Photobiomodulation, Photomedicine, and Laser Surgery
Volume 40, Number 6, 2022
© Mary Ann Liebert, Inc.
Pp. 1–9
DOI: 10.1089/photob.2021.0165

Original Research

Open camera or QR reader and scan code to access this article and other resources online.

Skin Fractional Scar Treatment with a New Carbon Dioxide Scanner: Histological and Clinical Evaluation

Giuseppe Scarcella, MD,[1] Laura Pieri, PhD,[2] and Irene Fusco, PhD[3]

Abstract

Background: The mechanism of action of fractional carbon dioxide (CO_2) laser in the management of skin scarring is stimulation of collagen and fibroblasts in the dermis, resulting in remodeling and shrinking of the skin.
Objective: The purpose of this research is to assess the safety and performance of a new CO_2 laser scanner for treatment of acne scars.
Methods: The study was carried out on 20 patients of both sexes, with a mean age of 25.7 ± 6.7 years. To assess the performance and safety of this new CO_2 scanner, a preclinical histological evaluation was done. A clinical evaluation of acne scars was performed using Goodman and Baron's quantitative global acne scarring grading system (GBQGASGS) and a crusting scale where crusting scores ranged from 1 = none to 4 = severe. Digital photographs were taken to obtain esthetic results.
Results: GBQGASGS showed a significant improvement in patients' scars and the treatment was well tolerated, with no lasting side effects.
Conclusions: The new scanner seems to be an effective and safe device for skin scarring treatment, speeding up the healing time of scars.

Keywords: skin remodelling, new CO_2 scanner, acne scars, clinical efficacy

Introduction

For a long time, fully ablative laser treatments, especially those performed with the carbon dioxide (CO_2) laser, have been considered the gold standard for resurfacing treatments due to strong skin remodeling. The CO_2 laser has been used successfully in the treatment of different types of scars, improving texture, color, and contracture.[1–5] Nevertheless, these invasive treatments resulted in adverse post-treatment responses such as pigmentary changes, swelling, erythema, blistering, crusting, and in some cases scarring.[6,7]

Fractional ablative lasers have the benefit of higher safety profile than traditional ablative lasers[8] with a reduction in the onset of erythema and recovery times.[9] These benefits in combination with the associated reduction in scarring and impaired pigmentation have contributed to the popularity of fractional laser treatments.

Fractional ablative laser causes immediate ablation at the epidermal/dermal level and within 48 h of treatment, the ablation area is completely replaced by invaginating epidermal cells. This microscopic ablative zone surrounds the epidermal tissue, and microscopic epidermal necrotic debris (MEND) can be observed in the stratum corneum. On the 7th day, MEND exfoliation is noticeable, and 1 month after the treatment, MEND is substituted by the normal stratum corneum.[10]

[1]General Secretary and National Head of Laser Department of ISPLAD, International-Italian Society of Plastic-Regenerative and Oncologic Dermatology, Verona, Italy.
[2]Biologist-Florence–Italy, Florence, Italy.
[3]Department of Pharmacology, University of Florence, Florence, Italy.

Compared with traditional lasers, the fractional ablative CO_2 laser can effectively improve skin regeneration, with shorter downtime and significantly fewer side effects. However, sometimes, in correlation with the quantity of energy used, even the fractional laser treatment can induce hyperpigmentation (PIH); Esmat et al.[11] reported the occurrence of persistent pixel stamping marks (PPSM), which represent miniature scarring at the sites of microscopic thermal zones, such as complications following the treatment of scars using high energy levels. These adverse post-treatment responses are associated with acute inflammatory responses to skin heat damage.

An increase in melanin synthesis may be due to an increase in the amount of arachidonic acid metabolites during the inflammatory process, which can stimulate melanocytes, particularly if the energy is concentrated at the level of the epidermis–dermis junction. Indeed, in PIH, anti-inflammatory treatments such as corticosteroids are employed to reduce postlaser inflammatory responses.[12]

Fractional ablative CO_2 lasers have proven to be a prospective therapy for improving burn scar function and appearance,[13–15] with a great number of studies reporting amelioration in the properties of the burn scar after treatment such as scar texture and color[16,17] and greater freedom of movement, especially around the joints.[18–20] Skin pretreatment with an ablative fractional laser is an effective method of enhancing topical drug absorption into the skin, and as a result, laser-assisted fractional drug delivery has become an established treatment modality.[21,22]

This technique is based on the fractional disruption of the epidermis, thereby creating a series of microscopic holes in the skin through which topical medication can be administered, minimizing the risk of scarring.[23]

Fractional systems have been on the market for a long time and there is proportionality between the energy supplied and the depth reached, which are consolidated over time.

Deep scars require greater ablation and therefore also greater energy. Indeed, the most severe scars require laser action depths >1 mm and this can be achieved by increasing the ablative power, which is related to the energy delivered by the system.[24–26]

Since an increase in the depth of action is directly related to the energy delivered, this consequently increases the risk of inflammation. For this reason, it became necessary to reduce the spot size of the DOT (columns of thermal damage).

To achieve greater ablation depths and, at the same time, reduce the amount of energy delivered to limit patient's pain and the risk of PIH onset, the optical mechanism of the DOT scanner was improved by reducing spot diameters, leading to the development of a new (SCAR3) scanner. The HiScan DOT scanner is an established CO_2 laser scanner (DEKA M.E.L.A., Florence, Italy) that can be used in dermatology and esthetic medicine for improvement and rejuvenation of the skin and acne scars.[27–31]

The SCAR3 scanner can be connected to the CO_2 family of lasers (DEKA M.E.L.A.) and is used to emit an energy/DOT of over 600 mJ. CO_2 laser emission with SCAR3 is fractionated, therefore it creates very thin and spaced columns of thermal damage (DOT), which penetrate deep into the skin layer.

Due to its particular features, the fractional CO_2 laser can achieve many different effects, further enhancing its great versatility. The shape and size of the scanner mode can be adapted to treat difficult regions such as the skin of the eyelids and the periorbital area.[32]

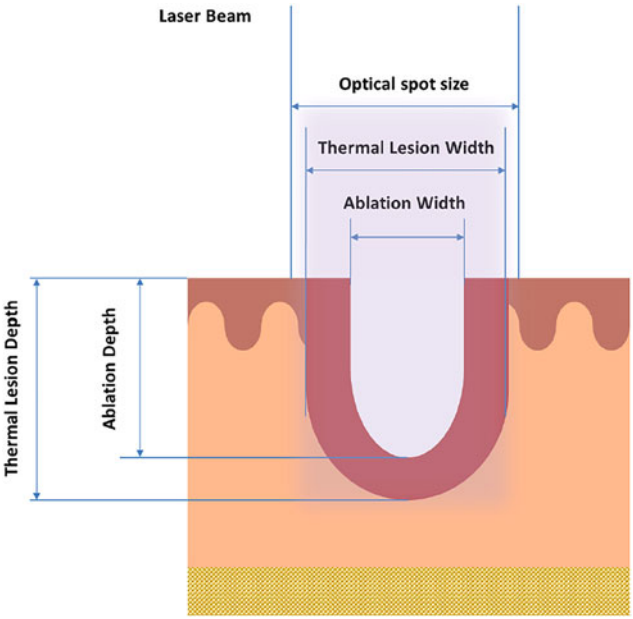


FIG. 1. A schematic graphical representation of the thermal lesion depth/width and ablation depth/width.

Treatment with fractional CO_2 causes a type of microablation of the epidermis that recovers in 24–48 h: epidermal tissue recovery happens rapidly through migration of keratinocytes and extrusion of damaged cells at the edges of the ablative and thermal zones. This treatment is safe with no serious side effects, with a reduction of downtime and an increase in patient satisfaction.[33]

Tenna et al. described the use and advantages of CO_2 laser emission in the induction of tissue shrinkage: complete reepithelialization was observed.[34]

Despite leading to bleeding in patients, this new method of fractional CO_2 laser emission using the same energy/DOT, in comparison with normal CO_2 (and Er:Yag) ablative lasers traditionally used in the resurfacing technique,[30,35–38] instead of reducing its therapeutic efficacy, seems to increase patient's acne scar healing time.

Based on these, the aim of this study is to assess the safety and performance of the new SCAR3 scanner (DEKA M.E.L.A.) in the treatment of acne scars, comparing its effectiveness on the acne scar healing rate with results from literature using previous CO_2 scanners by the same company (HiScan DOT) and using the same energy levels/DOT.

TABLE 1. DEMOGRAPHICS

No. of patients	20
Female patients	8
Male patients	12
Average age, years (±SD)	25.70 (±6.75)
Fitzpatrick skin type	II–IV

SD, standard deviation.

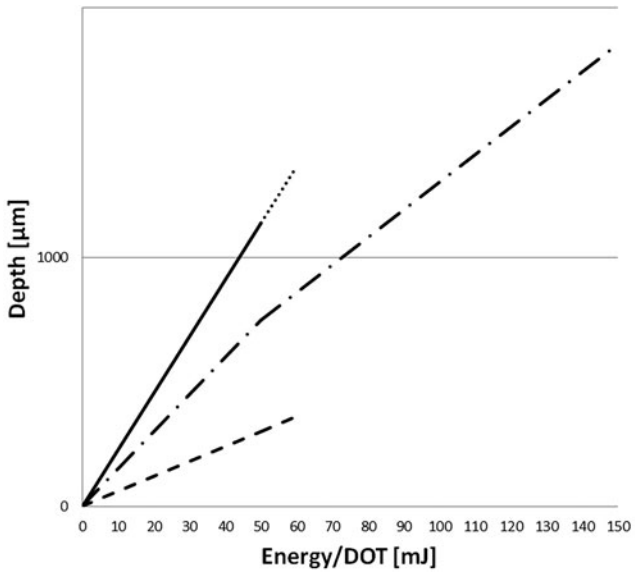


FIG. 2. Plot of the depth as energy increases: the thermal lesion depth achieved with SCAR3 (continuous line); ablation depth achieved with SCAR3 (dash–dot line); and ablation depth reported in literature data[40,45] with the HiScan DOT scanner (dashed line). DOT; SCAR3.

Materials and Methods

Ex vivo preclinical test

For the purpose of assessing the performance and safety of the SCAR3 scanner, a histological evaluation was done. An ex vivo sheep inner thigh skin sample was chosen due to its similarity with human skin tissue. Taking into consideration the entire range of energy levels available on the device, the following working points were chosen and divided in two groups (Groups 1 and 2) to better compare our data with those present in the literature for HiScan DOT, which are closest to the parameters used in Group 1 (Group1: energy levels/DOT ranged between 0 and 50 mJ).

With Group 2 (Group 2: energy levels/DOT ranged between 60 and 150 mJ), we investigated the effect of the SCAR3 scanner on histological samples also using higher energy levels than those presented in literature's data. We did not exceed 150 mJ/DOT due to lack of adequate skin sample thickness.

After laser exposure, all samples were fixed in 10% neutral buffered formalin, dehydrated through a crescent ethanol series, incorporated into paraffin, sectioned in series (4–5 μm thickness), stained with hematoxylin and eosin (H&E), and finally examined under an optical microscope. We recorded the morphological data of each pulse induced by both lasers on the tissue.

The following measurements were taken for each energy level/DOT (Fig. 1):

- Thermal lesion depth/width [μm]: depth/width at which coagulative thermal damage is observed.
- Ablation depth/width [μm]: depth/width at which ablation is observed.

Clinical evaluation

Patient selection. The clinical study included 20 patients of both sexes (8 females and 12 males), with an average age of 25.70 ± 6.75 (range 19–47 years) and Fitzpatrick skin type II–IV, affected by acne scars (Table 1). These patients were enrolled at the DermoLaser office in Verona, Italy. Patients who have recently undergone an exfoliation treatment or surgical treatments such as lifting and any patient with past skin disorders, including keloids and/or Koebner's phenomenon, were excluded.

Study protocol. In this study, patients were treated with the SCAR3 scanner (DEKA M.E.L.A.) with energy of 45–50 mJ/DOT and DOT spacing of 500 μm.

Before treatment, patients were well informed about the procedure and possible adverse effects, and an informed consent statement was signed by each patient.

The patients were subjected to a single-pass device, paying attention to avoid overlapping. After treatment, the skin was cooled with gauze soaked in cold water and an emollient cream was applied. The possible use of antibiotic creams or the oral administration of nonsteroidal anti-inflammatory therapies was also considered to be appropriate. The clinical examination of scars was carried out by using Goodman and Baron's quantitative global acne scarring grading system (GBQGASGS).[39]

Each patient was asked to complete a daily diary for 14 days following the procedure: a crusting grading scale was used in which crusting was graded, with scores ranging from 1 = none to 4 = severe.[40] Digital photographs were taken using a digital camera (Sony; Mod. DSCRX10M3, 14 M

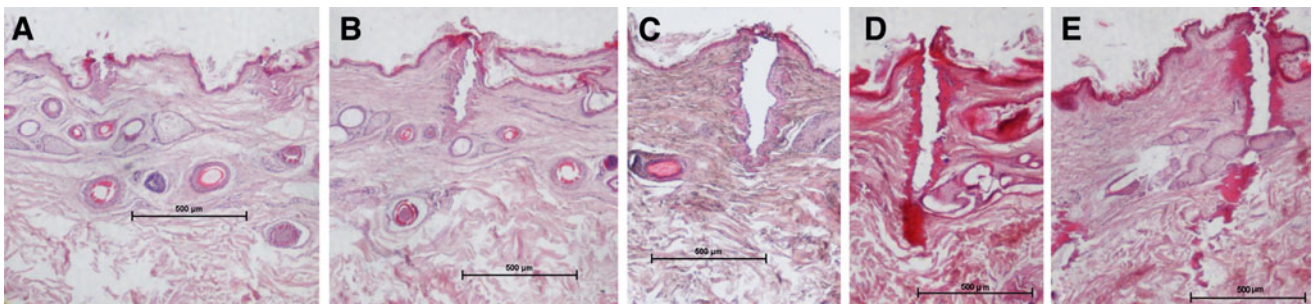


FIG. 3. Energy levels/DOT, 10–50 mJ (Group 1); changes in ablative, thermal, and total micron depths in ex vivo sheep skin after SCAR3 treatment (**A–E** scale bars 4×).

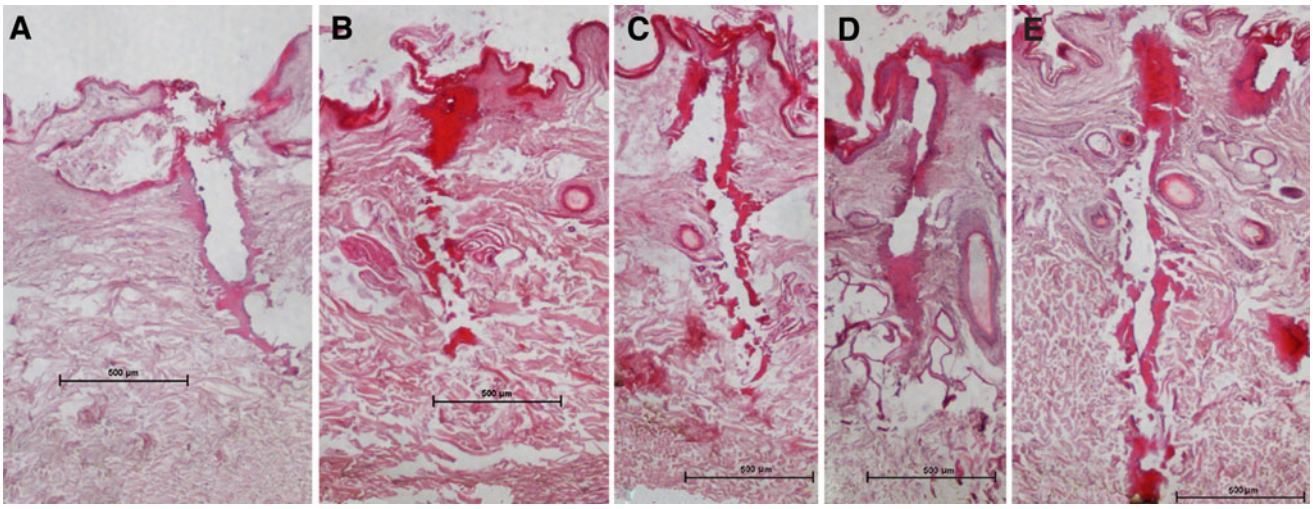


FIG. 4. Energy levels/DOT, 60–150 mJ (Group 2); changes in ablative, thermal, and total micron depths in ex vivo sheep skin after SCAR3 treatment (**A–E** scale bars 4×).

pixel) and Canfield Visia Facial Imaging System to obtain esthetic results: all subjects were evaluated and photographed before treatment, immediately after treatment, and 3 months after the last treatment. Adverse effects were evaluated and recorded.

Statistical analysis. The thermal lesion width and ablation width are shown as mean ± standard deviation (SD), while the trend lines of thermal lesion depth and ablation depth were analyzed. Paired Student's *t*-test was used to compare the clinical outcomes before and after treatment. The SPSS program, version 25.0 (IBM), was used for statistical analysis.

Preclinical Results with Histological Analysis

H&E-stained sections of sheep skin tissue subjected to laser treatment with the CO_2 fractional laser and scanning system (SCAR3; DEKA M.E.L.A.) showed narrow columns with increasing depth as the energy/DOT (mJ) increased; double depths were observed in comparison with histological studies by Bonan et al.[33] (for HiScan DOT); microablation columns of damage and coagulated microcolumns of collagen were observed from the epidermis into the underlying papillary and reticular dermis to various depths of the dermis. Higher energy settings caused deeper tissue injury and increased penetration into the reticular dermis (Fig. 2).

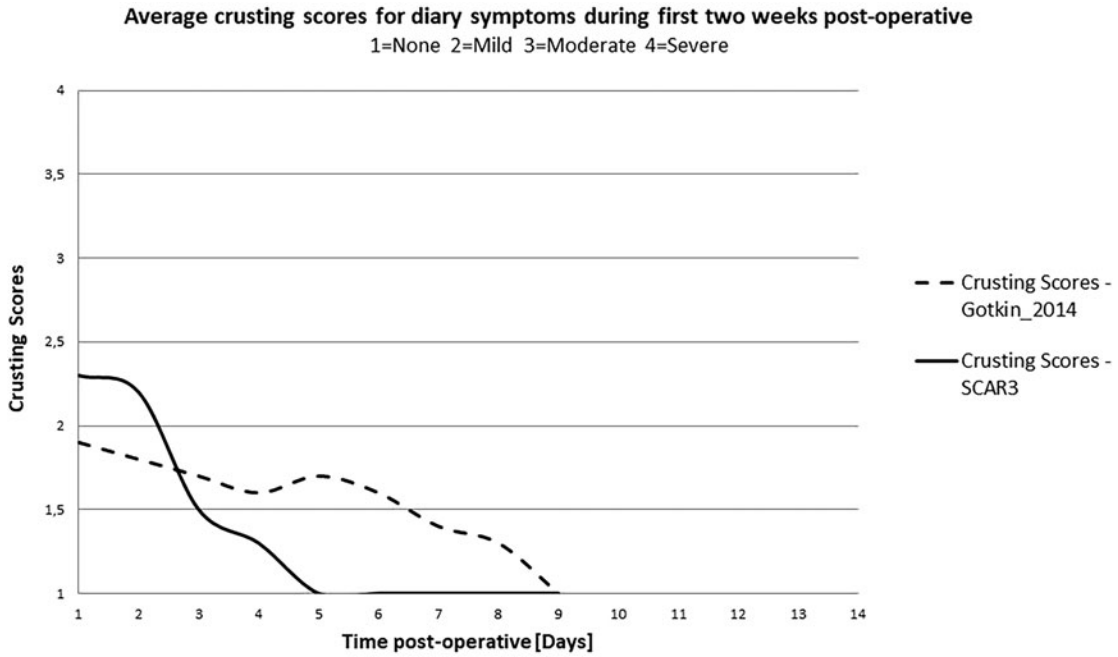


FIG. 5. Graphic representation of average crusting scores during the first 2 weeks postoperative, with the same energy/DOT.

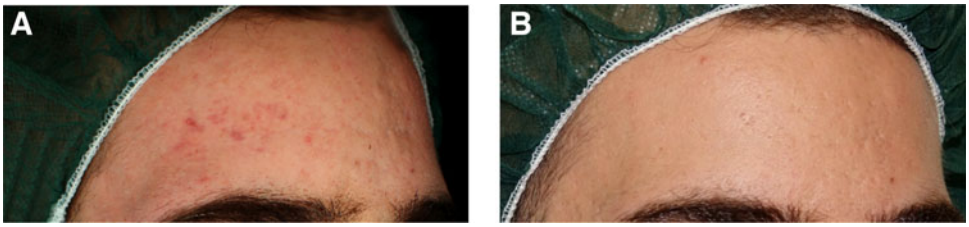


FIG. 6. View of patient's forehead at baseline **(A)** and 3-month follow-up **(B)**. An improvement in acne scars is observed.

The mean (±SD) ablation width was $118.8 \pm 78.0\ \mu$m, while the mean (±SD) thermal lesion width was $227.2 \pm 87.9\ \mu$m.

In conclusion, our histological findings (Figs. 3 and 4) show that for HiScan DOT, ablative depths achieved with the SCAR3 scanner using the same energy levels/DOT appear to be double in comparison with other similar histological findings published in literature.[34,41]

Assuming a linear trend of thermal lesion depth with increasing energy, we can observe that for the same energy/DOT, the SCAR3 scanner reaches greater depths compared with an established CO_2 scanner of the same system.

Clinical Results

We can observe that the treatment of skin scarring in patients using SCAR3 showed good results, even if this treatment showed more bleeding with the same energy/DOT used, compared with other traditional scanners of the same laser source.[34,41–45] However, several studies show longer healing times, as reported in the research by Gotkin and Sarnoff[40] for HiScan DOT, in which crusting scores reported in the crusting scale decreased more progressively than those observed after treatment with SCAR3 (Fig. 5) and in which crust appearance resolved in about 9 days, unlike that observed with the SCAR3 (crust appearance resolved in 5 days at the most, with the same energy/DOT used).

Patients' photographic evaluation showed an improvement of acne-scarred skin (Fig. 6). Significant improvement in acne scars in accordance with GBQGASGS was observed 3 months after the last treatment session (Table 2). The GBQGASGS scores decreased significantly ($p < 0.001$) from baseline (18.2 ± 5.2) to 3-month follow-up (9.8 ± 3.0) after the last treatment (Table 3; Fig. 7).

Immediately after treatment with the SCAR3 scanner, we observed mild erythema, which resolved within 48 h. Patients' compliance and comfort were positive also if temporary bleeding was observed immediately after the treatment. Even a faster and significant reduction in superficial erythema was also observed (maximum up to 2 days) in comparison with that in literature, which lasted up to 5 days[37] with the same energy/DOT used. No long-lasting side effects were observed.

Parameters of the two laser scanners (HiScan DOT and SCAR3) are shown in Table 4.

Discussion

Manstein et al.,[46] in 2004, first described the histological lesion of fractional laser devices. Fractional photothermolysis causes skin regeneration through creation of microscopic thermal/ablative lesions in the underlying epidermis or dermis.[35,36] The use of ablative fractional photothermolysis by CO_2 laser causes the formation of microscopic columns of thermal damage at the level of the epidermis/dermis, inducing superficial epidermal abrasion and thermal damage (both in ablation and in coagulation) down to the skin layers that must be treated, causing significant collagen stimulation.[47,48]

The CO_2 laser with a fractional scanning system (such as the SCAR3 scanner) produces microcolumns of thermal

Table 2. Goodman and Baron's Quantitative Global Acne Scarring Grading System

Grade/type	*Grade 1 (1–10 lesions)*	*Grade 2 (11–20 lesions)*	*Grade 3 (>20 lesions)*
A. Milder scarring (1 point each) Macular erythema or pigmentation Mildly atrophic, dish like	1 point	2 points	3 points
B. Moderate scarring (2 points each) Moderately atrophic, dish like Punched out with shallow bases, small scars (<5 mm) Shallow, but broad, atrophic areas	2 points	4 points	6 points
C. Severe scarring (3 points each) Punched out with deep, but normal, bases, small scars (<5 mm) Punched out with deep abnormal bases, small scars (<5 mm) Linear or troughed dermal scarring Deep, broad atrophic areas	3 points	6 points	9 points
D. Hyperplastic Papular Scars, keloidal/hypertrophic	2 points Area <5 cm^2 6 points	4 points Area 5–20 cm^2 12 points	6 points Area >20 cm^2 18 points

Table 3. Mean Score of Goodman and Baron's Quantitative Global Acne Scarring Grading System Evaluated Before Any Treatment and 3 Months After the Last Session

	Before, mean ± SD	*Three-month follow-up, mean ± SD*	*Significance*
Mean score of GBQGASGS	18.2 ± 5.2	9.8 ± 3.0	*p*- < 0.001

FU, follow up; GBQGASGS, Goodman and Baron's quantitative global acne scarring grading system.

damage surrounded by healthy tissue, which are able to create, through real microablation, vertical scaling of the epidermis: the microthermal zones (MTZs) promote growth factors and wound repair protein stimulation.[49]

MTZs, denominated as DOT in the laser system, have characteristics of specific emission to guarantee maximum effectiveness and minimal unwanted skin damage. The columns must have a constant ablation diameter from the impact with the skin surface to the layers below and the propagation of thermal and coagulative damage, which surrounds the area subjected to ablation at the level of the dermis, must maintain a constant shape and diameter throughout the depth of penetration to avoid the spread of uncontrolled heat in the surrounding tissue.

The skin around each column does not suffer the thermal damage just mentioned (ablation and coagulation), but only a biostimulation effect, and evaluation of the distance between each single DOT is fundamental to achieving a healing process that is fastest and with the best clinical result. Collagen stimulation and cutaneous rejuvenation effect depend on the depth of thermal damage at the level of dermis that triggers the formation of new collagen and tissue repair.[50]

Following resurfacing with the fractional CO_2 laser, various factors, including tumor necrosis factor-α, heat shock protein, transforming growth factor-β, and matrix metalloproteinase, from 2 days after treatment up to 3 months, lead to collagen remodeling and scar healing.[49–52]

The clinical effects are significant both in the treatment of aging skin of all degrees (according to Fitzpatrick classification) and in pigmented lesions and acne scarring. The treatment requires one or more sessions, which can also be done without anesthesia or with the application of a topical anesthetic, in subjects with less evident skin aging. The downtime is very minimal (a few days) and, according to Geronemus,[1] the side effects are significantly reduced as well as significantly less severe than those caused from the use of traditional ablative lasers.[53]

With the SCAR3 scanner, a faster and significant decrease in superficial erythema has also been observed (maximum up to 2 days) in comparison with the HiScan DOT scanner treatment, where erythema did not exceed 5 days in any patients.[37]

Healing of ablation zones and remaining thermal damage around the ablation zones contributes to the formation of a new and rearranged collagen pattern that is important in the neocollagenesis process[42]; moreover, if this is also associated with the greater depth of action of the SCAR3 scanner system (due to a small spot size) with a more pronounced bleeding and crusting process than a traditional scanner, an excellent result is certainly achieved.

The CO_2 laser system, with the use of the new SCAR3 scanning system and conservative parameters, reaches the deep layers of the dermis up to a depth of >1 mm. This implies that the potential effect of this laser, at the chosen parameters, covers all skin targets necessary to carry out superficial or deep treatments in any dermatological problem. Indeed, many scar areas are more than 1 mm thick and extend more than several millimeters in depth. To effectively treat these lesions, a laser ablation penetration depth greater than 1 mm is required, going as deep as possible to initiate the healing cascade and achieve good results in scar remodeling.

Traditional treatments with the fractional CO_2 laser,[29,33,37,40] which we have broken down with regard to the energy parameter used, do not report post-treatment bleeding events; bleeding of the treated areas accompanied by formation of blood serum crusting is given even greater emphasis in the cascade of events that normally result in stabilization of the collagenesis–collagenolysis cycle, which lead to faster scar healing.

It is known from literature that blood provides important and essential growth factors for tissue regeneration. After tissue injury, the resulting blood clot reestablishes hemostasis and provides a transient extracellular matrix for migration of cells. Platelets secrete many mediators for wound healing, but in the absence of bleeding, they do not exert these actions.

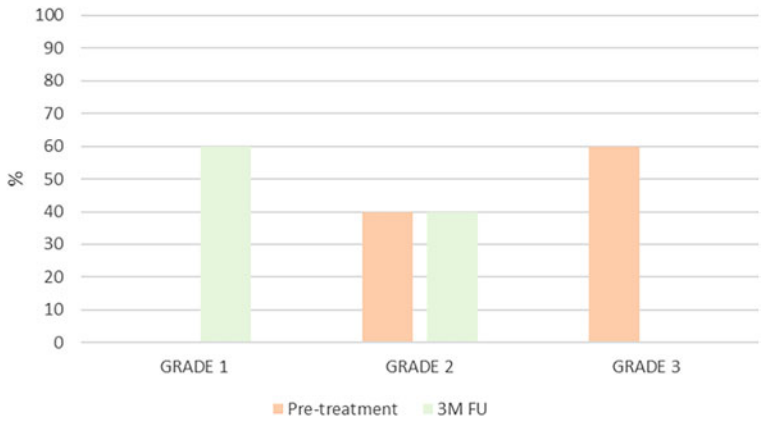


FIG. 7. Histogram representation of the GBQGASGS lesion grade, evaluated before treatment and 3 months after the last treatment. FU, follow up; GBQGASGS, Goodman and Baron's quantitative global acne scarring grading system.

Table 4. Laser Scanner Parameters

	HiScan DOT scanner (DEKA M.E.L.A.)	*SCAR3 scanner (DEKA M.E.L.A.)*
Energy/DOT [mJ]	Over 600	Over 600
Spacing [μm]	From 100 to 2000	From 100 to 2000
Scan area [mm^2]	225	225
Scan shape	Point, line, triangle, parallelogram, hexagon, square, ellipse, or annular ring	Point, line, triangle, parallelogram, hexagon, square, ellipse, or annular ring
Beam profile	Gaussian	Gaussian
Optical spot size [μm]	2.9E+02	2.1E+02
Optical area [mm^2]	0.067	0.033

Particularly, transforming platelet-derived growth factor and growth factor b1 probably stimulate fibroblast proliferation in the tissue around the wound and migration of integrin receptors into the wound space.[54] Three to 5 days after tissue injury, new capillaries visible as granulation tissue serve as a matrix for blood vessel proliferation and fibroblast migration.[55]

For this reason, the use of fractional ablative CO_2 laser is often combined with therapies that promote these growth factors, such as platelet-rich plasma[56] in reconstruction of depressed scars, which produce excellent results.[57]

In this study, it was also observed that with the use of the SCAR3 scanning system, patients have faster scar healing in comparison with the HiScan DOT scanner as it was possible to obtain an almost comparable effect in terms of depth of action, while halving the energy emission values, and consequently the possible onset of hyperpigmentation.

We can hypothesize that hyperpigmentation reduction is related to the depth of action of the subject system, which, by creating deeper holes in the epidermis, could further disperse the amount of arachidonic acid released following an inflammatory response,[58] as already discussed in the Introduction section. Further studies will be needed to validate this hypothesis.

The SCAR3 scanner may also be used for tattoo removal since its effectiveness has been observed when combined with the fractional Q-switch laser.[59]

Conclusions

Our preclinical and clinical findings show that the SCAR3 scanning system produces excellent results in scar treatment, using similar energy emission levels as those found in literature and decreasing the spot size to achieve a double depth effect. Although transient bleeding was observed, it led to faster scar healing after treatment, compared with the literature findings.

This new scanner system, in addition to reducing patient downtime and related recovery times, more importantly, improves treatment performance. This benefit is most evident in patients with conditions that affect their quality of life such as pervasive skin disease and morbid scar complications.

Authors' Contributions

G.S. performed the research and contributed substantially to the study design, interpretation, and data acquisition/analysis and I.F. and L.P. contributed to manuscript writing. All authors were involved in drafting and revision of the manuscript and approval of the version to be published.

Each author has agreed to be responsible for all aspects of the job to ensure that issues related to the accuracy or integrity of any part of the job are properly investigated and resolved.

Ethical Statement

The techniques performed in this study involving humans are in accordance with the ethical standards of the institutional national research committee and the Helsinki Declaration of 1975.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

No funding was received for this article.

Supplementary Material

Supplementary Figure S1

References

1. Geronemus RG. Fractional photothermolysis: current and future applications. Lasers Surg Med 2006;38:169–176.
2. Chapas AM, Brightman L, Sukal S, et al. Successful treatment of acniform scarring with CO2 ablative fractional resurfacing. Lasers Surg Med 2008;40:381–386.
3. Salles AG, Remigio AFDN, Zacchi VBL, Ferreira MC. Treatment of facial burn sequelae using fractional CO2 lasers in patients with skin phototypes III to VI. Braz J Plast Surg 2012;27:9–13.
4. Clementoni MT, Patel T. A new treatment for severe burn and post-traumatic scars: a preliminary report. Treat Strat Dermatol 2013;2:44–48.
5. EL-Hoshy K, Abdel-Halim M, Dorgham D, Sayed SS, El-Kalioby M. Efficacy of fractional carbon dioxide laser in the treatment of mature burn scars: a clinical, histopathological, and histochemical study. J Clin Aesthet Dermatol 2017;10:36–43.

6. Railan D, Kilmer S. Ablative treatment of photoaging. Dermatol Ther 2005;18:227–241.
7. Hunzeker CM, Weiss ET, Geronemus RG. Fractionated CO2 laser resurfacing: our experience with more than 2000 treatments. Aesthet Surg J 2009;29:317–322.
8. Alexiades-Armenakas MR, Dover JS, Arndt KA. The spectrum of laser skin resurfacing: nonablative, fractional, and ablative laser resurfacing. J Am Acad Dermatol 2008; 58:719–737.
9. Neaman KC, Baca ME, Piazza RC III, VanderWoude DL, Renucci JD. Outcomes of fractional CO2 laser application in aesthetic surgery: a retrospective review. Aesthet Surg J 2010;30:845–852.
10. Michael J Reilly 1, Marc Cohen, Akishige Hokugo, Gregory S Keller. Molecular effects of fractional carbon dioxide laser resurfacing on photodamaged human skin. resurfacing on photodamaged human skin. Arch Facial Plast Surg 2010;12:321–325.
11. Esmat SM, Abdel-Halim MRE, Gawdat HIet al. Persistent pixel stamping marks: a novel complication of fractional CO 2 laser in scar treatment. Lasers Med Sci 2019;34: 1125–1135.
12. Ou KL, Wen CC, Lan CY, Chen YA, Wang CH, Wang YW. The optimal application of medium potency topical corticosteroids in preventing laser-induced inflammatory responses-an animal study. Life (Basel) 2021;11:350.
13. Hantash BM, Bedi VP, Kapadia B, et al. In vivo histological evaluation of a novel ablative fractional resurfacing device. Lasers Surg Med 2007;39:96–107.
14. Anderson RR, Donelan MB, Hivnor C, et al. Laser treatment of traumatic scars with an emphasis on ablative fractional laser resurfacing: consensus report. JAMA Dermatol 2014;150:187–193.
15. Waibel JS, Gianatasio C, Rudnick A, Siegel A. Use of lasers in wound healing: how to best utilize laser technology to prevent scar formation. Curr Dermatol Rep 2018;7: 303–310.
16. Karmisholt K, Haerskjold A, Karlsmark T, Waibel JS, Paasch U, Haedersdal M. Early laser intervention to reduce scar formation—a systematic review. J Eur Acad Dermatol Venereol 2018;32:1099–1110.
17. Haedersdal M, Moreau KER, Beyer DM, Nymann P, Alsbjorn B. Fractional nonablative 1540 nm laser resurfacing for thermal burn scars: a randomized controlled trial. Lasers Surg Med 2009;41:189–195.
18. Waibel JS, Wulkan AJ, Shumaker PR. Treatment of hypertrophic scars using laser and laser assisted corticosteroid delivery. Lasers Surg Med 2013;45:135–140.
19. Shumaker PR, Kwan JM, Landers JT, Uebelhoer NS. Functional improvements in traumatic scars and scar contractures using an ablative fractional laser protocol. J Trauma Acute Care Surg 2012;73:S116–S121.
20. Kroonen L, Shumaker PR, Kwan JM, Uebelhoer N, Hofmeister E. Treatment of split-thickness skin graft-related forearm scar contractures with a carbon dioxide laser protocol: 3 case reports. J Hand Surg Am 2013;38: 2164–2168.
21. Krakowski AC, Goldenberg A, Eichenfield LF, Murray JP, Shumaker PR. Ablative fractional laser resurfacing helps treat restrictive pediatric scar contractures. Pediatrics 2014; 134:e1700-5.
22. Haedersdal M, Erlendsson AM, Paasch U, Anderson RR. Translational medicine in the field of ablative fractional laser (AFXL)-assisted drug delivery: a critical review from basics to current clinical status. J Am Acad Dermatol 2016; 74:981–1004.
23. Wenande E, Tam J, Bhayana B, et al. Laser-assisted delivery of synergistic combination chemotherapy in in vivo skin. J Control Release 2018;275:242–253.
24. Gordon HS, heather MT, Tucker B. Fractional CO2 laser resurfacing of photoaged facial and non-facial skin: histologic and clinical results and side effects. J Cosmet Laser Ther 2009;11:190–201
25. Oni G, Robbins D, Bailey S, Brown SA, Kenkel MJ. An in vivo histopathological comparison of double and single pulsed modes of a fractionated CO2 laser. lasers in surgery and medicine 2012;44:4–10.
26. Waibel JS, Rudnick A, Shagalov DR, Nicolazzo DM. Update of ablative fractionated lasers to enhance cutaneous topical drug delivery. Rev Adv Ther 2017;34:1840–1849.
27. Mu YZ, Jiang L, Yang H. The efficacy of fractional ablative carbon dioxide laser combined with other therapies in acne scars. Dermatol Ther 2019;32:e13084.
28. Ibrahim SM, Elsaie ML, Kamel MI, Mohammed EE. Successful treatment of traumatic scars with combined nonablative fractional laser and pinpoint technique of standard CO2 laser. Dermatol Ther 2016;29:52–57.
29. Ibrahim SM, Saudi WM, Abozeid MF, Elsaie ML. Early fractional carbon dioxide laser intervention for postsurgical scars in skin of color. Clin Cosmet Investig Dermatol 2019; 12:29–34.
30. Alexiades-Armenakas M, Sarnoff D, Gotkin R, Sadick N. Multi-center clinical study and review of fractional ablative CO2 laser resurfacing for the treatment of rhytides, photoaging, scars and striae. J Drugs Dermatol 2011;10:352–362.
31. Sarnoff D, Gotkin H, Doerfler B, Gustafson J, Hanke CW. The safety of laser skin resurfacing with the microablative carbon dioxide laser and review of the literature. J Drugs Dermatol 2018;17:1157–1162.
32. Fitzpatrick RE, Goldman MP, Satu NM, Tope WD. Pulsed carbon dioxide laser resurfacing of photo-aged facial skin. Arch Dermatol 1996;132:395–402.
33. Bonan P, Campolmi P, Cannarozzo G, et al. Eyelid skin tightening: a novel 'Niche' for fractional CO_2 rejuvenation. J Eur Acad Dermatol Venereol 2012;26:186–193.
34. Tenna S, Cassotta G, Brunetti B, Persichetti P. Hyperpigmentated scars of the face following a toxic epidermal necrolysis (TEN): a case report. Dermatol Plast Surg 2016; 1:1007.
35. Khatri KA, Ross V, Grevelink JM, Magro CM, Anderson RR. Comparison of erbium:YAG and carbon dioxide lasers in resurfacing of facial rhytides. Arch Dermatol 1999;135: 391–397.
36. Tanzi EL, Alster TS. Single-pass carbon dioxide versus multiple-pass Er:YAG laser skin resurfacing: a comparison of postoperative wound healing and side-effect rates. Dermatol Surg 2003;29:80–84.
37. Cannarozzo G, Sannino M, Tamburi F, et al. Deep pulse fractional CO2 laser combined with a radiofrequency system: results of a case series. Photomed Laser Surg 2014;32: 409–412.
38. Nanni CA, Alser TS. Complications of carbon dioxidelaser resurfacing. An evalutation of 500 subject. Dermatol Surg 1998;24:315–320.
39. Goodman GJ, Baron JA. Postacne scarring: a qualitative global scarring grading system. Dermatol Surg 2006;32: 1458–1466.

40. Gotkin RH, Sarnoff DS. A preliminary study on the safety and efficacy of a novel fractional CO_2 laser with synchronous radiofrequency delivery. J Drugs Dermatol 2014;13: 299–304.
41. Tenna S, Cogliandro A, Piombino L, Filoni A, Persichetti P. Combined use of fractional CO2 laser and radiofrequency waves to treat acne scars: a pilot study on 15 patients. Clinical Trial J Cosmet Laser Ther 2012;14:166–171.
42. Omi T, Kawana S, Sato S, Bonan P, Naito Z. Fractional CO2 laser for the treatment of acne scars. J Cosmet Dermatol 2011;10:294–300.
43. Scarcella G. Laser CO2 and radiofrequency: effective synergy for skin rejuvenation. J Plast Dermatol 2011;7, 3.
44. Prignano F, Bonciani D, Campolmi P, Cannarozzo G, Bonan P, Lotti T. A study of fractional CO_2 laser resurfacing: the best fluences through a clinical, histological, and ultrastructural evaluation. Randomized Controlled Trial. J Cosmet Dermatol 2011;10:210–216.
45. Campolmi P, Bonan P, Cannarozzo G, et al. Epub 2012 Apr 19. Highlights of thirty-year experience of CO2 laser use at the Florence (Italy) department of dermatology. Sci World J 2012;2012:546528.
46. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic Outcomes of fractional CO2 laser application in aesthetic surgery: a retrospective review patterns of thermal injury. Lasers Surg Med 2004;34:426–438.
47. Gotkin RH, Sarnoff DS, Cannarozzo G, Sadick NS, Armenakas MA. Ablative skin resurfacing with a novel microablative CO2 laser. J Drugs Dermatol 2009;8:138–144.
48. Wang YS, Tay YK, Kwok C. Fractional ablative carbon dioxide laser in the treatment of atrophic acne scarring in Asian patients: a pilot study. J Cosmet Laser Ther 2010;12: 61–64.
49. Prignano F, Campolmi P, Bonan P, et al. Fractional CO2 laser: a novel therapeutic device upon photobiomodulation of tissue remodeling and cytokine pathway of tissue repair. Dermatol Ther 2009;22(Suppl. 1): S8–S15.
50. Rinaldi F. Laser: a review. Clin Dermatol 2008;26: 590–601.
51. Sasaki GH. Fractional CO2 laser resurfacing of photoaged facial and non-facial skin: histologic and clinical results and side effects. J Cosmet Laser Ther 2009;11:190–201.
52. Reilly MJ, Cohen M, Hokugo A, Keller GS. Molecular effects of fractional carbon dioxide laser resurfacing on photodamaged human skin. Arch Facial Plast Surg 2010; 12:321–325.
53. Sorbellini E, Rinaldi F. Evaluation of CO2 fractional laser effect on the skin by confocal microscopy. J Plast Dermatol 2010;6:2.
54. Singer AJ, Clark RA. Cutaneous wound healing. Rev N Engl J Med 1999;341:738–746.
55. Honnegowda TM, Kumar P, Udupa EGP, Kumar S, Kumar U, Rao P. Role of angiogenesis and angiogenic factors in acute and chronic wound healing. Plast Aesthet Res 2015;2: 243–249.
56. Sharma S, Kaur J, Kaur T, Bassi R. Fractional carbon dioxide laser versus combined fractional carbon dioxide laser with platelet-rich plasma in the treatment of atrophic post-acne scars: a split-face comparative study. J Cutan Aesthet Surg 2021;14:41–46.
57. Ganio C, Tenewitz FE, Wilson RC, Moyles BG. The treatment of chronic nonhealing wounds using autologous platelet-derived growth factors. J Foot Ankle Surg 1993;32: 263–268.
58. Adalatkhah H, Sadeghi-Bazargani H. The Association between melasma and postinflammatory hyperpigmentation in acne patients. Iran Red Crescent Med J 2013;15:400–403.
59. Radmanesh M, Rafiei Z. Combination of CO2 and Q-switched Nd:YAG lasers is more effective than Q-switched Nd:YAG laser alone for eyebrow tattoo removal. Clin Trial J Cosmet Laser Ther 2015;17:65–68.

Address correspondence to:
Irene Fusco, PhD
Department of Pharmacology
University of Florence
Florence 50121
Italy

E-mail: irene.fusco@unifi.it

Received: November 18, 2021.
Accepted after revision: March 14, 2022.
Published online: May 25, 2022.