Epidermal Growth Factor in the Treatment of Diabetic Foot Ulcers : An Update

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PERSPECT VASC SURG ENDOVASC THER 2012 24: 37 originally published online 11 April 2012
DOI: 10.1177/1531003512442093

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Perspectives in Vascular Surgery and Endovascular Therapy
24(1) 37–44

DOI: 10.1177/1531003512442093
http://pvs.sagepub.com

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Abstract

Management of diabetic foot ulcers remains a rather challenging task. Epidermal growth factor (EGF) plays a central role in wound healing. It acts on epithelial cells and fibroblasts promoting restoration of damaged epithelium. However, its bioavailability is impaired in chronic diabetic foot ulcers. Current evidence suggests that application of human recombinant EGF in addition to standard treatment is able to achieve both partial and complete healing and to prevent foot amputations. Its efficacy has been tested at various concentrations and by various administration routes (topical application and intralesional injection). Intralesional injection has better availability on the deep wound layers, but pain at the injection site is a common complaint. Generally, adverse events have been minor to mild. Finally, numerous issues need to be further clarified before widespread use of EGF becomes possible in everyday practice. Such issues include optimal dosage and administration route, characteristics of the ulcers most likely to heal (severity and ischemic/neuropathic or both), and cost-effectiveness.

Keywords

epidermal growth factor (EGF), growth factors, diabetic foot, wound healing

Diabetic Foot: Introduction

The diabetic foot is a common complication of diabetes mellitus. Its main feature is ulceration, which is defined as full-thickness penetration of the foot dermis, and it represents a major cause of morbidity and mortality worldwide.[1-4] The etiology of foot ulcers is multifactorial, its cornerstones being neuropathy, ischemia, and infection.[1-4] First, peripheral neuropathy leads to reduced muscular innervation and muscular atrophy, ultimately resulting in a high plantar arch, prominent metatarsal heads, and toe deformities, such as claw toes and hammer toes.[1-5] Thus, static and dynamic pressures on the plantar aspect of the foot are redistributed, and certain foot areas sustain chronic high pressure. At the same time, neuropathy is accountable for stocking distribution sensory loss, which bereaves patients of protective sensation, so that chronically elevated foot pressures are not recognized.[1-5] There is also a less extensively studied autonomic component of peripheral neuropathy. This is responsible for diminished sweat secretion, which in turn leads to dry skin, hyperkeratosis, and callus formation, with a propensity for cracking and ulceration.[4-6] Second, peripheral arterial disease reduces tissue oxygenation and hinders wound healing. Third, diabetic patients are particularly prone to infection, mainly because of impaired cellular and humoral immunity—deficiencies that are more pronounced in cases of severe chronic hyperglycemia.[3,5] During the past decade, intrinsic perturbations of the wound site have been increasingly appreciated. Among these, impaired local bioavailability of growth factors is considered to play a key role. This abnormality is mainly attributed to nonenzymatic glycation of growth factors as a result of hyperglycemia.[5]

In specialized centers, therapeutic strategy for foot ulcers depends on ulcer severity. The most commonly used classification systems are the Meggitt-Wagner system and the University of Texas system.[1,5-8] The former

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uses 5 grades of increasing severity. Grade I ulcers are superficial and do not affect tissues underlying the skin. Grade II ulcers are deeper, affecting ligaments and muscles but not bone and with no abscess. Grade III ulcers are deep ulcers with cellulitis or abscess formation, often complicated with osteomyelitis. Grade IV denotes ulcers with localized gangrene and grade V ulcers with gangrene involving the entire foot.[1] The latter classification system uses 4 grades of ulcer depth (0 to 3) and 4 stages (A to D), based on ischemia and/or infection.[6]

Optimal management of diabetic foot ulcers and amputation prevention strategies are best offered by multidisciplinary foot clinics.[1-4] Prompt revascularization, especially when the risk is low and the benefit is high (including percutaneous transluminal angioplasty/stenting, subintimal angioplasty, vein or prosthetic patch, or bypass grafting or hybrid repair), to optimize blood flow, aggressive infection control, and meticulous off-loading currently represent the mainstay of treatment. Off-loading is accomplished by total contact cast, Aircast walker, Scotch cast boot, or similar orthotic devices, along with removal of pus and debridement of nonviable tissue.[1-5] Other emerging therapies include human cultured dermis, human skin equivalent, topical growth factors, wound dressings, systemic hyperbaric oxygen,[1-4,9] and statins.[10-14] By virtue of their pleiotropic effects (mainly improvement of endothelial dysfunction and anti-inflammatory, antioxidative, and direct antiatherogenic actions), the latter improve blood flow and promote healing.[10-14] This therapeutic progress notwithstanding, diabetic foot ulcers are still notoriously difficult to manage, as reflected in the high annual incidence of ulceration and amputation: 2.5% to 10.7% and 0.25% to 1.8%, respectively.[1-4]

The present review outlines progress hitherto achieved with epidermal growth factor (EGF), one of the promising emerging therapeutic adjuncts.

Epidermal Growth Factor

EGF was discovered in mouse salivary glands in 1962.[15] It was soon recognized that it belonged to an EGF family comprising 13 ligands, whose receptors consist of 4 transmembrane tyrosine kinase receptors.[16] The latter are also called ERBB receptors, in view of their molecular similarity to the erythroblastoma viral gene product v-erbB.[16] EGF is secreted by platelets, macrophages, monocytes, and fibroblasts, acting in an autocrine and paracrine manner on epidermal cells, smooth muscle cells, and fibroblasts.[17-19]

Specifically, EGF interacts with its receptor across the entire epidermis and particularly in the basal layer,[20] promoting epithelial growth through activation of several pathways. Binding of EGF to its receptor results in prompt dimerization and autophosphorylation of the latter. This process activates the mitogen-activated protein kinase pathway, ultimately effecting phosphorylation of numerous transcription factors and calcium release by activated protein kinase C.[21] EGF also promotes epidermal regeneration and corneal epithelialization by a number of actions. Such actions include enhancing epithelial cell proliferation and migration to the wound, stimulating the production of proteins such as fibronectin, and increasing the number of fibroblasts in the wound.[22]

It is interesting to note that the healing actions of EGF appear to differ in acute versus chronic wounds. Indeed, based on ex vivo research, EGF is upregulated after acute injury, resulting in increased expression of keratins K6 and K16, thereby enhancing re-epithelialization and increasing the tensile strength in wounds.[20] Conversely, downregulation of EGF and its receptor as well as a mislocalization of EGF receptor in the cytoplasm of keratinocytes instead of the membrane are seen in chronic wounds. This probably contributes to the inhibition of epithelialization. It is important to note that addition of metalloproteinase inhibitors can reverse the substantial degradation of exogenous EGF and its receptor in chronic ulcers, implying that EGF is susceptible to the proteolytic environment of such wounds.[20]

EGF has so far been used in several clinical situations. It has been documented to induce hyperplasia and hypertrophy of skin keratinocytes and fibroblasts, thickening of the corneous layer, and stimulation of peripheral nerve regeneration.[22] Local EGF application has been tested on diabetic and venous ulcers, ulcerations following radiotherapy, burns,[22] and skin graft donor-healing sites.[20] Furthermore, its administration as an enema or oral formulation turned out to be efficacious for healing of colitis or duodenal ulcers.[22] Studies have shown that these effects are dose sensitive.[23] Its safety has been demonstrated in experiments on toxicity,[23,24] but its systemic use has been limited by the concern of promoting abnormal epithelial growth and tumorigenesis.[16]

Clinical Studies

Methodology of Studies

Available data are derived from studies with considerable heterogeneity. Indeed, in the majority of the clinical trials, patients were of Asian (China,[25] Korea,[26] India,[27] and Vietnam[23]) origin, with the exception of 3 trials, which were conducted in Cuba.[22,28,29] Patients with either type 2 diabetes mellitus[23] or both type 1 and 2 diabetes mellitus[22,25-29] were included. Presence of other disorders possibly interfering with compliance, increasing morbidity and mortality, or undermining the reliability of the conclusions served as exclusion criteria.[22,23,25-29]

Table 1. Methodology of EGF Studies

Study	Design	EGF	Patients	Method
Tsang et al,[25] China	R C DB FU 1 year	Cream, 0.02% and 0.04% concentration	G1: 19 G2: 21 G3: 21	G1: Actovegin cream G2: 0.02% EGF plus Actovegin cream G3: 0.04% EGF plus Actovegin cream
Acosta et al,[22] Cuba	NR UC hospitalization	Intralesional injection, 25 mg/vial	29	Infiltrations ×3/wk until 8 weeks or complete granulation
Hong et al,[26] Korea	Prospective, open-label crossover	Spray, 0.005% concentration	C: 21 I: 68	C: dressing I: EGF + dressing ×2/d
Viswanathan and Pendsey,[27] India	C R DB, multicenter	Gel, 150 mg/g	C: 30 I: 30	C: placebo I: EGF ×2/d until 15 weeks or healing
Fernández-Montequín et al,[28] Cuba	R UC DB, multicenter FU 1 year	Intralesional injection, 75 or 25 mg/vial	G1:23 G2: 18	G1:75 mg EGF G2: 25 mg EGF ×3/wk
Tuyet et al,[23] Vietnam	UC FU 8w	Spray, 0.005% concentration	28	×2/d + Hydrocolloid dressing
Fernández-Montequín et al,[29] Cuba	R C DB 8 weeks, multicenter, crossover FU 1 year	Intralesional injection, 75 or 25 mg/vial	G1: 53 G2: 48 G3: 48	G1: 75 mg EGF G2: 25 mg EGF G3: placebo ×3/wk

Abbreviations: EGF, epidermal growth factor; R, randomized; C, controlled; DB, double-blinded; FU, follow-up; G, group; NR, nonrandomized; UC, uncontrolled.

Moreover, ulcer severity, as defined by the Meggitt-Wagner classification system, and ulcer type (ischemic vs neuropathic lesion) were quite variable. However, all author groups offered standard ulcer treatment and add-on EGF.[22,23,25-29] Finally, and of foremost importance, the route of EGF administration presented considerable variation: EGF was given either as a topical formula[23,25-27] or as an intralesional injection but at very diverse concentrations.[22,28,29] It should be noted that this variation in the mode of administration could alter not only EGF bioavailability but also its tolerance and adverse event profile. Tables 1 and 2 summarize these important methodological differences.

Efficacy of Studies

The main outcome was the effect of EGF on the healing rates of diabetic foot ulcers. Ulcer closure was achieved after treatment with various concentrations and pharmacological forms of EGF and depended on ulcer severity.

Use of EGF for the management of grade I to II diabetic foot ulcers has been examined by 2 randomized, double-blind, controlled studies. Tsang et al[25] found significantly higher complete healing rates (95.30%) in patients treated with a cream containing 0.04% EGF plus Actovegin cream for 12 weeks in comparison with those receiving 0.02% EGF cream plus Actovegin cream (57.14%) or Actovegin cream alone (42.10%). Moreover, healing time in the 0.04% group was significantly (P = .0003) shorter (median time: 6 weeks) compared with the other groups.[25] Similarly, Viswanathan and Pendsey[27] showed that 69% (21/30) of ulcers healed in the group treated with EGF 150 mg/g gel twice daily in comparison to 21% (6/30) of ulcers in the control group at the end of 10 weeks. Parametric analysis showed that it took 9 weeks for ulcers to heal in the EGF group versus 13 weeks in the control group.[27]

In grade II and III ulcers accurately treated for arterial insufficiency and infection, twice daily local application of a 0.005% EGF spray has been examined in combination with advanced (hydrocolloid or composite) dressing. Tuyet et al[23] found that 56.5% (13/23) of ulcers of patients who had finished the 8-week follow-up period and did not drop out because of either uncontrolled infection or skin grafting achieved complete healing within an average of 39 days. The rates of wound closure were 43.3%, 59.9%, 68.7%, and 84.8% at weeks 2, 4, 6, and 8, respectively, regardless of ulcer severity.[23] Likewise, Hong et al,[26] in an open-label, crossover trial found complete healing in 76% (52/68) of patients who showed minimal progress during the first 3 weeks of treatment with advanced dressing and crossed over to the group that used EGF as an add-on therapy within an average of 46 days. This compared with 24% (21/89) of patients improving

Table 2. Inclusion Criteria Used in the EGF Studies

	Inclusion Criteria		Exclusion Criteria	
Study	General	Foot	General	Foot
Tsang et al,[25] China	DM1/DM2	UG I-II ABI ≥ 0.7	HbA_{1c} ≥ 12%	UG III-V
Acosta et al,[22] Cuba	DM1/DM2	UG III-IV ABI < 0.7 or ABI > 0.7+ ↑risk of amputation	Pregnancy/Nursing Malignant/Autoimmune/Psychiatric disorders Immunosuppressing/Corticosteroid medication	UG I-II UG V
Hong et al,[26] Korea	DM1/DM2	UG II-III D ≥ 3 months	Uncontrolled DM	Ischemia Joint sepsis Osteomyelitis Abscess
Viswanathan and Pendsey,[27] India	DM1/DM2 >18 years <65 years	Size > 2 cm^2 Size < 50 cm^2 D > 2-3 weeks ABI ≥ 0.75	Pregnancy/Nursing Heart failure/Hypertension grade III Gastrointestinal/Hepatic/Renal/Endocrine/ Hematological/Immunological disorders Hypersensitivity to the incipient(s) Uncontrolled DM/diabetic ketoacidosis/coma Chronic alcohol abuse Medication that could impair wound healing Participation in another study	UG III-V Purulent drainage Osteomyelitis Failure of dressing treatment Failure of other growth factor treatment
Fernández-Montequín et al,[28] Cuba	DM1/DM2 >18 years	UG III-IV↑ Risk of amputation	Pregnancy/Nursing Anemia Coronary/Heart disease Diabetic ketoacidosis/coma Renal failure Malignant/psychiatric/neurological disorders	Size ≤ 1 cm^2
Tuyet et al,[23] Vietnam	DM2 >35 years <75 years	UG II-III Nonclosure wounds after toe amputation Clean/Uninfected wounds	Pregnancy/Nursing Hypersensitivity to topical preparations Malignant/Hepatic/Renal/Autoimmune disorders Coronary/Heart disease Active pulmonary tuberculosis Cerebrovascular accident Malnutrition Immunosuppressing/Corticosteroid medication	Arterial insufficiency Foot infection Osteomyelitis Charcot foot Electrical/Radiation trauma Transtibial amputation Skin flap/graft
Fernández-Montequín et al,[29] Cuba	DM1/DM2≥18 years	UG III-IV Size > 1 cm^2	Anemia Coronary/Heart disease Diabetic ketoacidosis/coma Renal failure Malignancy Psychiatric/Neurological diseases Pregnancy/Nursing	Revascularization Risk of surgery

Abbreviations: EGF, epidermal growth factor; DM, diabetic patients; UG, ulcer grade (Wagner classification); ABI, ankle-brachial index; HbA_{1c}, glycated hemoglobin A_{1c}; ↑, high; D, duration.

on hydrocolloid or composite dressing alone and the overall 58% (52/89) healing rate of the population studied.[26]

In grade III to IV ulcers, intralesion EGF infusion 3 times per week has yielded satisfactory results. In the randomized, double-blind, multicenter trial by Fernández-Montequín et al,[28] complete ulcer healing at 5 weeks was achieved in 73.9% and 50.0% of patients treated with 75 and 25 μg of EGF, respectively, These results were verified by an extension of the study.[29] Ulcer closure occurred in 77.4% (41/53), 52.1% (25/48), and 56.2% (27/48) of patients treated with 75 μg EGF, 25 μg EGF, and placebo, respectively, whereas time to ulcer closure was significantly shorter in the 75-μg group (3 weeks).[29]

Some data are also available on granulation and partial healing of diabetic foot ulcers. Partial (83%) healing of grade I to II ulcers with an average duration of 5.5 weeks was documented in the study of Viswanathan and

Pendsey[27] Additionally, grade II to III ulcers showed great improvement after twice daily local application of a 0.005% spray EGF in combination with advanced (hydrocolloid or composite) dressing. The study of Tuyet and colleagues[23] found that 100% (28/28) of ulcers had granulated, whereas wound size was reduced up to more than 80% in the eighth week, regardless of grade or size. The evidence from intralesional injection of EGF agrees with results from local application: 86% (25/29) of patients treated with 25 μg EGF showed a productive granulation (71.1% ± 18.3%) during a mean in-hospital period of 66.5 ± 4.9 days in the study of Acosta et al.[22] With a higher dose of 75 μg EGF, the probability for 50% of the wound area to be covered by granulation tissue was higher and was attained 1 week earlier, as shown by Fernández-Montequín et al.[28] These results were verified in the randomized, controlled, double-blind study of Fernández-Montequín et al.[29] The main end point was granulation tissue covering ≥50% of the ulcer at 2 weeks. This was achieved in 19/48 controls versus 44/53 in the 75-μg group (odds ratio [OR] = 7.5; 95% confidence interval [CI] = 2.9-18.9) and 34/48 in the 25-μg group (OR = 3.7; 95% CI = 1.6-8.7).[29]

Ulcer characteristics, such as size and etiology, have also received attention. Healing of ulcers with area >6 cm^2 was significantly better ($P < .002$) in patients with grade I to II ulcers treated with local application of 150 mg/g EGF in comparison to the patients treated with placebo.[27] This difference in healing was not identified in ulcers with area ≤6 cm^2.[27] Acosta et al[22] examined the differences in the healing process between ischemic and neuropathic lesions after intralesional injection of 25 μg of EGF. In both ulcer types, inflammatory infiltration was attenuated and granulation was clearly enhanced by the eighth session.[22] In the former, this was accompanied by the appearance of abundant new functional capillaries and less hypertrophic vascular endothelial nuclei. In the latter, granulation was accelerated, exhibiting less dehiscence and increased thickness of collagen bundles.[22]

Another important issue tested in the trials was the impact of EGF treatment on amputations. Tsang et al[25] reported that 2 patients underwent toe amputation in the control group and in the group with topical 0.02% EGF application in contrast with no amputations in the group with 0.04% EGF topical application at 12 weeks. A favorable effect on amputation rates has also been shown for intralesional EGF injection. Acosta et al[22] found that intralesional injection of 25 μg EGF prevented amputation in 17/29 (58.6%) patients who completed 24 infiltration sessions. Amputation was necessary in 5/18 (28%) and 3/23 (13%) patients treated with injections of 25 and 75 μg EGF, respectively.[22] Fernández-Montequín et al[28] found a mean time to amputation of 13.9 months in patients receiving 75 μg EGF and 15.6 months in those receiving 25 μg EGF. However, amputations registered by this team were not enough for statistical analysis. It is interesting to note that all amputations except for one in the EGF-treated groups were seen in ischemic patients, whereas 5 neuropathic patients receiving placebo also sustained amputations.[29]

Useful data accrued with follow-up of these studies. In the Tsang et al[25] trial, the mean follow-up of grade I to II ulcers was 24 weeks. Ulcer healing improved progressively: 7 additional patients in the placebo group and 5 additional patients in the 0.02% EGF group achieved complete healing in the second part of the observation (between the 12th and 24th weeks).[25] Hong et al[26] found no recurrence of grade III to IV ulcers during 6 months. Nevertheless, a new lesion different from the prior site developed in 5 patients, and further surgical interventions were required in 16 patients as a result of aggravated wound or no response.[26] In the trial of Acosta et al,[22] wound recurrence after 12 months of follow-up appeared in only 1 patient treated with intralesional injection of 25 μg EGF. In the study of Fernández-Montequín et al,[28] 1 patient did not achieve complete healing, although the lesion had considerably improved, and another was further amputated despite complete granulation after 12 months. Among patients treated with 75 μg EGF, ulceration relapsed in one and further amputation was needed in 5 patients.[28] Similar results were obtained after 1 year of follow-up in the trial of Fernández-Montequín et al[29] (25/48 controls, 25/48 with 25 μg EGF, and 40/53 with 75 μg EGF).

Finally, the effect of EGF on healing of diabetic foot ulcers has been tested using various drug concentrations. Of note, some studies had 2 treatment arms (ie, low and high concentration), rendering comparison easier and more robust because of the common inclusion and exclusion criteria. In the study of Tsang et al,[25] higher healing rates and shorter healing time were achieved in the 0.04% EGF group compared with the placebo and the 0.02% EGF groups. This supports the efficacy of 0.04% EGF in enhancing healing of grade I to II ulcers as well as a potential threshold for this action.[25] The 2 trials of Fernández-Montequín et al[28,29] were not adequately powered to determine differences between the 2 doses, but there was a trend in favor of the higher dosage in terms of earlier[28] and more complete[29] response in the 75-μg EGF group. Only this higher dose yielded significant differences when compared with placebo for some secondary variables, such as end-of-treatment complete granulation response, time-to-complete response, and wound closure after follow-up.[29]

Safety

Adverse events seen with EGF use were, generally, mild to moderate, as summarized in Table 3.[22,23,27-29] EGF injection was accompanied by pain at the administration

Table 3. Adverse Events With EGF Use

Study	Mild/Moderate Side Effects	Severe Side Effects
Acosta et al,[22] Cuba	Pain during infiltration and discomfort, except for neuropathic patients, topical sepsis	Chest pain, transient fever, muscular tremor, dizziness, and vomiting
Viswanathan and Pendsey,[27] India	Rash, topical pain, skin irritation	
Fernández-Montequín et al,[28] Cuba	Topical sepsis, burning sensation, tremors, chills, local pain	Anemia and chest pain, acute abdomen, and fatal arrhythmia
Tuyet et al,[23] Vietnam	Overgranulation	
Fernández-Montequín et al, [29] Cuba	Pain at administration site, burning sensation, shivering, local infection, chills, anemia, fever, nausea, vomiting	Severe infection, cellulitis, renal failure, myocardial infarction, pneumonia, acute pulmonary edema, knee abscess

Abbreviation: EGF, epidermal growth factor.

site, whereas skin irritation was the most common side effect of topical EGF treatment. More adverse events were seen with the higher EGF dose than with the lower dose. The severe and sometimes fatal events did not appear to be directly linked with EGF administration but rather attributable to the patient comorbidity.

Discussion

Given the magnitude of the health concern associated with the diabetic foot worldwide, alternative and/or add-on therapies are essential.[1-4] Use of growth factors has continuously become more important in our armamentarium over the past decades.[5]

EGF is a pivotal factor in the healing cascade, acting on epithelial cells and fibroblasts and thereby promoting the restoration of damaged epithelium. However, its bioavailability is impaired in chronic diabetic ulcers. Indeed, fibroblasts from chronic diabetic foot ulcers exhibit a diminished response to stimulation with EGF.[30,31] In addition, EGF is overexpressed in keratinocytes but inadequately expressed in endothelial cells in the ulcer margins. At the same time, the EGF receptor is markedly reduced in both keratinocytes and endothelial cells in the wound.[32] These irregular responses may, at least partly, account for poor granulation and epithelialization, leading to ulcer chronicity. Therefore, measurement of EGF levels has been used as a marker of success in experimental treatments for diabetic ulcers, such as inorganic elements,[33] homologous[34] and autologous platelet-rich gel,[35] as well as extracorporeal shockwave therapy and hyperbaric oxygen.[36]

Thus far, studies have been performed in diabetic ulcers of variable severity, as defined by the Wagner classification system. Treatment of grade I to IV ulcers with topical EGF application achieved both complete and partial healing, leading to a reduction in amputations as well.[23,25-27] EGF has not been tested in grade V ulcers because these demand urgent, extensive surgery. Topical administration was well tolerated with only mild to moderate untoward effects.[23,27]

The desired effects of EGF could vary according to the availability of the growth factor on deep wound layers. Achieving an adequate efficacy is a common limitation with topical formulations because diffusion of the active agent is affected by necrotic tissue, sepsis, inflammation, and the action of wound proteases. Alternatively, intralesional injection could bring the active agent into the desired region.[22] Bearing this in mind, multicenter trials have tested the effect of EGF intralesional infiltration in grade III to IV ulcers, documenting improved wound healing and reduced amputation rates compared with standard treatment alone.[22,28,29] The dose of 75 μg EGF has been consistently shown to achieve higher healing rates and shorter time to heal than the dose of 25 μg EGF[28,29] and placebo.[29] Adverse events did not differ from those reported with topical application, except for pain at the injection site.[22,28,29]

Regrettably, no trial was specifically designed to address the issue of optimal EGF dosage. Indeed, most studies were not adequately powered to ascertain any differences between dosing regimens. This inadequacy notwithstanding, a trend in favor of the higher dose has emerged. Accordingly, the next step should now be a trial with adequate design and enough power to identify optimal EGF dose. Not to be ignored, the ideal dose might also be dependent on ulcer severity and EGF administration route.

Of particular note, the beneficial effect of EGF treatment seems sustainable over a long period, as testified by patient follow-up. This efficacy notwithstanding, peripheral arterial disease and diabetic neuropathy may lead to new ulcerations. Consequently, advanced therapeutic modalities are continuously required. Such technological advances include gene therapy, polymers, and electrospun nanofibers, which could prevent growth factor degradation in the wound and maintain constant, high local concentrations.[20] The synergistic effect of growth factors and injectable silicone resin particles on the biological

activity of dermal fibroblasts has been examined in a preliminary in vitro study.[37] Both alone and in combination with silicone resin particles, growth factors have been documented to increase fibroblast proliferation, but the presence of particles did not significantly increase efficacy.[37] Alternatively, EGF can be used to stimulate multipotent stromal cells before injection in order to increase their availability in the ischemic tissue. These modified cells can then significantly improve blood flow by increasing new vessel formation, as shown in the ischemic hind limbs of diabetic mice.[38]

Finally, the utility of EGF therapy in diabetes is enhanced by the additional favorable effects shown with this growth factor in wound healing of diabetic corneas[17] and pancreatic β cells.[39,40] In the latter, EGF ligands may exert favorable actions not only in the differentiation of pancreatic acinar and ductal cells into endocrine islet cells but also in β-cell growth, via diminished apoptosis and increased regeneration.[39,40] In this context, EGF treatment could ultimately emerge as a useful therapeutic adjunct both to increase β-cell mass[41] and to improve diabetic foot care.[25,26,28,29]

Conclusions

EGF plays a pivotal role in wound healing. It acts on epithelial cells and fibroblasts, promoting restoration of damaged epithelium. However, its bioavailability is impaired in chronic diabetic foot ulcers. So far, available evidence has suggested that application of human recombinant EGF in addition to standard treatment is able to improve healing rates and to prevent foot amputations. Some evidence is now also emerging that this beneficial effect may be sustainable. The efficacy of EGF has been examined at various concentrations and by various administration routes (topical application and intralesional injection). Intralesional injection achieves better availability on the deep wound layers, but pain at the injection site is a common complaint. Generally, adverse events have been minor to mild. Thus, overall experience with EGF is very promising. However, several issues need to be further clarified before widespread use of EGF is possible in everyday practice. These include optimal dosage and administration route, characteristics of the ulcers most likely to heal (severity and ischemic/neuropathic or both), and cost-effectiveness. Adequately designed and powered trials to answer these queries are the need of the hour.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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