Clinical application of photobiomodulation with blue light on non-healing ulcers in diabetic patients: a case series study

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Diabetes is related to numerous comorbidities, including the severe complications of poor wound healing, often resulting in chronic ulceration and consequent limb amputation. In wound healing, diabetes leads to improper function at all stages, with severe impairment of the vascular network. Photobiomodulation positively influences tissue regeneration and healing, modulating the inflammatory response and promoting angiogenesis. This case series evaluated the effect of blue light treatment (EmoLED) on 11 patients with diabetes with recalcitrant ulcers of various aetiology that were not responding to standard therapies. Results show that blue light therapy provides a positive contribution to standard treatments for wound healing in patients with diabetes, significantly improving reepithelisation and allowing complete recovery of chronic ulcers in most cases.

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Type 2 diabetes (T2D) is a major global health epidemic, with 9% of adults aged 18 years or older suffering from the disease and related comorbidities in 2017 (International Diabetes Federation, 2019). Among the most common complications of T2D are diabetic skin wounds leading to common chronic ulcerations in the lower limbs due to diabetes-related angiogenic defects and impaired vascular flow, impeding proper reepithelisation, tissue regeneration and healing (Nathan, 1993). Approximately 15% of people with diabetes will present with a foot ulcer, and 14–24% of these subsequently experience a lower-extremity amputation (Alavi et al, 2014).

Diabetes causes misregulation of both pro-angiogenic and anti-angiogenic factors, leading to impaired cell migration and differentiation that cause non-healing (Okonkwo and DiPietro, 2017). Additionally, defects in coagulation due to hyperglycaemia further worsen the pathological status of chronic ulcers. The abnormalities observed involve all stages of coagulation, affecting both thrombus formation and its inhibition, fibrinolysis, platelet and endothelial function. The final result is an imbalance between thrombus formation and dissolution, favouring the former (Ceriello, 1993).

Although the standard of care for diabetic ulcers is broadly consolidated, often treatments are not sufficient, and the rate of infection and amputation due to chronic wounds remains very high (Martins-Mendes et al, 2014). There is an urgent need to implement novel treatments to improve clinical outcomes in patients with recalcitrant diabetic ulcers.

A growing body of evidence supports the positive effects of phototherapy on several pathologies, particularly on inflammation and wound healing. The term photobiomodulation (PBM) was coined in 2014 by the North American Association for Photobiomodulation Therapy (NAALT; 2021), defining "a form of light treatment … eliciting photophysical and photochemical events at various biological scales".

PBM has been shown to promote several therapeutic effects, including the mitigation of pain and inflammation, immunomodulation, and promotion of tissue regeneration and healing (Anders et al, 2015). Light-emitting diodes (LED) were particularly suitable light sources for therapeutical use.

Visible blue light has been found to be particularly beneficial to treat skin wounds, reduce inflammation and promote tissue regeneration (Lubart et al, 2007; Ishikawa et al, 2011; Landau et al, 2011). Blue light is effective on acute and chronic wounds because of photophysical and photochemical effects, resulting in PBM that promotes regeneration and healing.

Photochemical effects are primarily responsible for chronic wound healing, where vascularisation is poor and blue LED light acts on cytochrome C/ cytochrome C oxidase to enhance cell metabolism, as well as activating flavins and increasing reactive oxygen species that cause a "controlled inflammation", promoting the synthesis of pro-angiogenic factors and tissue regeneration (Prindeze et al, 2012; Passarella and Karu, 2014). Blue light can also modulate the activity of fibroblast cells, mainly responsible for extracellular matrix and collagen deposition during tissue remodelling (Cicchi et al, 2016).

Previous results showed that blue LED light induced a restored collagen organisation in the wound bed and led to faster healing. Moreover, rapid onset of inflammation was observed, probably the primary process promoting superficial wounds after irradiation (Magni et al, 2020). Blue LED light effectively promoted wound healing and reduced pain in patients affected by long-term venous leg ulcers, cutaneous vasculitis and traumatic ulcers that were not responding to standard treatments (Mosti and Gasperini, 2018; Marchelli et al, 2019; Dini et al, 2020). The previous promising results prompted the authors to assess the efficacy of blue light irradiation on recalcitrant ulcers in patients with diabetes.

This case series reports blue LED light irradiation on leg ulcers of various aetiology in patients with diabetes that were highly resistant to healing and not responding to standard care.

Materials and methods

The study consecutively enrolled 11 patients with diabetes, age range 53–84 years, with ulcers of various aetiology in the lower limbs that were not responding to standard care. Patients were enrolled from the Diabetic Foot Clinic, Department of Internal Medicine, Hospital Trust ARNAS Civico, Di Cristina, Benfratelli, Palermo, Italy. After a proper cleansing of the wound bed, all patients underwent blue light therapy following a schedule of 10 weekly treatments (60 seconds per wound area) and the trial protocol in Blue Light for Ulcers Reduction (2021). Wounds were treated according to the standard of care after each treatment. In cases of rapid healing before the 10th treatment, blue light therapy was discontinued.

The LED irradiation system is a portable device emitting blue light (400-430 nm), provided by EmoLED Srl (Florence, Italy). The EmoLED blue LED light device illuminates a circular 5 cm diameter area at a distance of 4 cm for 60 seconds, providing a LED radiation at 120 mW/cm^2 power density, corresponding to an energy density dose of 7.2 J/cm^2.

Results

This study reports the outcomes of 11 patients with type 1 diabetes (T1D) and with T2D with several related comorbidities and recalcitrant ulcers. Two patients had T1D, and nine had T2D, with a diabetes history ranging from 2 to 35 years. All patients had cardiovascular and neurological complications due to diabetes, with various comorbidities. The history and main comorbidities of all patients are summarised in *Table 1*.

Table 1: History of 11 patients with diabetes treated with EmoLED to reduce chronic non-healing ulcers.

Patient	Age (years)	Sex	Type of diabetes	HbA_{1c} (%)	BMI	Duration of disease (years)	Smoking (cigarettes/ day)	Artery obstructive disease	Neuropathy	Cardiovascular disease	Chronic renal disease*
1	56	M	T2D	9.3	29.9	20	15	Yes	Yes	Yes	Stage I
2	57	F	T2D	5.3	27.1	20	60	Yes	Yes	Yes	No
3	80	F	T2D	6.6	22.2	1	0	Yes	No	No	No
4	70	F	T1D	6.6	53.3	15	0	No	Yes	Yes	Stage I
5	75	F	T2D	6.7	48.5	10	0	No	Yes	Yes	Stage III
6	63	F	T2D	7.1	25.5	22	20	Yes	No	No	No
7	82	F	T2D	6.5	29.2	30	0	Yes	Yes	Yes	Stage IV
8	62	M	T2D	5.3	23.3	10	7	Yes	No	Yes	No
9	84	M	T2D	9.7	25.3	12	30	Yes	Yes	Yes	No
10	53	M	T2D	6.7	28.5	2	20	Yes	No	No	No
11	54	M	T1D	7.1	26.7	25	0	Yes	No	No	No

*Stage according to CDK-EPI. BMI = body mass index

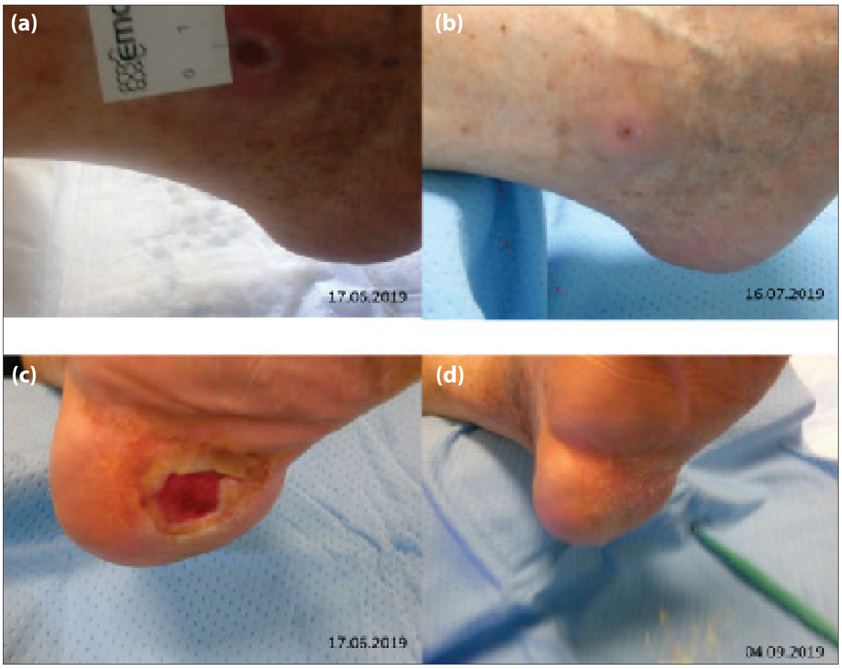

Figure 1. Patient 1 had two ulcers. The ulcer on the right malleolus (a) completely healed after five blue light treatments with EmoLED (b). The ulcer on the left calcaneus, of 6 years' duration (c), fully healed after 10 blue light treatments (d).

Four patients had a history of foot amputation and two patients had undergone amputation of part of the leg. All patients had ulcers in the lower limbs of at least 6 month' duration and had previously received standard treatments with unsatisfactory results.

The blue light therapy device was used to study the effect of PBM on the ulcers not responding to standard care. All patients also received standard care to promote revascularisation and reepithelialisation during this study.

Three patients also received an autologous skin graft or regenerative dermal substitute in combination with the blue light treatment. The blue light therapy allowed preparation of the wound bed for skin transplantation in the three cases observed, which led to complete reepithelialisation and healing. After blue light therapy, these three patients were ready to receive a graft, which allowed complete wound healing.

Results were evaluated as reduction of the wound area in percentage. Overall, 64% (*n*=7) of the patients completely recovered within 10 weeks of blue light treatment (100% reepithelialisation). Two patients had the lesion area reduced by 80% and 90%, respectively, and two patients had smaller reductions, with 30% and 50%, respectively.

Case studies

Three of the cases are described below. These are particularly interesting for the results obtained, given the initial conditions of the ulcers.

Case 1

Patient 1 was a 56-year-old man with T2D, managed by insulin, and rheumatoid arthritis. In January 2013, he had micro- and macro-angiopathy resulting from ischaemic heart disease, diabetic neuropathy and retinopathy, as well as peripheral obstructive arterial disease. Remarkably, the patient had previously undergone amputation of the right hallux and had a critical ischaemic condition in the left inferior limb, with several arterial occlusions and a reocclusion in the posterior tibial artery in the right leg, previously treated with percutaneous transluminal angioplasty (PTA).

In March 2013, he presented with a sizeable ulcerous wound and osteomyelitis in the left calcaneus. After revascularisation for severe ischaemia in the left leg (femoral, popliteus and anterior tibial artery), he underwent debridement, antibiotic therapy and negative pressure wound therapy (NPWT) for the ulcer, with unsatisfactory results. In December 2013, the patient received an autologous skin graft, with poor results. The wound did not heal over the next six years, although the patient received repeated antibiotic therapy, advanced medications, autologous skin graft, and dermal substitutes transplantation. Treatment with blue light was initiated in June 2019 on the wound in the left calcaneus (*Figure 1A*) and, at the same time, on a second ulcer in the internal right malleolus, which had developed 3 months earlier (*Figure 1C*).

Both ulcers visibly reduced and appeared more superficial with each blue light treatment. The one in the malleolus was also gradually less painful. Both lesions healed entirely with blue light treatment, with 100% reepithelialisation. The more recent ulcer in the malleolus completely healed with five treatments (*Figure 1B*), and the chronic ulcer on the calcaneus healed with 10 treatments (*Figure 1D*, right).

Case 2

Patient 2 was a 57-year-old man with T2D on insulin for 20 years, who also had micro- and macro-angiopathy. The patient had previously undergone a femoropopliteal bypass in the left leg and amputation of the left foot. At the first consultation, in November 2018, he presented with a severe ulcer in the stump area, with necrosis and sepsis, beside the open fracture of the tibial malleolus (*Figure 2A*). The ulcer was drained and disinfected,

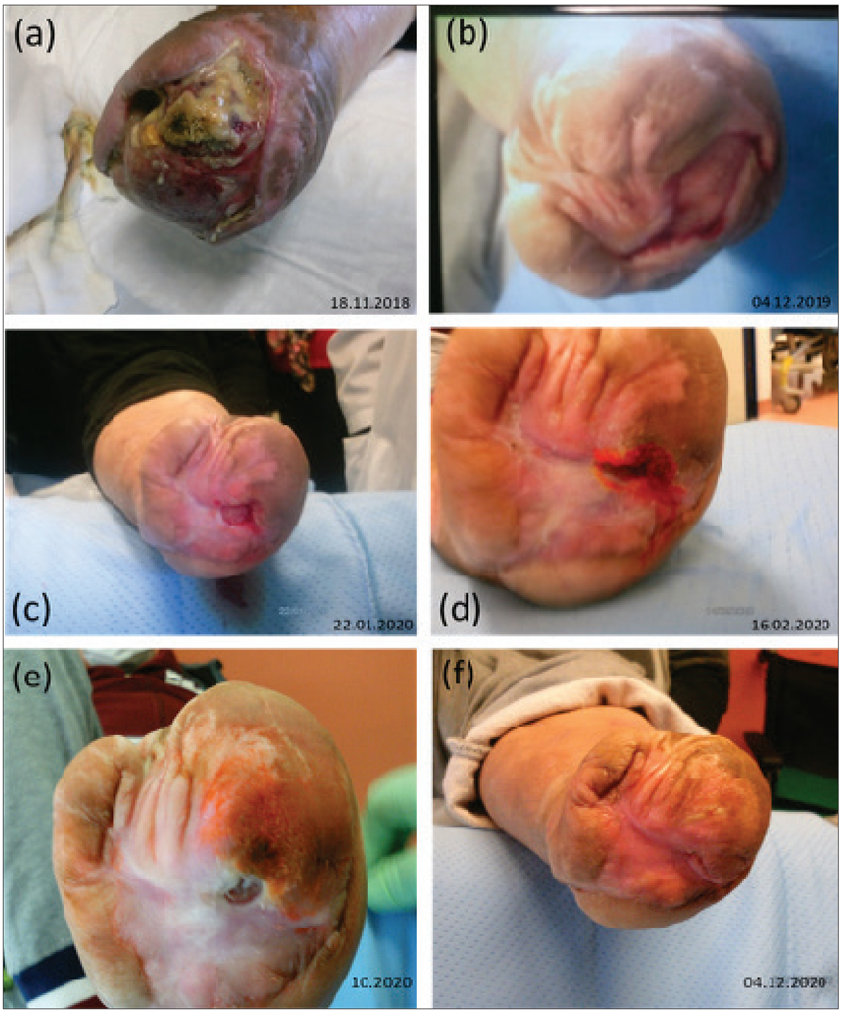

Figure 2. Patient 2 at first admission, with ulcer in the left leg stump with necrosis and sepsis (a). After surgery and standard care, with evident wound dehiscence (b). The wound after the first blue light treatment (c). and after 10 treatments (d), leading to 80% ulcer reduction. The stump about 8 months after first healing and an episode of heart failure, with ulcer recurrence, secretion and keratosis in the margins (e). The ulcer completely healed after seven blue light treatments (f).

and the patient hospitalised to evaluate the sepsis and vascular impairment. Computerised tomography angiography (CTA) showed severe stenosis in the right iliac artery and moderate stenosis of the superficial femoral artery, critical stenosis between the superficial femoral and popliteal artery and severe stenosis in the bifurcation of the right tibial artery. The left leg CTA revealed the complete occlusion of both the femoropopliteal bypass and the distal superficial femoral artery. The patient underwent revascularisation, an antibiotic for sepsis, and surgery to curtail the stump and reduce the fracture.

During postoperative hospitalisation, the clinical picture was further complicated by kidney failure. At follow-up the patient presented with wound dehiscence (*Figure 2B*). He was then treated with blue light therapy in December 2019, more than a year after the first observation.

Over the course of blue light therapy, exudate diminished and the wound bed appeared less infected, with bleeding. The margins were gradually less macerated; the wound reduced in size and became superficial (*Figure 2C*). After 10 treatments with blue LED light, the ulcer area had reduced by 80%, with the stump appearing rosy and the wound almost completely closed. (*Figure 2D*).

In August 2020, the patient reported heart failure and presented with periorbital and bilateral oedema in the lower limbs, bullous lesions in the legs and recurrence of the ulcer in the stump, with macerated margins and abundant exudate. After about 45 days, the oedema and bullous lesions resolved entirely with antibiotic and diuretic therapy, but the ulcer had slightly increased in diameter, with exudate and keratosis of the margins (*Figure 2E*). The patient underwent a further cycle of blue light treatment soon after to resolve the ulcer relapse.

After seven further blue light treatments, a 100% reduction of the lesion was observed, with full reepithelialisation and healing. At follow-up 15 days after the last treatment, clinical results were confirmed, with good trophism in the lesion area and adjacent tissues (*Figure 2F*).

Case 3

Patient 3 was an 80-year-old woman with T2D who had been on insulin for one year, and who also had macro-angiopathy, hypertension and obliterating arteriopathy of the lower limbs, previously treated with PTA. In April 2018, she presented with an infected ischaemic ulcer with tendon exposure in the middle and lower right leg that had developed about 3 months earlier (*Figure 3A*). She was treated with antibiotics and 10 NPWT treatments, with poor tolerability, which led to a partial reduction of the lesion and covering the tendon (*Figure 3B*).

In June 2019, 15 months after the first admission, blue light therapy was initiated. The wound bed improved, appearing gradually more cleansed, with less exudate and lower pain levels, and the lesion reduced and became more superficial. After 10 treatments, the ulcer had reduced in size by 50% (*Figure 3C*). Importantly, this improvement in reepithelisation allowed for a dermal substitute graft to be performed, leading to complete recovery.

Conclusion

Increasing evidence shows the efficacy of blue LED light therapy in promoting wound healing

Figure 3. Patient 3 at first admission, broad ischaemic-infected ulcer in the III middle and lower right leg with tendon exposure (a), after NPWT in (b), and after blue light treatment in (c), with 50% recovery.

and reducing inflammation and pain in patients affected by long-term venous leg ulcers, not responding to standard treatments. These encouraging results led us to assess the efficacy of blue light irradiation on recalcitrant ulcers in patients with diabetes, commonly not responding to the standard of care.

Blue light therapy significantly improved reepithelisation and healing in all the 11 patients studied, with the majority showing a complete recovery of the ulcers with no side effects. In the three cases presented, the treatment positively contributed to wound healing in patients with severe vascular impairment, and was also effective in managing ulcer recurrence in a patient with complex clinical pictures, including kidney and heart failure. The blue light therapy was particularly helpful in improving tissue replacement when applied.

These promising results indicate that blue LED light irradiation could be an effective and safe adjuvant therapy in managing recalcitrant ulcers in patients with diabetes, not responding to the standard of care. Further trials will be necessary to confirm our results. WINT

Disclosure

The authors report that EmoLED provided the blue LED light medical device.

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