Section: Surgery

Original Research Article

A STUDY OF CHANGES IN HISTOPATHOLOGICAL FEATURES OF DIABETIC FOOT ULCER BEFORE AND AFTER GLYCAEMIC CONTROL: A SEMIQUANTITATIVE ANALYSIS IN TERTIARY CENTRE

Utkarsh Kumar[1], Anjali Singh[2], Nivesh Agrawal[3], Sanjeev Kumar Gupta[4], Deepak Kumar Singhla[5]

[1]Associate Professor, Department of Surgery kalpana Chawla Government Medical College, India.
[2]Assistant Professor Ajay Singhal Institute of Medical Sciences, Shamli, India.
[3]Professor and Head Department of Surgery, Kalpana Chawla Government Medical College, India.
[4]Professor, Department of Surgery, IMS BHU, India.
[5]Professor, Department of Surgery, KCGMC, Karnal, India.

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Corresponding Author:
Dr. Utkarsh Kumar,
Associate Professor, Department of Surgery kalpana Chawla Government Medical College, India.
Email: utkarshkumar2009@gmail.com

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ABSTRACT

Background: Diabetes is a major health concern now days due to sedentary life style and diabetic foot ulcers are the common complication that is not being managed only by regular dressing but also by strict glycaemic control. Diabetic foot ulcers have higher risk of hospitalisation and sometimes amputation so, diabetic foot ulcers required more care to prevent morbidity.
Aim: To observe the histopathological changes in diabetic foot ulcers after glycaemic controls.
Materials and Methods: It was a prospective observational study including 30 patients in Department of Surgery, in tertiary care teaching hospital of North India for a duration of 1.5 years, with their demographic profile and wound characteristics and comparing histopathological changes before and after glycaemic control. Histopathological evaluation of the severity of edema, necrosis, granulation and extracellular matrix (ECM) was performed using semi-quantitative scoring
Results: This study, the Mean wound area before glycemic control was 32.43±24.72cm2 & after glycaemic control was reduced to 13.00±9.68 cm2 with complete healing of ulcers in two patients after 6 weeks. Semiquantitative analysis confirmed the prevalence of intercellular edema and cellular debris in patients before glycemic control ($P < 0.01$), whereas extracellular matrix and granulating tissue were more prevalent in patients after glycemic control ($P < 0.01$).
Conclusion: The study concludes that glycemic control plays an important role in decreasing the wound surface area and thereby, helps in healing of foot ulcer. The histopathological features after glycemic control, showed a shift towards a reparative pattern with prevalence of granulation tissue.
Keywords: Foot ulcers, Diabetes Mellitus, Blood glucose control, Pathology.

INTRODUCTION

A study of 18000 patients in India revealed that there are70% of undiagnosed case of diabetes which is quite high in number. Most common complication is the foot ulceration; affecting approximately 15% of diabetic patients. About 85% patients with diabetic foot ulcer (DFU) undergoes amputation.[1] At the cellular level, wound healing is commonly impaired in diabetes. Wound of diabetic patients take longer time to heal because of improper integration of angiogenesis, inflammation, expression of gap junction proteins, matrix metalloproteinases (MMPs) and disordered immune response, majority of which are also governed by toll-like receptor 2 (TLR2) expression.[2] A meta-

analysis of nine randomised controlled trials in nearly 11 000 participants showed that glycaemic control improved the healing of diabetic foot ulcer, decreased the risk of amputation and improved sensory nerve function.[3] Increased local hypoxia and impaired cellular responses to hypoxia are the factors that contribute to delayed wound healing.[4] Finally, recent evidence suggests a role for epigenetic alterations, including microRNAs, in delayed DFU healing due to the complex interplay between genes and the environment.[5] Education as well as multi-disciplinary helps in reduction of complication of diabetic foot. Offloading, use of negative-pressure wound therapy, Hyperbaric oxygen therapy recommended in management of complicated diabetic foot ulcers.[6] There are several modalities and products available to enhance wound healing, many of them are costly & beyond the reach of the poor people of the developing countries like India. Some of them are cumbersome to carry out on a day today basis. In this study, we observed the wound healing after good glycaemic control.

MATERIALS AND METHODS

It was a prospective observational study, carried out in Department of Surgery in tertiary care teaching hospital of North India for a duration of 1.5 years. Approval was taken from Institutional Ethical committee. It included 30 patients with diabetic foot ulcers. Informed written consent was taken from all the participants.

Inclusion Criteria

- Patients with diabetic foot ulcer for > 6 weeks

Exclusion Criteria

- Diabetic foot ulcer patients without glycemic control
- Diabetic Patients with ischemic foot ulcers
- Pregnancy
- Patients with concomitant malignancy

Detailed history with general and systemic examination of patients was carried out. Wound details were recorded. Wound grading was done by University of Texas Diabetic wound classification.[7] To calculate wound area, a sterile transparent graph paper was placed on the wound to mark its borders. The two largest perpendicular diameters were measured using a ruler (in millimeters) & these two diameters were multiplied to obtain wound area in mm^2. [Figure 1]

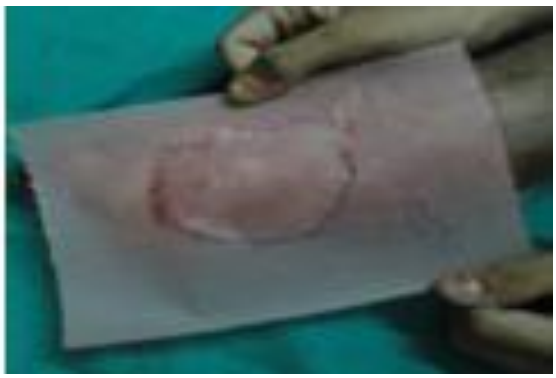


Figure 1: Wound size measurement using translucent graph paper

All the patients were followed up to 6 weeks from the date of first procedure and following data were kept in record:

- Photographic record
- All investigations were sent on day 1
- Wound biopsy on day 1 and after 6 weeks.
- Histopathological changes (H & E) on day 1 and after 6 weeks.

Post 6 weeks histopathological changes were assessed and compared to pre-glycaemic control level.

Histopathological analysis:

Histopathological evaluation of the severity of edema, necrosis, granulation and extracellular matrix (ECM) was performed using semi-quantitative scoring as follows:

+ negligible;
++ moderate;
+++ Abundant.

Necrosis was graded similarly, for convenience of grading based on viable necrotic foci under low power (10X).

+ barely visible on low power.
++ Recognizable necrosis in >1 low power field.
+++ Large necrotic area visible in low power.

Statistical analysis:

All the parameters studied during observation period were compared using chi-square test for parametric variables & Paired T test. The critical value of 'p' indicating the probability of significant difference was taken as < 0.05 for comparison. Statistical analysis was performed using SPSS 16.0 software Windows version (Inc., Chicago, USA).

RESULTS

In the study, the mean age of the diabetic foot patients was 53.50 ± 12.03 years ranging from 30 to 75 years. Male-to-female ratio was 1.5:1. The mean duration of diabetes was 6.38 ± 4.57 years. 36.67% cases had right foot ulcer, 50.0% cases had left foot ulcer and 13.3% cases had bilateral limb involvement.

Histopathological changes in the wound, including intercellular edema, necrotic tissue, granulation and extracellular matrix, were compared in the study, on

day 1 and after 6 weeks (i.e., after glycaemic control).

Wound area at presentation (i.e. before glycaemic control) was 32.43±24.7, whereas, mean wound area at 6 weeks (i.e. after glycaemic control) was reduced to 13.00±9.7. This difference was statistically significant (p<0.001). Early presentation of patients with diabetic foot ulcer and getting proper treatment (glycaemic control, regular debridement and dressing) helped in decreasing the wound size of ulcer and also prevented the progression of diabetic foot ulcer to higher grade.

Figure 2: HPE changes in Intercellular edema

Table 1

Edema	Day1 (%)	After 6 weeks (%)
1+	9 (30.0%)	10 (33.3%)
2+	11 (36.7%)	14 (46.7%)
3+	10 (33.3%)	6 (20.0%)
Total	30 (100.0%)	30 (100.0%)

$\chi 2=17.87$; p=0.0005

Figure 3: HPE of necrotic changes

Table 2

Appearance on T2-weighted image	Number of patients (n)	Percentage (%)
Low signal intensity or shading	13	30.2
Fluid–fluid level	15	34.9
Hyperintense signal intensity with suppression on TIRM	3	7.0
Hyperintense signal intensity without suppression on TIRM	12	27.9
Total	**43**	**100.0**

$\chi 2=32.96$; p=<0.001

Figure 4: HPE changes in Granulation formation

Table 3

Granulation	Day1 (%)	After 6 weeks (%)
1+	17 (56.7%)	1 (3.3%)
2+	10 (33.3%)	10 (33.3%)
3+	3 (10.0%)	19 (63.4%)
Total	30 (100.0%)	30 (100.0%)

$\chi 2=26.33$; p=<0.001

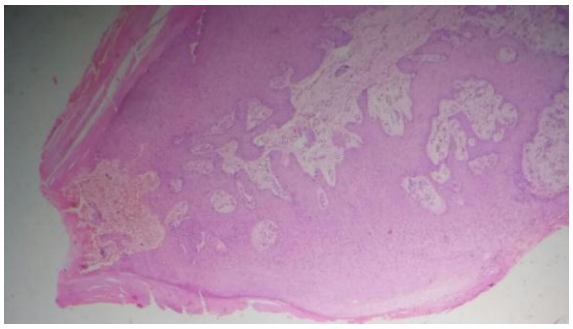


Figure 5: Hematoxylin & Eosin (H & E) stain of diabetic foot ulcer with more intercellular oedema and necrotic tissue (10x magnification)

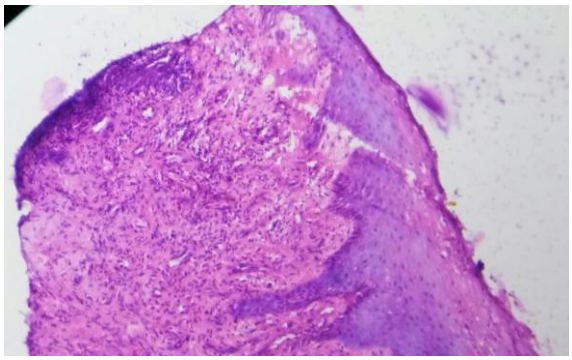


Figure 6: H & E stain of diabetic foot ulcer with less intercellular oedema and healthy granulation tissue (10x magnification)

Figure 7: HPE changes in ECM (Extracellular matrix)

Table 4:

ECM	Day 1 (%)	After 6 weeks (%)
1+	15 (50.0%)	13 (43.3%)
2+	14 (46.7%)	14 (46.7%)
3+	1 (3.3%)	3 (10.0%)
Total	30 (100.0%)	30 (100.0%)

$\chi 2=29.30$; p=<0.001

All wounds were initially characterized by marked intercellular edema (Figure 2), poorly organized ECM (Figure 7), significant inflammatory infiltration (figure 3) and the presence of young granulation tissue (Figure 4). Despite the fact that in many patients wound healing process was protracted

and resistant to local treatment, surgical treatment allowed a transformation from a chronic to an acute process. The majority of patients had wounds in inflammation phase. Hematoxylin & Eosin (H & E) stain of diabetic foot ulcer with more intercellular oedema and necrotic tissue with 10x magnification (Figure 5). H & E stain of diabetic foot ulcer with less intercellular oedema and healthy granulation tissue with 10x magnification. [Figure 6]

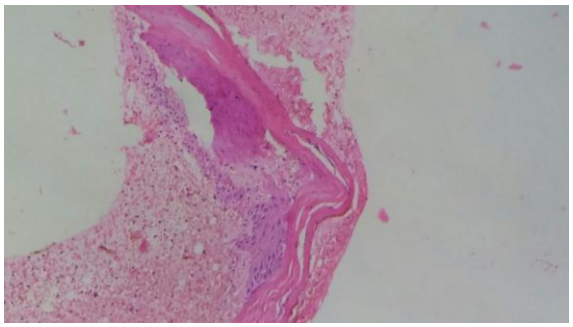
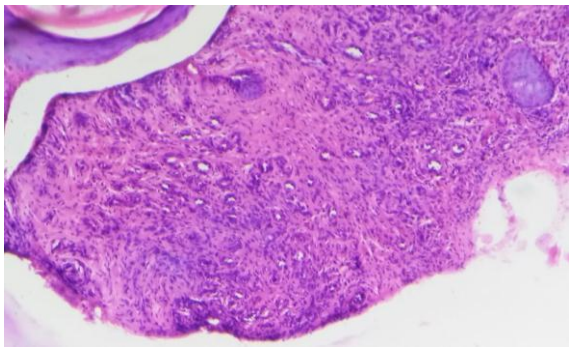


Figure 8: H & E stain of diabetic foot ulcer with more intercellular oedema and necrotic tissue and less extra cellular matrix (10x magnification)



Semiquantitative analysis confirmed the prevalence of intercellular edema, [Figure 2] and cellular debris (Figure 3) in patients before glycemic control ($P < 0.01$), whereas extracellular matrix (Figure 7) and granulating tissue (Figure 4) were more prevalent in patients after glycemic control ($P < 0.01$). H & E stain of diabetic foot ulcer with more intercellular oedema and necrotic tissue and less extracellular matrix (Figure 8), while, H & E stain of diabetic foot ulcer with less intercellular oedema, healthy granulation tissue and marked ECM. [Figure 9]

DISCUSSION

India has maximum number of diabetics in the world (50.3 million in 2010). As per W.H.O, between 2005 to 2025, there will be 170% increase in diabetic population in developing countries like India. In contrast, there will be only 42% increase in diabetics in developed countries during same period. Approximately 5% of the diabetic patients present with foot ulceration and this complication may further increase to 15%.[8]

The etiopathogenesis of diabetic foot ulcer is due to peripheral neuropathy or ischemia or both. The presence of infection compounds the problem and contributes to both morbidity and mortality in these cases.[9,10]

In this study we have excluded patients with diabetic foot ulcers with ischemia. The benefits of evidence-based multidisciplinary treatment, a 50% reduction in major lower-limb amputation risk has been achieved in people with diabetes.[11]

In this study, mean age in the diabetic foot patients was 53.50±12.03 years ranging from 30- 75 years.M:F ratio is 1.5:1. The mean duration of diabetes was 6.38±4.57 years. Study suggested that 36.67% of ulcers involved the right foot and 50.0% involved the left foot and 13.3% were bilateral limb involvement.

Wound area at presentation (i.e. before glycaemic control) was 32.43±24.7 & mean wound area at 6 weeks (i.e. after glycaemic control) was reduced to 13.00±9.7. This difference was statistically significant ($p<0.001$). Pscherer et al, 2010 found that patients with a mean HbA1c above 7.5% had 20% higher risk of amputation compared to patients with HbA1c level below 7.5%.

Most of the patients in our study were anemic with 60% patients having Hb <10 gm%. Low Hb leads to decreased oxygen delivery in the tissues and local hypoxia is known to be one of the major causes of delayed healing in such wounds though it can also be a sequela of chronic inflammation in these patients.[12] Poor socioeconomic status with resultant nutritional deficiency also contribute to low hemoglobin level.

In this study 26.7% of patients with diabetic foot ulcer had previous history of foot ulceration. It can presume that patients with history of ulceration possess all the risk factors necessary to produce another ulceration. Findings of this study are consistent with report of earlier studies, where role of previous ulceration and amputation have been recognized as risk factors for the development of new ulcers.[13] Diabetic patients if left untreated have high chances of ulcer progression. However, with proper treatment and control of hyperglycemia there is a progressive reduction in wound size eventually leading to wound healing.[14,15]

Diabetes affects the three phases of wound healing; the inflammatory phase through compromising the immune system, the proliferative phase through suppression of collagen deposition and formation of new vessels (angiogenesis) and the remodeling phase in which re-organization of collagen occurs to restore the tissue structural integrity.

There is marked histopathological changes after glycemic control in diabetic foot ulcers. Before glycemic control patients showed marked intercellular edema as well as matrix alterations and debris. After glycemic control, ulcers showed a shift toward a reparative pattern with prevalence of granulation tissue.[16,17] Semiquantitative analysis confirmed the prevalence of intercellular edema and cellular debris in patients before glycemic control ($P < 0.01$), whereas Extracellular matrix and

granulating tissue were more prevalent in patients after glycemic control ($P < 0.01$).

According to the histological study, patients with DFUs had marked intercellular edema, poorly organized ECM and wounds in the phase of inflammation and formation of granulation tissue. Histopathological changes were suggestive of decrease in inflammatory and reactive components with progression of reparative pattern.

Debridement removes devitalized tissue, bioburden, and senescent cells and promotes healing through bleeding. By debridement, a chronic ulcer becomes more of an acute state. All necrotic and non-viable tissue should be removed, and there should not be concern about the residual defect caused by the debridement as removal of this tissue is impor¬tant to attain closure.[18,19] Most wounds require serial debridement. DFUs that are debrided at each visit have a significantly greater chance of healing in 6 weeks than with debridement less often.

It is essential that healing in diabetic foot is optimized in order to improve patient outcomes and to minimize use of limited health care resources.[20]

Limitations of the study were

- small sample size
- histopathological changes before and after glycemic control were compared; no control group was included in the study

CONCLUSION

Glycemic control plays important role in decreasing the wound surface area and thereby help in healing of foot ulcers. The histopathological features are also markedly different in that after glycemic control, ulcers showed a shift towards a reparative pattern with prevalence of granulation tissue.

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