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Anti-fibrosclerotic effects of shock wave therapy in lipedema and cellulite

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Abstract. *In vivo* measurements in 26 female patients with lipedema and cellulite parameters were carried out before and after therapy by means of complex physical decongestive therapy (CPDT) including manual lymph drainage and compression as main components and/or shock wave therapy (SWT). Oxidative stress parameters of blood serum and biomechanic skin properties/smoothening of dermis and hypodermis surface were evaluated. Oxidative stress in lipedema and cellulite was demonstrated by increased serum concentrations of malondialdehyde (MDA) and plasma protein carbonyls compared with healthy control persons. Both MDA and protein carbonyls in blood plasma decreased after serial shock wave application and CPDT. The SWT itself and CPDT itself lead to MDA release from edematous tissue into the plasma. Obviously both therapy types, SWT and CPDT, mitigate oxidative stress in lipedema and cellulite. In parallel SWT improved significantly the biomechanic skin properties leading to smoothening of dermis and hypodermis surface. Significant correlation between MDA depletion of edematous and lipid enriched dermis and improvement of mechanic skin properties was demonstrated. From these findings it is concluded, that a release of lipid peroxidation (LPO) products from edematous dermis is an important sclerosis-preventing effect of SWT and/or CPDT in lipedema and cellulite. Expression of factors stimulating angiogenesis and lymphangiogenesis such as VEGF was not induced by SWT and/or CPDT and, therefore, not involved in beneficial effects by SWT and/or CPDT.

Keywords: Lipid peroxidation, malondialdehyde, protein carbonyls, sclerosis, lipedema, cellulite, shock wave therapy – SWT, lymph drainage

Abbreviations: SWT, shock wave therapy; CPDT, complex physical decongestive therapy; MDA, malondialdehyde; LPO, lipid peroxidation; HNE, 4-hydroxy-2,3-nonenal; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; HGF, Hepatocyte growth factor; IGF, Insulin-like growth factor(s); IGF BP3, Insulin-like growth factor binding protein, the most important binding protein for IGF-I and IGF-II; TBA, thiobarbituric acid.

1. Introduction

Clinical symptomatology, pathogenesis, diagnostics and therapy of lipedema and cellulite were reviewed by Stroessenreuther [1], Rossi and Vergnanini [2], Herpertz [3], Bilancini et al. [4,5], Gregl [6],

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Beninson and Edelglass [7], Singer [8] and others. Both lipedema and cellulite are characterized by lipid accumulation in the skin of the thighs. As therapy variants the CPDT, compression therapy, medical exercise, and surgical treatment are available. Surgical interventions such as lipectomia or liposuction are widely used [1,9,10]. Baumeister described tissue damages including damage of lymph vessels resulting in lymphedema as negative side effect of liposuction and possibilities to prevent those disturbances [11]. Additionally, sympathetic nerves are essentially destroyed in liposuction. This regional denervation results finally in repeating lipid accumulation [12]. Therefore, most authors advise against liposuction to prevent complications and favour CPDT as therapy of lipedema and cellulite [1,13,14]. CPDT was also shown to reduce oxidative stress in lymphedema and lipedema [13,15,16] due to MDA and HNE release from edematous tissue. Nevertheless, this method is time and personal consuming, and a succesful therapy needs months or years. At present, it can be safely stated that there is no topical medication or manipulative process to which advanced lipedema and cellulite visibly respond in a treatment period of less than 2 months [17].

Shock wave application is a new approach for the treatment of lipedema and cellulite. It represents an easy to handle, non-invasive, side effect free, local therapy type with short application periods. The original idea was to stimulate lipid mobilization and lipolysis in edematous regions which was already demonstrated for ultrasound application [18]. In this study the influence of shock wave applications alone and in combination with CPDT on oxidative stress and lipid peroxidation in lipedema and cellulite [13, 15,16] was investigated and related to changes of biomechanic skin properties and skin elasticity. Furthermore, influences of SWT on (lymph)angiogenic peptides should be analyzed.

2. Material and methods

2.1. Patients and therapy regimen

The study population included 26 women suffering from lipedema and/or cellulite who were patients of the Hufeland Hospital Bad Ems (Head Dr. Dr. R. Brenke) during the period 2004 and 2005. All subjects gave informed consent before the investigation was done. The study was conducted according to Good Clinical Practice and to E.U. guidelines for testing medical devices. The age of the patients was 45.3 ± 11.1 years (all patients together; mean $\pm$ S.E.). The age of the group of patients with lipedema was 45.2 ± 12.5 years, the age of the groups of patients with cellulite 45.8 ± 7.9 years (mean $\pm$ S.E.). The selection of individuals excluded supplementation with antioxidative substances, acute infections and chronic diseases. Further exclusion criteria were cardiovascular, renal or lung diseases, neoplastic disorders and/or chemotherapy, and recent surgical treatments. The study was allowed and confirmed by the Ethics Commission of the Landesaerztekammer Rheinland-Pfalz (Mainz, Germany).

The diagnosis was set up clinically by means of the typical symptoms of lipedema (symmetric swelling of thighs with pressure induced pain) and cellulite (typical skin changes). In this paper all patients both with lipedema and with cellulite were grouped together and compared with an age-matched healthy control group ($n = 80$).

The duration of serial shock wave treatment by means of a shock wave equipment DERMASELECT of Storz Medical AG, Kreuzlingen, Switzerland, was two weeks (15–16 days). The device which is usually applied in orthopedics, was modified for the special application in dermatology. The parabolic reflector was coupled to the skin with a silicon water cushion. The therapeutic head was rebuilt in the manner to localize the focussing point of shock waves into the water cushion leading to a diverging shock wave front which is skin compatible. Depending on the subjective pain sensitivity of patients the angle

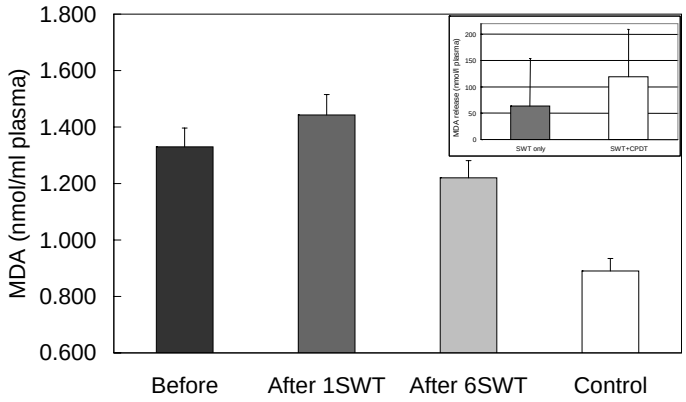

Fig. 1. Plasma MDA concentration in lipedema and cellulite before, after one SWT applicaton, and after serial therapy (SWT 6 times plus CPDT) compared with control. 26 female patients, 80 controls, values are given as μmol/l (mean $\pm$ S.E.); The inserted Fig. shows the MDA release after SWT only or after SWT plus CPDT in combination. Release was given as nmol/ml plasma, mean $\pm$ S.E.

of the shock wave path in the underlying tissue could be varied within 20 degrees (energy levels 0.1–8.0 of the machine) keeping the treatment area on the skin fixed. For this study a mean energy level of 3.5 has been used. This level corresponds to an energy flux density of 0.16 mJ/mm^2 (30 mm behind the focus). Three applications of SWT were carried out per week to six applications per patient within two weeks. A single therapy was carried out for 8 minutes (1,000 impulses). CPDT was carried out daily, in parallel to the SWT. CPDT was carried out at both thighs as usual, whereas SWT was used only for one thigh with the aim to compare the changes of the volume and biomechanic skin properties of treated and untreated thigh. Volume of the thighs was measured by means of a perometer of Perosystem, Messger äte GmbH, D-42347 Wuppertal, Germany.

2.2. Collection and storage of blood samples

Blood samples were collected into heparinized tubes. Samples were immediately centrifuged at 1500 g for 5 min and the plasma was separated and stored at $-80\,^{\circ}$C until the analyses were carried out. MDA and protein carbonyls were measured in plasma.

2.3. Evaluation of oxidative stress

MDA was determined according to Wong et al. [19] with modifications of Sommerburg et al. [20]. MDA was determined as the thiobarbituric acid (TBA) derivative. Therefore, a modification reaction was performed in a reaction mixture containing 750 μl of phosphoric acid (440 mM), 50 μl sample or MDA standard, 250 μl TBA solution (42 mM), and 450 μl of bidistilled water. The reaction mixture was incubated at 100°C for 60 min and then the samples and standards were cooled to 4 °C on ice. To neutralise and precipitate the proteins before injection into the HPLC system the samples and standards were diluted with methanol/1 N NaOH (1:1, v/v). Afterwards all samples were centrifuged at 13,000 RPM for 2 min. Sample volumes of 50 μl were injected. TBA-MDA complex was detected by means of fluorescence using an excitation wavelength of 525 nm and emission of 550 nm.

For determination of protein carbonyl groups the method of Buss et al. [21] with modifications of Sitte et al. [22] was used. After determination of the protein concentration, the samples were diluted

to the same concentration of protein (1 mg/ml) and 15 μl of these samples were derivatized with 45 μl dinitrophenylhydrazine solution. Sample loading and washing of ELISA plates was performed as described by Buss et al. 1997 [21]. Development was performed using a detection system described by Sitte et al. [22]. Absorbencies were determined at 492 nm. A standard curve of oxidized bovine serum albumin (BSA) was included in each plate. Blanks of PBS without protein were subtracted from standards and samples absorbencies. Oxidised BSA was prepared by modifying solved BSA with hypochlorite. The carbonyl content of the oxidised BSA was determined according to Buss et al. [21]. Reduced BSA was obtained as described by Buss et al. [22].

2.4. Determination of of regulatory peptides VEGF, HGF, IGF, and of IGF BP3

VEGF, vascular endothelial growth factor, was determined according to [23]. HGF, Hepatocyte growth factor, was measured as described in [24]. IGF, Insulin-like growth factor, and IGF BP3, Insulin-like growth factor binding protein, were analyzed as described in [25].

2.5. Measurement of biomechanic skin properties

For skin property evaluation a DermaLab equipment of Cortex Technology, Hudson, Denmark, was used (DermaLab base equipment DO 0200.01–471; elasticity sonde CO 500201–211). DermaLab is useful for the evaluation of skin elasticity (according to the elasticity modul of Young) or of smoothening of dermis and hypodermis. The physical dimension of Young modul is given as MPa. Due to the non-linearity of the measuring geometry it appears to be better to call the data stiffness-index, instead of Young modul.

3. Results

Both parameters of oxidative stress, plasma MDA and plasma protein carbonyl concentrations were increased in patients before starting the therapy. Initial MDA was 1.31 ± 0.57 μM compared with 0.89 ± 0.21 μM in healthy control persons ($n = 80$) (Fig. 1). The mean values of initial protein carbonyl concentrations in patients with lipedema and cellulite were 39 ± 15 pmol/mg protein and, therefore, more than twice the control values which are 17 ± 7 pmol/mg protein (Fig. 2). After serial SWT plus CPDT significant decreases of plasma MDA and protein carbonyls were measured (Figs 1 and 2) although the control values could not be reached. Obviously both therapeutic applications, SWT and CPDT, contribute to MDA and protein carbonyl reductions. Comparing the combined effect of SWT and CPDT with the SWT effect alone, one gets reductions of plasma MDA by 192 nmol/l by combined therapy and by 64 nmol/l by SWT alone within 15–16 days therapy periods. Observing the acute effects of SWT and CPDT, both methods lead to MDA release from edematous tissue. That is concluded from rapid plasma MDA increase immediately after SWT or CPDT. The mean MDA increase 10 min after SWT was 0.082 μmol/l plasma. Interestingly, 10 min after both SWT in CPDT-treated patients no significant increase of plasma protein carbonyl concentration in contrast to increased plasma MDA concentration was found.

The biomechanic skin properties measured as Young modul/stiffness index increased significantly by SWT. Figure 3 demonstrates the increase of Young modul/stiffness index from SWT application to application. After 6 SWT applications the Young modul/stiffness index was in the range of healthy control persons. Initial MDA concentration and MDA release by SWT correlated with the volume of the

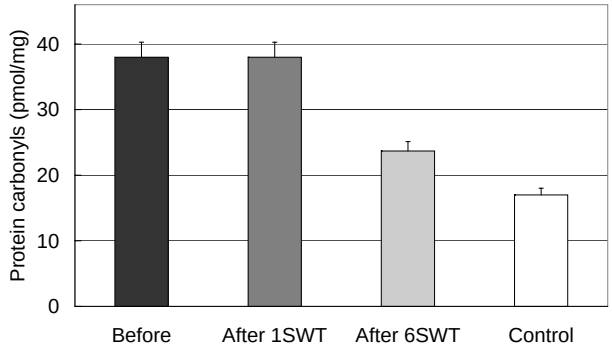

Fig. 2. Plasma protein carbonyl concentration in lipedema and cellulite before and after therapy (SWT plus CPDT) compared with control. 26 female patients, 80 controls, values are given as pmol/mg (mean ± S.E.).

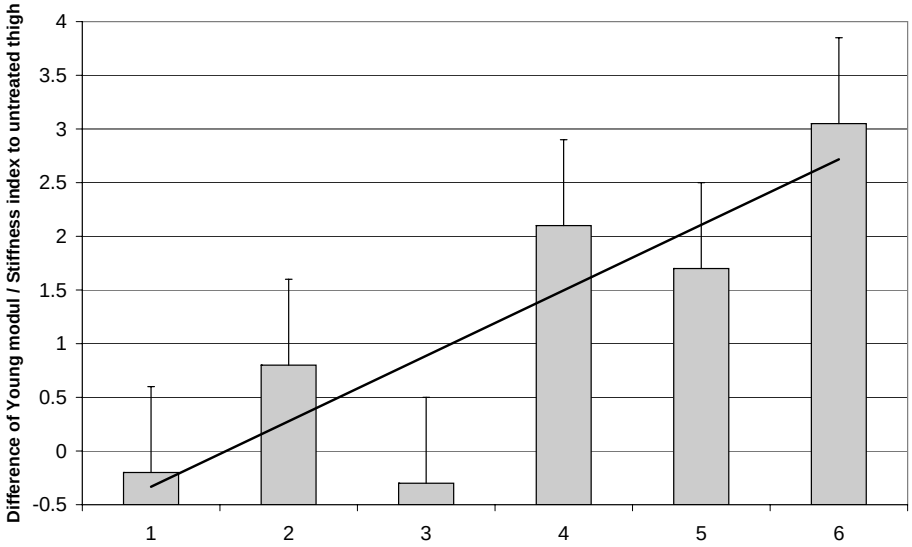

Fig. 3. Improvement of biomechanic skin properties during a 2 weeks-period with 6 sessions of shock wave application each for 8 minutes (1.000 impulses) in 5 patients with cellulite. In this part of the study the patients were treated only with SWT, but without parallel CPDT. Therefore, the increases 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 SWT. Values as Young modul/stiffness index without dimension; trend was calculated as linear trend.

edema (Fig. 4) or as lower the Young modul/stiffness index was (Fig. 5). In contrast to the significant changes of oxidative stress parameters and biomechanic skin properties in lipedema and cellulite there were no significant changes by SWT in plasma concentrations of regulatory peptides such as VEGF which could be related to lymphangiogenesis (Fig. 6). At least there was no increase of those regulatory peptides, rather a slight, but not significant, trend to decreased values in HGF.

4. Discussion and conclusions

The increased plasma MDA and protein carbonyl levels in lipedema and cellulite demonstrate a drastic oxidative stress including an accelerated lipid peroxidation in lipedematous tissue. Similar findings were

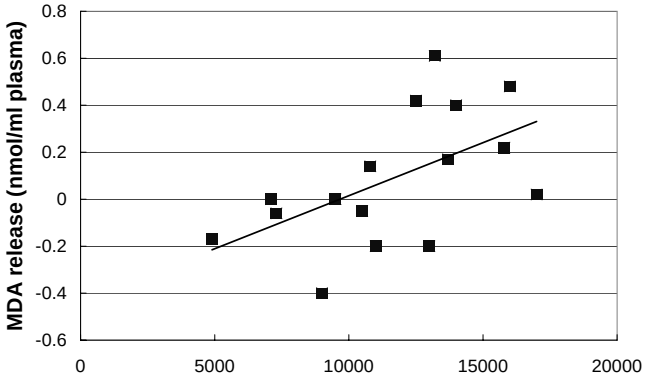

Fig. 4. Correlation between MDA/MDA release and thigh volume, i.e. degree of lipedema/cellulite in 15 patients. MDA/MDA release as μmol/l blood plasma, volume given as ml. Trend was calculated and inserted as linear (continuous line) correlation.

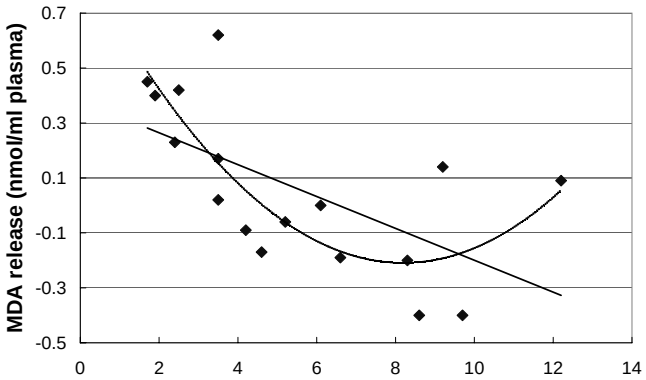

Fig. 5. Correlation between MDA release by shock wave therapy and skin elasticity (Young modul/stiffness-index) before starting the shock wave applications (initial value) in 16 patients. MDA values as μmol/l blood plasma; stiffness-index without dimension. Trend was calculated and inserted as linear (thin line) and polynomic (bold curve) correlation.

already found in chronic lymphedema [15,16].

Discussing the acute effect of SWT onto the MDA and protein carbonyl levels one should mention that MDA was liberated from edematous tissue into plasma. From the measured mean difference of 82 pmol/l one can estimate under conditions of rapid exchange within extracellular compartment 28 liters $\times$ 82 pmol/liter, i.e. about 2 to 3 μmol. Taking into account additionally the rapid reactions of MDA and its metabolism, one could estimate at least the tenfold amount of MDA release from edematous tissues, i.e. 30 μmol. Such amount is, of course of high importance for the conditions of skin and dermis. The fact, that every shock wave application induces an MDA release into the plasma, but not an increase of protein carbonyls leads to the conclusion, that by SWT the edematous tissue MDA is liberated without significant increase of protein carbonyls. We propose to call that an antioxidative deloading of edema without toxicity for the plasma proteins. In contrast to MDA (and further aldehydic LPO products) liberation which is stimulated by SWT, we could not find stimulating effects on angiogenic factors such as VEGF and other regulatory peptides. Such an effect could be observed after shock wave treatment of ischemic areas in the microcirculation of the limb and the heart [26–28].

The interrelationships between MDA and edema volume, which were shown in Fig. 4, were observed already in patients with lymphedema [15,16]. The correlation between MDA/MDA release and skin

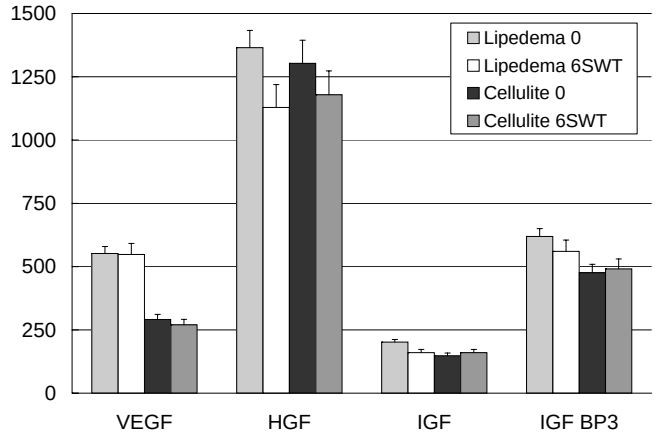

Fig. 6. VEGF, HGF, IGF, and IGF BP3 in plasma of patients with lipedema and cellulite before and after serial shock wave therapy. Number of patients in which these parameters were measured: $n = 8$ for lipedema, and $n = 5$ for cellulite.

elasticity (see Fig. 5) is of special importance because of its clinical relevance. The fibrosis of the skin usually is called sclerosis or fibrosclerosis. The ongoing sclerosis is the basis of skin remodeling leading to irreversible changes. From skin and also from other organs such as liver close interrelationships between oxidative stress or changes of the redox equilibrium and fibrotic processes are known [29–37]. The association of an alteration of intracellular redox equilibrium with excessive extracellular matrix deposition is a frequent feature in many chronic inflammatory processes. Moreover, the evidence that ROS play a causative role in fibrotic degeneration including stimulation of fibroblasts is growing. Independent of the tissue, two kinds of cells are involved in fibrogenesis, i.e. macrophages and fibroblasts or fibroblast-like cells which communicate through chemoattractants, growth factors and profibrogenic factors. In this context, ROS, free radicals and LPO-derived aldehydic products may up-regulate the transcription and synthesis of fibrogenic cytokines, above all TGFβ1 [31,33–35].

The possibility to control or down-regulate fibrogenic cytokine levels by means of antioxidant or dietetic treatments opens new potential pharmacological and nutritional horizons in the treatment of chronic diseases characterised by excessive fibrosis [33,35]. In analogy the possibility to down-regulate fibrogenic cytokine levels by means of shock wave induced removal of aldehydic LPO products from edematous tissue opens new therapeutic horizons for many women suffering from lipedema and cellulite.

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