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# The effect of human recombinant epidermal growth factor in the treatment of diabetic foot ulcers

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ABSTRACT

*Objectives*. Diabetic foot ulcer (DFU) is one of the most important and common complication of type 2 diabetes mellitus ($T_2DM$). A new therapy, consisting of intralesional administration of human recombinant epidermal growth factor (hrEGF), has been suggested to accelerate wound healing and prevent amputations. The effect of hrEGF on DFU treatment was investigated in this study. *Materials and Methods*. 20 patients with DFU were included in this study, all of whom were receiving insulin treatment for $T_2DM$. In addition, they received intralesional therapy with a dose of 75 µgr of hrEGF, three times a week. *Results*. In 18 patients, complete granulation response was achieved in approximately 3,3 weeks. There were 2 cases of recurrence at 6 months after EGF treatment. Between 6 and 12 doses of epidermal growth factor were used for this study. The most common side effects were tremor, chills, pain and burning at the site of administration. *Conclusions*. Our study shows that intralesional administration of hrEGF in $T_2DM$ can prevent amputations in DFU and also accelerate wound healing. Thus, intralesional application of hrEGF should be an option for standard care, as a second line of treatment (given its cost-effectiveness) when appropriate.

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## Introduction

Diabetic foot ulcers (DFU) are a major problem with serious consequences for the diabetic patient. The etiology of DFU is related to neuropathy, microangiopathy and infection. Such pathologies may occur separately or may coexist in the same patient. These destructive events add to the deterioration of collagen synthesis (due to the metabolic effects of diabetes) and the prolongation of wound healing. The neural and vascular structure of the foot is disturbed, followed by disturbance of both the functional and physical anatomy of the foot. DFU causes foot loss every 30 seconds in the world. DFU and infections are preventable complications of diabetes, leading to job loss, disabilities, psychosocial trauma, and high treatment costs. These complications can develop in one in six diabetic patients, while the infection can be seen in half of patients with DFU, all of which can cause amputation [1,2]. Hyperglycemia prevention, elimination of infection and immediate healing of wounds are the main principles of treatment in the prevention of these complications, which without treatment progress to the limb loss. In this study, the effect of recombinant human epidermal growth factor (hrEGF) on wound healing was investigated [3-5].

## Materials and Methods

Written informed consent was obtained from 20 patients admitted to our hospital's diabetes clinic between January 2016 and May 2019. The inclusion criteria of the patients were: age over 18 years, with DFU stage 3-4 according to the Wagner classification [2], without wound granulation despite surgical debridement and with a defect of at least 10 $cm^2$. Patients with malignancy, autoimmune disease, pregnancy, diabetic coma, decompensated heart, kidney or liver disease, and psychiatric disease were excluded from the study. Cases that were treated with corticosteroids were also excluded from this study. hrEGF

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sera produced from saccharomyces cerevisiae, using recombinant DNA technology, contain 75 µgr growth factor per mL. In each administration, 1 ml hrEGF was diluted with 4 ml saline and applied intralesionally. A dose of 75 µgr of epidermal growth factor was administered three times a week. Growth factor treatment was discontinued when complete granulation occurred in the lesion and the lesion area was less than 1 cm². Also, if the application time lasted more than 8 weeks, the treatment was stopped.

The epidermal growth factor was injected intralesionally (lesion contours) at a dose of 75 µgr each time with a 26 G needle. When the infiltration site was changed, the needle was changed each time so as not to spread or transmit the infection. After application, the lesions were covered with a sterile moist gauze. The result was assessed after eight weeks of treatment, as follows. If there was 75-100% granulation tissue formation, it was assessed as a complete response, if there was 50-75% granulation tissue formation, it was described as a partial response, and if there was 0-50% granulation tissue formation, was considered insufficient or minimal response.

## Results

The data of the 20 patients (8 men and 12 women) evaluated in the diabetes clinic of our hospital are summarized in Table 1.

**Table 1.** The relationship between demographic and medical data

| No. | GENDER | AGE | DM (years) | WOUND SIZE ($cm^2$) | NUMBER OF INJECTIONS | WAGNER CLASSIFY |
|---|---|---|---|---|---|---|
| **1** | ♂ | 44 | 11 | 16 | 7 | 4 |
| **2** | ♀ | 48 | 17 | 17 | 11 | 4 |
| **3** | ♂ | 49 | 9 | 24 | 12 | 4 |
| **4** | ♂ | 39 | 9 | 28 | 12 | 3 |
| **5** | ♀ | 77 | 18 | 19 | 6 | 3 |
| **6** | ♀ | 71 | 15 | 28 | 8 | 4 |
| **7** | ♂ | 68 | 13 | 22 | 7 | 4 |
| **8** | ♀ | 66 | 11 | 14 | 6 | 3 |
| **9** | ♀ | 67 | 14 | 17 | 7 | 4 |
| **10** | ♀ | 77 | 17 | 20 | 7 | 4 |
| **11** | ♀ | 58 | 9 | 18 | 8 | 4 |
| **12** | ♂ | 72 | 12 | 17 | 6 | 4 |
| **13** | ♀ | 49 | 9 | 25 | 11 | 3 |
| **14** | ♂ | 50 | 8 | 25 | 10 | 4 |
| **15** | ♂ | 47 | 7 | 22 | 12 | 3 |
| **16** | ♀ | 49 | 8 | 21 | 10 | 4 |
| **17** | ♀ | 59 | 9 | 27 | 9 | 4 |
| **18** | ♀ | 78 | 12 | 29 | 8 | 4 |
| **19** | ♂ | 77 | 14 | 17 | 9 | 4 |
| **20** | ♀ | 72 | 12 | 13 | 6 | 3 |

The lesions were reassessed after treatment. Complete response was observed in fifteen patients, partial response in three patients, and insufficient response in two patients. The relationship between wound size and healing time is summarized in Figure 1. Wound closure was achieved in 18 patients; by split thickness skin graft in five lesions, punch graft in five lesions, and secondary healing in eight lesions (Figures 2-3).

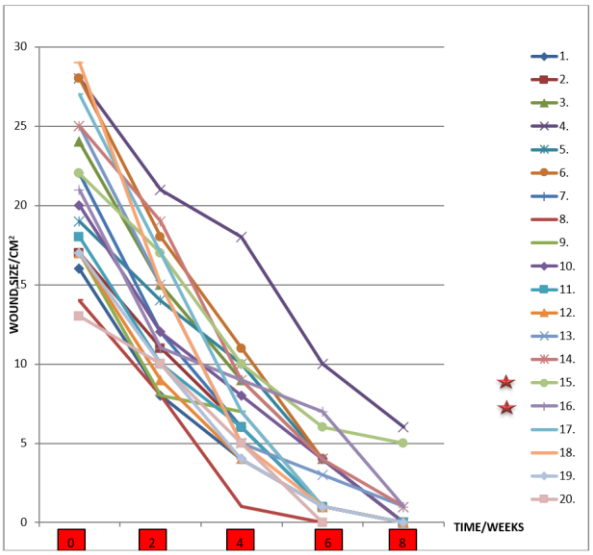


**Figure 1**. The relationship between wound size and healing time.
★ patients with insufficient response to treatment

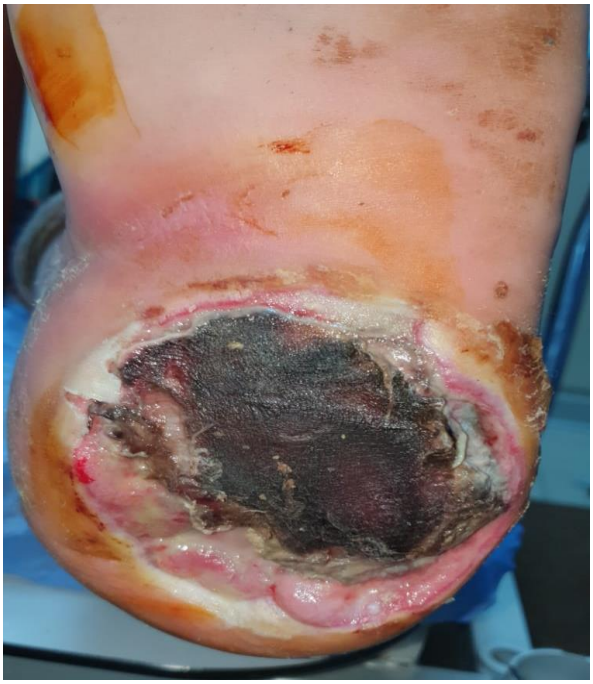

**Figure 2**. Case of DFU showing necrotic tissue prior to EGF treatment

During treatment of patients, pain occurred at the site of application in four (20%) patients, fever occurred in two (10%) patients, vomiting occurred in five (25%) patients and chillness and tremor occurred in five (25%) patients.

All of these complications did not have serious implications for patients, so treatment was not discontinued due to adverse events. Recurrent lesions were diagnosed in 2 (10%) of patients at the follow-up after 6 months of treatment; these two patients underwent amputations.

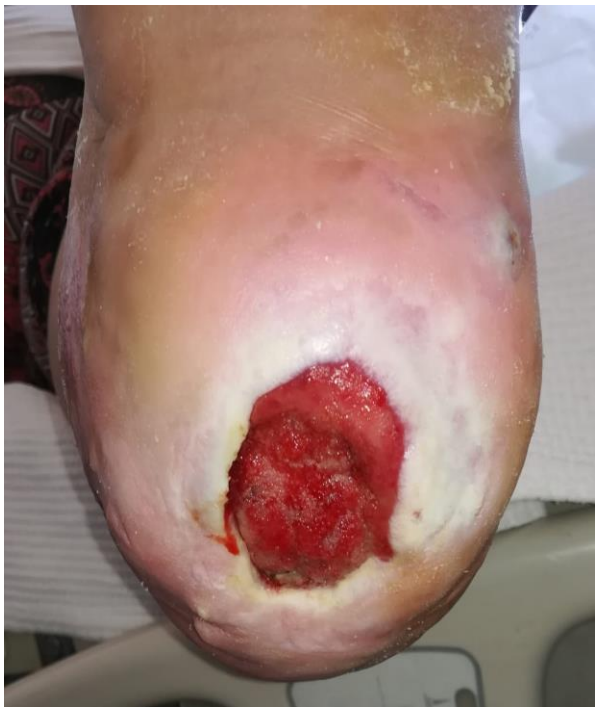

**Figure 3**. The appearance of the wound 8 weeks after EGF treatment

## Discussion

When they occur, wound control and care are very important in the treatment of DFU in patients with $T_2DM$ [6,7]. The most important therapeutic goal is to restore the anatomical and functional features of the foot. Concomitant peripheral arterial disease is often one of the complicating factors in treatment. In case of infection, the progression of the disease can be stopped by the administration of appropriate antibiotics. Debridement of necrotic and infected tissues accelerates granulation. The hrEGF stimulates the formation of granulation tissue in the wound (which is part of the surgical treatment), being also used to accelerate the closure of the wound by skin grafting. The epidermal growth factor is a polypeptide of 53 amino acids, its drug presentation being in the form of vials of 25 μgr and 75 μgr. These drugs are stored and transported at 4-8°C [8,9]. The hrEGF binds to specific cell membrane receptors, where it increases mitogenic activity, stimulates cell migration, increases the extracellular matrix and facilitates granulation tissue formation by enhancing angiogenesis and stimulating cell maturation [10,11]. The hrEGF can be neutralized by proteases present in the wound. For successful results, hrEGF is applied inside DFU lesions [12]. The growth factor may also be unavailable for its therapeutic biological activity due to the trapping/ binding to several molecules such as fibrinogen, macroglobulin or albumin [13-15].

Amputation rates have decreased in line with the increase in endovascular and surgical revascularization procedures for cases of DFU, so the diagnosis of peripheral arterial disease is very important for the treatment of diabetic foot ulcers [16-18]. In a multicenter double-blind placebo-controlled Phase III clinical study conducted by Fernández-Montequín et al., the intralesional infiltration of doses of 75 μgr /25 μgr EGF and placebo were compared. Both doses were proven to be more effective than placebo, with 75 μgr being significantly more effective than 25 μgr EGF in wound healing [19]. We decided to use a treatment dose of 75 μgr in our group of patients. Velazquez et al. similarly studied the effects of 75 μgr EGF on diabetic ulcers. In his study, the healing rate among all patients was up to 91%, and the duration of treatment was 26.5±8.9 days [20]. In terms of treatment time, we obtained similar results with this study group. In another study, Yera-Alos et al. summarized the available clinical information from the intralesional use of rh-EGF for advanced DFU. He showed that post-marketing experiences in over 2000 patients confirm the results of clinical trials with a 75% probability of a complete granulation response (61% healing), and an absolute (16%) or relative (71%) reduction in risk of amputation.

In our study, the relapse rate was almost similar to the studies reported and presented above. In their study, Yera-Alos et al. stated that treatment-related side effects were higher at 75μg dose than at 25μg. The rates and types of complications were similar to our group of patients. In this study, local infection was detected in 4% of patients after hrEGF administration, while no infection was found in our group of patients [21].

Our study was performed to confirm the observations related to the effectiveness of hrEGF in DFU treatment. Despite the successful results, there are limitations. The small number of patients is one of the limitations, so larger series are needed for clearer results. It is a study without a control group, but our patients were selected from patients who did not respond to wound care and hyperbaric oxygen treatments prior to hrEGF treatment. For this reason, the study group may be called a treatment-resistant group, thus suggesting that hrEGF treatment may be more effective than other treatments.

## Conclusions

As a result of the current study, intralesional administration of hrEGF to complete wound closure in DFU patients, in combination with good wound care measures, may accelerate wound healing. In addition, this study shows that intralesional application of EGF can prevent amputations in diabetic foot ulcers that are

nonresponsive to standard care, including the wound therapy with hyperbaric oxygen at negative pressure.

## Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

## Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

## Authors' contributions

Conceptualization: Bartin MK, Data collection: Bartin MK, Formal analysis: Okut G, Methodology: Bartin MK, Software: Okut G, Validation: Okut G, Investigation: Bartin MK, Writing - original draft: Bartin MK, Writing - review & editing: Okut G.

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