Impact of extracorporeal shock waves on the human skin with cellulite: A case study of an unique instance

Christoph Kuhn[1]
Fiorenzo Angehrn[1]
Ortrud Sonnabend[2]
Axel Voss[3]

[1]Klinik Piano, Biel, Switzerland;
[2]Pathodiagnostics, Herisau, Switzerland; [3]SwiTech Medical AG, Kreuzlingen, Switzerland

Abstract: In this case study of an unique instance, effects of medium-energy, high-focused extracorporeal generated shock waves (ESW) onto the skin and the underlying fat tissue of a cellulite afflicted, 50-year-old woman were investigated. The treatment consisted of four ESW applications within 21 days. Diagnostic high-resolution ultrasound (Collagenoson) was performed before and after treatment. Directly after the last ESW application, skin samples were taken for histopathological analysis from the treated and from the contra-lateral untreated area of skin with cellulite. No damage to the treated skin tissue, in particular no mechanical destruction to the subcutaneous fat, could be demonstrated by histopathological analysis. However an astounding induction of neocollageno- and neoelastino-genesis within the scaffolding fabric of the dermis and subcutis was observed. The dermis increased in thickness as well as the scaffolding within the subcutaneous fat-tissue. Optimization of critical application parameters may turn ESW into a noninvasive cellulite therapy.

Keywords: cellulite, extracellular matrix, fat tissue, high-resolution ultrasound of skin, extracorporeal shock wave, histopathology, scaffolding of subcutaneous connective tissue

Introduction

Affecting most post-adolescent women of all races, cellulite (gynoid lipodystrophy) – the dimpling of skin primarily on thighs and buttocks – can be considered as a normal macroscopic expression of the female skin (Müller and Nürnberger 1972; Pavicic et al 2006). It is uncommon in men. The majority of affected men also suffer androgen-deficiency disorders (such as Klinefelter-syndrome, hypo-gonadism or cirrhosis; Baker et al 1976). While cellulite was the ideal type of women at the times of impressionism, today this "orange peel" aspect of the skin is severely unacceptable, such that it may induce embarrassment and psychosocial inhibition in those suffering its consequences. In itself cellulite is not potentially hazardous to health (Smith 2002). A few treatments ensured by some evidence-based support are available today (such as the mechanical therapy of folding-unfolding and suction called endermology, topically applied caffeine and retinol, and the recommendation of exercise and weight loss; Pavicic et al 2006). Medium-energy, high focused extracorporeal shock waves (ESW) applied locally to the skin with cellulite may be a potential noninvasive therapy approach. Recently low-energy defocused ESW treatment showed some evidence of remodeling of the collagen within the dermis (Angehrn et al 2007). Shock wave treatments are to be distinguished from high intensity ultrasound used in liposculpturing (Adamo et al 1997; Rohrich et al 2000).

Physics of extracorporeal shock wave (ESW)

Shock waves such as lightning strikes with their subsequent thunder are acoustical longitudinal waves that transmit energy through a medium from the place of their

Correspondence: Fiorenzo Angehrn
Klinik Piano, Gottstattstrasse 24,
CH-2504 Biel, Switzerland
Tel +41 32 344 4040
Fax +41 32 344 4042
Email angehrn@klinikpiano.ch
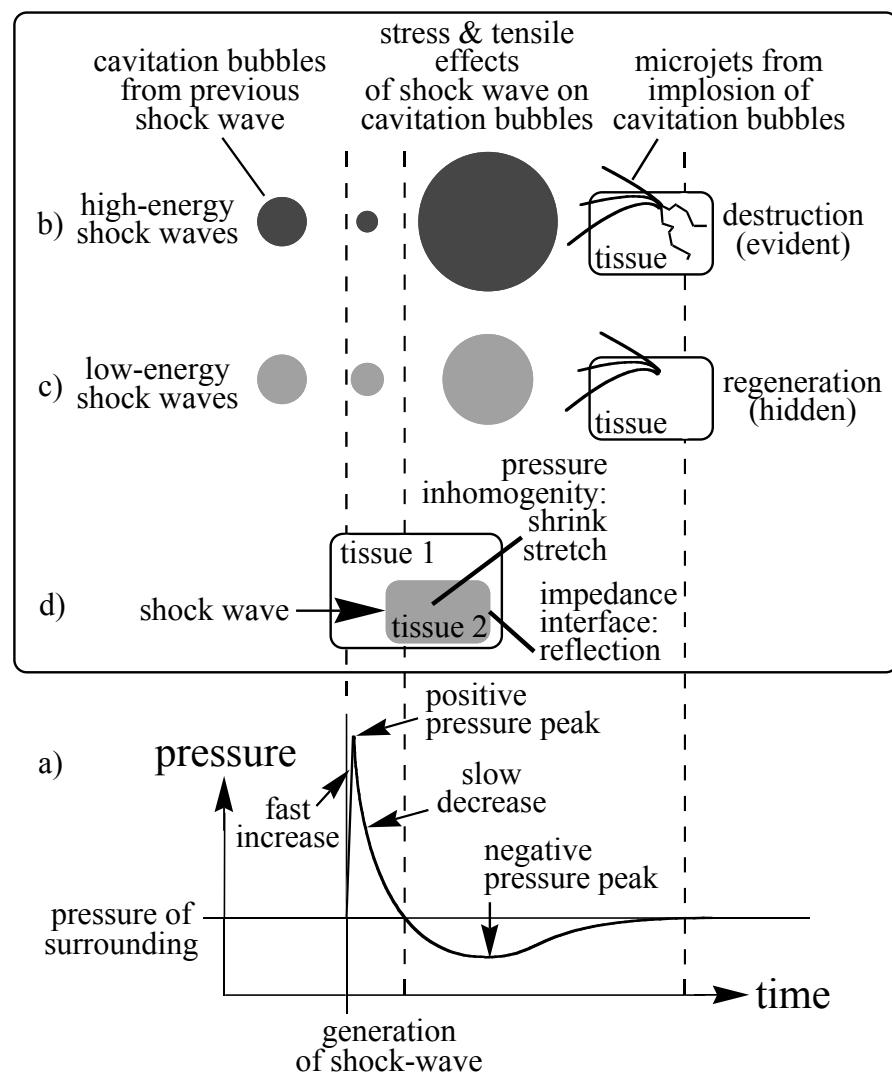
Figure 1 Shock-wave: its physics and main biological effects. **a)** A shock wave is a single, positive pressure pulse rising from surrounding's pressure followed by an exponential descent and a tensile amplitude below surrounding's pressure. The rising occurs within nanoseconds to large amplitude up to 10–100 MPa, whereas the tensile amplitude is of long duration of 2000 nsec with a comparatively small negative pressure peak between 10% to 20% of positive pressure peak. **b)** and **c)** In overcoming the cohesive forces of fluid cavitation bubbles are generated or enlarged by the shock-wave's tensile wave component (even in the case of a negative pressure peak of less than 1 MPa). The bubbles may grow to achieve radii of more than 30 μm. These cavitation bubbles collapse after the shock-wave propagated further and surrounding's pressure is re-established. Subsequent jet-streams can arise with velocities as large as 800 m/sec. **d)** The energy loss at acoustic impedance interfaces between tissues (Table 1) and even at sub-cellular structures (Bereiter-Hahn and Blase 2003; Lemor et al 2004) by refraction and diffraction contribute to the biological effect of ESW (Table 2).

generation to distant areas. Shock waves (Figure 1a) are presented by a single, positive pressure pulse followed by an exponential descent and a comparatively small tensile amplitude below surrounding's pressure (Gerdersmeyer et al 2002; Wilbert 2002; Wess 2006). Due to the high compressibility of gases, small pressure variations induce large changes in the density and temperature of the medium. In less compressible media such as liquids and solids, a shock wave with 10 MPa is still considered weak (Gerdersmeyer et al 2002).

Unfocused extracorporeal shock waves (ESW) radially spread with an energy flow density which decreases by the third power with distance from the applicator. *High-focused, focused,* or *partially focused* ESW (by using elliptic acoustic mirrors) have their maximum of energy flow density at a specific penetration depth. *High-energy* ESW have an energy flow density per pulse of 0.2–0.4 mJ/mm^2 at the focus, whereas *low-energy* ESW have energy flow density per pulse smaller than 0.1 mJ/mm^2 (Rompe et al 1997; Urhahne 2005) with a *medium-energy* focus between 0.1 mJ/mm^2 and 0.2 mJ/mm^2. The damage by high-energy ESW outside of the treatment zone is almost completely avoided by focusing. The ESW *application frequency* is another important physical parameter.

Biological effects of ESW

In overcoming the cohesive forces of fluid by the shock-wave's tensile wave component (Figure 1a) *cavitation bubbles* (Figure 1b and 1c) (Haeussler and Kiefer 1971; Sapozhnikov et al 2002; Wolfrum et al 2003; Wolfrum 2004; Wess 2006) are generated (low frequency range of ESW application) or enlarged (high frequency range). The implosion of large cavitation bubbles and the subsequent strong *jet-streams* (Figure 1c) are the primary cause of adverse effects such as tissue damage, destruction of blood vessels (loosening of endothelial cells; Steinbach 1993) and formation of blood clots in vessels (Brodmann 1998). Energy losses at *acoustic impedance interfaces* (Table 1) on the back side relating shock-wave influx (caused by reflections) as well as the shrink and stretch from pressure inhomogeneity within the shock-wave (Rompe et al 1997; Gerdersmeyer et al 2002) contribute to the biological effects (Figure 1d). High-energy extracorporeal shock wave therapy (ESWT) is worldwide the golden standard to treat urolithiasis through fragmentation of the kidney stone (Müller et al 2004).

On the subcellular level, the damages are the increase of permeability of the cell-membrane (Koshiyama 2006), lesions of the cytoskeleton (Moosavi-Nejad 2006), changes of mitochondria, endoplasmatic reticulum, and nuclear membrane of the cell that may lead to apoptosis (Kato 2007). Biological reactions of liberation of different agents (measured by immuno-histo-chemistry) such as vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (eNOS), and proliferating cell nuclear antigen (PCNA) are reported (Siems et al 2005; Wang et al 2006). ESW-application may induce intra- and extracellular signal-transduction and may generate NO-radicals and heat-shock proteins (HSP) (Neuland et al 2005).

The stimulating effect of low-energy (partially-focused as well as focused) extracorporeal generated shock waves on biological processes within the tissues reached has increasingly become the centre of interest in the last few years. The principle of action, that ESW induces self-regenerating processes within the healthy tissue surrounding the focus of affliction, appears to be universal. A multitude of very different indications like musculoskeletal diseases (calcaneal spur, tennis-elbow, golf-arm, lime-shoulder; Wang et al 2006), orthopedics (pseudarthrosis; Siebert and Buch 1997), chronic skin lesions (ulcus cruris) and burnings (Sparsa et al 2005; Schaden et al 2006) respond positively to shock wave therapy. Shock waves are also effective as a means to increase local blood circulation and metabolism. These mechanisms are considered responsible

for final healing (Delius et al 1995). Thus ESW is already used to treat myocardial ischemia (Nishida et al 2004). Additionally ESW seems to have a high antibacterial effect (Gerdesmeyer et al 2005). Low-energy defocused ESW treatment may be effective in treating cellulite by remodeling collagen within the skin (Angehrn et al 2007). Because of these diverse effects, we investigated the impact of medium-energy, high-focused ESW treatment on cellulite, examining skin and subcutaneous fat by histology.

The pathophysiology of cellulite

Based upon anatomy and histology of the skin, Nürnberger and Müller (1972, 1978) formulated a scheme for development of cellulite (Figure 2). Up to the 7th or 8th

Table 1 Acoustical impedance values related to human skin. Aqueous gel: optimal contact between ESW application device and skin

Substance tissue	Impedance [10^3 kg/s m^2] (lower and upper limits)
Air	429
Water	1480
Fat	138
Skin	1530–1680
Blood	1620
Muscle	1650–1740
Bone	3200–7400

Table 2 Estimates of the energy involved in metabolism (nutritional basic turnover) and of the physical energy of a shock wave (value higher by factor of $4*10^6$). Note that the physical focus of a shock wave (6 dB = 50% isobar) is much smaller than the tissue volume within which the shock wave (after many reflections and diffractions) is finally absorbed

| Metabolism (nutrition, caloric assessment):	
Basal metabolic rate (energy per day)	6480 kJ/86400s = 75 W
Total number of cells	$5.0*10^{13}$
Metabolic rate per cell	$1.5*10^{-12}$ W
Metabolic energy per cell in 1μs	$1.5*10^{-18}$ J
Shock wave (single, duration of 1μs):	
SW-energy in focus volume in 1μs	$3.1*10^{-3}$ J
Focus-volume (6 dB = 50% isobar, elipsoid length 21 mm and ∅ 7.2 mm)	$5.7*10^{-7}$ m^3
Total body volume (cellular fraction: 75%)	$7.5*10^{-2}$ m^3
Mean cell volume	$1.1*10^{-15}$ m^3
Number of cells in focus-volume	$5.2*10^8$
SW-energy per cell in 1μs	$6.0*10^{-12}$ J
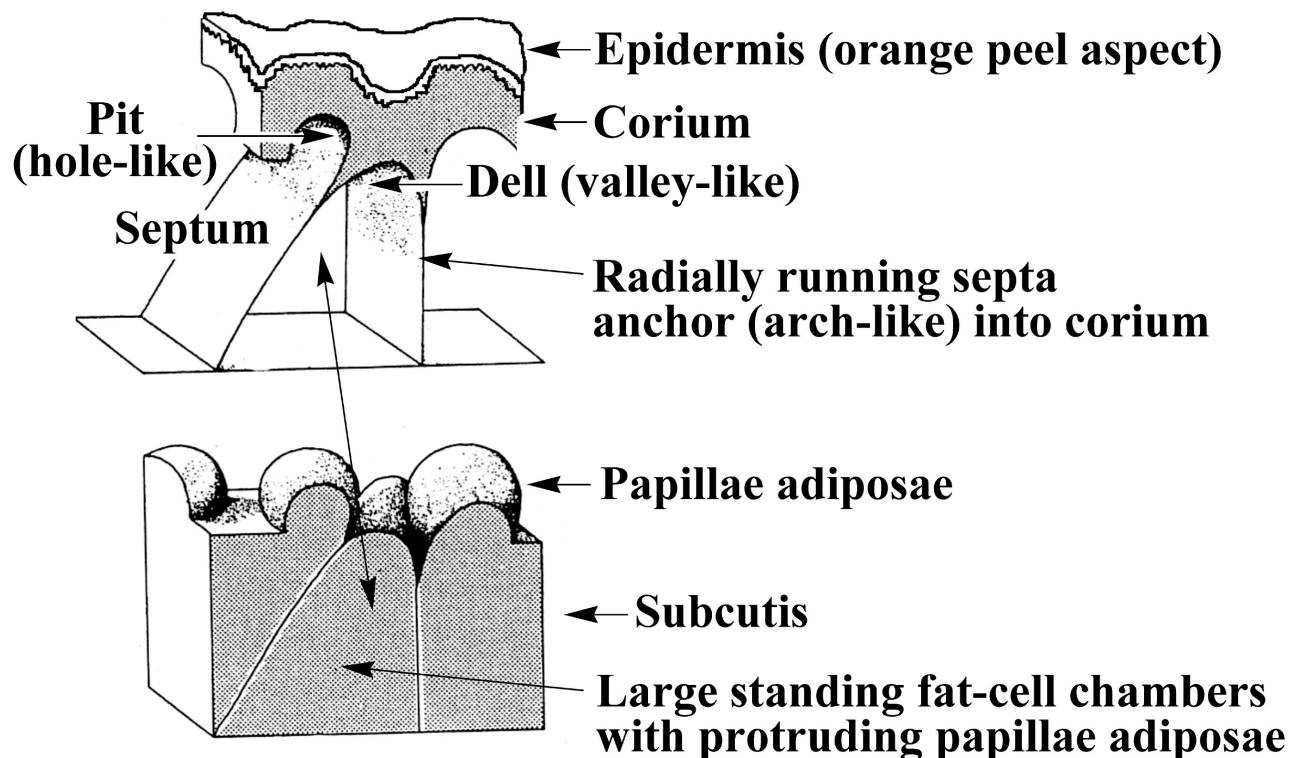
Figure 2 Inner structure of the female skin and the underlying subcutaneous tissue. Partitioned border zone between corium and subcutis. The plane of the subcutis with papillae adiposae rising into dells (valley-like) and pits (hole-like) on the undersurface of the corium. Modified from Nürnberger and Müller 1978.

fetal month in both sexes, the upper part of the subcutaneous tissue just below the corium consists of standing fat-cell chambers and septa running radially similar to those of the adult woman. At birth, sex-typical differences are clearly manifest: in male newborns, small, polygonal fat-cell chambers and septa of netted, angled and parallel to the surface, crisscrossing connective tissue are distinctly those of adult males in addition to the corium being thicker and coarser in fibrous structure. These sex-typical structural differences probably are called forth by the proliferative effect of androgens on the mesenchyme (fibroblast activity) during the last third of fetal life.

Incipient cellulite recognized by an "orange peel" appearance represents focally enlarged fibro-sclerotic strands partitioning the hypodermis and limiting the out pouching of fat lobules (Quatresooz et al 2006). In contrast, full-blown cellulite recognized by a dimpled skin surface represents subjugation of the hypertrophic response of the hypodermal connective tissue strands when the resistance is overcome by progressive fat accumulation (in subjects with high body mass indexes) forming papillae adiposae that protrude into the lower reticular dermis (Quatresooz et al 2006). A simple grading-score of cellulite by inspection is given (Nürnberger and Müller 1978) (Table 3).

Prospective design study: Methods, materials and human resources
Human resource
A woman aged 50 with colored skin and cellulite grade 3 at her thighs and buttocks had to have surgery on both hips. After giving her informed consent, she agreed to have the skin at her left thigh treated with ESW several times (Table 4) before the operation. The hip-surgery was carried out under lumbar anesthesia and on this occasion two representative full-thickness skin samples were taken at the same time, one at the site of the ESW application and one at the contra-lateral, symmetric untreated side to be examined by means of histopathology. The following regime was carried out:

Table 3 Cellulite grading (Nürnberger and Müller 1978)

Grade	Definition
0	• Smooth surface of skin while lying down and standing. • Wrinkles upon pinch-test.
1	• Smooth surface of skin while lying down and standing. • Mattress-phenomenon upon pinch-test.
2	• Smooth surface of skin while lying down. • Mattress-phenomenon spontaneously while standing.
3	• Mattress-phenomenon spontaneously while standing and lying down.

Table 4 ESW application and therapy documentation scheme

		Left	Right
Day 0	LCCT	•	•
	Collagenoson	•	•
	1. ESWT application	•	
Day 7	*2. ESWT application*	•	
Day 14	*3. ESWT application*	•	
	LCCT	•	•
Day 21	LCCT	•	•
	4. ESWT application	•	
	Collagenoson	•	•
	Surgery: skin samples	•	•

ESW-Device

The shock waves are produced by electro-hydraulic means with the device ActiVitor-Derma®, the probe ActiVitor Probe D0 and along with the following adjustments (Table 5).

Collagenoson®

The high-resolution ultrasound of the skin (Tikjob et al 1984) represents an imaging-producing and noninvasive diagnostic tool, which is able to give an exact representation of the skin and its adnexa. The ultrasound system used in this study included a probe of 22 MHz (yielding a high-resolution axial of 50 µm, lateral of 200 µm, and a depth of 6 mm) that was placed upon wet skin. It measured the microstructure of the mesenchymal connective tissue and the collagen structures within the extracellular matrix of the dermis (collagenometry), showing both the epidermis and the boundary between dermis and subcutis. With this device, the structure and the quality

Table 5 ESW application adjustments

Focus	High-focused
6 dB (= 50%) isobar	
Length (z)	21 mm
Diameter ⌀ (x,y)	7.2 mm
Penetration depth	5.0 mm
Pressure rising-time	10–15 nsec
Shock-wave duration	1–2 µsec
Positive pressure peak	40 MPa
Negative pressure peak	1–2 MPa
Energy flow density	0.115 mJ/mm^2
Frequency	4 Hz
Number of pulses	200/cm^2
Treated area	2 x 2 cm^2
Total duration	3 min + 20 sec

of the collagen and thus the result of cellulite therapy can be exactly evaluated (Mole et al 2004).

LCCT-device

Liquid crystal contact thermography (LCCT) measures minor differences in skin temperature (Hoffmann et al 1989). Here we use LCCT to detect a change in micro-perfusion of the surrounding tissue treated by ESW.

Results and discussion

Hyperemia was clearly visible by LCCT at the site of ESW treatment, starting from immediately thereafter and lasting days (Figure 3). Comparing high frequency, high resolution ultrasound measurements of medium-energy, high-focused ESW-treated and untreated skin areas, we could see some improvement in the epidermis and the extracellular matrix of the dermis (Figure 4).

Impact of ESW on extracellular matrix of skin with cellulite

In a recent study (Angehrn et al 2007) the hypothesis was stated that low-energy defocused ESW treatment (12 therapy sessions) is effective in treating cellulite through the remodeling of skin's collagen. This effect can be corroborated by the subjective comments of the subjects (where improvement from treatment may have a latent period of from 2 to 6 months) as well as by measuring the microstructure of the skin using high frequency ultrasound (Collagenoson®). The present prospective design study (medium-energy, high-focused ESWT, 4 therapy sessions) supports this hypothesis by a histopathologic sample. On this sample no signs of tissue repair are visible. However an amazing induction of neocollageno- and neoelastino-genesis is observed within the scaffolding fabric of dermis resulting in increased in thickness of the dermis (Figure 5).

Impact of ESW on subcutaneous fat tissue

Besides tightening the skin and improving its quality, an ideal therapy of cellulite should assure a reduction of subcutaneous fat. In our case of ESW treatment and the follow-on by histological analysis, we could not ascertain any direct or indirect signs of mechanical destruction or liquefying of fat tissue on any one of the histological slices. Signs of necrosis as well as the infiltration of leucocytes and macrophages were absent. In the course of our limited facility of histological methods, we could not entirely role out fat reduction by apoptosis. On the other hand, we could detect a substantial increase in the scaffolding of the subcutaneous fat tissue and we thus
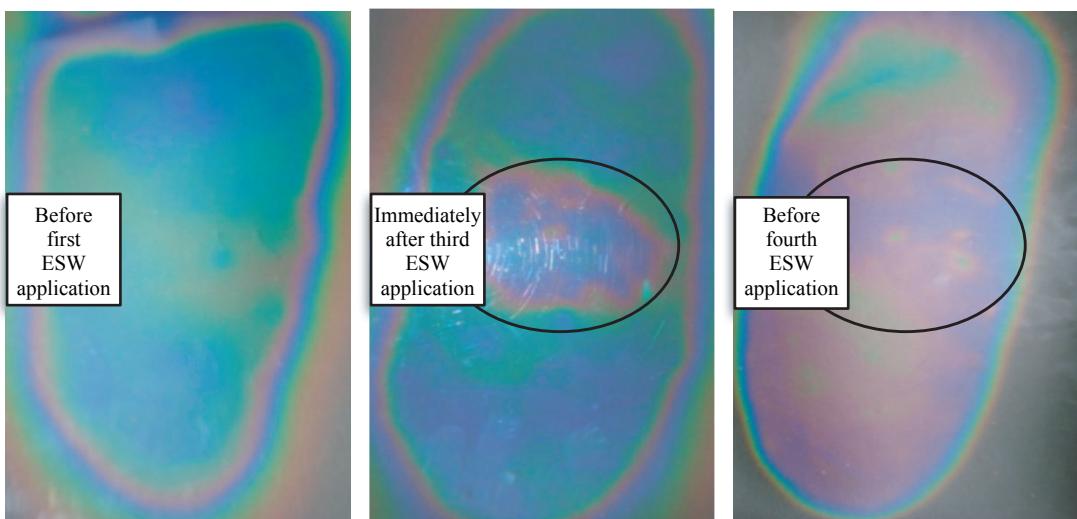
Figure 3 LCCT (Liquid crystal contact thermography, RW27ST with colors corresponding to temperature steps of 0.70 Celsius) of left, proximal, lateral thigh: before 1st ESW-application (control, left), immediately after 3rd ESW-application (middle) and before 4th ESW-application (right). Note the hyperemia at the site of ESW-treatment.
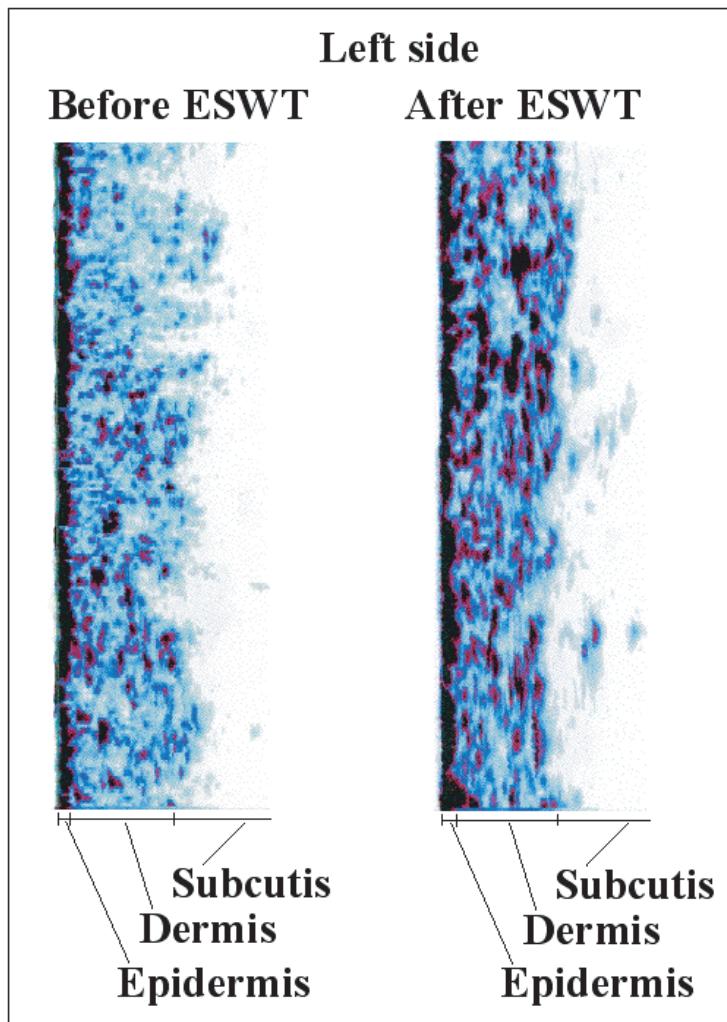

Figure 4 High-frequency high-resolution ultrasound measurement of skin (Collagenoson®) of left thigh before treatment (control) and after treatment (same site). Treatment: medium-energy, high focused ESW. Notice: increased collagen contentment after treatment.

a) HE   not treated   ESW-treated
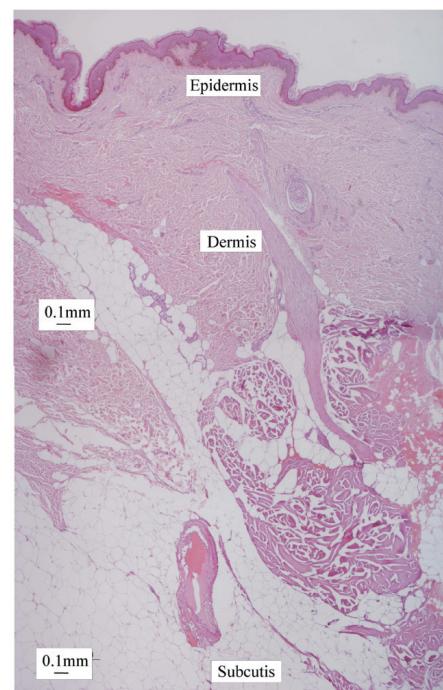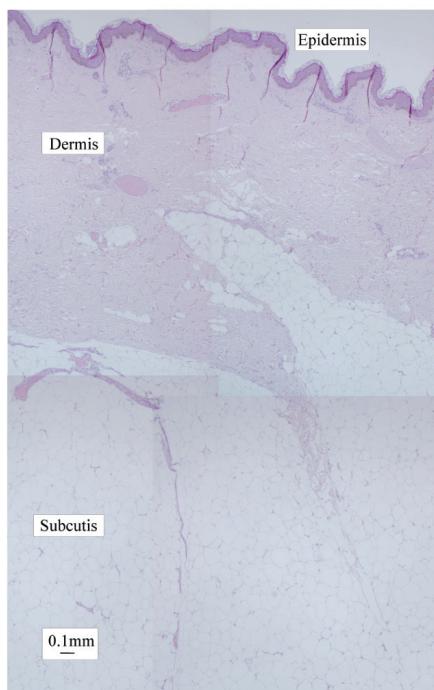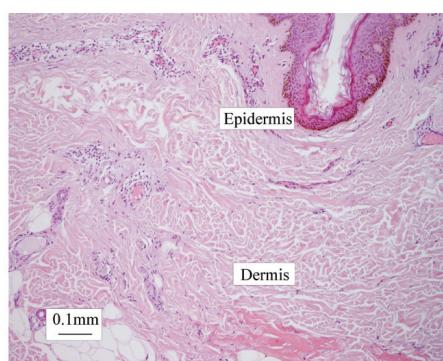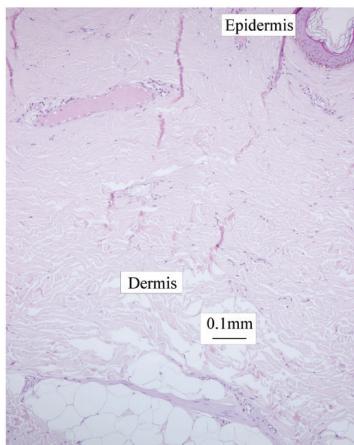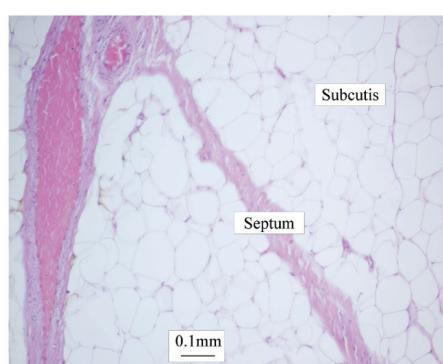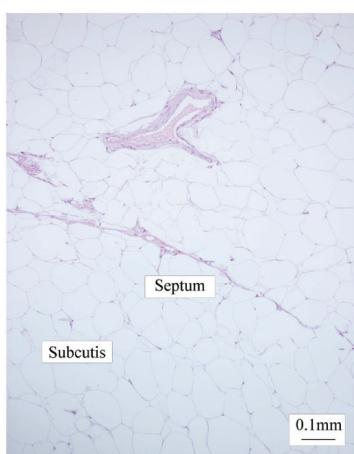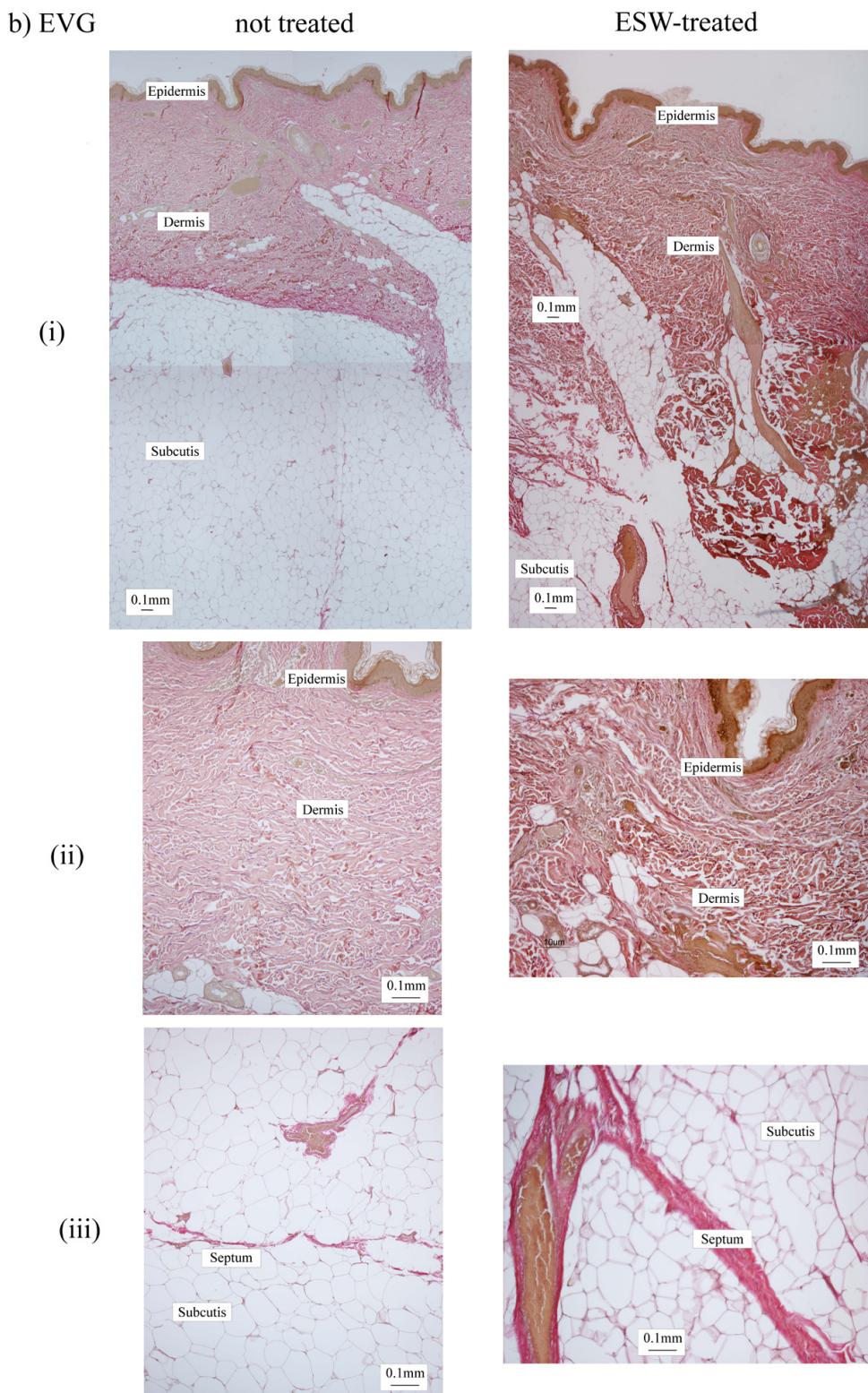
Figure 5 Histopathology of skin and of subcutaneous fat tissue. **a**) Hematoxylin Eosin stain (HE, nuclei: blue; cytoplasma and connective tissue: red-pink), **b**) Elastin Van Gieson stain with Resorcin-Fuchsin (EVG, elastic fibers: black, collagen: red, muscle tissue: yellow). One characteristic and representative slide taken from the central (ESW-treated) part of the skin-sample (surface: 75 mm*28 mm, depth: 40 mm, evenly spaced slides) and a corresponding slide (control) of the not treated skin-sample (surface: 70 mm*25 mm, depth 40 mm). Photographs focusing (**i**) epidermis/dermis/subcutis (4×-objective), (**ii**) epidermis/dermis (10×-objective), (**iii**) subcutis (10×-objective).
Note: Magnification of each image indicated by bar. No signs of tissue repair are visible – such signs of a response to an injury would be tissue-necrosis, extravasation of erythrocytes, the infiltration of neutrophils lymphocytes and macrophages and the subsequent scar-formation. However an increase of the skin's connective tissue, the extracellular matrix, particularly collagen and possibly elastin is observed resulting in increased thickness of the dermis and of the scaffolding within the subcutaneous fat tissue.

conjecture a stupendous induction of neocollageno- and neoelastino-genesis within the subcutaneous tissue by ESW.

Conclusion

The application of external and internal forces are considered to be able to regulate gene expression and cell behavior. In particular, cell stretch is considered to be a stimulus supporting cell proliferation (skin expanders). The signaling pathways linking mechanical stretch to cell proliferation and survival (eg, activation of anti-apoptotic kinase PKB/Act) are still not well described (Kippenberger et al 2005).

These encouraging results put forward that optimization of critical application parameters may turn ESW into a noninvasive cellulite therapy, not by reduction of subcutaneous fat, but by strengthening the skin's scaffolding fabric, particularly of the dermis and the subcutaneous fat tissue.

Further studies should show whether parameters such as the patient's age (adolescent, adult or elderly females), body-composition (obesity), and the stage of cellulite have an influence on the outcome of ESW treatment. In our case, a histological analysis was possible by a planned operation symmetrical and at the same sites. In implementing a study with many participants, a noninvasive method of analysis must be applied such as high-resolution ultrasound.

Acknowledgments

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