Effectiveness of autologous leucocyte and platelet-rich fibrin (L-PRF) in management of chronic diabetic foot ulcers

Original Article

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ABSTRACT

Background: Necrotic tissues debridement, revascularization surgery, infection control, mechanical offloading, blood glucose monitoring, and patient education are the standard treatments for persistent diabetic foot ulcers. Platelet-rich fibrin has positive benefits in the stomatology fields. Leukocyte-PRF aids in soft tissue healing, bone regeneration and rich in growth factors.

Aim & Objectives: This study measured changes in wound area and documented adverse events to evaluate the efficacy of L-PRF administration in the treatment of chronic diabetic foot ulcers.

Patients and Methods: Twenty patients with persistent diabetic foot ulcers lasting longer than three months were enrolled in prospective quasi-experimental study. The patients' ulcers did not heal even after receiving the best possible wound care, which included appropriate offloading, daily dressing and proper control of infection. For six weeks, L-PRF applied topically to each patient once every five to seven days, either as an injectable and/or membrane form. Following each session, diameters of the ulcers were measured and recorded and carefully examined if there were any signs of infection or newly formed ulcers on the foot.

Results: There was a statistically significant decrease in all three ulcer dimensions, length ($p=.002$), width ($p=<.001$),depth ($p=.020$) after 6 weeks and the surface area ($p=<.001$). There was a statistically significant strong positive correlation between the change in ulcer length vs. the change in ulcer width and strong positive correlation between ABPI vs. The change in ulcer depth. It also shows a marginally significant negative correlation of moderate strength between the change in ulcer length vs. the hemoglobin A1c percentage and marginally significant positive correlation of moderate strength between the change in ulcer length vs. the change in ulcer depth.

Conclusion: The use of L-PRF can lower the burden of the illness and greatly accelerate the healing of chronic diabetic foot ulcers. It is a speedy, affordable, and accessible modality.

Key Words: Diabetic foot ulcers, ankle brachial pressure index, fibrin rich in leukocytes and platelets.

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INTRODUCTION

Diabetic foot ulcers (DFUs) that are difficult to heal represent a clinical issue to medical professionals and healthcare systems around the globe. It is estimated that in tertiary care facilities in Europe, 77% of DFUs recover in less than a year. They are a major source of morbidity and are linked to expensive treatment expenditures[1]. Debridement of necrotic tissues, revascularization surgery, infection control, mechanical offloading, blood glucose monitoring, and patient education about foot care are some of the basic treatments for persistent diabetic ulcers[2]. For some individuals, complete wound closure may take months or even years, and in as many as half of the cases, wound closure may not even succeed[3].

If this kind of therapy is unsuccessful, "advanced wound care" is advised. Many novel treatments have been put out in the past ten years, but it is unclear how successful they will be overall or whether they will have side effects. Unfortunately, the majority of advanced treatments come at a high cost and aren't always obviously better than the best possible basic wound care[2]. As surgical adjuvants, fibrin matrix and platelet components-especially growth factors-offer promising healing capabilities. Because of this, a lot of PRP techniques are still available on the market and are used to treat skin wounds. Unfortunately, in spite of favorable outcomes, these methods have little effect in treating refractory ulcers and are unable to heal large, refractory wounds. Furthermore, most patients globally cannot afford them due to their complexity and expense of usage each application[4]. Leukocyte- and platelet-rich

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fibrin (L-PRF) is an autologous blood-derived product that may be manufactured rapidly and affordably. It is a second-generation platelet concentrate intended for topical application with better effects than conventional PRPs[5].

platelet-rich fibrin (PRF) has positive benefits in the fields of plastic surgery and stomatology. There are several varieties of PRF with various applications and preparations. Numerous growth factors are included in leukocyte-PRF (L-PRF); these factors and proteins can be released gradually, aid in the regeneration of bone and soft tissues locally, and promote the body's normal healing and tissue-repair processes[6, 7].

This study measured changes in wound area and documented adverse events in order to track the benefits and evaluate the efficacy of L-PRF treatment in the management of chronic diabetic foot ulcers (DFU).

PATIENTS AND METHODS:

This prospective quasi-experimental study was carried out at the cardiothoracic and vascular surgery center at Mansoura University Hospital from May 2022 to December 2023. Patients with chronic diabetic foot ulcers (DFU) who did not improve after more than three months of appropriate offloading and optimal standard wound care were enrolled in the study. During the six weeks of this research, each patient got a topical treatment of L-PRF, either as an injectable and/or membrane, every five to seven days.

Patients who had an active infection at the site of the wound, patients who received subpar standard wound care (such as incorrect offloading or infection control), patients with peripheral artery disease (distal pulses absent or an ankle brachial index of less than 0.8 or more than 1.2), patients who were malignant or who were taking long-term steroidal and/or immunosuppressive medications, and patients with varicose vein ulcers were all excluded.

Methods

All patients were subjected to full history taking for comorbid medical conditions and risk factors. The clinical examination included inspection of foot (status of skin, muscular condition and bone structure, deformities of the feet such as claw toe and hallux valgus) and footwear. And those with Charcot's foot (diabetic neuronal-osteoarthropathy). Signs of PAD as pallor and trophic changes were also checked. The palpation of foot was done to search for signs of infection (hotness, crepitus and osteomyelitis) and signs of PAD (coldness and bruit). And assessment of distal pulsation (of ATA, PTA and DPA) was assessed.

Laboratory investigations included CBC, serum creatinine, HBA1C, and serum albumin while imaging investigations included duplex on the infrainguinal vessels with special attention of infragenicular waveform analysis of ATA, PTA, plain X-ray and CT angiography (if needed). ABPI was measured and documented with using of Hi Dop vascular Doppler with 8MHZ probe and mercurial sphygmomanometer.

Ethical Consideration

The study was submitted for approval by Institutional Research Board (IRB) (code number was MS.22.04.1969). Approval of the managers of the health care facilities in which the study was conducted. Informed verbal consent was obtained from each participant sharing in the study. Confidentiality and personal privacy were respected at all levels of the study. Collected data was not used for any other purpose.

Method of PRFM Preparation

A blood sample was taken without anticoagulant in 10-mL tubes which are immediately centrifuged at 3000 rpm for 10 minutes. The absence of anticoagulant implied the activation in a few minutes of most platelets of the blood sample in contact with the tube walls and the release of the coagulation cascades. Fibrinogen is initially concentrated in the high part of the tube before the circulating thrombin transforms it into fibrin. A fibrin clot was then obtained in the middle of the tube in 10 to 20 min after centrifugation, just between the red corpuscles at the bottom and acellular plasma at the top. Platelets were theoretically trapped massively in the fibrin meshes. After collection of the PRF itself, resistant autologous fibrin membranes were easily obtained by driving out the serum from the clot and shaped on sterile surface according to the size of the ulcer (Figure 1). Injectable L-PRF was obtained by immediately aspiration and injection of the L-PRF after centrifugation and not waiting until fibrin clot formation.

Fig. 1: After collection ofthe PRF itself (A,B), resistant autologous fibrin membranes are easily obtained by driving out the serum from the clot (C) and applied directly inside the ulcer(D)

Procedure Description

The ulcer was prepared by debridement of eschar, necrotic or devitalized tissues if present. Proper hemostasis and wound irrigation were done with normal saline. Length, width, and depth of the ulcer were measured and documented. L-PRF was obtained. Regarding the clotted L-PRF, the clot was shaped and compressed against the ulcer by sterile gauze to form a membrane, regarding the liquid L-PRF, it was injected into the floor of the ulcer in circular manner. Sterile gauze and adhesive plaster were used to cover the ulcer.

Follow Up

Ulcer dimensions were measured and documented after each session. A careful foot examination for any signs of infection or newly developed ulcers was done.

Statistical Analysis

Software used:

Data were entered and analyzed using IBM-SPSS software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

Data expression:

Qualitative data were expressed as N (%).

Quantitative data were initially tested for normality using Shapiro-Wilk's test with data being normally distributed if $p>0.050$. The presence of significant outliers (extreme values) was tested for by inspecting boxplots.

Quantitative data were expressed as mean (standard deviation) if normally distributed or median and interquartile range (Q3 or 75^{th} percentile minus Q1 or 25^{th} percentile) if not.

Data comparison:

Paired Quantitative data:

The Wilcoxon's signed ranks test was used to compare non-normally distributed paired data.

Correlations:

Spearman's correlation

The Spearman's correlation test was used to determine whether there is a linear relationship / association between two non-normally distributed quantitative data. The strength of association was considered low, medium, or high if the correlation coefficient (r) was > 0.1 to <0.3, 0.3 to <0.5, or 0.5 or more, respectively.

Significance level:

For any of the used tests, results were considered as statistically significant if $p\ value \leq 0.050$.

RESULTS:

This study involved 20 diabetic patients with foot ulcers. Their mean age (standard deviation) was 52.4 (8.1), ranging from 35 to 70 years. They were 15 males (75%) and 5 females (25%).

Hypertension was present in 18 cases (90%). Eleven patients were currently smokers (55%).

The type of off-loading was Air-Walker in two cases (10%) and Off-Sole in 18 cases (90%).

Ray amputation of the toe closely related to the ulcer occurred in two cases (10%). The surface area change (mm2/week) ranged from zero (no change) to 15 mm2/week, with a median of 3.3 mm2/week). (Table 1): Categorical characteristics of the studied cases. (Figure 2): Bar chart for categorical characteristics of the studied cases. (Table 2): Numerical characteristics of the studied cases. (Figure 3): Bar chart for numerical characteristics of the studied cases.

Table 3 shows a statistically significant strong positive correlation between the change in ulcer length vs. the change in ulcer width and strong positive correlation between ABPI vs. the change in ulcer depth. It also shows a marginally significant negative correlation of moderate strength between the change in ulcer length vs. the hemoglobin A1c percentage and a marginally significant positive correlation of moderate strength between the change in ulcer length vs. the change in ulcer depth. (Figure 4): Scatterplot of change in ulcer length vs. change in ulcer width. (Figure 5): Scatterplot of change in ulcer length vs. change in ulcer depth. (Figure 6): Scatterplot of change in ulcer length vs. hemoglobin A1c (%). (Figure 7): Scatterplot of change in ulcer depth vs. ABPI. (Table 4) shows a statistically significant decrease in all three ulcer dimensions, length ($p=.002$), width ($p=<.001$), depth ($p=.020$) after 6 weeks and the surface area ($p=<.001$). (Figure 8): Median of ulcer dimensions. (Figure 9) shows a female patient 50 years, diabetic, presented with Rt foot ulcer resistant to heal for 14 months. (Figure 10) shows a male patient 45 years, diabetic, presented with Rt foot ulcer resistant to heal for 6 months.

Table 1: Categorical characteristics of the studied cases

Characteristic	N	%
Sex		
Male	15	75
Female	5	25
Hypertension	18	90
Current smoking	11	55
The type of off-loading		
Air-Walker	2	10
Off Sole	18	90
Ray amputation of the toe closely related to the ulcer	2	10

Notes: N = absolute frequency. % = Relative frequency (percentage).

Table 2: Numerical characteristics of the studied cases

Characteristic	Mean	SD
Age (years)	52.4	8.1
Hemoglobin A1c (%)	8.8	1.04
Ankle-Brachial Pressure Index (ABPI)	1.17	0.11
	Median	**Q1-Q3**
Number of cellulitis attacks	0	0-1
Surface area change (cm) per week	0.33	0.19-0.63

Notes: SD = standard deviation. Q1-Q3 = 25^{th} – 75^{th} percentiles.

Table 3: Correlations of changes in ulcer dimensions:

Parameter	Change in ulcer length		Change in ulcer width		Change in ulcer depth	
	r_s	**Sig.**	**r_s**	**Sig.**	**r_s**	**Sig.**
Change in ulcer length	-	-	.903	**<.001**	.443	.050
Change in ulcer width	.903	**<.001**	-	-	.405	.077
Change in ulcer depth	.443	.050	.405	.077	-	-
Age (years)	-.059	.805	.084	.725	-.050	.834
Hemoglobin A1c (%)	-.443	.051	-.244	.299	.276	.240
Ankle-Brachial Pressure Index (ABPI)	.245	.297	.183	.439	.575	**.008**
Number of cellulitis attacks	.238	.158	.294	.208	.118	.621

Notes: rs = Spearman's correlation coefficient. Sig. = significance (*p-value*). The change in ulcer dimensions was calculated by subtracting dimension at presentation minus dimension after 6-weeks. The test of significance is Spearman's correlation.

Table 4: Changes in ulcer dimensions after 6-weeks

Dimension	At presentation		After 6-weeks		Change		Sig.
	Median	**Q1-Q3**	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	
Length	3	2.6-3.4	2.5	1.5-3	0.5	0-1	**.002**
Width	2.5	2-3.4	2	1.05-3	0.5	0.08-1	**<.001**
Depth	1	1-1.5	1	0.5-1.4	0.5	0-.05	**.020**
Surface area (cm^2)	7.5	5.3-12	5	1.6-10.1	1.95	1.1-3.75	**<.001**

Notes: Q1 = 25^{th} percentile. Q3 = 75^{th} percentile. Change = dimension at presentation minus dimension after 6-weeks. Sig. = significance (*p-value*). Surface area = length * width. The test of significance is Wilcoxon's signed ranks test.

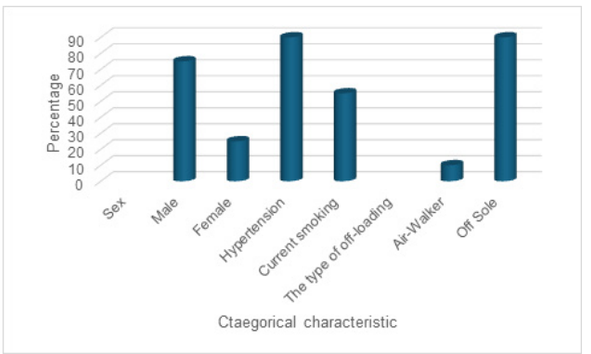

Fig. 2: Bar chart for categorical characteristics of the studied cases

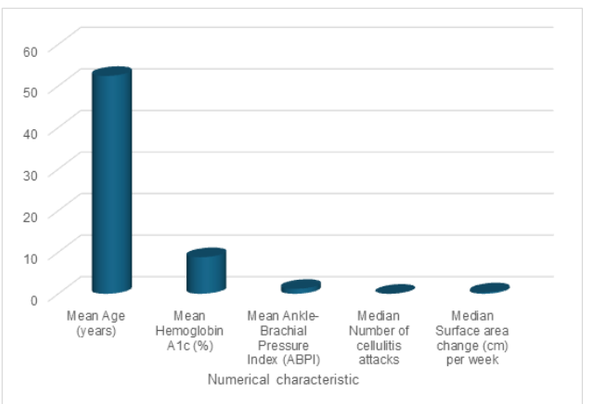

Fig. 3: Bar chart for numerical characteristics of the studied cases

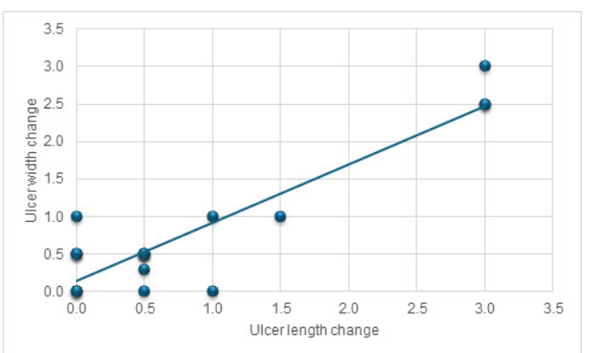

Fig. 4: Scatterplot of change in ulcer length vs. change in ulcer width:

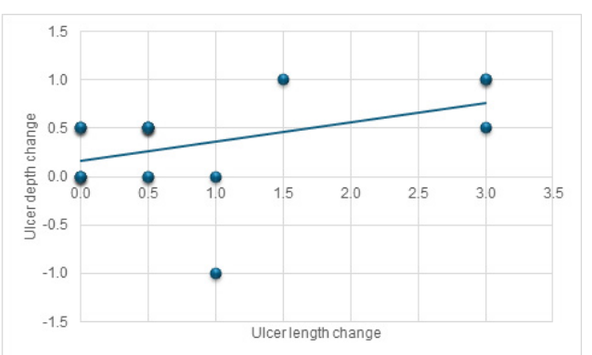

Fig. 5: Scatterplot of change in ulcer length vs. change in ulcer depth:

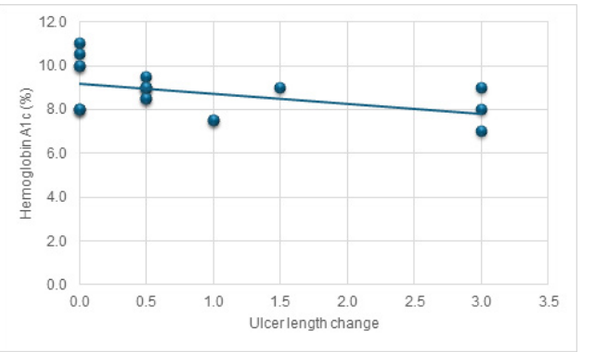

Fig. 6: Scatterplot of change in ulcer length vs. hemoglobin A1c (%):

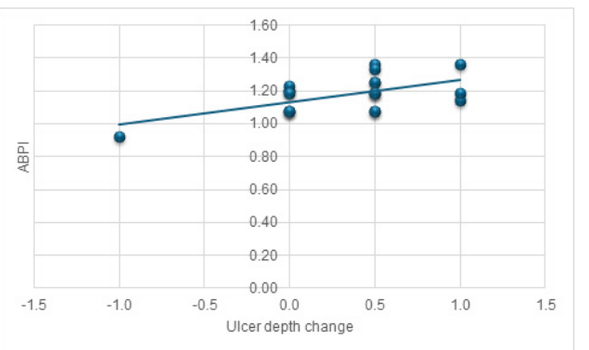

Fig. 7: Scatterplot of change in ulcer depth vs. ABPI:

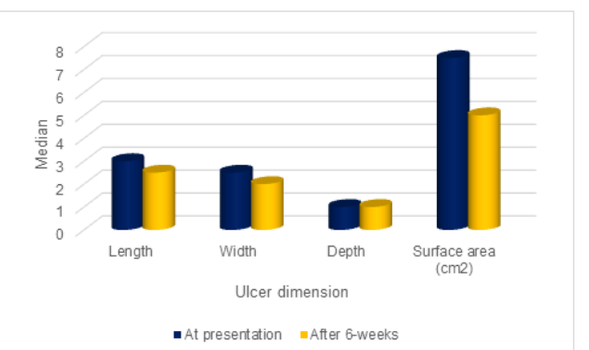

Fig. 8: Median of ulcer dimensions:

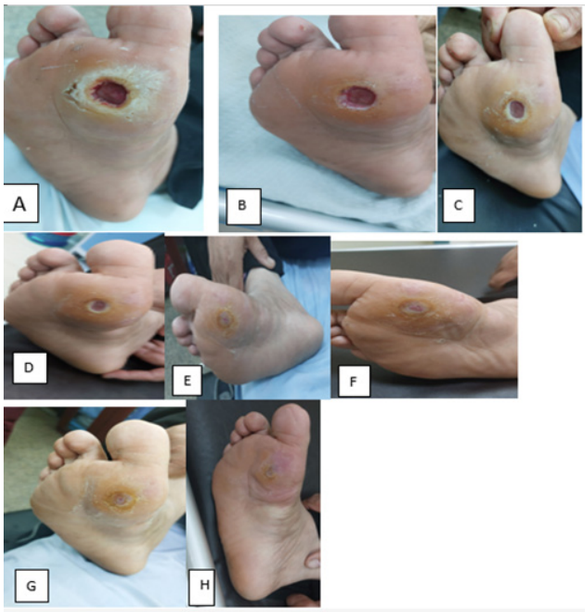

Fig. 9: Female patient 50 years, diabetic, presented with Rt foot ulcer resistant to heal for 14 months. A) Ulcer dimensions at presentations 3x2.5x1 cm. B) The ulcer after surgical curettage of the callus. C) ulcer dimensions after 1 week 2.8x2.3x0.8 cm. D) ulcer dimensions after 2 week 1.8x1.3x0.4 cm. E) ulcer dimensions after 3 week 0.5x0.5x0.2 cm. F) ulcer dimensions after 4 week 0.5x0.5x0.2 cm. G) ulcer dimensions after 5 week 0.3x0.2x0.1cm. H) ulcer after 6 week with complete healing

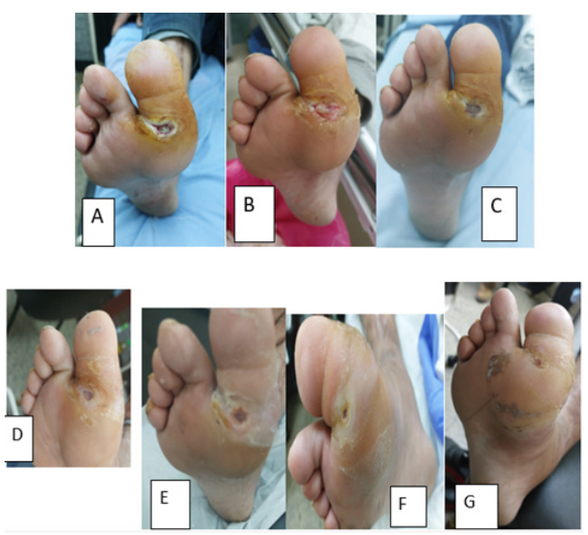

Fig. 10: Male patient 45 years, diabetic, presented with Rt foot ulcer resistant to heal for 6 months. A) Ulcer dimensions at presentations 2.5x2x1 cm. B) The ulcer after application of platelet rich fibrin (PRF) membrane. C) Ulcer dimensions after 1-week 2x1.4x0.8 cm. D) ulcer dimensions after 2 weeks 1x1x0.4 cm. E) ulcer dimensions after 3 weeks 0.7x0.5x0.2 cm. F) ulcer dimensions after 4 weeks 0.5x0.3x0.2 cm.

DISCUSSION

In individuals with peripheral neuropathy, recurrent stress over a region prone to high shear or vertical stress is often the etiology of diabetic foot ulcers. When it exists, peripheral artery disease also plays a role in the formation of foot ulcers[13].

The expense of treating DFUs makes up around one-third of the overall cost of diabetes treatment. About 20% of patients have unhealed DFUs in a year, despite these exorbitant treatment expenses. Recurrences of DFUs are prevalent even after wound resolution, occurring in around 40% of patients within a year after the initial wound closure. Even though there are well-established guidelines for handling DFUs, treating DFUs is frequently difficult[14].

The amount of time required to heal is the main issue with DFUs. Chronic inflammation is associated with increased levels of tissue inhibitor of metalloproteinase (TIMP) and matrix metalloproteinase (MMPs), both of which are major factors in the delayed healing process. Cytokines, such as interleukins (e.g., IL-1 and IL-6) and tumor necrosis factor-α (TNF-α), are released by inflammatory cells. In DFUs, neuroischemic illness restricts the flow of nutrients and oxygen to the wound, impeding the healing process. Owing to insufficient oxygen and nutrients, epithelial cells at the site of the wound are unable to express proteins that are necessary for the healing process, including platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). The lowered amounts of growth factor will prolong the healing process[12].

Numerous innovative therapies have been researched to enhance wound healing in DFU patients. A strategy approach that addresses several factors, including as changing one's lifestyle, treating the underlying cause, using antibiotics, and taking good care of wounds, is necessary for the treatment of DFUs[15].

A dressing that has the ability to lower inflammation and include growth factors is required as an adjuvant to topical DFU therapy[1].

Combination of platelets and released cytokines in a fibrin clot was initially reported by Choukroun *et al*. in 2001 as PRF. Compared to PRF, PRP contains a greater concentration of platelets. But, PRF is still more effective than PRP. This is explained by the presence of fibrin, which, when compared to standard PRP, multiplies the mean concentration of growth factors several times. Dohan *et al*.'s study demonstrated that PRF exhibited superior healing compared to PRP because to its delayed release of growth factors and cytokines. These results have led to the recent use of PRF in the treatment of chronic, non-healing leg ulcers[6].

In this study, all patients received a topical application of L-PRF either membrane and/or

injectable every 5-7 days for 6 weeks. In this study, this study involved 20 diabetic patients with foot ulcers. Their mean age (standard deviation) was 52.4 (8.1), ranging from 35 to 70 years. They were 15 males (75%) and 5 females (25%). Hypertension was present in 18 cases (90%). Eleven patients were currently smokers (55%). The type of off-loading was Air-Walker in two cases (10%) and Off-Sole in 18 cases (90%). Ray amputation of the toe closely related to the ulcer occurred in two cases (10%) due to infection. The surface area change (mm2 / week) ranged from zero (no change) to 15 mm2/week, with a median of 3.3 mm2 / week).

The current study demonstrated statistically significant strong positive correlation between the change in ulcer length vs. the change in ulcer width and between ABPI vs. the change in ulcer depth. It also shows a marginally significant negative correlation of moderate strength between the change in ulcer length vs. the hemoglobin A1c percentage and a marginally significant positive correlation of moderate strength between the change in ulcer length vs. the change in ulcer depth.

It also shows a statistically significant decrease in all three ulcer dimensions, length ($p=.002$), width ($p=<.001$), depth ($p=.020$) after 6 weeks and the surface area ($p=<.001$).

Consistent with the present findings, PRF has been demonstrated by Dorjay *et al*. 2021[16] to be effective in treating chronic or nonhealing ulcers; it is recommended that these ulcers get at least three to four sittings to promote healing. The beneficial effects of L-PRF on wound healing in DFU ulcers were shown by Yuqi Wang *et al*. in 2021[17], although there were drawbacks when treating wounds with deep bone exposure and inadequate blood supply. One of the most feared side effects of L-PRF injection is infection, which has been linked in our study to recurrent cellulitis bouts and amputation of two digits in certain patients.

Limitations in this study included a small number of cases and the use of manual method for measuring ulcer dimensions. Thus, more studies including more cases and more objective methods for measuring of ulcer dimensions should be conducted in the near future.

CONCLUSION

Our results indicate that using L-PRF can significantly promote the healing of chronic diabetic foot ulcers and reduce the severity of the condition. It is a fast, affordable, and accessible modality.

CONFLICT OF INTEREST

There are no conflicts of interest.

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