

# Improvement in skin elasticity and dermal revitalization in the treatment of cellulite and connective tissue weakness by means of Extracorporeal Pulse Activation Therapy: EPAT

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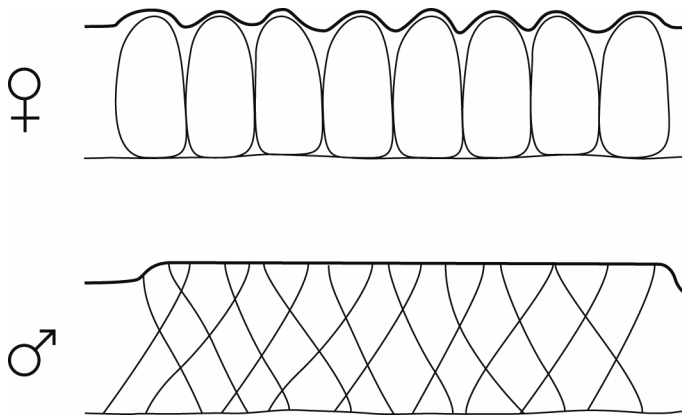
## Summary

The Extracorporeal Pulse Activation Therapy (EPAT) in dermatology may become the first non-invasive treatment method to ensure effective and long-lasting therapy of age-related connective tissue weakness in the extremities, especially in the treatment of unsightly cosmetic skin defects referred to as cellulite. Acoustic pulses stimulate microcirculation in fat tissue and improve existing metabolic regulation disorders to reduce the visible signs of cellulite. The measured elasticity values gradually improve in the course of EPAT therapy. The measured parameters of the mechanical skin properties, skin structure and degree of satisfaction of the female subjects are very promising in terms of the long-term effectiveness (>6 months) of this therapy. No clinically relevant side effects were observed in the course of the long-term study.

## Purpose

The frequently described cosmetic condition known as cellulite is caused by an increase in fat deposits on the buttocks and thighs on the one hand, and by skin ageing due to thinning collagen layers on the other hand. Cellulite typically affects women owing to their genetic pre-disposition to the disorder. In fact, females have 21 to 22 billion fat cells, whereas males only have around 17 to 18 billion. Female fat tissue stores fat more easily and quickly than male tissue as the accumulated fat cells in females act as energy reserve during pregnancies (1,2).

The main cause of cellulite – which from a cosmetic defect may develop into a medical problem in the form of lipedema – is to be found in the structure and condition of the connective tissue. In the female thigh, arched and almost perpendicular collagen fiber bundles run through the subcutis. These structures determine the skin texture at the interface between the corium and subcutis. If one pinches the skin between the thumb and index finger (so-called pinch test), the fat cell chambers bulge out and produce the typical orange peel appearance (1,8). All in all, female skin is more elastic than male skin.



**Fig. 1:** When compared to the fiber orientation in male skin, the structure of the subcutaneous fat tissue on the female thigh clearly explains why the orange peel appearance revealed by the pinch test only occurs in women.

The objective of this study was to stimulate metabolic activity in the subcutaneous fat tissue by using the method of the Extracorporeal Pulse Activation Therapy (EPAT) in order to enhance connective tissue firmness and significantly improve the skin texture and skin structure to visibly reduce the appearance of cellulite.

### **Introduction: loss of skin elasticity**

The fact that the skin, and female skin in particular, is a hormonally influenced organ causes accelerated skin ageing in women when the hormonal milieu changes during menopause. The skin of climacteric women becomes lax and often dry, and facial features begin to lose vitality and firmness. Estrogens in the epidermis stimulate cytogenesis and the production of collagen fibers (9). However, as the estrogen level drops with menopause, collagen neoformation decreases and the quality of the new collagen deteriorates. The number of elastic skin fibers declines and their structure changes. The epidermal tissue becomes weaker, whereas the subcutaneous tissue gradually hardens (1,8,9).

Moreover, skin ageing gradually weakens the skin's natural defense mechanisms. Protein molecules, changed by the influence of oxygen radicals, increasingly accumulate in the skin. However, free radicals are not only produced in response to external stimuli such as sunlight or ozone. They may also result from factors such as smoking, stress, unhealthy diet or excess weight and accumulate in the tissue.

Another factor to be considered is the blood circulation in the skin, which determines the transport of oxygen and nutrients and the migration of immune cells. Lack of exercise due to long sitting or lying, for example, seriously affects lymphatic drainage. This leads to increased fat deposits and causes the skin to gradually develop the distinctive orange peel appearance of cellulite (1,5).

## **Patients and methods**

### **Groups of patients**

A total of 69 female patients with advanced cellulite (stage 2 to 3, revealed by pinch test) and age-related connective tissue weakness were divided into three groups for which slightly different treatment regimens were used:

- 1) Group 1 (Study beginning 2004/12), undergoing 6 therapy sessions within 3 weeks, treated with planar acoustic wave
- 2) Group 2 (2005/ 10) undergoing 8 therapy sessions within 4 weeks, with the planar acoustic wave.
- 3) Group 3 (2006/11) 10 patients were treated only with the D-Actor, the radial pressure pulses.

### **Methods**

Group 1) and 2) were treated between December 2005 and April 2006 in the Utoquai Clinic for Aesthetic Plastic Surgery, Zürich. After completion of preliminary examinations, extracorporeal acoustic waves generated by means of a new therapy system CELLACTOR SC1 were applied to the outer and inner thigh areas and to the gluteal region. Group 3) were treated between November 2006 and February 2007 at the Rosenparkklinik, Darmstadt with the same treatment protocol.

The number of applied pulses per patient and therapy session was identical in both groups. Group 3 was treated with 4000 pulses/treatment area.

Exclusion criteria for three groups were the following:

- pregnancy / breast-feeding,
- anamnesis of phlebitis or deep venous thrombosis in leg,
- inflammations in therapy region,
- liposuction treatment in therapy region more than 6 months prior to the study.

### **Therapy system:**

Extracorporeal acoustic pulses are characterized by high pressure amplitudes, short pressure rise time, short and asymmetric pulse characteristics. They are capable of temporarily transmitting energy from the point of generation to remote regions.

Medically used acoustic pulses are generated extra corporeally and introduced into the body without causing skin lesions. In order to minimize reflection losses as the waves enter the body, acoustic waves must not be generated in air, but in a medium whose acoustic properties are similar to those of human tissue.

For this purpose, the applicator of the CELLACTOR SC1 system, developed by the Swiss company Storz Medical, features a water immersed electromagnetic acoustic wave source with a coupling membrane which is applied to the skin of the female patient. In addition to this, ultrasound gel is applied to the applicator and skin to avoid energy loss through air inclusions.



**Fig. 2:**  
**2-1 Planar applicator**, so-called C-Actor  
CELLACTOR SC1



**2-2: Radial pressure applicator**, so-called D-Actor



**Fig. 3: CELLACTOR SC1**

The previously defined gluteal and femoral therapy regions were treated with 800 pulses with the C-Actor at an average energy level of 0.25 mJ/mm<sup>2</sup> which means that a total of 3200 pulses were applied per patient. With the D-Actor applicator 4000 pulses were applied/ treatment region.

Each treated therapy region had a size of approx. 20 by 30 cm. Treatment was performed by "scanning" the therapy region with the applicator, that is by moving the applicator both horizontally and vertically over the therapy region to ensure uniform tissue treatment.

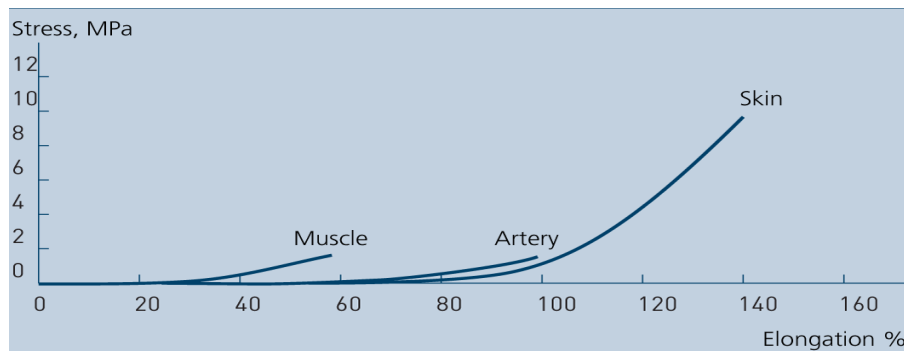
### **Evaluation of skin structure**

Measurements conducted in this study were performed with the DermaLab<sup>®</sup> system developed by Cortex Technology. This system is designed to determine the modulus of elasticity. It works on the basis of the stress-strain relation which is created under vacuum conditions (0 - 65 kPa). The measured values are in MPa. The measuring accuracy specified by the manufacturer is  $\pm 2\%$ . Measurements were always performed in the same skin area and before each therapy session.

Changes in the connective tissue structure in the corium and at the interface with the subcutis were identified by using the DermaScan C<sup>®</sup> ultrasound system, also developed by Cortex Technology. The 20 MHz ultrasound transducer offers a 60 by 130 micron resolution and a 10 mm penetration depth.

Echo-free structures are displayed as black regions in the ultrasound image. Connective tissue structures appear in green, red or yellow. The basic requirement for the measurement and analysis of ultrasound images is that all images are produced with the same system and by using identical amplification settings. As the ultrasound reflection intensity relates to the relative density of the targeted tissue, it also provides information on the arrangement of the collagen and elastic fibers. The color scale indicates the intensity of ultrasound reflection: from white which represents highest reflection down to black which represents lowest reflection.

### Skin elasticity literature values



**Fig. 4:** Stress-strain curve for three different tissues: skin, arteries and muscle [Duck,38]

The literature values found for comparison with the measurements in our observation series were very few and differed significantly between each other. The lack of standardization of methods for the determination of mechanical skin properties has already been criticized in medical literature (16).

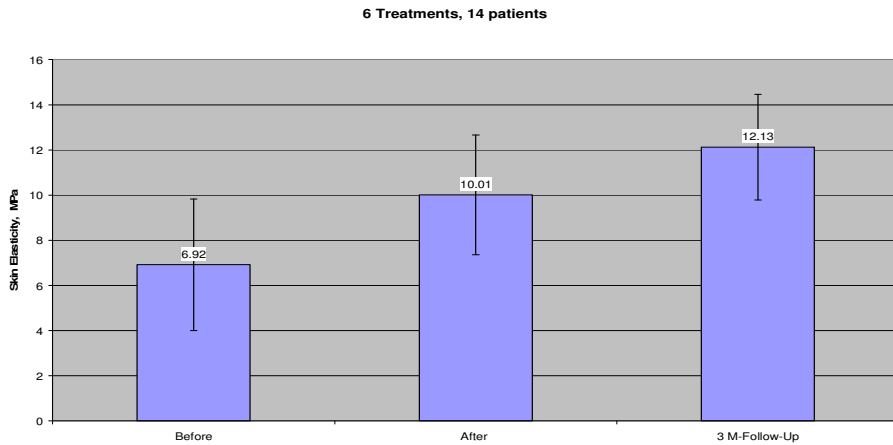
As a result, only values obtained with the same measuring system can be compared, as in this case the stress applied and the tensile speed remain unchanged.

**Results:**

**Changes in skin elasticity**

**Group with 6 therapy sessions, 3-months follow-up  
C-Actor Mode**

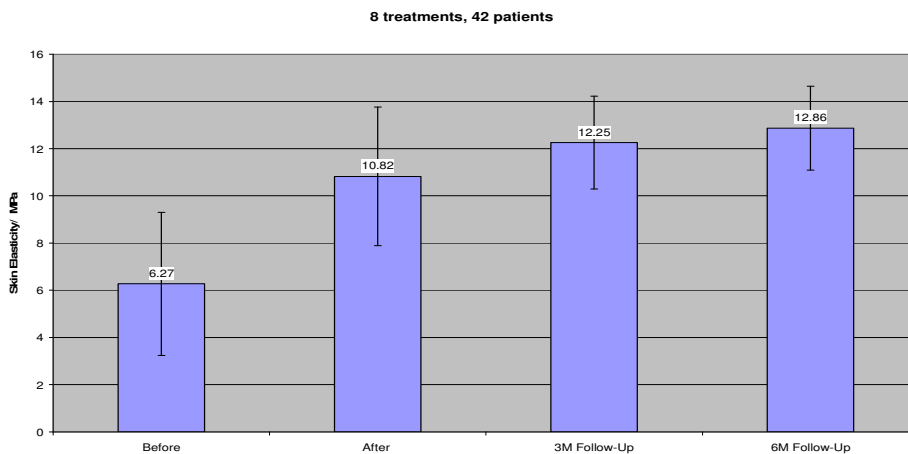
High MPa values mean that higher vacuum were required to lift the skin and thus reflect higher skin firmness. As demonstrated in Fig. 5 skin elasticity increases continuously. The differences between the mean values were highly significant.



**Fig. 5:** Wilcoxon signed rank test: group of n=14 patients out of a total of 15 subjects undergoing 6 therapy sessions and a 3-months follow-up after the last therapy. The measuring values of one patient had to be excluded from the statistics due to non-participation in one of the therapy sessions.

**Group with 8 therapy sessions; 6-months follow-up  
C-Actor Mode**

In Fig: 6 a 6 months follow up was additionally measured in the group with 42 sessions with 8 treatments.



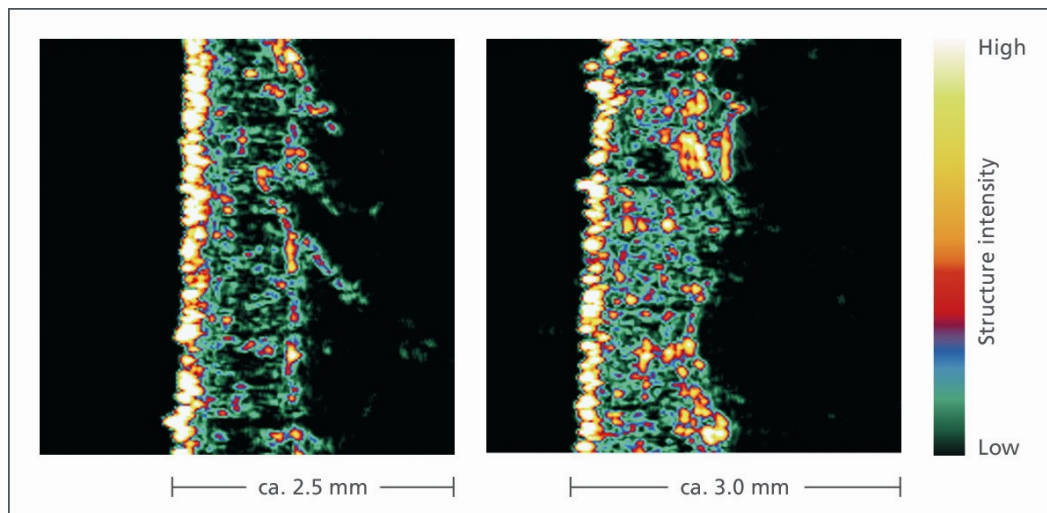
**Fig. 6:** Wilcoxon signed rank test: group of n=42 patients (total n=44) undergoing 8 therapy sessions and 3- and 6-months follow-ups after the last therapy. Two patients had to be excluded from the group due to the lack of measuring data.

The skin elasticity values measured at the end of the therapy (group b) revealed a 73% mean increase (significance  $p < 0.001$ ). At the 3- and 6-months follow-ups, skin elasticity had even improved by 95% and 105% respectively. (significance  $p < 0.001$ ).

By contrast, the improvement in skin properties achieved with chemical skin care products (creams, lotions) generally ranges between 12% and 25% and may reach just over 30% in single cases only. According to Voss and Schlippe from large dermatological studies an improvement of over 40% is to be considered an exceptional result (2).

EPAT - therapy is assumed to reduce significantly existing disorders of the skin by stimulating microcirculation in fat tissue. Acoustic waves tailored specifically for application to the subcutis have only minimal side effects, such as minor pain during therapy or slight skin reddening. This has been confirmed in 95% of the subjects who were treated (2).

### Analysis and evaluation of ultrasound images



**Fig. 7: DermaScan image of cellulite skin in 54-year-old female patient**

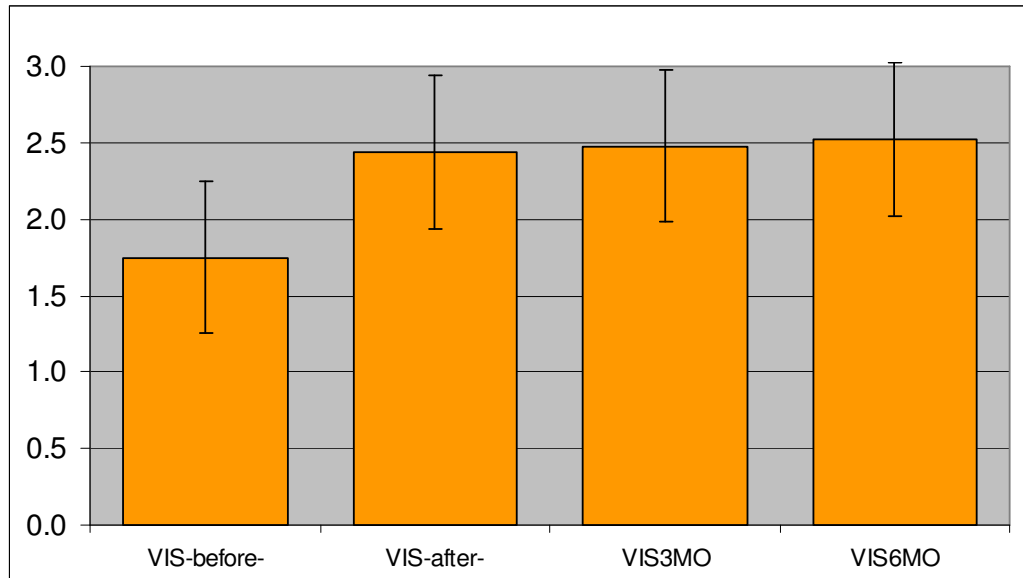
Left (before therapy): the interface between the corium and the subcutis appears as a broken, irregular line; the black structures are fat cells and lymphatic fluid.

Right (after therapy): the skin tissue has become measurably more compact; echo-free interspaces (black) have been reduced.

The ultrasound images were blinded on the basis of the manufacturer's image coding per patient and rated by an independent group of reviewers according to the following criteria:

score 1 = weak structure; score 2 = medium structure; score 3 = firm structure. The images were inserted into a PowerPoint presentation and submitted to the 4 independent reviewers in arbitrary order.

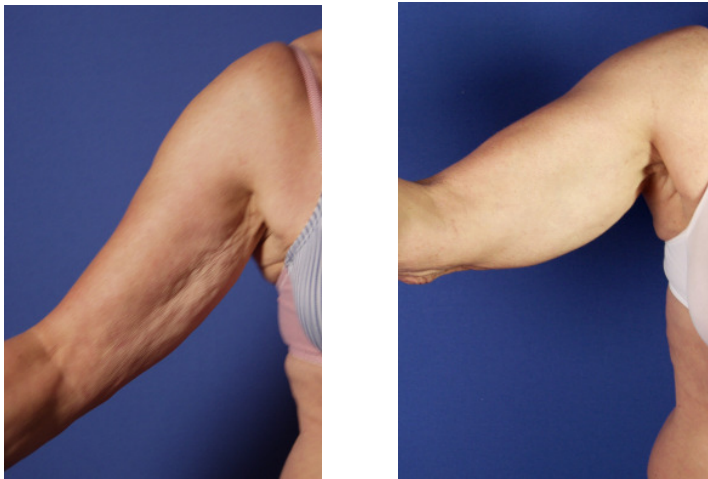
The result of this objective visual evaluation is summarized in the following chart:



**Fig. 8:** Evaluation of score ratings of DermaScan images, including follow-up examinations

The evaluation revealed an upward trend in the visually determined skin firmness values, which had significantly increased from baseline.

### Cosmetic evaluation



**Fig. 9:** Before and after EPAT-Therapy

Cosmetic appearance of upper arms of female patient before and after 6 EPAT/D-Actor Therapy is shown in Fig. 9.





**Fig. 10:** Cosmetic appearance of cellulite on thighs before (left) and after (right) 6 EPAT sessions. Patient with age-related connective tissue weakness.

During the investigations no clinical side effects were observed except minimal pain in 3 of 69 patients. Also this minimal pain was observed 2 to 3 days before the period of the female patients. During these days the applied energy level was reduced.

## Discussion

The observations and results of this study confirm the acoustic wave effects on biological tissue such as the stimulation of microcirculation and the improvement in cell permeability (18,19,20).

Cellulite is associated with a reduced transport capacity of the lymphatic vessels. At an advanced stage of cellulite (lipedema), the lymphatic vascular system is no longer able to return a sufficient amount of protein molecules from the interstitial space into the venous blood system. The high concentration of plasma proteins in the interstice causes fibrosis and thus alters the tissue properties.

This leads to an increase in the impedance jump where the cavitation effect of acoustic pulses takes place. The older the subjects were at the time of treatment and the longer their history of cellulite was, the better was the therapeutic efficacy.

In-vitro tests have shown that the application of acoustic pulses leads to short-term cell permeability increase to allow distinct active substances (e.g. cytostatic agents) to be transferred to the cells (22). In the application under discussion, this cell permeability may stimulate the exchange of substances of fat cells and activate fat-splitting enzymes (phospholipases) through the beta-receptors on the fat cell membranes (3,5,6).

The evaluation of the ultrasound images documents a visually detectable change in the tissue structure. The network of collagen/elastic fibers in the dermis and subcutis becomes denser and measurably firmer. The biochemical examinations conducted so far as part of this study series suggest that

oxidative stress in tissue is reduced, which is assumed to promote collagen synthesis (23).

This would also corroborate the described long-lasting improvement in skin elasticity of up to 6 months.

### **Molecular-biological considerations concerning collagen synthesis**

As already mentioned application of acoustic waves to lipedema and cellulite has proved to significantly reduce the concentration of aldehydic lipid peroxidation products, such as malon dialdehyde, under in-vivo conditions (23).

If the extent of lipid peroxidation (LPO) processes and the accumulation of cytotoxic LPO products can be influenced favorably, i.e. decreased, then this is an indirect though reliable indication of a reduced consumption of low-molecular antioxidants. This means that especially the most important low-molecular antioxidants, such as glutathione, tocopherol (vitE) and ascorbic acid (vitC), are used to a lesser extent, so that intracellular and extracellular concentrations of these compounds remain at a higher level.

The fact that in the case of ascorbic acid this phenomenon is closely related with the protection and improved biosynthesis of collagen is basic textbook knowledge (25). L-ascorbic acid is believed to act both as a classic water-soluble antioxidant and as an electron donator or protective enzyme in hydroxylation.

Hydroxylase is essential for collagen and carnitine biosynthesis. During the normal reaction cycle of prolyl-4-hydroxylase, a hydroxyprolyl peptide develops, with the simultaneous decarboxylation and oxidation of alpha-ketoglutarate to succinate. The valence of the enzyme-bound iron remains unchanged. Uncoupled reaction cycles are characterized by the decarboxylation and oxidation of alpha-ketoglutarate, where oxygen is separated as superoxide radical and the bivalent iron oxidizes to trivalent iron. Since this would inactivate the enzyme required for the following reaction cycles, Fe<sup>3+</sup> must be reduced by ascorbic acid. As a result, ascorbic acid plays an important protective role for the hydroxylases involved in collagen metabolism and carnitine biosynthesis (25).

After all, it is not without reason that scurvy, which develops in case of a massive lack of ascorbic acid, is associated with severe disorders in the connective tissue metabolism and especially with an insufficient collagen formation resulting from a serious disturbance of the hydroxylation reactions of collagen biosynthesis. Consequently, the vitC-dependent hydroxylation of collagen is absolutely essential for the collagen structure and function.

An extensive series of experimental and clinical results as well as clinical studies support the close positive interaction between vitamin C and collagen stability in the skin (26,27,28,29,30,31,32,33,34,35,36,37).

A European study, published in 1997, into the effectiveness of a suction roller massaging device for cellulite treatment (25) revealed an up to 60% reduction of echo-free structures at the corium/subcutis interface, based on the same ultrasound parameters as those used in our study. However, the authors of

the European study confirmed that the achieved improvement in the tissue status only lasted 1.1 months (24).

Judging by the findings gathered to date from stage 2 studies into the effectiveness of EPAT Therapy, the improvement in the tissue status resulting from EPAT lasts up to 6.5 months after completion of the last session.

EPAT is a non-invasive therapy method that requires relatively little time from doctors and patients (that is not highly time-consuming for doctors and patients). Serious side effects have not been found so far. Nevertheless exclusion of side effects has to be observed also in ongoing applications to guarantee the safety of the methodological approach.

EPAT therapy may be developed into a promising, side-effect-free therapy method with long-lasting effectiveness in the field of body shaping and skin rejuvenation.

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