

**Anti-fibrosclerotic effects,
improvement in skin elasticity
and dermal revitalization in the treatment of
cellulite and connective tissue weakness by**

Acoustic Wave Therapy

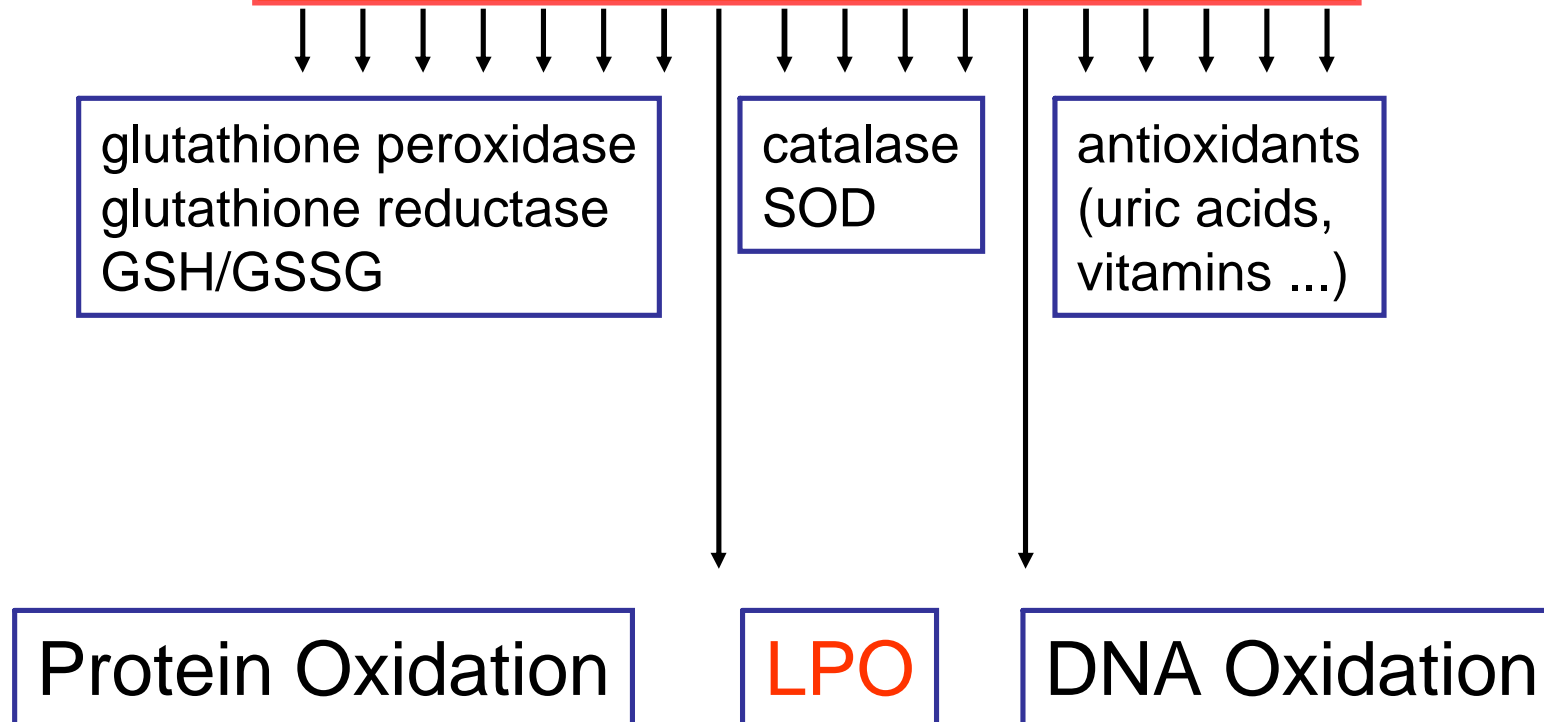
Futureperfect Body Management Workshop

May 12-13, 2007, Dallas

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Primary Antioxidative Defense

Free Radicals and Oxidants



Products of Lipid Peroxidation

- lipid hydroperoxides
- hydroxylipids
- conjugated dienes
- modified phospholipids
- oxidized cholesterol and cholesterol esters
- alkanes (ethane, pentane)
- 'soluble' aldehydic products
 - alkanals (ethane, pentane)
 - alkanals (hexanal)
 - alkenals (hexenal)
 - hydroxyalkenals (HNE)
 - bifunctional aldehydes (MDA)

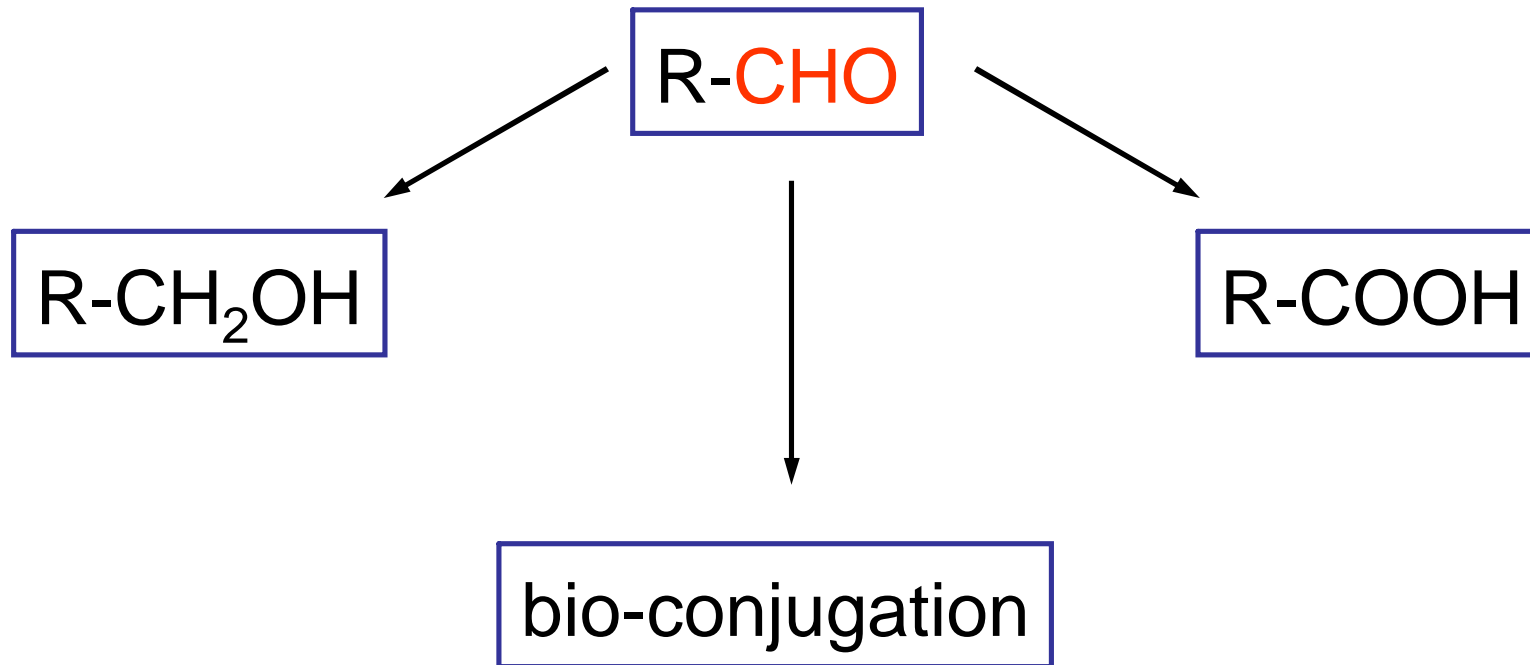
Detection of HNE

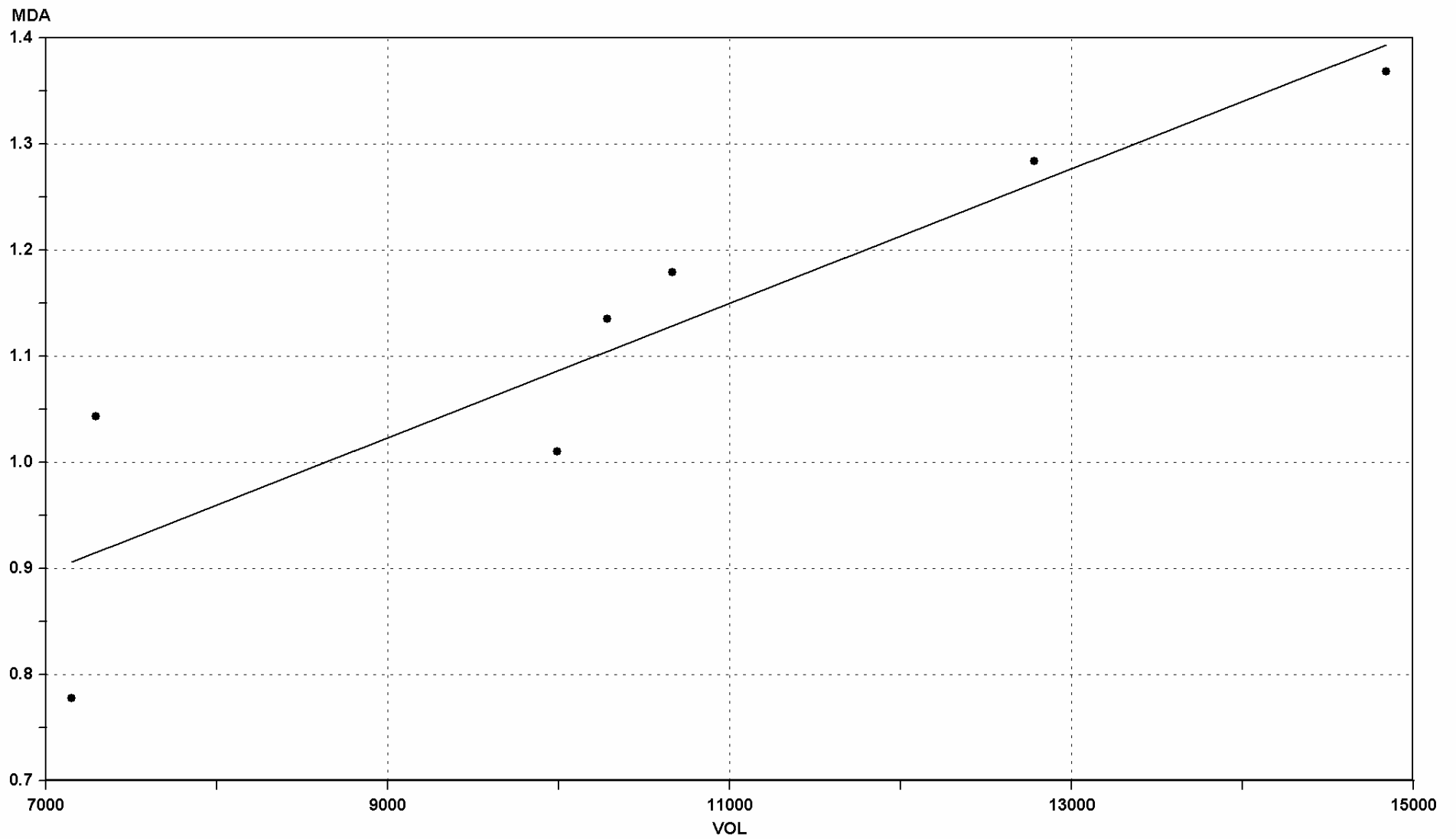
- direct HPLC measurement (223 nm)
- DNPH derivatisation (TLC, HPLC)
- Derivatisation and GC/MS
- Antibodies to HNE-protein-adducts

Common Detection Methods of MDA

- Direct measurement (HPLC, urine)
- TBA reaction
 - spectrophotometric ($E_{535\text{nm}}$ or $E_{535-520\text{nm}}$)
 - fluorometric (515/550 nm)
 - HPLC with fluorometric detection

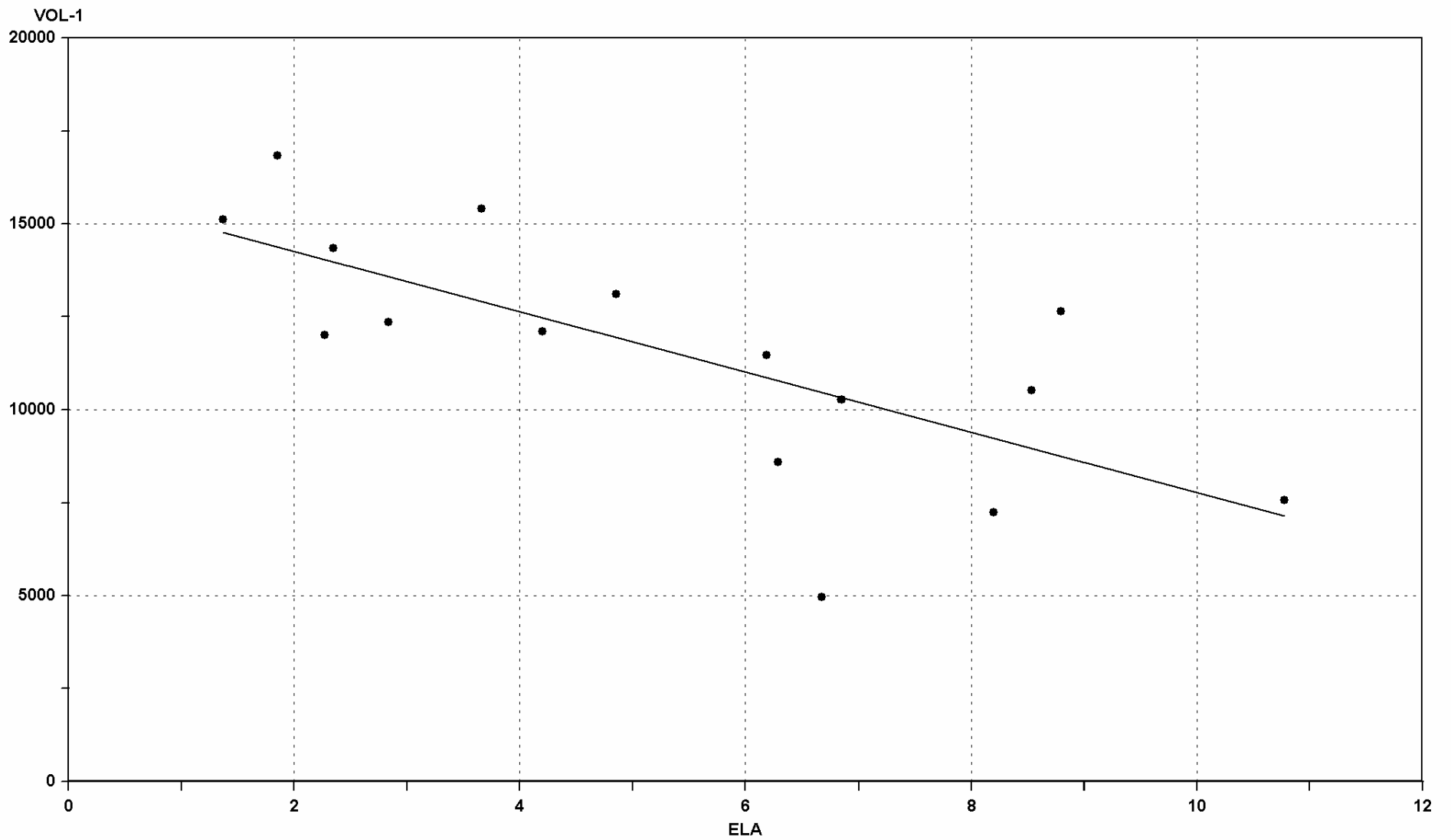
Biochemical Reactions of Aldehydic Lipid Peroxidation Products





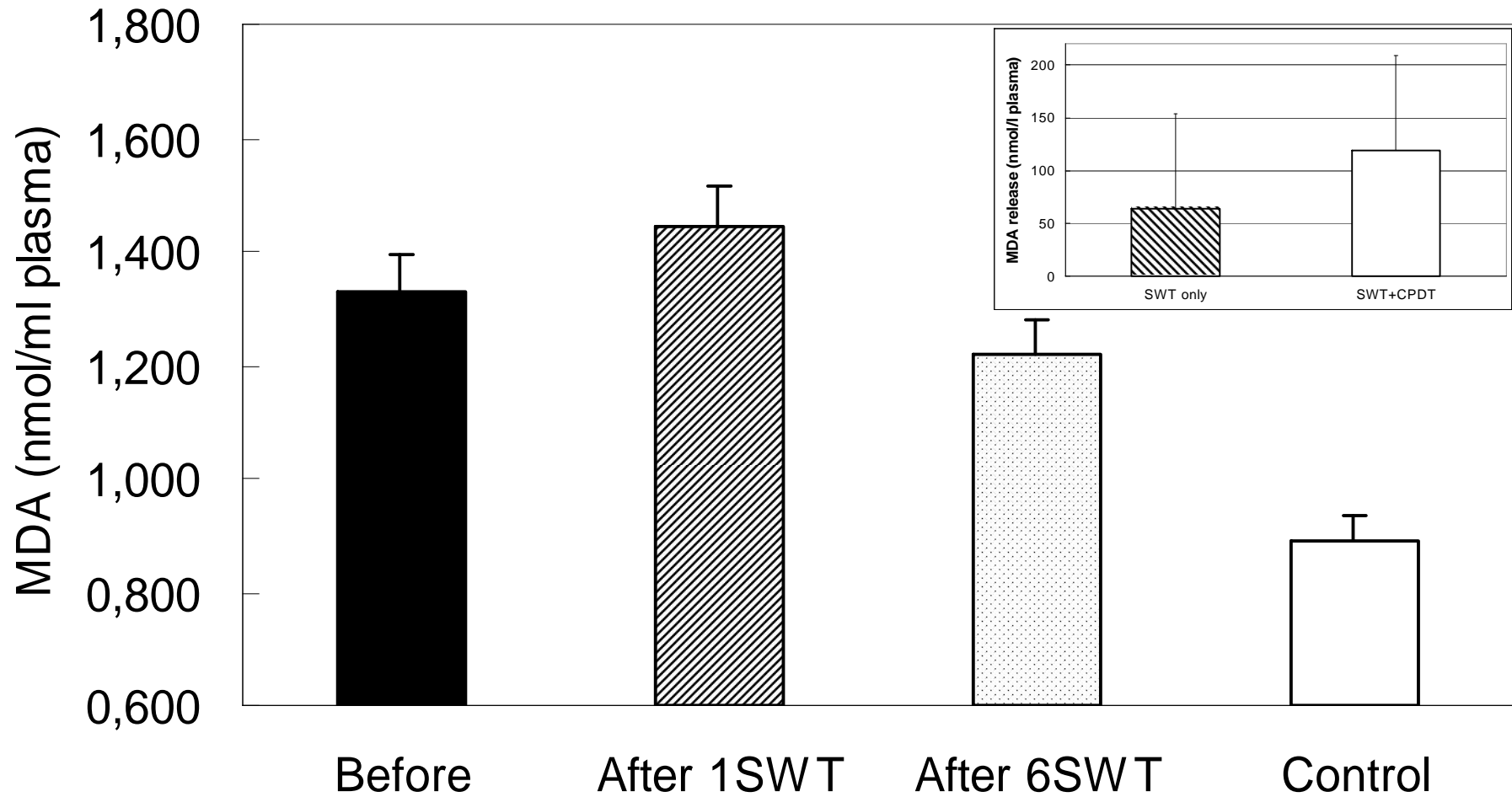
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p = 0.0058

se = 0.09285
y = 0.00006331*x + 0.4535

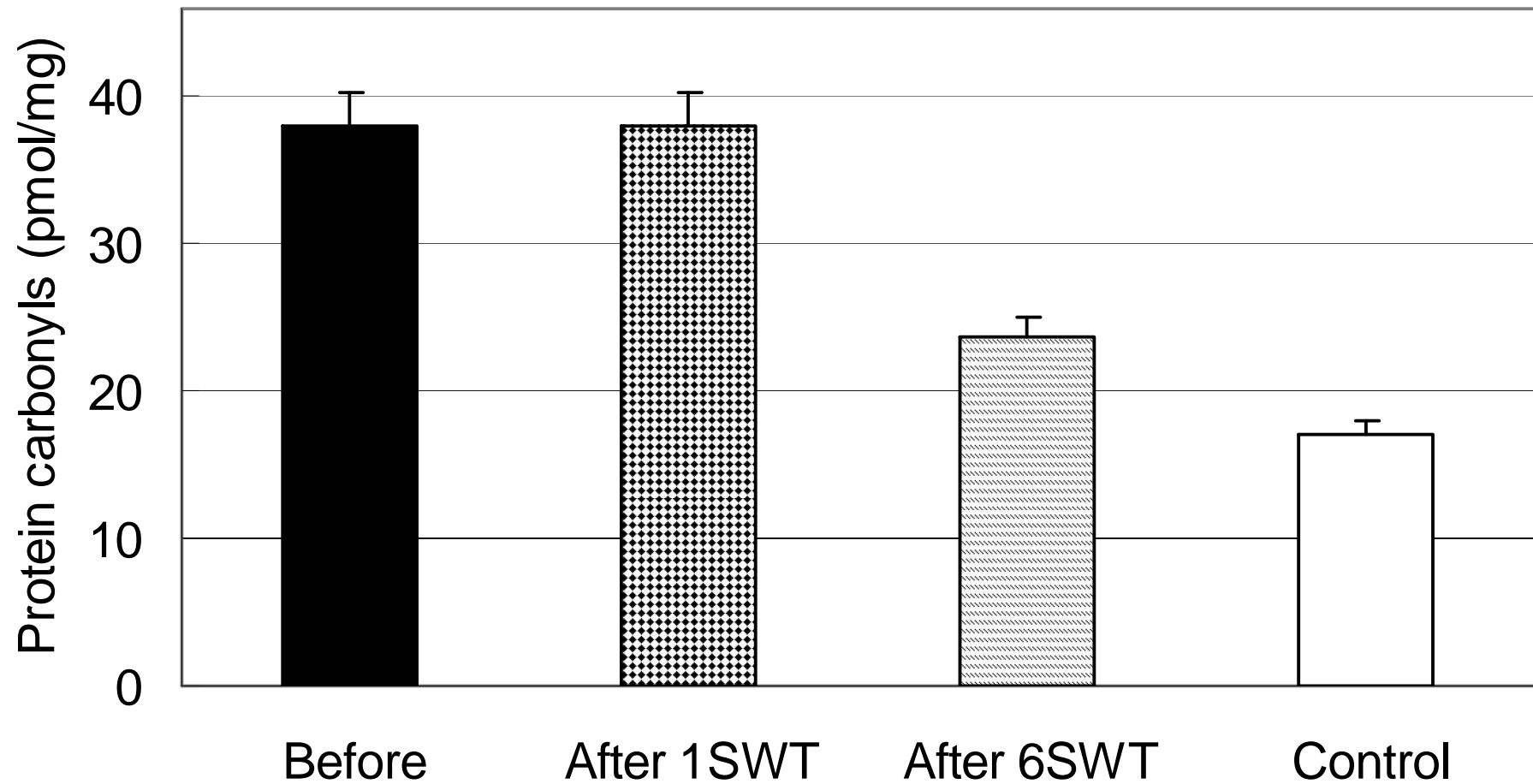


r=-0.7153 n=16
p = 0.0018

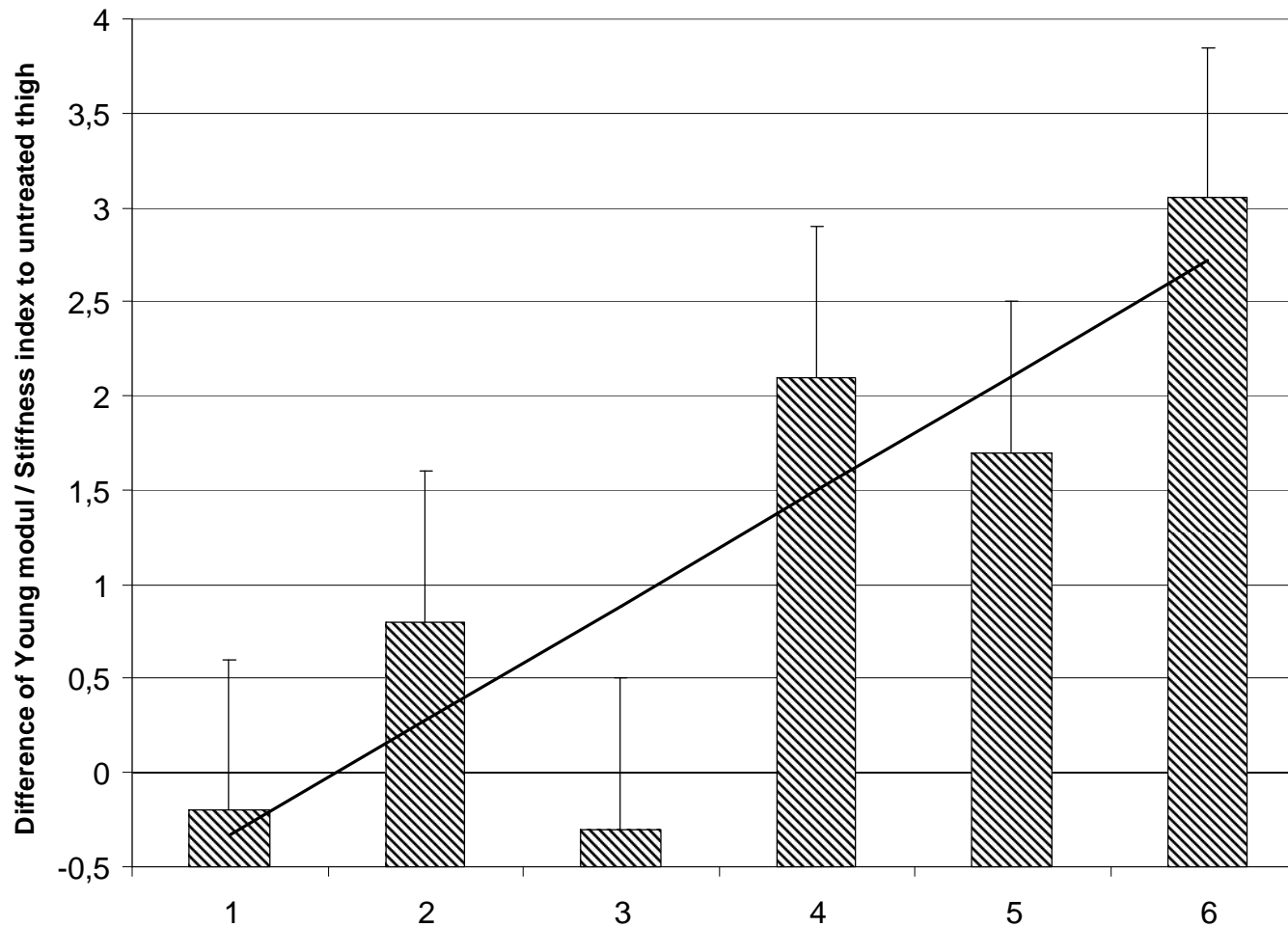
se = 2343.9
y = -810.67*x + 15877



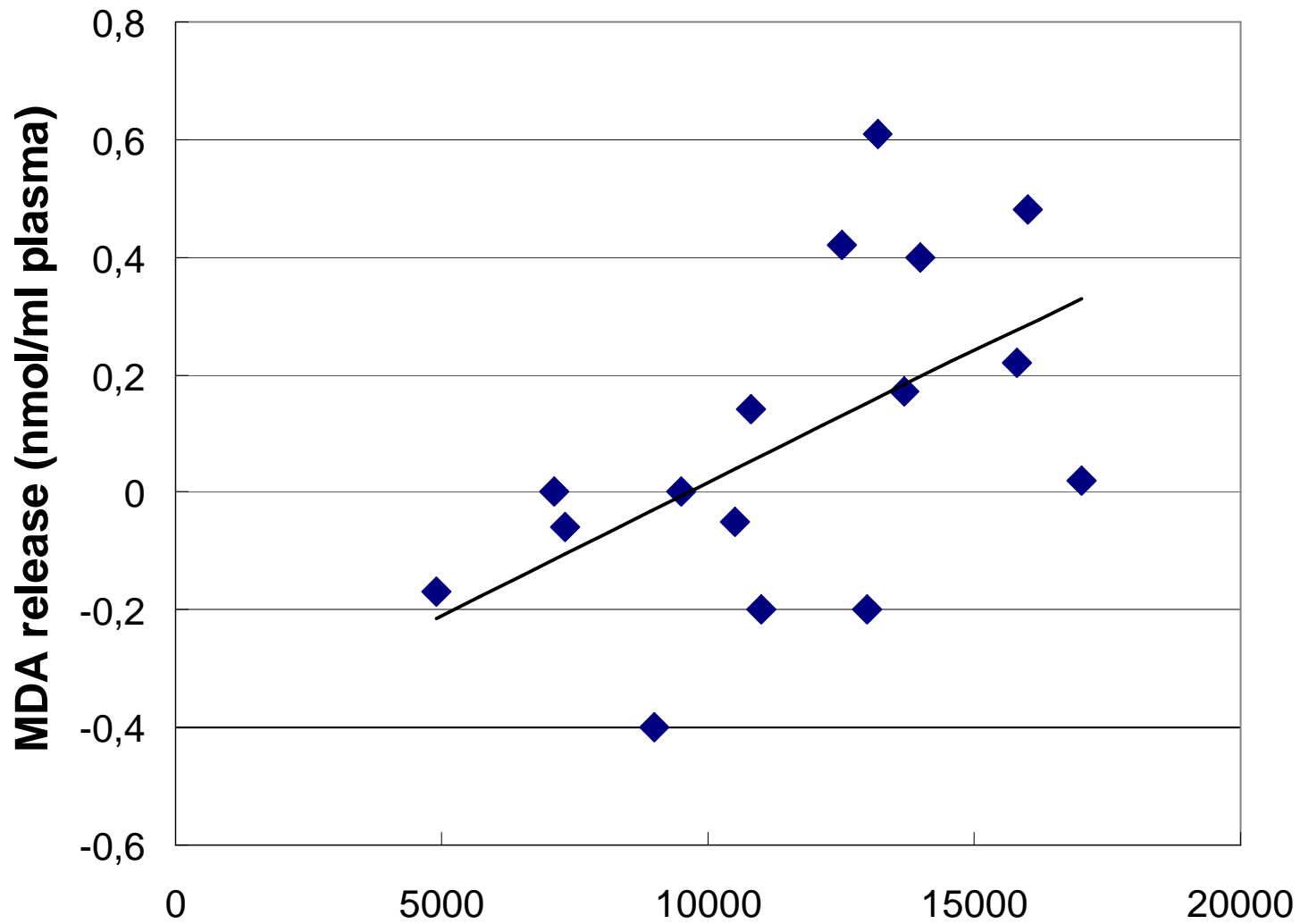
Plasma MDA in cellulite before, after one AWT application, and after serial therapy (AWT 6 times plus CPDT = complex physical decongestive therapy) compared with control. 26 female patients, 80 controls, values as $\mu\text{mol/l}$ (mean \pm S.E.); as insertion the MDA release after AWT only or after AWT plus CPDT in combination. Release was given as nmol/ml plasma, mean \pm S.E.



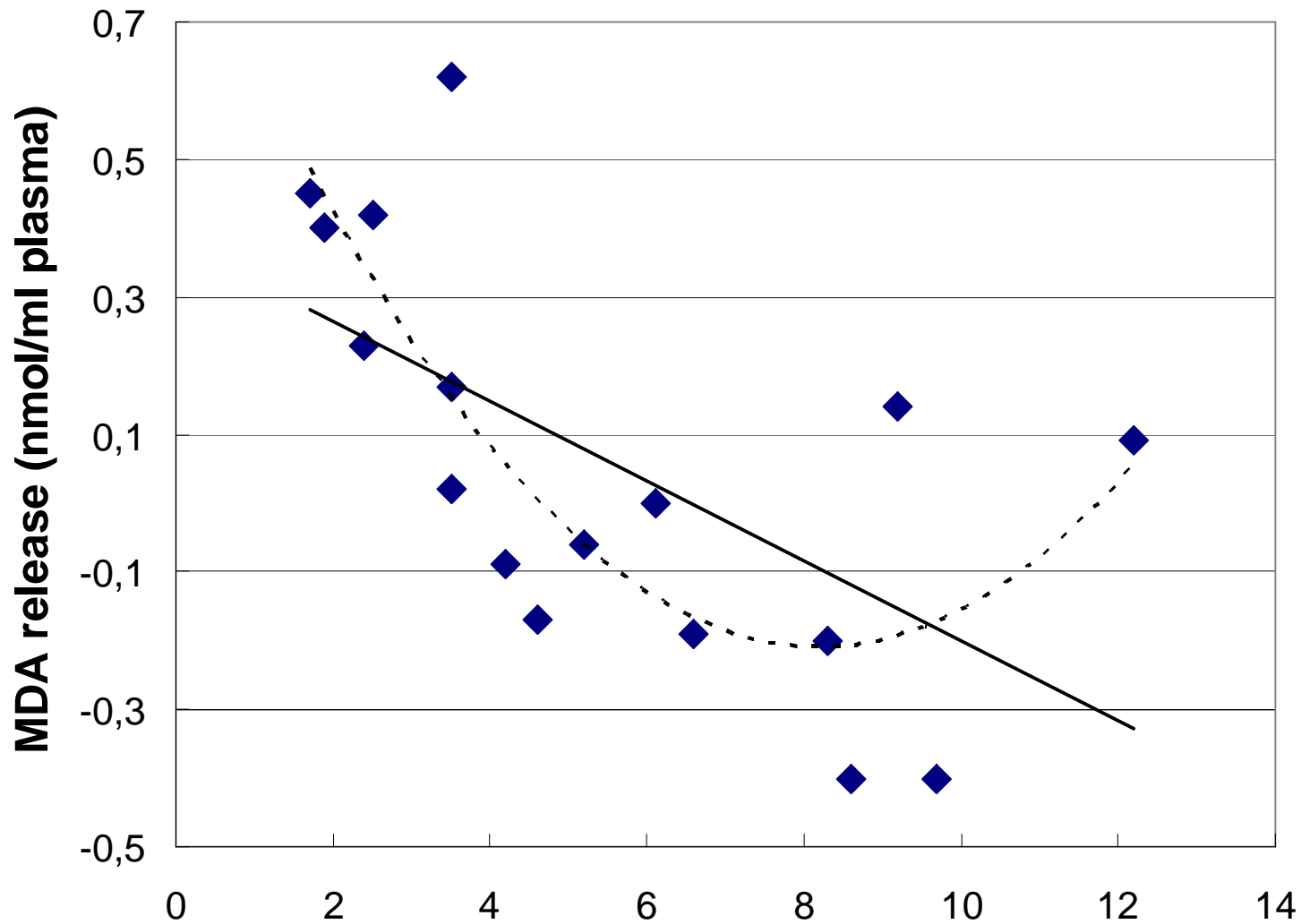
Plasma protein carbonyl concentration in cellulite before and after therapy (AWT plus CPDT) compared with control. 26 female patients, 80 controls, values are given as $\mu\text{mol/mg}$ (mean \pm S.E.)



Improvement of biomechanic skin properties during a 2 weeks-period with 6 sessions of AWT each for 8 min (1.000 impulses) in 5 patients with cellulite. In this part of the study the patients were treated only with AWT, but without parallel CPDT. Therefore, the increases of smoothening and elasticity (Young modul or stiffness index) which are given as difference between Young modul / stiffness index of the treated and untreated extremity are completely due to AWT. Values of Young modul / stiffness index without dimension; trend was calculated as linear trend.



Correlation between MDA / MDA release and thigh volume, i.e. degree of cellulite in 15 patients. MDA / MDA release as $\mu\text{mol/l}$ blood plasma, volume given as ml. Trend was calculated and inserted as linear correlation.



Correlation between MDA release by AWT and skin elasticity (Young modul /stiffness-index) before starting the AWT applications (initial value) in 16 patients. MDA values as $\mu\text{mol/l}$ blood plasma; stiffness-index (x-axis) without dimension. Trend was calculated and inserted as linear (full line) and polynomic (dashed line) correlation.

Patients and methods

Dec 2004 to Nov 2006 (69 female patients with cellulite)

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



Planar applicator,
so-called C-Actor
CELLACTOR SC1



Radial pressure applicator, so-called
D-Actor

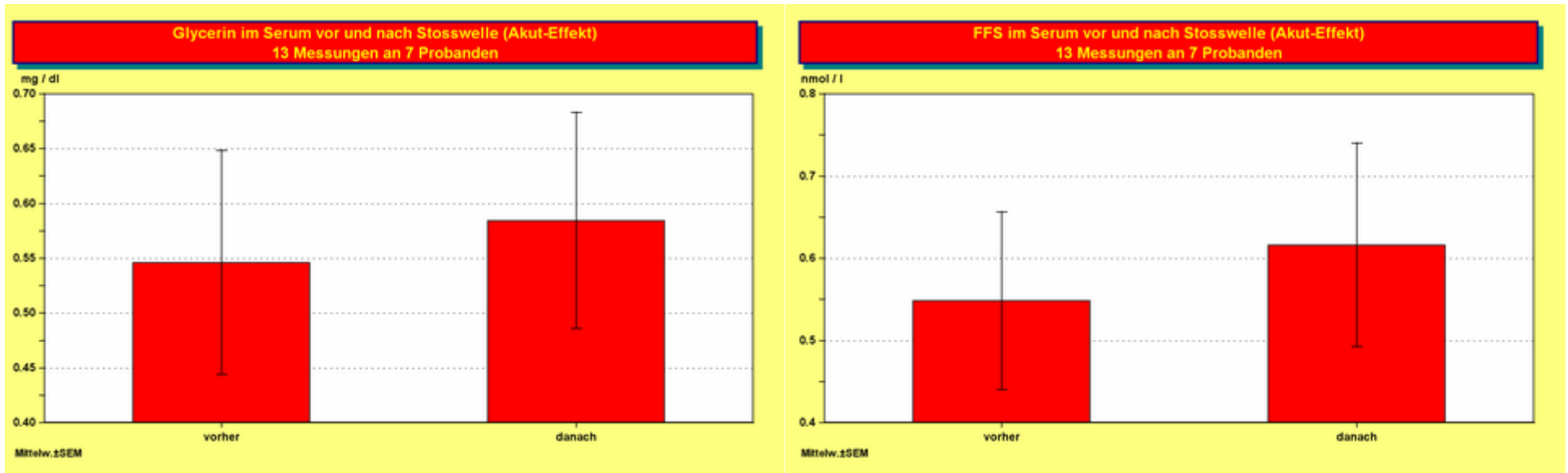
- **Group 1) and 2) were treated between December 2005 and April 2006 in the Utoquai Clinic for Aesthetic Plastic Surgery, Zürich. After completion of preliminary examinations, extracorporeal acoustic waves generated by means of a new therapy system CELLACTOR SC1 were applied to the outer and inner thigh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



Methodology

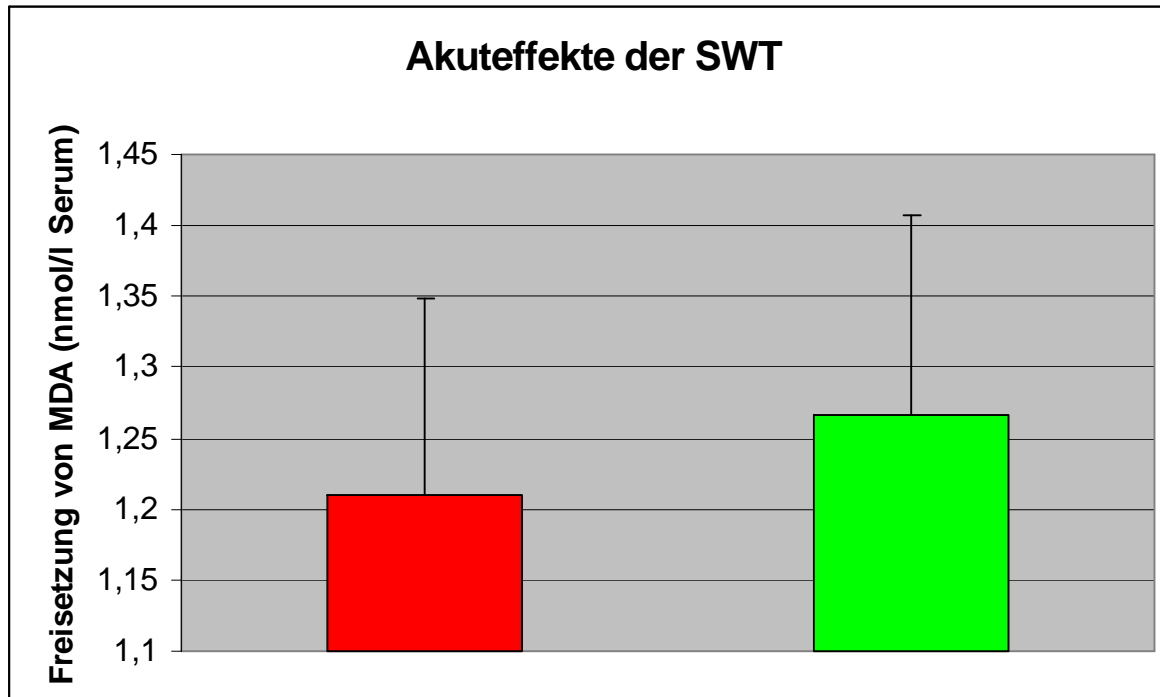
- The previously defined gluteal and femoral therapy regions were treated with 800 pulses with the C-Actor at an average energy level of 0.25 mJ/mm² which means that a total of 3200 pulses were applied per patient. With the D-Actor applicator 4000 pulses were applied/ treatment region.
- Each treated therapy region had a size of approximately 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.

Release of lipids from lipedema into the blood as acute effect of EPAT = Stimulation of lipolysis



Glycerin release from lipedematous tissue Free fatty acid release from lipedematous tissue

Release of MDA into the blood plasma



Rapid mobilization of LPO products (MDA) from lipedematous tissue into blood plasma by EPAT; we propose to call it anti-oxidative deloading

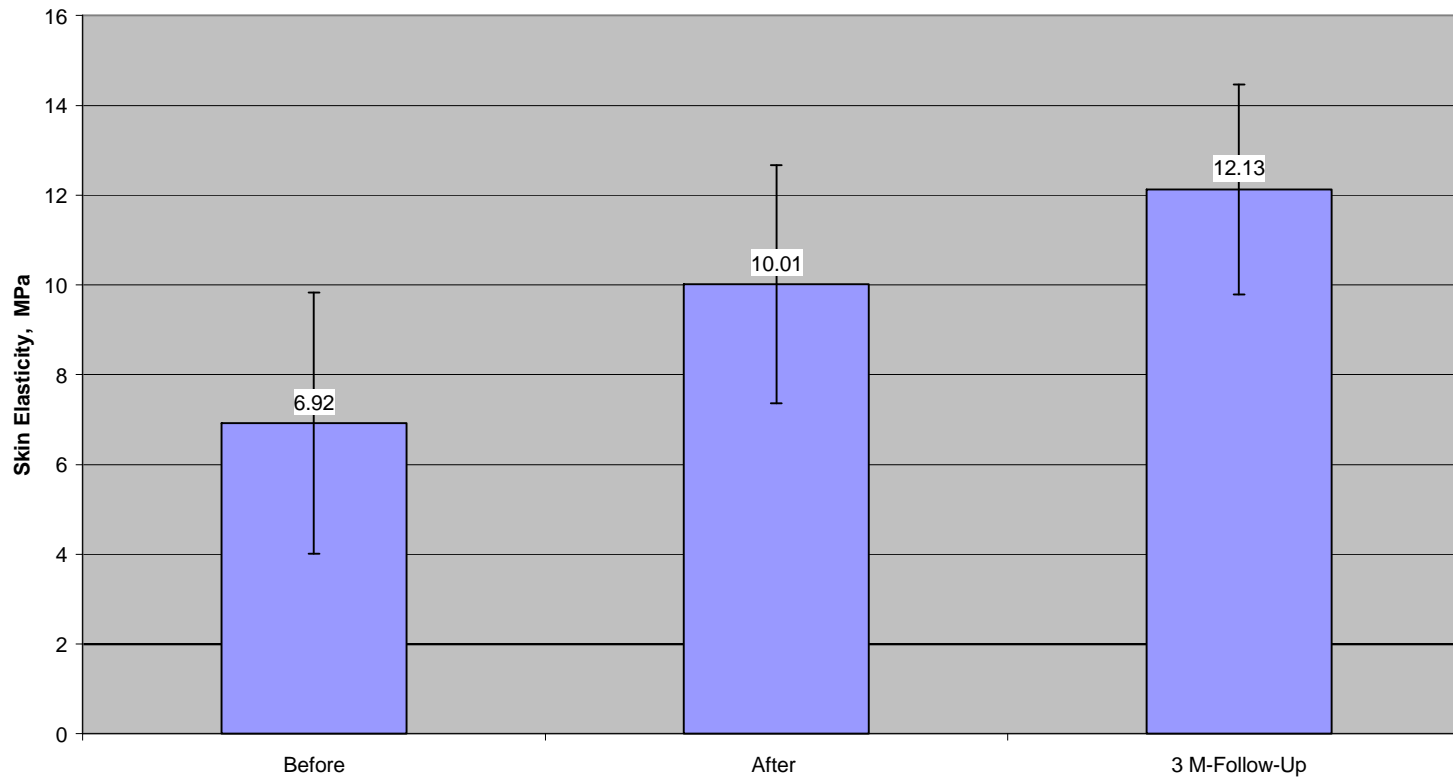
Evaluation of skin structure

- Measurements conducted in this study were performed with the DermaLab® 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® 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.

Changes in skin elasticity

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

6 Treatments, 14 patients

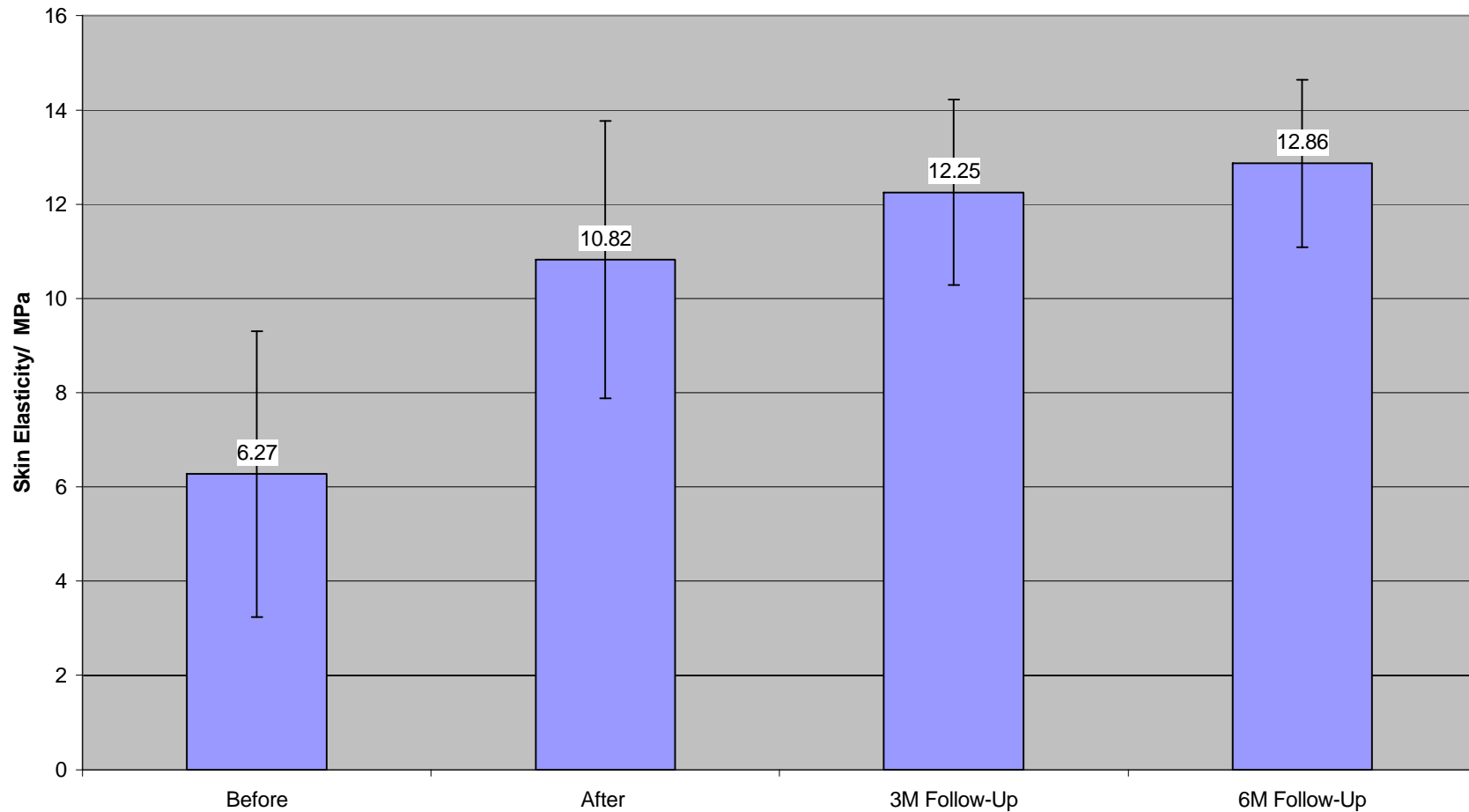


Skin elasticity increases continuously during AWT

Changes in skin elasticity

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

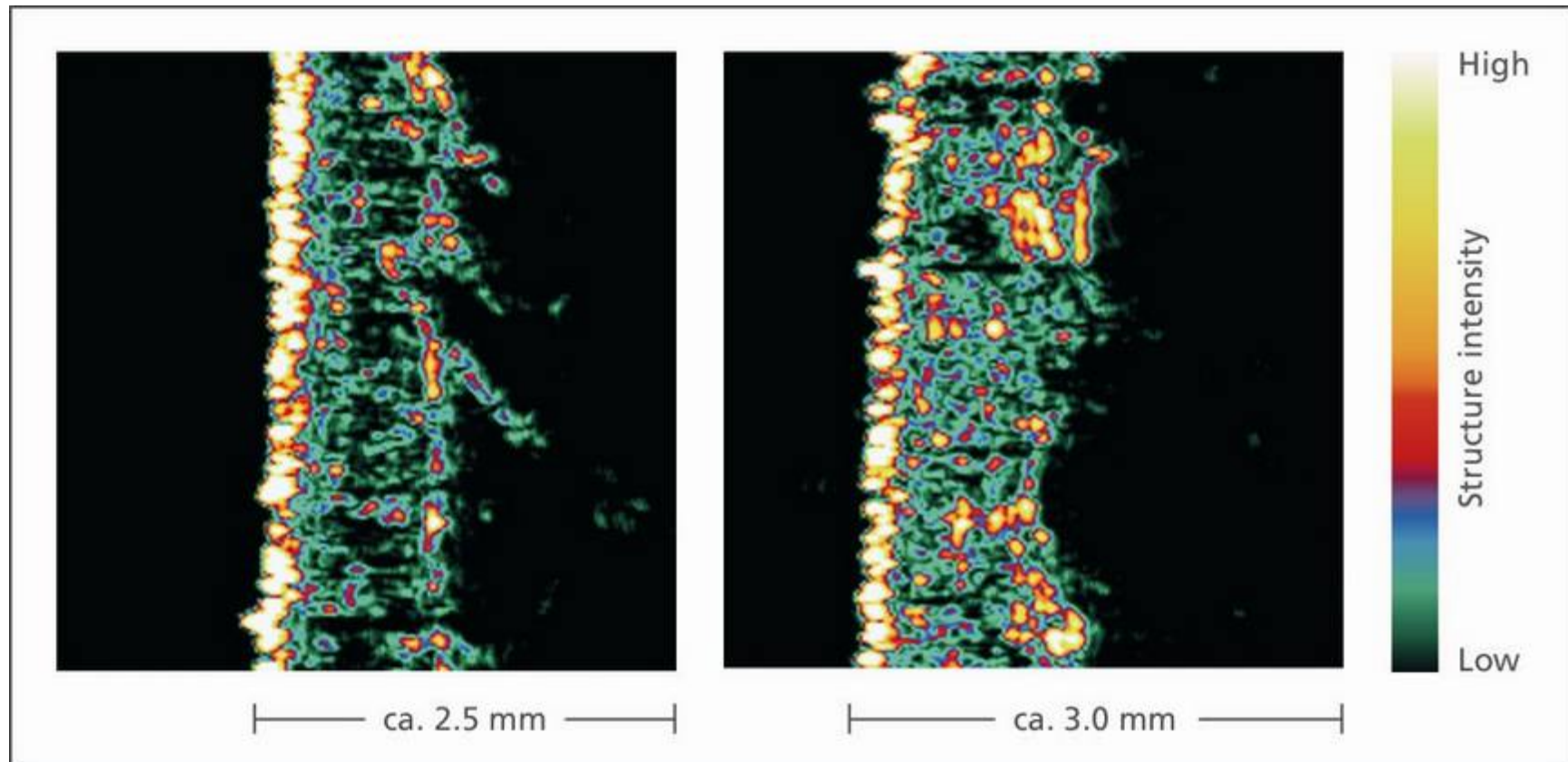
8 treatments, 42 patients



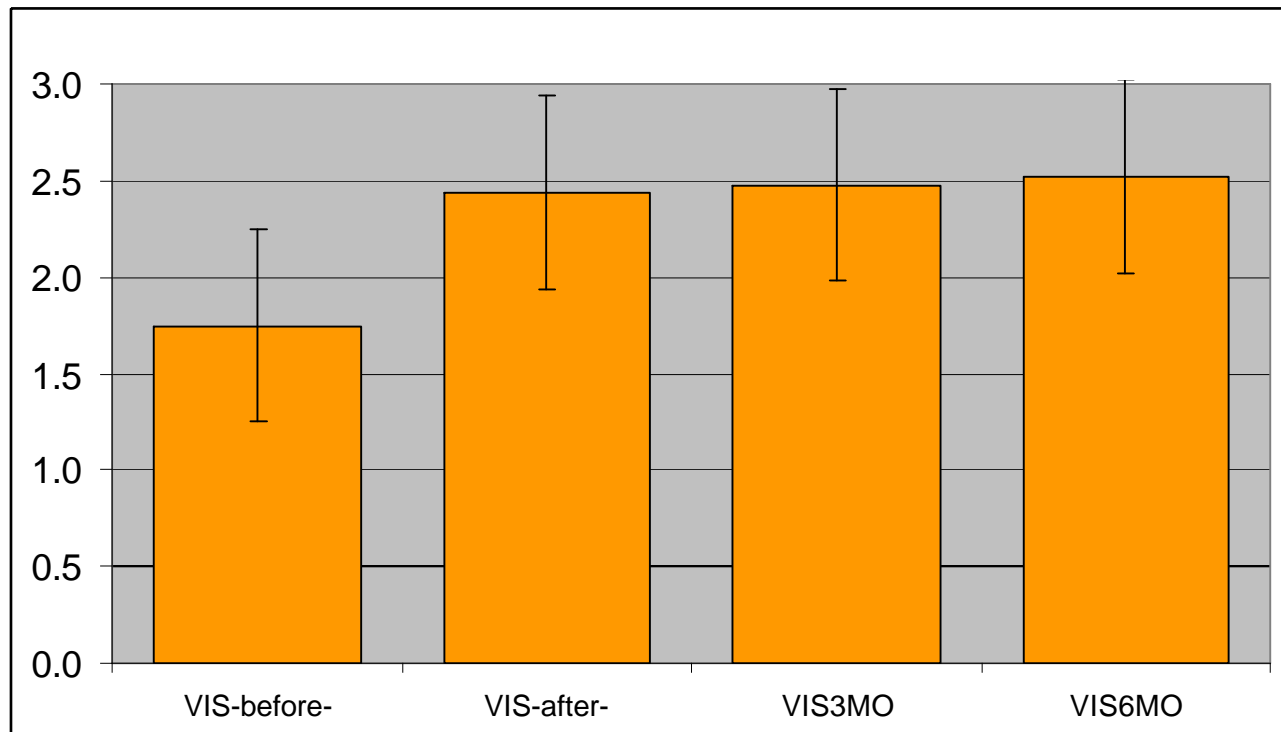
Impressive skin elasticity improvement by AWT

- 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.
- AWT - 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.

Analysis and evaluation of ultrasound images



Result of objective visual evaluation



Evaluation of score ratings of DermaScan images, including follow-up examinations: The evaluation revealed an upward trend in the visually determined skin firmness values.

Discussion / Interpretation of data

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

Comparison of planar and radial heads

Planar head

Radial head

Penetration
Depth

6.5 cm

3 cm

Therapeutic
target

body sculpting

cellulite

Lipolysis

stimulated (glyc,ffa)

not detected

Collagen
synthesis

stimulated

not influenced

Long-/short-
term effect

long-lasting effects

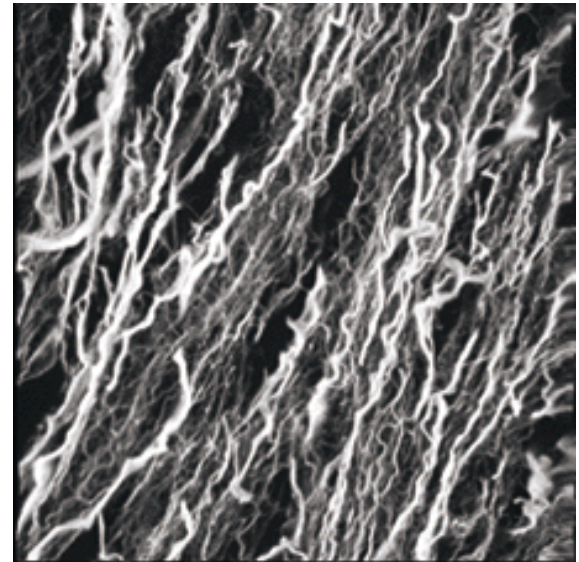
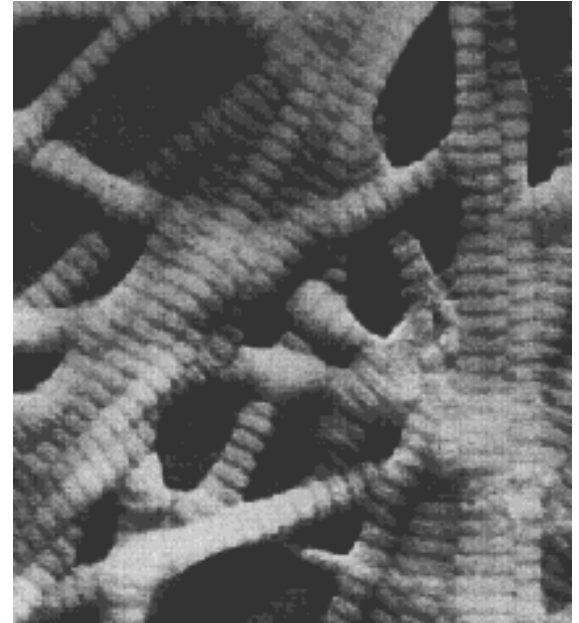
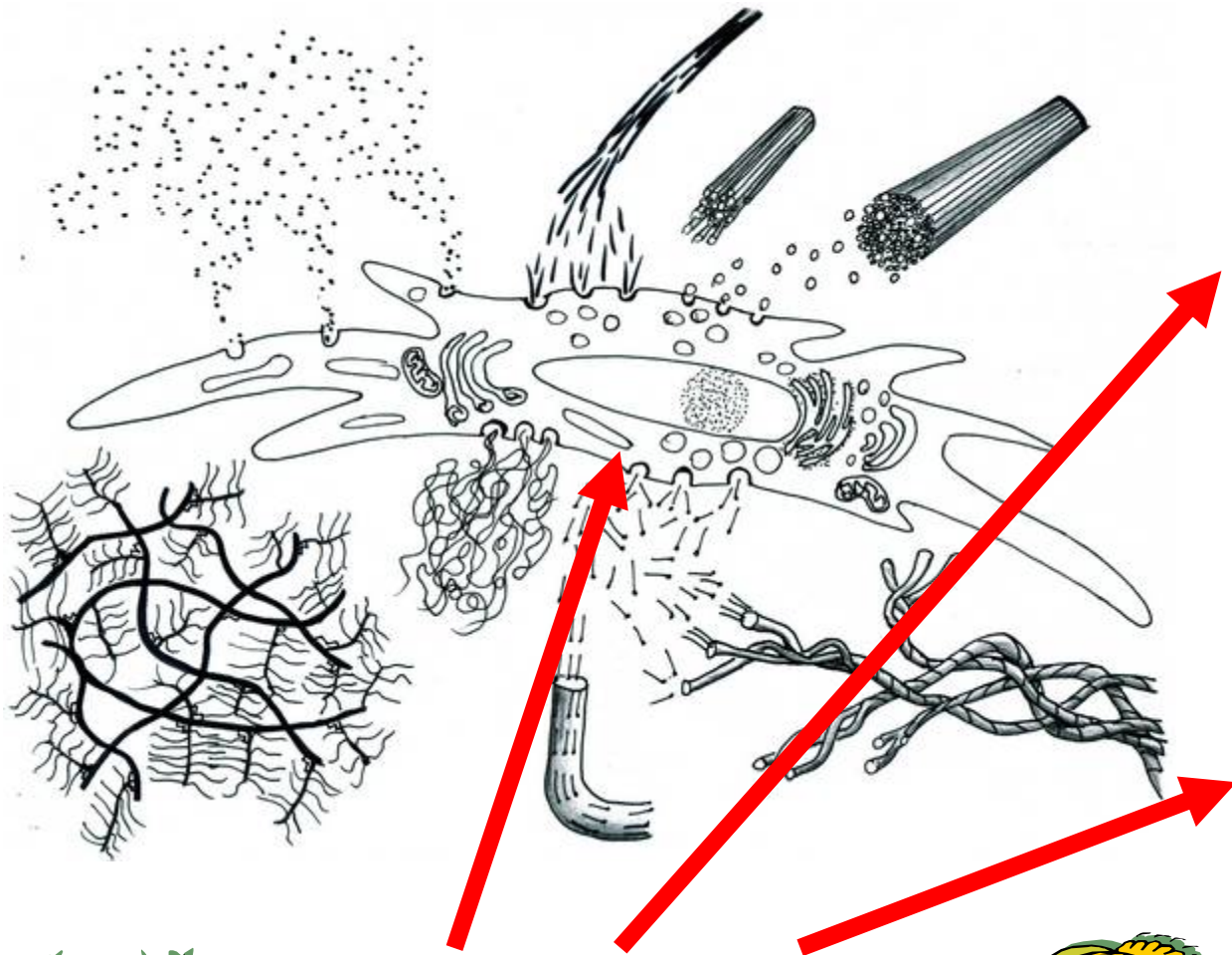
short-term effects

Molecular-biological considerations concerning collagen synthesis

- Application of acoustic waves to lipedema and cellulite has proved to reduce the concentration of aldehydic lipid peroxidation products, such as MDA, under in-vivo conditions.
- If the extent of LPO processes and the accumulation of cytotoxic LPO products can be decreased, then this is an indication for reduced consumption of low-molecular antioxidants.
- 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.

Molecular-biological considerations concerning collagen synthesis

- Ascorbic acid is closely related to the protection and improved biosynthesis of collagen.
- 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.



Vitamin C

Conclusions

- AWT 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. Nevertheless exclusion of side effects has to be observed also in ongoing applications to guarantee the safety of the methodological approach.
- **AWT may be developed into a promising, safe therapy method with long-lasting effectiveness in body shaping and skin rejuvenation.**