Efficacy of topical epidermal growth factor in healing diabetic foot ulcers

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Background: Peripheral neuropathy, vascular disease and immune dysfunction contribute towards the pathogenesis of the diabetic foot. Given that the only growth factor approved by the US Food and Drug Administration for the treatment of diabetic foot ulcers is platelet-derived growth factor-BB, and that controversy remains regarding the role of epidermal growth factor (EGF) in the management of this disorder, we conducted a study to assess the efficacy of EGF in accelerating the healing of diabetic foot ulcers.
Methods: In a single-blind, placebo-controlled clinical trial, 30 diabetic patients, (14 women and 16 men, age range: 27–77 years) were treated with topical EGF, and 20 controls (11 men, 9 women, age range: 32–75 years) were treated with placebo. Both groups were otherwise treated by wound debridement and irrigation with normal saline solution, systemic antibiotic therapy and daily wound dressing. The treatment and follow-up period was 4 weeks. **Results:** After 4 weeks, average wound closure in the treatment group was significantly greater than in placebo (71.2 vs. 48.9%, p = 0.03). Complete wound closure as a result of treatment was observed in seven patients and in one patient from the placebo group. EGF was significantly more effective than placebo in stimulating diabetic foot ulcer healing (relative risk: 3.4; 95% confidence interval: 1.84–13.61).
Conclusions: This study demonstrates a potential effect of topical EGF in significantly speeding up wound healing in diabetic foot ulcers; however, further multicenter studies are required in the future to confirm these results in a larger population.

Keywords: diabetes mellitus, epidermal, growth factor, foot ulcer

Diabetic patients are prone to foot ulcerations as a result of a combination of abnormal pressure to certain areas of the foot with cycles of repetitive stress, peripheral neuropathy and vascular disease. Peripheral vascular disease is rarely the cause of ulceration but does play a significant role in the level of amputation required [1,2]. These etiologies can result in severe outcomes, including gangrene and amputation [1,3]. Diabetes, one of the causes of over 50% of nontraumatic lower-limb amputations; although such statistics are eminently reducible by a mixture of risk-factor reduction, patient education, foot care, topical treatments and vascular surgery [4,5]. The annual incidence of foot ulceration in diabetic patients is 2–10%, and the annual risk of amputation in this group is between 0.2–2% [6], which is 15 to 20-fold higher than in patients without diabetes [2,3,7]. High-quality patient care and education has reduced the risk of amputation by 40–50% [8,9].

Normal wound healing results from the complex interaction of different cell types within the wound area and their ability to produce and respond to a number of growth factors. These growth factors regulate cell migration and proliferation, synthesis of the extracellular matrix, enzymatic activity and the production of more growth factors. Current belief therefore states that the healing process is, to a large extent, regulated by locally acting growth factors [10–12]. These are usually small polypeptides that stimulate, in a paracrine or autocrine fashion [12], the proliferation and biologic activity of cells [12,13]. Epidermal growth factor (EGF) is a 6 kDa protein found in platelets and vascular and duodenal glands. EGF activates mesenchymal and epithelial cells in readiness for proliferation and stimulates epidermal repair after injury [12,14,15]. It activates epidermal and stromal cell division and migration, stimulates angiogenesis, and is a potent mitogen in keratinocytes [13,15].

Given that the only growth factor approved by the US Food and Drug Administration (FDA) for the treatment of diabetic foot ulcers is platelet-derived growth factor-BB (PDGF-BB), and that controversy remains regarding the role of EGF in the management of this disorder, we conducted a study to assess the efficacy of EGF in accelerating the healing of diabetic foot ulcers.

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Patients & methods

Patients

The study was a single-blind placebo-controlled clinical trial. Patients were entered to the study randomly until a total of 50 patients (30 EGF and 20 placebo) were recruited. The patient population consisted of diabetic patients with foot ulcers presenting with the following inclusion criteria:

- Ulcer with Grade I or II, as defined by the Wagner Classification (Grade I: superficial ulcer; Grade II: deep ulcer to tendon, capsule, or bone; Grade III: deep ulcer with abscess, osteomyelitis, or joint sepsis; Grade IV: localized gangrene of forefoot or heel; Grade V: gangrene of entire foot) [16]
- Ulcer with adequate perfusion, as indicated by an ankle–brachial index (ABI) and ultrasound

After wound debridement and infection control, and following approval by the treating orthopedic or vascular surgeon, subjects were assigned to in- or out-patient therapy with either EGF or placebo. Informed written consent was obtained from each patient prior to recruitment. The study was approved by the medical ethics committee of the Research Secretariat of the Tehran University of Medical Sciences (Tehran, Iran) and carried out at Tehran's Doctor Shariati University Hospital between October 1998 and September 2001.

Methods

Patients enrolled were treated with EGF and evaluated once every week for 4 consecutive weeks with respect to wound size and severity, the presence of granulation tissue, edema, erythema and infection, fasting blood glucose and 4 pm blood glucose, smoking and the development of neurological and vascular complications. Each examination was carried out by two physicians and neuropathy was diagnosed by electromyography and nerve-conduction velocity studies. Vasculopathy was diagnosed by clinical examination (ABI) and Doppler ultrasound.

Patients in both the EGF and placebo groups had their wounds washed with normal saline and dressed every day. Wound dressing consisted of sterile gauze and adhesive tape only. No disinfecting solution, such as betadine, was used. EGF or placebo was applied once a day, every day, for 28 consecutive days, at the time of wound dressing. Wound length and width was measured (in cm) using a measuring tape, from which the surface area of the wound was calculated using the formula for calculation of the regular geometric figure that best approximated to the shape of the wound. All examinations and measurements were carried out in a blinded fashion. Examination by the same clinicians at each step, together with the single-blind design of the study, greatly reduced observer bias. Fasting blood sugar (FBS) and 2-h postprandial blood glucose (2hPP) were measured by the glucose-oxidase method and glycosylated hemoglobin ($HbA1_C$) by affinity chromatography at the beginning and end of the study. Other biochemical variables were estimated by standard laboratory methods.

EGF Formulation

The EGF formulation (Hebermin®:Heber Biotec®) used in this study contained 1 mg of recombinant human EGF/1000 mg of 1% silver sulfadiazine in a hydrophilic base. The placebo formulation contained just 1% silver sulfadiazine in the same hydrophilic base, manufactured by the pharmacy at Doctor Shariati University Hospital. No patients present in the study suffered from a sulfa allergy.

Data collection & statistical analysis

Initial study data were gathered with the use of questionnaires. Percentage wound closure was calculated using the formula:

$$\frac{\text{initial wound size after 4 weeks}}{\text{initial wound size}} \times \frac{100}{1}$$

Data were analyzed using the Chi-squared, logistic regression, Mann-Whitney U and Mantel-Hanszel tests.

Results

A total of 30 diabetic patients (14 women, 16 men; age range: 27–77 years) were assigned to the EGF group and 20 (9 women, 11 men; age range: 32–75 years) to the placebo group. Age, sex, type and duration of diabetes, history of hypertension, hyperlipidemia and smoking, wound size and duration, diabetes medication for the treatment and placebo groups can be seen in **Table 1**. All ulcers examined were present in the lower limb and in particular in the foot (75%), leg (13%) and other site (12%). Of these, three patients had ulcer on malleoli. Biochemistry results, consisting of FBS, 2hPP, $HbA1_C$, white blood cell count (WBC), erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), creatinine, total glyceride and total cholesterol, together with calculated mean blood glucose over the 4-week period of the study, were the same in treatment and placebo groups (**Table 1**).

Table 1. Preintervention features of the treatment and placebo groups .

Variable	Treatment group	Placebo group	P-value
Age (years)	56.9 ± 12.7	59.7 ± 12.3	0.50
Sex (% male)	72.7% M	53.3% M	0.22
Duration of diabetes (years)	12.6 ± 7.5	14.9 ± 7.1	0.42
BMI (kg/m^2)	24.0 ± 3.4	22.8 ± 3.8	0.30
Smoking	40%(12)	45%(9)	0.37
Wound size (mm^2)	87.5 ± 103.2	103.4 ± 147.8	0.22
Duration of wound (days)	42.9 ± 38.4	59.7 ± 55.5	0.57
Infection	70%(21)	60%(12)	0.29
Nephropathy*	76.7%	80%	0.60
Neuropathy‡	93%	100%	0.55
Vasculopathy§	43.3%	40%	0.57
Retinopathy¶	83.3%	100%	0.21
ABI < 1	46.4%	50%	0.56
Initial fasting blood sugar (mg/dl)	137.9 ± 53.9	157.6 ± 53.2	0.36
Fasting blood sugar (mg/dl) at end point	126.7 ± 49.9	134.5 ± 50.2	0.48
$HbA1_C$ (%)	10.5 ± 2.6	10.9 ± 1.65	0.22
ESR (mm/h)	47.9 ± 25	47.9 ± 22	0.54
Leukocyte count (10^9/ml)	9405 ± 3736	8730 ± 3093	0.63
Creatinine (mg/dl)	1.2 ± 0.83	0.99 ± 0.33	0.27
Triglyceride (mg/dl)	184 ± 100	148 ± 64	0.40
Total cholesterol (mg/dl)	186 ± 58	169 ± 48	0.47

Mann-Whitney U Test used for nonparametric variables not meeting criteria for normality.

**Glomerular filtration rate < 80 ml/min, with GFR calculated from plasma creatinine and 24 h urine protein and creatinine values.*

‡*by clinical examination and electromagneticlnerve conduction studies.*

§*by physical examination and Doppler ultrasound.*

¶*by fundoscopic examination by an ophthalmologist.*

ABI: Ankle-brachial index; BMI: Body mass index; ESR: Erythrocyte sedimentation rate; HbA1: Glycosylated hemoglobin.

As can be seen from **Table 2**, complete wound closure was observed in 23.3% of patients (7 out of 30 wounds) in the EGF and in 10% of patients (2 out of 20 wounds) in the placebo group. In the EGF group, wound healing greater than 70% was observed in 15 wounds (50%) and of less than 70% in 15 (50%). The corresponding figures in the placebo group were 3 and 17, respectively. The 70% cut-off point was chosen because it showed a significant correlation with EGF use; that is, at this value, EGF was 3.4 times more effective than placebo (relative risk [RR] = 3.4; 95% confidence interval [CI] = 1.84–13.6). Average hospital stay was 29.6 ± 20.95 days in the EGF group and 28.9 ± 15.1 days in placebo. **Figure 1** shows the efficacy of EGF in terms of the percentage of wounds that recovered by 70% or more, at the same time underlining the detrimental effect of neurologic and vascular complications, wound severity (Wagner staging) [16], and poor glycemic control on wound healing, even in patients receiving EGF. Note that in the patients without neuropathy, 100% of EGF-treated wounds closed by 70% or more, and that in patients with an average FBS above 140 mg/dl, less than 20% of EGF-treated wounds and none of the placebo-treated group closed by 70% or more.

Comparing patient age, duration of diabetes, duration of ulcer, and average FBS between patients with more or less than 70% closure and those with less than 70% closure, the only significant difference was in average FBS (Mann-Whitney U = 87.500, p = 0.031), again confirming the importance of tight glycemic control in the management of diabetes mellitus and its complications (**Table 3**). Patients tolerated treatment with topical EGF well. There were no topical or generalized adverse effects to report.

Discussion

In this study, we have shown the potential efficacy of EGF as an adjunct to conventional

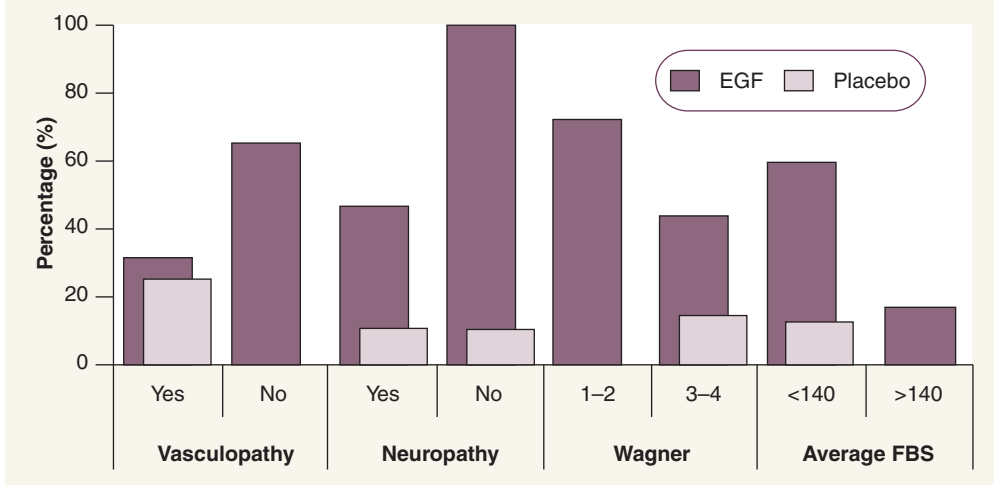
Table 2. Wound closure in treatment and placebo groups after 4 weeks.

	Group	EGF		Placebo		Test outcome
Closure		***N***	***%***	***N***	***%***	
I*	<70%	15	50	17	85	p = 0.05
	>70%	15	50	3	15	p = 0.05
II‡	Partial	23	76.7	18	90	p = 0.3
	Complete	7	23.3	2	10	p = 0.3

Closure rate is determined by the equation [(initial wound size - wound size after 4 weeks)/initial wound size] ×100; Partial closure is defined as <100%; Complete closure is defined as 100%.
EGF: Epidermal growth factor.
**Cut-off point: 70%; ‡Cut-off point: 100%*

wound care in patients with diabetic foot ulcers. The efficacy of EGF is reduced in the presence of neuropathy, vasculopathy, increasing wound severity and poor glycemic control. These findings underline the overall usefulness of EGF therapy, but even more importantly, the need for careful patient selection in order to achieve a clinically relevant response. Evidence for the efficacy of EGF as an adjunct to the treatment of chronic foot ulcers, regardless of cause, is still equivocal. A number of *in vitro* and animal studies, specifically in mice, have confirmed the importance of EGF in wound repair [12,13,15], even though strain-specific differences in wound-healing rates may distort the true effect of EGF in the mouse models studied. In 1989, Knighton and colleagues were the first to show that locally acting factors (obtained from an autologous blood sample) accelerated wound healing [17–20]. The same group also found that the use of a platelet-derived wound-healing factor as adjunct to adequate wound care in diabetic patients significantly reduced the incidence of amputation [21,22]. The therapeutic efficacy of topical recombinant human EGF (rhEGF) has been confirmed by, among others, Brown and colleagues, in a study of nine patients, five of whom had diabetes [18]. Brown also carried out a large trial of EGF efficacy on 12 nondiabetic patients with chronic wounds, again with successful results [23]. They treated their patients initially with silvadene alone, which was ineffective in spite of its antibacterial action, for a period of 3 weeks to 6 months. This was followed by treatment with EGF–silvadene, the addition of EGF producing a highly significant response. However, Cohen and colleagues failed to detect any significant difference in healing rate or speed between placebo and topical EGF in 17 healthy volunteers with artificially induced wounds. The wound environment in a healthy volunteer and a chronic diabetic are not the same; however, and

Figure 1. Efficacy of EGF versus placebo in patients whose wounds healed by more than 70%.



EGF: Epidermal growth factor; FBS: Fetal bovine serum.

Table 3. Patient characteristics by degree of healing.

Closure	<70% closure	≥70% closure	p-value
Characteristic			
Age (years)	57.6 ± 11.0	57.5 ± 14.9	0.648
Duration of diabetes (years)	14.0 ± 7.6	12.1 ± 7.2	0.406
Duration of ulcer (days)	45.0 ± 32.8	51.1 ± 57.7	0.541
Average FBS (mg/dl)	132.3 ± 32.5	110.5 ± 19.1	0.031

Values are given as mean ± standard deviation. Statistical analysis performed by the Mann-Whitney U test with a level of significance of p = 0.05. FBS: Fasting blood sugar.

any therapeutic effect of exogenous EGF in the former group may be lost in the background of an intact endogenous healing response [24].

No significant side effect has been reported in association with the use of EGF. Steed and colleagues reported that the majority of side effects were mild or moderate in severity [10]. Furthermore, they reported the overall incidence of infection – including cellulitis, wound infection, and osteomyelitis – in their treatment (PDGF) group at 11.4%, compared with 26.3% in their placebo group. This study confirms the efficacy of topical EGF in the treatment of diabetic foot ulcers. A greater than 70% reduction in wound size was observed in 3.4 times as many patients in the EGF treatment arm than placebo. The absence of any significant side effect indicates that EGF could well become part of routine therapy for diabetic foot ulcers.

Expert commentary & outlook

In spite of a number of confounding factors, our study demonstrates that EGF is superior to placebo in improving objective parameters of wound healing. Factors that reportedly influence the healing effects of EGF include vasculopathy, poor glycemic control, depth and severity of the wound, and cigarette smoking. Our findings showed that poor glycemic control decreased the healing effect of EGF. A recent study by Portero-Otín and colleagues shows that the activation of the EGF receptor (EGFR)-signaling pathway is inhibited by advanced glycation end product (AGE) precursors, in a time- and dose-dependent manner, which therefore abrogates EGF-induced EGFR autophosphorylation and the activation of two of the major EGFR downstream-signaling pathways, extracellular signal-regulated kinase (ERK) and phospholipase C (PLC)-γ [25]. These findings establish a clear link between molecular and functional events, and explain the finding that EGF efficacy is reduced in patients with poor glycemic control. They also emphasize the importance of tight glycemic control not only in the prevention of complications but also in improving the outcome of complications under treatment. In addition, in one study of the effects of PDGF on neuropathic diabetic foot ulcers, a statistically significant improvement in ulcer healing was demonstrated with a cream with 100 µg/g in PDGF but not when the cream contained 30 µg/g of the peptide [26]. However, our results were contradictory.

The involvement of non-EGF pathways in wound healing, at least in animal models [27], means that it is unlikely that EGF therapy alone can meet the therapeutic requirements of patients. This is partly confirmed by recent evidence that better response rates can be achieved by treatment with a combination of growth factors (EGF, insulin-like growth factor [IGF]-1, basic fibroblast growth factor [bFGF] and PDGF-AB) than with any factor individually [28].

There was, nevertheless, no significant difference in length of hospital stay between treatment and placebo groups (29.6 ± 20.95 days versus 28.8 ± 10.1 days). This may be explained by the fact that during the initial stage of the study, the difficulties we had in co-ordinating regular visits by the various specialties involved in the management of diabetic foot ulcers meant that patients in the EGF group had to stay longer in hospital than they really needed to. It is clear that this study had some limitations in that there were no facilities available for computerized measurement of ulcers which can result in decreased accuracy of results, as well as the small sample size, heterogeneous diabetic ulcers in nature and limited significance. Hence, this single-center study needs validation with a larger, multicenter trial.

In conclusion, our results support the contention that hEGF, in addition to good foot care, is more effective than placebo in healing diabetic ulcers, and that it may assist in reducing healing times.

Highlights

- The main goal of this study was to assess the efficacy of epidermal growth factor (EGF) in the healing of diabetic foot ulcer.
- This study was a single blind placebo-controlled clinical trial.
- In total, 50 diabetic patients with foot ulcer entered the study (30 patients received EGF and 20 placebo).
- Duration of the study was 4 weeks.
- EGF was significantly more effective than placebo in stimulating diabetic foot ulcer healing

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