ORIGINAL STUDY

Оценка клинико-морфологических особенностей заживления язвенных дефектов при синдроме диабетической стопы

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Цель. *Провести сравнительную оценку клинико-морфологических параметров заживших и незаживших нейропатических язвенных дефектов при синдроме диабетической стопы (СДС).*

Материалы и методы. *Были проанализированы 43 образца раневых дефектов при СДС, которые в зависимости от исхода течения заживления раны были разделены на две группы: группа 1 – биоптаты ран, заживших самостоятельно (n=30), группа 2 – биоптаты ран, не заживших самостоятельно (n=13). Анализировались следующие параметры: пол, возраст, уровень HbA_{1c}, длительность существования раны, своевременность обращения за специализированной медицинской помощью, степень выраженности диабетической периферической полинейропатии, наличие поздних осложнений сахарного диабета (СД), плантарная локализация раны, соотношение грануляционной ткани, некроза, фиброза, степень экспрессии Ki 67.*

Результаты. *Пациенты обеих групп не отличались по возрасту, уровню HbA_{1c}, степени выраженности поздних осложнений СД, плантарной локализации ран. Статистически значимые отличия получены по следующим параметрам: скорость обращения за специализированной медицинской помощью [50 vs 132 (дня), p=0,03]; наличие грануляционной ткани [61±25 vs 32±21 (%), p=0,001], фиброза [24±24 vs 49±22 (%), p=0,002], грануляции/фиброз [7,5±8,1 vs 1,9±4,6 (%), p=0,02], степень экспрессии Ki67 [15±8 vs 5±6 (%), p=0,001]. В условиях одновременного влияния на заживление раны множества параметров основным являлся показатель содержания грануляций. Если их количество превышало 50%, то вероятность заживления составляла 1.0. Если грануляций содержалось менее 50%, то прогноз заживления определялся экспрессией Ki67. При уровне Ki67>7% вероятность заживления раны составляла 0,75, при уровне Ki67≤7% вероятность заживления составляла 0,17, а незаживления – 0,83.*

Заключение. *В условиях оказания специализированной помощи больным с СДС основным показателем, влияющим на прогноз заживления раны, являлась своевременность обращения больного за специализированной помощью. В многомерной модели заживления ключевым параметром являлось количество грануляционной ткани. При содержании грануляций в ране менее 50% прогноз определяется уровнем экспрессии Ki67.*

Ключевые слова: *сахарный диабет; синдром диабетической стопы; предикторы заживления язвенных дефектов; грануляции; фиброз; некроз; Ki67*

Clinical and morphological characteristics of wound healing in diabetic foot syndrome

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Aim. *To assess the clinical and morphological characteristics of neuropathic diabetic foot ulcers (DFUn)*

Materials and Methods: *Forty-three specimens of DFUn were analysed. Depending on the outcome, samples were divided into 2 groups: group 1—healed ulcers (30 samples), group 2—unhealed ulcers (13 samples). The following characteristics were analysed: age, sex, glycated haemoglobin (HbA_{1c}), ulcer duration, time of admission to the specialised clinic, severity of neuropathy, presence of late complications, plantar localisation, percentage of necrotic tissue, granulation and fibrotic tissue and, Ki-67expression.*

Results. *Patients were similar in age, HbA_{1c}, severity of late complications and plantar localisation. There was a significant difference in the time of admission to the specialised clinic [50 vs 132 days, p = 0.03], percentage of granulation [61 ± 25 vs 32 ± 21 %, p = 0.001] and fibrotic tissue [24 ± 24 vs 49 ± 22 %, p = 0.002], the granulation/fibrosis coefficient [7.5 ± 8.1 vs 1.9 ± 4.6 (%), p = 0,02] and expression of Ki-67 [15 ± 8 vs ± 21 (%), p = 0.001] between groups. A multidimensional model revealed granulation tissue as the main parameter influencing healing. The probability of healing was 1.0 if the percentage of granulation tissue was <50%. If the percentage of granulation tissue was <50%, the prognosis of healing was determined by the expression of Ki-67. When Ki-67 levels were >7%, the probability of healing was 0.75. For Ki-67 levels ≤7%, the probability of healing was 0.17 and the probability of not healing was 0.83.*

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Conclusion. *The time at which a patient was admitted to the specialised clinic and the percentage of granulation tissue were key factors affecting the prognosis of wound healing in DFUn.*
Keywords: *diabetes mellitus; diabetic foot syndrom; predictors of neuropathic diabetic foot ulcers healing; granulation tissue; fibrosis; Ki67*

Diabetic foot syndrome (DFS) is a major complication of diabetes mellitus (DM), characterised by the presence of infection, ulceration and/or the destruction of deep tissues, which are associated with neurological disorders and/or limb ischaemia of varying severity [1]. This definition of DFS covers the mechanisms underlying the development of skin damage and the reasons for slow wound healing. Therapeutic measures are usually aimed at eliminating factors that impede healing. Thus, unloading the affected limb is a key component of therapy for patients with plantar wounds. Individuals with lower limb ischaemia require the restoration of blood flow for effective wound healing. In the case of infection, systemic antimicrobial therapy should be used; otherwise, infection can spread rapidly and lead to limb amputation and lethal outcomes. In addition, we should not underestimate the utility of local treatment, including regular wound cleansing, the removal of necrotic tissue and proper wound dressing, in accordance with the healing phase. In specialised centres, patients with DFS usually receive comprehensive treatment that includes all the measures described above (if necessary), according to the standards of care [2]. Timely administration of appropriate therapy is crucial for these patients. Many experts consider it one of the main factors for preventing lower limb amputation for patients with DM [3]. However, even specialised medical care does not guarantee rapid healing and favourable outcomes. According to our data, approximately 16% of cases fail to achieve effective healing within a year [4]. Therefore, studying the clinical and morphological features of healed and unhealed wounds may provide important information for the optimisation of treatment strategies.

Aim

The aim of this study was to assess the clinical and morphological parameters of healed and unhealed wounds of patients with neuropathic DFS.

Materials and methods

We enrolled patients who were admitted to the Diabetic Foot Unit at the Endocrinological Dispensary of the Moscow Healthcare Department. To be enrolled, each patient had to have the following inclusion criteria characteristics:

- Type 1 or type 2 DM (T1DM or T2DM) and over 18 years of age;
- agreement to sign an informed consent form;
- Presence of a neuropathic ulcer;
- No visible signs of any infectious inflammatory process;
- No signs of critical ischaemia;
- Ability and willingness to follow treatment recommendations for ulcers.

All patients underwent assessment of magistral blood flow and peripheral neuropathy. Reduced magistral blood flow was diagnosed by the palpation of tibial arteries in the lower limbs, Doppler ultrasound tests and Dopplerometry with assessment of the pulse wave. The following tests were also performed as necessary: 1. duplex scanning of lower limb arteries and transcutaneous oximetry in the affected limb (TcPO2). Patients with TcPO2 < 40 mmHg were excluded from the study. Peripheral neuropathy was evaluated by the examination of tactile, pain and vibration sensitivity, as well as by the detection of abnormalities in knee jerk and Achilles reflexes. The neuropathy disability score (NDS) was used for the total estimation of these parameters [5].

All patients received special treatment for neuropathic ulcers, depending on the localisation, the presence of infection and the depth of the wound. Adherence to a special regimen, which included unloading the affected limb, was obligatory for patients with plantar wounds. Individuals with suspected wound infection received systemic antibiotics with the possibility of treatment regimen correction after microbiological examination. The tools for local therapy were selected in accordance with specific characteristics of the wound and the stage of the healing process. If, despite the therapeutic measures undertaken, the wound size decreased by less than 10% after 12 weeks of treatment [6], the patient was referred to an orthopaedic surgeon to choose an appropriate method of surgical treatment (including orthopaedic correction), depending on the wound condition and presence of foot deformation.

Morphological methods

We performed an incisional biopsy from the centre and the edges of each ulcer to be sampled after an initial rinsing with saline solution and the removal of necrotic tissues. The upper layer of the wound, approximately 0.5 cm3, was removed with a scalpel, fixed in 10% neutral-buffered formalin and embedded in paraffin wax. Serial paraffin sections were stained with hematoxylin and eosin. A morphometric technique was used to estimate the relative areas of necrosis, granulation and fibrosis (in %).

The nuclear protein Ki67, which is expressed in most phases of the mitotic cell cycle, was used as a marker of proliferation. Cells from wounds less than 1 year old have significantly higher levels of Ki67 expression [7].

Immunohistochemical staining was performed according to a standard protocol, with initial antigen unmasking performed in a microwave oven. A 3% solution

of hydrogen peroxide was used for endogenous peroxidase blocking in the deparaffinised sections.

Anti-Ki67 monoclonal antibodies (Dako, Denmark, 1:100 dilution) were used as primary specific antibodies. Ultimately, the relative number of stained cells in the granulation tissue (% per 300 cells) was evaluated.

The following clinical parameters were analysed: age, HbA1c level, age and localisation of the wound, severity of diabetic peripheral polyneuropathy as estimated by measurement of vibration sensitivity and NDS, and the presence of late complications of DM, including proliferative retinopathy and end-stage diabetic nephropathy. Morphological parameters analysed included the ratio of granulation tissue, necrosis and fibrosis. Immunohistochemical analysis included the level of Ki67 expression.

We analysed samples collected between 2013 and 2015. The condition of a wound (healed or unhealed) was assessed in September 2016. Ulcerations that showed complete epithelialisation were considered self-healed in response to the conservative therapeutic measures used. Ulcerations without complete epithelialisation or those that healed only after surgical treatment (various orthopaedic corrections) were considered non-self-healed.

Statistical data analysis

We calculated the means with standard deviations (M ± SD) for data with normal distribution; the median (Me) with 25th–75th percentile (Q25; Q75) values were calculated for data with a non-normal distribution. The Mann–Whitney U-test was used for the comparison of independent continuous variables; the Pearson's χ^2 test was used for the comparison of categorical variables. The difference was considered significant for $p < 0.05$. We constructed a decision tree for assessing the prognostic value of the multivariate model.

Ethical review

The study protocol was approved by the Ethics Committee of the Endocrinological Dispensary of the Moscow Healthcare Department on January 18, 2013.

Results

Thirty-nine patients with neuropathic DFS were included in this study. A total of 43 samples were collected (in four patients, specimens were taken from two ulcers of different ages). Table 1 contains the clinical characteristics of patients with DM and neuropathic ulcers.

All patients included in the study had had DM for a long time; the mean HbA1c level was 8.1% ± 1.5%. All participants had signs of peripheral polyneuropathy; 28% were diagnosed with proliferative diabetic retinopathy. Among the seven patients with end-stage diabetic nephropathy, five (12%) were on haemodialysis and two patients (5%) each had a transplanted kidney. In most cases, ulcers had a plantar location. Thirty wounds (70%) healed during the follow-up period after conservative treatment. Particular attention should be paid to the age of the wound, which varied significantly in the study group. The Q25 and the Q75 demonstrate that 25% of patients sought medical assistance within 3 weeks of the emergence of a wound and 75% of patients sought medical assistance within 2 months.

One of the main morphological characteristics of samples taken from the ulcers of patients with DFS is the simultaneous presence of tissues typical of different stages of re-epithelialisation, including a high percentage of granulation and fibrosis and a low percentage of necrosis. These are signs of a chronic healing process in the ulcers tested.

All specimens were divided into one of two groups, depending on the treatment outcome: the first group included biopsies of wounds that healed after conservative treatment (n = 30) and the second group included biopsies of non-self-healed wounds (n = 13). A comparative analysis of clinical parameters in both groups is shown in Table 3.

We observed a significant difference in the promptness of seeking medical assistance between the two groups. Patients from the first group came to see a doctor an average of 50 days after the emergence of a wound, whereas in the second group, it was more than 70 days. This parameter varied significantly in the group with non-self-healed wounds: some of the patients sought medical assistance within 2 weeks, whereas others sought medical assistance after 2.3 years (849 days). The number of males was significantly higher in the group with healed wounds ($p = 0.04$). Age, HbA1c level, frequency of late severe complications (proliferative retinopathy and end-stage nephropathy) and the number of patients with plantar wounds did not vary significantly between the groups.

Table 4. Comparative microscopic analysis of morphological and immunohistochemical parameters of specimens obtained from ulcers of patients with neuropathic DFS.

Table 1

Clinical characteristics of patients with DFS	
Number of patients, n	39
Number of samples, n	43
T1DM/T2DM, n (%)	6/33 (16/84)
Age, years (M ± SD)	59±6
Gender (Male/Female), n (%)	30/13 (70/30)
Duration of DM, years (M ± SD)	14±8
Insulin therapy, n (%)	28 (65)
HbA1c, % (M ± SD)	8.1 ± 1.5
Proliferative retinopathy, n (%)	12 (28)
End-stage nephropathy, stage 4–5 chronic renal disease, n (%)	7 (17)
Neuropathy disability score, points (M ± SD)	14±4
Vibration sensitivity, volts (M ± SD)	46±11
Age of the wound at the time of admission, days [Me (Q25; Q75)]	43 (19; 111)
Plantar wounds, n (%)	32 (74)
Number of healed wounds, n (%)	30 (70)

Table 2

Morphological characteristics of specimens obtained from ulcers of patients with neuropathic DFS	
Number of patients, n	39
Number of specimens, n	43
Relative content of granulation tissue, %	51±27
Relative content of necrotic tissue, %	17±21
Relative content of fibrous tissue, %	32±26
Ki67 expression, (%)	11±8

As shown in table 4 patients with healed wounds had higher levels of granulation and lower levels of fibrosis. We calculated a relative coefficient for the granulation tissue (%) and the fibrous tissue (%). In most patients with healed wounds, this coefficient was four times higher than in those with unhealed wounds ($p = 0.02$). The level of Ki67 expression was three times higher in the group with healed wounds than in the group with unhealed wounds.

To identify prognostic factors for effective wound healing among the multiple factors that probably contribute to this process, we constructed a decision tree. It allowed us to create a model addressing the impact of multiple factors on a specific event (wound healing, in our case) and identify the significant factors. The following variables were included in the model: type of DM, HbA1c level, finger amputation in anamnesis, wound localisation (plantar or non-plantar), level of vibration sensitivity, ratio of necrotic tissue, granulation tissue and fibrosis, Ki67 expression level (%) and age of the wound.

According to the model, the percentage of granulation tissue in the sample is a key parameter. If the degree of granulation exceeds 50%, wounds heal in 100% of cases. The level of Ki67 expression was 15% in this group. If the degree of granulation is below 50%, there are two possibilities: variant 1 (Ki67 > 7%) – the probability of wound healing is 0.75; variant 2 (Ki67 ≤ 7%) – the probability of the wound failing to heal is very high (0.83).

The level of Ki67 expression is closely associated with the amount of granulation tissue in the sample. The Pearson correlation coefficient was 0.6 for these variables ($p < 0.001$). The scatter plot (Fig. 1) shows the relationship between the degree of granulation and the level of Ki67. However, in some cases with a high degree of granulation (40%–60%), the level of Ki67 expression was low (<7%) (circled in red). We can assume that these were samples with so-called 'flaccid' granulation tissue, which has a low capacity for repair.

Discussion

The dynamics of wound size is the main predictor of effective healing in clinical practice. More than 50% reduction of the wound during the first 4 weeks of treatment is a good prognostic factor for complete healing within 12 weeks [8].

As previously discussed, the main factors affecting wound healing and the speed of healing (estimated by the dynamics of wound size) are the presence of infection, magistral blood flow and adherence to a special regimen, which includes unloading the affected limb. In this study, we have not identified factors affecting the speed of wound healing. Healing that occurred after conservative treatment was considered a primary endpoint.

The majority of ulcers are epithelialised within 1 year in cases where appropriate medical care is based on the elimination of the factors discussed above. For instance, the average rate of healed ulcers in European countries reaches 77% [9], in Germany, the rate varies between 57% and 93%, depending on the condition of the magistral blood flow [10], and in the United Kingdom, it is 66% [11].

Table 3

Comparative analysis of clinical parameters in both groups			
Parameter	Group 1 (N = 30)	Group 2(N = 13)	p
Age, years	58±5	61 ± 6	p=0.08
Age of the wound by the time of admission, days [Me; Q25; Q75]	50 (16; 70)	132 (14; 849)	p=0.03
HbA1c, %	8.2±1.6	7.8±1.4	p=0.41
Vibration sensitivity, volts	45±10	47±14	p=0.61
NDS, points	14 ± 4	15 ± 4	p=0.17
Proliferative retinopathy, n (%)	9 (38)	3 (27)	p=0.2
End-stage nephropathy, n (%)	6 (20)	1 (8)	p=0.4
Plantar wounds, n (%)	22 (73)	10 (77)	p = 0.8

Table 4

Comparative microscopic analysis of morphological and immunohistochemical parameters of specimens obtained from ulcers of patients with neuropathic DFS			
Parameter	Group 1 (N = 30)	Group 2 (N = 13)	p
Necrosis, %	16±22	18±19	p=0.7
Granulation, %	61±25	32±21	p=0.001
Fibrosis, %	24±24	49±22	p=0.002
Granulation, fibrosis,%	7.5±8.1	1.9±4.6	p=0.02
Ki67 expression, %	15±8	5±6	p=0.001

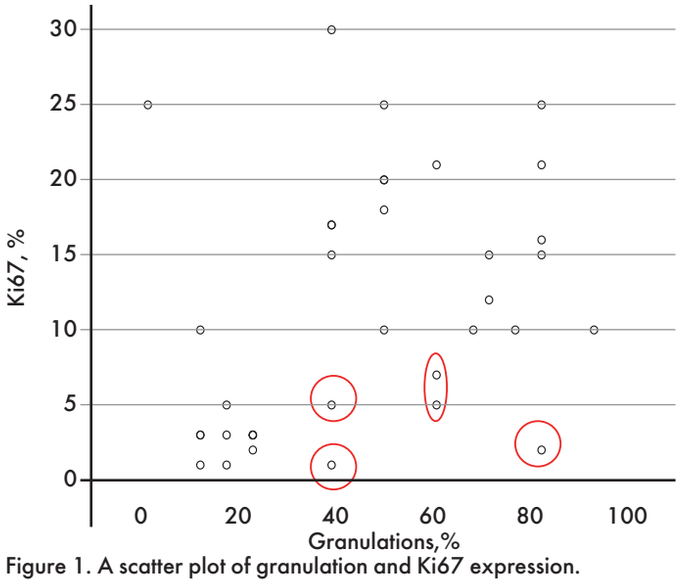

Figure 1. A scatter plot of granulation and Ki67 expression.

According to our data (without considering the magistral blood flow), the rate of healed ulcers is 78% per year; for patients with neuropathic DFS, it reaches 84% [12].

However, in some cases, even addressing all the factors described above does not lead to the reduction of wound size and subsequent healing. There may be so-called 'stagnation' of the wound in cases where a doctor does not see any deterioration or improvement of the healing process over a long time. Our observations suggest that the frequency of such cases among patients with neuropathic DFS is 16% [12]. These patients are particularly interesting for further investigation. The identification and subsequent analysis of parameters typical for this category of patients will improve the evaluation of treatment prognosis and patient management. Nevertheless, the number of healed wounds in this 'stagnation' group was twice as high as the number of unhealed wounds. These data confirm that the absence of healing in cases where all risk factors have been eliminated is an exception rather than a rule.

According to our results, the only clinical parameter significantly associated with ulcers failing to heal was the promptness of seeking medical assistance. Timely medical treatment is one of the main factors in preventing major amputations [3]. This parameter is also important for wound healing. The impact of timely medical care on wound healing has not been previously described.

Among other clinical parameters in this analysis, chronic renal failure (CRF) may influence the healing of ulcers. Preliminary comparative analysis of Ki67 expression did not demonstrate any significant differences between patients with and without CRF. Therefore, we decided to not allocate these patients to a separate group. The number of patients with CRF did not vary between groups.

The results of our comparative analyses revealed that several morphological parameters (the relative coefficient for the granulation tissue and the fibrous tissue and the level of Ki67 expression) varied significantly between the groups. The main determinant of effective wound healing is the amount of granulation tissue. It has a prominent role in the healing process [13, 14]. According to our data, the amount of granulation should not be less than 50% for the effective healing of chronic wounds. In addition, healing depends on the proliferative ability of the tissue. We assessed the level of Ki67 expression to estimate this ability. Ki67 is a universal marker of active proliferation and is mainly used in cancer diagnostics. We analysed the possibility of its use to determine the prognosis of healing. Currently available publications lack data on the expression of Ki67 for the assessment of healing in chronic wounds. Our results suggest that the Ki67 index should exceed 7% for effective healing, i.e. at least 7% of the granulation tissue should be actively proliferating. Since Ki67 is a universal marker of proliferation, it can be considered a surrogate marker for wound healing prognosis.

Our study has a number of limitations, including the relatively low number of specimens and the large number of parameters analysed. This highlights the difficulties of selecting an adequate model for assessing prognostic factors with multiple variables. In addition, some parameters demonstrated significant variability within a single group (the promptness of seeking medical assistance and the duration of in-patient treatment), which may have an impact on the results and their interpretation. However, patients with chronic non-healing wounds are quite rare in real clinical practice.

Conclusions

1. The main factor that has a significant impact on wound healing is the promptness of seeking medical assistance.
2. Among multiple parameters affecting the process of ulcer healing, the amount of granulation tissue in a wound has a prominent role.
3. A morphological examination algorithm for healing prognoses should include the following stages:
   - Evaluation of granulation in a wound (%). If the degree of granulation exceeds 50%, the probability of effective healing is 1.0;
   - If the degree of granulation is below 50%, assessment of Ki67 expression is recommended. When Ki67 expression occurs in >7% of tissue, the probability of healing is 0.75; Ki67 expression ≤7% is associated with a high risk of failing to heal (0.8).

Additional information

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Conflict of interest

The authors declare no conflict of interest related to this manuscript.

Authors contribution

M. B. Antsiferov contributed to the development of the research concept and study design, editing and final approval of the manuscript;

E. A. Kogan performed laboratory testing, data analysis, data interpretation and editing of the manuscript; E. Yu Komelyagina contributed to the development of the research concept and study design, data collection, data analysis, data interpretation and drafting of the manuscript.

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