLUs with complete wound healing as final outcome.

## CASE SERIES

The 14 patients had undergone fat grafting for treatment of CLU in our prospective observational study at plastic and reconstructive centre of a tertiary care hospital from December 2015 to December 2019.

### *Study population*

Inclusion criteria being patients with CLU's (any etiology, not responded to conventional therapies for >3 months and multiple ulcers were counted as individual cases if >3 cm apart) and coagulopathies, uncontrolled diabetes mellitus (Hba1c >9 mmol/mol) were exclusions.

### *Procedure*

Fat was harvested using standard Coleman's technique. Debridement was done under local anesthesia and fat cells were transferred after multiple passes in retrograde manner underneath and around the ulcers until the desired volume was achieved. Soft compression dressing was given and active pressure over the grafted area was avoided for next 3 weeks.

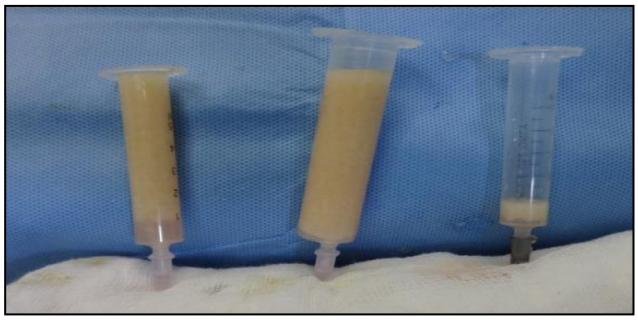

**Figure 1: Harvested fat cells.**

**Figure 2: Post centrifuged fat cells.**

**Figure 3: Fat grafting in progress.**

### *Follow up*

Patients were evaluated at 1 week, 1, 3 and 6 months.

### *Case 1*

Pre op picture of a 51 years old lady with chronic ulcer with unhealthy granulation in right heel. She was operated for Cauda equina in past. Post op picture at 6 months following fat grafting showing complete healing.

**Figure 4: Pre and post fat grafting.**

***Case 2***

Pre operative picture of a 45 years old lady with repeated breakdown of split thickness graft in left insole area leading to chronic ulcer. She was operated for RTA with crush avulsion of left foot and she is a known case of Diabetes mellitus on medication for past 05 years. Post operative picture 6 months of fat grafting showing complete wound healing.

**Figure 5: Pre and post fat grafting of case 2.**

***Case 3***

Pre op picture of a 63 years old gentleman showing chronic ulcers right leg. He is on insulin therapy for his Diabetes mellitus for past 15 years and also have chronic venous insufficiency in both lower limbs. Post op picture 6 months of fat grafting showing complete healing.

**Figure 6: Pre and post fat grafting of case 3.**

***Case 4***

Pre operative picture of a 69 years old gentleman showing CLU's. He was having these ulcers since past 8 years and was a known case of chronic venous insufficiency with DVT for past 10 years. His multiple ulcers were considered separate cases as per our inclusion criteria. Post operative picture at 6 months showing complete healing of one ulcer and marked improvement in other two ulcers in form of reduction of size and healthy ulcer bed. He underwent fat grafting again at 6 months with minimal gains and was subsequently was done split thickness skin graft for remaining wounds at 9 months. At 12 months graft has consolidated well, donor site healed well and there are minimal raw areas remaining.

**Figure 7: Pre and post fat grafting of case 4.**

***Age distribution***

Fourteen patients of CLU irrespective of etiology with complete data were included in study. Mean age for cases were 48.71 years. More than 70% of the patients were above 45 years of age.

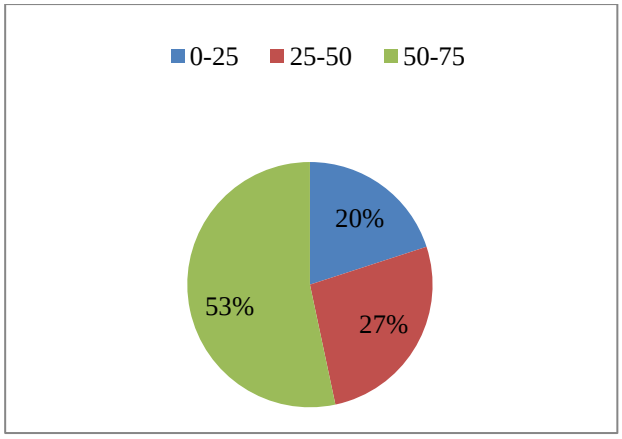


**Figure 8: Age distribution.**

***Sex distribution***

Out of 14 patients, 9 were male and 5 female patients.

***Co-morbidities associated***

Chronic venous insufficiency was noted in 5/14 patients (3 with DVT and 1 has diabetes milletus type 2 who was on insulin therapy), diabetes milletus was seen in 4/14 patients (one was on dialysis and other had chronic limb ischemia), one case each of Australian antigen positive status, operated case of cauda eqina and meningomyelocele, metastatic carcinoma cervix post radiation, and tramatic paraplegia was there to complete the list.

***Site of ulcer***

All the subjects included in the study had ulcers over the foot and lower leg.

***Size of ulcer and amount of fat grafted***

Average size of ulcer was 16.46 $cm^2$ and maximum size was 45 $cm^2$ seen in one of the patients. A total 4.9 cc of average fat was transferred underneath and around ulcer.

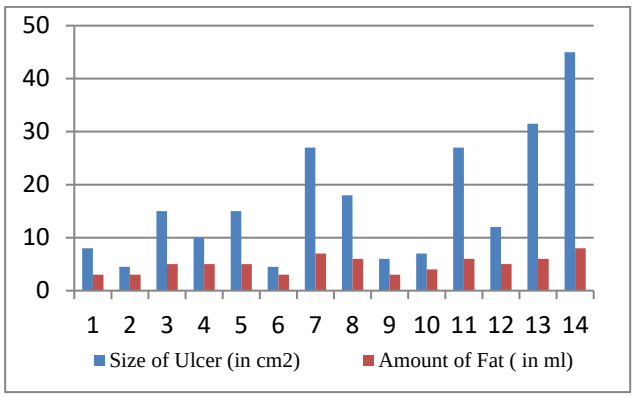


**Figure 9: Relation between size of ulcer and amount of fat grafted.**

***Donor site and type of anaesthesia***

Thigh was used as donor for fat grafts. 12 out of 14 were comfortable with Local anaesthesia with tumescent and 2 opted for Spinal anaesthesia. Pain was assessed at donor site using VAS in immediate post operative period till 48 hours (Telephonically) with average score of 3.8 and in one paraplegic patient it was not applicable.

***Time since ulcer and complete healing time***

Average age of ulcers before intervention was 33.34 months. 3 out of 14 were having these ulcers for past 8 years and post procedure one patient healed and other two showed marked improvement. 11 out of 14 ulcers healed completely within average 27.4 days and final outcome was not achieved in rest of the 3 patients. Two out of these 3 patients in which primary outcome was not achieved but improvement in terms of reduction in ulcer size and healthy granulation tissue was noted. In view of these gains, they were offered second sitting of fat grafting at 3 months and subsequently split thickness skin grafted was done for residual ulcers. Patients were evaluated at 1 week, 1 month, 3 months and 6 months.

***Early complications***

Mild pain which was settled after the first 48 hours of procedure (average VAS of 3.8) and was not a major concern of the patient. One patient developed infection with abcess inspite of the adequate management. He underwent debridement and local flap cover for the defect.

## DISCUSSION

CLU are commonly associated with high morbidity and markedly reduced quality of life.[21-23] With increasing prevalence of diabetes mellitus and its common sequelae chronic wounds are a financial burden.[24-26] Autologous fat cells have abundant ADSC and are easily harvested as compared with bone marrow derived stem cells (BMSC) under LA or GA with minimal complications. With limited research literature available, it is believed that stem cells work by taking part in inflammatory process and their transformation into different cells which mediate healing.[27-33] Caviggioli et al demonstrated complete healing of a post traumatic ulcer in their case report using fat grafting which was visible at 4 weeks compared to ~27.4 days (<4 weeks) in our study and their results stayed till 1 year while it is 24 months in our study.[34] They also reported that after the second sitting of fat grafting the quality and elasticity of skin was improved which was almost comparable to the normal skin but in our study we used it for further improvement of the residual ulcers. In Zuk et al and other studies demonstrated that adipose tissue contains ADSC's and their reparative and regenerative properties.[35-39] Smith et al in 2020 have provided valuable information on the feasibility of conducting a large-scale RCT for fat

grafting ± PRP in diabetic foot ulcers.[40] A total of 18 patients were included in the trial at a single site over 17 months and follow-up completed by 21 months whereas in our study we recruited 14 patients over a period of 24 months and subsequently followed up for 24 months. In Smith et al majority of 15 patients were type 2 diabetics on insulin therapy in late 50's, raised body mass index with ex-smoker status or at least one significant co morbidity.[40] More men (83%) were recruited than women with exclusion criteria in the beginning being kidney failure, vascular disease, wound dimensions, transport/follow-up issues, and chronic infection. In our study, 14 patients (9 were male and 5 female) of CLU irrespective of etiology with complete data were included. More than 70% of the patients were above 45 years of age with mean age was 48.71 years and at least one co morbidity. Chronic venous insufficiency was noted in 5 patients (3 with DVT and 1 had Diabetes milletus type 2 who was on insulin therapy), diabetes milletus was seen in 4 out of 14 patients (one was on dialysis and other had chronic limb ischemia, all were on insulin therapy), one case each of Australian antigen positive status, operated case of cauda eqina and meningomyelocele, metastatic carcinoma cervix post radiation therapy and tramatic paraplegia was there to complete the list. In Smith et al all patients had undergone procedures on day care basis compared to 12 patients who were given treatment on OPD basis and only 2 were admitted for day care services in our study.[40] In their study, 11 out of 12 patients required local anaesthesia and none got admitted for same as compared to ours, where 12 underwent procedure in LA and 2 opted for spinal anaesthesia, who required admission. No adverse events were noted in our study whereas 5 adverse events were seen in Smith et al.[40]

In our study, 3 patients out of 14 were having these ulcers for past 8 years and post procedure one patient healed completely and other two showed marked improvement in the form of reduction of raw area and resulted in healthy wound bed. No significant differences seen in wound volume and area, healing time, PUSH score and cost of dressings between the two groups in Smith et al and complete healing of the five wounds (28%) was seen within the 12 weeks whereas 11 patients showed complete healing (79%) in ~4 weeks (27.4 days) in our study.[40] The 10 published case series evaluated by them found that an average time required for healing was 15 weeks after fat therapy. Three published articles on fat/PRP have never reached any conclusion with accuracy with healing as an outcome was there in two articles. Healing at 20 weeks seen in 34% (n=53) and 48% (n=54) in two multi-centre trials in which hard-to-heal diabetic foot ulcers were evaluated respectively. Therefore, to assess the results properly the follow up period should be more than 20 months which was 24 months in our study. Cost of treatment was tried to be quantified with evaluation of cost of dressing but accuracy not achieved as the cost arising from the community care, hospital and society was found to be significant. All the subjects included in our study had ulcers over the foot and lower leg with average age of ulcer before intervention 33.34 months. 3 patients out of 14 were having these ulcers for past 8 years (no evidence of malignancy in biopsy done in other department) and post procedure one patient healed completely and other two showed marked improvement. Average size of ulcer was 16.46 $cm^2$ with maximum size of 45 $cm^2$ seen in one of the patients and total 4.9 cc of average fat was transferred underneath and around the ulcer. Thigh was used as donor for fat grafts in all the patients. 12 out of 14 were comfortable with Local anaesthesia with tumescent and 2 opted for Spinal anaesthesia. Pain was assessed at donor site using VAS in immediate post operative period till 48 hours with average score of 3.8 (mild and tolerated well) and in one paraplegic patient it was not applicable. 11 out of 14 wounds healed completely within average 27.4 days and final outcome was not achieved in rest of the 3 patients. 2 out of these 3 patients in which primary outcome was not achieved but marked improvement in terms of reduction in ulcer size and healthy granulation tissue was noted. In view of these gains, they were offered second sitting of fat grafting at 3 months and subsequently split thickness skin grafted was done for residual ulcers. Patients were evaluated at 1 week, 1 month, 3 months, and 6 months. One patient developed infection with abcess inspite of the adequate management. He underwent debridement and local flap cover for the defect. Our study is suggestive of the fact that the autologous fat grafting in management of CLU's found feasible, easy, cost effective, tolerable OPD procedure under minimal anaesthetic requirement in majority of cases, repeatable with minimal or negligible early complications.

### *Limitations*

Our study was conducted at single tertiary care centre and had a small sample size. Cost analysis, imaging (3-D), histological and biochemical evaluation of scar did not form a part of our study.

## CONCLUSIONS

CLU's are causing misery to mankind since stone age. CLU's have been managed with conventional therapies for years and none of them is proven to be the gold standard. Daily dressings, multiple hospital visits etc are a constantly causing the physical and mental trauma. Fat grafting has gained popularity over the last few years due to its regenerative and reparative properties. All patients tolerated outpatient procedure well, except for 2 patients who opted for spinal anesthesia and were provided day care. Fat grafting procedure is easy and convenient and can be repeated (if required) with minimal morbidity, minimal self-limiting complications and adjunct in improving the outcomes of CLU's. Complete wound healing was achieved in 11 patients and out of 3 failures one required flap cover and other two patients had marked reduction in size of ulcers for which a second sitting of fat grafting was offered at 3 months and

subsequently split thickness grafting was done for the residual ulcers. Early ambulation and lesser visits to the hospital resulted in better financial and mental wellbeing/outcomes. Our study is only suggestive but for further evaluation of favorable outcomes multi-centric randomized controlled trials will be required.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

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**Cite this article as:** Saroha R, Langer V, Singh SK Fat grafting: an adjunct in management of chronic leg ulcers. Int Surg J 2023;10:268-74.