The use of epidermal growth factor in diabetic foot ulcers in South Africa

TG Mothabeng,[1] TK Ngcobo,[1] N Singh,[1] SC Deprés,[2] MA Valdés,[3] AD Tuero Iglesias,[4] AB Minkova,[3] JA Buxadó,[3] JE Baldomero,[3] A del Río Martín,[3] VLM González[3]

[1] Surgical Medical Services, 1 Military Hospital, South Africa

[2] Department of Angiology and Vascular Surgery, Hospital Militar Central Doctor Carlos J Finlay, Cuba

[3] Center for Genetic Engineering and Biotechnology, Cuba

[4] Laboratory of Bioequivalence, Centre for Research and Development of Medicines (CIDEM), Cuba

Corresponding author, email: jose.acosta@cigb.edu.cu

Background: Treatment of complex diabetic foot ulcers (DFU) with intra- and peri-lesional injection of recombinant human epidermal growth factor (rhEGF) has been safe and effective in clinical trials. Here, we report results on the efficacy and safety of this treatment in South Africa.

Methods: A case series of 24 patients with DFU was conducted in a tertiary hospital in Tshwane, South Africa. Patients were treated between 1 March and 15 December 2019; with good wound care (GWC) and rhEGF through section 21 (compassionate care using an unregistered medicine). The rhEGF was administered intra- and peri-lesional, three times a week. The evolution of their ulcers was monitored and documented.

Results: Twenty-two of the 24 patients completed treatment, but all patients' wounds/ulcers were analysed and the outcomes reported. Satisfactory granulation was noticed in the two patients who withdrew. Complete granulation response and wound closure were observed in the 22 patients who completed treatment, demonstrating a treatment efficacy of 91.7%. Most (88%) reported adverse events (AEs) were mild. Serious AEs were observed in two patients, and none were judged to be directly related to the treatment.

Conclusion: This case series demonstrates that intervention with rhEGF in complex DFU has a 91.7% efficacy in a sample of South African patients, and was well tolerated. This treatment regimen suggests a milestone in the management of a complication of diabetes. It could be the answer to the high rates of amputations that plaque patients presenting with DFU.

Keywords: diabetes, wound, healing, EGF, granulation, angiology

Wound Healing Southern Africa 2022;15(1):16-21

Introduction

Diabetes mellitus (DM) represents a global health problem and is a significant risk factor for other diseases of vascular origin that are among the leading causes of death.[1,2] More than 463 million adults suffer from DM, and 578 million have been estimated by 2030.[3] The diabetic foot ulcer (DFU) is one of the most harmful complications of DM.[4,5] DF, a complex pathology, defined as a neuropathic etiopathogenic-based clinical alteration induced by sustained hyperglycaemia, in which, with or without coexistence of ischaemia and previous traumatic trigger, produces injury or ulceration of the foot.[5]

Foot ulceration is a significant complication of DM with an annual incidence slightly higher than 2%, which ranges between 5–7.5% in those with peripheral neuropathy.[6] The prevalence of diabetic foot reported in several populations is between 2–10%.[7] An estimated 15% of patients with DM develop ulcers at some point in life,[8] and 10–30% of diabetic patients with ulcers progress to amputation. An important factor contributing to this unfavourable outcome is ulcer infection – 60% of amputations are preceded by infected ulcers,[9] and a 5-year mortality rate of 50–60.0% has been observed after lower limb amputation.[10]

In Africa, 19 million adults aged 20–79 years suffer from DM, which has been estimated to increase to 47 million by 2045. South Africa has the highest prevalence in Africa, with 4.6 million people with DM.[11] DFU has been identified in 28% of diabetic patients in South Africa at primary healthcare services,[12] and studies conducted in this country have found a growing trend of DM prevalence, as an important cause of non-traumatic amputations.[13,14] Efficacy and reproducibility of treatments for healing DFU have been low, and reported results come from interventions in neuropathic and small-sized lesions.[15,16] Safe and effective treatments of DFU are urgently needed.

Treatment of complex DFU with intra- and peri-lesional injection of recombinant human epidermal growth factor (rhEGF) (Heberprot-P®, CIGB, La Habana) has been safe and effective in a randomised, placebo-controlled, double-blind clinical trial.[17] Post-marketing information from 2 702 patients confirmed results obtained in clinical trials.[18,19] These results led us to hypothesise that wound closure would be observed in more than 90% of patients, and major amputation would be indicated in less than 5%, without serious adverse events (AEs) in South African patients, after treatment of DFU with rhEGF and good wound care (GWC). Following this line of reasoning, we conducted a case series in 24 patients with DFU grades 3 and 4, according to Wagner's classification,[20] in a South African hospital.

Methods

Trial oversight

Patients with complicated DFU and non-healing ulcers were selected and treated with rhEGF in a South African health institution. The treatment protocol was initiated after approval was obtained from The South African Health Products Regulatory Authority (SAHPRA) through Section 21 of the Medicines and Related Substance Act, Act 101 of 1965 as amended.[14] SAHPRA's guidelines were observed, and so were principles for medical intervention in humans established in the Helsinki Declaration amended by the 52nd General Assembly in Edinburgh, Scotland, October 2000, including the clarifications of paragraph 29 in Washington 2002, as agreed by the 59th Assembly of the World Medical Association in October 2008 and approved at Fortaleza, Brazil 2013. Authors assume responsibility for the accuracy and completeness of the data and analyses and the fidelity of this report and case presentation.

Patients

Twenty-four patients aged ≥ 18 years, with type 1 or 2 DM, complex DFU, 16 with neuropathic and eight having ischaemic/infective aetiology; most at risk of amputation, and having understood and signed informed consent for the use of unregistered medicine were selected. Patients were invited to participate when a suitable case was identified.

Evaluation

All patients were evaluated with blood investigations: urea and electrolytes, creatinine, random blood glucose, full blood count, HBA1C, C- reactive protein (CRP), the neutrophil-lymphocytes and lymphocytes-platelets indexes, which are considered predictive markers of healing with the use of rhEGF, were analysed upon admission of patients; X-rays of the chest and affected limb, echocardiogram. Any patient with features or suspicion of peripheral arterial occlusive disorder was further evaluated with arterial Doppler and CT angiography when indicated.

Treatment protocol

The treatment protocol started with an evaluation of metabolic changes, presence and severity of infection and assessment of arterial occlusive disease. Patients included in the treatment protocol were evaluated and followed up, as stipulated, in compliance with the intent-to-treat analysis. Patients who withdrew or who were withdrawn from the treatment were not replaced; they continued to be offered GWC and further management through the hospital's wound clinic. When a patient had more than one ulcer, the largest one was chosen for treatment with rhEGF, and lesions less than two cm were only treated with GWC. Patients with a critical degree of ischaemia were included after vascular intervention. Infectious processes affecting lesions were treated before including each patient in the protocol. The standard of care and GWC were continued with the use of rhEGF.

Trial procedures

Participants received rhEGF 75 µg, intra- and peri-lesional, three times per week on alternate days, for a maximum of eight weeks, and GWC. Lyophilised rhEGF was dissolved with 5 ml of water for injection, and injected using a standard disposable syringe with either a 22 G or 25 G x 0.5" insulin needle (5–10 injections of 0.5–1 ml), first into the dermo-epidermal junction at equidistant points all over the lesion contours,

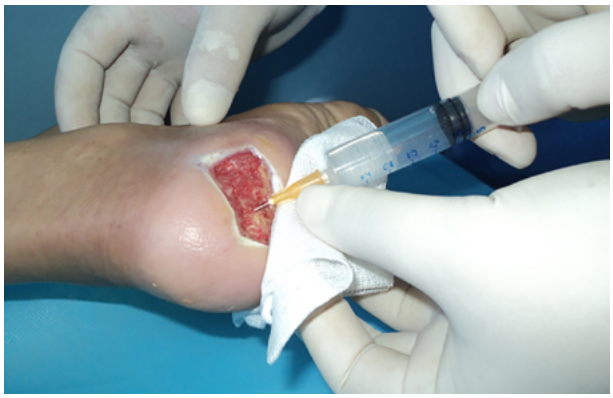


Figure 1: Intra- and peri-lesional injection of rhEGF 75 µg into the diabetic foot ulcer

and then deeply downward into the wound bottom in circles and centripetally to ensure a uniform distribution (Figure 1). Wounds were dressed with sterile gauze, and all patients were seen at follow-up visits three times per week until the end of the trial. No other dressing was used. An active search was conducted for AEs, and all medical incidents occurring from the administration of the first dose of rhEGF were considered as such. All serious AEs and suspected drug-related AEs were recorded from the first day of treatment.

Outcomes

The primary outcomes expected were wound granulation, reduction in ulcer size and depth, complete closure, tolerance of the treatment and AEs. The secondary outcomes were time to complete granulation, time to complete wound closure, time to closure by skin graft, treatment failure and need for amputation, and type of amputation. All patients were analysed, whether or not they completed the treatment protocol. AEs were classified as mild, where no therapy was necessary; moderate, if specific treatment was needed; and severe, in case of life-threatening reactions, need for hospitalisation or prolonged hospitalisation in those already admitted, and death. Type, duration, intensity, severity, and causal relationship of AEs were recorded.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (25th and 75th percentiles). Categorical variables were given as absolute values and percentages. Absolute frequency, per cent of granulation, and wound closure were estimated in categories: satisfactory and unsatisfactory. Normality (QQPlot) and fitness tests (Shapiro–Wilk and Kolmogorov–Smirnov) were performed to verify if data were uncorrelated with one another and came from a normal distribution, and if random components had fixed variation. Evaluation of safety was performed from frequency of patients with AEs. Two-sided *p*-values of 0.05 or less were considered to indicate statistical significance. The Bayes factor test was used for benefit-risk ratio analysis, considering wound closure as benefit criterion, and amputation and interruption due to AE as risk criteria.[21,22]

Results

Characteristics of the patients

From March to December 2019, a total of 24 patients with complicated DFU were treated using rhEGF, through section 21 compassionate

Table I: Demographic and baseline characteristics of patients

Characteristics	*n*	%
	24	100
Sex		
Male	22	91.7
Female	2	8.3
Age (years)		
Mean ± SD	60 ± 11	
Median ± QR	57 ± 12	
(Minimum; Maximum)	(49; 94)	
Diabetes type		
Type 1	1	4.2
Type 2	23	95.8
Diabetes evolution time (years)		
Mean ± SD	12.2 ± 8	
Median ± QR	10. ± 9	
(Minimum; Maximum)	(0*; 35)	
Glucose control treatment (%)		
Metformin	15	62.5
Insulin	12	50
Sulfonylureas	1	4.2

* Diabetes evolution time: one patient with one month of evolution

Table II: Distribution of included patients according to characteristics of lesions

Characteristics	*n*	%
	24	100
Affected lower limb		
Right	18	75
Left	6	25
Wound location		
Toe	11	45.8
Sole	8	33.3
Dorsum	3	12.5
Transmetatarsal	2	8.3
Calcaneus	1	4.2
Internal edge	1	4.2
Extreme edge	1	4.2
Wound area (cm²)		
Mean ± SD	19.1 ± 23.2	
Median ± QR	9.6 ± 27.3	
(Minimum; Maximum)	(0.8; 101)	
Wound evolution time (day)		
Mean ± SD	112 ± 125	
Median ± QR	60 ± 83	
(Minimum; Maximum)	(7; 365)	

care. The predominant sex was male, with 22 patients (91.7%). Most patients were black Africans (54.2%), type 2 DM (95.8%), and on oral hypoglycemic agents.

Table III: Distribution of patients according to response to treatment with rhEGF

Response to treatment	*n*	%
	24	100
Granulation response		
Yes	23	95.8
No	1	4.2
Complete closure		
Yes	22	91.7
No	2	8.3

Table IV: Characteristic of lesions according to surgical procedures

Characteristic	*n*	%
	24	100
Indication of minor surgical procedures		
Yes	22	91.7
Toilette	13	59.1
Toilette + disarticulation	5	22.7
Disarticulation	3	13.6
Transmetatarsal	1	4.5
Occlusive type patterns		
Without change	16	66.7
Femoropopliteal	6	25
Distal	2	8.3
Infection		
Yes	13	54.2
No	11	45.8
Osteomyelitis		
Yes	5	20.8
No	19	79.2
Revascularisation		
Yes	3	12.5
No	21	87.5

Twenty out of 24 patients (83.3%) had associated comorbidities, with arterial hypertension as the predominant pathology. The lower right limb was the most affected (75.0%), predominant ulcer locations were the toe (45.8%), sole (33.3%), and dorsum of the foot (12.5%). The mean DFU size was 19.1 ± 23.2 cm^2, and the mean wound evolution time was 112.0 ± 125.0 days, with a maximum of 365 days (Table II). Lesions treated in 83.3% of patients were deep grade 3, according to the Wagner classification, with bone and tendon exposures, and 20.8% corresponded to type B II, according to the Texas classification.

Follow-up and outcomes

Treatment was completed in 23 (95.8%) patients. One patient withdrew from the study, signed himself out of the hospital and apparently resulted in a below-knee amputation several weeks later in another hospital; he cited personal family issues for his decision to withdraw from treatment. Satisfactory granulation response was achieved in all patients that completed the treatment (Table III). Wound closure was obtained in 22 patients (91.7%), at a mean time of 12.6 weeks, and a

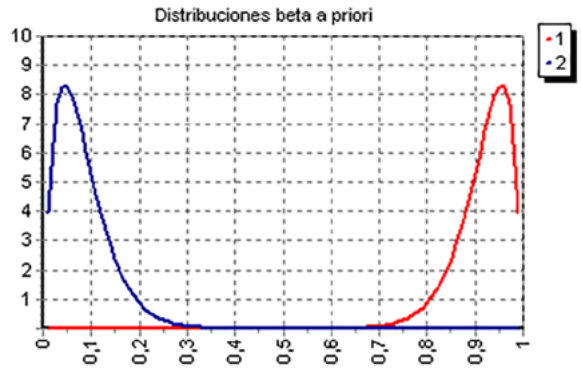
Table V: Distribution of interventions with rhEGF according to DFU severity

Applications	Neuropathic	Neuroischaemic	Total
n	16	8	24
Mean ± SD	9.0 ± 8.0	12.0 ± 6.0	10.0 ± 7.0
Median ± QR	6.0 ± 15.0	12.0 ± 11.0	8 ± 14.0
(Minimum; Maximum)	(1.0; 24.0)	(3.0; 22.0)	(1.0; 24.0)

maximum of 19.7 weeks. Closure time was higher in neuroischaemic (14.6 ± 2.6 weeks) than in neuropathic patients (11.7 ± 2.4 weeks). There were no major amputations, and no recurrence of ulcers up to a year in 18 patients following treatment. Four patients were lost to follow-up after six months.

During treatment, a significant number of patients needed surgical procedures (Table IV). Debridement was performed in 59.1% of patients, followed by limited amputations of toes and forefoot (22.7%). Three revascularisations were performed, which presented a femoropopliteal occlusive pattern detected by physical examination, and arteriography, with satisfactory results. There were more injections of rhEGF in neuroischaemic (9 ± 8) than in neuropathic patients (12 ± 6).

Complete closure response was satisfactory in 91.7% of patients. In neuropathic patients, the mean closure time was 11.7 ± 2.4 weeks, and in neuroischaemic cases, 14.6 ± 2.6 weeks. Bayes factor, representing the ratio of the likelihood of benefit (red) to the likelihood of risk (blue), was 11.5, representing more evidence in favour of the benefit of the treatment with rhEGF. In both neuropathic and ischaemic patients, the absence of interceptions between probability distribution functions for benefit (wound closure) and risk (amputation and interruption) were observed (Figure 2).



Benefit: Complete closure (22/24)
Risk: Interruption of the treatment for any cause (2/24)

Distributions beta a priori	Population 1	Population 2
Parameter a	22.0	2.0
Parameter b	2.0	22.0
Mean	0.92	0.08
Standard deviation	0.06	0.06

Figure 2: Risk-benefit analysis (Bayes factor = 11.5) of patients treated with rhEGF, benefit (red; wound closure) and risk (blue; amputations and treatment interruption due to adverse events) probability distributions of the outcome of patients treated with intra-lesional rhEGF

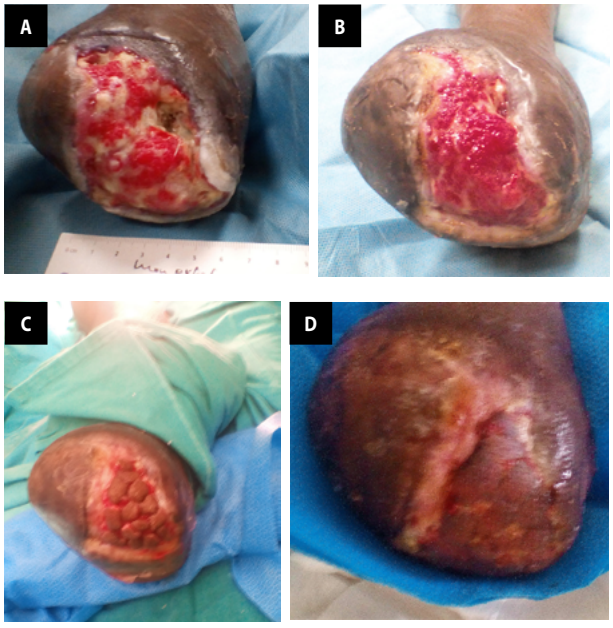


Figure 3: (A) First day of intervention with rhEGF, (B) application 16 and end of treatment, (C) type Davis skin graft, and (D) complete closure at day 45

Table VI: Frequency of adverse events

Adverse events	*n*	%
Total	24	100
Patients with at least one AE	6	25
Total AE	9	100
Type of AE (*n*)		
Pain at administration site (4)	5	55.5
Local infection (2)	2	22.2
Tremors (1)	2	22.2
Intensity of AE		
Light	8	88.9
Moderate	1	11.1
Severity of AE		
No serious	7	77.8
Serious	2	22.2

We present two examples of patients with complex DFU treated with the medicine (Figures 3 and 4). The first is a 64-year-old male with diabetes for 19 years on metformin. He presented five months before the introduction of rhEGF with septic ulcers on the second and third toes; the patient (reluctant to have toe amputation) had several debridements, challenging to manage sepsis even after the toes were ultimately amputated, and GWC in hospital. He later had a transmetatarsal amputation and was offered rhEGF treatment as soon

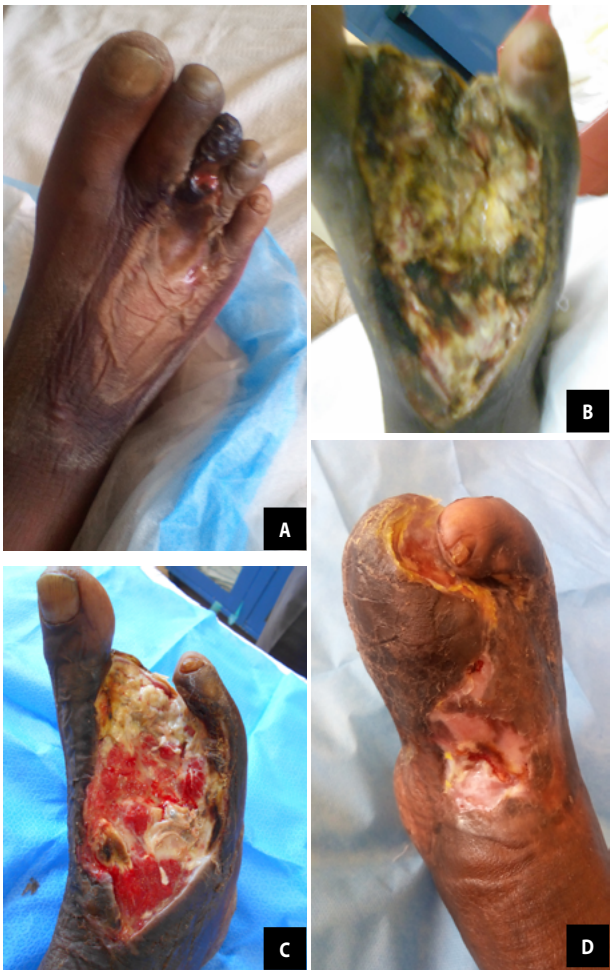


Figure 4: (A) Initial wound, (B) after surgical intervention and first day of treatment with rhEGF, (C) tissue granulation and epithelisation after 22 applications, and (D) healed wound

as it was available and section 21 permission obtained. The patient had 16 injections over five weeks, with complete granulation skin graft possible. This patient was facing a below-knee amputation and achieved wound closure in 45 days of rhEGF treatment and GWC.

The second patient was a 55-year-old male with undiagnosed type two DM, presenting to the surgery clinic with an ulcer (area 55 cm^2) on the dorsum of the right foot affecting the second, third, and fourth toes. After amputation of the affected toes, rhEGF intervention was performed. Complete granulation response was achieved in 10 weeks with 22 rhEGF injections; complete wound closure was achieved in 12 weeks.

Safety

AEs (9) are listed in Table VI. The most frequent AEs were pain at the injection site (55.5%), local infection (22.2%), shivers, and chills (22.2%). More than 88% of AEs were classified as mild, 11.1% as moderate intensity, and none were attributable to the treatment with rhEGF. Non-serious AEs accounted for 77.8%, and serious AEs were reported in two patients (local infection) who required hospitalisation.

Discussion

Results obtained in this case series report support the hypothesis of the efficacy and safety of the treatment of DFU with rhEGF, since complete closure was obtained in 91.7% of patients, with a total of 9 ± 8 interventions in neuropathic patients, and 12 ± 8 in neuroischaemic patients, without major amputations. It is interesting to note that three patients with neuroischaemic DFU with previous revascularisation, complete closure was achieved. This type of lesion usually heals after 5–16 months, which shows in these cases that the intervention with intra- and peri-lesional infiltration of rhEGF significantly reduces the closing time after revascularisation.

Treatment protocols for diabetic foot include metabolic control, debridement, treatment in a humid environment, dressings, relief of local pressure, antimicrobial treatment of infection, growth factors, and revascularisation methods. These components of treatment protocols have shown advantages, but healing of these lesions is slow, and recurrence is usually high in the first year after healing. Relapse rates reported in the literature are higher than 30%.[23,24] Recurrence in the United Kingdom has been reported at 50–70%, after one-year follow-up.[25] This represents a serious problem since delayed healing and recurrence are predisposing factors for infection and amputation, in addition to personal, family, social and health costs associated with an open lesion.

In a study conducted in a district hospital of KwaZulu-Natal in South Africa, lower-limb amputations due to DM were reported in 660 patients, which represented an annual cost higher than 398 million ZAR.[26] Personal, family and socioeconomic costs higher than 5 million ZAR per amputees were estimated, resulting in an additional cost of 6 155 million ZAR per year for KwaZulu-Natal. Extrapolation of these data to 11 provinces of South Africa represents an additional cost of at least 68 billion ZAR. Therefore, timely treatment of DFU with effective actions and healthcare reduces healing time, amputations, and hospitalisation costs and increases patients' quality of life.

It should be noted that intra- and peri-lesional application of rhEGF is a first-in-class treatment and has been indicated for initial and advanced stages of DFU of ischaemic and neuropathic aetiology. The intervention with rhEGF stimulates granulation and accelerates healing of DFU, reduces debridement and recurrence, effectively counteracts ageing of fibroblasts present in ulcers, and stimulates their proliferation. This treatment reduces hospital stays by being able to treat injuries on an outpatient basis and makes the reincorporation of patients into society possible.

Limitations of study

This work aimed to provide a case series of the intervention with rhEGF in complex DFU. This was intended to demonstrate the efficacy and safety of a treatment that has been used in many countries since 2006, when it was approved in Cuba. No statistical sample size calculation was performed a priori, and it was equal to the number of patients treated during the case series, which is an important limitation of the study. The present case series is limited by the small number of patients and the absence of a control group for comparison. Although a higher sample size would have yielded more certainty for the interpretation of results, a population of 24 patients with complex DFU at risk of amputation seems to be enough for drawing relevant conclusions and designing further clinical trials in South Africa including more patients and a longer duration of follow-up. Despite these limitations, this case series

reinforced the argument in favour of intra-lesional administration of rhEGF to improve healing of chronic DFU.

Conclusion

The safety and efficacy of the intervention with rhEGF were demonstrated in 24 patients with complex DFU. An efficacy of 91.7% in the treatment of DFU grade 3 and 4, with complete wound closure in less than 15 weeks, and serious AEs in two out of 24 patients represents a significant advance in the treatment of this devastating disease. Finally, implementing this method in South Africa could be the starting point to reducing the amputation rate and health costs in the management of DFU, which may allow relocating resources to other health priorities.

Acknowledgements

We wish to thank Lotty Ledwaba, the nurses, and administrative personnel working at the hospital for making the collaboration and treatment protocol with rhEGF a success and for their roles. We also appreciate the kind gesture of the Cuban government, the Center for Genetic Engineering and Biotechnology (La Habana, Cuba), and the Ministry of Public Health for assistance with the donation of rhEGF and for providing angiologists and vascular surgeons for medical advice.

Conflict of interest

VLM González, JE Baldomero-Hernández, MA Valdés, AB Minkova and JA Buxadó are employees of the CIGB, owner of the product's patent and sanitary registrations, where the product Heberprot-P® is produced. The rest of the authors have no conflict of interest to declare.

ORCID

TG Mothabeng https://orcid.org/0000-0001-5605-7311
TK Ngcobo https://orcid.org/0000-0002-9265-6562

References

1. Brownlee M. The pathobiology of diabetic complications. A unifying mechanism. Diabetes. 2005;54 (6):1615-25. https://doi.org/10.2337/diabetes.54.6.1615.
2. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet. 2014;383(9922):1068-83. https://doi.org/10.1016/s0140-6736(13)62154-6.
3. International Diabetes Federation (IDF). Atlas of Diabetes of the IDF, 10th ed. Brussels, Belgium; 2020. Available from: http://www.idf.org/diabetesatlas. Accessed 10 Jun 2022.
4. Armstrong DG, Wrobel J, Robbins JM. Are diabetes-related wounds and amputations worse than cancer? Int Wound J. 2007;4(4):286-87. https://doi.org/10.1111/j.1742-481x.2007.00392.x.
5. Costa RHR, Cardoso NA, Procopio RL, et al. Diabetic foot ulcer carries high amputation and mortality rates, particularly in the presence of advanced age, peripheral artery disease and anemia. Diabetes Metab Syndr. 2017;11 Suppl 2:S583-87. https://doi.org/10.1016/j.dsx.2017.04.008.
6. Marinello J, Blanes JI, Escudero JR, et al. Consenso sobre pie diabético. Angiología. 1997;49(5):193-230.
7. Reiber GE. The epidemiology of diabetic foot problems. Diabet Med. 1996;13 Suppl 1:S6-11.
8. Lipsky BA. Medical treatment of diabetic foot infection. Clin Infect Dis. 2004;39 Suppl 2:104–14. https://doi.org/10.1086/383271.
9. Perich AP, González SRM, Valdés RE, et al. Development of diabetes mellitus in patients with impaired glucose tolerance: An 18-year follow-up. Rev Cubana Endocrinol [Online in Spanish]. 2002;13(2). Available from: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1561-29532002000200002&lng=es&nrm=iso&tlng=es.
10. Berlanga J, Cibrian D, Guillén I, et al. Methylglyoxal administration induces diabetes-like microvascular changes and perturbs the healing process of cutaneous wounds. Clin Sci (Lond). 2005;109(1):83-95. https://doi.org/10.1042/cs20050026.
11. Berlaga J, Fernández JI, López E, et al. Heberprot-P: un nuevo producto para el tratamiento de las ulceras complejas del pie diabético. MEDICC Review [Online in Spanish]. 2013;15(1). Available from: https://mediccreview.org/heberprot-p-un-nuevo-producto-para-el-tratamiento-de-las-ulceras-complejas-del-pie-diabetico.
12. Dessie G, Mulugeta H, Amare D, et al. A systematic analysis of prevalence and sub-regional distribution of undiagnosed diabetes mellitus among adults in African countries. J Diab Metab Disord. 2020;19(2):1931-41. https://doi.org/10.1007/s40200-020-00635-9.
13. Ntuli S, Swart A, Lambert CV. Risk factors for diabetic foot ulceration. South African J Diab Vasc Dis. 2018;15(1). https://journals.co.za/doi/10.10520/EJC-10055042ca.
14. Bertram MY, Jaswal AVS, Van Wyk VP, Levitt NS, Hofman KJ. The non-fatal disease burden caused by type 2 diabetes in South Africa, 2009. Glob Health Action. 2013;6:19244. https://doi.org/10.3402/gha.v6i0.19244.
15. Manickum P, Ramklass SS, Madiba TE. A five year audit of lower limb amputations below the knee and rehabilitation outcomes: the Durban experience. Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2019;24(2):41-45. https://doi.org/10.1080/16089677.2018.1553378.
16. 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(5):822-27. https://doi.org/10.2337/diacare.21.5.822.
17. Margolis DJ, Bartus C, Hoffstad O, Malay S, Berlin JA. Effectiveness of recombinant human platelet-derived growth factor for the treatment of diabetic neuropathic foot ulcers. Wound Repair Regen. 2005;13(6):531-36. https://doi.org/10.1111/j.1524-475x.2005.00074.x.
18. Fernández-Montequín JI, Valenzuela-Silva CM, González-Díaz O, et al. Intra-lesional injections of recombinant human Epidermal Growth Factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomized, placebo-controlled, double blind study. Int Wound J. 2009;6(6):432-43. https://doi.org/10.1111/j.1742-481x.2009.00641.x.
19. López-Saura PA, Yera-Alos IB, Valenzuela-Silva C, et al. Medical practice confirms clinical trial results of the use of intralesional human recombinant Epidermal Growth Factor in advanced diabetic foot ulcers. Adv Pharmacoepidem Drug Safety. 2013;2(2):128. https://doi.org/10.4172/2167-1052.1000128.
20. Yera-Alos IB, Alonso-Carbonell L, Valenzuela-Silva CM, et al. Active post-marketing surveillance of the intralesional administration of human recombinant epidermal growth factor in diabetic foot ulcers. BMC Pharmacol Toxicol. 2013;14:44. https://doi.org/10.1186/2050-6511-14-44.
21. Wagner FW. Algorithms of diabetic foot care. In: Levin ME, O'Neal FW, editors. The Diabetic Foot. St Louis, MO: Mosby; 1983. p. 290-95.
22. Jeffreys H. Theory of probability. 3rd ed. Oxford, UK: Clarendon Press; 1961.
23. Lee MD, Wagenmakers EJ. Bayesian cognitive modeling: A practical course. Cambridge University Press; 2013.
24. Matricali GA, Deroo K, Dereymaeker G. Outcome and recurrence rate of diabetic foot ulcers treated by a total contact cast: short-term follow-up. Foot Ankle Int. 2003;24(9):680-84. https://doi.org/10.1177/107110070302400905.
25. Frigg A, Pagenstert G, Schäfer D, Valderrabano V, Hintermann B. Recurrence and prevention of diabetic foot ulcers after total contact casting. Foot Ankle Int. 2007;28(1):64-69. https://doi.org/10.3113/fai.2007.0012.
26. Boulton AJM, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005;366(9498):1719-24. https://doi.org/10.1016/s0140-6736(05)67698-2.
27. Sommasundram P, Davashni P, Deepak S, Romashan P. Diabetes-related amputations in the public healthcare sector in KwaZulu-Natal: a five-year perspective. Are we winning? Journal of Endocrinology, Metabolism and Diabetes of South Africa 2019;24(1):32-36. https://doi.org/10.1080/16089677.2018.1550956.