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ESTUDIOS CLÍNICOS

bi-one®

Lifetouch. Therapy

BIODERMOGENESI®
THE LIFE-TOUCH THERAPY

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ESTUDIOS CLÍNICOS

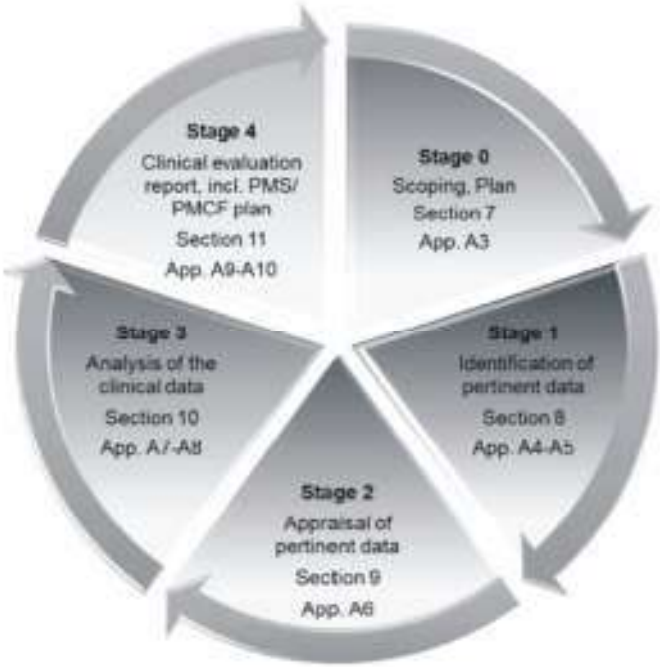
bi-one®
Lifetouch Therapy

ESTUDIOS GENERALES

BIODERMOGENESI®
THE LIFE-TOUCH THERAPY

1. Introduction

The clinical evaluation is based on a complete analysis of the available relevant pre and post-sale data relating to the destination of the device in question, including performance data and clinical safety data.
There are several stages in carrying out a clinical evaluation, as shown in the flow chart below:



This clinical evaluation was prepared following the European Commission's guidelines, Enterprise and Industry Directorate-General, MEDDEV 2.7.1 Rev. 4, complying with the Directive 2007147/EC standards. Its structure reflects these guidelines.
The working group that drew up this document is indicated below.

Maurizio Busoni	Owner of Expo Italia Srl Teacher since 2008 in the II level Master of Aesthetic Medicine and Surgery at the University of Barcelona. Lecturer in the II level Aesthetic Medicine Masters at Siena, Pavia, Camerino, Palermo, Verona, Tor Vergata, and Pisa.
Dr. Domenico Amuso	Surgeon Teacher in the II level Masters at the Universities of Pescara, Verona, and Chieti. He has published dozens of works and ten indexed on PubMed and various mono-thematic books related to aesthetic pathologies.
Eng. Lorenzo Spinelli	External consultant, owner of STUDIO LS and the ELETTRA Srl laboratory He collaborated to prepare the Technical File of the product and coordinated the electrical safety checks and electromagnetic compatibility of the devices at the Elettra Srl laboratories. He specializes in the legislative and regulatory framework and collaborates to register the product in the Ministry Database. **Electronic engineer, an external consultant for more than 30 years, an inspector for the Medical Devices Directive since 2002, assisted in the setup of this report.**

2. Purpose

The purpose of this evaluation, made up of this chapter and the attached report, is to identify clinical support information that allows us to define a starting point for product validation, comparing it to competitors' products or experimental tests.
This report was created to describe the methodologies used to identify relevant scientific publications to prove the device's safety and performance. Expo Italia Srl is the manufacturer.

The research protocol, a research report, and copies of the most relevant articles and the corresponding bibliographies are integral to the technical documentation.
To simplify the understanding of this text, we will make use of equivalent terminology, identified below:

Vacuum	that is:	negative pressure, void
Electroporation	that is:	square wave stimulation
Capacitive radio frequency	that is:	electromagnetic field, Marconi-therapy, Tecar-therapy
I/O	that is:	operating microprocessor, power board
CPU	that is:	supervisor microprocessor, user interface
Hundredth atmosphere	that is:	10 mb, 7.6 mmHg

3. Objectives

The objectives of this report are as follows:

- Report and describe the studies regarding our technology
- Report and describe the data obtained from the scientific literature survey pertinent to the device in question.

These data must support the equipment mentioned above in terms of performance and safety and must be an integral part of the guarantees regarding its performance. Therefore, the method used consists of choosing similar devices and comparing the versions obtained with those already on the market and currently considered to comply with the applicable specifications.

- Illustrate the research strategy and present the results.
- Document how the shared data were obtained and trace them back to the device's performance in question.
- Present the final selection of the chosen literature to provide clinical evidence of the validity of the device.

4. Identification of the device

Bi-one® LifeTouchTherapy is a device intended for dermatologic therapies thanks to the synergy between capacitive radiofrequency (otherwise called "electromagnetic field"), negative pressure (otherwise called "vacuum"), and electrostimulation (otherwise called "electroporation"). The device is intended for use by properly trained medical and paramedical staff within medical practices or clinics. The device has no particular limitations and does not expose the patient or the operator to side effects.

Bi-one® LifeTouchTherapy is found inside a metal case that acts as a Faraday cage, and it is powered at 15VDC through a specific switching power supply certified for medical use. The case houses a power board (I/O), an expansion that houses the vacuum sensor. This expansion houses the electrical stimulation delivery module, one or more vacuum pumps, a battery of solenoid valves. In contrast, the upper head houses the control board (CPU), the keyboard, and the display.
The following outputs are present on the container:

STIM	delivers square wave electric signal at a frequency of 5 Hz
ACTIVE	provides negative pressure from 90 to 250 mb
	produces square wave electric signal at a frequency of 5 Hz
	delivers capacitive radiofrequency from 0.5 to 1.0 MHz
RIF	closing reference of the capacitive radiofrequency

5 The mechanism of action

The Bi-one® LifeTouchTherapy device provides various applications in the field of dermatology. The therapies provided are the following:

- Post-surgical and burn scars therapy
- Stretch marks therapy

The Bi-one® LifeTouchTherapy device acts thanks to the biological effect of the synergy between electromagnetic field, vacuum, and electroporation.
This section will describe the known effects of the various forms of energy adopted, the synergies, and the relevant therapeutic areas.

5.1 The synergy between vacuum, electromagnetic fields, and electroporation

Onboard a specific hand-piece called "ACTIVE PLUS," available in three different versions for the face and body, three distinct forms of energy are adopted: the electromagnetic field, the vacuum, and the electroporation. These energies are all known in therapeutic applications and boast numerous publications in high-impact journals and on the official bodies of various Aesthetic Medicine Societies, national and international.

To understand the Bi-one® LifeTouchTherapy device's effectiveness and intrinsic safety, we must learn how it interacts with the skin tissue and how the adopted hardware and software solutions ensure the highest standards.

The biological effect induced by the device is described below. It analyzes its action, the induced reactions, the risk elements found up-to-the-minute, and the solutions implemented to avoid their emergence, first examining each form of energy in its own right and then applied jointly.

5.2 The vacuum

The Bi-one® LifeTouchTherapy device delivers the vacuum to the patient by adopting safe parameters. Vacuum is generated with pumps and is choked downstream before being applied to the patient, thanks to a group of differentiated loss solenoid valves. The opening of each solenoid valve is activated by the I / O. Simultaneously, the CPU monitors every leak's entrance, detecting the solenoid valve's consumption and the vacuum applied and that foreseen by the operating protocols through a Motorola® sensor. It indicates any anomalies on display. The vacuum level adopted for the currently planned therapies varies from 90/100 mb (step 1) to 140 mb (step 4), therefore within the safe value based on the experience of Moortgat and coll. A01, which indicates an effective and safe level of vacuum applied equally to 200 mb. The vacuum reaches the edge of the handpiece thanks to a pneumatic cable with ultra-fast couplings; on the handpiece, a heading is designed to contact the patient's skin, made of Tecason® or similar certified ISO 10993.

The nominal value of the vacuum produced is then verified in real-time with a Motorola® production sensor, which sends information on the actual vacuum level produced to the CPU microprocessor. The software provides more and fewer tolerance thresholds of the value of each step. It is related to the oscillation of the vacuum value generally found with the operation of the therapy or the pressure variables exerted by the operator. As long as the vacuum value read falls within these standards, the treatment continues without messages. In addition to these tolerances, there are two others. The first has a more significant oscillation than the nominal value and still allows the delivery of the therapy in safety, but sends a WARNING message to the operator to inform an actual deviation of the value. This WARNİNG message does not indicate danger for the patient but invites the operator to replace the external filters, as the presence of impurities inside them modifies the actual value of the vacuum delivered. If the oscillation of the vacuum level increases again, the device sends an ALARM message and informs the operator that he must send the apparatus for assistance. If the technology continues to be used without the due calibration of the vacuum levels, the machine stops and sends the message "ALARM! SAFE MODE ". From that moment on, it will be necessary for the device to undergo a new calibration at an authorized service center before activating the vacuum delivery to the patient again.

The vacuum is used for many therapies in the state-of-the-art, from scars to skin regeneration to extracellular matrix remodeling. However, modern technologies and applications make side effects unusual, limited to redness, skin sensitization, and modest edema or hematomas. The technology incorporated in Bi-one® LifeTouchTherapy prevents the patient from taking risks above-written. İt is because the device reads the vacuum level delivered to the patient and indicates an eventual overdose of energy with messages like WARNİNG, ALARM, ALARM! SAFE MODE.

It is also important to point out that the use of the device is reserved for doctors or paramedics who have undergone a specific training course, thus eliminating the risk factor linked to the operator's inexperience.
Furthermore, our online training platform Edu-Care, reserved for owners of the Bi-one® LifeTouchTherapy device, keeps updated for all the usage and new fields of application.

5.3 The electromagnetic field

Even the delivery of the electromagnetic field to the patient takes place by adopting parameters of absolute safety, thanks above all to the device's architecture that allows the highest safety standards.
The action of the electromagnetic field has been known since 1939, when Clayton in London demonstrated, for the first time, the possibility of regenerating damaged muscle tissue faster, thanks to what he called "Marconi therapy." The

electromagnetic field does not transmit energy as traditionally understood within the biological tissue but rather reactivates the physiologically present electrical charges. Suppose we activate a positively charged electromagnetic field (corresponding to the positive peak of every single pulse of the radio frequency). In that case, we will have the sodium (Na+), and potassium (K+) ions move towards the inside of the cell membranes (having themselves a positive electric charge) through the electro-pores consisting of intrinsic proteins. Note that these ions are biological carriers that allow the introduction of nutritional factors into the cell membranes. Therefore the positive charge given by the electromagnetic field favors and accelerates the action, allowing a higher intake of these elements inside layers.
Consequently, the passage to the negative peak of every radiofrequency pulse determines an electromagnetic field of negative charge. Therefore, the energy becomes attractive towards sodium and potassium, which in this case, carry out their carrier action by removing the waste material of the cellular metabolism, moving these elements towards the matrix. At the end of the negative phase, we will have these ions present in the matrix, ready for another crossing of the cell membranes and further supply of nutrients. The repeated action of crossing the membranes determines the transformation of the kinetic energy into a mild increase in skin temperature, attested to be between 39 and 40° C, unlike the physiological 36°/37° C. This phenomenon, well-known today, allows the implementation of Van't Hoff's Law (Nobel Prize in Chemistry in 1901), according to which cellular and molecular regeneration multiply by four in case of temperature between 39° and 40° C, with concomitant good cellular nourishment and good activity of skin microcirculation.

In managing the device and safety of the therapy, the reference handpiece of the ACTIVE phase is extremely important. This antenna receives all the energy that is not biologically active (and therefore "consumed" by the skin tissue); the device receives this data thanks to its hardware architecture. The device is equipped with an electronic card called I/O, intended to supply and modulate the three forms of energy. Another electronic card called CPU, designed for the user interface (display and keyboard) and to supervise I/O activity. The software involves the following steps:

phase 1	activation	CPU	commands the I/O to deliver the radio-frequency
phase 2 (*)	bio-feedback	CPU	reads the feedback value and calculates the difference (energy supplied - minus bio-feedback) to know the quantity of biologically active energy
phase 3 (*)	modulation	CPU	changes the frequency and intensity of the radio-frequency delivered by the I/O

(*) From the beginning of the treatment, phases 2 and 3 are repeated at each significant variation of the bio-feedback, which changes the effective dose of a biologically active electromagnetic field.

This solution allows constant monitoring of the active energy dose, modifying intensity and frequency in real-time, based on the response obtained with the bio-feed-back method, also developed based on the experiences of Eilebrecht and coll. B02 has developed a system that brings the impedance measurement in parallel with biopotential measures that allow a better "coupling" of the patient with the technology in question. Thanks to this procedure and a proprietary algorithm, the device aligns the induced thermal effect between 39 ° and 40 ° C, effectively preventing any side effects.

If the device fails to read the bio-feedback for a period equal to or greater than 60 seconds, block itself. Therefore, it informs the operator by producing an acoustic signal and a message on display. At this point, the operator must reactivate the appliance before proceeding with the delivery to the patient.

The electromagnetic field is generated with a capacitive radiofrequency variable between 0.5 and 2 MHz, generally delivered between 0.6 and 0.9 MHz. The radiofrequency is produced with a maximum power of 4 W and oscillates between 1.1 and 1.8 KVPP. It reaches the dispensing hand-pieces via an RG58 shielded cable, which possesses BNC connectors at its terminals. It is covered with a black PVC protective cylinder to preserve its mechanical and electrical integrity electrical insulation towards external elements.
The radiofrequency produced by the device then arrives on the handpiece, or the tin plating of a vetronite disc, with the isolated part facing the patient. The vetronite is placed inside the Tecason® or similar surface (see description of the "vacuum"), and it is hermetically sealed and galvanically isolated.
Before applying the handpiece to the patient, the operator should cover the vitrinite disc with a thermoformed PVC disposable cap. This ISO 10993 certified cap is the guarantee for the treatment's biocompatibility.

The disposable Pentamed® pads also increase the safety of the treatment, as documented by Tomura et al. B03. This solution allows obtaining the desired thermal effect with a smaller amount of energy produced and reduces the side effects. The adoption of this kind of disposable insulator eliminates the risks associated with both to an emitter minimally chipped or in any case not intact, which exposes to the direct passage of radiofrequency towards the patient

with consequent skin damage, and towards any even minimal lesion of the cornea (through which the flow of the electromagnetic field would be centralized, which notoriously favors the best quality conductors). The concentration of the electromagnetic flux exposes you to the risk of excessive localized overheating, which could lead to micro-crusting.

5.4 Electroporation

Electroporation is a technique that boasts dozens of published studies, which demonstrate the ability of the system to convey active ingredients of low molecular weight through the corneal layer to the epidermis[8, 9]. All this takes place without noting side effects, thanks to the most reduced dosages and the break period between one pulse and the other, usually at least as long as the delivery time. The only incidents observed are limited to redness and skin sensitization.
To prevent these potential incidents, we programmed the production of square wave stimulation at a frequency of 5 Hz with a hardware limitation that does not allow delivery of a value higher than 1 V.
The engineering of the device involves the physical, mechanical and electrical separation of the circuit intended to generate the square wave stimulation, on which some optoisolators allow the total galvanic decoupling of the patient from the electronics. The hardware provides the signal generation with the FDS9435A MOSFET, which enables the output to the limitation below the most prudent safety parameters. This component can be adjusted through software and checked by the CPU in every activation of the device.
Before starting the therapy, the signal is delivered to a closed channel inside the device, where it is possible to perform a qualitative check of the electrical impulse delivered. If the delivery is correct, the device activates the output channels and continues dispensing; if, on the other hand, the signal read inside the closed channel turns out to be different from the expected standards, the electroporation delivery is not activated. The message STIM ERROR appears on display.
The signal generated inside the device reaches the handpiece thanks to a shielded multipolar cable. The terminals split parallel on the handpiece, with two pairs of cables to stimulate the patient's skin. This pair is represented on the handpiece by blu and greed LEDs. The two pairs of cables intended for skin stimulation are welded onto two pairs of circular terminals of AISI 316 surgical steel. These pairs of electrodes are activated one after the other, with a delivery time of 5 seconds per pair; while delivering the first pair, the blue LED lights up, while the green light up when the delivery takes place via the second pair.
This mechanism allows reversing the direction of the stimulation delivered. It starts with the negative pole on the right side of the handpiece for five seconds; after changing the polarity, the right side becomes positive. The polarity change prevents the galvanization of the tissue and eliminates the risk of redness and skin sensitization. Precisely due to galvanization, which can be described as the concentration of ions of similar polarity (negative towards the positive pole and vice versa), rare but potential collateral events may occur in other electroporation technologies.

6 Bibliography selection criteria

The bibliography adopted to document the effectiveness and safety of the technology in question is divided into three groups:

• bibliography relating to prototype versions of the Bi-one® LifeTouchTherapy 03 device;

• bibliography relating to technologies that can be superimposed on the Bi-one® LifeTouchTherapy 01, 02 device;

• bibliography relating to the forms of energy cited, generic or retrospective, or relating to particular aspects of these forms of energy, aimed at demonstrating the intrinsic safety of the solutions adopted.

In the selection of the literature, we avoided mentioning studies with similar or redundant contents.

7. Selected similar devices and publications cited

As indicated in chapter 5, Bi-one® LifeTouchTherapy adopts three distinct forms of energy: capacitive radiofrequency, vacuum, and electroporation. For the drafting of this document, we have selected a device called Bi-one® or Bi-one® 2.0 MD 01, 02 also produced by Expo Italia Srl and already present on the market, chosen for the perfect overlap of the form of energy supplied, the fields of application, the main characteristics of the applied parts.
The Bi-one® 2.0 MD device was produced starting from 2013. The same year Professor Angela Faga, Professor of Plastic and Reconstructive Surgery at the University of Pavia, asked the competent Ethics Committee for authorization to carry out a study on this technology in the field of scar therapy (see attachment). The study took place in 2015 and was subsequently published in 2016 under the title *Scar Remodeling with the Association of Monopolar Capacitive Radiofrequency, Electric Stimulation, and Negative Pressure* [01]. After the study's publication, many doctors have started

to use this technology for dermatological therapies, including stretch marks, for which it has shown highly positive results 02.

The Bi-one® LifeTouchTherapy device was developed in 2019 as a derivation of the Bi-one® 2.0 MD device. The new model, created exclusively for dermatological therapies, differs from the previous one for the following improvement characteristics:

• More advanced feedback system

Unlike the previous model, this provides a much more compelling reading of the feedback relating to the energy absorbed by the skin tissue. The old version of the feedback system was active upon switching on and align the device to the characteristics of the tissue. Bi-one® LifeTouchTherapy, on the other hand, provides for continuous monitoring that takes into account the variation in the conductivity of the tissue as a result of the thermal variation given by the capacitive action and the greater vascularization of the tissue provided by the vacuum.

• Self-regulation equipment

Thanks to the continuous reading of the feedback, the device constantly receives information on the ideal frequency and intensity for delivering the capacitive radiofrequency. Thanks to an algorithm, it automatically adjusts these values avoiding the risk of incorrect setting by the operator.

• Device safety lock

Bi-one® LifeTouchTherapy provides a safety blocking of the delivery if it cannot read the feedback correctly for more than 60 seconds, effectively preventing the delivery of incorrect frequencies and intensities for the therapy in progress, thus eliminating any risk of overdose.

• Extension of the intermediate steps of the frequency delivered

The device delivers capacitive radiofrequency with variable frequency from 0.5 to 2 MHz with a more significant number of intermediate steps than the previous version. The increase in the middle stages of the frequency delivered allows greater precision in therapy.

• Creation of dedicated programs

Combining an improved feedback system, self-regulation, safety block of the device, and an increase in the steps of the frequencies supplied has made it possible to develop dedicated programs. These programs provide by default a certain range of restricted frequencies dedicated to the specific characteristics of the skin tissue, based on its electromagnetic conductivity and thickness.

As a result, specific programs have been developed for body, breast, and face and neck therapy.

All of the abovementioned elements made it possible to stabilize the average intensity of the capacitive radiofrequency delivered from nominal 6W potential to 4W effective. İn this way, keeping the therapy's effectiveness unchanged thanks to the more exact real-time calibration of frequency and intensity, increasing the therapy's safety and eliminating the risk of energy overdoses.

7.1 Description of the devices

Bi-one®

The Bi-one® device is built on a self-supporting trolley with an external 110/250 VAC - 15VDC switching power supply, capable of delivering electrical stimulation in the form of a square wave, a capacitive radiofrequency, and vacuum. The combined action of these forms of energy determines: The favorable results observed in our study on mature scars might be related to a synergic effect of three different well-known physical energies currently used in clinical practice. The total absence of side effects is also appreciated from experience gained by the University of Pavia. In December 2018, a new version of this device was developed, later called Bi-one® 2.0 MD, when it was introduced on the market, i.e., at the beginning of 2019.

To document the perfect equality between the two models and their complete overlap, the test reports relating to electrical safety and electromagnetic compatibility, issued by Elettra Srl of Calenzano, are attached. The test reports

and photographs show that they use the same hardware, except for the finishes of the handpieces, and that the energy supplied is identical in characteristics such as intensity and frequency.

The same perfect uniformity is obtained with the Bi-one® LifeTouchTherapy device. Consequently, we can say that these devices are perfectly stackable and that the study carried out by Bacci and co. 03 cannot be defined as a pre-market study. Because it is related to a device already present on the market and there are already published studies 1, 2.

The attachments are the followings:

Bi-one® Device	R-EL-289-0114-02A – R-EM-289-0114-01A-1
Bi-one® detto Bi-one® 2.0 MD Device	R-EL-289-1118-01A – R-EM-289-1018-01A

Bi-one® LifeTouchTherapy

The new version of the device was made in a stand-alone version, bringing the 110/250 VAC - 15VDC switching power supply directly inside the case, making it more manageable and compact. The new version also delivers electrical stimulation in a square wave, capacitive radiofrequency, and vacuum.

Technical characteristics

Bi-one® / Bi-one® 2.0 MD	**Bi-one® LifeTouchTherapy**
Weight Kg. 33,4	Weight Kg. 9
Power Supply 110/250 VAC +/-10% - 50/60 Hz Secondario switching 15 VDC x 4,2 A Consumption max 65W External Fuses 2 - 2 A/250 V delayed	Power Supply 110/250 VAC +/-10% - 50/60 Hz Secondario switching 15 VDC x 4,2 A Consumption max 65W External Fuses 2 - 2 A/250 V delayed
Classification EN 60601-1 Class I type BF	Classification EN 60601-1 Classe I type BF
Vacuum from 0 to -0,35 kPa (+/- 10%)	Vacuum from 0 to -0,35 kPa (+/- 10%)
Capacitive radiofrequency with variable frequency from 0.2 to 2 MHz with a maximum power of 6W	Capacitive radiofrequency with variable frequency from 0.5 to 2 MHz with nominal power of 6W and average power output of 4W **
A square wave with a frequency of 5 Hz and a maximum value of 3.5 VPP on a load of 500 Ohm	A square wave with a frequency of 5 Hz and a maximum value of 3.5 VPP on a load of 500 Ohm
38 mm Ø x 3 mm deep vacuum bell	38 mm Ø x 3 mm deep vacuum bell Also available in the following sizes ***: Vacuum bell 30 mm Ø x 3 mm deep Vacuum bell 30 mm Ø x 1 mm deep
20 mm Ø capacitive RF emitter	20 mm Ø capacitive RF emitter
Square wave stimulation emission with four circular electrodes in AISI 316 steel	Square wave stimulation emission with four circular electrodes in AISI 316 steel

Chart I

* Bi-one® and Bi-one® 2.0 MD appliances have the same technical and mechanical characteristics and are perfectly stackable.

** Despite having all the three technologies in question a nominal RF output value of 6W on a load of 500 ohms, the Bi-one® LifeTouchTherapy device was also subjected to the measurements required by the EN 60601-2-2 standard: 2018 (see Test Report R-EL-289-0720-04A), which showed an average emission of 4 W.

Since the hardware of the devices in question is identical, it is believed that the Bi-one® and Bi-one® 2.0 MD models also have a similar average emission value. It is essential to point out that these measurements were not performed as they were not required.

*** In addition to the handpiece equipped with a vacuum bell with the same diameter and depth compared to the model adopted by the Bi-one® device, the new version also includes handpieces of different shapes that allow more outstanding ergonomics in the treatment of scars placed in small areas (for example in the face).

Bi-one® 2.0 MD	Bi-one® LifeTouchTherapy
 Picture 1 – Bi-one® / Bi-one® 2.0 MD	 Picture 2 – Bi-one® LifeTouchTherapy

From comparing the forms of energy delivered, their frequency and intensity, and the mechanics of the applied components, the perfect overlap of the Bi-one® and Bi-one® LifeTouchTherapy devices are evident.

The studies of Alberti and Laura 02 and Bacci and co. 03 focused on the therapy of stretch marks. The qualification of the stretch mark as a natural dermal scar is widely present in scientific literature, as summarized by You Jin Yang and co.: ***Striae distensae are atrophic dermal scars*** B04. Similarly, Alexiades-Armenakas and coll. B05 stated that on ***histopathologic analysis, a stria alba is similar to a scar. F***or this reason, they unite 31 adult patients in a study, 22 burdened with scars and 9 with stretch marks. A similar definition of the striae is given by Trelles et al. B06; the ***histopathology shows that striae distensae are very similar to scars***, while Tretti Clementoni defines them as B07 ***atrophic dermal scars*** and Yong-Kwan Tay et al. B08 ***dermal scars with flattening and atrophy of the epidermis.***

In addition to the definitions mentioned above, the in-depth histological analysis of Pinkus and coll. B09***:Identical histologic features were found in all 17 cases. They were characterized by the scar-like arrangement of parallel collagen bundles in the upper part of the dermis associated with numerous thin and straight or wavy elastic fibers extending across the stria. A similar picture was encountered in the distended surgical scar***.

The work of Bacci and co. 03 has as its object the therapy of stretch marks with prototypes of the Bi-one® LifeTouchTherapy device; in agreement with the Scientific team, it was decided to document the safety and effectiveness of this technology for the following reasons:

• the absolute similitude between the Bi-one® and Bi-one® LifeTouchTherapy devices;

• the same intended use object of the study by Nicoletti and coll. 01, or the dermal scars defined as stretch marks.

In light of this, the Scientific team considered it plausible to carry out the study based on the authorization issued by the Ethics Committee of the University of Pavia. In this sense, the Clinical Investigation Plan, a copy of the Informed Consent Form and the Patient Information Document, and the Final Report signed by the President of the Scientific Managers Committee and the Head of the Sponsor are attached.

Anecdotally we note that the perfect overlap between the Bi-one® device used by Nicoletti and co. and the Bi-one® LifeTouchTherapy technology is given by the title of the published article: ***Scar Remodeling with the Association of Monopolar Capacitive Radiofrequency, Electric Stimulation, and Negative Pressure***, or the same forms of energy delivered.

On July 20, 2021, yet another search was carried out on the Italian Ministry of Health website. There are no "Safety warnings on medical devices" for the technologies mentioned above that can be superimposed on Bi-one® LifeTouchTherapy, nor for the manufacturers of these devices.

8 Critical analysis of the literature

The three forms of energy described above combined in the technology, and thanks to previous models, was the subject of studies. The first study was preceded by the resolution of September 19, 2013, of the Ethics Committee of the University of Pavia, which authorized its use to treat scars produced in the Annex.

This survey was conducted by Nicoletti and coll. 01 of the Chair of Plastic Surgery of the University of Pavia, which with ***Scar Remodeling with the Association of Monopolar Capacitive Radiofrequency, Electric Stimulation, and Negative Pressure*** have demonstrated the effectiveness of our technology in the treatment of post-surgical and burn scars.
The conclusions are exemplary: *The combined sequential local treatment of hypertrophic scars with low-intensity electromagnetic and electric stimulation associated with negative pressure demonstrated a favorable synergic effect on the scar collagen and elastic fibers network remodeling.* ***Amplification of the impact of three different well-known physical energies was therefore obtained without any side effect***.

The experiences of Nicoletti and co. demonstrate the efficacy and safety of the treatment by specifically documenting a functional improvement of the scars. Among them, we would like to underline two burn scars on the neck that limited the motility of the patient's head and caused chronic pain, wholly recovered with the therapy. We obtained the reorganization of the elastic fibers and collagen in the treatments, with instrumental evidence of skin regeneration and repair with the total absence of side effects.

The two subsequent studies are performed on patients burdened with stretch marks or dermal scars.

Engaging in this sense is the results documented by Alberti and co. 02 is very interesting. This study highlighted the tissue regeneration and the reorganization of the skin layers on a group of twenty patients burdened by consolidated ultra-twenty-year stretch marks, which are assimilable in all respects to hypotrophic skin scars as they destructure the basement membrane and prevent the skin from activating melanin production (notoriously, old striae do not tan due to the alteration of the basement membrane). After the therapy, we obtained skin regeneration with the filling of the atrophy and a reorganization of the skin layers in all subjects. Furthermore, the treatment reactivated the melanin production process, which is also in the total absence of side effects. The authors conclude the study with the following considerations: ***The uniformity of outcomes is appreciated, as all patients reacted positively to the therapy in the absence of side effects.*** The study was conducted with the Bi-one® 2.0 MD device.

Even more interesting is the study carried out with Bi-one® 2.0 MD devices and Bi-one® LifeTouchTherapy prototypes. In this study, 917 patients were involved, with 1,256 body areas treated for 9,784 sessions performed. Bacci and co. 03 demonstrate bioptically a skin regeneration evidenced by new collagen and elastic fibers and a fundamental dermo-epidermal reorganization with restoring the correct skin layers, in the total absence of side effects. The study in question was developed with Professors from Pisa and Barcelona, the Director of the Level II Master of the University of Verona, and Level II Master Professors from the Universities of Palermo, Siena, Marconi, Chieti. Pescara and Cattolica del Sacro Cuore and other researchers.

Analyzing the device in question and its previous models, significant results were always highlighted in the total absence of side effects 01, 02, 03. This result was possible thanks to the careful design of the device, referring to parameters explicitly cited in the scientific bibliography, and adopting advanced software and hardware solutions.

Although not related to the synergy applied by Bi-one® LifeTouchTherapy, the literature abundantly demonstrates the efficacy and safety of the three forms of energy used in compliance with specific parameters, all adopted by our technology.

The benefits of biological action, which is brought by vacuum and mechanotransduction towards dermal regeneration, are many findings in the scientific literature. For example, Moortgat et al. A01 state: ***A variety of physiological effects are reported in the literature, for example, an increased number of fibroblasts and collagen fibers accompanied by an alteration of fibroblast phenotype and collagen orientation***. Benefits are found in the treatment of post-surgical and burn scars A01, A03 where Meirte et al. observe: ***The statistically significant changes in the dermal layers suggest edema formation and an increased extracellular matrix production, which could be attributed to an immediate mechanotransduction effect of vacuum massage on the remodeling of the extracellular matrix***. However, it is evident that the vacuum therapy did not show significant side effects A01, A03, A04 if used at low values, however lower than 200 mb A01. Studies on mechanotransduction confirm the effectiveness in all its fields of application: ***A proper formal definition of mechanotransduction might be the processes whereby cells convert physiological mechanical stimuli into biochemical responses*** A05.
In this sense, please note that the vacuum level delivered by Bi-one® LifeTouchTherapy varies from 90 to 140 mb, perfectly respecting the standards indicated by Meirte and coll. A01. In addition to appreciating the parameters proven to be safe, the technology can monitor the actual vacuum level delivered in time and allows the device to be blocked when the safety thresholds are exceeded, effectively eliminating the risk of overdose with consequent side effects for the patient.
As already reported, the application of electromagnetic fields in sports medicine dates back to 1939, when Clayton demonstrated for the first time the possibility of faster regeneration of injured muscle tissue, except to write together with Scott in 1967 the first text that describes it in detail. The fields of application and effects expanded in the current edition in 1975 B01. Franco Astolfi and co. in his monograph also masterfully documented the efficacy, versatility, and safety of electromagnetic fields. B10, since 1986 a point of reference for researchers attentive to this form of energy and its infinite applications.
For the capacitive RF, we appreciate the affirmations of Da Silva A06, as claims to obtain the best results exactly with the temperatures adopted by Bi-one® LifeTouchTherapy: ***Observed a thickening and realignment of interlobular septae using temperatures between 39° and 41° C. with radiofrequency***.

In any case, until today, no significant side effects have been found in the various fields of application of electromagnetic fields. Any possible side effects are generally linked to two distinct factors: an overdose of energy or applying an applied part that is not intact, which determines a direct discharge of the RF towards the patient's skin. Bi-one® LifeTouchTherapy was designed and built to reduce these risks further.

To prevent the risk of overdose, Bi-one® LifeTouchTherapy constantly monitors the dose of active energy in a closed chain with the patient, modifying intensity and frequency in real-time, based on the response obtained with the bio-feed-back method, also developed based on the experiences of Eilebrecht et al. B02. They have developed a system that brings impedance measurement in parallel with biopotential measures that allow a better "coupling" of the patient with the technology in question. Thanks to this procedure and a proprietary algorithm, the device aligns the induced thermal effect between 39 ° and 40 ° C, effectively preventing any side effects. The device is equipped with a safety block system. It activates when the delivery of the energy cannot be read by the feedback system correctly for more than 60 seconds, effectively preventing incorrect frequencies and intensities for the therapy in progress, thus eliminating any risk of overdose.

Regarding the risk of direct RF discharges towards the patient due to the non-perfect integrity of the applied part, Bi-one® LifeTouchTherapy adopts special disposable caps made with a certified non-cytotoxic PVC film under the ISO standard. 10993. These caps have been designed and built based on the study by Tomura and co. B03 demonstrated a significant increase in the effectiveness of capacitive RF therapy thanks to the interposition of a film between the applied part and the patient's skin. This solution allows obtaining the desired thermal effect with a smaller amount of energy produced, consequently further reducing the risk of side effects, always linked to energy overdoses. It is understood that the adoption of a disposable insulator eliminates the risks associated with an emitter minimally chipped or, in any case, not intact, which exposes the direct passage of radiofrequency towards the patient with consequential skin damage.
This review of the bibliography concludes concerning electroporation, which allows the delivery of active medicinal ingredients beyond the stratum corneum in the total absence of side effects A02.

All the studies cited relating to the Bi-one® LifeTouchTherapy device and the totally or partially overlapping devices demonstrate the effectiveness of the technologies under study and their absolute safety. None of the studies cited

reported collateral events or damages suffered by patients, even minor or temporary. As further confirmation of the safety of the Bi-one® LifeTouchTherapy device, please note that Nicoletti and Coll. 01 conclude their study with the following words: ***Therefore, an amplification of the effects of three different well-known physical energies was obtained without any side effect***.
Bacci and co. 03 when talking about the study which 917 patients were involved for 9.784 sessions confirm: ***In light of the previous experiences uniformity of results obtained, patients' compliance, an almost total absence of side effects and downtime, and renewed ability of stretch marks to tan, it can be asserted that Biodermogenesi® [the name of the therapy, which the Bi-one® LifeTouchTherapy device is the executor N.d.R.] is considered as the most suitable treatment for its effectiveness, safety, tolerability and replicability on stretch marks regardless the age of the stria and phototype of the patient.***

8.1 Complete Bibliography

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02 Alberti G, Laura S. Treatment of stretch marks aged more than twenty years with the synergy of electromagnetic field and vacuum. Clinical case studies and subsequent follow-up – Aesthetic Medicine Volume 5, n° 1, January/March 2019 pp. 14/21

03 Bacci P.A., Alberti G., Amuso D., Artigiani A., Benitez Roig V., Di Nardo V., Garcia V., Greco D., Laura S., Pagano M., Reale A., Sarracco I., Saracoglu S., Urbani C., Venditti E., Wade M., Zunica R. The synergy between vacuum and electromagnetic fields in the treatment of striae distensae: retrospective study on 917 patients with clinical and histological case records – Journal of Applied Cosmetology Volume 39 Iss. 1 (January-June 2021)

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The part relating to the intended use and additional safety procedures implemented in the device in question

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B02 Eilebrecht B, Willkomm J, Pohl A, Wartzek T, Leonhardt S. Impedance measurement system for determination of capacitive electrode coupling – IEEE Trans Biomed Circuits Syst. 2013 Oct;7(5):682-9

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B08 Yong-Kwang Tay, Colin Kwok, Eileen Tan. Non-Ablative 1,450-nm Diode Laser Treatment of Striae Distensae. Lasers in Surgery and Medicine 38:196–199 (2006)

B09 H. Pinkus, M.K. Keech, H. Mehregan. Histopathology of striae distensae, with particular reference to striae and wound healing in the Marfan syndrome. The Journal of Investigative Dermatology Vol. 48 n. 3:283-292 (1966)

9 Identification of relevant data, including literature

a) Data held by the manufacturer

The data pertinent to the clinical evaluation conducted by the manufacturer include:

- Pre-sale clinical investigations carried out with the Bi-one® LifeTouchTherapy device
- Data deriving from PMS (*Post-Marketing Surveillance*) includes adverse events reports, return information, accident reports, and customer complaints.
- Clinical studies were performed with the Bi-one® LifeTouchTherapy device.
- Relevant clinical studies, such as tests, essays, validations, etc., were carried out on similar devices.
- Similar or equivalent devices. A list of comparable devices is given in the report attached to Section 1.4. These devices have been classified as *similar devices*; that is to say, the performance in terms of use is used to define the minimum acceptable performance levels.

Equivalence is defined following MEDDEV 2.7.1 according to the following:

- *clinical correspondence:* similar devices are chosen because they are used in the same clinical application in a similar population (including age, anatomy, physiology).
- They have equivalent efficacy and mainly report the same *intended use*.
- *Technical equivalence:* similar devices are used in similar conditions, have identical technical specifications, deliver similar forms of energy, and have similar operating principles.
- *Biological equivalence:* similar devices are manufactured with the same materials or with "comparable" materials.

b) Post-Marketing Surveillance

- Accidents

A system to collect surveillance data from the market on similar or equivalent devices has been set up since no problems or complaints have been encountered on the product in the market.

Accordingly, a search was carried out on the Italian Ministry of Health website (HTTP: //www.salute.qovit/portale/news/p3213.isp?Linqua=italian&menu=news&p=warnings) to find accidents, safety notices, and other problems related to this category of devices, not directly highlighted in the Risk Analysis.

Accident reports/safety warnings in the last five years have been evaluated for similar or equivalent products on the market. No safety warnings were found on the Ministry of Health website for any device similar or identical to the one being assessed.

However, the device's clinical method is already in use with diathermy products that have already been manufactured, certified, and marketed by the company for some time. For this reason, a module has been created for customers who already use the previous device, which has enabled us to have a history of the accidents encountered and their management and the level of satisfaction of the doctor and patient.

c) Pre-clinical studies

Electromagnetic safety and compatibility

The device has undergone safety tests according to EN 60601-1 and electromagnetic compatibility tests according to EN 60601-1-2. The procedures for the evaluation and implementation of the tests follow the regulatory updates.

Biocompatibility
See specific biocompatibility assessment in the relevant section of this technical document.
Validation of the software
The device has undergone software validation; see Section 6.6 of this technical document.
Usability validation
The device has undergone usability validation with the simulation of the identified scenarios; see specific attachment 7 of this technical document.

d) Data deriving from the literature

The search for relevant literature on evaluating similar devices and research with clinical relevance was carried out by a person with good experience. The corresponding curriculum is reported in the Annex to the validation report.

Period covered by the research
The clinical investigation covered 2000 to today, with articles present in the bibliography from an earlier period.
This type of investigation has made it possible to detect the present-day condition in the fields of application of the Bi-one® LifeTouchTherapy device, with specific reference to the forms of energy adopted (capacitive radiofrequency, otherwise called electromagnetic field, Marconi Therapy or Tecar therapy), negative pressure (otherwise called vacuum) and square wave stimulation (otherwise called electrotraction).
These are further combined with articles relating to the device in question.

Methodology used
This report provides documentation on the methods used in the literature search so that the work can be evaluated, verified, and possibly reproduced.
The literature search was carried out using these methods:
• use of an internet search engine
• identification of articles containing clinical data and experience acquired with equivalent devices

Literary resources used to identify data
The search engines *http://www.ncbi.nlm.nih.gov/pubmed* and https://www.scopus.com/home.urs were mainly used to carry out this literature search.
This research portal is universally recognized as a scientifically valid source of literature in the clinical field and, particularly, on the effectiveness of the various devices.
Alternatively, research was carried out on the websites of the leading national and international Aesthetic Medicine companies.
In addition to scientific information, research was carried out on the competitors identified as manufacturers of similar devices. These searches made it possible to download technical and commercial documentation on these devices.

Selection criteria for choosing articles
The selection criteria of the articles that result from the output include the following two steps:
1) Determination of the relevance of the content. References deemed irrelevant are discarded.
2) Evaluation of the content reported in the reference (carried out only on articles that pass screening). Only the "highest weight" items are considered "pivot" for the clinical evaluation at the end of this second step.

The acceptability criteria of the input data for the evaluation are as follows:

Origin of the Document	**Completeness of document**	**Degree of compatibility between devices cited in the source and Univet EOS HP**	**Benefit/risk analysis**
A (high degree of reliability): Document produced by University, Publicly recognized institutions recognized scientific structures	**A** Significant number of patients (10+ patients) or Laboratory tests on in vitro cells	**A** (high): devices completely overlapping in performance	The study highlights benefits for the user and does not report important side effects
B (medium degree of reliability): Source: Private research, clinical documents drawn up by consultants of the manufacturing company	**B** Number of patients not significant but enough to make it a valid study (5 - 10 patients)	**B** (sufficient): devices not entirely overlapping but with characteristics such as to replicate the analyzed treatment	**B** The study highlights benefits for the user but it also reports cases of worsening of clinical conditions of the patient
C (insufficient degree of reliability): Source: documents without reference to the editor	**C** Insufficient number of patients (less than 5) (these studies can however, be taken under consideration if the evaluator believes that the reported data and the clinical findings have support)	**C** (insufficient): Devices with not-overlapping characteristics and with different intended use	**C** The study emphasizes that the benefits to the patient are less than the adverse effects related to the application of treatment

Table I

9.1 Destination of use and bibliographical references

The following are all the device's possible and most common applications, identifying the bibliographic section for each; the reference article is indicated for each section.

Intended use	Bibliographic reference	Contraindications	Limitations of use	Significant parameters
Scars	Bi-one® [01] Vacuum [A03]	Controindications: A, B, C, D, E, F, G, H, I, J, K, L, M Effetti Collaterali emersi dalle pubblicazioniSide effects arisen from the pubblications: None	We only intervened on completely cicatrized tissue and no earlier than three months after the formation of the post-surgical scar and twelve months for the burn scar	Vacuum between 100 and 140 MB Use the ACTIVE PLUS SMALL handpiece (max 3 mm dermal dilation) for scars on the body and the ACTIVE PLUS FACE handpiece (1 mm dermal dilation) on the face and neck Session time: <20 minutes
Stretch marks	Bi-one® 2.0 MD [02] Bi-one® LifeTouchTherapy [03]	Controindications: A, B, C, D, E, F, G, H, I, J, K, L, M Effetti Collaterali emersi dalle pubblicazioniSide effects arisen from the pubblications: None	We only intervene on intact and not injured and inflamed skin It is preferred not to intervene in the period of childhood but from adolescence, after the age of 12	Vacuum between 100 and 140 mb Use the ACTIVE PLUS LARGE handpiece for the body and the ACTIVE PLUS SMALL handpiece for the breast (max dermis dilation 3 mm) Session time: 25 minutes

Table III

The limits of application for this device vary according to the different therapeutic fields. In this list, they are all listed, characterized by an alphabetical letter with which they will be identified in Table II, in the column "Limitations of use." The indicated limits are of two types: the first group concerns those for which the patient must not carry out therapy, the second group, identified by (*), involves the clinical features for which the patient may have a lower therapeutic benefit than the usual standards; in such cases, it is recommended to defer therapy.

A. Cardiac insufficiency
B. Pacemaker bearer
C. Ongoing or recent (in the last five years) oncological therapy
D. Sensitivity problems in the area to be treated
E. Epilepsy
F. Skin phlogosis in the area to be treated
G. Vascular diseases such as thrombosis, thrombophlebitis in progress, varicose veins in the area to be treated
H. Injuries, cuts, and skin abrasions not healed in the area to be treated
I. Use of anticoagulant drugs and thinners
J. Severe renal impairment
K. Phenomena of anorexia or bulimia in progress or the past two years
L. Current pregnancy or breastfeeding
M. No use of therapy under the age of 12

9.2. Input data analysis

The analysis of the data for evaluation is as follows:

Document analyzed Stored in attached "clinical validation"	Source of the document	Completeness of the document	Degree of compatibility between devices mentioned in the source and the Bi-one® LifeTouchTherapy device	Benefits/ risks analysis	Overall assessment of the document
01	A	A	A	A	High reliability. High completeness. Total compatibility. Benefits without side effects
02	B	A	A	A	Significant reliability. High completeness. Total compatibility. Benefits without side effects
03	A	A	A	A	High reliability. High completeness. Total compatibility. Benefits without side effects
A01	B	A	C	A	Significant reliability. High completeness. Moderate compatibility. Benefits without substantial side effects
A02	B	A	C	A	Significant reliability. High completeness. Moderate compatibility. Benefits without substantial side effects
A03	B	A	B	A	Significant reliability. High completeness. Discreet compatibility. Benefits without substantial side effects
A04	B	A	C	A	Significant reliability. High completeness. Moderate compatibility. Benefits without substantial side effects
A05	B	A	C	A	Significant reliability. High completeness. Moderate compatibility. Benefits without substantial side effects

Document analyzed Stored in attached "clinical validation"	Source of the document	Completeness of the document	Degree of compatibility between devices mentioned in the source and the Bi-one® LifeTouchTherapy device	Benefits/ risks analysis	Overall assessment of the document
A06	B	A	C	A	Significant reliability. High completeness. Moderate compatibility. Benefits without substantial side effects

Table IV

From the numerous studies cited and the even more, numerous that are not mentioned in this document because they constitute a repetition, we suggest some aspects that we want to emphasize as significant:
• the third-party technologies taken as reference have high similarities with the application of the same forms of energy provided for Bi-one® LifeTouchTherapy;
• all the articles cited indicate a benefit for the patient, of a variable entity but always present and the general absence of side effects;
• the high number of studies relating to the device in question allows the consolidation of its effectiveness and safety, with particular reference to works (01, 02, and 03) done by the universities of Pisa, Pavia, and Verona;
• the high number of patients (961 patients) documented by the specific studies related to Bi-one® LifeTouchTherapy consolidates the fact that all have had a more than positive response to therapy in the total absence of side effects and with stabilization of the outcomes documented by follow-ups.

10. Conclusions

From the documents presented, it can be deduced that Bi-one® LifeTouchTherapy, although proposing an unusual synergy, does not constitute a novelty in medical therapies.
It does not have significant contraindications and limitations of use, except the generic ones indicated in this document.
Another essential feature of the Bi-one® LifeTouchTherapy device is the total absence of documented side effects.
There are also no particular contraindications or limitations of use except those mentioned above. Moreover, the device provides well-established methods and physical parameters; similar products are already present on the European market, with CE labeling for the EEC Directive 93/42 relating to medical devices with similar uses and technical characteristics.

Summarizing the above, Expo Italia Srl company has carried out a first clinical validation investigation of its devices with:

clinical study on prototypes of the device in question
- A bibliographic survey on comparable devices for indications of use and possible contraindications
- performed an annual analysis of the product complaints
- has carried out a clinical evaluation of its products and the treatments provided by its customers
- has acquired scientific bibliography on its own devices and competitors' devices
- updated the available literature with critical analysis conducted with users regarding the product support documentation
- verified the contents of the risk analysis based on the evidence acquired by the users of the products and post-production experiences
- performed a usability assessment of the equipment
- reassessed the risk at the annual review

As stated above, the devices can be considered safe and aligned with the state of the art criteria, subject to the commitments to monitor the scientific literature and to get feedback from the market annually, or in the case of

significant changes to the product to assess the risks and subsequent review of the analysis whenever deemed necessary.

The research identified the following equivalences:

- **clinical**
  - use in the same conditions and medical indications
  - use in the same areas of the body
  - use in similar populations (age, gender, anatomy, physiology)
  - significant side effects not expected
- **technical**
  - overall characteristics comparable and overlapping as regards to the forms of energy supplied, their intensity, and biological effects
  - operated under the same terms of use
  - similar technical specifications and performance
- **biological**
  - use of the same materials in contact with human tissues

The settings described in this document and the related attachments also constitute a management procedure for post-market surveillance to audit the produced documentation and any update of the risk analysis as indicated for management.

- **Harmonized standards**

The standards listed in Section 2 of the Technical Documentation File have been applied to construct the device.

- **Complaints:**

The Technical Assistance Service is established to admit, manage and communicate with anyone who has to intervene after the sale, as indicated in the corresponding internal procedures; the collection of reports from the market is, therefore, the primary tool for monitoring any problems not previously assessed. The complaints concerning the Bi-one® LifeTouchTherapy device lead the company to determine the product's safety and whether these are relevant for risk management purposes or if the ascertained risks are unacceptable. In the latter case, the company will re-evaluate the entire risk management process for the product.

- **Recalls and notifications**

There were no recalls or notifications related to devices already on the market, similar to the device in question by 20-07-2021.

- **Adverse events:**

There are no known adverse events related to devices already on the market, similar to the device in question by 20-07-2021.

Through the Ministry of Health website, it has been verified that there are no reports of accidents or near misses involving devices with characteristics similar to the Bi-one® LifeTouchTherapy device.

Based on the above, the device is VALIDATED clinically, and its intended use is confirmed.
The compliance of the device with the essential requirements in terms of efficacy and safety has been assessed and demonstrated in the documents attached to this technical file:

- Annex of the technical file "Safety Test Report”
- Annex “Usability”
- Annex of the "Software Validation" Technical File
- Annex of the Technical File "Risk Analysis"

- Section 3 of the "Labeling" Technical File
- Annex of the "Manuals" Technical File

12. Post-marketing clinical follow-up

At the start of this document, the Bi-one® LifeTouchTherapy device has not yet obtained certification and approval from a notified body. However, the clinical method used by the device is already used in diathermy products that have been made, certified, and marketed by the company for some time.
It is, therefore, a method already adapted and consolidated for some time. In any case, it is expected that during this year, any operations and research carried out on the product itself will be mentioned in this document with particular reference to:

- Data from doctors who use the device in Italy:
- Doctor satisfaction level, patient satisfaction level,
- number of patients treated,
- any side effects, their management,
  outcome.

At present, specific research aimed at targeted populations or applications is not needed. From 2021, it is planned to extend this monitoring abroad, involving foreign distributors to carry out the same research with their customers.

- New scientific publications
- Technological innovations inherent to the product
- Regulatory adjustments
- Information from institutional sites about products similar to the Bi-one® LifeTouchTherapy device or with protocols used by Bi-one® LifeTouchTherapy
- Priority communications: *accidents, analysis of complaints, NC that cause modification; other urgent communications*

At the end of the evaluation period or in case of evidence that necessitates an immediate action such as withdrawal or necessary modification of the Technical Documentation File, a final report is to be prepared, pointing out, if needed: any HW or SW changes, changes to the protocols, changes to the manuals or the labeling, technical changes of materials, changes to the Technical Documentation File (risk analysis, validation and others), any communications to the notified body, ministry or other entities, possible contacts to customers, assessing possible retirement of the product or intervention.

Scheduled date	*Active schedule*	*Identified cues (also indicate alleged actions to take from what has been detected)*	*Action to take:* *Point out if it involves the variation of the Technical File* *Indicate whether urgent modification of the Technical File is necessary*	*Research is done by*
December 2021	Information from institutional Regulatory Adjustments sites	Search on Italian Ministry of Health website: Home > News e media > Notizie > Avvisi di sicurezza > Avvisi di sicurezza sui dispositivi medici.		Maurizio Busoni

December 2021	New scientific publications Any new products or technological innovations on products Evaluation data from customers			
December 2021	Information from institutional Regulatory Adjustments sites New scientific publications Any new products or technological innovations on products Evaluation data from customers			
Annually from January 2022	Data from doctors who use the device			Customer care for Italy Export for abroad

12. Documentazione attached

With version 0.3 of this clinical validation document, the following attachments have been added:

CER_2.1_R-EL-289-0114-02A Bi-one® appliance electrical safety report test
CER_2.1_R-EM-289-0114-01A-1 Bi-one® 2.0 MD device EMC test report
CER_2.1_R-EL-289-1118-01A Bi-one® 2.0 MD appliance electrical safety test report
CER_2.1_R-EM-289-1018-01A Bi-one® 2.0 MD appliance EMC test report
CER_2.1_BDG2019-02_PIC PIC - Clinical Investigation Plan (see Bibliographic ref. 03) Available in Italian
CER_2.1_BDG2019-02_CIP CIP - Informed Patient Consent (see Bibliographic ref. 03) Available in Italian
CER_2.1_BDG2019-02_SIP SIP - Patient Information Sheet (see Bibliographic ref. 03) Available in Italian
CER_2.1_BDG2019-02_REPORT REPORT - Final report (see Bibliographic ref. 03) Available in Italian

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Document: Clinical Validation:

Revision	Date	İssued by	Approved by
1.0	October 20th 2020	Marco Bargigli	Maurizio Busoni
2.0	November 29th 2020	Domenico Amuso	Maurizio Busoni
3.0	Januart 19th 2021	Domenico Amuso	Maurizio Busoni

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ESTUDIOS CLÍNICOS

bi-one®
Lifetouch Therapy

ESTUDIOS DE ESTRÍAS

BIODERMOGENESI®
THE LIFE-TOUCH THERAPY

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The synergy between vacuum and electromagnetic fields in the treatment of striae distensae: retrospective study on 917 patients with clinical and histological case records

A possible treatment for striae distensae

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key words: *Striae distensae, striae atrophicae, striae rubrae, striae albae, stretch marks, Biodermogenesi, laser, radiofrequency, needling, dermabrasion, IPL*

Abstract

Striae distensae (SD) are dermal lesions that cause evident and unwanted imperfections. They may occur on arms, shoulders, breasts, abdomen, gluteus and legs, usually during puberty and pregnancy. At an early stage they feature a reddish-purple colour (striae rubrae) with an inflamed appearance; at the second stage, which is defined as the chronic stage, they are also marked by hypopigmentation and dermo-epidermal atrophy. During the past twenty years, various technologies have been put forth in the treatment of striae, which have shown encouraging outcomes in some cases. This retrospective study has been conducted on 917 patients that presented stretch marks on their body. Patients underwent a treatment based on the synergy between electromagnetic fields and vacuum; 6 to 9 sessions of treatment were performed for each patient once or twice a week. Clinical evaluation was carried out at the end of the treatment cycle; patients and doctors each rated their level of satisfaction on a scale from 0 to 100%. The outcome was documented through biopsies taken on 20 patients. All patients demonstrated an improvement of their stretch marks and 83% of the patients declared being very/extremely satisfied with the result. The results of the biopsies demonstrated a reorganization of the skin layers and a qualitative and quantitative increase of collagen and elastic fibres and all patients declared a total absence of side effects. The uniformity of the results, patient compliance and lack of adverse reactions proved that the synergy between electromagnetic fields and vacuum is an effective and safe treatment for stretch marks.

Introduction

During the first half of the XXI century stretch marks proved to be the most widespread aesthetic pathology in the world, affecting males and females indifferently from puberty. To date, according to the existing literature, there is no therapy that can be considered totally satisfactory and safe.

Dermabrasion provides a moderate improvement of red striae (1, 2). The percutaneous collagen induction therapy for treating red striae seems to be more effective (1, 3). Manuskiatti et al. (4) reported improvements on stretch marks treated with non-invasive resistive radiofrequency, whilst Dong-Hye Suh et al. (5) had minor results combining resistive radiofrequency with PDL (Pulsed Dye Laser). Shokeir et al. (6) compared IPL (Intense Pulsed Light) with PDL, which turned out to be more effective, obtaining good results only on red striae. Lee et al. (7) noted an improvement on each patient treated with 10,600-nm CO2 (carbon dioxide) fractional laser, while Khater et al. (8) claimed to not have observed any improvement in 50% of the cases. According to Yang et al. (9) 41.67% of the patients were unsatisfied with the results, while Tehranchinia et al. (10) achieved unsatisfying results on SD on high phototypes. In a preliminary study on 4 patients, Nouri et al. (11) had no improvement and nullified the research.

Wanitphakdeedecha et al. (12) had good results on almost all patients with Er:YAG fractional laser, on the other hand, Gungor et al. (13) claimed that "We observed no satisfactory clinical improvement in striae distensae alba lesions although histopathological changes were seen". With 858 nm. Pulsed Dye Laser (PDL)

Jiménez et al. (14) had modest results on 20 patients, while Nouri et al. (11) did not achieve any improvement.

Applying 1.064-nm Nd:YAG laser, Goldman et al. (15) reported positive results on early-stage red stretch marks. Elsaie et al. (16) documented a reduction from 5.73% to 13.47% in width of the stretch marks, although the biopsies demonstrated that "clinical improvement on striae are not relevant". Lastly, Gungor et al. (13) did not recommend it for striae alba.

Positive outcomes were consistently reported by De Angelis et al. (17) using a non-ablative fractional laser on 51 patients; Tretti Clementoni et al. (18) documented that the area of stretch marks showed filling in more than 50% of the cases. According to Guertler et al. (19), initially the reduction in depth of the furrow is equal to 32.07%, which lowers to 28.77% after six months. Contradictory outcomes were demonstrated by Yang et al. (9), a study conducted on 24 Asian patients. Stotland et al. (20) presented the blind evaluation of the results obtained on 8 patients, all of whom declared to have an improvement. Malekzad et al. (21) confirmed a lower performance of treatment on high phototypes.

Materials and methods

This retrospective study involved 917 healthy patients with intact skin burdened by stretch marks that were treated with a synergy between electromagnetic fields and vacuum in 2018-2019. The treatments were carried out in medical practices in Italy, Spain, United Kingdom and Turkey; each doctor documented the results observed on at least twenty patients.

For this study, patients between 15 and 60 years of age were selected, that presented stretch marks of any sort, location and cause, with no limitation of skin phototype.

Exclusion criteria were epilepsy, pacemakers, oncologic therapy undergone in the last 5 years, pregnancy and breast-feeding, open wounds, severe skin inflammation, varicose veins, phlebitis or thrombophlebitis in the area to be treated. All the patients signed the informed consent and agreed to share their personal data for this study. The total of 917 patients showed Fitzpatrick skin type between I and VI (Table I) with different dating of the striae (Table II), located in different body areas (Table III). Some of them underwent stretch mark treatments on multiple parts of the body, therefore on these 917 patients the results that were documented were obtained on 1.256 different body districts with on average 7.9 sessions per treated part for a total of 9.784 treatments delivered. The causes of the onset of the striae were detected (Table IV, V) and a total of 172 patients with striae rubrae and 745 patients with striae alba were treated. The patients declared to not have undergone other stretch mark treatments in the previous three months and that they would not wear any cosmetic products in the 24 hours preceding each treatment session. The treatments were performed by Bi-one® 2.0 MD and Bi-one® LifeTouchTherapy devices (Expo Italia Srl, Florence, Italy).

Phototype	I	II	III	IV	V	VI
Patients	22	325	348	105	73	44

Table I. *Patients phototype*

Less than 2 years	2-5 years old	6-10 years old	11-20 years old	Over 20 years old
263	165	278	372	178

Table II. *The age of striae (of the 1.256 treated areas).*

Arm	Breast	Abdomen	Kidney area	Gluteus	Thigh	Calf	Shoulder
90	146	322	63	346	215	42	32

Table III. The body parts with stretch marks (of the 1*.256 treated areas).*

	Women	Men
15-20 years old	92	18
21- 30 years old	309	34
31- 40 years old	291	11
41- 50 years old	99	4
41- 50 years old	65	0

Table IV. *Patient age and sex.*

Pregnancy	Puberty	Weightlifting	Hormone therapy	Other	No idea
407	221	9	85	64	131

Table V. *The suspected cause.*

These appliances function thanks to the synergy between electromagnetic fields and low-suction vacuum, usually between 10 and 15 hundredths of bar and with only 3-millimetre

skin dilatation, where the mechanotransduction activates (22). Mechanotransduction converts mechanical information into biochemical signs, increasing cellular conversation and activity; this determines a synergy with the electromagnetic fields also known as "shielded electrode" and affects epidermis and dermis, in fact, a relevant interaction between sodium (Na+) and potassium (K+) ions - noted for their cell membrane permeability - is appreciated (25). When the shielded electrode is positively charged, it pulls sodium and potassium ions, which are also positive, across the cell membranes though intrinsic proteins (26), consequently enhancing the supply of oxygen and nourishment. A negative phase follows the early positive one of the same duration and intensity. During this phase, sodium and potassium are attracted towards the outside of the cell membrane and become available for a new pumping action.

This technology uses a frequency ranging from 0.5 to 2 MHz and a 4-to-6 W mean power automatically set by the device's bio-feed-back system capable of reading the amount of the energy absorbed by the skin in real time, thus guaranteeing the maximum yield of the treatment and preventing overdose-related risks (27).

The synergy between the electromagnetic fields and the vacuum used is called Biodermogenesi®. A neutral non-alcoholic-based detergent was used to clean the skin before starting the treatment. On wide and sunken striae, a mechanical peeling was performed with a handpiece equipped with an interchangeable abrasive head, made of ISO 5832 standards-compliant non-cytotoxic steel, provided with the device. Afterwards, treatment was carried out by following the operating protocols to guarantee performance uniformity. The treatment lasted 25 minutes, during which a stimulation of the striae and of the surrounding tissue was provided by the movement of the handpiece along set paths, allowing to combine stretch marks regeneration and skin reshaping, and reduce the effects of gravity.

To corroborate Alberti and Laura's experience (28), who witnessed how stretch marks on 20 patients treated with the technologies that are subject of this study got tanned in total absence of side effects, the patients were invited to expose skin to the sun during the period of treatment.

During the first session, the patients with white stretch marks, excluding stretch marks on the inner thighs, were asked to expose to the sun and check whether the striae were able to positively react to ultraviolet rays and reactivate their tanning ability. Two-hundred-and-ninety-seven patients out of 312, exposed themselves to the sun regularly, encouraged by the fact that the treatment period coincided with Summer. The doctors compared the pictures taken of these patients before and after the treatment cycle and evaluated whether the pearly-white colour of the striae changed after exposure to sun and tanning. Seven days after the last session, the doctors who performed the treatments evaluated the outcome achieved, identifying 5 levels of result using an evaluation form based on the Likert Scale (I - none; II - mild improvement 1-25%; III - moderate improvement 26-50%; IV- good improvement 51-75%; V - excellent improvement 76-100%); in addition, the patient satisfaction score was rated using the following scale: 0 = not satisfied, 1 = slightly satisfied, 2 = satisfied, 3 = very satisfied, 4 = extremely satisfied.

Punch biopsy samples were taken from the most atrophic site of the stretch marks on 18 volunteers with over 20-year-old striae 3mm, before the first treatment and one week after the last one. On 2 volunteers, the second biopsy was taken after 2 sessions done 2 days apart. The sections of the excised skin were stained with haematoxylin and eosin and Masson trichrome stains; a dermatologist and an anatomopathologist evaluated the histological samples.

The doctor's evaluations and the patients' satisfaction were assessed using the Wilcoxon Signed Rank test to compare the final data and the starting point; P less than 0.05 was considered significant.

Results

The outcomes of the treatments were documented with VAS scale according to participants and doctors (Table VI). No patient declared to be unsatisfied, 2.47% of the patients declared slight satisfaction of the results (31 body areas), 14.57% declared to be satisfied (183 body areas), 41.64% declared to be very satisfied (523 body areas) and 41.32% extremely satisfied (519 body areas).

	VAS doctor	**VAS patient**	
No improvement	0 (0%)	0 (0%)	Unsatisfied
1-25% of improvement	24 (1.91%)	31 (2.47%)	Slightly satisfied
26-50% of improvement	184 (14.65%)	183 (14.57%)	Satisfied
51-75% of improvement	485 (38.61%)	523 (41.64%)	Very satisfied
76-100% of improvement	563 (44.83%)	519 (41.32%)	Extremely satisfied

Table VI. *VAS scale according to the participating patients and doctors.*

The evaluation of the doctors basically confirmed what had been declared by the patients: no improvement on 0 body areas (0%), mild improvement between 1-25% on 24 body areas (1.91%), moderate improvement between 26-50% on 184 body areas (14.65%), good between 51-75% on 485 body parts (38.61%) and excellent improvement between 76-100% on 563 body areas (44.83%). The renewed ability of stretch marks to gradually tan has been particularly appreciated by the patients.

One week after the end of the treatment cycle,

the doctors examined the 297 patients that exposed themselves to the sun; the pigmentation of the striae was evident in all of them. Stretch marks were darker in colour, more similar to the surrounding skin tissue and in some cases perfectly uniform and becoming invisible.

Upon first sun exposure which took place after 3/4 treatment sessions, the striae almost reached erythema and started to gain colour progressively, sometimes with less intensity than the surrounding tissue. In contrast to reports regarding other types of technologies, the vacuum stimulates skin remodelling, as documented by Moortgat et al. (23) while the electromagnetic field enables cellular and molecular multiplication (24) and skin reparative actions.

The electromagnetic field is generated through a high-frequency electrical signal directed to a specific handpiece with an electro-conductor inside. The external part is covered with a dielectric to prevent the signal from being discharged on the patient. The dielectric, relevant and uniform outcomes have been achieved on patients with phototypes V and VI as well as tanning of the striae.

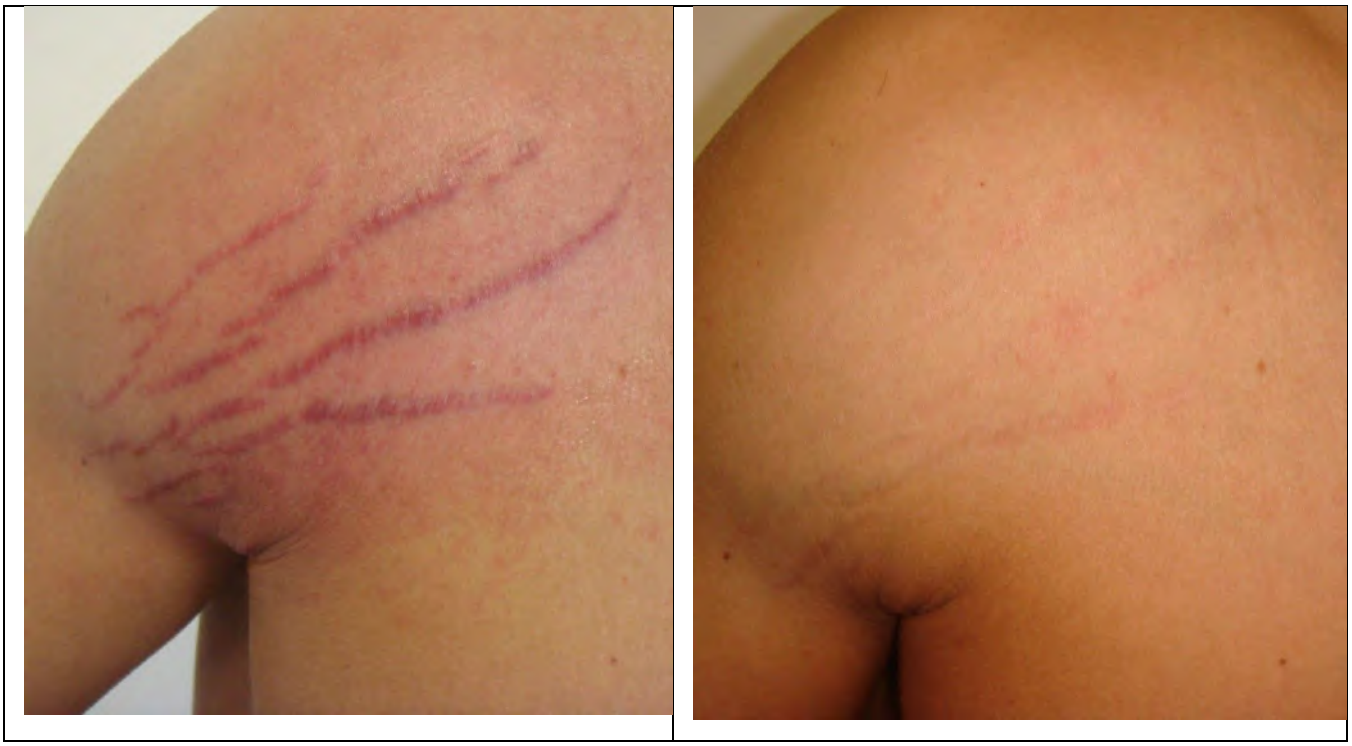

Fig. 1. *A young man with striae rubrae probably due to heavy weightlifting workout. After a treatment cycle the stretch marks are less evident and now tanned in a similar way to the surrounding skin tissue. Courtesy P.A. Bacci, Arezzo – Italy.*

The treatment was found to be safe, in fact only two patients out of 9.784 total sessions monitored by us had adverse reactions limited to mild skin erythema that dissipated on its own within a week. A few minutes after the therapeutic treatment the patient felt a pleasant

warmth, which lasted at least a few hours after the treatment terminated. Once the session was completed, the skin appeared blood-bedewed but not reddened. Since the treatment does not have any downtime, the patients can return to their normal daily routine without any limitation.

The biopsies taken on the 20-year-old white stretch marks confirmed the doctor's evaluation. Before starting the treatment session, all patients presented loss of volume of stretch mark epidermis and dermis, flattening of basement membrane, and collagen fibres destructured and parallel to the stratum corneum. In the bioptic analysis conducted at the end of the treatment cycle, an overall restructuring of the skin layers was noticeable: the epidermis was well-structured; the basement membrane has recovered its correct sinusoidal shape, a fundamental element to melanocytes, which, founding their correct position, enable stretch marks to tan when exposed to the sun; and the dermis has gained volume and new collagen fibres, being no longer parallel to the stratum corneum as in the case of the skin tissue featuring stretch marks.

The biopsies taken after two sessions confirm the presence of skin regeneration and show a mild but evident increase in collagen and elastic fibres.

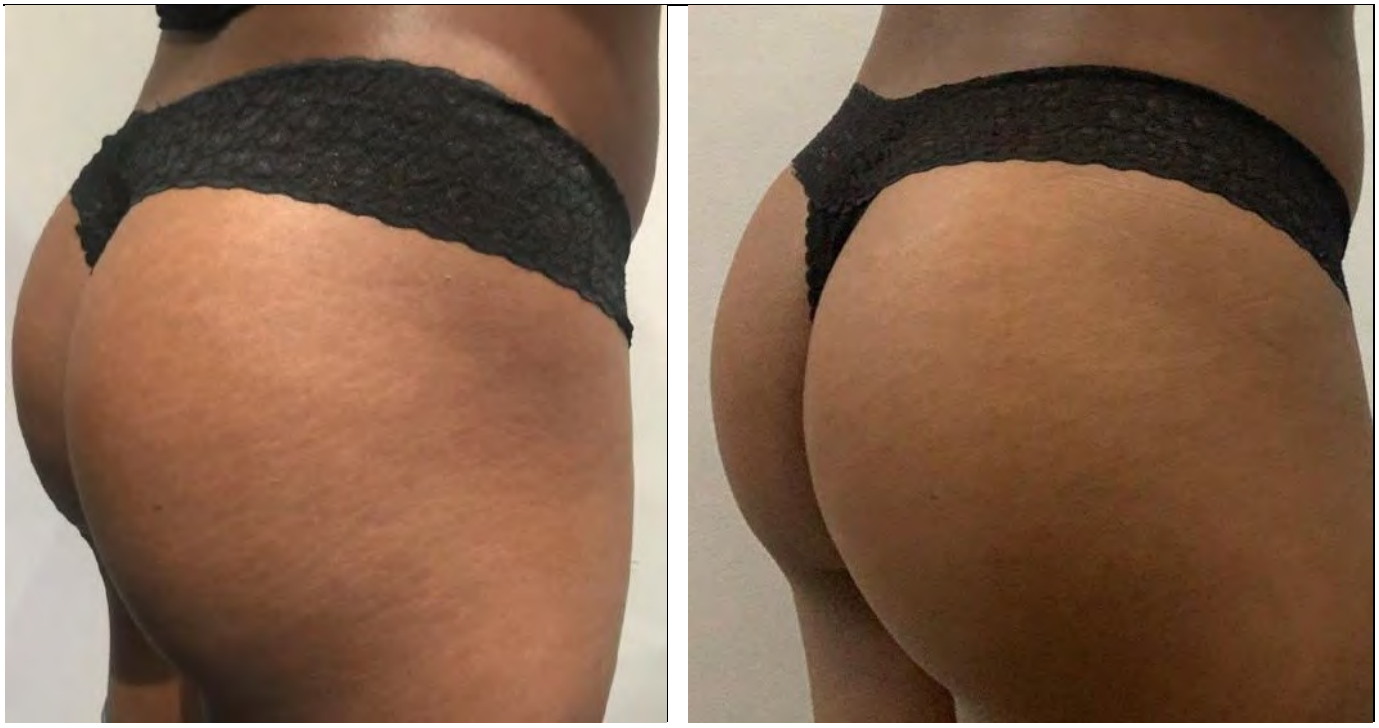

Fig. 2. *A patient with skin phototype V and 18-year-old stretch marks. After a 6-session Biodermogenesi® treatment cycle the stretch marks are filled and have the same colouring as the surrounding skin. Courtesy M. Wade – London, UK.*

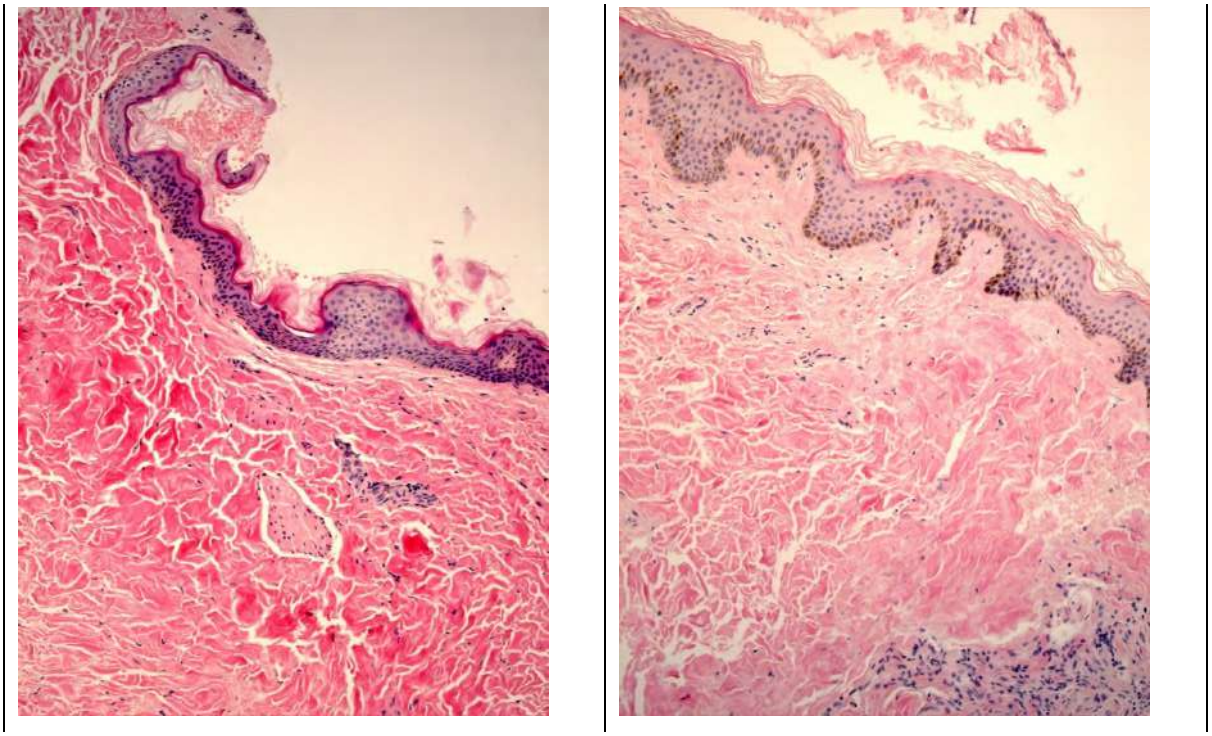

Fig. 3. *The biopsies before and after a 7-session Biodermogenesi® treatment cycle on a patient with skin phototype VI and 25-year-old striae are presented above. We witness the reorganization of epidermis, basement membrane and dermis, where a qualitative and quantitative increase in collagen fibers is noticeable. Courtesy A. Artigiani, Pisa, Italy.*

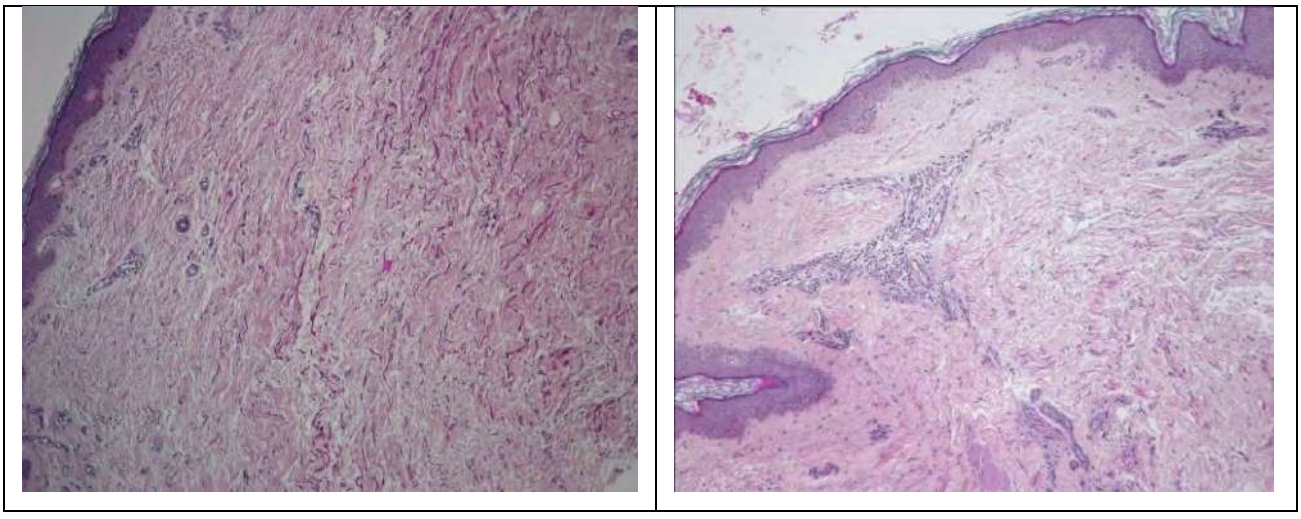

Fig. 4. *The biopsies before and after two Biodermogenesi® treatment sessions, two days apart on a patient with skin phototype II and 20-year-old striae. The microscopic analysis shows a mild but evident increase in collagen fibers. Courtesy P.A. Bacci, Arezzo, Italy.*

Discussion

We have to reflect on many limits of the previous studies executed on stretch marks treatments. The outcomes are generally documented on a low number of patients, sometimes 1 or 2, mostly between 10 and 40, with only one exception of a maximum of 51 patients (17) (non-ablative fractional laser). Another limit is the lack of objective reports on the outcomes, like biopsies;

moreover, when the biopsies are present, they are usually very few, from 1 to 4, and basic factors like the age of the patient, the dating and the severity of the striae are not provided. Through the comparison of those biopsies with Hague's (29) description of red and white striae's structural alterations, much more affinities with red stretch marks are found. A further limit is the often contradictory results mentioned in the pre-existing studies, where the researchers observed different outcomes although they used the same technologies.

Our perceptions are validated by other researchers (29) who claim that "No treatment has proved to be completely effective", Elsaie et al. (30) states that "None of the existing therapeutic options offer a complete treatment", Sardana (31) argues that in literature there are no high-quality studies involving a large number of patients and objective checks to guarantee a therapeutic prospect replicable on a high number of patients. First of all, the current study differs from the others for the significant number of patients with heterogeneous features and different skin phototypes coming from various Countries, which means for the first time there is a relevant sample for purpose of replication; having 20 biopsies taken on stretch marks of which dating and patient's phototype are known, together with the amount of information provided, makes this study more reliable than the others, with the awareness of the fact that such a wide pathology is worth a more detailed and specific comparative histological investigation.

The other difference is the patients' high level of satisfaction, with the 83% of patients rating the result as "good" or "excellent"; an additional confirmation is the assessment of the tanning, as a matter of fact stretch marks on all 297 patients who regularly exposed to the sun regained pigmentation.

All this data, together with the total absence of side effects, allows us to affirm that Biodermogenesi® is an effective and safe therapy that opens new and interesting perspectives in stretch mark treatment.

The comparison between the side effects arising from the synergy between vacuum and electromagnetic fields and other cutting-edge technologies is simple; comprehending that the contraindications of other treatment methods are mild, short-lived or statistically rare, the synergy matter of this study is preferred to the other methods for its lack of side effects, its safety and tolerability.

From 2008, P.A. Bacci conducted many studies on this technology (32), which have formed the basis for more recent developments. It is worth mentioning that, in the treatment of striae, Artigiani et al. (33) of the School of Dermatology at the University of Pisa achieved an actual regeneration of the skin tissue in total absence of side effects and histologically documented a qualitative and quantitative increase in the collagen and the elastic fibres. Alberti et al. (28) presented the restructuring of the skin featuring stretch marks by documenting its renewed ability to tan when exposed to sun and consequently the reorganization of the basement membrane and the reactivation of melanocytes.

Nicoletti et al. (34) documented the effectiveness of the treatment on post-surgical and burn scars by underlining the reorganization of elastic fibers and collagen with no side effects. Considering

the previous experiences, uniformity of the results obtained, patient compliance, the almost total absence of side effects, the downtime and the renewed ability of stretch marks to tan, it can be asserted that Biodermogenesi® is considered the most suitable treatment for its effectiveness, safety, tolerability, and replicability on stretch marks regardless of the age of the striae and the phototype of the patient.

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A New Treatment for Stretch Marks and Skin Ptosis with Electromagnetic Fields and Negative Pressure: A Clinical and Histological Study

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Abstract

Background:

Stretch marks (SM) are nowadays the most common aesthetic pathology of the body; in the XX century, it mainly affected pregnant women, while today it also affects teenagers during puberty, boys and girls without distinction. The aim of this study was to evaluate possible variations in the histological structure of the skin—in terms of quality/quantity of the extracellular matrix and of the collagen and elastic fibers—following the electromagnetic fields and negative pressure (V-EMF) treatment as regards hypotonia and SMs.

Materials and Methods:

For the current study, 60 women, aged between 25 and 45, were examined. All of them presented deep, white or pearly white colored SMs having had them for between 12 and 25 years. These were documented, asking patients their level of satisfaction, through pictures and biopsies. All patients underwent a cycle of 6 or 8 weekly sessions; everyone was highly satisfied with the results obtained.

Results:

Biopsies proved that the tissue was reorganized and restored to the original volume, characterized by the production of new, high-quality collagen and elastin molecules, by the reorganization of the basement membrane and by the correct positioning of the melanocytes. No side effects were observed during the treatments. This synergy stands as the most suitable treatment of striae rubra and alba.

Conclusion:

V-EMF enhances the keratinocyte migration base, melanocytes, and promotes neoangiogenesis with the result of improvement in the SM.

Keywords: Electromagnetic fields, negative pressure, skin aging, stretch marks

I. TRODUCTION

Stretch marks (SM) are nowadays the most common aesthetic pathology of the body; in the XX century, it mainly affected pregnant women, whereas today it also affects teenagers during puberty, boys and girls without distinction. Microdermabrasion, needling therapy, and various types of lasers have been used for the treatment of SM, but to date none is able to deal with this aesthetic pathology with certain, satisfactory and systematic outcomes on all patients, both from the point of view of reducing the depth of the line and the typical hypopigmentation of the mature striae.[1,2,3] No current therapeutic option offers complete treatment, although there are a few emerging new modalities that are encouraging.[1] Microdermabrasion was probably the first instrumental method applied to SM and yet it does not have a significant bibliographical reference. Anyhow, the therapy showed an improvement in only the stria rubra and limited or nil improvement of the stria alba.[4,5] Histological analysis documents an increase in procollagen I.[4] Lasers have become the most common technology in the treatment of striae; these include pulsed-day laser (PDL), excimer lasers (ELs), the short-pulsed carbon dioxide fractional lasers (CO_2FLs), Nd: YAG lasers, the non-ablative Er:Glass fractional lasers (NAFL), diode lasers, and fractional photothermolysis. Below we analyze what emerges from the published studies.

Magnets have been used in clinical practice since ancient times by Egyptians, Greeks, and Chinese.[6] Electromagnetic fields and negative pressure is a new treatment for hypotonia and SM. The aim of this study was to evaluate the effectiveness of the electromagnetic fields and negative pressure in the treatment of SM through a clinical and histological evaluation of variations of quality/quantity of the extracellular matrix and of the collagen and elastic fibers.

Materials and Methods

This study was conducted in a private office of Verona (Italy), in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2008.pdf) and the additional requirements of Italian law. The sample included 60 healthy adult Caucasian female patients, suffering simultaneously from cutaneous hypotonia and SM. The selected patients were between 25 and 45 years of age, and body mass index (BMI) was between 21 and 27 and historically healthy.

The subjects were normal-weight or slightly overweight without complications of any diagnosis of degenerative diseases and lifestyle habits that would have favored aging, such as smoking, alcohol abuse, etc.

Each patient signed informed consent on the adopted procedure, but none of the patients knew which pathology the treatment was aimed at.

The diagnosis for all was a simultaneous presence of cutaneous hypotonia, cellulite, and white SM (whose onset time has not been documented).

The exclusion criteria for patients were as follows:

- pacemaker carriers,
- surgery or cancer treatment in the last 5 years,
- epilepsy,
- vascular insufficiency located in the area to be treated (thrombosis, thrombophlebitis, varicose veins),
- skin inflammation of the area to be treated,

- open wounds in the area to be treated,
- ongoing anticoagulant therapy,
- pregnancy or breastfeeding,
- incidents of anorexia or bulimia in the last 2 years,
- previous treatment of SM with other therapies.

The patients belonging to the study group underwent a cycle of six to eight sessions, with weekly treatments, without the addition of any active ingredients. The patients were all in the phototypes II and III of the Fitzpatrick scale with skin areas affected with white SM, hypotonia, and cellulite. The treatments were administered between March 18 and May 2019 with follow-up of 90 days. The clinical study, developed in an observational and microscopic manner using histology, followed the double-blind control procedure randomized in parallel groups.

At the end of the course of treatment, all the patients expressed a rate of satisfaction on the result achieved.

Electromagnetic fields and negative pressure device therapy (V-EMF)

The device that generates the V-EMF (Expo Italia Srl, Florence, Italy) was used in the present study.

The device was equipped with a generator of electromagnetic fields, an electron flow generator, a pair of vacuum pumps, and a series of handpieces. The apparatus acts through the use of magnetic fields. The electromagnetic field, fundamental for this technology, which is based on the synergy between the electromagnetic field, vacuum effect, and low-intensity electrical stimulation, is generated with an electric signal with a variable frequency between 500 and 1000 Hz, projected toward handpieces that are completely covered with a dielectric material. Even the passage of the electrical signal, from the device toward the handpiece, takes place inside a special electric cable covered with a high-density metal mesh, destined to create a real Faraday cage that prevents the signal from being dispersed in the environment. The part of the handpiece in contact with the skin of the patient is covered with a dielectric material of very high electrical resistance, intended to constitute an insulating barrier. The insulating structure thus created is placed in contact with the patient's skin with which it interacts, creating an effect similar to that of a capacitor.

The dielectric coating prevents the passage of the electrical signal from the device to the patient's skin, but, instead, allows the stimulation of the electric charges present inside the biological tissue.

The charges move in relation to the electric potential supplied by the device, which acts by rejecting the similar ones and attracting the opposites. The continuous polarity change leads to a continuous flow of endogenous electric charges, which move inside these tissues, with particular attention to the activity of sodium Na+ and potassium K+ ions whose action of permeability of cell membranes increases per unit of time. The continuous kinetic activity of the ions and the rapid rotation of the dipoles present cause a partial transformation of the motion kinetic energy into stabilized thermal energy, never below 39°C and never above 40°C utilizing the biofeedback system provided in the device. The brushless vacuum pumps allow the delivery of negative pressure with absolute precision and stability, with a maximum value of –0.35 atm.

Histology processing

Each patient underwent biopsies at different times during the therapeutic procedure before and after treatment.

The biopsies were carried out to document:

- epithelial basal cells;
- epithelial thickness;
- number of melanocytes;

- vessel number;
- qualitative evaluation of type III collagen with multiple stained histology;
- qualitative evaluation of elastic fibers with multiple stained histology.

The treated area and site of the biopsy was the culotte de cheval.

Each patient underwent two biopsies, before and after treatment; a total 120 biopsies were performed. These were performed with a circular punch biopsy of 2 mm diameter (KAI Industries, Oyana, Japan).

The histological tests were performed and validated at the Department of Neuroscience, Biomedicine, and Movement, Anatomy and Histology Section, University of Verona, Italy.

The specimens were stained with hematoxylin and eosin, Masson's trichrome, and Van Gieson. Four fields of 2000 μm in diameter and 4000 μm long were evaluated for each sample.

Statistical analysis

A power analysis was performed using clinical software for determining the number of samples needed to achieve statistical significance for quantitative analyses of cell numbers for:

- epithelial basal cells;
- epithelial thickness;
- number of melanocytes;
- vessel number.

A calculation model was adopted for dichotomous variables (yes/no effect) by using the incidence effect designed to discern the reasons (80% for the test group and 20% for the control group), with alpha = 0.05 and power = 95%.

The optimal number of samples for analysis was 60 patients per group.

Numerical results are presented as means±SD for all the experiments.

The data outcome was collected and statistically evaluated by the software package GraphPad 6 (Prism, San Diego, CA, USA). The normal distribution of the study data was evaluated by the Kolmogorov–Smirnov test to evaluate the normal distribution. The Wilcoxson signed-rank test was performed to compare the study variables' means in each group. The level of significance was set at $P < 0.05$.

Results

Patients were questioned at the end of the study on any changes of the skin: of the total 60 patients, 57 responded that they had observed considerable changes especially in the brightness of the skin in the treated area, and three responded that they noticed only a slight change but that the skin was different.

However, all 60 patients expressed a positive judgment of skin compactness and tactile sensation. The objective results are shown with photographic images before and after the completed treatment in some of the patients treated [Figure 1]. We observed decreased striae and initial tanning, leading to a reorganization of the skin layers and to a restoration of the melanocytes.

Histological analysis

After an initial objective evaluation using photographic images before and after treatment, an associated histological evaluation was performed with different staining, to highlight the ultrastructural aspects of the epidermis and dermis.

The histological results of the slides were read by two pathologists working in two different medical universities, Verona and Modena Reggio Emilia, to minimize the possibility of misinterpretation.

Before treatment

The epidermis of the SM demonstrated loss of the rete ridge pattern and collagen bundles perpendicular to the surface, which appeared disorderly spaced [Figures 1–5]. Additionally, alteration of the microcirculation was evident before treatment. Few melanocytes were observed. No inflammatory cells were observed in the epithelium or epidermis. The histomorphometric results are shown in Figure 6 and Table 1.

After treatment the epidermis showed increased thickness; moreover, the visible collagen appeared reorganized and the microcirculation was present. The epidermis had a basket weave appearance and well-formed rete ridges. Additionally, normal dermis demonstrated collagen bundles parallel to the surface, which were evenly spaced. There was a clear increase in epidermal thickness and the presence of melanocytes; no inflammatory cells were observed in the epithelium or epidermis [Figures 1–5]. The histomorphometric results are shown in the table and [Figure 6] (Table).

Discussion

The results of the present study indicate that the treatment adopted is associated with an increased and structural regulation of collagen in the dermis, increase in cellular replication of the epidermis with increased thickness, and repositioning with the regulation of melanocytic cells, with considerable synthesis of elastic fibers that lose their point-like structure.

In addition to the general reorganization of the treated tissue, good angiogenesis with good microcirculation architecture was evident. Patients' statements on improved skin brightness and compactness are linked to the aforementioned: improvement of the quality of hyaluronic acid, increase in type 3 collagen concentration, and regularization of epidermis metabolism.

In addition to the clinical evidence of the results, it was observed that the treatment was considered pleasant and relaxing by all patients, who could maintain their normal lifestyle. Furthermore, no side effects nor down time occurred. The choice of the range of frequencies adopted, i.e. low frequencies, allows a real activity of crossing of the cell membranes by the Na+ and K+ ions due to an effective action of induced ionic migration, unlike what happens with higher frequencies with which one obtains at most an ionic vibration and therefore only a thermal effect but not the action of Na+ and K+ carriers on cells and fibroblasts. This difference is essential in the histological evaluation, which allows us to understand the regeneration obtained, or rather the increase in the presence of collagen and elastic fibers and the greater cellular mitosis, a consequence of the cellular nutrition induced by the Na+ and K+ pumps and not by the induced thermal effect.

The stimulation induced by the V-EMF device determines a series of clinically appreciable benefits in the cutaneous areas affected by various pathological conditions, such as relaxation, micro-wrinkles, spots, acne, cellulite, and SM.

The benefits can be attributable to the combined effect of three mechanisms:

(a) the increase of the blood microcirculation, which facilitates the oxygenation of the treated tissues;

(b) stimulation of tissue cellular metabolism which, among other things, favors the transmission of any active ingredients;

(c) stimulation of fibroblasts (both mechanical and respiratory), which induces the production of collagen and elastin.

Starting from these assumptions, the present study aims to evaluate the effect of the V-EMF treatment on the histological framework of the skin, in order to help clarify the efficacy detected, from a clinical point of view, in the different conditions in which the technique is indicated.

The choice of this experimental approach seems to be the most suitable to document the observed clinical effectiveness in an objective way, so as to make both the doctor and the patient confident, also in terms of safety and risk/benefit ratio.

Similar results were achieved by Artigiani *et al.*[7] This technology has already shown a great potential in the regeneration of the striae, claiming to witness a "real restructuring of the stretch mark without any side effects," documenting the outcomes on white SM aged between 7 and 35 years, also on patients with high levels of skin phototypes. The researchers also state that the therapy was found to be effective on all treated patients. The most interesting aspect of this article is the abundant bioptic documentation, which demonstrates a real cutaneous repair of the striated tissue, with the reorganization of the basement membrane and multiplication of collagen and elastic fibers.

In a similar way, Nicoletti *et al.*[8] documented a significant reparative action in the treatment of post-surgical and burn scars, stating that the combined sequential local treatment of hypertrophic scars, with low-intensity electromagnetic and electric stimulation in association with negative pressure, demonstrated a favorable synergic effect on the scar collagen and remodeling of the elastic fibers network. An amplification of the effects of three different well-known physical energies was therefore obtained without any side effects.

Analyzing the results obtained, we see that after three sessions two out of 10 patients left the study, three out of 10 patients reported no results (no improvement) and five reported little result (poor). The same patients after a 3-month follow-up declared the following: no result in 2 out of 10 and little result in 6 out of 10. The photos document a poor outcome. In addition to the dubious outcomes encountered by the authors, the NAFL is characterized by a moderate pain during therapy,[9,10,11] micro-crusting,[10] recurrent edema, and hyperpigmentation,[9,11,12] which is generally reabsorbed in 5/10 days, with a maximum duration of hyperpigmentation of 8 weeks.[13]

de Angelis *et al.*[14] recommend prophylaxis to patients in the month before the treatments and in the following 6 months. Therefore, the limitations due to the heterogeneity of the laser trials (wavelength, protocols) have an unclear effect on the SM. There is evidence that EMF promotes bone formation and therefore can be used in regenerative applications aimed at bone fracture healing[15] and bone augmentation procedure.[16] EMF has positive effects during cartilage regeneration[17] and can be used for its positive impact on epidermal stem cell proliferation which may result in beneficial effects.[18] Many clinical practice guidelines recommended that NP can be used for reducing the healing time of surgical wounds.[19]

In conclusion, the results of the present study show that V-EMF enhanced an increased rate of the epithelium thickening, the number of melanocytes, and vascularization with improved color of the SM.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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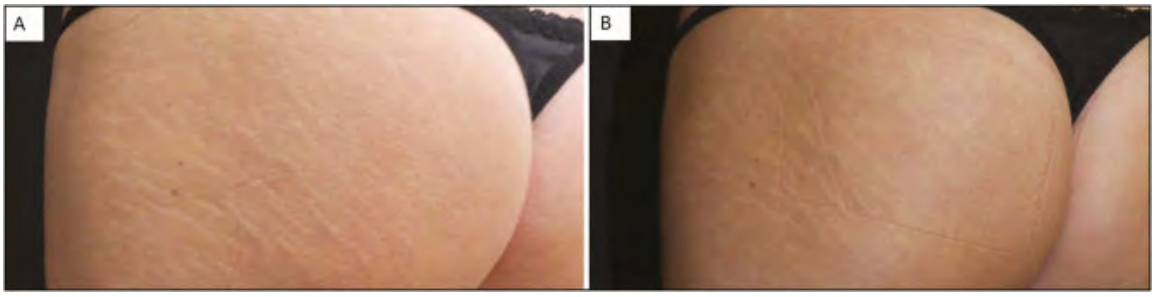
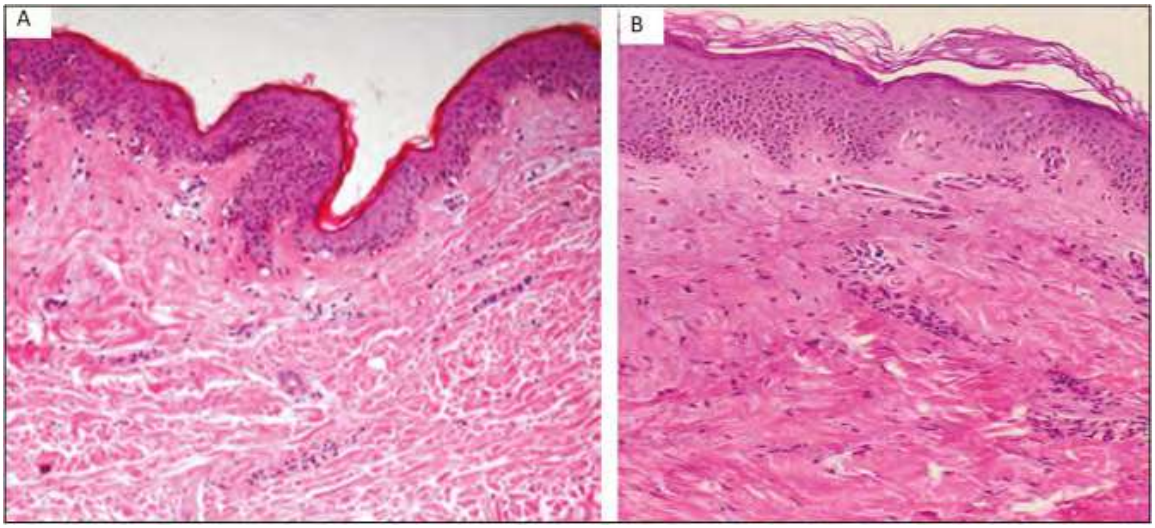
Figures and Tables

Figure 1



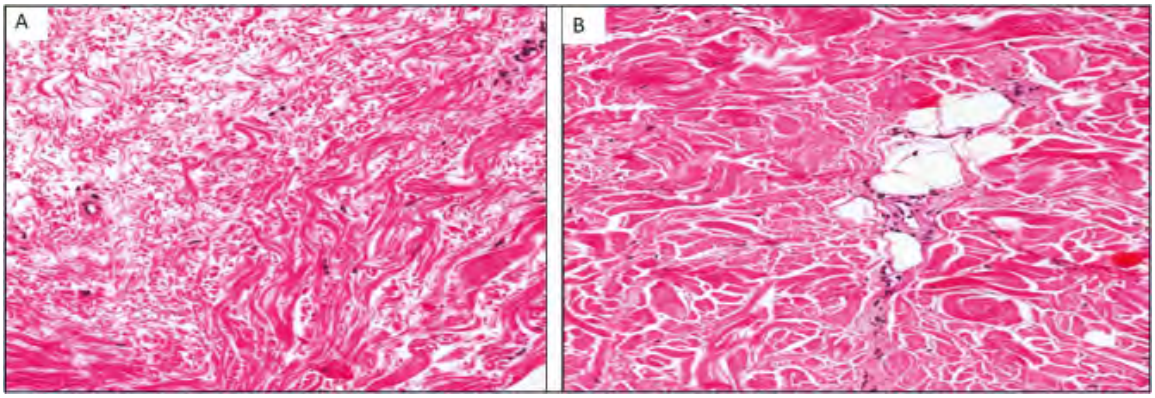
Before (A) and after (B) 9 V-EMF treatment. The evident and deep striae appear now filled, soft to touch and their color is much more similar to the surrounding normal skin, all this due to a better vascularization

Figure 2



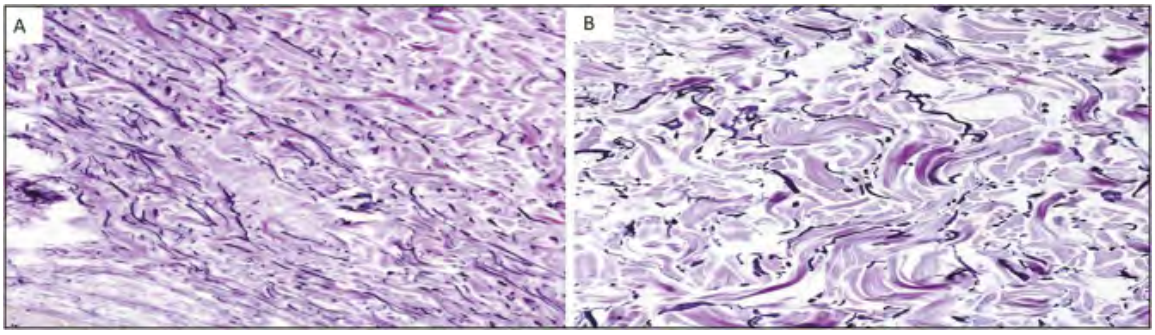
A. Section of skin including epidermis and dermis. Before treatment. Hematoxylin and eosin. ×10. White SM. B. After treatment. The epidermis shows up with increased thickness; moreover, the visible collagen appears reorganized and the microcirculation is present. Hematoxylin and eosin. ×10. White SM

Figure 3



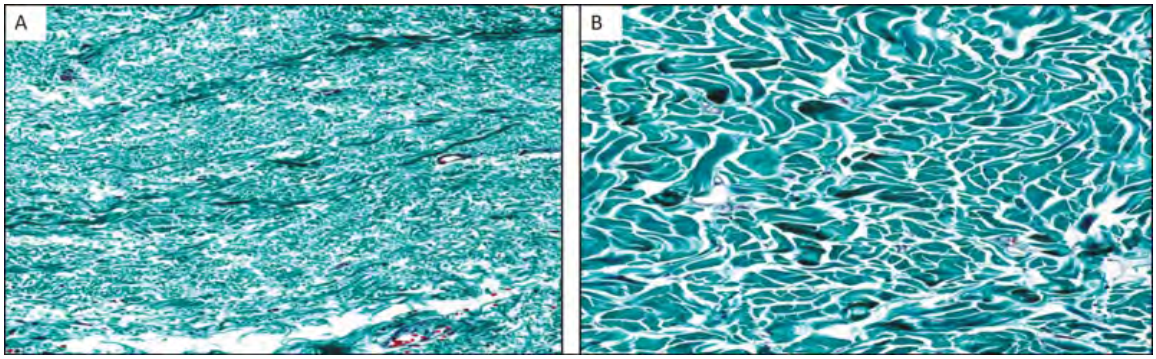
A. Skin section, specific to the dermis, before treatment. Disorganized collagen fibers with different volumes. Hematoxylin and eosin. ×40. B. After treatment. Collagen fibers increased in volume and reorganized. Hematoxylin and eosin. ×40

Figure 4



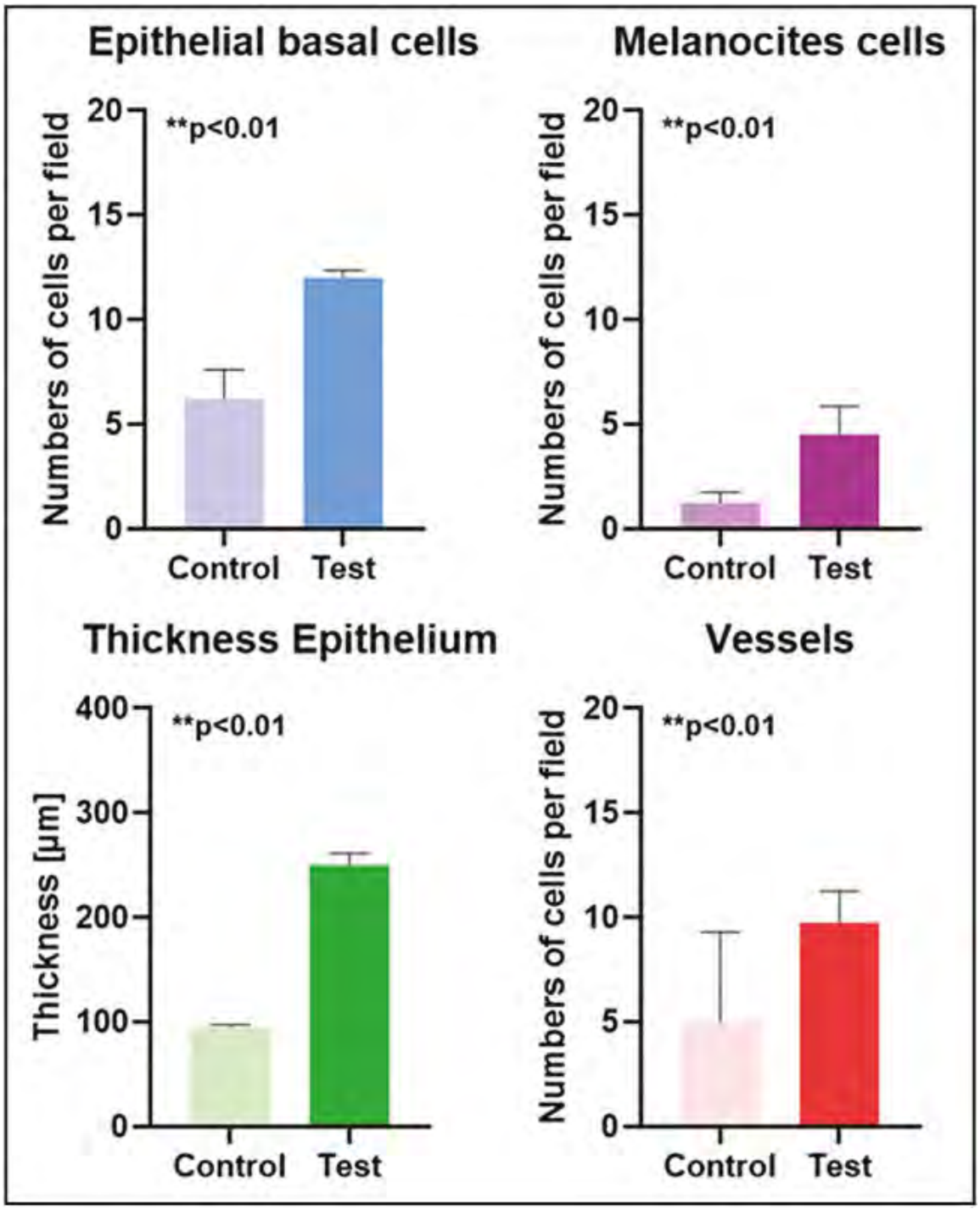
A. Before treatment. Elastic fibers disorganized. Weigert. ×40. B. After treatment. White SM. Elastic fibers, well-formed, long, and stretched. Weigert. ×40

Figure 5



A. Before treatment. Disorganized collagen fibers with differing volumes, with this staining the alteration of the microcirculation is more evident. Masson Gold Trichrome. ×40. B. After treatment. Well-organized collagen fibers of constant volume. Masson Gold Trichrome. ×60

Figure 6



Open in a separate window

The bar graphs show the epithelial basal cells, epithelial thickness, melanocytes, and vessel number (mean, standard deviation)

Table 1

Summary of the means count of Epithelial Basal Cells, Thickness Epithelial, Melanocites, Number Vessel

Groups	Epithelial basal cells		Epithelial thickness (µm)		Number of melanocytes		Vessel number	
	Control	Test	Control	Test	Control	Test	Control	Test
Average (SD)	6.21 ± 1.4	12.01 ± 0.4	95.5 ± 2.22	250 ± 11.77	1.25 ± 0.7	4.52 ± 0.33	5 ± 4.4	9.75 ± 1.5
P-value	$P < 0.01$		$P < 0.01$		$P < 0.01$		$P < 0.01$	

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Original Article

Treatment of stretch marks aged more than twenty years with the synergy of electromagnetic field and vacuum. Clinical case studies and subsequent follow-up

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Abstract

Objective: the aim of this study was to verify the efficacy of the synergy between electromagnetic field, electron flow and vacuum realized with Biodermogenesi® method. This synergy was applied on very old (more than twenty years) stretch marks (striae albae - SA) on female patients. The type of stretch marks treated were selected not by location or cause, but by the age of stretch marks. In this case, the study will allow to open a discussion on the possibility to intervene successfully also against the notoriously more difficult types of striae, analyzing the results obtained and the absence of side effects.

Method: 20 women with stretch marks aged more than twenty-years were treated with a treatment program of 9 Biodermogenesi® sessions executed weekly. The treatment was performed with Bi-one® 2.0 MD device, equipped with a generator of electric impulses, electromagnetic fields and vacuum integrated with a bio-feedback system that allows the automatic variation of frequencies and intensities of the electromagnetic field delivered. A subjective evaluation of the outcomes was asked separately to the patients and the researchers; they were asked to evaluate: the filling of the hallow area of the stretch marks, the feeling to the touch of the stretch marks, the discoloration and the eventual tanning of the stretch marks. The evaluation was carried out at T0 (before the sessions - 0%), T1 (after the ninth treatment session) and T2 (after six months from the end of the ninth session cycle). The evaluation scale is as follows:

- Level 0	No improvement	+ 0%
- Level 1	Poor improvement	from +1% to +20%
- Level 2	Minimal improvement	from +21% to +40%
- Level 3	Moderate improvement	from +41% to +60%
- Level 4	Good improvement	from +61% to +80%
- Level 5	Excellent improvement	from +81% to +100%

Results: the improvement of the SA has been evidenced with a tangible filling of those same marks, evident both to the touch and to the sight, and with the recovery of its initial color and subsequently uniform with the surrounding skin tissue. In the subsequent or simultaneous exposure to ultraviolet, we appreciated the tanning of the striae with an intensity very similar to the surrounding skin, in total absence of side effects.
There was also a general increase in the elasticity and compactness of the treatment area.

Conclusions: the synergy offered by Biodermogenesi® method has proven to regenerate even very old SA, which are the most difficult ones to treat. These imperfections were significantly reduced, and in some cases were completely eliminated their evidence to touch and sight, thanks to the newfound power to tan the striae with the exposure to ultraviolet rays. The uniformity of outcomes is appreciated, as all patients reacted positively to the therapy in the absence of side effects.

Keywords
Stretch marks, Biodermogenesi, electromagnetic field, vacuum, electroporation, capacitive radiofrequency

Abbrevations

T0	assessment made before the treatment program
T1	assessment made at the end of the treatment program
T2	follow-up made from 6 to 12 months after the end of the treatment program
PIH	post-inflammatory hyperpigmentation
SA	striae albae
SR	striae rubrae

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Introduction

Since the second half of the twentieth century, stretch marks have increased exponentially among the female gender and has gradually started to affect young boys as well, becoming probably the most widespread imperfection in the new generations.

Biodermogenesi® has shown remarkable effectiveness in the regeneration of stretch marks[1] and post-surgical scars and burns[2], favoring the production of collagen and elastic fibers. The aim of this study is to verify the outcomes of the new synergy developed by Biodermogenesi® on a group of female patients, all burdened by very old stretch marks that are white and opaque in color with a deep and rigid structure.

The new synergy, which combines electromagnetic fields with electron flow and vacuum, provides a number of sessions drastically reduced compared to the previous Bi-one® technology, to regenerate a twenty-year stria; before it required at least 20 sessions.

Stretchmarks that are more than twenty years old are more difficult to work on to obtain a significant improvement.

The existing literature has recently focused on the analysis of the results obtained with various types of lasers, facing some consolidated limits: the greater efficacy documented regarding only the red stretchmarks, and therefore newly formed stretch marks. However, we saw that at the end of laser treatment programs the results were varying from moderate to none and were not replicable on all the patients, especially on SA.

Furthermore the laser procedure caused the constant presence of edema and PIH and a recurrent pain detected by patients.

Briefly analyzing the existing literature in support of laser therapy, we note various evaluations of the results obtained. The results obtained with a non-ablative fractional laser in the experience of Katz et al.[3], limited to only two young patients (12 and 13 years) with striae dated 3 and 10 months, appear positive.

Other experiences speak instead of appreciable results on a part of the patients treated, compared to others whose outcomes have been minimal or none. In this sense, we recall the experiences of Bach and his colleagues[4]: "six of the 22 patients (27%) showed good to excellent clinical improvement from baseline, whereas the other 16 (63%) showed various degrees of improvement".

This is confirmed also by Stotland and his colleagues[5] who confirm that: "photographs of 8 randomly selected patients showed an overall improvement of 26% to 50% in 63% (5 of 8 patients)". Even the experience of Tretti Clementoni has obtained greater uniformity of results[6], he confirms that some patients treated with non-ablative fractional laser do not show significant outcomes: "the volume of SD depressions improved by more than 50% (mean improvement 58%) in the majority of patients (11 of 12 patients) and the color of the lesions improved by more than 50% (mean improvement 54%) in 83,33% of patients (10/12)".

Apart from Katz's experience[3], the other researchers[4,5,6] do not mention the visual appearance of stretch marks (white or red) and their dating.

The experience of De Angelis et al.[21] is based on 51 patients treated with 1540-nm fractional nonablative Er: Glass laser and the evaluation was done both by researchers and blinded, always with positive outcomes, noting a reduction in striae generally greater than 50%.

With the same technology, Farhad Malekzad and coll.[22] evaluated the efficacy on patients with skin phototype between II and V burdened by SA with different outcomes. We note that after 3 sessions, 2 out of 10 patients left the study, 3 out of 10 patients declared no results (no improvement) and 5 poor results (poor); the same patients, after a follow-up of three months, 2 out of 10 declared no results and 6 out of 10 little result.

In addition to the controversial outcomes found by the authors, the non-ablative fractional laser is characterized by moderate pain during therapy[4,6], micro-crusting[6], recurrent edema and hyperpigmentation[4,6] generally reabsorbed in the course of 5/10 days.

De Angelis and coll.[21] recommend to patients a prophylaxis in the month before the treatments and in the following six months.

Particular attention of the present study is reserved to the hypochromia of the dated striae and to the possibility to recover the faculty of tanning by the same ones. This aspect has already been studied in the past, with a therapy based on excimer lasers. Goldberg[22] treated 75 patients with 8/9 sessions per patient, with an attenuation in 60 cases, while in 15 there was no improvement. Alexiades-Armenakas et al.[23] have always performed 9 sessions per patient and have documented a 68% improvement in hypopigmentation but only stable between 1 and 6 months. At the end of the 6 months no residual outcome was found.

The practically zero stabilization of the improvements obtained has limited the spread of this therapy, leaving the problem of hypopigmentation unresolved.

Materials and methods

We analyzed a group of 20 patients aged between 34 and 66 years, all with SA aged between 20 and 35 years, and treated them with a cycle of 9 sessions of Biodermogenesi® on a weekly basis.

The patients were all healthy and did not have any preconditions for being excluded from the trial.

The exclusion criteria are as follows: Pace-Maker users; cancer therapy in progress or during the last 5 years; epilepsy; vascular alterations such as varices, phlebitis and thrombophlebitis; pregnancy or breastfeeding; alterations and hormonal therapies manifested during

the last 6 months; anti-coagulant therapy; phenomena of anorexia or bulimia during the last 2 years.
Biodermogenesi® treatment was performed with an electro-medical device called Bi-one® 2.0 MD, combined with three synergistic active ingredients.
Treated stretch marks were present on the breasts, arms, abdomen, hips, buttocks, thighs, calves; for the cases in question we treated a single area on each patient, as required by the official protocols.

Technology
The treatment was performed with a non-invasive electro-medical device "Bi-one® 2.0 MD" and protected by some international patents (Expo Italia S.r.l., via Segantini, 34, Firenze, Italy). The apparatus was equipped with a generator of electromagnetic fields, an electron flow generator, a pair of vacuum pumps and a series of handpieces.
The generator of electromagnetic fields emits a capacitive shielded signal at a variable frequency, ranging from 0.5 to 1 MHz ± 10%, and variable intensity up to a maximum value of 6W on a 500 Ohm resistance. The device is equipped with a bio-feedback system that allows to change independently the intensity and frequency of the signal delivered according to the different biological characteristics of each individual patient, increasing the temperature of the treated area between 39° C and 40° C.
The electron flow generator emits a 5 Hz square wave signal with a maximum intensity of 0.36 mA on a 500 Ohm load. Generators of the electromagnetic field and of the electron flow are separated mechanically and galvanically from each other and towards the network plant. The brushless vacuum pumps allow delivering negative pressure with absolute precision and stability, with a maximum value of - 0.35 atmospheres.

Procedures
The treatment procedure was divided into two distinct phases, during which several forms of energies are present for different biological actions.
The first phase was about a light mechanical peeling. For this phase, we used a single-use abrasive pad placed inside the PEELING handpiece.
PEELING handpiece works with a gentle vacuum action, designed to lift the tissue with the stretchmarks, bringing the hollow area of the imperfection outwards. The complete deconstruction of the elastic fibers that characterizes very old striae[1,7] allows the striae to extend outwards, bringing the dense and compact corneous layer in relief, favoring a selective reduction.
The second phase, called ACTIVE PLUS, provides the synergistic action of vacuum and biocompatible electromagnetic field generated thanks to a capacitive radiofrequency with variable frequency and intensity. The combination of these forms of energy activates a greater action by the arterial capillaries, it increases the caliber and brings to the matrix oxygen and nutritional elements, stimulates the lymphatic microcirculation, and helps to drain part of the toxins present[11]. The simultaneous flow of electrons, object of the new technology, allows a reduction to the electrical resistance of the skin tissue, effectively amplifying the yield of the electromagnetic field.
As the effectiveness and the useful dose of the applied electromagnetic field is inversely proportional to the electrical resistance; the flow of electrons reduces this value and consequently increases the regenerative efficacy of the electromagnetic field.
At the same time we observe a strong pumping of the Na + / K +, able to increase the fibroblast activity, leading to the synthesis of collagen and elastic fibers[1,7] and favoring a tissue repair [11, 12, 13].
The technology adopted for the present study provides a platform developed by NXP, a company owned by Philips, able to compare the acceleration obtained with sodium and potassium through the cellular barriers:

Previous Bi-one® technology from 300 to 450 mV
New Bi-one® 2.0 MD technology from 750 to 850 mV

Documenting an effectiveness on average by double with respect to the previous technology.
The full treatment session takes about 25 minutes in total. The protocol provides a preliminary evaluation system of stretch marks that determines the level of difficulty and therefore anticipates the patient what the result will be, how many sessions will be needed to obtain this result and how long the treatment cycle will take to be completed. All the patients examined, respected the indications provided by the protocol.

Evaluation
The evaluation of the results of the treatment of stretch marks was carried out by using the VAS (Visual Analogue Scale) scales of the patient and the doctor.
Assessments were made before the start of treatment, during the preliminary visit (T0), after the last treatment (T1) and after a period between 6 and 12 months from the end of the sessions (T2).
The VAS scale asks the patient to make the most of the following parameters:
- Improvement of the stretch marks to the touch (depth and fibrosis)
- Improvement of the visual stretch marks (color and opacity)
- Increase in the faculty of the stretch mark to get a tan

The values are expressed from 0 = 0% (no improvement), from 1 = 1% to 20% (poor improvement), from 2 = 21% to 40% (minimal improvement), from 3 = 41% to 60% (moderate improvement), from 4 = 61% to 80% (good improvement), from 5 = 81% to 100% (excellent improvement).

Results
The results obtained are summarized in the following *Tables 1, 2* (patient's VAS scale) and *Table 3* (doctor's VAS scale). The scales measure the perceived improvement on the treated stretch marks.

VAS Scale - Patient
At the end of the treatment program (T1), 11 patients (55%) found an improvement between 41% and 60%, while 9 patients (45%) found an improvement between 61% and 80%. The perception of the improvement obtained was increased when the follow-up (T2) was performed

Patient	Patient's Age	The presence of stretch marks in years	Area	Patient T1	Patient T2	Doctor T1	Doctor T2
RK	34	> 20	Buttocks	4	5	4	5
CS	52	25	Abdomen	3	5	4	4
GF	43	20	Thighs	3	4	4	4
MR	38	20	Abdomen	3	5	5	5
ML	39	20	Breasts	3	5	4	5
SA	42	22	Abdomen	3	5	4	5
VA	43	20	Abdomen	4	5	3	4
ST	53	30	Abdomen	3	5	4	4
GA	42	20	Thighs	3	3	2	3
IR	66	> 30	Thighs	3	5	4	4
CN	35	22	Breasts	3	4	4	5
LM	58	> 30	Arms	3	4	4	5
SL	43	20	Abdomen	4	5	5	5
SM	41	25	Flanks	4	5	4	4
FM	38	21	Abdomen	4	5	5	5
LA	42	25	Inner Thighs	4	4	4	4
VD	40	24	Flanks	3	4	4	4
LB	48	33	Buttocks	4	4	4	5
HR	36	21	Thighs	4	5	4	5
PMG	34	21	Buttocks	4	5	4	5

Table 1 *- VAS scale of the doctor and the patient.*

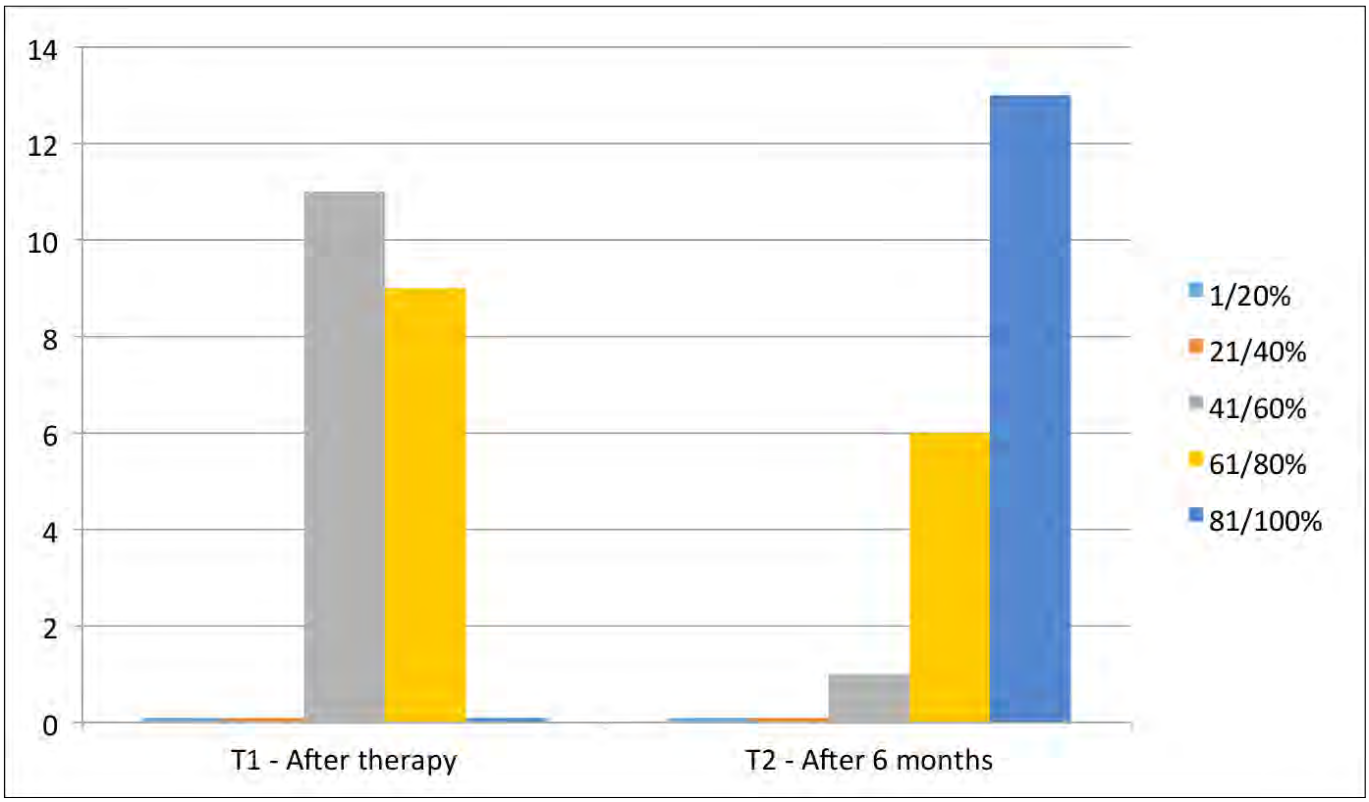


Table 2 *- Patient's VAS scale.*

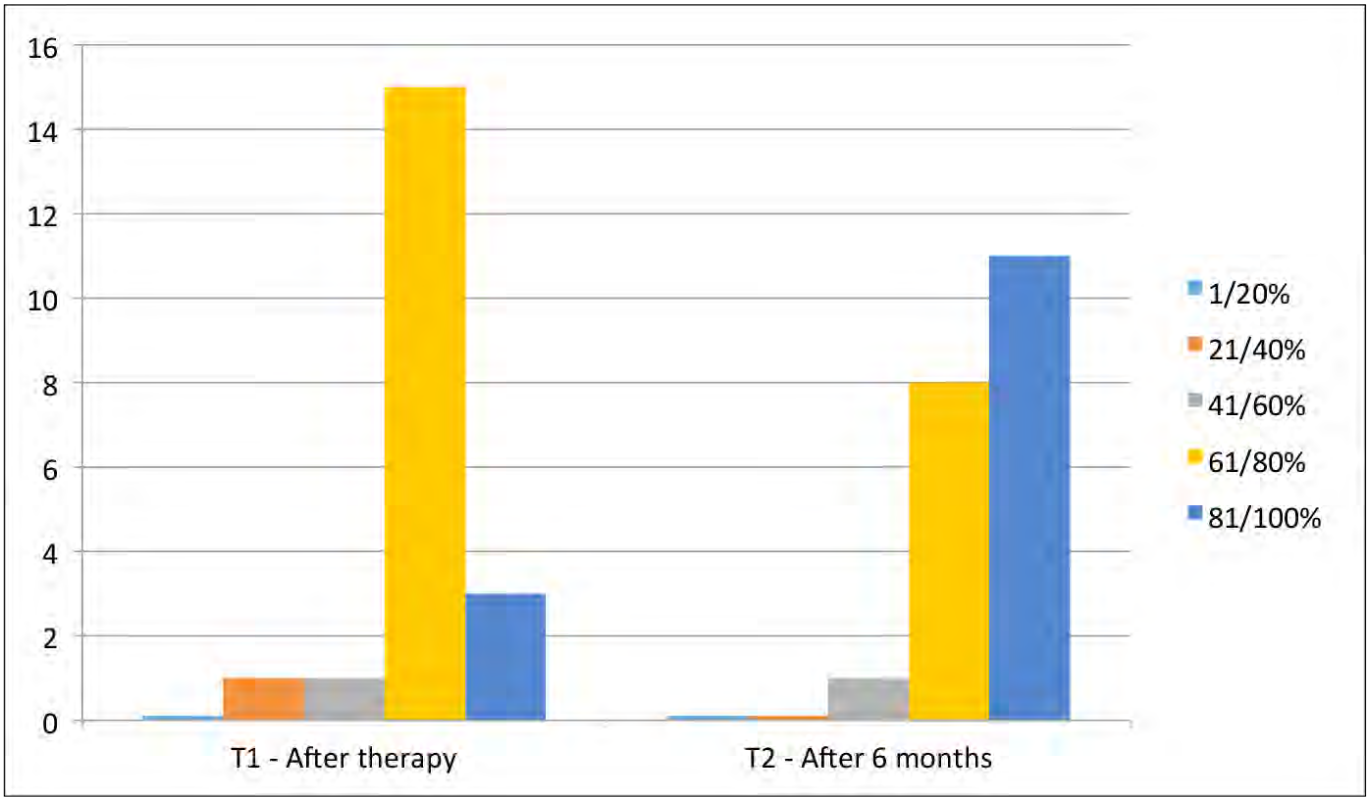


Table 3 - VAS scale of the doctor.

after more than 6 months from the end of the treatment program: 1 patient (5%) found an improvement between 41% and 60%, 6 patients (30%) found an improvement between 61% and 80%, while 13 patients (65%) found an improvement between 81% and 100%.

VAS scale - Doctors

At the end of the treatment program (T1) the doctors in one case (5%) evaluated an improvement between 21% and 40%, on another patient (5%), between 41% and 60%, on 15 patients (75%), between 61% and 80% and on 3 patients, between 81% and 100%. Also the evaluation of the improvements obtained was increased by the doctors during the follow-up (T2): in one patient (5%) they evaluated an improvement between 41% and 60%, on 8 patients (40%) between 61% and 80% and on 11 patients (55%) between 81% and 100%.

Analyzing the documented results, a noticeable overall improvement of the treated stretch marks is evident, both in the evaluation of the patients and the doctor.

In the T1 test, we notice an overall improvement of the SA, which tends to increase in the months after the treatment. The progression of the improvement is due to the activation of virtuous reactions, which we have also found with the previous version of the technology. The reactivation of the sodium and potassium pump allows restoring a better activity of the fibroblast, which physiologically manifests itself in the course of a few weeks after the treatments, during when the maximum regenerative response is obtained by the treated tissue. Another aspect that the patients have greatly appreciated is given by the newfound ability of striae to tan with the sun exposure another aspect that we had found with the previous technology. Early experiences, first of Dr. Artigiani and coll.[1] had documented a recovery of the ability to tan by the stretch marks treated with Biodermogenesi®. This aspect has allowed patients to expose themselves to ultraviolet also during the treatments, highlighting a progressive tanning of the striae. Of course, for the patients living in Sanremo and Palermo who were part of this study, it was much easier to obtain the tanning of the stria as both of the cities are known for their beach attractions.

The stabilization and progression of the outcomes, as shown by the conclusions made in T2, where the appreciation of patients and doctors is consolidated, is confirmed by Bacci[14], who performed a follow-up after more than 5 years from the end treatment with Biodermogenesi®. In his study, Bacci highlighted a general improvement of the results previously achieved, without any regression of the outcomes obtained on the patients.

Unlike what was found with other technologies, the treatment of striae with Biodermogenesi® did not cause pain, discomfort, or any side effects, even minimal, at the end of each treatment session. Patients were able to regain their lifestyle immediately without any limitation.

The choice of evaluating the results obtained with the present therapy by means of the VAS scale exposes to the risk of subjectivity that would not occur with instrumental or bioptic tests. However, we believe that the type of result obtained, which is the filling of the striae, even if they are present for more than twenty years, and their subsequent tanning makes this assessment acceptable. In fact, the filling and the rediscovered capability of tanning of the stretched skin derives exclusively from a reorganization of the epidermis

and the dermis, a restored basal membrane, a correct positioning of the melanocytes and from an adequate dermal vascularization. Basically, to completely tan the striae, it is essential to fully regenerate the skin tissue. In our opinion, the results obtained on all patients adopting t the VAS scale is certainly subjective, but in the specific case it is not questionable.

Discussion

Biodermogenesi® opens up a new perspective in the treatment of SA by applying for the first time a non-invasive method that is not based on damage and subsequent repair. We know that collagen fibers change between 52° and 55° C[15] and contract at 65° C[16] and come to denature between 60° and 70° C[17].
The thermal effect induced by Biodermogenesi® stabilizes the dermis temperature between 39° and 40° C and therefore the variation of collagen and elastic fibers documented bioptically by Bacci[6] and by Artigiani et all. 1 gives us a curiosity about the induced regenerative mechanism, presumably related to the Van't Hoff law.
In the case of Biodermogenesi®, it is believed that the thermal effect is the consequence of the increased activity of Na+ / K+ across the membranes, favored by the applied electromagnetic field [18,19], it determines this reaction for mere friction.
The regenerative faculty of the tissues subject to greater activity by these carriers is amply demonstrated by the literature in sports medicine, in the field of recovery of muscle injuries [11,12,13].
However, the evident improvement of the treated striae is obtained in total absence of side effects.

Conclusions

Biodermogenesi® can be used successfully in the treatment of SA, even if they are very old (more than twenty years), favoring both an aesthetic result and an effective regeneration of dermis and epidermis, as evidently demonstrated by the renewed ability to tan by the striae as a result of correct skin reorganization. All patients treated in accordance with the protocols have noticed a significant improvement in the imperfection, also confirmed by the doctors, with no side effects and without limitations to a normal lifestyle.

Conflict of interest

The authors declare that they have no conflict of interest.

Documented cases

Case 1

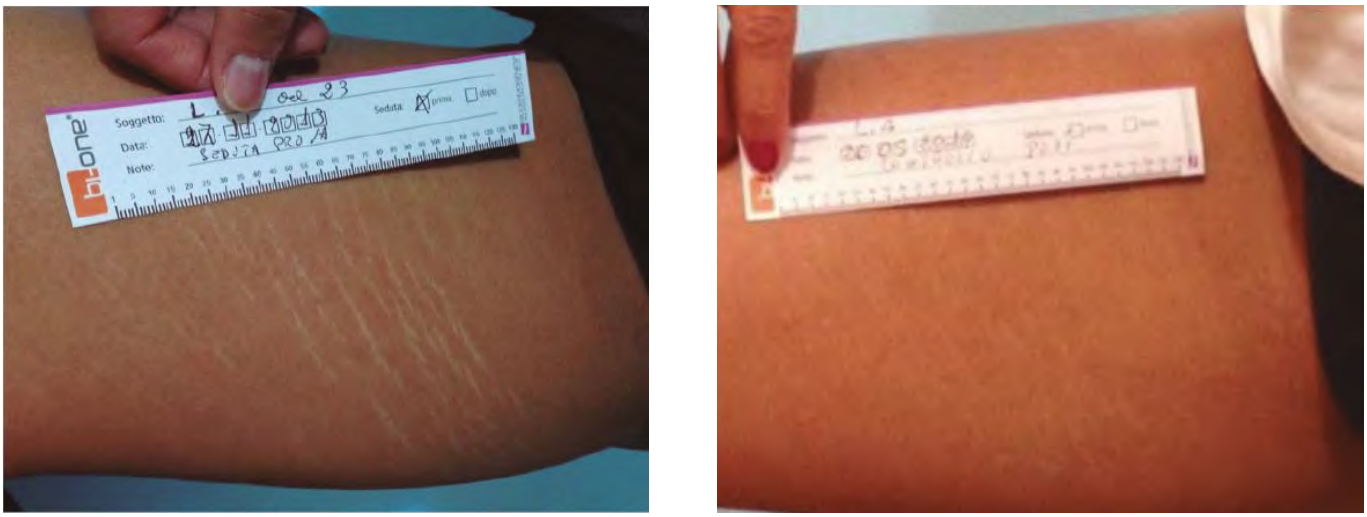


Figure 1 *- L.A., a 42-year-old patient with striae present for 25 years. Pictures taken at T0 and T1 + 6 months. Stretch marks are filled and tanned, uniform to the touch and to the sight.*

Case 2

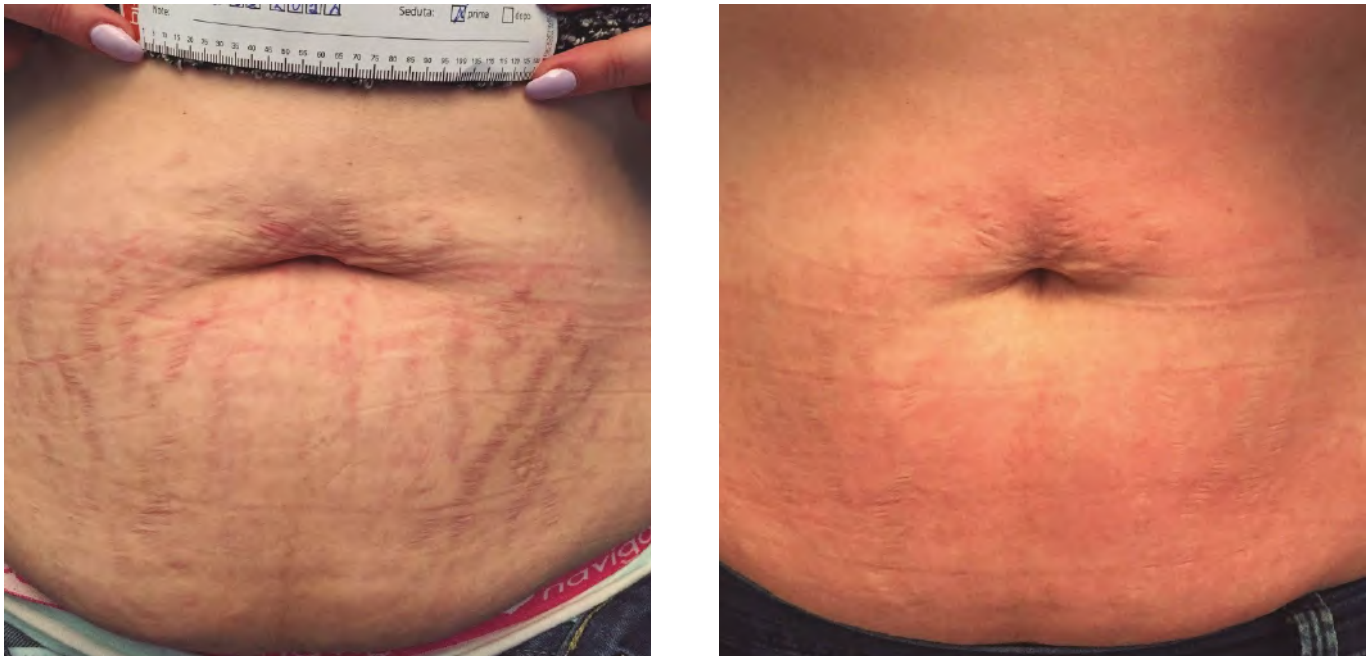
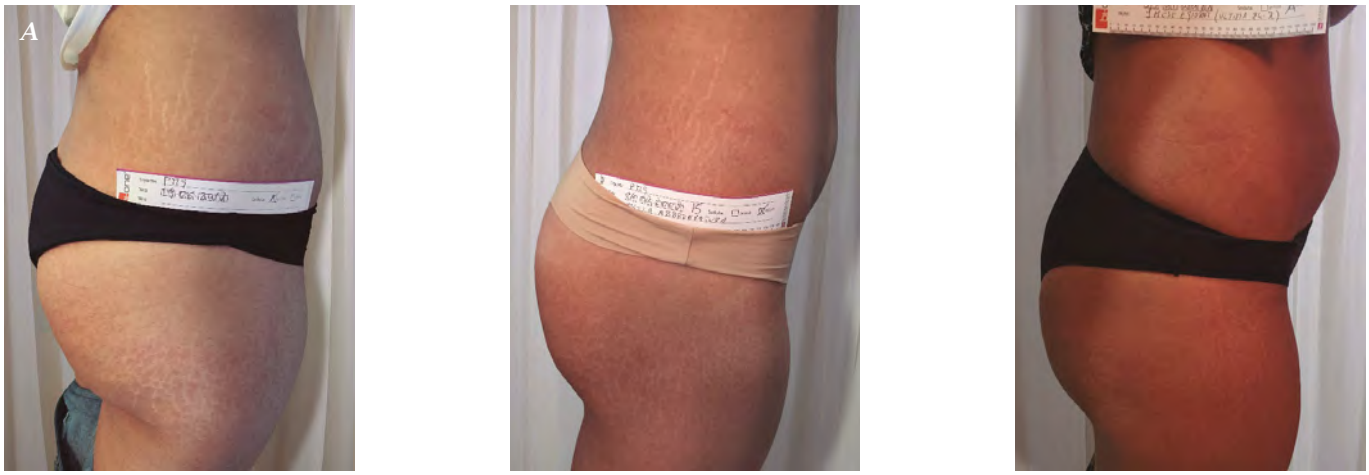
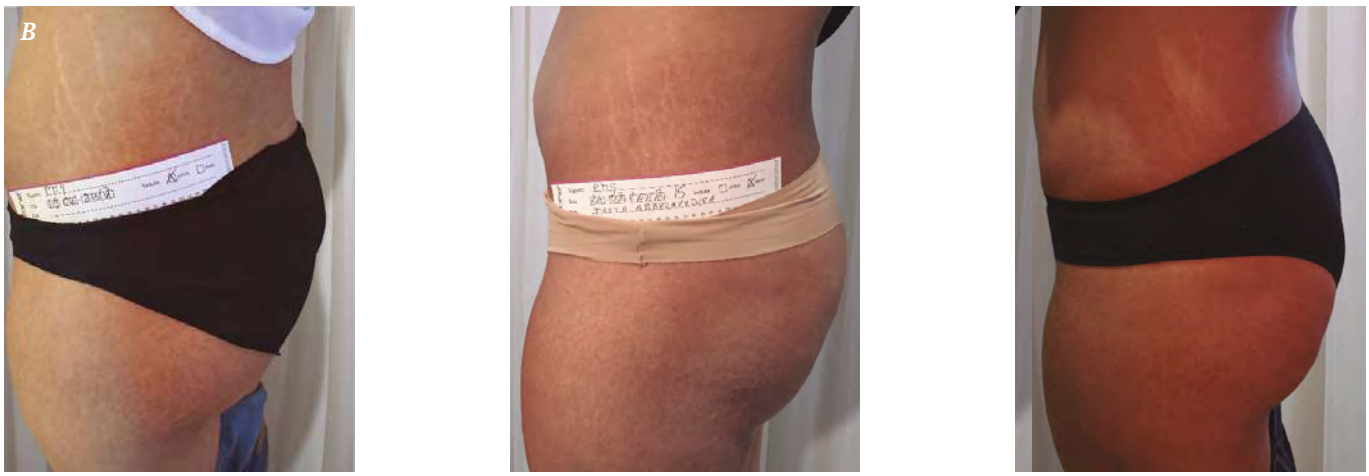


Figure 2 *- S.L., a 43-year-old patient with stretch marks present for 20 years. Pictures taken at T0 and T1 + 6 months. Stretch marks are filled and tanned and at the same time, skin tone has improved. The abdomen is more compact and firm and the navel has reopened.*

Case 3 dx



Case 3 sx



Figures 3 (A-B) *- P.G.M., a 34-year-old patient with stretch marks present for 21 years. Pictures taken at T0, T1 and T1 + 6 months. In the patient in question we appreciate the filling of stretch marks since T1, where they started to pigment due to limited sun exposure. The photo taken at T1 + 6 months highlights an excellent tanning of stretch marks thanks to subsequent sun exposure and the achievement of substantial uniformity with the surrounding tissue.*

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UNIVERSITÀ DI PISA

A. Artigiani, G. Cervadoro, B. Loggini, A. Paolicchi
Biodermogenesi: la soluzione non invasiva nel trattamento delle smagliature

Scuola di specializzazione in Dermatologia e Venereologia
U.O. Dermatologia, Fisioterapia, e Follow-up Ustioni
Università di Pisa

BIODERMOGENESI®: LA SOLUZIONE NON INVASIVA NEL TRATTAMENTO DELLE SMAGLIATURE

Dallo studio eseguito dalla Scuola di Specializzazione in Dermatologia e Venereologia dell'Università di Pisa è stato estratto un articolo pubblibato sulla rivista La Medicina Estetica

INTRODUZIONE

La Scuola di Dermatologia e Venereologia dell'Università di Pisa è stata tra le prime a promuovere studi inerenti a Biodermogenesi®. Lo staff dei ricercatori dell'Ateneo pisano ha analizzato gli esiti della terapia su 18 pazienti di fototipo compreso tra II e VI con smagliature bianche vecchie tra 7 e 35 anni, di lunghezza media di 8,2 centimetri ed ampiezza media di 7,3 millimetri. I pazienti sono stati sottoposti a sedute effettuate due volte a settimana, eseguite direttamente nei locali della Scuola di Dermatologia e Venereologia.

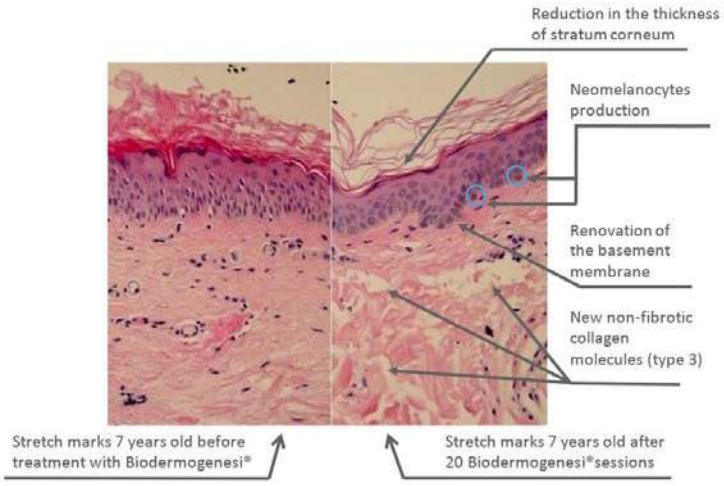
Per lo studio non si sono ammessi pazienti gravati da pacemaker, epilettici, anoressici o bulimici, con pregressi da chirurgia o terapia oncologica negli ultimi 5 anni, con ferite aperte o con varici, flebiti o tromboflebiti nell'area da trattare. La valutazione degli esiti si è basata sui seguenti fattori:

- biopsie sulle smagliature prima e dopo il ciclo delle sedute;
- ecografie prima e dopo il ciclo delle sedute;
- fotografie prima e dopo il ciclo delle sedute;
- valutazione tridimensionale del riempimento del solco delle strie;
- verifica dell'abbronzatura al termine del ciclo delle sedute;
- analisi degli effetti collaterali;
- valutazione del livello di soddisfazione del paziente espresso in cinque livelli di risultato, sviluppati con questionario ispirato alla Scala Likert (I – Nessun miglioramento - non soddisfatto; II – miglioramento da 1 a 25% - moderatamente soddisfatto; III – miglioramento da 26 a 50% - mediamente soddisfatto; IV – miglioramento da 51 a 75% - molto soddisfatto; V – miglioramento da 76 a 100% - estremamente soddisfatto).

ANALISI DEGLI ESITI

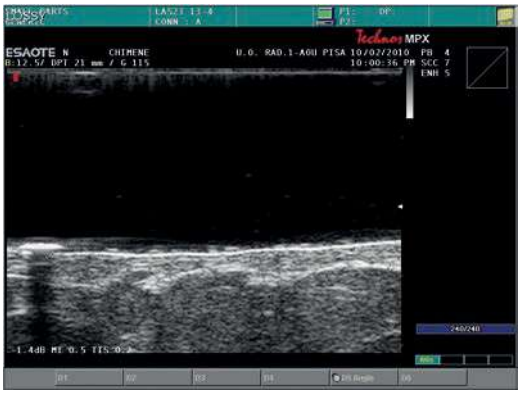
Biopsie

L'analisi comparativa delle biopsie eseguite prima e dopo il ciclo delle sedute evidenzia una riorganizzazione degli strati cutanei: il corneo si riduce, l'epidermide recupera spessore, la membrana basale si riorganizza e recupera la corretta forma sinusoidale ed evidenzia la presenza di melanociti, il derma si presenta ricco di collagene di tipo III di ottima qualità.

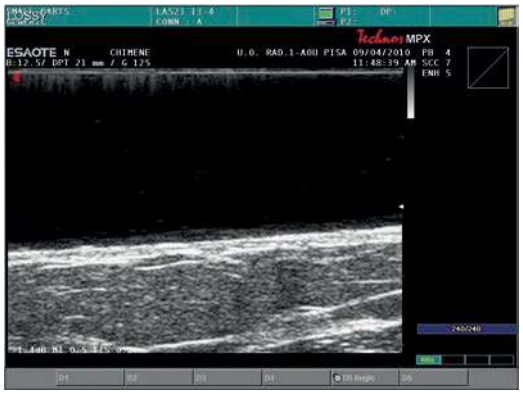


Ecografie

L'ecografia eseguita prima delle sedute evidenzia una stratificazione del corneo, che si presenta denso e compatto, tanto da essere fortemente iperecogenico, come mostra il cilindro anecoico sottostante. Il rilievo eseguito dopo le sedute evidenzia invece una uniformità della stria con il tessuto circostante, eliminando l'area anecoica.



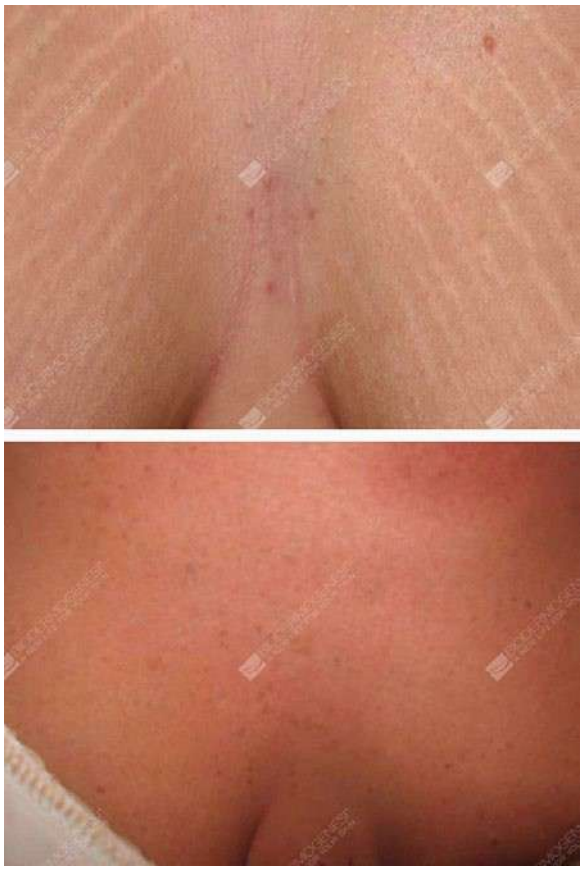
Prima delle sedute



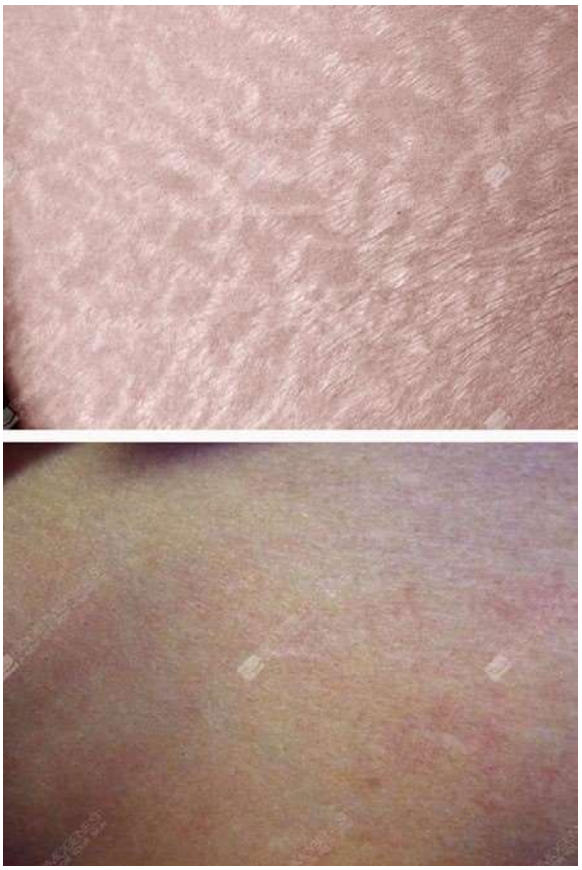
Dopo le sedute

Fotografie

Le fotografie scattate prima e dopo le sedute presentano un evidente miglioramento delle strie, che si presentano riempite ed abbronzate; al posto del solco bianco e madreperlaceo si apprezza il livellamento sia del volume del tessuto che del colore, grazie alla nuova capacità di abbronzarsi con naturalezza.



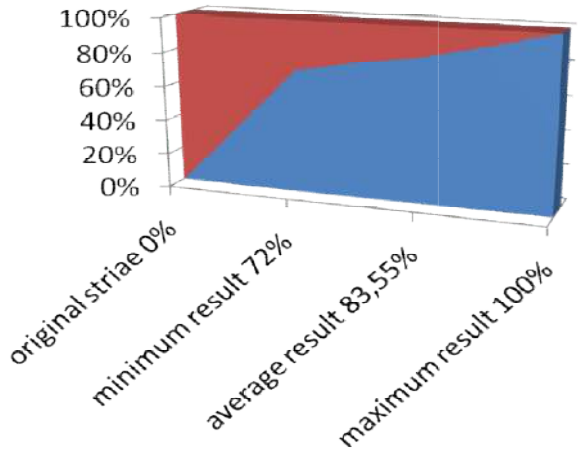
Paziente di 21 anni con smagliature bianche, opache e profonde vecchie oltre 7 anni. Dopo la terapia con Biodermogenesi® si apprezza un netto miglioramento delle strie, riempite e livellate ma anche perfettamente abbronzate, che si presentano del tutto simili al tessuto circostante.



Paziente di 45 anni di fototipo IV con smagliature bianche, opache e profonde vecchie oltre 20 anni, dovute a gravidanza. Dopo un ciclo di sedute con Biodermogenesi® si apprezza un netto miglioramento delle strie, riempite e livellate, che si presentano estremamente simili al tessuto circostante.

Valutazione tridimensionale delle strie

L'analisi tridimensionale delle smagliature evidenzia un riempimento minimo del 72%, un valore medio dell'83,55% ed in due casi del 100%. Il rilievo tridimensionale è stato rilevato con uno strumento sviluppato dallo staff dell'Università di Pisa.



Valutazione dell'abbronzatura

Tutti i pazienti trattati, anche quelli con fototipo elevato, si sono regolarmente esposti al sole subito dopo le terapie ed hanno visto le strie abbronzarsi senza avere effetti di iperpigmentazione di alcun genere. Le strie si presentano quindi abbronzate e cromaticamente integrate con il tessuto circostante.

Effetti collaterali

Con lo studio in oggetto non si sono riscontrati effetti collaterali, neppure di lieve entità. In maniera analoga abbiamo riscontrato la totale mancanza di downtime in quanto il paziente può recuperare i suoi normali stili di vita immediatamente dopo la sedute e può anche esporsi ai raggi solari in maniera diretta.

Valutazione dei pazienti

Tutti i pazienti si sono dichiarati molto soddisfatti o estremamente soddisfatti, grazie soprattutto alla nuova facoltà della pelle smagliata di abbronzarsi.

Conclusioni

Alla luce dello studio dello staff dei ricercatori pisani Biodermogenesi® risulta essere efficace e sicura nel trattamento delle smagliature bianche, anche in pazienti di fototipo IV, V e VI per i quali molte delle altre terapie offerte sono decisamente sconsigliate. L'analisi bioptica dimostra una strutturale riorganizzazione cutanea e permette di comprendere perché la stria si riempia (mitosi cellulare e moltiplicazione di collagene e fibre elastiche) e si abbronzi (organizzazione della membrana basale e presenza dei melanociti), mentre le ecografie dimostrano l'uniformità al tatto della stria con il tessuto circostante. L'elevato livello di soddisfazione espresso da tutti pazienti e la totale assenza di effetti collaterali permette di ritenere Biodermogenesi® quale terapia elettiva nei confronti della smagliatura.

Le conclusioni letterali dei ricercatori dell'Università di Pisa sono le seguenti:

Con il presente studio abbiamo per la prima volta constatato una reale ristrutturazione della smagliatura in totale assenza di effetti collaterali. L'aspetto sicuramente più rilevante è dato dalla uniformità dei risultati, tali da portarci ad affermare come questi siano sicuramente replicabili su qualsiasi soggetto, a condizione di rispettare il protocollo operativo.

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Articolo Originale

Trattamento di strie alba ultraventennali con la sinergia ottenuta con campi elettromagnetici e vacuum. Casistica clinica e successivo follow-up*

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Riassunto
Obiettivo: lo studio si pone l'obiettivo di verificare l'efficacia della sinergia tra campi elettromagnetici, flusso di elettroni e vacuum massaggio realizzata con Biodermogenesi®, applicata su smagliature ultraventennali (striae alba – SA) su pazienti donne. La scelta del tipo di smagliature trattate, selezionate non per localizzazione o causa, ma per datazione, permette allo studio di aprire una discussione sulla possibilità di intervenire con successo anche nei confronti delle strie notoriamente più ostiche, analizzando i risultati ottenuti e l'assenza di effetti collaterali.
Metodo: 20 pazienti donne gravate da smagliature ventennali sono state trattate con un ciclo di 9 sedute di Biodermogenesi® a cadenza settimanale. Il trattamento è stato eseguito con Bi-one® 2.0 MD, equipaggiato con un generatore di impulsi elettrici, campi elettromagnetici e vuoto integrati ad un sistema di bio-feedback che permette la variazione automatica di frequenze ed intensità del campo elettromagnetico erogato. Si prevede una valutazione soggettiva degli esiti effettuata separatamente dai pazienti e dai ricercatori chiamati a valutare il riempimento del solco, l'evidenza al tatto, la discromia e l'eventuale abbronzatura delle smagliature. La valutazione è effettuata a T0 (prima delle sedute – 0%), T1 (al termine del ciclo di 9 sedute) e T2 (dopo sei mesi dal termine del ciclo di 9 sedute). La scala di valutazione è la seguente:

- Livello 0	Nessun miglioramento	+ 0%
- Livello 1	Miglioramento scarso	da +1% a +20%
- Livello 2	Miglioramento lieve	da +21% a +40%
- Livello 3	Miglioramento medio	da +41% a +60%
- Livello 4	Miglioramento buono	da +61% a +80%
- Livello 5	Miglioramento ottimo	da +81% a +100%

Risultati: il miglioramento delle SA si è evidenziato con un tangibile riempimento delle medesime, evidente sia al tatto che alla vista, e dal recupero di un colorito inizialmente compatibile con il tessuto circostante e successivamente uniforme. Nella successiva o contemporanea esposizione agli ultravioletti si è apprezzata l'abbronzatura delle strie con intensità progressivamente similare alla cute integra, in totale assenza di effetti collaterali.
Si è constatato inoltre un generale aumento dell'elasticità e compattezza delle aree trattate.
Conclusioni: la sinergia offerta da Biodermogenesi® ha dimostrato di rigenerare anche SA ultraventennali, notoriamente le più complesse da trattare, riducendone significativamente, ed in alcuni casi eliminandone del tutto, l'evidenza al tatto ed alla vista, grazie anche alla ritrovata facoltà di abbronzare le strie con l'esposizione agli ultravioletti. Si apprezza l'uniformità degli esiti, in quanto tutti i pazienti hanno reagito positivamente alla terapia in assenza di effetti collaterali.

Parole chiave
smagliature, Biodermogenesi, campi elettromagnetici, vacuum, elettroporazione, radiofrequenza capacitiva

Abbreviazioni:

AV	valore medio rilevato
T0	rilievo effettuato prima del ciclo dei trattamenti
T1	rilievo effettuato al termine del ciclo dei trattamenti
T2	rilievo effettuato nel follow-up eseguito tra 6 e 12 mesi dalla fine dei trattamenti
PIH	post-inflammatory hyperpigmentation
SA	striae alba
SR	striae rubra

*Treatment of stretch marks aged more than twenty years with the synergy of electromagnetic field and vacuum. Clinical case studies and subsequent follow-up pubblicato sulla Rivista *Aesthetic Medicine*, 2019; 5(1):30-37.

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Introduzione

A partire dalla seconda metà del XX secolo la smagliatura ha aumentato in modo esponenziale la propria incidenza nell'ambito del genere femminile ed ha progressivamente iniziato ad interessare anche i giovani ragazzi, arrivando ad essere probabilmente l'inestetismo più diffuso nelle nuove generazioni.
Biodermogenesi® ha dimostrato una notevole efficacia nella rigenerazione delle smagliature[1] e delle cicatrici post-chirurgiche e da ustione[2], favorendo la produzione di collagene e di fibre elastiche.
Lo scopo di questo studio è verificare gli esiti della nuova sinergia sviluppata da Biodermogenesi® su un gruppo di pazienti donne, gravate tutte da smagliature ultraventennali che si presentano alla vista bianche ed opache mentre al tatto risultano profonde e rigide. La nuova sinergia, che unisce campi elettromagnetici a flusso di elettroni e vacuum, prevede un numero di sedute drasticamente ridotto rispetto alla precedente tecnologia Bi-one® per la quale abbiamo constatato come la rigenerazione di una stria ultraventennale richiedesse in genere 20 sedute.
L'elevata datazione delle strie determina una maggiore difficoltà nell'ottenere un miglioramento significativo dell'inestetismo.
La letteratura esistente, ultimamente concentrata sull'analisi degli esiti ottenuti con varie tipologie di laser, mette di fronte ad alcuni limiti ormai consolidati: la maggiore efficacia documentata nei confronti delle strie rosse, e quindi recenti, la non certa replicabilità degli esiti su tutti i pazienti trattati, la costante presenza di edemi e PIH ed un ricorrente dolore rilevato dai pazienti.
Analizzando brevemente la letteratura esistente a supporto della terapia laser si notano diverse valutazioni degli esiti conseguiti. I risultati ottenuti con un laser frazionato non ablativo nell'esperienza di Katz e coll.[3], limitata a due sole giovani pazienti (12 e 13 anni) con strie datate 3 e 10 mesi appare positivo. Altre esperienze parlano invece di risultati apprezzabili su una parte dei pazienti trattati, a fronte di altri i cui esiti sono stati minimi o nulli. In tal senso si ricordano le esperienze di Bach e coll.[4], "six of the 22 patients (27%) showed good to excellent clinical improvement from baseline, whereas the other 16 (63%) showed various degrees of improvement", confermata anche da Stotland e coll.[5] che dichiarano: "photographs of 8 randomly selected patients showed an overall improvement of 26% to 50% in 63% (5 of 8 patients)". Pur ottenendo una maggiore uniformità di risultati anche l'esperienza di Tretti Clementoni e coll.[6] conferma come alcuni pazienti trattati con laser frazionato non ablativo non evidenzino esiti significativi: "the volume of SD depressions improved by more than 50% (mean improvement 58%) in the majority of patients (11 of 12 patients) and the color of the lesions improve by more than 50% (mean improvement 54%) in 83,33% of patients (10/12)".
A parte l'esperienza di Katz[3], gli altri ricercatori[4, 5, 6] non fanno menzione dell'aspetto visivo delle smagliature (bianche o rosse) e della loro datazione.
L'esperienza di De Angelis e coll.[20] è basata su 51 pazienti trattati con 1540-nm fractional nonablative Er:Glass laser e la valutazione è stata fatta sia dai ricercatori che in cieco, sempre con esiti positivi, rilevando una riduzione delle strie generalmente superiore al 50%. Con la medesima tecnologia Farhad Malekzad e coll.[21] hanno valutato l'efficacia su pazienti di fototipo compreso tra II e V gravati da SA con esiti differenti. Si nota che dopo 3 sessioni 2 pazienti su 10 hanno abbandonato lo studio, 3 su 10 pazienti dichiarano nessun risultato (no improvement) e 5 poco risultato (poor); gli stessi pazienti, dopo un follow-up di tre mesi, dichiarano 2 su 10 nessun risultato e 6 su 10 poco risultato.
Oltre agli esiti controversi riscontrati dagli autori, il laser frazionato non ablativo si caratterizza per un moderato dolore durante la terapia[4, 6], micro-crusting[6], ricorrenti edema ed iperpigmentazione[4, 6] generalmente riassorbiti nel corso di 5/10 giorni. De Angelis e coll.[20] consigliano ai pazienti una profilassi nel mese precedente ai trattamenti e nei sei mesi successivi.
Particolare attenzione del presente studio è riservata alla ipocromia delle strie datate ed alla possibilità di recuperare la facoltà di abbronzarsi da parte delle medesime. Questo aspetto è stato già in passato oggetto di studio, con una terapia basata sui laser ad eccimeri. Goldberg[22] ha trattato 75 pazienti con 8/9 sedute per paziente, con un'attenuazione in 60 casi, mentre in 15 non si è riscontrato miglioramento. Alexiades-Armenakas e coll.[23] hanno sempre effettuato 9 sedute a paziente ed hanno documentato un miglioramento dell'ipopigmentazione pari al 68% stabile però soltanto tra 1 e 6 mesi. Al termine dei 6 mesi in nessun caso si è riscontrato un esito residuo. La stabilizzazione praticamente nulla dei miglioramenti ottenuti ha limitato la diffusione di questa terapia, lasciando irrisolto il problema dell'ipopigmentazione.

Materiali e metodi

Si è analizzato un gruppo di 20 pazienti di età compresa tra 34 e 66 anni, tutte gravate da SA vecchie tra 20 e 35 anni, trattate con un ciclo di 9 sedute di Biodermogenesi®, a cadenza settimanale. Le pazienti sono risultate essere sane e non presentano presupposti per essere escluse dalla sperimentazione.
I criteri di esclusione sono i seguenti: portatori di Pace-Maker; terapia oncologica in atto o nel corso degli ultimi 5 anni; epilessia; alterazioni vascolari quali varici, flebiti e tromboflebiti; gravidanza od allattamento; alterazioni e terapie ormonali manifestate nel corso degli ultimi 6 mesi; terapia anti-coagulante; fenomeni di anoressia o bulimia nel corso degli ultimi 2 anni.

Il trattamento di Biodermogenesi® si esegue con un apparato elettromedicale chiamato Bi-one® 2.0 MD, abbinato a tre principi attivi sinergici.
Le smagliature trattate si presentavano localizzate su seno, braccia, addome, fianchi, glutei, cosce, polpacci; per i casi in esame abbiamo trattato una singola zona su ciascun paziente, come previsto dai protocolli ufficiali.

Tecnologia

Il trattamento è stato eseguito con un apparato elettromedicale non invasivo chiamato Bi-one® 2.0 MD e tutelato da alcuni brevetti internazionali (Expo Italia S.r.l., via Segantini, 34, Firenze, Italy). L'apparecchio è dotato di un generatore di campi elettromagnetici, di un generatore di flusso di elettroni, di una coppia di pompe per il vuoto e di una serie di manipoli.
Il generatore di campi elettromagnetici emette un segnale schermato capacitivo a frequenza variabile, compresa tra 0,5 ed 1 MHz ±10%, ed intensità variabile sino ad un valore massimo di 6W su carico di 500 Ohm.
Il sistema è dotato di un sistema di bio-feedback che permette di variare autonomamente intensità e frequenza del segnale erogato in base alle differenti caratteristiche biologiche di ogni singolo paziente, determinando un innalzamento della temperatura dell'area trattata compresa tra 39°C e 40°C.
Il generatore di flusso di elettroni emette un segnale ad onda quadra a 5 Hz con intensità massima di 0,36 mA su carico di 500 Ohm.
I generatori del campo elettromagnetico e del flusso di elettroni sono meccanicamente e galvanicamente separati tra loro e verso l'impianto di rete.
Le pompe per il vuoto brushless permettono di erogare una pressione negativa con assoluta precisione e stabilità, con un valore massimo di - 0,35 atmosfere.

La procedura

Il trattamento contempla due fasi distinte, nel corso delle quali si adottano più forme di energia, finalizzate a diverse azioni biologiche.
La prima fase prevede un leggero peeling meccanico effettuato tramite una spugna abrasiva monouso collocata all'interno del manipolo PEELING.
Il manipolo PEELING lavora con una blanda azione di vuoto, destinata a sollevare il tessuto striato portando l'interno del solco verso l'esterno. La completa destrutturazione delle fibre elastiche che caratterizza le strie datate[1, 7] permette di estendere le strie verso l'esterno, portando lo strato corneo denso e compatto in rilievo, favorendone una selettiva riduzione. La seconda fase, definita ACTIVE PLUS, prevede l'azione sinergica di vacuum e di campo elettromagnetico biocompatibile generato grazie ad una radiofrequenza capacitiva a frequenza ed intensità variabili.
L'abbinamento di queste forme di energia permette di innescare una maggiore azione da parte dei capillari arteriosi, incrementandone il calibro ed apportando alla matrice ossigeno ed elementi nutrizionali, stimolando il microcircolo linfatico, contribuendo a drenare parte delle tossine presenti[11]. Il contemporaneo flusso di elettroni, oggetto della nuova tecnologia, permette di ridurre la resistenza elettrica del tessuto cutaneo, amplificando di fatto la resa del campo elettromagnetico. Si ricorda che l'efficacia e la dose utile del campo elettromagnetico applicato è inversamente proporzionale alla resistenza elettrica; il flusso di elettroni riduce questo valore e di conseguenza aumenta l'efficacia rigenerativa del campo elettromagnetico.
Contemporaneamente assistiamo ad una forte spinta della pompa Na+/K+, in grado di mobilitare velocemente il fibroblasto, portando alla sintesi di collagene e di fibre elastiche[1, 7] e favorendo una riparazione del tessuto[11, 12, 13]. La tecnologia adottata per il presente studio prevede una piattaforma sviluppata da NXP, azienda di proprietà di Philips, in grado di confrontare l'accelerazione ottenuta nei confronti di sodio e potassio attraverso le barriere cellulari:
Precedente tecnologia Bi-one® da 300 a 450 mV
Nuova tecnologia Bi-one® 2.0 MD da 750 a 850 mV
documentando un'efficacia mediamente doppia rispetto alla precedente tecnologia.
Il trattamento completo richiede circa 25 minuti complessivi. Il protocollo prevede un sistema di valutazione preliminare delle smagliature che ne determina il livello di difficoltà e di conseguenza anticipa al paziente quale sarà il risultato finale, in quante sedute questo sarà ottenuto ed in quanto tempo il ciclo dei trattamenti dovrà essere completato. I pazienti esaminati hanno rispettato le indicazioni previste dal protocollo.

Valutazioni

La valutazione degli esiti del trattamento delle smagliature è stata effettuata adottando le scale VAS (Visual Analogue Scale) del paziente e del medico.
Le valutazioni sono state effettuate prima dell'inizio dei trattamenti, nel corso della visita preliminare (T0), dopo l'esecuzione dell'ultimo trattamento (T1) e dopo un periodo compreso tra 6 e 12 mesi dal termine delle sedute (T2). La scala VAS chiede al paziente di valorizzare complessivamente i seguenti parametri:
- miglioramento della smagliatura al tatto (profondità e fibrosi)
- miglioramento della smagliatura alla vista (colore ed opacità)
- Incremento della facoltà della smagliatura di abbronzarsi
I valori sono espressi da 0 = 0% (nessun miglioramento), da 1 = 1% a 20% (miglioramento scarso), da 2 = 21% a 40% (miglioramento lieve), da 3 = 41% a 60% (miglioramento medio), da 4 = 61% a 80% (miglioramento buono), da 5 = 81% a 100% (miglioramento ottimo).

Risultati

I risultati ottenuti sono riassunti nelle seguenti ***Tabelle A*** (scala VAS del paziente) e ***B*** (scala VAS del medico).
Le scale misurano il miglioramento percepito nelle strie trattate.

Scala VAS del paziente e del medico

Paziente	Età	Datazione	Area	Paziente T1	Paziente T2	Medico T1	Medico T2
RK	34 anni	> 20 anni	Glutei	4	5	4	5
CS	52 anni	25 anni	Addome	3	5	4	4
GF	43 anni	20 anni	Coscia	3	4	4	4
MR	38 anni	20 anni	Addome	3	5	5	5
ML	39 anni	20 anni	Seno	3	5	4	5
SA	42 anni	22 anni	Addome	3	5	4	5
VA	43 anni	20 anni	Addome	4	5	3	4
ST	53 anni	30 anni	Addome	3	5	4	4
GA	42 anni	20 anni	Coscia	3	3	2	3
IR	66 anni	> 30 anni	Coscia	3	5	4	4
CN	35 anni	22 anni	Seno	3	4	4	5
LM	58 anni	> 30 anni	Braccia	3	4	4	5
SL	43 anni	20 anni	Addome	4	5	5	5
SM	41 anni	25 anni	Fianchi	4	5	4	4
FM	38 anni	21 anni	Addome	4	5	5	5
SL	42 anni	25 anni	Int. Coscia	4	4	4	4
VD	40 anni	24 anni	Fianchi	3	4	4	4
LB	48 anni	33 anni	Glutei	4	4	4	5
HR	36 anni	21 anni	Coscia	4	5	4	5
PMG	34 anni	21 anni	glutei	4	5	4	5

Tabella 1 *- Scala VAS medico e paziente.*

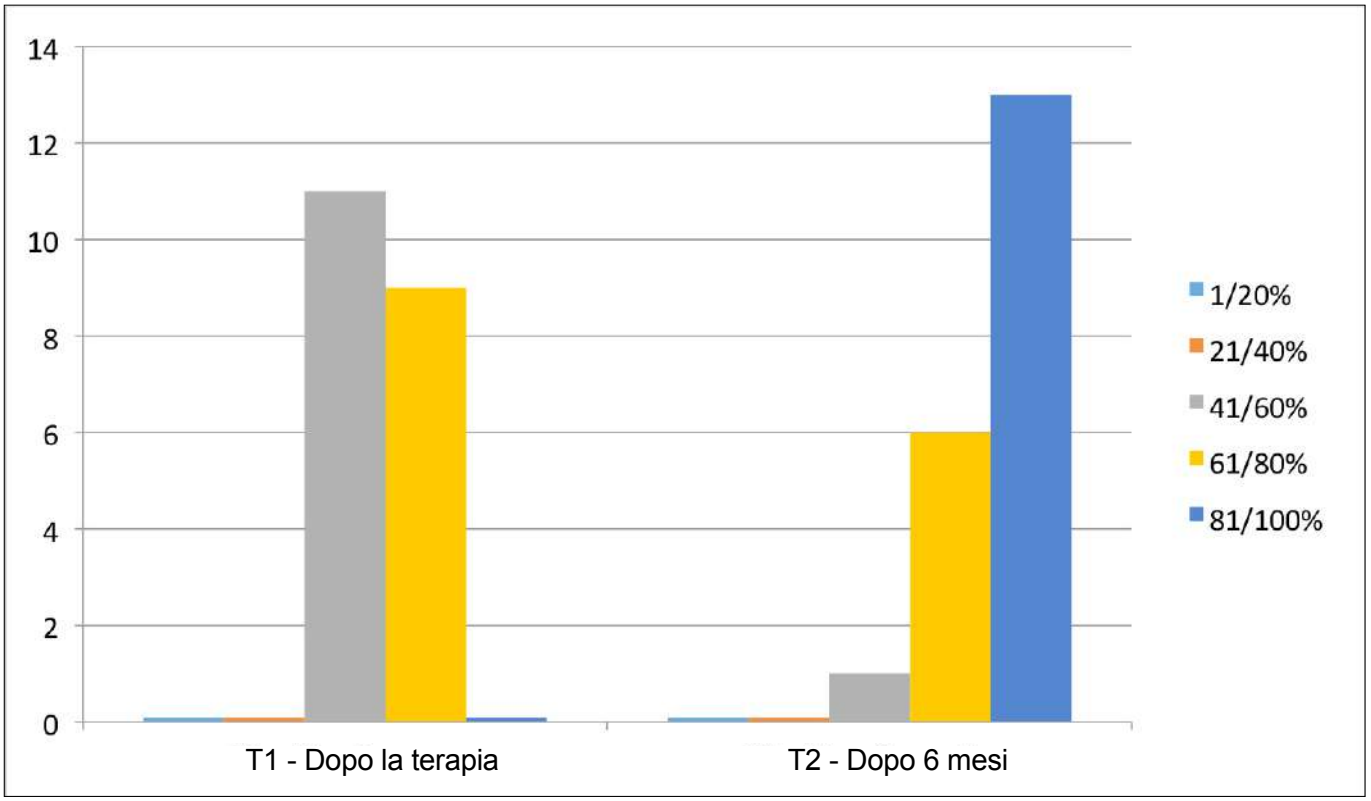


Tabella A *– Scala VAS paziente*

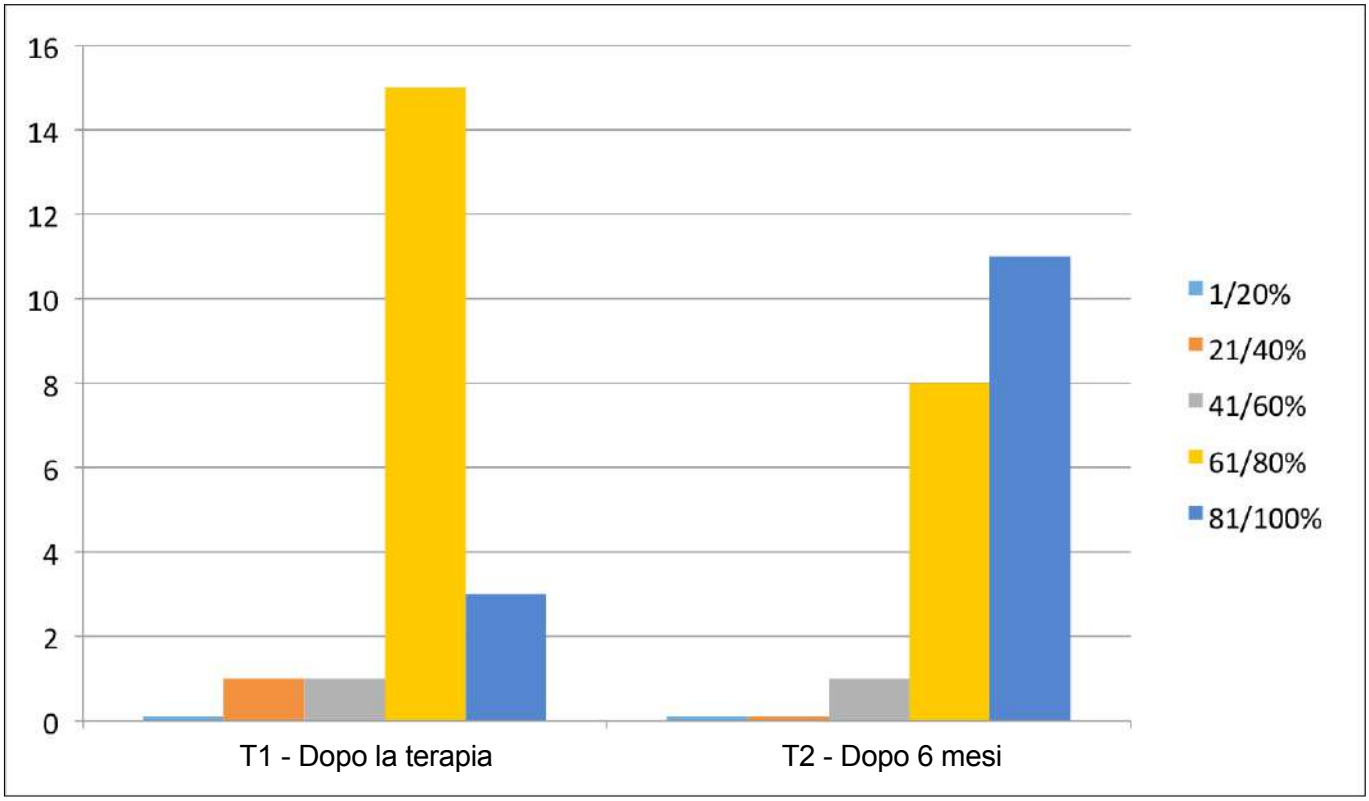


***Tabella B** – Scala VAS medico.*

Scala VAS paziente
Al termine del ciclo delle sedute (T1) 11 pazienti (55%) hanno constatato un miglioramento tra il 41% ed il 60%, mentre 9 pazienti (45%) hanno constatato un miglioramento tra il 61% e l'80%. La percezione del miglioramento ottenuto è aumentata quando è stato effettuato il follow-up (T2) eseguito dopo oltre 6 mesi dal termine del ciclo delle sedute: 1 paziente (5%) ha constatato un miglioramento tra il 41% ed il 60%, 6 pazienti (30%) hanno constatato un miglioramento compreso tra 61% e 80%, mentre 13 pazienti (65%) hanno constatato un miglioramento compreso tra l'81% ed il 100%.

Scala VAS medico
Al termine del ciclo delle sedute (T1) i medici in un caso (5%) hanno valutato un miglioramento compreso tra il 21% ed il 40%, in un paziente (5%) hanno valutato un miglioramento compreso tra il 41% ed il 60%, su 15 pazienti (75%) hanno valutato un miglioramento compreso tra il 61% e l'80% e su 3 pazienti hanno valutato un miglioramento compreso tra l'81% ed il 100%. Anche la valutazione dei miglioramenti ottenuti è aumentata da parte dei medici in occasione del follow-up (T2): in un paziente (5%) hanno valutato un miglioramento compreso tra il 41% ed il 60%, su 8 pazienti (40%) hanno valutato un miglioramento compreso tra il 61% e l'80% e su 11 pazienti (55%) hanno valutato un miglioramento compreso tra l'81% ed il 100%. Analizzando i risultati documentati appare evidente un notevole miglioramento globale delle strie trattate, sia nella valutazione dei pazienti che del medico. Nella verifica T1 si nota un complessivo miglioramento delle SA, che tende ad aumentare nel corso dei mesi successivi al trattamento. La progressione del miglioramento è dovuta all'attivazione di reazioni virtuose, da noi riscontrate anche con la precedente tecnologia. La riattivazione della pompa di sodio e potassio permette di ripristinare una migliore attività del fibroblasto, che fisiologicamente si manifesta nel corso di alcune settimane successive ai trattamenti, nel corso delle quali si raggiunge la massima risposta rigenerativa da parte del tessuto trattato. Un altro aspetto che i pazienti hanno molto apprezzato è dato dalla ritrovata facoltà delle strie di abbronzarsi con l'esposizione solare, aspetto, anche questo, che avevamo riscontrato con la precedente tecnologia. Precedenti esperienze, prima tra tutte quella di Artigiani e coll.[1] avevano documentato un recupero della facoltà di abbronzarsi da parte della smagliatura trattata con Biodermogenesi®. Questo aspetto ha permesso alle pazienti di esporsi agli ultravioletti anche nel corso dei trattamenti, evidenziando una progressiva abbronzatura delle strie. Tale aspetto è stato indubbiamente facilitato anche dalle aree geografiche in cui vivono le pazienti trattate (Sanremo e Palermo), note per le proprie attrazioni balneari.
La stabilizzazione e la progressione degli esiti, come dimostrano i rilievi effettuati in T2, dove l'apprezzamento delle pazienti e dei medici risulta essere consolidato, viene confermato da Bacci[14], che ha eseguito un follow-up dopo oltre 5 anni dal termine dei trattamenti con Biodermogenesi®, evidenziando un generale miglioramento degli esiti originariamente ottenuti, senza alcun regresso degli esiti ottenuti nei pazienti verificati.
A differenza di quanto riscontrato con altre tecnologie il trattamento delle strie con Biodermogenesi® non ha

causato dolore o fastidio né alcun effetto collaterale, neppure minimo, al termine di ogni seduta, quando le pazienti hanno potuto riprendere immediatamente il proprio stile di vita senza alcuna limitazione.

Riflessioni

Biodermogenesi® apre una nuova prospettiva nel trattamento delle SA applicando per la prima volta un metodo non invasivo che non si basa sul danno e la conseguente riparazione. Sappiamo che le fibre di collagene si modificano tra 52° e 55° C[15], si contraggono a 65° C[16] e arrivano a denaturarsi tra i 60° ed i 70° C[17]. L'effetto termico indotto nel derma da Biodermogenesi® si stabilizza tra 39° e 40° C e quindi la variazione di collagene e fibre elastiche documentata biopticamente da Bacci[6] e da Artigiani e coll.[1] pone interessanti domande sul meccanismo rigenerativo indotto, presumibilmente correlabile all'equazione di Van't Hoff. Appare comunque oggettivo il miglioramento delle strie trattate in totale assenza di effetti collaterali, normalmente connessi all'eccessivo innalzamento della temperatura cutanea, sino ad oggi ritenuta essenziale per ottenere una riorganizzazione del collagene.
Nel caso di Biodermogenesi® si ritiene l'effetto termico non la causa della neocollagenogenesi quanto piuttosto la conseguenza dell'incrementata attività di Na+/K+ la cui maggiore motilità, favorita dal campo elettromagnetico applicato[18, 19], determina tale reazione per mero attrito; la facoltà rigenerativa dei tessuti oggetto di maggiore attività da parte di tali carrier è ampiamente dimostrata dalla letteratura in medicina dello sport, nell'ambito del recupero di lesioni muscolari[11, 12, 13].

Conclusioni:

Biodermogenesi® può essere utilizzata con successo nel trattamento delle SA, anche ultraventennali, favorendo sia un risultato estetico che una rigenerazione effettiva di derma ed epidermide, come palesemente dimostrato dalla ritrovata facoltà di abbronzarsi da parte delle strie trattate, derivata dalla corretta riorganizzazione cutanea. Tutti i pazienti trattati nel rispetto dei protocolli hanno constatato un rilevante miglioramento dell'inestetismo, confermato anche dai medici, in assenza di effetti collaterali e senza limitazioni del normale stile di vita.

Conflitto d'interesse

Gli autori dichiarano di non avere conflitto di interessi.

Casi documentati

Caso 1

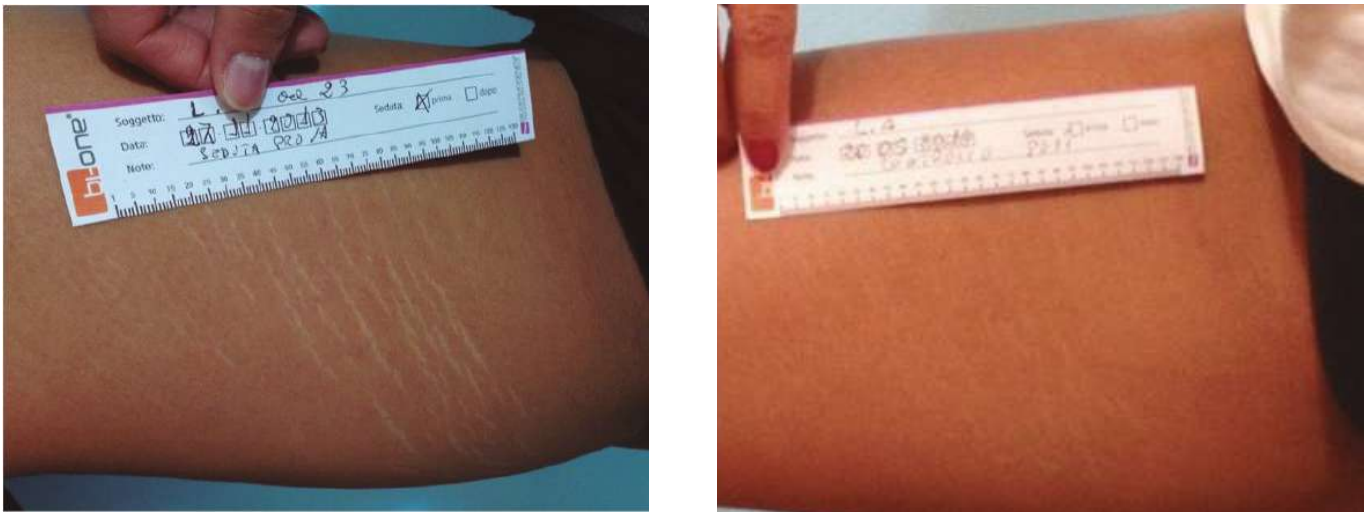


Figura 1 *- L.A., paziente di 42 anni con striae presenti da 25 anni. Foto scattate a T0 e a T1 + 6 mesi. Le smagliature sono riempite e scurite, uniformi al tatto e alla vista.*

Caso 2

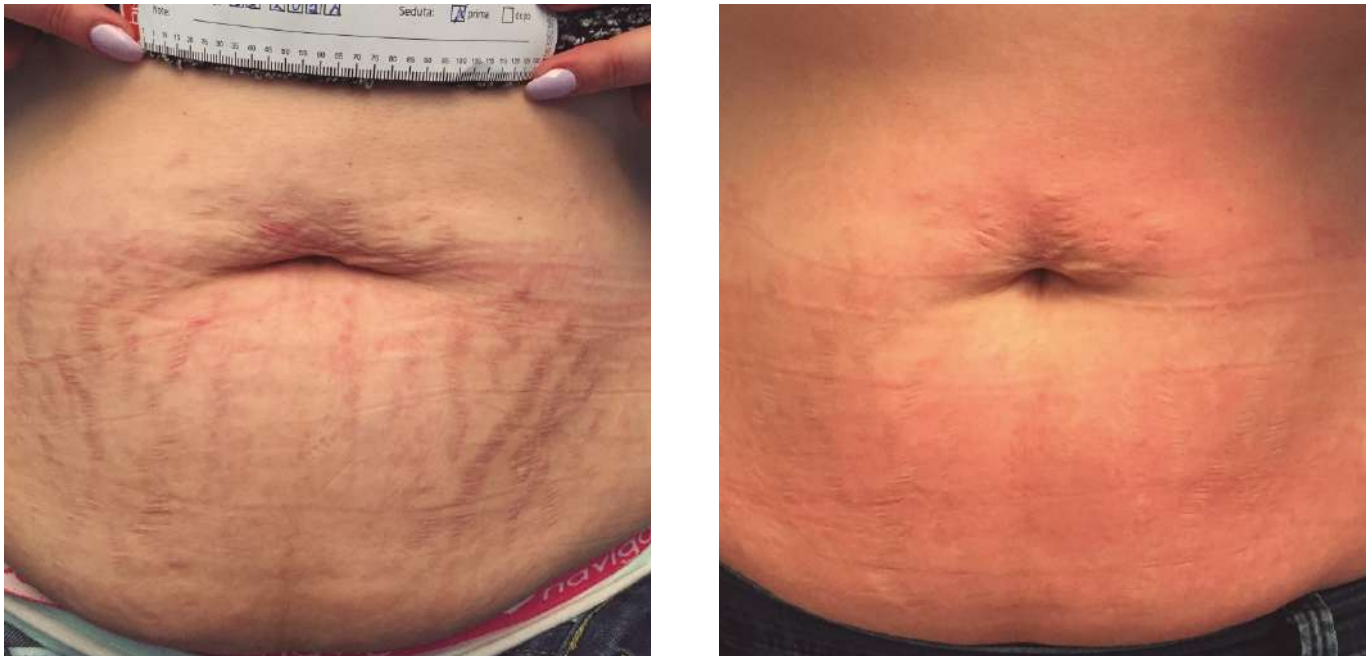
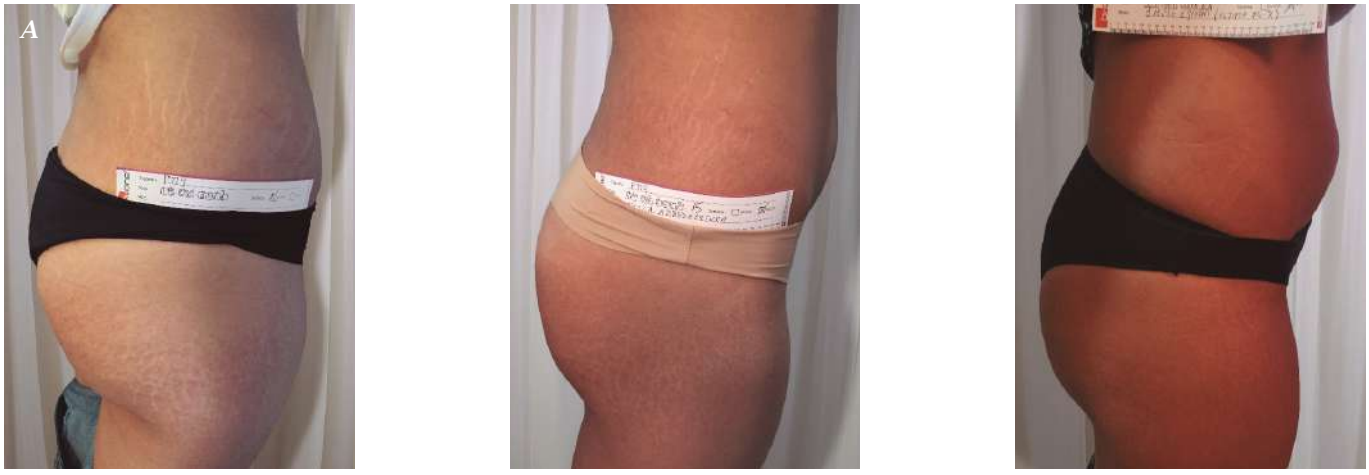


Figura 2 *- S.L., paziente di 43 anni con smagliature presenti da 20 anni. Foto scattate a T0 e T1 + 6 mesi. Le smagliature sono riempite e scurite allo stesso tempo, il tono della cute è migliorato. L'addome è più compatto e rassodato e l'ombelico risulta nuovamente aperto.*

Caso 3 dx



Caso 3 sx

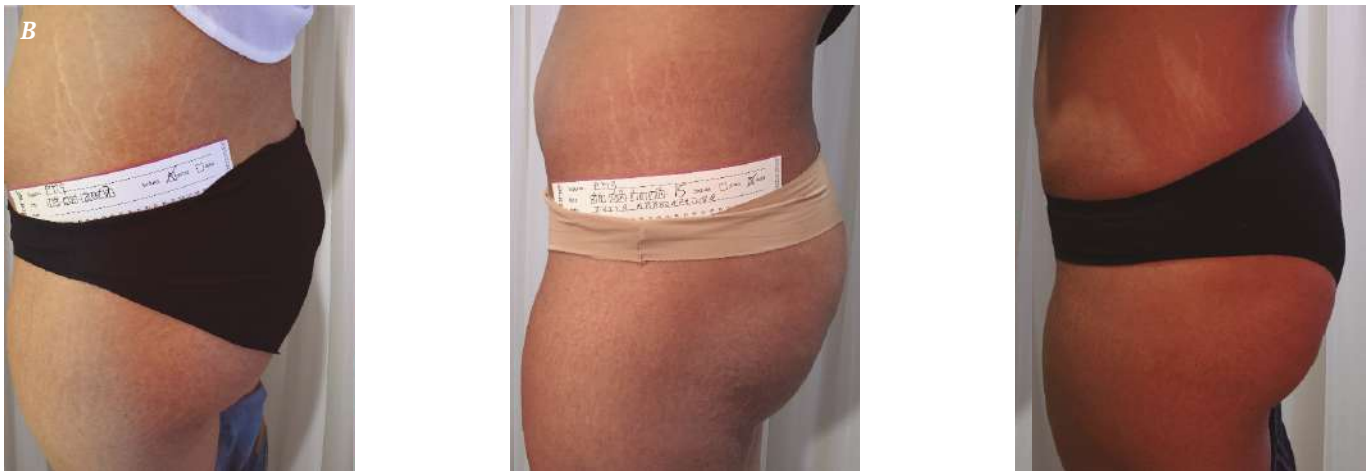


Figura 3 (A-B) *- P.G.M., paziente di 34 anni con smagliature presenti da 21 anni. Foto scattate a T0, T1 e T1 + 6 mesi. Nella paziente in questione abbiamo rilevato il riempimento delle smagliature già a partire dal T1, quando hanno iniziato a pigmentarsi per la limitata esposizione al sole. La foto scattata a T1 + 6 mesi evidenzia un'eccellente scurimento delle smagliature grazie alla conseguente esposizione al sole e il raggiungimento di una uniformità sostanziale con il tessuto circostante.*

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Photobiomodulation

Scar Remodeling with the Association of Monopolar Capacitive Radiofrequency, Electric Stimulation, and Negative Pressure

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Abstract

Objective: A study was established to objectively assess the effects of low-intensity electromagnetic and electric stimulation plus negative pressure on mature scars. ***Background:*** Radiofrequency plus negative pressure therapy demonstrated a favorable reorganization and regeneration of the collagen and elastic fibers and was proposed for the treatment of cellulitis and skin stretch marks. ***Methods:*** Twenty-six mature scars in 20 Caucasian patients (15 females and 5 males) were enrolled in the study. The treatments were carried out with a Class I, BF-type electromedical device equipped with a radiofrequency generator, an electric pulse generator, and a vacuum pump twice a week for 3 months. Corneometry, transepidermal water loss, elastometry, colorimetry, and three-dimensional skin surface pattern were objectively assessed with Multi Probe Adapter System MPA and PRIMOS pico. A subjective assessment was carried out with the VAS and PSAS scales. Each scar was compared before and after the treatment and with the skin in the corresponding healthy contralateral anatomical area at the same times. ***Results:*** Reduction of the scar surface wrinkling and overall scar flattening were demonstrated after the treatment. The scar slightly tended to approach the color and elasticity of healthy skin too. ***Conclusions:*** The combined local treatment of mature scars with low-intensity electromagnetic and electric stimulation in association with negative pressure might suggest a favorable synergic effect on the scar collagen and elastic fiber remodeling.

Keywords: scar, radiofrequency, negative pressure, electrical stimulation therapy

Introduction

Scar formation is the ultimate outcome of wound repair in humans that takes place as a cascade consisting of overlapping inflammatory, proliferative, and remodeling phases. When the process of wound healing is uneventful after completion of the remodeling phase, the scar enters the so-called mature state according to the scheme proposed by the International Advisory Panel on Scar Management.[1] Scar has no epidermal appendages and displays a collagen pattern of densely packed fibers. The tensile strength of wounded skin at best reaches only approximately that of unwounded skin.[2] In addition, scar is brittle and less elastic than normal skin, although the regeneration of elastic fibers in the scar is still debated.[3] In addition, scars are usually hypopigmented after full maturation even if they can become hyperpigmented in dark pigmented individuals or in lighter pigmented ones after exposure to UV radiation. In conclusion, the scar itself does not reproduce the features of normal skin, and therefore, it is still an unsolved functional and cosmetic issue despite the large number of treatment proposals: surgery, silicone gel sheeting, injected corticosteroids,

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pressure therapy, radiotherapy, laser therapy, cryotherapy, adhesive microporous hypoallergenic paper tape, and a number of miscellaneous therapies based on an anecdotal basis.[1]

A large number of literature reports demonstrate the effectiveness of radiofrequencies on favorable collagen remodeling through both immediate ultrastructural changes in the fibrils architecture and subsequent induced regeneration of new collagen and elastic fiber network.[4,5] Therefore, radiofrequencies have been supposed to have favorable effects on scar remodeling, although such a correlation is actually controversial as suggested by a large number of literature reports that failed to prove any sound evidence.[6,7]

The association of radiofrequency, electric stimulation, and negative pressure has been reported effective for the treatment of cellulitis and skin stretch marks[8–11] through the reorganization and regeneration of the collagen and elastic fibers. On that basis, the authors established a study to objectively assess these combined effects on mature scars in a human sample.

Materials and Methods

A prospective controlled open clinical pilot trial was carried at the Advanced Technologies for Regenerative Medicine and Inductive Surgery Research Centre, University of Pavia, Pavia, Italy, in cooperation with the Plastic Surgery Unit, Department of Clinical Surgical, Diagnostic, and Pediatric Sciences and the Department of Drug Sciences of the University of Pavia, Italy.

The study was approved by the University of Pavia Ethical Committee on September the 19th, 2013.

The inclusion criteria were as follows: ages between 18 and 65 years and body mass index between 15 and 35. Exclusion criteria were as follows:

- Pacemaker implant
- Current or past 5 years history of chemotherapy
- Local sensation disturbances
- Epilepsy
- Local skin inflammation
- Local vascular diseases (thrombosis, thrombophlebitis, varicose veins)
- Difficult to heal wounds
- Anticoagulation therapy
- Severe renal failure
- Current or past 5 years history of anorexia or bulimia
- Current pregnancy or breastfeeding
- Patients with very poor skin compactness and elasticity requiring surgical treatment (mastopexy, abdominoplasty, brachioplasty, and so on)
- Thyroid diseases
- Adrenal diseases
- Current or recent past history of oral contraception
- Adult acne
- Recent development of hypertrichosis
- Menstrual cycle alterations
- History of frequent and massive body weight changes
- Current hypocaloric diet
- Past 6 months history of hormone regulating therapy
- Current pharmacological treatments of any type
- Use of any topical scar treatment within 3 months before the enrollment.

According to the former criteria, a homogeneous sample of 19 consecutive Caucasian patients (14 females and 5 males, 12 subjects Fitzpatrick photo-type 2 and 7 subjects Fitzpatrick photo-type 3) with an overall of 25 mature scars was enrolled in the study. Mean age was 31 years (minimum 21, maximum 58, median 24). The trial was carried out over a period of 17 months, from October 2013 to February 2015.

The scar was considered the experimental unit of the study, irrespective of the number of scars per patient. Multiple scars per patient were calculated as a single measurement value corresponding to the mean value of multiple measures. All of the scars had a history longer than 1 year (range 1–23, mean 8, median 7) and were considered mature and not hypertrophic according to the International Advisory Panel on Scar Management.[1] Twenty scars were the outcome of a primary intention wound healing process and 6 followed a secondary intention wound healing (Table 1).

The equipment

The treatments were carried out with a Class I, BF-type electromedical device patented for noninvasive cosmetic applications called BiOne® (Expo Italia Srl, Firenze, Italy).

It is equipped with a radiofrequency generator, an electric pulse generator, and a vacuum pump.

The radiofrequency generator emits a shielded capacitive variable radiofrequency signal (frequency range 0.5–1 MHz ±10%, maximum power 6 W at 500 Ohm, temperature output range 39°C–40°C). A biofeedback system allows for an automatic output frequency adjustment according to the individual patient's skin biological features.

The electric pulse generator emits a 5 Hz square wave with adjustable output up to 0.36 mA at 500 Ohm.

The two generators are mechanically, galvanically, and optically isolated.

The vacuum pump provides an adjustable negative pressure up to max 0.35 atm.

The device is provided with a number of probes interacting with the human body (Fig. 1).

- The peeling probe is a resin bodied handle with a polyvinyl chloride (PVC) head covered with single use abrasive disks (diameter 150 mm, grain S1000) connected to the vacuum pump providing a negative pressure up to max 0.35 atm.
- The stimulating probe, connected to the electric pulse generator, are polyvinyl nitrate bodied handles, provided with an Anticorodal (Aluminum alloy) 110 plate supporting a set of AISI 316 (austenitic stainless steel alloy) spheres (14 spheres for the large probe and 4 spheres for the small one).
- The active probe is a resin-bodied handle provided with a white PVC disk connected to the same vacuum pump as the peeling probe, centered by a red epoxy glass core connected to the radiofrequency generator. Both the electric square wave and the radiofrequency are returned back to their generators through a neutral electrode, consisting in an Aluminum cylinder, held in the palm of the patient's hand.

The procedure

Each treatment takes place in four steps.

Table 1. The Scars Sample

Scar	*Wound healing*	*Aethiology*	*Site*	*Size (mm)*
1	Primary	Abdominoplasty	Lower abdomen	200×15
2	Primary	Abdominoplasty	Lower abdomen	260×10
3	Primary	Appendicectomy	Right iliac fossa	26×6
4	Primary	Appendicectomy	Right iliac fossa	70×20
5	Primary	Appendicectomy	Right iliac fossa	40×10
6	Primary	Arthroplasty	Left knee	100×10
7	Primary	Fracture ORIF	Left elbow	150×10
8	Primary	Fracture ORIF	Left arm	210×15
9	Primary	Fracture ORIF	Right arm	140×10
10	Primary	Mole excision	Back	31×12
11	Primary	Mole excision	Right upper abdomen	25×10
12	Primary	Mole excision	Right arm	110×15
13	Primary	Hysterectomy	Lower abdomen	160×3
14	Primary	Trauma	Left knee	13×4
15	Primary	Trauma	Left iliac fossa	75×20
16	Primary	Cardiac surgery	Sternum	185×5
17	Primary	Arthroplasty	Left knee	35×9
18	Primary	Male genital surgery	Left iliac fossa	50×5
19	Primary	Vascular malformation excision	Left thigh	240×10
20	Secondary	Trauma	Left scapula	120×20
21	Secondary	Trauma	Left knee	40×8
22	Secondary	Burn	Left neck	60×60
23	Secondary	Burn	Left leg	80×80
24	Secondary	Burn	Left neck	86×50
25	Secondary	Trauma	Left arm	30×30

ORIF, open reduction and internal fixation.

First step: a soft peeling with the peeling probe is performed with a mechanical gommage implemented by the negative pressure; it lasts a few minutes, until the skin surface turns light red.

Second step: electric stimulation with the stimulating probes; it lasts from 2 to 6 min; the intensity of the square wave is regulated by the operator according to the patient's sensory threshold.

Third step: activation with the active probes; it lasts 10 min starting with the vacuum pump and then switching to the radiofrequency generator as a slight skin erythema shows.

Fourth step: stimulation of the lymphatic drainage by moving the active probe switched on radiofrequency mode along the course of the lymphatic vessels.

To enhance the thermal and electrical contact between the treatment tip and the skin, in the second, third, and fourth steps, a water gel containing Hyaluronic acid and plant extracts acting as a conductive medium is applied on the skin surface.[12,13]

Assessments

The objective assessments were carried out at the Laboratory of Pharmaceutical Chemistry of the Department of Drug Sciences at the University of Pavia, Italy, using two instrumental devices:

1. Multi Probe Adapter System MPA (Courage and Khazaka, Koln, Germany) equipped with Cutometer MPA 580, Corneometer CM825, Tewameter TM300, Mexameter MX18, and Colorimeter CL 400 allows assessment of skin corneometry, transepidermal water loss (TEWL), elastometry, and colorimetry.
2. PRIMOS pico (GFMesstechnik; GmbH, Teltow, Germany) allows a three-dimensional (3D) skin scan.

These diagnostic techniques already proved their effectiveness in the objective anatomical functional assessment of the skin in several previous reports in the literature.[14–19]

All of the devices are CE certified and passed the safety tests before use.

The anatomical functional parameters under study in our sample of scars were corneometry, TEWL, elastometry, colorimetry, and 3D skin surface pattern.

As the sample included scars with different size, the smallest was considered as the unit of measurement and the assessments were carried out in the midpoint of this unit. The larger sized scars were approximately divided in segments corresponding to the unit of measurement, and the

FIG. 1. The device probes interacting with the human body: **(A)** the peeling probe connected to the vacuum pump; **(B)** the stimulating plates; and **(C)** the active probe.

arithmetical average from all the units' values was assumed as the value for the whole scar.

Corneometry. As skin is a dielectric medium, all variations in hydration correspond to changes in the skin capacity. The hydration of the stratum corneum was assessed with a 49 mm^2 surface probe allowing precise measurement in 1 sec within a 10–20 μm depth range.

TEWL. TEWL was assessed in terms of $gr/m^2/h$ by a skin evaporimeter made of a small cylindrical open chamber (1 cm in diameter, 2 cm in height) with a couple of hygrometric sensors connecting to a microprocessor plugged into a computer workstation. The device allows recording of the TEWL (ranging from 0 to 90 $g/m^2/h$), the relative humidity (ranging from 0% to 100%), and the probe temperature.

Elastometry. The cutaneous elasticity was assessed through a Cutometer measuring the vertical deformation of the skin induced by vacuum aspiration. A negative pressure of 450 mbar was applied on the skin for a time of 1–3 sec through a 2 mm diameter probe. Each aspiration is followed by a release time, allowing the skin to return to its resting condition. The probe is provided with an optic sensor assessing variation of light transmission due to the aspirated skin bulking inside the probe.

The following parameters have been considered reliable indicators of the skin elasticity:

- Skin compactness (R0): the passive skin behavior following application of negative pressure
- Skin resistance (R2): the resistance against the return to the rest conditions at the end of suction
- Net skin elasticity (R5): the ratio between the maximum skin extension and the residual skin deformity.
- The parameters were expressed on an arbitrary score scale.

Colorimetry. Skin colorimetry was measured using two methods: Mexameter and Colorimeter.

In the Mexameter method, a 5 mm diameter probe emits light at three different wavelengths (568, 660, and 870 nm). An optic sensor measures such a light after reflection on the skin. The device measures the emitted light absorption rate by both the melanin and hemoglobin, providing an arbitrary melanin index (MI) and an arbitrary hemoglobin index, respectively, range 0–999.

In the Colorimeter method, an 8 mm diameter probe emits white LED light. An optic sensor measures the light after reflection on the skin using an arbitrary score scale for the following parameters:

- Luminosity (L): range 0 (black)–100 (white)
- Green and red (A): tolerance −120/+120
- Blue and yellow (B): tolerance −120/+120

The skin color is calculated using the formula: $L \times A \times B = ITA$

3D skin scan. The PRIMOS (Phaseshift Rapid *In vivo* Measurement of the Skin) system provides high-resolution assessment of skin surfaces by using phase-shifted light stripes projected by micromirrors to generate a 3D profile (area 18×13 mm). The reflected light is captured by a high-resolution camera, and a software package converts the image into a color-coded picture, with different colors for different heights. Skin reliefs and hollows are measured as follows:

- Maximum absolute height in μm of the skin profile calculated from the maximum depth of the skin hollows to the top of the skin reliefs
- Mean furrows depth (μm)
- Mean depth of the deepest furrow (μm)
- Maximum depth of the deepest furrow (μm)
- Furrow count
- Furrow overall volume (mm^3)
- Overall furrow surface (mm^2)
- Furrow surface ratio: percentage of the skin area with furrows versus the area without furrows
- Furrow overall length (mm): length sum of all furrows.

The 3D synthetic assessment of the skin surface was expressed by the function integral of the skin surface profile (Ra) and by the difference between the highest skin surface spot and the deepest skin furrow in μm (Rmax).

The subjective assessments were carried out using the VAS and PSAS scales.

Two separate VAS Scales (score range: 1–10) assessing the overall subjective perception of the scar were blindly submitted both to the patients and to a single dedicated medical researcher. The patients were also given a PSAS Scale (score range: 1–10) assessing the scar-related pain, color, stiffness, and thickness.

Trial planning

A complete treatment cycle had a duration of 3 months. Each patient enrolled in the study underwent a preliminary consultation (t_0) for the pretreatment baseline assessments. Then, 24 sequential treatment sessions with a 2 weekly schedule followed (t_1–t_{24}). Each treatment lasted 30 min. The effects of the sequential treatments were assessed at the time of the final consultation (t_{25}), 3–13 (median 5) days after the last application.

A formal informed written consent for both the procedure and medical photography was obtained from all of the patients, and the study conformed to the Declaration of Helsinki.

The patients filled the VAS and PSAS questionnaires at the time of enrollment (t_0), after 2 months of treatment (t_{16}), and at the end of the treatment (t_{25}).

The scars were assessed at the beginning and at the end of the study (t_0 and t_{25}), and a comparison was carried out between the measurements at these times. Patients were advised to not apply any topical moisturizing ointments 24 h before the measurements.

In addition, each scar was compared with the skin in the corresponding healthy contralateral anatomical area at the same times, to exclude all of the changes in the scars that might not be related to the treatment, thus providing an intrapatient control.

All of the collected data were gathered into a patient's comprehensive individual chart.

Statistical methods

Individual-level measurements were calculated as the mean value of multiple measures for each individual patient (if >1 measurement was available) or by a single measurement otherwise. Quantitative variables distribution is described by median [25^{th}, 75^{th} percentiles or interquartile range (IQR)]. The presence of statistically significant variations in terms of quantitative variables distribution between repeated measurements was performed by the *t*-test for paired samples or by the Wilcoxon test for paired samples when variables deviated from the normal distribution (Shapiro–Wilk test p value <0.05). The presence of statistically significant differences in terms of quantitative variables distribution between scar and the contralateral corresponding healthy skin was assessed by the *t*-test for unpaired samples or by the Wilcoxon rank-sum test for unpaired samples when variables deviated from the normal distribution (Shapiro–Wilk test p value <0.05). The correlation between individual-level variations observed by comparing before (t_0) versus after the treatment (t_{25}) measurements and age at scar was evaluated by the Pearson or Spearman correlation tests as appropriate. The presence of statistically significant differences in terms of individual-level variations observed by comparing before (t_0) versus after the treatment (t_{25}) measurements among aethiology classes was assessed by the one-way ANOVA test or by the Kruskal–Wallis test as appropriate. p values <0.05 were considered statistically significant. All statistical tests were performed by the R statistical software version 3.2.2 (www.r-project.org).

Results

The results from the objective instrumental assessments are summarized in Table 2 and Fig. 2 (*a* to *m*).

Corneometry

The *t*-test for paired samples failed to demonstrate any statistically significant difference in the scars before (t_0) and after the treatment (t_{25}).

Transepidermal water loss

The *t*-test for paired samples failed to demonstrate any statistically significant difference in the scars before (t_0) and after the treatment (t_{25}). The healthy contralateral skin displayed no changes at the same times.

Elastometry

R0. The *t*-test for paired samples failed to demonstrate any statistically significant difference in the scars before (t_0) and after the treatment (t_{25}).

A statistically significant difference was appreciated in the healthy contralateral skin at the same times ($p=0.0076$).

The scars showed a statistically significant lower R0 index versus the healthy contralateral skin before the treatment (t_0), while no difference was appreciated at the end of the treatment ($p=0.0228$).

R2. The Wilcoxon test for paired samples failed to demonstrate any statistically significant difference in the scars before (t_0) and after the treatment (t_{25}).

R5. The *t*-test for paired samples failed to demonstrate any statistically significant difference both in the scars and in the healthy contralateral skin before (t_0) and after the treatment (t_{25}). A statistically significant difference was demonstrated between the scar and the healthy contralateral skin before the treatment ($p=0.0042$); such a difference persisted after the treatment, although with a lesser degree ($p=0.0116$).

Colorimetry

Mexameter method

Melanin. A statistically significant reduction in the MI was appreciated in the scars after the treatment ($p=0.0063$) and in the healthy contralateral skin at the same time ($p=0.0006$). No statistically significant difference was appreciated in the scars versus the healthy contralateral skin both before and after the treatment.

Erythema. The *t*-test for paired samples failed to demonstrate any statistically significant difference both in the scars and the healthy contralateral skin before (t_0) and after the treatment (t_{25}).

Colorimeter method

L: the *t*-test for paired samples failed to demonstrate any statistically significant difference in the scars before (t_0) and after the treatment (t_{25}), while a statistically significant increase in the L index was appreciated in the healthy contralateral skin after the treatment (t_{25}; $p=0.0197$).

A: the *t*-test for paired samples failed to demonstrate any statistically significant difference in the scars before (t_0) and after the treatment (t_{25}), although a trend was appreciated in the A index that approached the healthy contralateral skin, displaying a drift toward the green section of the light spectrum. No changes were appreciated in the healthy contralateral skin before (t_0) and after the treatment (t_{25}).

B: the *t*-test for paired samples failed to demonstrate any statistically significant difference in the scars before (t_0) and after the treatment (t_{25}), although a trend was appreciated in the B index that approached the healthy contralateral skin as demonstrated by the loss of statistically significant difference between the scars and the healthy contralateral skin after the treatment with a drift toward the blue section of the light spectrum. A statistically significant difference was appreciated in the healthy contralateral skin before (t_0) and after the treatment (t_{25}), displaying a drift toward the blue section of the light spectrum too ($p=0.0427$).

ITA: the *t*-test for paired samples failed to demonstrate any statistically significant difference in the scars before (t_0) and after the treatment (t_{25}). A statistically significant difference was appreciated in the healthy contralateral skin at the same times ($p=0.0045$).

3D skin scan

Ra. A statistically significant difference ($p=0.0002$) was appreciated in the scars before (t_0) and after the treatment (t_{25}), with a lower Ra index after the treatment. No changes were appreciated in the healthy contralateral skin.

Rmax. A statistically significant difference ($p=0.0002$) was appreciated in the scars before (t_0) and after the

TABLE 2. VARIABLES DISTRIBUTION AT T_0 AND T_{25} AND CORRESPONDING COMPARISONS

Variable	*St_0 Median (IQR)*	*St_{25} Median (IQR)*	*$HCSt_0$ Median (IQR)*	*$HCSt_{25}$ Median (IQR)*	*St_0 vs. St_{25}* p	*$HCSt_0$ vs. $HCSt_{25}$* p	*St_0 vs. $HCSt_0$* p	*St_{25} vs. $HCSt_{25}$* p
Corneometry	36.09 (30.03, 43.11)	34.67 (32.2, 42.77)	40.73 (32.2, 57.72)	39.91 (37.59, 46.63)	0.8640	0.4582	0.1737	0.1882
TEWL	6.85 (4.78, 8.75)	8.9 (5.5, 11.6)	8.35 (4.77, 11.22)	6.85 (4.25, 12.1)	0.4932	0.2702	0.3792	0.6849
Melanin	188.46 (140, 223.25)	146.83 (128, 191.08)	163.29 (135.09, 218.17)	144 (112.54, 185.66)	0.0063*	0.0006†	0.7694	0.3569
Erythema	299.84 (263.84, 357.55)	291.5 (255.41, 325.5)	250.83 (170.92, 317.08)	241.84 (199.29, 296.17)	0.3803	0.7084	0.0892	0.0941
L	65.48 (63.19, 68.51)	66.62 (63.25, 68.5)	66.25 (59.75, 68.83)	66.98 (64.01, 69.37)	0.9134	0.0197*	0.7075	0.6588
A	12.84 (10.88, 13.74)	12.28 (11.28, 12.98)	11.26 (9.9, 13.44)	10.96 (9.91, 12.04)	0.6813	0.3378	0.4238	0.0787
B	12.03 (10.61, 13.16)	11.95 (10.49, 13.5)	13.73 (12.09, 15.38)	12.44 (10.98, 13.55)	0.5289	0.0427*	0.0223*	0.3483
ITA	53.16 (43.83, 58.42)	52.67 (48.5, 57.71)	50.34 (36.42, 55.75)	52.84 (45.17, 58.5)	0.8590	0.0045**	0.2187	0.9892
Ra	21.75 (19, 24.38)	19.25 (17.75, 22.75)	20.5 (19, 22.75)	20 (19, 23.25)	0.0002†	0.3075	0.7449	0.3356
Rmax	153.25 (123.75, 175)	139 (120.88, 157.5)	133 (121.25, 161.25)	141.5 (126.75, 155.75)	0.0002†	0.8959	0.5338	0.5323
R0	0.12 (0.08, 0.2)	0.12 (0.06, 0.19)	0.20 (0.13, 0.27)	0.12 (0.08, 0.24)	0.3424	0.0076*	0.0228*	0.2447
R2	0.75 (0.68, 0.84)	0.83 (0.62, 0.86)	0.79 (0.73, 0.83)	0.80 (0.71, 0.83)	0.4222	0.2984	0.1969	0.4488
R5	0.47 (0.4, 0.55)	0.51 (0.32, 0.57)	0.66 (0.56, 0.76)	0.63 (0.57, 0.69)	0.8698	0.3225	0.0042*	0.0116*

Comparisons between time points (i.e., St_0 vs. St_{25} and $HCSt_0$ vs. $HCSt_{25}$) were performed by the Student's *t*-test for paired samples or by the Wilcoxon test for paired samples; comparisons between treatments at the same time point were performed by the Student's *t*-test for unpaired samples or by the Wilcoxon rank-sum test for unpaired samples (i.e., St_0 vs. $HCSt_0$ and St_{25} vs. $HCSt_{25}$).

St_0 = median (25^{th}, 75^{th} percentiles, IQR) of each variable's distribution in scars at t_0.

St_{25} = median (25^{th}, 75^{th} percentiles, IQR) of each variable's distribution in scars at t_{25}.

$HCSt_0$ = median (25^{th}, 75^{th} percentiles, IQR) of each variable's distribution in healthy contralateral skin sites at t_0.

$HCSt_{25}$ = median (25^{th}, 75^{th} percentiles, IQR) of each variable's distribution in healthy contralateral skin sites at t_{25}.

St_0 versus St_{25} = *p* value deriving from the comparison of each variable's distribution between t_0 and t_{25} measurements in scars.

$HCSt_0$ versus $HCSt_{25}$ = *p* value deriving from the comparison of each variable's distribution between t_0 and t_{25} measurements in healthy contralateral skin sites.

St_0 versus $HCSt_0$ = *p* value deriving from the comparison of each variable's distribution between measurements in scars and healthy contralateral skin sites at t_0.

St_{25} versus $HCSt_{25}$ = *p* value deriving from the comparison of each variable's distribution between measurements in scars and healthy contralateral skin sites at t_{25}.

Variable = analyzed variable.

HCS, healthy contralateral skin sites; IQR, interquartile range; S, scars; TEWL, transepidermal water loss.

* *p* Value <0.05.

† *p* Value <0.004 based on the Bonferroni correction for multiple testing.

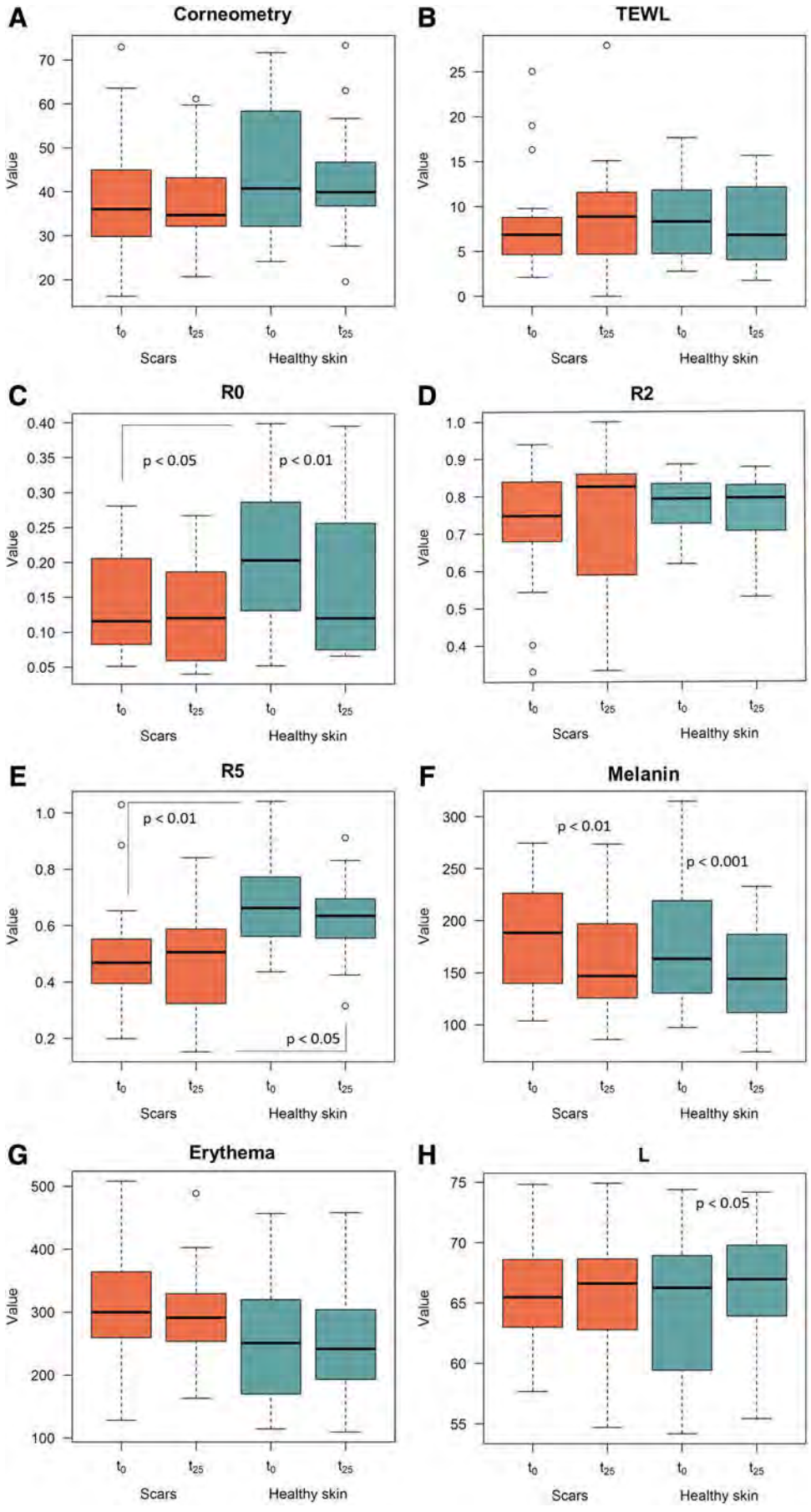

FIG. 2. The parameters distribution: **(A)** Corneometry; **(B)** TEWL; **(C)** R0; **(D)** R2; **(E)** R5; **(F)** Melanin; **(G)** Erythema; **(H)** L; **(I)** A; **(J)** B; **(K)** ITA; **(L)** Ra; and **(M)** Rmax. Each boxplot graphically represents (from bottom to top) the lower nonoutliers limit, the 25th percentile, the 50th percentile (median value), the 75th percentile, and the upper nonoutliers limit of each parameter's distribution at t_0 and t_{25} for scars and healthy skin, respectively. Each dot represents an outlier measurement with respect to the corresponding distribution. TEWL, transepidermal water loss.

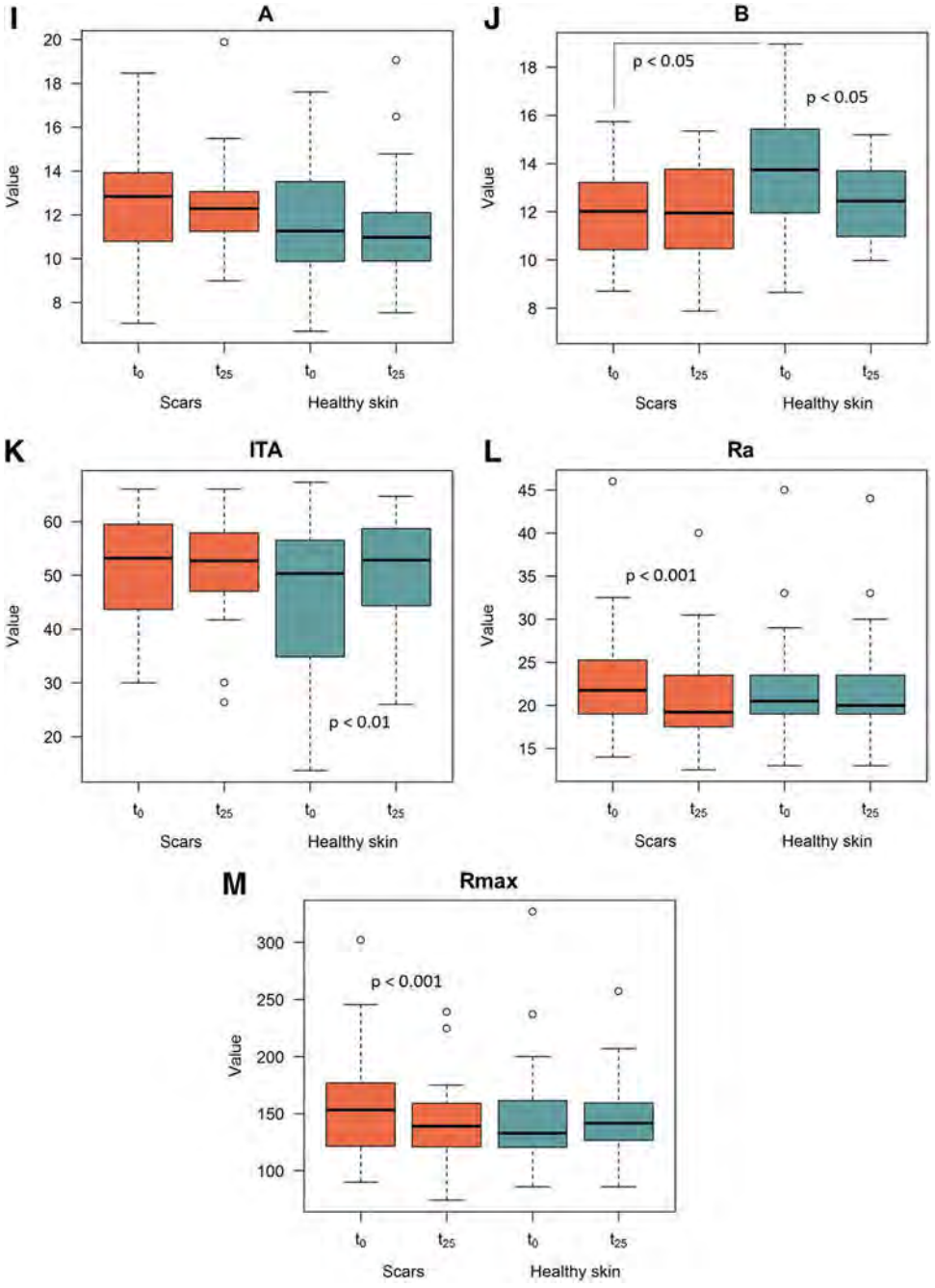

FIG. 2. *Continued.*

treatment (t_{25}) with the scar tending to approach the wrinkling of the normal skin. No changes were appreciated in the healthy contralateral skin.

Impact of confounding factors

The impact of potential confounders on the statistically significant variations identified was also tested. The individual-level variations observed by comparing before (t_0) versus after the treatment (t_{25}) measurements showed evidence of weak correlation with scar age ($r^2 < 0.05$) and did not vary significantly among aethiology classes ($p > 0.05$). These observations suggest that the identified variations were not influenced by the effect of confounding factors.

VAS and PSAS questionnaires

The results from the subjective assessments are summarized in Table 3.

The VAS and PSAS questionnaires demonstrated a statistically significant improvement in all of the items in the pretreatment (t_0) versus the post-treatment time (t_{25}). A similar statistically significant improvement was also appreciated in the pretreatment versus midtreatment time (t_{16}).

Discussion

Our results demonstrated an overall fair improvement in the scar connective tissue after the combined sequential local treatment with low-intensity electromagnetic and

Table 3. Variables Distribution of VAS and PSAS Questionnaires at Different Time Points and Corresponding Variations

Variable	t_0 Median (IQR)	t_{16} Median (IQR)	t_{25} Median (IQR)	$\Delta\ (t_{16}-t_0)$ Median (IQR)	p	$\Delta\ (t_{25}-t_{16})$ Median (IQR)	p	$\Delta\ (t_{25}-t_0)$ Median (IQR)	p
VAS researcher	6 (5, 8)	4 (3, 6)	3 (2, 4)	−2 (−2, −1.5)	0.0002*	−1 (−1.62, −0.88)	0.0007*	−3 (−3.62, −2)	2.52×10^{-09}*
VAS patient	7.25 (6, 8)	5 (2.38, 6.25)	3 (1.75, 5)	−2 (−3.25, −1.5)	2.52×10^{-06}*	−1 (−2, −0.5)	6.06×10^{-05}*	−3.5 (−5, −2.5)	3.18×10^{-08}*
PSAS	20 (16.75, 23.25)	11.5 (7, 14)	9.5 (6.5, 12.25)	−7.5 (−10.25, −6)	9.45×10^{-08}*	−2 (−4, −1.5)	2.31×10^{-05}*	−11 (−13, −6.75)	2.12×10^{-10}*

Median (IQR) = median value (25^{th}, 75^{th} percentiles) of each variable's distribution;
p value = p value from the Student's t-test for paired samples [variables following the normal distribution (Shapiro test $p \geq 0.05$)] or from the Wilcoxon Signed Rank test for paired samples [variables deviating from the normal distribution (Shapiro test $p < 0.05$)], comparing variables values between different time points.
IQR, interquartile range.
*$p < 0.05$.

electric stimulation in association with negative pressure (Figs. 3 and 4) as demonstrated by the changes in the following objectively assessed anatomical functional parameters: net skin elasticity (R5) expressed as the ratio between the maximum skin extension and the residual skin deformity, blue and yellow light reflection (B), skin surface profile (Ra), and the difference between the highest skin surface spot and the deepest skin furrow (Rmax).

The final assessment was carried out shortly after the last application. Such a schedule was considered the best compromise to meet both the patients' compliance and the onset of biological effects induced by the sequential treatments, as the ultrastructural changes in the collagen fibril architecture are demonstrated to occur shortly after the radiofrequency application.[5,20] The patients were advised to contact the research staff in case of unfavorable mid and long-term scar evolution after the treatments, but no complaints were referred.

Although some degree of elastic fiber network regeneration has been reported in mature scars, the latter are demonstrated to be still remarkably stiffer than the normal skin.[3]

Skin compactness (R0) did not demonstrate any change in the scars after the treatment, although the healthy contralateral skin underwent a decrease in such an index at the same time, likely due to a seasonal change, not influent on the scar tissue. No changes were appreciated in skin resistance (R2), both in the scar and in the contralateral healthy skin. However, the lesser significance in the difference of net skin elasticity (R5) between the scars and the contralateral healthy skin at the end of the treatment might suggest a slight improvement of the overall scar elasticity.

Elastic fiber regeneration has been reported following radiofrequency treatments[21] with evidence of a juvenile reticular pattern.[22] Therefore, our results are likely to be related to the radiofrequency sequential applications.

In our sample, the significant similar decrease of the MI in the scars and in the healthy contralateral skin is likely to be related to seasonal regression of skin tanning.

Skin owes its color to four pigments:[23] oxyhemoglobin, reduced hemoglobin, melanin, and carotene. Blue color is an optical effect due to a Tyndall phenomenon as light reflected

FIG. 3. Mature scar in the right iliac fossa. Pretreatment view.

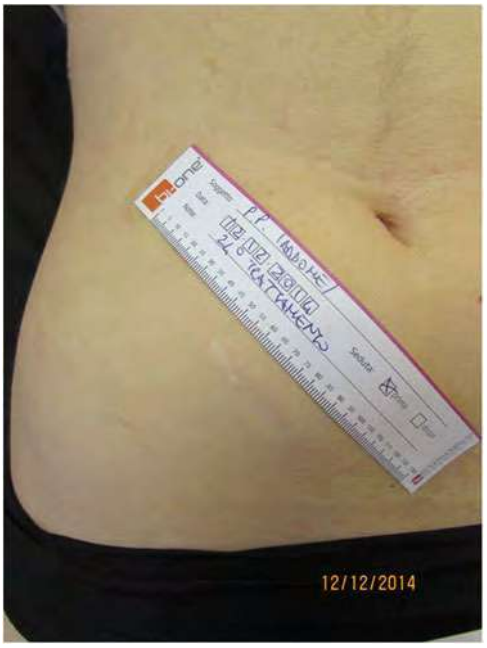

FIG. 4. Post-treatment view with overall scar improvement.

in vivo from the melanin, according to an exponential dependence on wavelength,[24] is scattered by the turbid medium of the basal epidermis.

Evidence has been produced to suggest that the overlying epithelium contributes nothing to the blue colors, and it has been proposed that the brown pigment in the corium appears blue because of subtractive mixing of colors.[25] Collagen reflects blue by withdrawal of longer wavelengths of light spectrum.[25–27]

In our sample, the colorimetry displayed some interesting outcomes in the scars after the treatment.

The B-index showed an interesting trend, although no statistically significant difference was appreciated in the scars after the treatment; their B-index tended to approach that of the normal skin at the end of the applications, thus

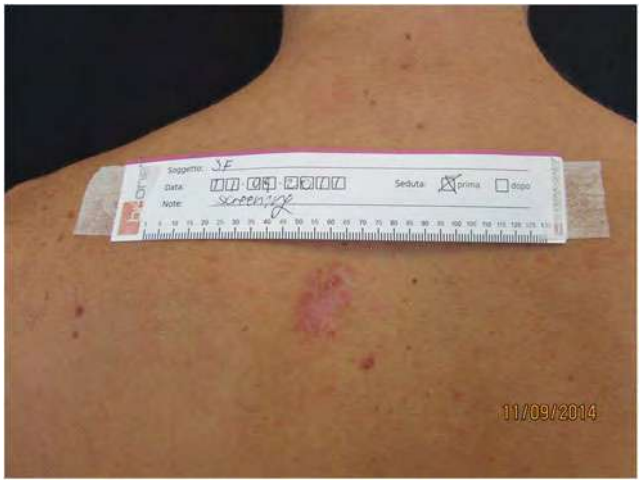

FIG. 5. Mature scar in the dorsum. Pretreatment view.

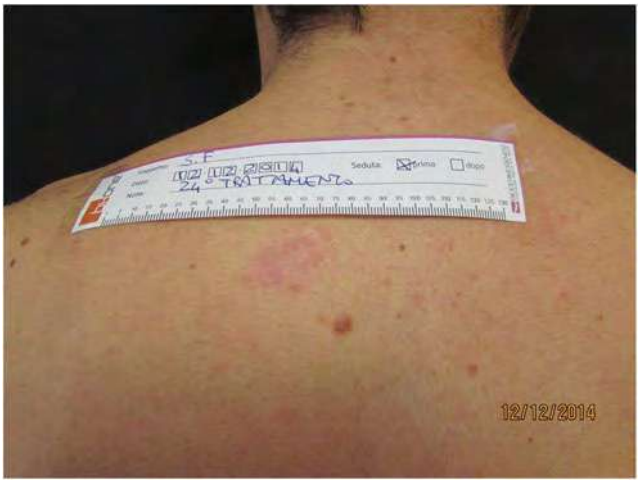

FIG. 6. Post-treatment view with improved scar thickness and color.

suggesting that the scars tended to drift toward the blue section of the light spectrum and to approach the color of healthy skin (Figs. 5 and 6).

The A-index in the scars displayed a drift toward the green section of the light spectrum after the treatment, thus approaching that of the healthy contralateral skin too.

The absence of any significant effect of the treatment on both melanin and erythema indexes suggests that the drift toward the cold section of the light spectrum might be related to collagen fiber rearrangement.

The 3D synthetic assessment of the skin surface, expressed by the Ra and Rmax indexes, demonstrated that the surface wrinkling was more represented in the scars versus the healthy contralateral skin before the treatment. A significant improvement with a lower Ra and Rmax indexes in the scars versus the healthy contralateral skin was demonstrated at the end of the treatment. The treatment, therefore, yielded both a reduction of the scar surface wrinkling and an overall scar flattening.

All of the latter changes observed in the assessed anatomical functional parameters are likely to be related to the alterations of the scar collagen structure induced by the treatment.

The favorable objective results consistently matched the outcomes from the VAS and PSAS questionnaires. Actually the VAS Scale demonstrated a significant overall improvement in the scar perception both in the patients and in the medical researcher; according to the PSAS Scale, the patients referred a significant reduction of scar-related pain, stiffness, thickness, and color after the treatment.

All of the modifications observed in the scars after the treatment are likely to be related to the peculiar action of radiofrequency, which allows selective heat transfer to the dermis and subcutaneous tissue, yielding a controlled collagen alteration. Several literature reports[5,22,28,29] demonstrated that radiofrequencies provide an immediate heat-induced rearrangement of native collagen fibers that are gently progressively denaturated and progressively metabolized by the macrophages and that a late fibroblastic response yields regeneration of the normal dermal collagen and elastic fiber network. These effects might, therefore,

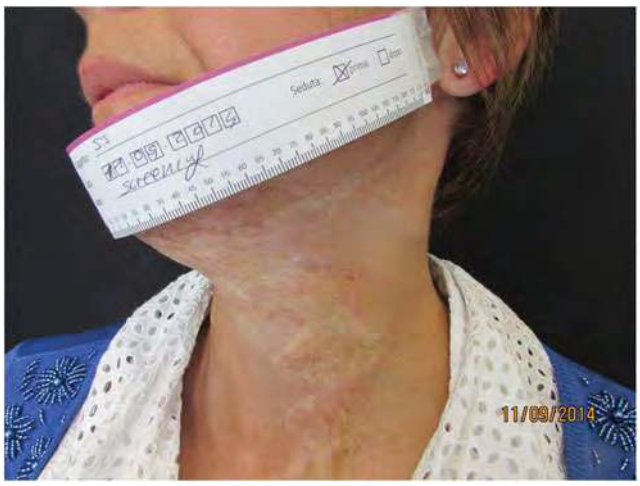

FIG. 7. Mature scar in the left side of the neck. Pretreatment view.

explain the reduction of the scar surface wrinkling, the overall scar flattening, the changes in the skin light absorption properties, and the favorable trend of slight net scar elasticity increase after the treatment in our sample (Figs. 7 and 8).

Actually, the radiofrequency-related changes in the connective tissue are not entirely explained by a simple temperature rise. It is demonstrated that collagen fibers begin to curve at 52°C–55°C,[30] contract at 65°C,[31] and the denaturation threshold falls between 60°C and 70°C.[32] As the maximum power output in our device provides a the temperature range of 39°C–40°C, the supposed changes of the collagen and elastic fibers might also be related to a spatial rearrangement in the absence of complete denaturation.[22]

The absence of any significant effect on corneometry, transepidermal water loss, and MI confirms that radiofrequencies within the therapeutic range power selectively act on the dermis and spare the epidermis.[22] Therefore, the procedure under study can be considered safe without side effects on epithelia and melanocytes.

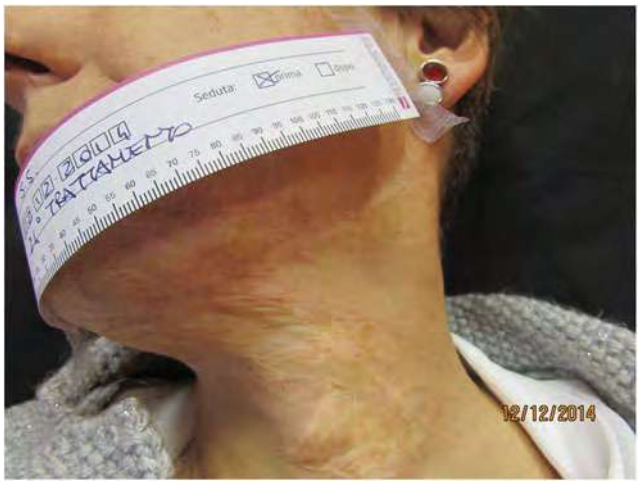

FIG. 8. Post-treatment view with scar elasticity improvement.

The applied negative pressure improves the radiofrequency effects mainly providing a dermal neoangiogenesis that, in turn, supports all of the regenerative processes.[33–35]

A further improvement of the effects of the combined application of radiofrequency and negative pressure is also related to the square wave electric pulses whose favorable effects on the cells' activity have been long demonstrated.

The favorable effects of monopolar capacitive radiofrequencies have been long investigated in the orthopedic pathology where they are widely used in therapy-related clinical practice for their thermal effects, mainly relieving pain and inflammation and improving tissue extensibility. Even if the most commonly used and researched are shortwave therapies, new electrophysical agents employing much lower frequencies have emerged, but, to date, they remain largely unexplored.[36–39]

Our experience, therefore, would bring new knowledge about the use of capacitive radiofrequency into new fields of clinical application.

The objective assessment of scars is a difficult matter as the recruitment of an actual homogeneous sample is hampered by the extreme variability of the individual response of the wound healing process, which is only partially related to the scar aethiology and clinical features.[40]

Recruiting a homogeneous sample of scars from patients with a high degree of personal compliance is even more difficult. Such pitfalls undoubtedly represent a limitation in this trial. Nevertheless, the results from this study might suggest further investigations in the field of the interactions between the physical energies and the living tissues and might contribute to increase the treatment options for scars.

Conclusions

The combined sequential local treatment of mature scars with low-intensity monopolar capacitive radiofrequency and electric stimulation in association with negative pressure objectively demonstrated an overall favorable synergic effect in the scar connective tissue.

Collagen fiber rearrangement likely yielded to a change in the color features with a drift toward the cold section of the light spectrum and to a reduction of the surface wrinkling with an overall flattening.

Net skin elasticity slightly improved too, likely following elastic fiber network remodeling.

These objective results matched the favorable outcomes from the subjective VAS and PSAS questionnaires.

No side effects on epithelia and melanocytes were appreciated, thus demonstrating a selective action of the treatment on the dermis without involving the epidermis.

Therefore, the favorable results observed in our study on mature scars might be related to a synergic effect of three different well-known physical energies currently used in clinical practice.

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Author Disclosure Statement

No competing financial interests exist.

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V-EMF treatment of facial scar: First results

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ABSTRACT

Aim of study: This is a retrospective study aimed at evaluating the effectiveness of the use of electromagnetic fields and negative pressure treatment (V-EMF) for facial scars, from an aesthetic and functional point of view, and considering the variations in the levels of hydration.
Material and methods: 25 subjects with facial scarring were re-evaluated after being treated with the V-EMF method. The hydration levels of the scars before and after treatment were compared. The results were evaluated considering the satisfaction levels of the patients with the VAS, and of the medical specialists who performed the treatment, and of 3 independent dermatologists with the Likert scale.
Results: Mean hydration levels of scars went from 41.8 to 53.3, with mean hydration levels of healthy reference points equal to 54.6. The minimum patient satisfaction level was 2 in the VAS. The minimum level of satisfaction of specialists and dermatologists was equal to IV on the Likert scale for all patients, except for 1 subject in which it was III for the specialist who had treated him. Anti-aging and re-pigmentation effects were also noted as secondary results.
Conclusions: From an aesthetic and functional point of view, and for the overall anti-aging effect of the treated area, V-EMF applied to facial scars has shown extremely promising results.

1. Introduction

In developed countries alone, about 100 million new wound cases resolve into visible scars each year. Of these scars, 55 million are outcomes of elective surgeries, 25 million are outcomes of emergency surgery to resolve trauma, and 20 million have different causes [1]. These numbers do not include a very large number of injuries, again resulting from traumatic events, that do not require surgery.

The impact of scars is not only physiological, but the more they are visible, the more they cause a sense of discomfort in the subjects, with consequent effects on social life, reduction of self-esteem and worsening of interpersonal relationships [2]. These effects are exacerbated when scars are found on the face. They can escalate into emotional blocks and anxiety [3–5].

Although the wounds are of different nature, they all involve, on a superficial level, the laceration of the epidermis, in particular of the stratum corneum, with consequent alteration of the functionality of the epithelial barrier. This functionality is restored only after the complete restructuring of the stratum corneum, with a timing of over a year from the traumatic event [6].

One of the main functions of the epidermis is to maintain the balance of skin homeostasis, which includes the prevention of excessive transepithelial water loss (TEWL) [7]. An increase in TEWL, which causes an alteration in skin hydration levels, also results in a delay in wound healing, and in the formation of hypertrophic forms of scars or other skin alterations [8,9]. The lesion of the stratum corneum alone can consequently induce an alteration of skin homeostasis, an increase in TEWL, and the subsequent alteration of keratinocytes [8].

The risk of a scar degeneration is particularly relevant on the face, which has one of the thinnest stratum corneum in the human body [10], and for this reason it is subject to a greater physiological TEWL.

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Abbreviations

TEWL = transepithelial water loss
V-EMF = vacuum and electromagnetic fields
VAS = visual analog scale

Table 1
Demographics.

Patient	Gender	Age	Cause of scar	Previous therapies
P01	F	28	Trauma	No
P02	F	32	Cut	No
P03	F	25	Trauma	No
P04	F	21	Cut	No
P05	M	35	Trauma	No
P06	M	56	Surgery	No
P07	M	61	Burn	No
P08	F	50	Cut	NAFL
P09	F	48	Trauma	No
P10	M	36	Trauma	No
P11	M	57	Trauma	No
P12	F	48	Burn	No
P13	F	51	Surgery	NAFL
P14	M	51	Burn	No
P15	F	25	Cut	No
P16	F	32	Trauma	Needling
P17	F	41	Trauma	No
P18	F	46	Cut	No
P19	M	37	Surgery	Carboxitherapy
P20	M	41	Surgery	No
P21	F	36	Trauma	No
P22	M	45	Trauma	Carboxitherapy
P23	F	32	Cut	No
P24	F	53	Cut	Needling
P25	M	55	Trauma	No

Abbreviations: F, female; M, male; NAFL, non-ablative fractional laser.

An effective restoration of the epithelial barrier, and the reduction of TEWL, with increased hydration of the stratum corneum, allow both the improvement of the scarring process and of the entire epidermal structure, with morphological restoration of the stratum corneum, increase in cell volume, and a regenerative action similar to an anti-aging effect [11].

The therapies currently used for the reduction of the visual effect of the scars and the functional restoration of the tissues involved in the wound do not always produce appreciable results, especially in the presence of hypertrophic scars and keloids [12–14]. New therapies based on the use of medical devices are gaining momentum, but verifying their effectiveness requires further studies [15–17].

In this study we want to evaluate the use of electromagnetic fields and negative pressure treatment (V-EMF) for facial scars, both from an aesthetic and functional point of view, paying particular attention to the changes in hydration induced in the tissues.

2. Material and methods

This is a retrospective study that analyzes data from a group of subjects undergoing V-EMF treatment for the resolution of facial scars. Written informed consent was collected to use the data, in full compliance with complete anonymity to ensure respect for privacy.

2.1. Subjects

The data from 25 subjects between the ages of 25 and 61, 10 males and 15 females, i.e. 25 scars on the face, of which 3 caused by burns, 4 post-surgical, 7 caused by cuts, and 11 caused by trauma, were re-evaluated. 18 scars had never undergone any treatment, while 7 had undergone minimizing treatments, with no effect. Further personal and etiological data are shown in Table 1.

Patients were selected for treatment based on the following inclusion criteria: healthy (specifically, non-epileptic) subjects with fully healed facial wounds.

The criteria for exclusion from treatment were: presence of pacemakers, presence of acute inflammatory conditions of the skin, subject to oncological pathologies in the previous 5 years, with problems of anemia and bulimia in the previous 2 years.

2.2. Treatment

All subjects were appropriately informed about all the procedures implemented, and signed a written informed consent. The treatments were conducted in private clinics in Italy, in full compliance with ethical principles. All procedures and subsequent evaluations were conducted in accordance with the Declaration of Helsinki, as revised in 1983.

Before each session, the patients' skin was cleaned with a neutral non-alcoholic cleanser.

The V-EMF technique, already used for stretch marks [18,19], was adapted for application on scars. The treatments were delivered according to the Biodermogenesi® method, using the Bi-one® LifeTouchTherapy device (Expo Italia Srl, Florence, Italy). The subjects underwent a cycle of 4–8 sessions, lasting 6–20 min each (depending on the size of the scar), with a frequency of 1–2 sessions per week, based on the clinical evaluation of the scar.

The vacuum was delivered in the range of 100–130 mbar, in order to induce a dilation of the epidermal tissue equal to 1 mm, according to the principle of mechano-transduction [20,21], for the conversion of mechanical stimuli into biochemical signals, aimed at increasing the cellular metabolism [22,23]. In a vacuum regime on the face, this increase also induces an anti-aging action [24,25].

During the vacuum state, an electromagnetic field was applied to promote cell and molecular proliferation [26]. The magnetic field was generated by means of a capacitive system with a capacitor composed of a 1st type armature, covered with electrical insulating material, and a 2nd type armature, consisting of a return electrode and the tissues themselves. The application of the magnetic field induces a migration of ionic charges (principally, Na+, K+) towards the opposite poles of the generator, and, due to the Joule effect, a localized temperature increase, not higher than 1–2 °C with respect to the basal body temperature [27]. It is known that the crossing of the ions of the membranes of fibroblasts and dermal cells favours the absorption by the cells of both nutrients and oxygen [28,29].

It should be noted that the device used for the treatment was able to carry out an automatic feedback control of the telemetry of the subjects, to adapt the output frequency (between 0.5 and 2 MHz) and the power supplied (average power = 4 W), in order to avoid side effects, such as the subject's thermal discomfort [18,30].

At the end of the various sessions no protective, soothing or moisturizing product was applied.

2.3. Evaluations

Before the first (T0) and 2–3 days after the last treatment (T1) a comparison was made between the hydration level of the scar and the hydration level of a control point. The control point was taken at a distance of 3 cm from the scar. If it was impossible to consider this reference, the mirror point on the other side of the face was taken as a control point. The degree of hydration was measured using the Corneometer CM825 instrument (Courage + Khazaka electronic GmbH, Köln, Germany), and levels in the 50–70 range were assumed to be normal hydration levels.

At T1, patient satisfaction was assessed using the transepithelial water loss (TEWL with scores of 0 = not satisfied, 1 = slightly satisfied, 2

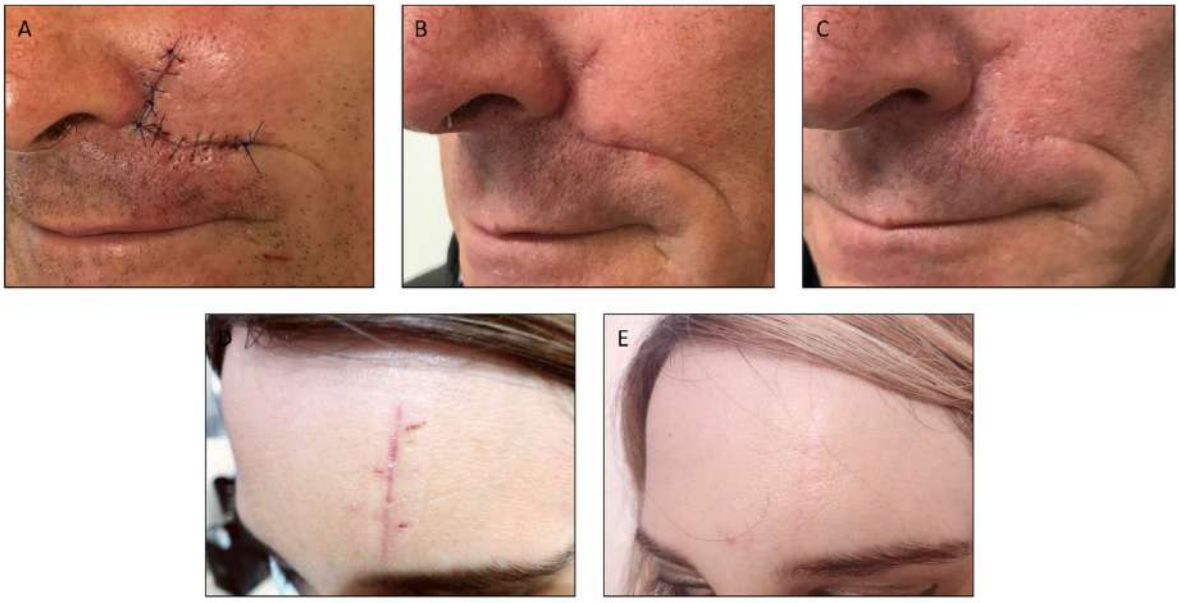

Fig. 1. Examples of the results obtained with the treatment. Man with surgical scar along the nasal sulcus and nasolabial line on the left, immediately after surgery (A), after complete wound healing (B), and after treatment with V-EMF (C). Woman with frontal longitudinal scar on the left, after complete wound healing (D), and after treatment with V-EMF (E).

Table 2
Mean hydration levels.

Normal range	T0			T1		
	Scars	Reference points	Scars and intact skin difference	Scars	Scars and intact skin difference	Scars hydration improvement
50/70	41.8 range: 36.2–46.5[a]	54.6 range: 51.1–57.8[a]	−23.45%	53.3 range: 49.8–57.1[a]	- 2.44%	+21.01%

[a] Range of hydration values available for 16 of the 25 subjects.

Table 3
Rating scale at T1.

VAS – Patients [number of subjects (percentage of subjects)]		Likert scale [number of subjects (percentage of subjects)]		
			Specialists	Independent dermatologists
Not satisfied	0 (0%)	No improvement	0 (0%)	0 (0%)
Slightly satisfied	0 (0%)	Mild improvement	1 (4%)	0 (0%)
Satisfied	2 (8%)	Moderate improvement	3 (12%)	2 (8%)
Very satisfied	11 (44%)	Good improvement	11 (44%)	10 (40%)
Extremely satisfied	12 (48%)	Excellent improvement	10 (40%)	13 (52%)

= satisfied, 3 = very satisfied, 4 = extremely satisfied. The medical specialists who performed the treatment evaluated the results obtained using the Likert Scale (I = none, II = slight improvement 1–25%, III = moderate improvement 26–50%, IV = good improvement 51–75%, V = excellent improvement 76–100%). Analyzing the photographic data collected at T0 and T1, three independent dermatologists, completely unaware of the type of treatments performed evaluated the final results using the Likert Scale.

3. Results

A sample of the visual differences observed before and after full treatment, in both a male and a female, is shown in Fig. 1.

Table 2 reports the hydration values measured at T0 and T1 for all subjects, both at the scar level, and at the reference point. At T0 the mean hydration level of the scars showed the presence of TEWL. The reference points had average values in the normal range of hydration. At T1, the mean hydration level of the scars was significantly increased, and the values returned to the normal range, with a minimal difference from the reference points.

Table 3 shows the results of the rating scales at T1. On the VAS scale, patients indicated level 2 as the minimum level of satisfaction. Therefore, no patients were dissatisfied or slightly satisfied with the treatment results. On the Likert scale, all medical specialists assigned scores between IV and V, with the exception of one specialist who chose a level III, for one of the subjects treated. All the independent dermatologists classified the final results of the treatments at levels IV and V.

The entire treated area also visually showed an anti-aging effect, and an unexpected secondary outcome, i.e. exposure to the sun, led to an increase in scar pigmentation.

4. Discussion

Facial scars are particularly critical both because they are difficult to treat, given that the skin of the face has a very thin stratum corneum which determines a greater physiological predisposition to TEWL [10], and because they often involve psychological outcomes relevant to people [2–5].

The thickness of the stratum corneum differs significantly in a subject in the various anatomical sites [10]. This is related to TEWL. On average, the face has TEWL values > 10 $gm^{-2}h^{-1}$, much higher than other parts of the body. It should be noted that these are average values, since a considerable variability has also been demonstrated in the different parts of the face [10]. However, this allows us to state that the

treatment of scars on the face is more complex than the treatment of scars in other locations, precisely because of the greater difficulty and longer times that the wounds show to heal in dry environments compared to humid ones [31,32].

The lesion of the stratum corneum causes a further increase in TEWL levels, and a consequent overproduction of inflammatory cytokines. In cascade, this determines the stimulation of the uncontrolled production of myofibroblasts [8,33,34]. In the face, a wound causes an exacerbation of TEWL, resulting in an increased susceptibility to the formation of hypertrophic scars, keloids, and skin fibrosis [6]. Taking into account that profibrotic growth factors TGF-β1 and TGF-β2 are predominantly present in adult wounds [34], it is clear that a scar on the face in an adult subject almost certainly has fibrotic sequelae, with associated chronic inflammation [35]. Fibrosis consists mainly of an alteration of the extracellular matrix, with structural and functional impairment. Initially there is an increase in the generation of type III collagen, followed in a short time by the production of type I collagen, which increases the mechanical resistance of the scar, thus determining a deteriorative evolution [36–38].

The methods most commonly used for the treatment of scars, especially if hypertrophic or keloid, do not seem to be particularly effective [39,40], and further studies are need, also aimed at optimizing them [12,15,41]. Silicone gel sheeting and topical therapies with extra-moisturizing creams appear to be particularly promising therapies [8]. In fact, these are methods that aim to restore the right level of skin hydration, reducing TEWL, and preventing the scar from degenerating into hypertrophic scar or keloid [16,42]. Both procedures allow the restoration of the functionality of the epithelial barrier, with a consequent reduction of both the existing inflammations and the secretion of proinflammatory cytokines [43–45].

The method described in this study fully embraces the principle of regeneration of epidermal lesions in order to fully restore the structure and functionality of all the layers involved in the scar. The results obtained in terms of improving the hydration levels of scars seem to confirm the effectiveness of the technique in this sense. Further studies are needed to re-evaluate long-term hydration to understand if the results obtained are consolidated, and the formation of hypertrophic and keloid scars is prevented.

The same technology applied to stretch marks has shown, from a histological point of view, an increase in the thickness of the epidermis, the reorganization of collagen, and the restoration of microcirculation [18,19]. It makes sense to expect the same kind of results on scars. But further studies with adequate histological evaluations are needed.

The correspondence between the levels of patient satisfaction and the satisfaction levels of both medical specialists and independent dermatologists is noted. The coincidence of the evaluations of the two different groups of doctors is particularly relevant, considering that medical specialists could overestimate the results of the treatments, having chosen them.

The anti-aging effect was expected, considering that the technique combines vacuum application and simultaneous electromagnetic stimulation [24,25,28,29]. The tanning effect of the scars was also predictable, as already evidenced in their studies, on the treatment of stretch marks with the same technology, by Bacci et al. [18] and by Scarano et al. [19].

5. Conclusion

A scar is a permanent aesthetic, functional and psychological damage. Identifying a method that solves all these aspects is undoubtedly a challenge for regenerative medicine.

The method described in this study, applied to what are considered the most difficult scars to treat, i.e. facial scars, has shown extremely interesting and promising results, from an aesthetic and functional point of view, with the restoration of hydration levels, and for the overall anti-aging effect of the treated area. Undoubtedly, further studies involving a larger number of patients and with longer follow-ups are needed.

What is certain is that the synergy of multiple treatments, vacuum and electromagnetic fields combined in a single instrument and in a single method, is a fascinating novelty both in the treatment of scars, and in regenerative medicine in general.

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Declaration of competing interest

All authors have no conflicts of interest to disclose.

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Article

Vacuum and Electromagnetic Fields Treatment to Regenerate a Diffuse Mature Facial Scar Caused by Sulfuric Acid Assault

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Abstract: Acid attacks are on the rise, and they cause extensive and deep burns, especially on the face. The treatments used to improve the aesthetic, functional and social impact of non-acid scars do not always prove useful for acid scars. This article reports the case of a woman with an extended, mature, acid facial scar, caused by sulfuric acid assault, treated with a recent new procedure that combines the application of vacuum and electromagnetic fields. Before and after the treatment, the aesthetic appearance, and motor function of the face and neck were evaluated, as well as the level of hydration, the amount of sebum, the elasticity, and the pH of the skin. The improvements highlighted after the treatment of the aesthetic and functional characteristics of the face and neck, and of the physical parameters of the skin seemed to indicate that this particular treatment induces tissue regeneration, even in the nerve component. However, it is evident that the rehabilitation pathways of facial wounds and scars must be personalized, and must include continuous psychological support for the patient.

Keywords: acid attack; burn; scar; V-EMF; regenerative treatment

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1. Introduction

The data on the increase in the number of chemical attacks are alarming [1–5]. Mortality associated with these actions is very high [4–8], and, considering that the victim is often attacked in the face, the sequelae completely destroy her/his life because the damage is aesthetic, functional and social [9–17].

Among the acids most used to perform the attacks is sulfuric acid, which on the skin has a double action, both chemical and thermal, due to its properties [4,7,18,19]. The effects of prolonged and massive exposure to this acid, if the victim survives, are both disfiguring and dysfunctional [4,5,7,8,20–22] due to the long healing times of the wounds and the fact that numerous reconstructive surgeries are often necessary [7,23,24].

There are numerous more or less invasive treatments aimed at improving residual aesthetic stigmatizations and facial dysfunctions (Table 1, [25–43]), but an optimal treatment has not yet been identified [44,45]. In fact, although many interventions appear promising, sometimes the results reported in the literature are conflicting [32–35], or interventions suitable for some types of scars are not effective for others [29,43–45]. This may depend on the extreme variability of individual situations, for each of which a personalized medical-surgical-rehabilitation path should be identified.

In this report we present the case of a woman with a mature scar, extending to the whole face, caused by a sulfuric acid attack and treated with a new recent multi-technique procedure. The latter is a form of therapy, generally used for small scars [46], which combines the application of vacuum and electromagnetic fields (V-EMF).

Table 1. Most common scar treatments.

Invasiveness	Type	References
Non-invasive	Silicone sheet coating	[25]
	Topical treatment	[26,27]
	Application of mesenchymal stem cells in tissue scaffolds	[28]
Minimally invasive (principally injectable therapies)	Corticosteroid injection	[29]
	Botox injection	[30]
	Mesenchymal stem cells injection (principally obtained from fat grafting)	[31–33]
	Hyaluronic acid filler	[34,35]
Invasive	Cryotherapy (generally applied after surgical excision)	[36]
Others (more/less invasive)	Laser - minimally invasive—non-ablative - invasive—ablative	[37–39]
	Shock wave therapy	[40]
	Radiofrequencies application	[41]
	Microneedling	[42]
	Dermabrasion (combined with regenerative agents)	[43]

V-EMF Treatment

In V-EMF therapy, a medium frequency electromagnetic field is applied in a vacuum regime, directly to the affected area. The waves used are radio waves with a frequency range of 450–2000 kHz (the frequency range generally used in resistive-capacitive diathermy is 450–1200 kHz). Energy is transferred to the tissues in a capacitive way, by means of a single metal electrode, suitably shielded by insulating material. The second conductive plate of the capacitor is given by the body tissue, and this implies that the electromagnetic charge is concentrated near the isolated electrode, i.e., in the superficial tissues [47–49].

From the biomedical point of view, an endogenous diathermic effect and a magneto-mechanical effect are simultaneously induced on the treated tissues. The thermal effect is due to the transformation of the kinetic energy of the ions, which move due to electromagnetic waves, into heat (Joule effect) [50–52]. The magneto-mechanical effect is linked to the piezoelectricity of some tissues, i.e., to their ability to mechanically alter their structure following a magnetic stress [53,54].

The first effect determines an increase in metabolic reactions. There is an increase in microcirculation, with a consequent increase in the number of gaseous exchanges between blood and tissues. The catabolic products are drained more quickly and the diapedesis of granulocytes, macrophages, and of the cells involved in inflammatory and reparative processes increases. In addition, the "cell killing" effect of senescent and damaged cells occurs [48,49,55–58]. The rise in temperature extends deeper [48,49,55], although the actual amount progressively decreases as it deepens from the surface of the skin [47,58]. However, this involves an overall analgesic effect [47,49,56,59], and consequently a well-being after therapy, with muscle relaxation, an increase in muscle flexibility [60,61], a reduction in pain associated with movements, and an increase in the elasticity of the connective tissue [49,56,61,62].

The second effect occurs mainly at the level of connective tissue, which is the body tissue with the most significant piezoelectric characteristics. The structural deformation of this tissue favours the resolution of fibrotic states, and the rebalancing of the extracellular matrix [63,64].

The combination of the two effects improves the repair of all involved tissues, and wound healing. We can speak of a real regenerative effect, given that there is an overall tissue regeneration [49,58,59], including that of the neural component [65–68].

The application of electromagnetic waves in a vacuum regime (100–150 millibar) amplifies the effects that these waves induce on the tissues. In particular, the vacuum appears to play a fundamental role in the restructuring of the extracellular matrix, since the induced mechanical stimulus activates the endothelial cells, the fibroblasts and the cutaneous myofibroblasts [69,70].

2. Materials and Methods

2.1. Case

We present the case of a 63-year-old female, attacked with sulfuric acid on 28 May 2012 and hospitalized from 28 May 2012 to 2017 at the Cardarelli Hospital in Naples, Italy. Here she underwent 27 surgeries for the reconstruction of the face and neck, through autologous skin grafts taken from different parts of the body, and 3 autologous lipofilling procedures. After the surgeries, she did not use an elastic compression mask at home. From the event, the patient has been followed from a psychological point of view by the Association "Women for Women Against Violence".

After 10 years from the attack, on the face and neck, she visually showed retraction of the skin and marked dyschromia. Evident were the flattening of the nose, presumably due to the retraction of the peri-labial tissue, and the deformation of the neck, with the absence of the typical right-angled conformation of the platysma and the presence of a diagonal line shape.

Face and neck showed hardening and thickening of the skin surface, and loss of sensation, with absence of both slight tactile perception and pinching.

From a functional point of view, the deformation of the nose involved the reduction of the nasal rostrums, resulting in the need to breathe through the mouth. The deformation of the neck reduced its motility. The rotational movement of the head appeared limited and sometimes painful on the side opposite to that of rotation. The retraction of the skin tissue at the level of the face induced traction of the lower lip with consequent involuntary opening of the mouth, in case of extension of the head.

2.2. Methods

The patient underwent V-EMF treatment, that was delivered according to the Biodermogenesi® method, using the Bi-one® LifeTouchTherapy device (Expo Italia Srl, Florence, Italy), and with the protocol already detailed in Veronese et al. [46]. Specifically, the subject underwent a cycle of 12 sessions, lasting 25 min each, with the frequency of one session a week, in the period April–May 2022. The vacuum was applied at 100–150 millibars. The frequency used for the generation of the EMF varied between 0.5 and 2 MHz, i.e., the supplied power was on average 4 W. The variability was linked to an automatic self-regulation system of the device, linked to an automatic feedback control of the quantity of energy absorbed by the skin. This amount is, in turn, related to the thickness of the treated skin.

A neutral alcohol-based cleanser was used on the skin before starting the procedure. Before each session, the operator identified the main fibrous excerpts present by palpation. In an initial phase lasting about 15 min, the handpiece was applied to the fibrotic excerpts, first parallel to their progression (10 min), to obtain a progressive softening action, and subsequently (5 min), tangentially. In the remaining 10 min, the handpiece was passed over the whole face and neck, to generalize the action.

Before the first treatment session (T0) and a week after the last session (T1) the level of hydration, the quantity of sebum, the elasticity, and the pH of the skin were measured at the level of the center of the forehead, of the left and right cheekbones, and in the center of the chin. To make the measurements the Skin Plus® device (Lemi s.r.l., Casalbuttano and Uniti, Italy) was used. Measurement was performed 2 times per test type and per location. The value obtained from the first survey was considered valid if confirmed by a second survey, with a tolerance of 5%. In the presence of greater differences, the average of the 2 measured values was taken.

At T0 and T1, photographs of the forehead, middle third of the face, nose in profile, and lower third of the face were taken for a qualitative evaluation of the effects of the treatment. A Nikon D500 camera was used, at a distance of 1 m from the patient, with artificial light.

3. Results

The level of hydration, the amount of sebum, the elasticity, and the pH of the skin recorded at T0 and T1 are shown in Table 2. For all tests and all sites, the 2 measurements taken differed by 2–3%. Therefore, the first value detected was considered valid.

Table 2. Skin parameters.

	Forehead		**Right Cheekbone**		**Left Cheekbone**		**Chin**	
	T0	T1	T0	T1	T0	T1	T0	T1
Hydration Level	12	18 *	32	46	35	86	34	73
normal value					>44/100			
Sebum Quantity	27	43 **	25	65 **	27	70 **	29	63 **
normal value					<40/100			
Skin Elasticity	18	48	16	45	16	44	15	63 **
normal value					>20/50			
Skin pH	3.7	4.9	3.6	5.0	3.6	4.8	3.2	4.9
normal range					4.1–5.8			

* increase below normal levels; ** increase above normal levels.

After the treatment, 2 of the 4 tested parameters did not normalize in the forehead area. The level of skin hydration remained practically unchanged, while the amount of sebum produced exceeded the upper limit of the norm. The latter data was common to all the facial areas considered.

In the cheek there was an increase above the normal range of skin elasticity. Therefore, even for the cheek 2 out of 4 parameters did not normalize.

On the surface, the skin appeared less tight. Some scar furrows appeared smooth. On palpation, the fibrotic tissue mainly present in the nose, chin and neck was softer and less adherent. The structure of the nose and the lower middle third of the face were particularly reshaped, presenting a more natural conformation. The photographic comparison at T0 and T1 is shown in Figure 1.

Finally, it should be noted that during the single treatment sessions the subject did not report any discomfort. No side effects or pain were reported during treatment and at T1.

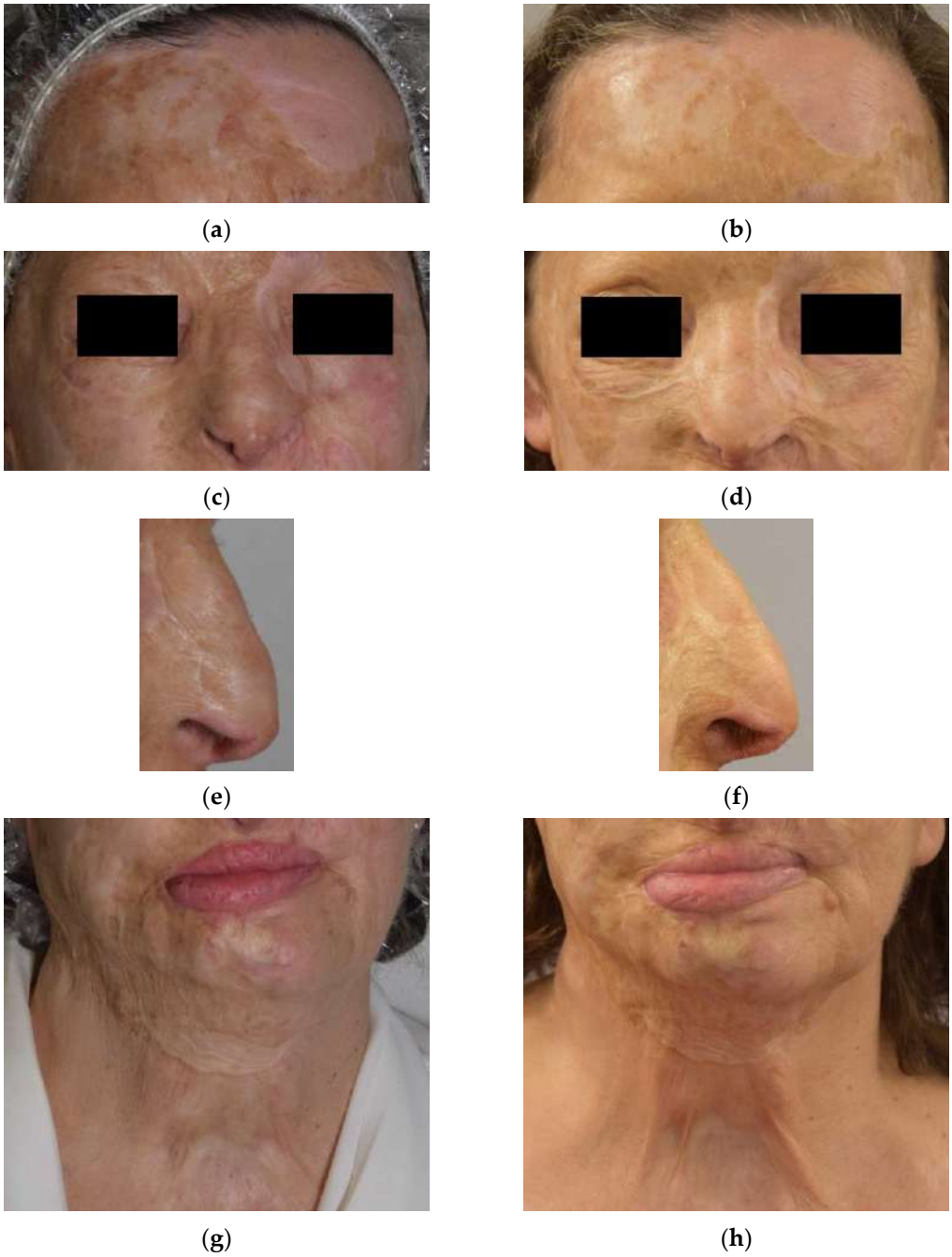

Figure 1. Photographs just before, and 1 week after the V-EMF treatment of the forehead (**a**,**b**), middle third of the face (**c**,**d**), nose (**e**,**f**), and lower third of the face (**g**,**h**).

4. Discussion

In cases of acid assault, the face is generally the most affected part of the body [3–5]. The first necessity when a patient arrives at the hospital with this type of injury is always to save her/his life. Only when the survival of the subject has been guaranteed is it possible to intervene to try to preserve all the functions of the face (primarily the visual one), promote rapid healing, and minimize visual stigmatization [19,71].

The precocity of treatments seems to indicate a better functional and aesthetic wound healing, with the formation of less extensive and shallow scars [24,72,73]. Unfortunately, timeliness is not always possible, as in the case described in this study, where healing times were very long. In addition, there are people who have old scars and/or who have not benefited from the various treatments performed [44,45]. In these cases, a long time passes

after the initial injury. Thus, a treatment may, instead of promoting regeneration (as in the proliferative/modulating phase of healing), cause a resumption of an inflammatory process. This process may ultimately culminate in a major proliferative phase, but first by inducing a major distress phase in the treated subject.

The V-EMF procedure has the advantage of being completely non-invasive and the results obtained with the treatment of small scars are highly encouraging [46]. The application of this treatment on an extensive scar like that of the case described, although not a bet, did not guarantee the results obtained. The latter are extremely interesting, especially from a functional point of view. It should be noted that even the aesthetic results achieved are not trivial. For instance, the regeneration of the nose is evident, both in the skin and in the redefinition of the nasal rostrums (Figure 1c–f).

The reappearance of tactile sensitivity and the improvement of cranio-cervical motility further highlight the regeneration of the tissues damaged by the burn, a regeneration that also includes the neural components. Furthermore, the changes in skin characteristics after treatment (Table 2) demonstrate the regeneration of the skin texture and the normalization of many of its properties. The authors believe that the fact that sebum production increases beyond normal levels underscores the skin's strong natural response to treatment. And, therefore, it is not seen as a negative datum. The greater elasticity of the cheek could be linked to the greater amount of adipose tissue generally present in this area.

Given the results obtained, in the absence of any discomfort, it can be concluded that the procedure did not reactivate a situation of pain and inflammation, but a tissue regenerative activation was directly induced. This is particularly interesting also considering the age of the treated subject, an age in which the regenerative capacity in general, and of the face in particular, can be the subject of discussion.

In the literature there are not many analyses relating to this technique for the treatment of scars, given that it was recently introduced. In the two works that describe it [46,74], for ethical reasons, no invasive analyzes (e.g., biopsy analysis) were performed to evaluate the effectiveness of the method. The outcomes of the various treatments were evaluated by non-invasive measurements and were considered satisfactory in both studies. Nevertheless, in three studies V-EMF therapy was applied to stretch marks, often referred to as atrophic scars [75–77]. Two of these studies also reported histological evaluations of biopsies taken after the treatments [76,77]. These evaluations highlighted a tissue reorganization with restoration of the original volume. A neoformation of collagen shoots and elastin fibers was observed, with restructuring of the basement membrane, and of the extracellular matrix underlying the striae. Although the degree of tissue degeneration linked to chemical burn scars is undoubtedly not comparable to the structural alteration linked to the presence of a stretch mark, the reported observations highlight a regenerative reaction in the tissue treated with V-EMF therapy. This is certainly an important fact.

Studies in the literature described different types of treatment for burn cases, with excellent results for some aspects and absent or negative results for others [31,35,37,40,41]. One wonders if the combination of several different treatments can be significant for the full aesthetic and functional recovery, and for the improvement of all aspects of the quality of life of burned subjects. For this particular category of patients, it seems not only useful, but necessary to define a personalized therapeutic path. V-EMF treatment, which is a multi-technique procedure, appears to respect this principle. Perhaps in these particular subjects, with extensive and deep burn scars and the presence of painful fibrotic shoots, it may be necessary for patients to undergo multiple cycles of V-EMF therapy, to progressively resolve/improve their pathological state.

Finally, it is essential not to forget the fact that people with scars due to acid attacks are first of all victims, which must be followed from a psychological point of view, even during treatments, given the strong emotional impact that aesthetic-functional recovery can have [78–80].

5. Conclusions

Undoubtedly, the application of V-EMF treatment to a greater number of subjects is necessary to confirm the results obtained for the subject of this report. Considering this case, it can be concluded that V-EMF therapy appears to be beneficial for mature and widespread scars in burn outcomes. It is very promising that both aesthetic and functional recovery have been observed.

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Informed Consent Statement: Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement: All the data used for this study are present in the text.

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ORIGINAL ARTICLE

Vacuum and electromagnetic field in synergy for skin rejuvenation: A retrospective study on 217 patients

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Abstract

Background: There are many aesthetic treatments aimed at combating aging. In the most common and frequently used ones there are often side effects, albeit minor ones. However, sometimes it is necessary to use medications before or after treatments.

Objectives: To evaluate the anti-aging efficacy and application safety of a therapy based on the combination of vacuum and electromagnetic fields (EMFs).

Methods: A retrospective study was conducted to evaluate the aesthetic effects of the treatment on 217 subjects. Before treatment (T0) and after the last session (T1), skin hydration levels, the amount of sebum present and the pH were measured. The presence of discomfort during the sessions and side effects at T1 was verified. At T1, the levels of satisfaction of the patients and of the doctors who performed the treatment were assessed. At 3 and 6 months of follow-up the aesthetic results were re-evaluated.

Results: For all treated subjects, an evident qualitative improvement was observed in the quality of the skin of the neck and face, with an increase in tone and a reduction in wrinkles. The instrumental tests highlighted a normalization of skin hydration, pH, and sebum values. High levels of satisfaction at T0 and good stability of results up to 6 months of follow-up were reported. No discomfort was referred during the treatment sessions, nor any side effects after the entire treatment.

Conclusions: The treatment that exploits the synergy between vacuum and EMFs is very promising given the effectiveness and safety of the technique.

KEYWORDS
aging, Biodermogenesi, electromagnetic field, regenerative medicine, vacuum

1 | INTRODUCTION

Parallel to the increase in social well-being and the average life span, requests for aesthetic treatments have also increased, primarily face, and neck rejuvenation. In medicine, there are many treatments used to combat skin aging. In addition to injections and topical therapies, various methodologies based on different types of medical devices have been consolidated. The most common are needling, radiofrequency (RF), laser and focused ultrasound (fU).

Needling is performed using devices equipped with microneedles, which create micro-lesions on the skin, triggering the stimulation of the fibroblasts present in the dermis. Consequently, the fibroblasts produce collagen and elastin, in an induced process of natural skin regeneration. Needling side effects are generally limited to short-lasting erythema and edema.[1,2] It rarely caused hyperpigmentation, localized superficial infections, allergic reactions.[1–3] Topical antibiotic therapy may be prescribed based on skin reaction.[3]

The RFs used for anti-aging treatments are non-ablative. They can be monopolar or bipolar, depending on whether they are applied to the surface, or through intradermal needle-electrodes.[4] They can also be resistive or capacitive, but the former is preferred because it allows better control of the temperature variation. The resistive RF (rRF) is supplied as high frequency alternating current through one or more conductors applied to the skin, called "poles". This energy passes through the skin tissue, which is transformed into an electrical resistance, and tends to overheat quickly and intensely. This phenomenon called "thermalization" leads to the denaturation of collagen and a consequent repair drive. The use of RFs generally leads to non-persistent episodes of erythema and edema.[4,5] In addition, the treatment is perceived as painful by many patients. Out of 25 patients treated with superficial rRF, Riuz-Esparda found painful sensations during treatments in 13.64%.[6] In a study by de Felipe et al, of 290 patients treated with intradermal rRF, 9.3% experienced intense pain during treatment, and 6.22% reported second degree burns.[5] Antibiotic prophylaxis is indicated for intradermal RF.[7,8] In superficial RF, the use of antibiotics is necessary in case of burns from contact with the surface electrode.[9]

Lasers are divided into non-ablative or ablative depending on whether their action involves only the lower layers of the skin or even the outer surface. The CO_2 laser (10 600 nm) and the erbium laser (Er:YAG; 2940 nm) are ablative lasers, and are used for deep treatments. Non-ablative lasers perform softer treatments than ablative lasers, but are widely used in rejuvenation treatments. Among them are the Q-switch lasers, which are the ruby laser (694 nm), the alexandrite laser (755 nm) and the Nd: YAG laser (aluminum garnet and neodymium yttrium; 1064 or 532 nm). Other non-ablative lasers are the pulse-dye laser (PDL; 585–595 nm), the diode laser (800–980 nm), the KTP laser (potassium-titanium-phosphate; 532 nm). Both ablative and non-ablative lasers can be fractionated and non-fractionated. The former during the treatment leave microscopic columns of untreated tissue in the treatment area, to help limit the temperature increase. The laser beam is collimated and acts on individual skin components, in particular hemoglobin and water. Thermal micro-damage of the coagulation type is induced, and repaired through the production of new cells and, above all, collagen. Although the use of fractional tools increases the safety margin of treatments, side effects ranging from mild to severe have been reported.[10] Among the mild complications, the most common are the appearance of milia (19%), acne (2%–10%) and erythema (1% non-ablative laser; 12.5% ablative laser with persistence of symptoms for up to 3 months). Among the moderate complications, the most common is infection (0.3%–2%). Other complications are rare. Especially following the onset of acne and infections, the use of antibiotics may be necessary and these should be used as prophylaxis if other treatment sessions are planned.[10]

In fU, the thermal shock produced inside the tissue causes mini-coagulation points at the level of the middle and deep reticular layer of the dermis and hypodermis. Consequently, a reparative action is triggered. The main limitation of this technology is the pain felt by patients during treatment, which sometimes involves the use of anesthetics.[11,12] Side effects associated with this method are mild and are mainly transient erythema, edema, and bruising.[11,12] Less common effects are the appearance of skin streaks,[11,12] wheals, post-inflammatory hyperpigmentation, muscle weakness, transient numbness.[12] Trigeminal or mandibular motor nerve palsy is rare.[11]

What binds all the procedures described above, except needling, is the thermal shock that is induced at the level of the middle and deep layers of the skin. The effects related to thermal shock can persist even up to 7 days after treatment, spreading beyond the directly targeted area.[13] This can be positive because it shows that the healing process continues after the acute phase of the treatment and covers a larger area than the target area.[13] But the thermal effect on healthy tissues, if not controlled, can compromise their vitality.[14,15] Some treatments are able to induce thermal rises that can liquefy the collagen beyond any possible contraction,[12,15] preventing the beginning of the healing and tissue regeneration phase. These increases can also be linked to an incorrect duration of skin exposure, caused by the prolonged duration of treatments.[15]

The aim of this study is to evaluate the efficacy and safety of a non-invasive technology that combines the application of vacuum and the irradiation of an electromagnetic field (V-EMF), verifying its action through the detection of some skin parameters, and evaluating the presence of side effects.

2 | MATERIALS AND METHODS

We performed a retrospective chart review of 217 patients scheduled for aging treatment in 2021. All subjects had not received other antiaging treatments in the 3 months prior to initiation of V-EMF therapy. In conjunction with this one, they did not perform any other anti-aging treatments. In the 24 h preceding each single V-EMF treatment session they had not used any cosmetic product. The study was conducted in full compliance with the ethical norms and standards in the Declaration of Helsinki. An informed consent statement was obtained from all the subjects.

2.1 | Patients

The patients ranged in age from 35 to 81 years. The treatment was performed on a greater number of women than men (185 females; 32 males). A more detailed characterization by gender and age is shown in Table 1. All subjects considered had skin phototype IV.

All patients were healthy subjects with intact skin. The subjects were selected on the basis of the application limits of the V-EMF method, which are: pacemaker bearers, epileptics, people with severe skin inflammation, subjects with wounds that have not completely healed, subjects who have undergone oncological therapy in the last 5 years, subjects who have suffered from anorexia or bulimia in the past 2 years.

2.2 | V-EMF therapy

A detailed description of the principles underlying this therapy is given by Veronese et al.[16] For the anti-aging on the face, the therapy was carried out using the Bi-one® Life Touch Therapy device (Expo Italia Srl).

The electromagnetic field (EMF) was generated by applying a capacitive RF (cRF). Unlike rRF, cRF does not deliver energy directly to the patient's skin. A high-frequency signal is directed to a specific "shielded electrode", that is, an electrode whose outer part is covered by an insulating shield (dielectric material). The application electrode and the deep structures of the skin, separated from the electrode shield and tissues with insulating properties (such as the epidermis) form a capacitor, in which the action of the EMF takes place. A flow of positive ions (including sodium, $Na^+$and potassium, K^+) moves into the underlying tissue of the epidermis, crossing cell membranes and delivering nutrients to the cells. The inversion of the electric charge determines the opposite action in the cells, with an increase in the catabolic fluxes. These actions are due to the magneto-mechanical effect induced by the therapy, an effect which is linked to the piezoelectric properties of the tissues, that is, their ability to alter their own structure in response to magnetic stress. The connective tissue of the skin has important piezoelectric properties and its structural deformation, induced by EMFs, favors the rebalancing of the extracellular matrix (ECM).

Furthermore, the electromagnetic waves determine the movement of the ions present in the skin tissue, that is, the development of a kinetic energy. Part of this energy is transformed into thermal energy, and determines an endogenous diathermic effect. This leads to a slight heating of the dermis, which allows tissue regeneration and an increase in clearance, according to Van't Hoff's law. In fact, an increase in metabolic reactions is determined, with an increase in the microcirculation, and in the number of gaseous exchanges between blood and tissues. The results are: a more rapid drainage of catabolites associated with a "cell kill" effect of senescent and/or damaged cells, and an increase in the diapedesis of granulocytes, macrophages and cells involved in inflammatory and reparative processes. At the tissue level, there is relaxation of muscle contractures and an increase in the elasticity of the connective tissue.

Unlike other technologies based on EMF where the output frequency is fixed, Biodermogenesi® uses a variable frequency from 0.5 to 2 MHz and an average power between 4 and 6 W, automatically regulated by a biofeedback system. The amount of energy absorbed by the skin is constantly calculated to ensure that the induced thermal excursion does not lead to increases in tissue temperature above 39°–40°C.

The application of electromagnetic waves in a vacuum amplifies tissue reactions, with consequent activation of endothelial cells, fibroblasts and skin myofibroblasts. The vacuum was supplied at 100–150 millibars. This pressure allows the skin tissue to dilate by one millimeter and, consequently, mechano-transduction is activated, that is, the conversion of mechanical stimulation into biochemical signals,[17] which determine a metabolic, catabolic, and regenerative reaction of the tissues in which these signals propagate.

TABLE 1 Gender and age of the patients.

Age (years)	Females	Males
≤ 40	30	8
41–50	43	14
51–60	57	10
61–70	37	0
≥ 71	18	0

2.3 | Treatments

All subjects underwent five treatment sessions on the face and neck. Usually the Biodermogenesi® method involves performing a weekly treatment session or two sessions a week, depending on the skin type of the individual subject.

A neutral alcohol-based cleanser was used on the skin before starting the procedure. Subsequently, the handpiece of the device was positioned on the skin and slid over the face and neck, to guarantee uniformity of action on the whole area. The duration of each single session was 20 min.

At the end of the treatment, no protective, soothing, or moisturizing products were applied to the skin.

2.4 | Analysis

Before the treatment (T0) and after the last session (T1), skin hydration levels, the amount of sebum present and the pH on the forehead, cheeks, and chin were measured. The measurements were carried out using the instruments Corneometer CM825 (Courage+Khazaka electronic GmbH, Köln, Germany), Sebumeter SM810 (Courage+Khazaka electronic GmbH, Köln, Germany), and skin pH-meter PH 900 (Courage+Khazaka electronic GmbH, Köln, Germany). Anatomically, the exact points of the survey were:

1. the central point of the forehead from the glabella to the hairline;
2. considering the line of junction of the ala of the nose with the tragus, the point at 1/3 of lateral distance from the ala, bilaterally;

3. the central point of the chin.

These points correspond to points 2, 18, and 26 described by Voegeli et al.[18]

A comparison was made between the values recorded at T0 and T1, and with the values of optimal skin condition. The Wilcoxon signed-rank test was used for the analysis, with significance for $p < 0.05$.

The impressions of the patients during the treatment sessions were collected (no sensation, comfortable, uncomfortable, painful treatment), and the side effects recorded after the individual sessions and at the end of the entire cycle.

Furthermore, at T1 the levels of satisfaction with respect to the aesthetic effects, after the entire treatment, of both the doctors who performed the treatments and the patients were evaluated using a 5-point Likert scale (I = no improvement, II = slight improvement 1%–25%, III = moderate improvement 26%–50%, IV = good improvement 51%–75%, V = very good improvement 76%–100%), named Likert scale A. At 3 (T2), and 6 (T3) months of follow-up, the aesthetic results of the treatment were re-evaluated by the doctors who performed it using another 5-point Likert scale (I = marked attenuation of the results ≥21%, II = attenuation of results 11%–20%, III = moderate attenuation of results ≤10%, IV = unchanged/stable results, V = improvement of results), named Likert scale B.

3 | RESULTS

In all the subjects considered there was an overall increase in skin tone with tighter skin, and an improvement in the appearance of the wrinkles present, which were less deep. These results appeared evident already at time T1, as highlighted in Figure 1.

The values of the levels of hydration, the amount of sebum present and the pH are shown in Table 2. An overall increase in skin hydration levels, a reduction in the amount of sebum present and a rebalancing of pH levels were found in all three area tested. All three parameters were characterized by an initial situation of alteration, which normalized on average at the end of the treatment. For all subjects, in fact, normalization of skin hydration levels was highlighted, while for some subjects who started from a significant alteration of sebum production (in excess) and with a particularly basic pH, the levels improved, remaining however slightly outside the normal range.

As regards the impressions of the patients during the individual treatment sessions, they reported a pleasant feeling of warmth when

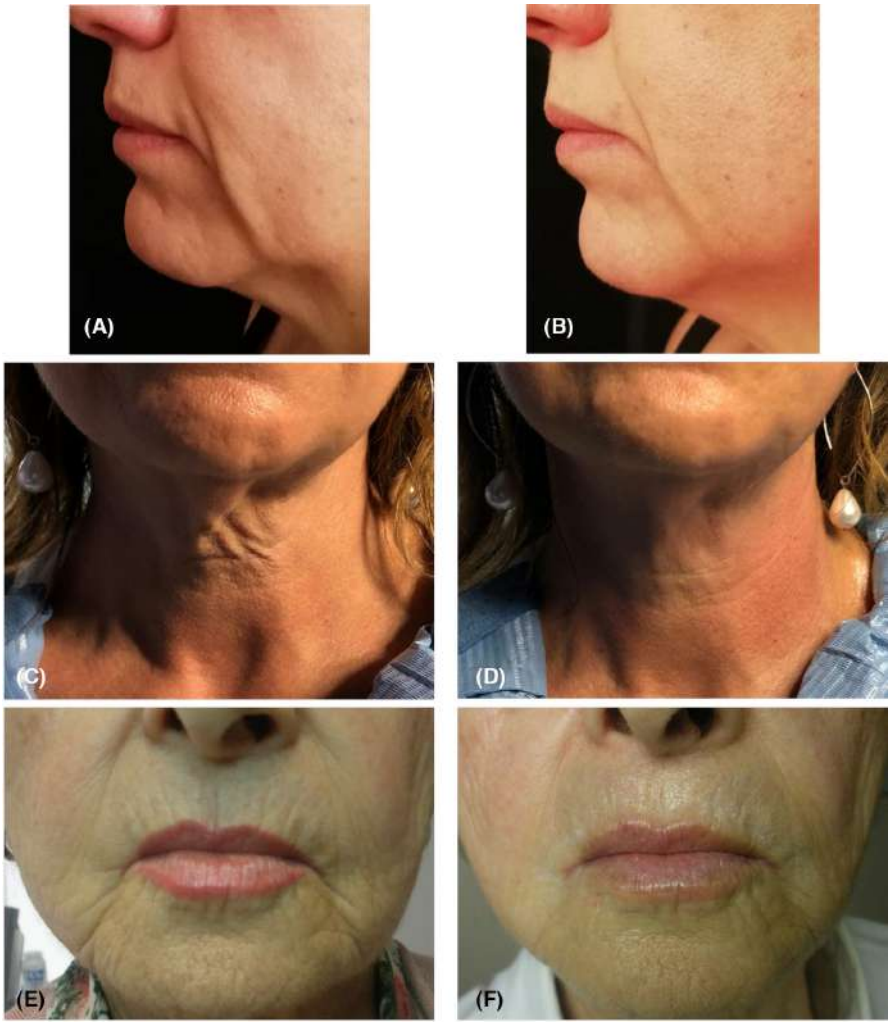

FIGURE 1 Aesthetic results obtained after the last session of treatment (T1) at three independent clinics. In all 3 cases there is a general improvement in skin tone and a reduction in wrinkles. (A) Profile of the lower third of the face of a 56-year-old female before the treatment (courtesy of Dr. Fulgione's archive). (B) Profile of the female in (A) after the treatment. The profile of the jawline and neck is defined and plumped (courtesy of Dr. Fulgione's archive). (C) Frontal view of the chin and neck of a 48-year-old female (courtesy of Dr. Alberti's archive). (D) Frontal view of the chin and neck of the female in (C) after the treatment. Correct repositioning of the platysma is appreciated (courtesy of Dr. Alberti's archive). (E) Frontal view of the lower third of the face of a 81-year-old female (courtesy of Dr. Laura's archive). (F) Frontal view of the lower third of the face of female in (E) after the treatment. Both perioral wrinkles and marionette lines appear less defined, with skin tighter (courtesy of Dr. Laura's archive).

TABLE 2 Skin parameters pre- and post- the entire treatment.

Skin parameters	Normal value range	Site	T0	T1	Net variation	Perceptual variation (%)
Hydration levels	50–70	Forehead	43.55	58.24	+14.69*	+33.73*
		Right cheek	41.55	59.80	+17.93*	+43.92*
		Left cheek	42.35	60.20	+17.85*	+42.15*
		Chin	42.55	52.08	+9.53*	+22.4*
		Mean	42.55	57.60	+15.05*	+35.37*
		(min-max)	(32,72-47,15)	(50,96-61,19)		
Amount of sebum	100–130	Forehead	150.32	129.86	−20.46*	−13.61*
		Right cheek	146.74	128.18	−18.56*	−12.75*
		Left cheek	145.58	127.89	−17.69*	−12.15*
		Chin	147.36	128.79	−18.57*	−12.6*
		Mean	147.50	128.68	−18.82*	−12.76*
		(min-max)	(135,12-151,61)	(122,17-131,65)		
pH levels	5.5–6.5	Forehead	7.36	6.54	−0.82*	−11.14*
		Right cheek	6.94	6.41	−0.53*	−7.64*
		Left cheek	6.97	6.44	−0.53*	−7.6*
		Chin	7.45	6.53	−0.92*	−12.35*
		Mean	7.18	6.48	−0.7*	−9.75*
		(min-max)	(6,62-7,48)	(6,22-6,82)		

*$p < 0.05$ in Wilcoxon signed-rank test.

sliding the handpiece, with an effect that lasted for a few hours after the end of the sessions.

No side effects were reported, neither in the short term (after each session), nor in the medium term (1 month after the end of the entire session cycle). It was also observed that the treatment sessions were not followed by downtime, that is, that all subjects immediately resumed all their activities, without any limitation.

The levels of satisfaction with the aesthetic results obtained at T1 are shown in Table 3.

Re-evaluations of doctors who performed treatments at 3 and 6 months are reported in Table 4. These re-evaluations were performed on 112 of the initial patients. Among these subjects, 12 had persistence of results up to 3 months of follow-up. All 12 subjects were < 50 years old (8 were < 40 years old, 4 were 41–50 years old).

4 | DISCUSSION

In evaluating the efficacy of V-EMF therapy, two substantial aspects emerge. First, the aesthetic, clinical, and functional results. Second, the absence of side effects during treatment, and in the short and medium term.

As far as effectiveness is concerned, the synergy of vacuum and EMFs induced by cRF has already been tested in various applications.[19–23]

Aesthetic improvement was evidenced in stretch marks, with reduction of visual stigmatization of both striae rubrae and albae.[19,20,22] A profound action at the level of the ECM has been demonstrated. Neo-activation of melanocytes has been observed following exposure to the sun.[20] This reaction was previously absent. Furthermore, an overall restructuring of the collagen and elastin fibers was found, with a rebalancing of the tensile properties.[19,22]

Similar results have been described in scar treatments.[21,23] In addition to the reduction of visual stigmatization, the rebalancing of the physical-mechanical properties of the skin was measured, synonymous with restructuring of the ECM.

Finally, an increase in skin firmness and a rebalancing of collagen and elastin fibers in the ECM were observed in skin ptosis.[19]

The rebalancing of the ECM fibers, with the reactivation of the metabolic and catabolic activities, and the regeneration linked to the activation of the stem cell niche, are the basis of all anti-aging therapies. Therefore, the result obtained in the present study could almost be defined as obvious. In reality, the vacuum and electromagnetic emissions calibrations are independent, but closely related to the achievement of the objectives. For example, an excessive increase in temperature, linked to too strong magnetic fields, could not only impede the regenerative action, but even worsen the tissue texture, with the formation of fibrotic layers and/or cellular apoptosis.

In all the aforementioned studies,[19–23] which include more than 1000 subjects treated with V-EMF for various problems, the absence of distress during the treatment sessions was reported and no side effects were reported, both in the short and medium term. This is a particularly interesting data, especially when compared with the data of the most widespread anti-aging treatments.

TABLE 3 Levels of satisfaction at T1.

	Patients' satisfaction		Doctors' satisfaction (referred to individual patient's improvements)	
Likert scale A levels	Number of subjects	Percentage of subjects (%)	Number of patients	Percentage of patients (%)
I	0	0	0	0
II	0	0	0	0
III	19	8.8	18	8.3
IV	60	27.6	46	21.2
V	138	63.6	153	70.5

TABLE 4 Doctors' evaluation related to the stability of individual patient results, at 3 and 6 months of follow-up.

	Doctors' evaluation (related to the stability of individual patient results)			
	3 months of follow-up		6 months of follow-up	
Likert scale B levels	Number of patients	Percentage of subjects (%)	Number of patients	Percentage of patients (%)
I	0	0	7	6.2
II	4	3.6	72	64.3
III	10	8.9	28	25.0
IV	86	76.8	5	4.5
V	12	10.7	0	0

The pleasantness of the V-EMF treatment contrasts with the painful states of the treatments with rRF[5,6] and with fUs.[11,12] For the latter, the use of anesthetics may even be necessary, but the pre-treatment administration of diazepam is also widespread.[12]

Side effects are always described for needling, rRF, laser and fU, and among these the most common, although not serious, is erythema.[1,2,4,5,10–12] However, the variety of side effects is very wide and may be such as to require the use of antibiotics.[3,9,10] In infra-dermal RF, their prophylactic use is even recommended.[7,8]

The fact that it is necessary to resort to the use of drugs, such as anesthetics and anxiolytics, to make the treatment bearable for patients, and drugs, such as antibiotics, to resolve situations created by the treatment, may be the subject of discussion. In fact, these are all procedures performed for purely aesthetic purposes. Therefore, the use of drugs should be severely limited. In this sense, the data on V-EMF therapy are very encouraging. It seems to overcome these problems, given that neither in the current study, nor in previous studies,[19–23] did any subject have to resort to the use of pre- or post-treatment drugs.

A possible limitation of this study derives from the fact that specific measurements of skin elasticity, an important parameter for the analysis of skin rejuvenation, were not performed. However, given that skin hydration levels are strongly correlated with skin elasticity,[24] the improvement recorded in hydration levels can be considered an indirect index of the improvement in the degree of elasticity.

Nevertheless, direct measurement of this parameter will also be performed in further studies.

Finally, the data on the duration of the effect of V-EMF therapy are extremely interesting. Only 7 of 112 subjects had >21% worsening of outcomes at 6-month follow-up. Twelve out of 112 subjects even showed a progressive improvement up to 3 months of follow-up, to underline how profound the action of the therapy is on the tissues. It should be noted that it is not surprising that all of these 12 subjects were < 50 years old, given that the ability to react to a stimulus is undoubtedly greater in more intact tissues. However effective an anti-aging therapy may be, if applied to sclerotic tissue, it can improve the tissue's tone and consistency, but the effects can only be limited and will certainly have a shorter duration. This supports the increasingly widespread line of thought of anticipating the start of anti-aging treatments, to make them preventive and not restorative treatments.

5 | CONCLUSIONS

The results, both qualitative and quantitative, obtained with V-EMF therapy, lead to the conclusion that this procedure is effective. In fact, the synergy between vacuum and EMFs provides results comparable to those achieved by the main anti-aging technologies. Furthermore, the absence of both discomfort during treatment sessions, and post-treatment side effects, make it a very safe technique.

AUTHOR CONTRIBUTIONS

Simona Laura, Giovanni Alberti, Annalisa Beatini, Elisabetta Fulgione and Claudio Urbani performed the research. Sheila Veronese, Pier Antonio Bacci, and Annalisa Beatini designed the research study. Simona Laura, Giovanni Alberti, Pier Antonio Bacci, Annalisa Beatini, Elisabetta Fulgione and Claudio Urbani analyzed the data. Simona Laura, Sheila Veronese, Pier Antonio Bacci and Annalisa Beatini wrote the paper.

FUNDING INFORMATION

No funding was received for this study.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study (deidentified patients photographs, raw measurements of skin parameters for individual patients, and statistical analyses) upon reasoned request, from trained practitioners and dermatologists, from the corresponding author for 3 years after the publication of this study. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Authors declare human ethics approval was not needed for this study. The study was conducted in full compliance with the ethical norms and standards in the Declaration of Helsinki. All the participants gave informed consent for the publication of their data.

INFORMED CONSENT

All the participants gave informed consent for the publication of their data.

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Communication

Hyper- and Hypopigmentation in a Subject with Fitzpatrick Skin Phototype VI: A New Treatment Option

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Abstract: Background: Laser therapies can cause hyper- and hypopigmentation of the skin. There is little evidence in the literature of effective treatments for these types of problems in Fitzpatrick skin phototypes IV–VI. The main aim of this retrospective study is to evaluate the effects of a new therapy that combines the application of electromagnetic fields and vacuum on a subject with Fitzpatrick skin phototype VI, who presented extensive, laser-induced facial dyschromia. The secondary aim is to test the effectiveness of a free imaging software for assessing skin pigmentation. **Methods**: The level of improvement after therapy was evaluated, with a 5-point Likert scale, one month after the end of the treatment by the subject and by the doctor who performed the treatment, and by two blinded dermatologists. With the free software, a three-dimensional reconstruction of the treated area and the evaluation of the color distribution were performed. **Results**: Both the subject and the doctors involved in the study positively evaluated the effects of the treatment. The image analysis highlighted the homogenization of the skin color in the treated area. **Conclusions**: The combination of electromagnetic fields and vacuum for dyschromia treatments appears promising. The new method of assessing melanin levels resulted particularly efficient.

Keywords: dyschromia; dark color skin; laser side effects; electromagnetic field; vacuum

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1. Introduction

Some skin types may develop more side effects than others when subjected to certain cosmetic treatments. Examples of the latter can be laser and non-ablative energy therapies in Fitzpatrick skin phototypes IV–VI [1]. Although in these skins the adverse effects are mainly post-inflammatory hyperpigmentation and erythema [2], irreversible hypopigmentation situations may occur [2,3]. All these effects, in addition to causing aesthetic damage, can also lead to psychological damage, and to a worsening of quality of life (QoL), as already highlighted for other pigmentation disorders [4,5]. Therefore, it is essential to identify corrective and resolution systems and procedures.

Hypopigmentation is treated, not always with benefit, using systems that try to reactivate the melanocytes, or repopulate the affected area, and rebalance the production of melanin [3,6]. The use of various therapies and techniques for the resolution of aesthetic damage is documented in the literature. These techniques range from completely non-invasive topical therapies, to phototherapy with UV rays, to laser therapies, to the combination of more or less invasive therapies, up to the transplantation of melanocytes-keratinocytes [3,6] and skin grafting [6]. However, the studies performed concern almost exclusively Fitzpatrick skin phototypes I–III, and the results are not always entirely satisfactory.

Post-inflammatory hyperpigmentation tends to resolve spontaneously over time. If treated, the goal of interventions is to slow pigment production, increase cell turnover, decrease inflammation, and break down pigmented product [7]. Its main clinical solution

is the application of topical lightening creams. [8]. More invasive solutions are laser therapy [9] and chemical peels [10]. Topical treatments have variable effects and can induce side effects, depending on the skin phototype [11]. Chemical peels are the most effective treatment for hyperpigmentation [12–14]. Laser therapy is less effective than chemical peels, and should be used with extremely caution in dark skin [9]. Generally, hyperpigmentation disorders of dark skin should be treated combining the use of sunscreens with a high sun protection factor against UVB and high protection against UVA, especially long UVA [15].

The main aim of this retrospective study is to report the effects of a new aesthetic therapy that combines the application of electromagnetic fields and vacuum (V-EMF therapy) on a subject with Fitzpatrick skin phototype VI, who presented extensive facial dyschromia, induced from laser treatment. The secondary aim is to present a completely free imaging reprocessing model for the assessment of skin pigmentation.

2. Materials and Methods

The present retrospective study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. The treatment has been approved by the Cardiff Cosmetic Clinic. The same device was used in a previous study on the aesthetic treatment of post-surgical and burn scars, a study authorized by an ethics committee [16]. In the present study, the device was used off label for dyschromia secondary to burn scars. The subject in this manuscript has given written informed consent for the details of his case to be published.

2.1. Subject

A 34-year-old man was admitted to the Cardiff Cosmetic Clinic (UK) with a diagnosis of hyperpigmentation associated with diffuse hypopigmentation of the face and neck. He reported that the aesthetic damage had arisen due to a hair removal treatment, performed 2 months earlier, with an 808 nm diode laser (unknown model) at another aesthetic clinic.

The subject had Fitzpatrick skin phototype VI and the macules or patches of both hyper- and hypopigmentation had the clear shape of the laser probe used previously (Figure 1).

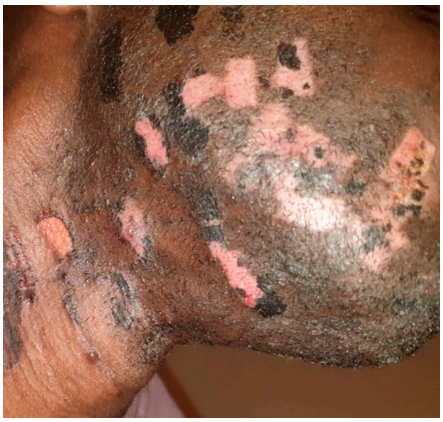


Figure 1. Before treatment, the skin showed both macules of post-inflammatory hyperpigmentation and patches of hypopigmentation throughout the beard area.

2.2. Choice of Treatment

The overlapping picture of hyper- and hypopigmentation made the choice of treatment particularly complex. The post-inflammatory hyperpigmentation pattern would regress over time or could be effectively treated using chemical peels. However, in subjects with Fitzpatrick skin phototype VI, these treatments cause high rates of side effects, including hypopigmentation [17,18]. If the subject did not present hypopigmentation spots, a chemical peel could have been opted for, after applying sunscreen protection, an application probably not performed during the laser procedure that had induced the dyschromia. The

aesthetic doctor preferred not to intervene on hyperpigmentation, focusing his attention on the hypopigmentation spots, the main aesthetic problem, as they are generally considered irreversible or only partially reversible.

In this case, the choice to resort to topical therapies did not appear adequate, given the high degree of dyschromia. UV phototherapy could worsen hyperpigmentation. The use of an additional laser device was totally excluded, since the cause of dyschromia was a laser treatment. It was possible to opt for more invasive treatments, such as melanocyte transplant or skin grafting, treatments linked to surgical risks [3,6].

Having noted the effects of the reactivation of melanin function on subjects treated with V-EMF therapy on surgical and burn scars [16], and stretch marks (SMs) [19], and the absence of side effects in both previous utilizations, and considering that it is a non-invasive procedure, the aesthetic doctor decided to propose the same treatment to the subject, without guaranteeing any results. This method, in fact, had never been applied to specific problems of dyschromia and dark complexions.

2.3. V-EMF Therapy—Principles

V-EMF therapy is a completely non-invasive aesthetic therapy, which combines the simultaneous application of an electromagnetic field (EMF), with a frequency varying from 0.5 to 2 MHz (average power 4–6 W), with a vacuum of 100–150 millibars.

The principles underlying this therapy have been extensively described in Veronese et al. [20].

Briefly, the EMF is generated by a capacitive type radio frequency, in which the capacitor plates are an electrode, which transmits a high frequency signal, and the tissues to be treated. The insulation that must be present between the two plates is composed by a dielectric material, which covers the electrode and the epidermis. The current passing from the electrode to the subepidermal tissues generates the EMF.

EMFs have magneto-mechanical transduction (MMT) as their main effect on tissues. This means that the flow of ions present in the treated tissues is activated, in particular sodium Na+, and potassium K+ ions. Both metabolic and catabolic exchanges are promoted, with consequent proliferative and clearance actions of the tissues and all the cells present in the treated areas [21]. MMT is also strongly related to the piezoelectric activation of tissues, particularly connective tissue, present in the extracellular matrix (ECM) [22]. This activation corresponds to the repair of ECM alterations. Finally, the ionic movement, corresponding to the development of kinetic energy, determines a thermal effect, with an increase in intradermal temperature of 1–2 °C [23], which further promotes the proliferation and clearance of tissues and cells [24].

The application of EMFs in vacuum conditions determines an amplification of the effects obtainable with the sole application of EMFs. Negative pressure promotes mechano-transduction [25], intensifying the effects of the therapy in all skin layers [26–28].

2.4. V-EMF Therapy—Treatment

The subject underwent 9 weekly sessions of 15–20 min each of V-EMF therapy. The therapy was delivered via the Bi-one® Life Touch Therapy device (Expo Italia Srl, Florence, Italy). This device is capable of delivering EMFs and vacuum, both variable, thanks to an automatic feedback control system, which allows the adjustment of the frequency applied based on the thickness of the skin and the heating of the area.

Before each session, the subject's skin was cleaned with a neutral non-alcoholic cleanser. The treatment was delivered with the subject lying supine on a table. The handpiece of the device was positioned on the skin and slid over the face and neck, to ensure the uniformity of action over the entire area.

At the end of each session, no protective, smoothing, or moisturizing products were applied to the skin. The subject was asked not to use topical products during the entire treatment cycle.

2.5. Analysis

One month after V-EMF therapy, the level of satisfaction with the results was tested. Both the subject and the doctor who performed the treatment evaluated the aesthetic results, using a 5-point Likert scale (I = no improvement; II = slight improvement 1–25%; III = moderate improvement 26–50%; IV = good improvement 51–75%; V = very good improvement 76–100%).

Additionally, anonymized facial images before and after treatment were analyzed by two blinded independent dermatologists. They rated the improvements using the same Likert scale mentioned above.

2.6. Imaging Acquisition

For photographic acquisition, the subject was seated in a chair, with his back firmly supported against the backrest. The head was tilted at 45 °C. The photos were acquired using a common smartphone, positioned 15 cm from the patient's face, avoiding the shadow effect. The ambient light was natural.

2.7. Imaging Analysis

Melanin rebalancing was assessed using a new procedure. Skin coloration analysis was performed indirectly with the free software ImageJ.JS v0.5.6 (National Institute of Mental Health, Bethesda, MD, USA). This software was chosen because it was created specifically for the processing of medical and biological images and their analysis, from the visualization of three-dimensional living cells, to the processing of images in radiology, and from the comparison of data from multiple imaging systems, up to the automated analysis of hematological systems.

Photographs taken of the subject before and after treatment were converted to greyscale images (transforming them from RGB colors to 8-bit images).

Using the "Surface Plot" function, three-dimensional greyscale reconstructions were performed of both the areas of the face affected by the dyschromia and the adjacent intact areas. This allowed to qualitatively evaluate both the extent of the damage and the improvement after treatment. The more intact the area, the more uniform the three-dimensional representation.

A quasi-quantitative analysis was performed by evaluating the greyscale distribution with the function: "Histogram". The more intact the area, the narrower the peak in the Gaussian distribution, because there are fewer color deviations.

3. Results

3.1. Aesthetic Results

One month after V-EMF therapy, skin color appeared homogeneous, with both hyperpigmentation macules and hypopigmentation patches disappearing (Figure 2). It should be noted that the post-inflammatory hyperpigmentation had already resolved during the treatment sessions, before the end of the entire cycle. No discomfort or pain on the part of the subject was highlighted during the treatment sessions. No side effects were found after the complete treatment.

As regards the aesthetic effects of the therapy, both the treated subject and the doctor who performed the treatment said that they were extremely satisfied, defining the final result as an excellent improvement (level V on the Likert Scale). The two blindly consulted dermatologists also gave the same score to the improvement observed by comparing the photos of the subject before and after the treatment.

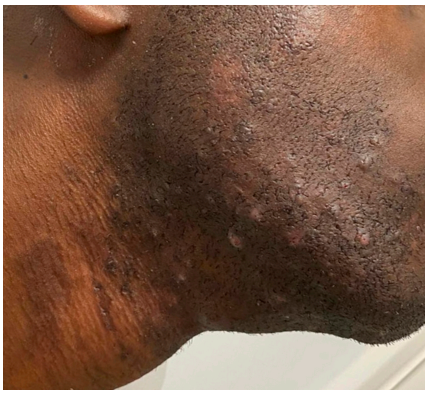
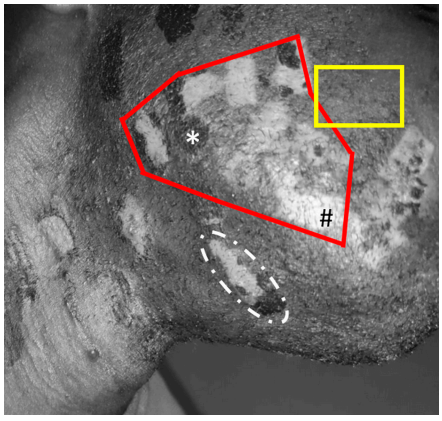


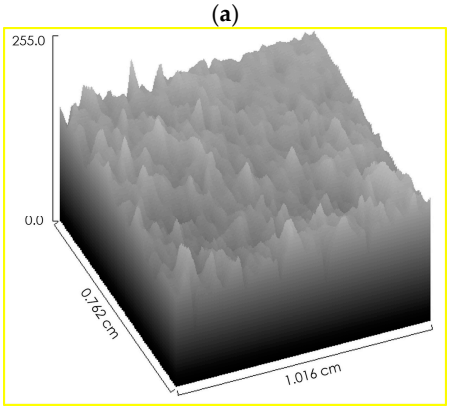
Figure 2. After the treatment, the excellent resolution of the dyschromia was noted. Melanocytic reactivation was evident.

3.2. Imaging Evaluations

After converting the pre-treatment photo to greyscale (Figure 3a), selecting two areas of the face, one healthy and one damaged, the three-dimensional representation of the two areas allowed a qualitative assessment of the levels of melanin present (healthy—Figure 3b; discolored—Figure 3d). The healthy area presented a uniform distribution (Figure 3b), while the damaged area presented a notable inhomogeneity, with the presence of depressions, corresponding to the hypopigmentation patches, and protuberances, corresponding to the hyperpigmentation macules (Figure 3d). Subsequently, the calculation of the distributions of grey values allowed the values of melanin levels to be simulated. Before treatment, the intact area exhibited a narrow-band mono-peak distribution (Figure 3c), confirming the uniformity of the staining. The laser-damaged area had a multi-peak distribution with wide-range values (Figure 3e), confirming the inhomogeneity of the staining.



(**a**)



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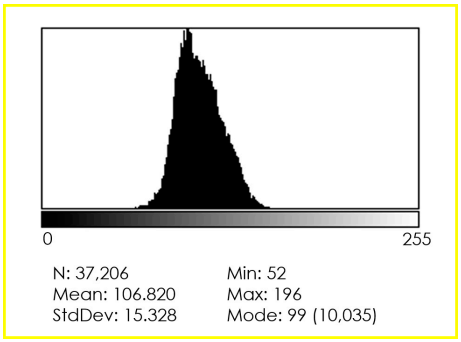
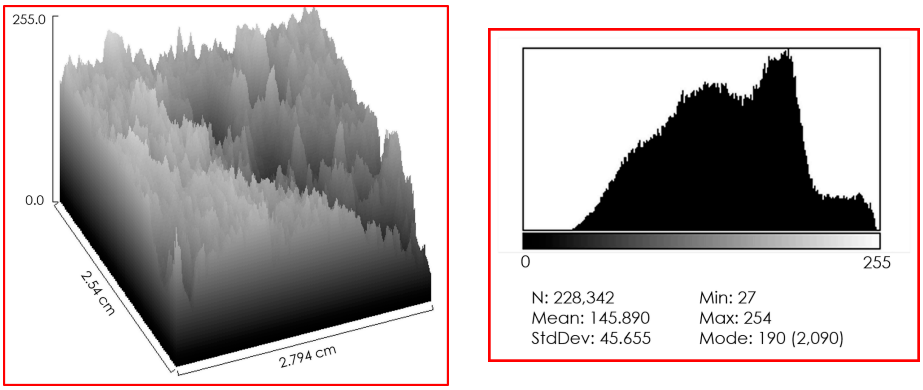


(**c**)

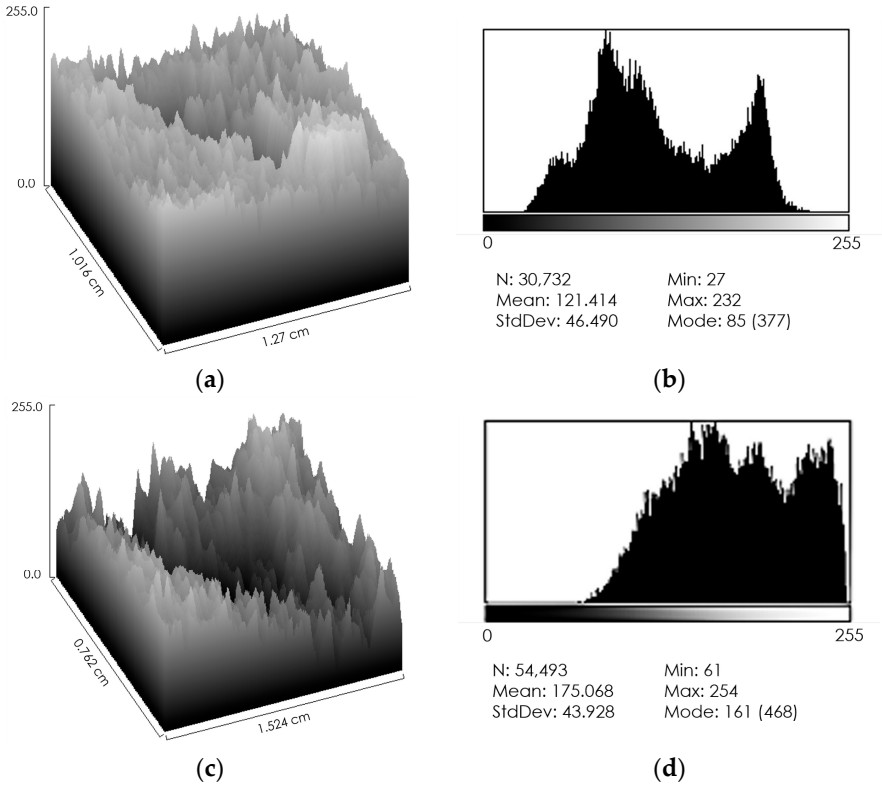
Figure 3. *Cont.*



(**d**) (**e**)

Figure 3. Assessment of pre-treatment melanin levels. (**a**) Conversion of the subject photo to a greyscale image (range 255 pixels). Clearly defined areas of hypo- (#) and hyperpigmentation (*), and areas where the two effects overlap are evident (dotted selection). (**b**) Three-dimensional representation of the healthy area, which has a uniform texture (yellow selection in (**a**)). (**c**) Grey level distribution of the healthy area; levels directly related to melanin levels. Intact, untreated skin shows a single-peak distribution with a narrow range of values, indicating uniform staining. (**d**) Three-dimensional representation of the area treated with the 808 Nm diode laser for hair removal (red selection in (**a**)). The skin texture appears irregular with depressions and bumps. (**e**) Grey level distribution of the treated area. The multi-peak profile indicates uneven skin pigmentation.

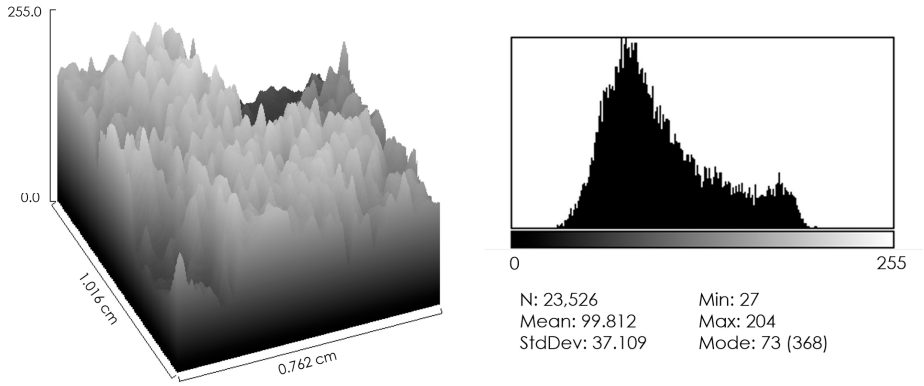
To verify the effectiveness of the method, smaller areas with different types of dyschromia were selected: an area that presented both hyper- and hypopigmentation (Figure 3a—dotted selection), an area with hypopigmentation only (Figure 3a—*), and an area with hyperpigmentation only (Figure 3a—#). Both the three-dimensional reconstruction and the calculation of the distribution of grey levels were performed, confirming the correspondence of depressions for hypopigmentation and bumps for hyperpigmentation (Figure 4).



(**a**) (**b**)

(**c**) (**d**)

Figure 4. *Cont.*



(**e**) (**f**)

Figure 4. Details of skin alterations induced by laser treatment. (**a**) Three-dimensional representation of an area where the effects of hypo and hyperpigmentation overlap (dotted selection in Figure 3a). Both a depression and a bump are present. (**b**) Grey level distribution of the same area shown in (**a**). A multi-peak distribution with a wide range of values is evident, indicating non-uniform staining. (**c**) Three-dimensional representation of an hypopigmented area (# in Figure 3a). A deep depression is evident. (**d**) Grey level distribution of the same area shown in (**c**). A multi-peak distribution with a wide range of values is shown, but this distribution differs from that in (**b**) because the range of values is shifted towards light colors, indicating low levels of melanin. (**e**) Three-dimensional representation of an hyperpigmented area (* in Figure 3a). A protuberance shaped like the laser probe is clearly visible. (**f**) Grey level distribution of the same area shown in (**e**). A multi-peak distribution with a wide range of values is present, but this distribution differs from that in (**b**,**d**) because the range of values is shifted towards dark colors, indicating high levels of melanin.

After converting the post-treatment photo to greyscale (Figure 5a), two areas corresponding approximately to those selected in the pre-treatment photos were selected. Three-dimensional representation was performed for both. The healthy area maintained a uniform distribution (Figure 5b), comparable to the pre-treatment reconstruction (Figure 3b). On the contrary, the area damaged by the laser presented a complete modification, with a three-dimensional reconstruction that was once again homogeneous, free of depressions and protuberances, significant for a normalization of melanin levels (Figure 5d). The greyscale distribution retained its narrow-band mono-peak shape for the healthy area (Figure 5c). A slight difference was noted compared to the pre-treatment distribution (Figure 3c). The most represented values were similar (on the scale of 255 grey tones, 196 pre-treatment vs. 197 post-treatment), while the average value was different (on the scale of 255 grey tones, 106,820 $\pm$ 15,328 pre-treatment vs. 132,837 $\pm$ 15,286 post-treatment). This variation is attributable to the different brightness of the two original photos. By comparing the pre- and post-treatment photos, the difference in brightness was quantified, calculating the average deviation of the two healthy areas, which was equal to 10.2%. It is believed that the different brightness of the photos does not affect the results, since the brightness is homogeneously different in both photos, and no bright spots are noticeable. The greyscale distribution for the damaged area took on a narrow-band mono-peak shape (Figure 5d), thus highlighting the normalization of the structure, i.e., the uniformity of the staining. The difference between the damaged treated area and the adjacent healthy area was attributed to the presence of shaved hair in the treated area.

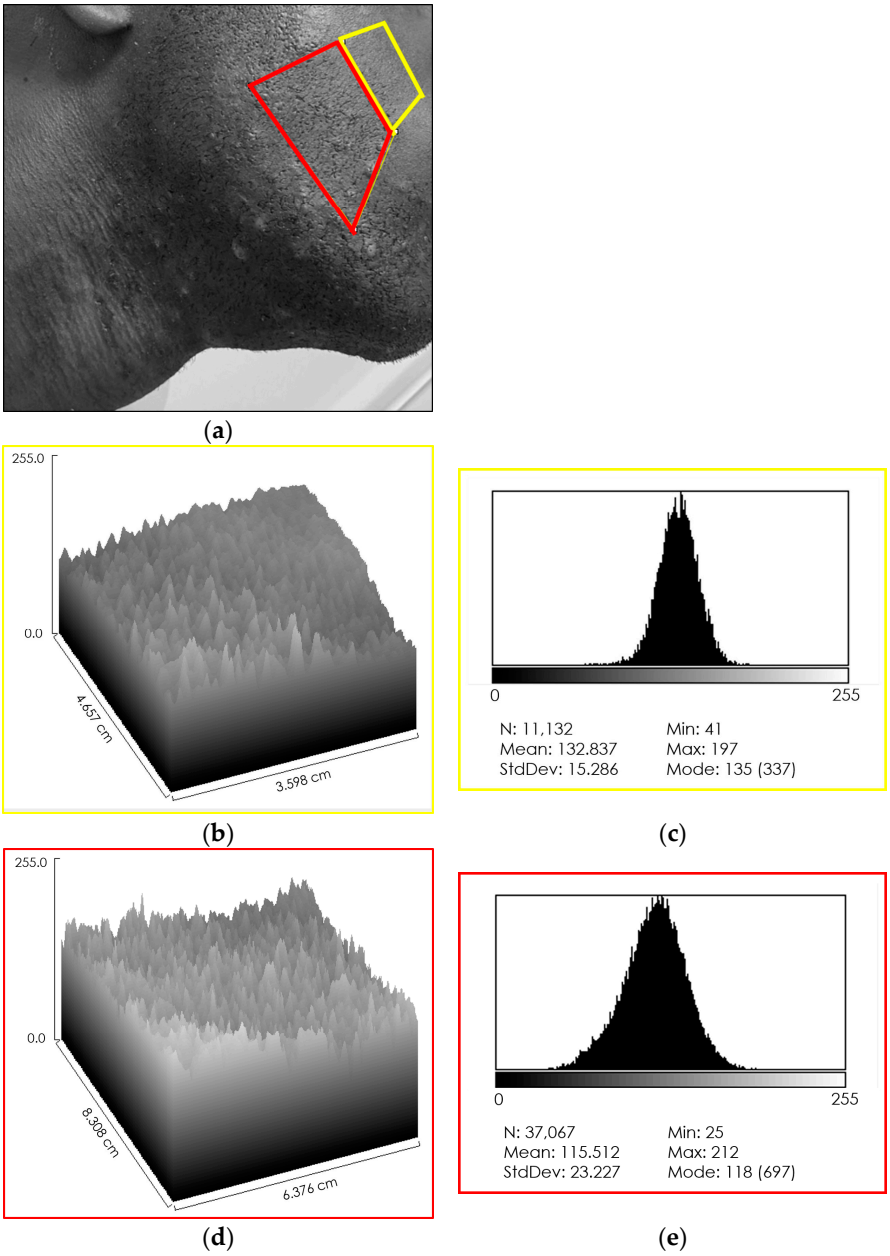


Figure 5. Assessment of post-treatment melanin levels. (**a**) Conversion of the subject photo to a greyscale image with two selections, yellow for intact untreated skin and red for treated skin. (**b**) Three-dimensional representation of the healthy area (yellow selection in (**a**)). (**c**) Grey level distribution of the healthy area. (**d**) Three-dimensional representation of the treated area, where the skin assumes the same profile as intact skin, both with respect to (**b**), and with respect to Figure 3b. (**e**) Grey level distribution of the treated area, which appears mono-peak, signifying the effectiveness of the treatment performed.

4. Discussion

The treatment of irreversible hypopigmentation in individuals with Fitzpatrick skin phototypes IV–VI remains a challenge in dermatology. A recent work by Rao et al. [3] exhaustively documents the possible causes of skin hypopigmentation and the corrective treatments known so far. Compared to hypopigmentation caused by viruses, bacteria, and fungi, which is mainly treated pharmacologically, iatrogenic hypopigmentation is mainly treated with mechanical devices. The literature documents several cases. However, overall, there are few cases of treatments for Fitzpatrick skin phototypes IV–VI.

Kang et al. [29] highlighted the ineffectiveness of many techniques in the treatment of dyschromia in African Americans and Hispanics. However, they also highlighted that interventions on these people are scarce, mainly for economic reasons. In fact, since these are problems understood almost exclusively as purely aesthetic, the costs are totally borne by the interested parties. This fact is extremely serious, if we consider that pigmentation disorders often lead to the onset of psychological effects and the worsening of QoL [4,5].

The case described in this study can be considered rare, as both hyper- and hypopigmentation were present, and the dyschromia was widely spread on the face and neck. This made the choice of treatment particularly difficult, having to resolve opposite situations, with the risk of healing one problem and worsening the other. Since hyperpigmentation spots are often post-inflammatory, and tend to resolve or reduce over time, even without specific treatments, the aesthetic doctor focused on depigmentation.

V-EMF therapy had already been tested in a clinical trial on surgical and burn scars [16]. In this work, the reduction of the visual stigmatization of scars was observed and the unexpected result of the newfound ability of the skin affected by the lesions to tan was noted. Furthermore, the effectiveness of this therapy had already been demonstrated in other studies concerning the treatment of SMs [19] and other facial scars [20,30]. A reduction in the visual stigma of the lesions was noted in all treated patients. In all these studies, an effect of increased metabolism and catabolism in the treated areas was observed, with the regeneration of the extracellular matrix and the rebalancing of the physical characteristics of the skin [16,19,20,30]. In particular, in the treatment of albae SMs, biopsy analysis highlighted an increase in the number of melanocytes after therapy. This was considered the cause of the newfound ability of SMs to tan after sun exposure [19]. At the same time, no hyperpigmentation effects were reported in the areas adjacent to the scars [16] and SMs [19]. This means that the treatment favored the proliferation of melanocytes, and reactivated the function of the few residues present in the depigmented areas, without unbalancing the number and functionality of the melanocytes present in the surrounding undamaged areas. For this reason, the application of this type of treatment to the case described was not considered a gamble, but a possible practice.

The results obtained were excellent, both from an aesthetic point of view and the speed with which they were achieved. The resolution of hypopigmentation spots is clearly attributable to a proliferation of melanocytes, with their functional reactivation. As expected, there were no hyperpigmentation effects in non-depigmented areas. On the contrary, the present hyperpigmentation resolved, with shorter times than those reported in the literature, relating to natural healing [31], times of no less than 6 months for spots a few shades darker than the natural color of the skin. This is attributable to the increase in the metabolism and catabolism of the treated areas.

The negative aspect to highlight is that the treatment was performed in a private aesthetic clinic and the entire cost was borne by the interested subject. That is, the ethical and not irrelevant problem of covering the costs relating to the treatment of dyschromia of dark phototypes remains [29].

However, the use of completely free treatment effectiveness evaluation systems, such as the one used in this study, could help reduce the cost of the treatments themselves, as it would reduce the economic burden on dermatology clinics. The image analysis system used in the present study made it possible to obtain qualitative and semi-quantitative data from the photos, i.e., indirect measures of the effectiveness of the treatment performed. There are numerous non-free software systems on the market for reprocessing facial images, and numerous devices equipped with probes that measure skin parameters. These parameters detect values of the external surface and allow to obtain, again indirectly, information on the intradermal effects of the treatments. A free system, like the one used in this study, could represent a step forward for systems evaluating the effects of skin care. Furthermore, by helping to reduce clinical costs, it could help reduce the costs of treatments, making them accessible to a wider population.

5. Limitations

V-EFM therapy is a new non-invasive medical treatment, used mainly in the aesthetic field. In this study, it was applied to a very particular case. Like all studies that report the experience of a single case, this study, although reporting excellent results, does not allow definitive conclusions to be drawn on the validity of the new therapy presented. The latter, to be applied systematically as a standard in the resolution of problems of dyschromia in general, and of dyschromia in subjects with dark skin in particular, must be appropriately validated through complete clinical trials, on an adequate number of subjects. For this reason, the results obtained, although excellent, can only be defined as promising.

Similarly, the new method for assessing melanin levels also appears to be particularly effective, but it also needs to be tested in a pilot phase, on a larger number of subjects, to be validated.

Finally, for the acquisition of photographic images, it is necessary to develop a standardized process, which allows to avoid errors in the evaluation of the results linked, for example, to environmental conditions, such as the brightness of the room.

6. Conclusions

Considering the results of the case described and the previous applications reported in the literature, V-EMF therapy can be considered a promising technique, guaranteeing rapid effects and resulting painless for the treated subjects. The effects on dyschromia make us reflect on its possible extension to problems of vitiligo and forms of scleroderma. The new system for assessing melanin levels also appears to be extremely promising.

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Institutional Review Board Statement: The present retrospective study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. The treatment has been approved by the Cardiff Cosmetic Clinic. The same device was used in a previous study on the aesthetic treatment of post-surgical and burn scars, a study authorized by an ethics committee [16]. In the present study, the device was used off label for dyschromia secondary to burn scars.

Informed Consent Statement: The subject in this manuscript has given written informed consent for the details of his case to be published.

Data Availability Statement: All relevant data are included in the article.

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