TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 1500-1504
© TÜBİTAK
doi:10.3906/sag-1703-153

# Intralesional epidermal growth factor therapy for diabetic foot ulcers: an evaluation of 15 cases

**Meltem IŞIKGÖZ TAŞBAKAN[1], Ilgın YILDIRIM ŞİMŞİR[2,*], Sinan MERMER[1], Serhat UYSAL[3], Murat ÖZTÜRK[4], Şevki ÇETİNKALP[2]**

[1]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Ege University, İzmir, Turkey
[2]Department of Internal Medicine, Division of Endocrinology and Metabolism Disorders, Faculty of Medicine, Ege University, İzmir, Turkey
[3]Clinics of Infectious Diseases and Clinical Microbiology, Buca Seyfi Demirsoy Public Hospital, İzmir, Turkey
[4]Department of Orthopedics, Faculty of Medicine, Ege University, İzmir, Turkey

**Received:** 22.03.2017 • **Accepted/Published Online:** 28.05.2017 • **Final Version:** 13.11.2017

**Background/aim:** Intralesional recombinant epidermal growth factor (EGF) is a new treatment approach for diabetic foot ulcer, approved in 2006. EGF therapy is given as an adjunct to the standard treatment regimen of antibiotics, surgery, and hyperbaric oxygen. EGF accelerates the healing of diabetic foot ulcers and reduces healing time. This single-center study was conducted to evaluate the outcomes of intralesional EGF therapy in patients with diabetic foot ulcers.

**Materials and methods:** We present the data of the follow-up patients treated in our clinics. Fifteen patients with diabetic foot ulcers or infections, who had been followed up and treated in our clinics, were included in this retrospective study. All patients were administered intralesional injections of 75 µg of EGF after treatment for infection on their diabetic foot ulcers, three times a week on alternate days. The patients were monitored with respect to treatment response and side effects of EGF.

**Results:** Thirteen patients (86.7%) developed new granulation tissue, 10 patients (66.7%) had complete wound closure, and three patients (20%) showed partial wound closure. No serious side effects requiring discontinuation of EGF therapy were observed. A total of twenty-one bacterial agents were isolated in thirteen patients, and no bacterial growth was observed in the tissue cultures of two patients. *Pseudomonas aeruginosa* was the most common isolated infectious agent in the tissue cultures (n: 6, 28%).

**Conclusion:** Intralesional injection of EGF on top of the standard treatment regimen appears to be a useful adjuvant therapy option in selected patients.

**Key words:** Diabetic foot, intralesional epidermal growth factor, wound healing

## 1. Introduction

The prevalence of diabetes mellitus and diabetes-related complications is continuously increasing. Diabetic foot ulcers represent one of the most common complications of diabetes and negatively affect patients' quality of life. Current estimates indicate that 15% of the entire diabetic patient population experiences diabetic foot ulcers at some point in their lives (1). This generates a significant burden in terms of healthcare costs. Diabetic foot ulcers impair the patients' quality of life, increase treatment costs substantially, lead to lower extremity amputations, and eventually increase mortality. The average duration of hospital stay among diabetics with foot ulcers is at least 50% longer than that of diabetics without foot ulcers. In the first 4 years after a lower limb amputation, amputation of the other leg becomes a matter of concern in more than 50% of patients. The relative risk of mortality has been shown to increase by almost 2.5-fold in diabetics who developed new foot ulcers.

The basic treatment approach to diabetic foot ulcers is based on metabolic control, good wound care, debridement, and appropriate antimicrobial therapy. New treatment methods, such as graft closure and intralesional injection of epidermal growth factor, have been developed for lower-stage wounds and neuropathic ulcers. However, alternative therapy options are still limited for higher-stage wounds, and amputation may become inevitable in such cases (2,3). Clinical trials have previously demonstrated the beneficial effects of intralesional epidermal growth factor (EGF) therapy in lower-stage neuropathic ulcers (4).

* Correspondence: ilginyildirim@hotmail.com

This single-center study was conducted to evaluate the outcomes of intralesional EGF therapy in patients with diabetic foot ulcers.

## 2. Materials and methods

Fifteen patients, who had been followed up with diabetic foot ulcers or infections, and had been given intralesional EGF therapy after the treatment of infection in our clinics between January 2014 and May 2016, were included in this study. We present the data of follow-up patients in our clinics. The patients were grouped by data records such as age, sex, duration of diabetes, previous history of diabetic foot, history of peripheral artery disease, history of osteomyelitis, nephropathy, and localization of the ulcer. All the data were recorded on patient follow-up forms. Foot pathologies were assessed by trained physicians, based on the criteria of the International Working Group on the Diabetic Foot [PEDIS (Perfusion, Extent/size, Depth/tissue loss, Infection, Sensation classification)]. Tissue samples were obtained from all patients at the time of admission. In total, 6–8 intralesional EGF injections at a dose of 75 μg/day were administered to the patients three times a week on alternate days. Before each EGF injection, necrotic and infected tissue at the injection site was debrided by a physician. Intralesional EGF therapy was initiated in all patients after the infection was controlled through adequate surgical debridement and antibiotherapy. EGF vials, supplied in cold chain, were stored at +4 °C. EGF was dissolved in 5 mL of sterile water and injected deep into the tissues surrounding the lesion.

According to the prespecified criteria, wound healing was assessed by measuring the area of granulation tissue on the lesion surface and calculating the ratio of the area of granulation tissue to the total lesion area. A ratio of <25% was considered to indicate lack of response, whereas the ratios of 26%–50%, 51%–75%, and >76% were considered to imply minimal response, partial response, and complete response, respectively. Side effects were monitored daily. All patients attended regular follow-up visits after completion of EGF therapy.

## 3. Results

A total of 15 patients were included in the present study. All patients had Type 2 diabetes mellitus and were undergoing insulin therapy. Table 1 summarizes the demographical and clinical data of the patient population. Thirteen (86.7%) patients had a history of debridement or minor amputation. Microbiological investigations were performed for all patients. A total of 21 bacterial agents were isolated in 13 of 15 cases, while no bacterial growth occurred in the tissue samples obtained from two cases. The most commonly isolated bacteria were *Pseudomonas aeruginosa* (n: 6, 28%). The other infectious agents are listed in Table 2.

**Table 1.** Demographic and clinical characteristics of patients.

| Demographic and clinical characteristics | N (%) |
|---|---|
| Age (mean ± SD) | 59.47 ± 9.3 |
| Sex (male) | 11 (73) |
| Duration of diabetes (mean, years) | 17.67 ± 8.8 |
| History of debridement | 13 (86.7) |
| Duration of ulcers (days) | 198.13 ± 227.9 |
| Previous history of diabetic foot | 7 (46.7) |
| History of peripheral artery disease | 8 (53.3) |
| History of osteomyelitis | 8 (53.3) |
| Nephropathy | 7 (46.7) |
| Baseline PEDIS | |
| Mild | 4 (26.7) |
| Moderate | 10 (66.7) |
| Severe | 1 (6.7) |
| Right foot wound | 6 (40) |
| Left foot wound | 11 (73.3) |
| Localization of the ulcer | |
| Toes, distal foot | 7 (46.7) |
| Foot sole | 8 (53.3) |
| Heel | 3 (20) |
| Dorsum, lateral foot | 5 (33.3) |
| Ankle | 1 (6.7) |
| Calf | 4 (26.7) |
| Outcome | |
| Complete response (granulation tissue >75%) | 10 (66.7) |
| Partial response (granulation tissue 51%–75%) | 3 (20) |
| No response | 2 (13.3) |

**Table 2.** Bacteria isolated from diabetic foot infections.

| Agent | N (%) |
|---|---|
| Gram positive cocci | 6 (29%) |
| *Staphylococcus aureus* | 4 |
| *Methicillin sensitive* | 3 |
| *Methicillin resistant* | 1 |
| *Streptococcus agalactiae* | 1 |
| *Enterococcus faecalis* | 1 |
| Gram negative bacilli | 15 (71%) |
| *Pseudomonas aeruginosa* | 6 |
| *Proteus spp.* | 3 |
| *P. mirabilis* | 2 |
| *P. vulgaris* | 1 |
| *Enterobacter cloacae* | 2 |
| *Klebsiella pneumoniae* | 1 |
| *Stenotrophomonas maltophilia* | 1 |
| *Serratia marcescens* | 1 |
| *Citrobacter braakii* | 1 |
| Total | 21 (100%) |

Ten patients (66.6%) developed >75% and three (20%) developed 51%–75% granulation tissue on the wound surface. Two (13.3%) did not respond to intralesional EGF therapy. Two patients, who experienced skin eruption, pruritus, and temperature increase of the extremity during the first injection, responded to symptomatic therapy (paracetamol and antihistaminics). Subsequent EGF injections were uneventful after administration of premedications. No serious side effects requiring discontinuation of EGF therapy were noted during the follow-up period. Two of the patients with complete response are shown in the Figure.

## 4. Discussion

Prevention and treatment of diabetic foot ulcers can be very challenging, as there are several factors that significantly contribute to their development, and each of these factors should be addressed separately. The ultimate goal of treatment of diabetic foot ulcers is to achieve complete wound closure whenever possible. While the basic treatment approaches are based on tight metabolic control, good wound care, debridement, and appropriate antimicrobial therapy, there is still a medical need for novel therapies (5). In this context, intralesional EGF therapy stands out as one of the complementary therapy options that may provide some benefit to selected patients.

Growth factors are proteins that regulate intracellular and intercellular signals. These proteins regulate controlled cell growth, proliferation, and differentiation; thus, they ensure that the skin maintains a healthy structure to function normally. EGF plays a mitogenic role in wound healing and induces migration of the cells responsible for wound closure to the site of ulceration, formation of the granulation tissue, angiogenesis, contraction of the wound borders by myofibroblasts, proliferation of epithelial cells, and their migration to the site of ulceration (6). Chronic wounds are characterized by decreased growth factor expression in wound tissue. Several studies have demonstrated that it is possible to accelerate wound healing by therapeutic use of growth factors.

In a study by Acosta et al. (2006), three-times-weekly EGF therapy at a dose of 25 μg/day was administered for 8 weeks to 29 patients at high risk (Wagner 3–4) of amputation with ischemic and/or neuropathic components. After the

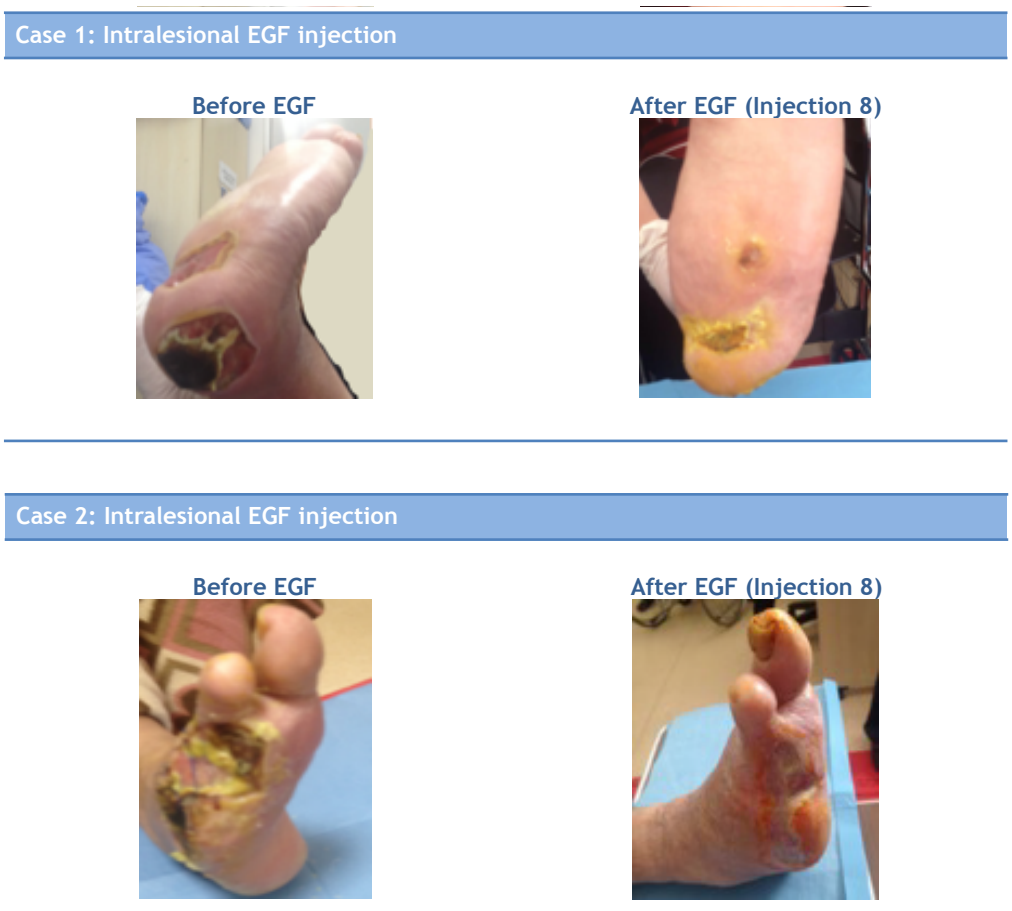


**Figure.** Descriptive case images before and after intralesional EGF injection.

eighth injection, 86% of the patients developed granulation tissue and re-epithelialization was achieved on the day 66 on average in 77% of the patients. The authors reported that a potential amputation was prevented in 17 (58%) patients, and underlined the efficacy of intralesional EGF therapy in decreasing amputation rates (7).

In their 2007 study comparing intralesional EGF doses of 75 μg (n: 23) and 25 μg (n: 18), Fernandez-Montequin et al. reported faster and more frequent formation of granulation tissue under a higher dose of EGF therapy (83% and 61%, respectively) (8).

In a multicentral Turkish study published in 2015, Ertugrul et al. assessed the efficacy of intralesional EGF therapy in 17 patients with diabetic foot ulcers. All patients were given three-times-weekly intralesional EGF at a dose of 75 μg. Wound closure was achieved in three patients (18%), whereas 13 patients (76%) developed >75% granulation tissue (9).

In the present study, 10 patients (66.7%) had moderate diabetic foot ulcers, 4 (26.6%) had mild, and one (6.7%) had severe, based on the PEDIS classification. Ten patients (66.7%) developed >75% granulation tissue on the wound surface, whereas three patients (20%) developed 51%–75% granulation tissue. Two patients (13.3%) did not respond to intralesional EGF therapy. One of the unresponsive patients had severe ulcers and the other had moderate ones, based on the PEDIS classification.

Diabetic foot infections are usually polymicrobial (10). Causative agents may include gram positive cocci, gram negative bacilli, and anaerobes. In the study by Ertugrul et al., no bacterial growth was observed in the tissue cultures of two of 17 patients given intralesional EGF therapy, and a total number of 21 bacteria species were isolated from the tissue cultures of the remaining 15 patients. In that study, the most frequently isolated bacteria specie was *Pseudomonas aeruginosa* (n = 7, 33%). Moreover, the most commonly reported side effects in their patients were tremor (n = 10, 59%) and nausea (n = 6, 35%). EGF therapy was discontinued in one patient due to a serious side effect (9). Microbiological investigations were performed in all cases in the present study, and the most frequently isolated species was *Pseudomonas aeruginosa*. In terms of side effects, two patients experienced skin eruption, pruritus, and temperature increase of the extremity during the first injection, and then responded to symptomatic therapy (paracetamol and antihistaminics). Subsequent EGF injections were uneventful after administration of premedications, and no serious side effects requiring discontinuation of EGF therapy were noted.

Although intralesional EGF may be a good complementary treatment option in appropriate cases, it continues to be an expensive therapy. In Turkey, a single vial costs 2210.98 TL (as of 5 April 2016) and the total treatment cost (three-times-weekly for 8 weeks) can amount to approximately 53,000 TL ($17,700). In a recent study by Eggert (2016), the total healthcare expenditure of a patient with lower extremity amputation due to diabetic foot infection was reported to range between $66,300 and $73,000 (11). Although intralesional EGF therapy appears to be an expensive option, it can still be cost-effective compared to the lower extremity amputations performed due to diabetic foot infections. Preserving the extremity is the most important advantage of this complementary treatment modality for appropriate patients.

In conclusion, the number of patients with diabetic foot ulcers continues to increase, and unfortunately these ulcers can result in major amputations. Intralesional EGF is a promising treatment option for preventing progression of diabetic foot ulcers and decreasing the rate of amputations among appropriate patients with diabetic foot ulcers. Previous studies and currently available data indicate that intralesional EGF can be an effective complementary treatment option in selected patients with diabetic foot ulcers.

To the best of our knowledge, this study involves the largest patient series reported so far from a single center in Turkey. Nevertheless, additional studies and long-term follow-up data are required to obtain more detailed clinical information on intralesional EGF therapy.

## References

1. Muhtaroğlu S, Barlak D, Ünlühizarcı K. Investigation of ischemia-modified albumin levels and some atherosclerosis-related serum parameters in patients with diabetic foot. Turk J Med Sci 2016; 46: 126-132.
2. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. Diabetes Care 1998; 21: 822-827.
3. Veves A, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. Diabetes Care 2001; 24: 290-295.
4. Hong JP, Jung HD, Kim YW. Recombinant human epidermal growth factor (EGF) to enhance healing for diabetic foot ulcers. Ann Plast Surg 2006; 56: 394-398.

5. Rubio JA, Aragón-Sánchez J, Jiménez S, Guadalix G, Albarracín A, Salido C, Sanz-Moreno J, Ruiz-Grande F, Gil-Fournier N, Álvarez J. Reducing major lower extremity amputations after the introduction of a multidisciplinary team for the diabetic foot. Int J Low Extr Wound 2014; 13: 22-26.

6. Berlanga-Acosta J. Diabetic lower extremity wounds: the rationale for growth factors-based infiltration treatment. Int Wound J 2011; 8: 612-620.

7. Acosta JB, Savigne W, Valdez C, Franco N, Alba JS, del Rio A, López-Saura P, Guillén G, Lopez E, Herrera L et al. Epidermal growth factor intralesional infiltrations can prevent amputation in patients with advanced diabetic foot wounds. Int Wound J 2006; 3: 232-239.

8. Fernandez-Montequin JI, Infante-Cristia E, Valenzuela-Silva C, Franco-Pérez N, Savigne-Gutierrez W, Artaza-Sanz H, Morejón-Vega L, González-Benavides C, Eliseo-Musenden O, García-Iglesias E et al. Intralesional injections of Citoprot-P (recombinant human epidermal growth factor) in advanced diabetic foot ulcers with risk of amputation. Int Wound J 2007; 4: 333-43.

9. Ertugrul BM, Buke C, Ersoy OS, Ay B, Demirez DS, Savk O. Intralesional epidermal growth factor for diabetic foot wounds: the first cases in Turkey. Diabet Foot Ankle 2015; 6: 28419.

10. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, LeFrock JL, Lew DP, Mader JT, Norden C et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2004; 39: 885-910.

11. Eggert JV, Worth ER, Van Gils CC. Cost and mortality data of a regional limb salvage and hyperbaric medicine program for Wagner Grade 3 or 4 diabetic foot ulcers. Undersea Hyperb Med 2016; 43: 1-8.