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Boosting skin elasticity and revitalising the dermis in cellulite and connective tissue weakness by means of extracorporeal Acoustic Wave Therapy (AWT)

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Abstract

Extracorporeal Acoustic Wave Therapy (AWT) has been successfully used in dermatology in the course of several clinical application studies, initially as a non-invasive method for providing effective long-term therapy for age-related connective tissue weakness at the extremities, specifically the cosmetically blemishing condition referred to as cellulite. The acoustic pressure waves improve microcirculation in the fatty tissue and existing disruptions of the metabolic regulation, thereby reducing the externally visible signs of cosmetic cellulite. The measured elasticity values improve significantly under treatment by acoustic pressure waves, while having a low-level and justifiable side-effect profile. The measured parameters for mechanical skin properties, the skin structure and the subjects' personal satisfaction levels make it possible to issue a favourable prognosis for long-term effectiveness (beyond 6 months). No clinically relevant side effects were observed during the application.

Problem

The cosmetic problem of cellulite, which has often been described, is caused firstly by increased fat deposits around the buttocks and thighs, while secondly the skin's ageing process contributes to this appearance because the collagen layers become thinner and thinner. The predisposition is genetic and is described as a typical female problem: Women have 21 to 22 billion fat cells, men only 17 to 18 billion. Women's fatty tissue stores fat more quickly and easily than men's does, because the fat reserves serve as an energy store during pregnancy (1,2). The main cause of this problematical cosmetic factor, which can also lead to medical problems in the form of a lipodema, lies in the structure and condition of the connective tissue. In the region of a woman's thigh, arc-

shaped collagenic fibre tracts standing almost perpendicular subdivide the subcutis. These structures determine the skin relief in the transitional area between the corium and the subcutis. In what is referred to as the pinch test, a woman's skin displays protrusion of the systems of fatty chambers and the typical orange-peel pattern results (1,8). A woman's skin is overall more distensible than male skin.

The objective of this investigation was to apply AWT treatment in order to mobilise the metabolic processes in the subcutaneous fatty tissue to such an extent that the connective tissue structure would be reinforced, the skin relief and therefore skin structure would be significantly increased and therefore that there would be a significant visible reduction in cellulite.

Introduction: Loss of skin elasticity

The skin, particularly female skin, is an organ that is dependent on hormones. For example, the changes in the hormone balance during the menopause result in accelerated skin ageing. The skin of menopausal women becomes more flaccid, is frequently dry and the contours of the face lose their freshness and tautness. In the epidermis, oestrogens promote new cell formation and the production of collagenic fibres (9). With the loss of oestrogens, the formation of new collagens declines and the quality of the newly formed collagens is impaired. The number of elastic skin fibres declines and their structure changes. The epidermic tissue becomes more flaccid whereas the subcutis becomes harder (1,8,9).



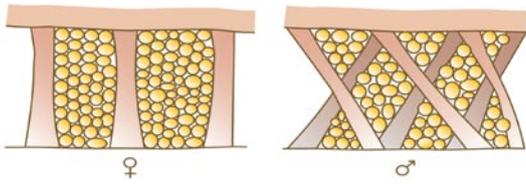


Fig. 1: The structure of subcutaneous fatty tissue in the female thigh compared to the structure of male fibre profiles shows why the „orange-peel effect“ only occurs with women in the pinch test.

The defensive forces of female skin also decline gradually due to ageing processes. There is an increased buildup of protein molecules in the skin that have been modified by interaction with oxygen radicals. Free radicals are not only formed by external effects such as sunlight or ozone. Processes such as smoking, stress, poor diet or obesity can lead to a buildup of free radicals in the body's tissue.

Another point concerns the blood flow through the skin which makes it possible to transport oxygen and nutrients as well as allowing immune cells to circulate. The flow of lymphatic fluid is markedly disrupted by an excessively sedentary lifestyle, e.g. lengthy sitting or lying down, fat deposits build up and if the procedure continues this leads to optically visible changes referred to as orange-peel skin or cellulite (1,5).

Subjects and methodology

A population of 69 women with pronounced cellulite (stage 2-3 in the pinch test) and age-related connective tissue weakness was divided into three groups with somewhat different treatment regimes:

- a) Group 1 with only six therapy sessions in three weeks, only treated with planar waves (C-Actor®).
- b) Group 2 with eight therapy sessions in four weeks, only treated with planar waves (C-Actor®).
- c) Group 3 with ten subjects, also with six therapy sessions, only treated with radial waves (D-Actor®).

The first two groups were treated during the period from December 2005 to April 2006. The women were subjected to a preliminary medical examination, then treated on the outer and inner thigh region as well as the gluteal area using a new therapy instrument, the Cellactor® SC1 (Storz Medical AG) for generating extracorporeal acoustic waves. The third group was treated in autumn 2006, involving the same treatment regime.

The number of pulses applied per patient and per therapy unit was the same in the first two groups. Group 3 was treated with 4000 pulses in each treatment region using the radial applicator.

The exclusion criteria for both groups were as follows:

- Pregnancy/breast feeding
- Phlebitis or deep leg vein thrombosis in the anamnesis
- Inflammations in the treatment area
- Liposuction in the treatment area more than six months in the past.

Therapy instrument

Acoustic pulses generated extracorporeally propagate through the tissue in the form of acoustic waves that are characterised by their high pressure amplitudes, rapid pressure rise and brief, asymmetrical pulse waveform. They can briefly transmit energy from the place of generation to distant areas and induce specific effects there.

Acoustic pulses used for medical purposes are generated outside the body and directed into the body without injuring the skin. In order to prevent reflection losses as much as possible during the transition into the body, the acoustic wave must not be generated and transmitted in air but in a medium with similar acoustic properties as those of human tissue. The planar applicator of the Cellactor® SC1 device developed by the Swiss company Storz Medical has a coupling diaphragm for this purpose, which is brought into contact with the patient's skin. Contact is assisted by applying ultrasound gel in order to avoid energy losses due to air inclusions.

Fig. 2a: Radial applicator, referred to as D-Actor®, of the Cellactor® SC1



Fig. 2b: Planar applicator, referred to as C-Actor®, of the Cellactor® SC1



Fig. 3 Cellactor® SC1



800 pulses were applied to the previously defined regions in the gluteal and femoral area using the C-Actor®, therefore each subject received 3200 pulses with an average energy level of 0.25 mJ/mm².

The radial application involved 4000 pulses/region administered using the radial applicator (D-Actor®). Each treatment region covered an area of about 20 x 30 cm which was „scanned“ using the applicator in both the horizontal and vertical directions. In this way, it was possible to ensure that the tissue was evenly treated.

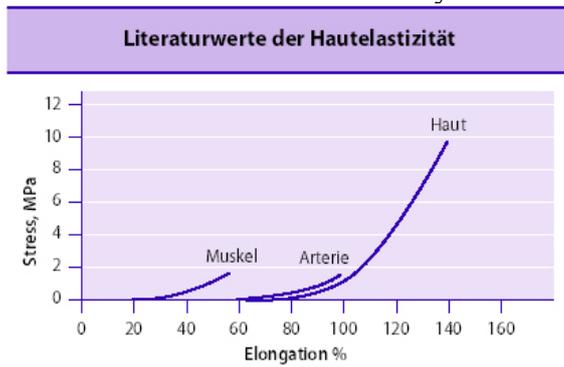
Measurement methodology

Current application observation made use of the Derma-Lab®, an instrument for measuring the modulus of elasticity, from Cortex Technology. It is based on the stress/elongation relationship that is generated by means of a vacuum (0 – 65 kPa). The measurements are given in MPa. According to the manufacturer's figures, the accuracy is in the region of 2 percent. A measurement was taken at the same location on the skin before each session.

The Derma Scan C® ultrasound device from the same company was used for determining the change in the connective tissue structure in the corium and the transition to the subcutis. A resolution of 60 x 130 µm with a penetration depth of 10 mm can be represented using the 20 MHz ultrasound head.

Fig. 4: Stress/elongation diagram for three different tissues: Skin, arteries and muscle; (Duck, 38)

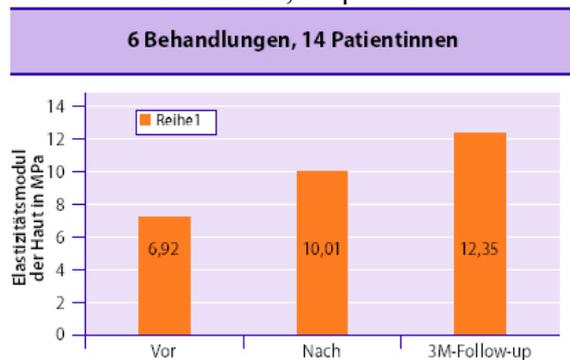
Published values for skin elasticity



Stress, MPa - Elongation%
Muscle, Artery, Skin

Fig. 5: Wilcoxon signed rank test normality test: Group 1 with n = 14 patients from a population of 15 people, who were treated six times. A follow-up was performed three months after the last treatment. One subject could not be included in the evaluation because of one missing measurement value.

Series 1: 6 treatments, 14 patients



Modulus of elasticity of the skin in MPa

Pre, Post, 3M follow-up

Zero-echo structures show up as black areas, connective tissue structures are reflected as green, red or yellow. It is a basic requirement for measurement or analysis of ultrasound images that the images have to be created with the same instrument and the same gain setting. The intensity of ultrasound reflection makes it possible to determine the relative density of the tissue and therefore to draw conclusions about the arrangement of collagenic and elastic fibres. The colour scale provides information about the magnitude of the reflection: White = maximum reflection descending to black = no reflection. Only few published values are available for comparing our observation series with, and the published values also vary rather widely. The lack of standardised measuring methods for determining mechanical skin properties has already been criticised in the medical literature (6). For this reason, only measurement values taken using the same measuring instrument can be compared with one another. In this case, it is possible to ensure that the mechanical stress applied and the traction speed are identical.

Results

1) Change in skin elasticity:

- a) Group 1 with six therapy units; C-Actor® application: 3-month follow-up (see Fig. 5). Elevated MPa values indicate that greater pressure was needed to raise the skin, therefore that the skin resilience was higher.
- b) Group 2 with eight therapy units; C-Actor® application: 6-month follow-up (see Fig. 6)

The values measured at the end of therapy for the skin elasticity indicated an increase of 74 percent, whilst in the follow-up after three months the increase was actually in the region of 95 percent. The increase in elasticity values measured in the 6-month follow-up was 105 percent. Normally, the improvements to skin properties achieved by chemical skin preparations (creams, lotions) are in the region of 12 to 25 percent, with just over 30 percent recorded in individual cases. According to Dr. Voss (consultant dermatologist and the head of Dermatest GmbH), above 40 percent represents an extraordinary result (2).

It can be assumed that AWT therapy stimulates the microcirculation in fatty tissue and therefore significantly improves the disruptions localised there. The side effects of an acoustic pressure wave attuned to the subcutis are reduced to a minimum; all that is to be expected is a painful sensation during the course of the treatment application or a reddening of the skin. This was confirmed by the patients' experience in 95 percent of the cases (2).

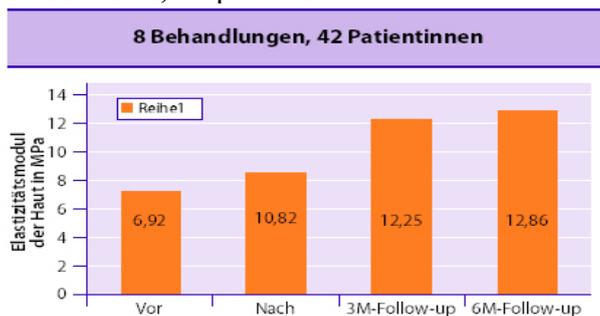
2) Analysis and evaluation of the ultrasound images

The ultrasound images (see Fig. 7) were anonymised using the manufacturer's image coding and subjected to a blind evaluation by an independent group in accordance with the following criteria:

Score 1 = Looser structure; Score 2 = Firmer structure; Score 3 = Firm structure.

Fig. 6: Wilcoxon signed rank test normality test; group 2 with n = 42 patients (population n = 44) who were treated on eight occasions and who attended the follow-up both three months and six months after the last treatment. Two subjects were excluded from this group due to missing measurement data.

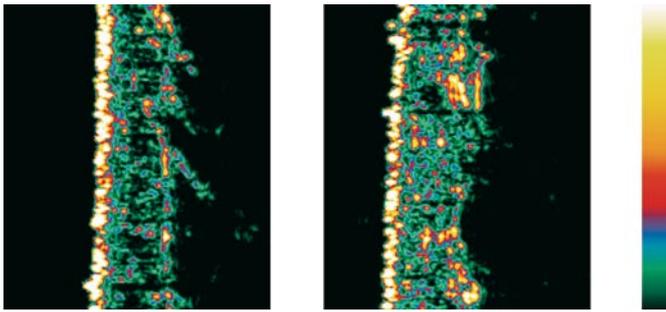
8 treatments, 42 patients



Modulus of elasticity of the skin in MPa

Series 1: Pre, Post, 3M follow-up, 6M follow-up

Fig. 7: Dermascan image of a 54-year old patient with cellulite. Left (pre): The dermis/subcutis transitions appear as a very discontinuous, irregular line; the black structures are fat cells and lymphatic fluid. Right (post): The skin structure has become measurably more compact; the zero-echo spaces (black) have reduced further.



The images were collated in a PowerPoint presentation and shown to the evaluators in a random sequence independently of one another.

The result of this objective, visual assessment is as follows (see Fig. 8):

The evaluation of the ultrasound images revealed a rise in cell density. The trend in the visually ascertained resilience values can be evaluated as significant.

3) Cosmetic assessment

Cosmetic effect on the upper arms of a female patient before and after AWT therapy, group B with six treatment units (see Fig. 9); effect in gluteal area (see Fig. 10).

Discussion

The observations and results indicate the possibility of AWT therapy influencing biological tissue, in particular by promoting microcirculation and influencing cell permeability (18,19,20).

In the case of cellulite, it is to be assumed that the transport capability of the lymph vessels is restricted. In the advanced stages of cellulite, lipodema, the system of lymph vessels is unable to return sufficient protein molecules from the interstitium into the venous bloodstream. The high concentration of plasma proteins in the interstitium leads to fibrification and therefore a modification of the tissue properties. This results in an increase in the impedance jump and this is where the acoustic pulse wave exerts its effect. The older the subjects with cellulite described in their records for many years, the greater the measured therapeutic effect.

in vitro experiments have shown that cells exposed to sound with acoustic pulses briefly become permeable and this allows active substances (such as cytostatic agents) to be introduced (22). In the application described here, it is this cell permeability that could be promoting the metabolism of the fat cells and leading to the activation of enzymes that break down fat (phospholipases) by means of receptors on the fat cell membrane (3,5,6).

The evaluation of the ultrasound images documents a visually detectable tissue conversion. The collagenic/elastic network of fibres in the skin and subcutis increases and becomes measurably firmer. Biochemical investigations conducted so far as part of this series of application observations indicate that the oxidative stress in the tissue is reduced, something which presumably represents a favourable condition for collagen synthesis (23). This would also help explain the described long-term effect on skin elasticity values lasting up to 6 months.

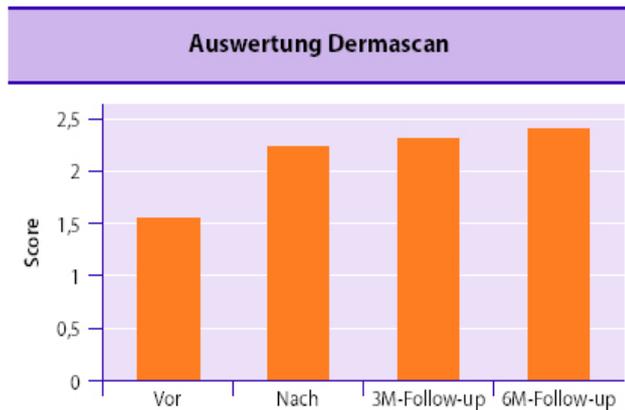
Microbiological observations on collagen synthesis

As already emphasised, it has been demonstrated that AWT therapy applied to lipodemas and cellulite enables the concentration of aldehydic lipid peroxidation products such as malondialdehyde to be reduced significantly under in vivo conditions (23). If the extent of lipid peroxidation (LPO) processes and the accumulation of

cytotoxic LPO products can be reduced, by which is meant favourably influenced, then this represents a reliable although indirect indication that low-molecular antioxidants are being curtailed. Consequently, it is above all the most important low-molecular antioxidants such as glutathione, tocopherol (VitE) and ascorbic acid (VitC) that are consumed to a reduced extent, with the effect that the intracellular and extracellular concentrations of compounds of this kind remain elevated.

Fig. 8: Evaluation of the score appraisals of the Dermascan images, including 3 and 6-month follow-up investigations.

Dermascan evaluation



Score / Pre, Post, 3M follow-up, 6M follow-up

The text books state that, in the case of ascorbic acid, this is closely connected with protecting and improving the biosynthesis of collagen (25). As such, L-ascorbic acid is not only accredited with acting as a classic water-soluble antioxidant, but also as an electron donor or protective enzyme in hydroxylations.

Hydroxylases are required for the biosynthesis of collagen and carnitine. In the normal cycle of reactions of prolyl 4-hydroxylase, a hydroxyprolyl peptide is created involving the decarboxylation and oxidation of alpha-ketoglutarate to succinate. The valency of the enzyme-bound iron does not change. Non-concatenated reaction cycles result in the decarboxylation and oxidation of alpha-ketoglutarate. In this case, oxygen is split off as a superoxide radical and the bivalent iron is oxidised to trivalent iron. Since this means the enzyme would be deactivated for the next reaction cycles, Fe³⁺ must be reduced by ascorbic acid. This means ascorbic acid undertakes an important protective function in the hydroxylases involved in collagen metabolism and carnitine biosynthesis (25).

It is not for nothing that scurvy, an illness which occurs when there is a massive lack of ascorbic acid, is associated with serious disruptions to the connective tissue metabolism and in particular also lack of collagen formation. This is because the hydroxylation reactions of collagen biosynthesis are severely impaired. Vitamin C-dependent hydroxylation of collagen is therefore essential for its structure and function.

An extensive series of experimental and clinical results as well as clinical application observations 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 massage instrument on cellulite (25) did show a therapeutic effect of up to 60 percent using the same ultrasound parameters in terms of reducing zero-echo structures in the corium/subcutis transition. However, the authors merely described the achieved tissue status as enduring for 1.1 months (24).

Based on the current status of observing the effectiveness of AWT treatment, the achieved tissue status can be demonstrated for up to 6.5 months following completion of the last therapy unit.

AWT treatment is a non-invasive therapy process and its application requires relatively little of both the doctor's and the patient's time. No serious side effects have been observed, although long-term observations should continue to be carried out. AWT treatment could develop into a promising therapy process without side effects in the fields of body shaping and skin rejuvenation with a real long-term effect.

Fig. 9: Before and after AWT therapy. (© Rosenpark Clinic Darmstadt)



Fig. 10: Cosmetic effect of cellulite, in this case reinforced in the gluteal area before (left), after (middle) and in the follow-up of six sessions of AWT therapy. (© Rosenpark Clinic, Darmstadt)



Literature

1. Dr. med. Werner Voss; Dr. Stefan Siebrecht „Gesunde Haut“; Trias Verlag, 2005; pages 102 ff.
2. Dr. med. Werner Voss; Dr. med. Gerrit Schlippe; „Gutachten zur Wirkung der Stoßwellentherapie auf das subkutane Fettgewebe und ihrer Wirkung auf die kosmetische Cellulite“; Dermatest GmbH, Medical Research Company, (12.2005)
3. R.H.K. Stroessenreuther: „Lipödem und Cellulitis sowie andere Erkrankungen des Fettgewebes“, Viavital Verlag 2001
4. Thoma H.: Lymphologica, 1996 bound volume, Stroessenreuther, Roman: Physikalische Maßnahmen bei Venenerkrankungen
5. Horst Weissleder and Christian Schuchhardt: „Erkrankungen des Lymphgefäßsystems“, Viavital Verlag, 2000
6. M. Földi / F. Tischendorf: „Lipödem und Zellulitis“ a symposium, Medizinischer Verlag Erdmann-Brenner, Munich, 1988
7. M. Földi / R. Stroessenreuther: „Grundlagen der manuellen Lymphdrainage“, 3rd edition, Urban&Fischer 2003
8. Dini G., Ghersetich I., Grappone C., Lotti T.: Proteoglycans in so-called cellulite. International Journal Dermatology 20 (1990), 272-274
9. Busch S: Vergleichende Untersuchungen der bindegewebigen Binnenstrukturen des Oberschenkels von Männern und Frauen, Mainz University, Med. Diss., 1976
10. Beate Rossbach, „Aesthetische Dermatologie“, pg. 20 ff. Sonntag Verlag; 2004
11. Hendriks FM, Brokken D, van Eemeren JT, Oomens CW, Baaijens FP, Horsten JB; A numerical-experimental method to characterize the nonlinear mechanical behaviour of human skin, Skin Res Technol. 2003 Aug, 9(3):274-83
12. Laura E. Edsberg, PhD; Robert E. Mates, PhD; Robert E. Baier, PhD; Mark Lauren, ME; Mechanical characteristics of human skin subjected to static versus cyclic normal pressures; Journal of Rehabilitation Research and Development, Vol.36 No.2, April 1999
13. Maass, Kühnapfel, Noninvasive measurements of elastic properties of living tissues
14. Hendriks FM, Brokken D, van Eemeren JT, Oomens CW, Baaijens FP, Horsten JB, A numerical- experimental method to characterize the nonlinear mechanical behaviour of human skin; Skin Res Technol. 2003 Aug; 9(3):274-83
15. Diidollou S, Patat F, Gens F, Vaillant L, Black D, Lagarde JM, Gall Y, Berson M; In vivo model of the mechanical properties of the human skin under suction; Skin Res Technol. 2000 Nov;6(4):214-221
16. Pedersen L, Hansen B, Jemec GB; Mechanical properties of the skin: a comparison between two suction cup methods; Skin Res Technol. 2003 May; 9(2):111-5
17. Carrino DA, Onnerfjord P, Sandy JD, Cs-Szabo G, Scott PG, Sorrell JM, Heinegard D, Caplan AI; Age-related changes in the proteoglycans of human skin. Specific cleavage of decorin to yield a major catabolic fragment in adult skin; J Biol Chem. 2003 May 9;278(19):17566-72. Epub 2003 Mar 5
18. O. Wess, Storz Medical AG, Kreuzlingen, in J Mineral-Stoffwechs. 2004; 11(4): 7-8
19. Gambihler S. Delius M, Ellwart JW. Permeabilization of the plasma membrane of L1210 mouse leukaemia cells using lithotripter shock waves. J. Membr. Biol. 141:267:275, 1994
20. C.E. Bachmann; „ESWT und Sonographie der Stütz- und Bewegungsorgane“, Steinkopf Verlag Darmstadt, 1999, page 4
21. Thoma H. Lymphologica, 1996 bound volume; Stroessenreuther, R.H.K. Physikalische Maßnahmen bei Venenerkrankungen, Lymphologica, 1996 bound volume)
22. M. Delius; F. Ueberle; L.Guo; „Anwendung von Stoßwellen für den Transfer von Molekülen in Zellen“; Biomedizinische Technik, vol. 47; part 1, pages 382 ff.; 2002
23. W. Siems, T. Grune, P. Voss, R. Brenke; „Anti-Fibrosclerotic effects of shock wave therapy in lipedema and cellulite“; BioFactors 24(2005); IOS Press; page 275-282.

24. G.W. Lucassen, W.L.N. van der Sluys, J.J. van Herk; "The effectiveness of massage treatment on cellulite as monitored by ultrasound imaging"; *Skin Research and Technology* 1997; Denmark; 154-160
25. Georg Löffler, Petro E. Petrides: *Biochemie und Pathobiochemie*, 7th edition, Springer Berlin, Heidelberg, New York, Hong Kong, London, Milan, Paris, Tokyo 2003, pg. 737-738
26. Farris PK., Topical vitamin C: a useful agent for treating photoaging and other dermatologic conditions, *Dermatol Surg.* 2005 Jul;31(7 Pt 2):814-7; discussion 818. Review., PMID: 16029672 [PubMed - indexed for MEDLINE]
27. Catani MV, Savini I, Rossi A, Melino G, Avigliano L., Biological role of vitamin C in keratinocytes., *Nutr Rev.* 2005 Mar;63(3):81-90. Review, PMID: 15825810 [PubMed - indexed for MEDLINE]
28. Kaplan B, Gonul B, Dincer S, Dincer Kaya FN, Babul A. Relationships between tensile strength, ascorbic acid, hydroxyproline, and zinc levels of rabbit full-thickness incision wound healing. *Surg Today.* 2004; 34(9):747-51. PMID: 15338346 [PubMed - indexed for MEDLINE]
29. Senturk N, Keles GC, Kaymaz FF, Yildiz L, Acikgoz G, Turanli AY. The role of ascorbic acid on collagen structure and levels of serum interleukin- 6 and tumour necrosis factor- alpha in experimental lathyrism. *Clin Exp Dermatol.* 2004 Mar; 29(2):168- 75. PMID: 14987276 [PubMed - indexed for MEDLINE]
30. Kockaert M, Neumann M. Systemic and topical drugs for aging skin. *J Drugs Dermatol.* 2003 Aug; 2(4):435-41. PMID: 12884471 [PubMed -indexed for MEDLINE]
31. Humbert PG, Haftek M, Creidi P, Lapiere C, Nusgens B, Richard A, Schmitt D, Rougier A, Zahuouani H. Topical ascorbic acid on photoaged skin. Clinical, topographical and ultrastructural evaluation: double-blind study vs. placebo. *Exp Dermatol.* 2003 Jun;12(3):237-44. PMID: 12823436 [PubMed - indexed for MEDLINE]
32. Bates CJ, Tsuchiya H., Comparison of vitamin C deficiency with food restriction on collagen cross-link ratios in bone, urine and skin of weanling guinea-pigs, *Br J Nutr.* 2003 Mar;89(3):303-10. PMID: 12628025 [PubMed - indexed for MEDLINE]
33. Jagetia GC, Rajanikant GK, Rao SK, Evaluation of the effect of ascorbic acid treatment on wound healing in mice exposed to different doses of fractionated gamma radiation. *Radiat Res.* 2003 Mar;159(3):371-80. PMID: 12600240 [PubMed - indexed for MEDLINE]
34. Nusgens BV, Humbert P, Rougier A, Richard A, Lapiere CM. Stimulation of collagen biosynthesis by topically applied vitamin C. *Eur J Dermatol.* 2002 Jul-Aug;12(4):XXXII-XXXIV. No abstract available. PMID: 12120619 [PubMed - indexed for MEDLINE]
35. Garcia-Mercier C, Richard A, Watier E, Chesne C, Rougier A. Effect of a water/oil emulsion containing for MEDLINE].
38. Duck; *Physical Properties of Tissue*; ISBN 0-12-222800-6 (page 151) ascorbic acid on collagen neosynthesis in human full thickness skin discs in culture. *Eur J Dermatol.* 2002 Jul-Aug;12(4):XXXXXXI. No abstract available. PMID: 12120618 [PubMed -indexed for MEDLINE]
36. Boyce ST, Supp AP, Swope VB, Warden GD. Vitamin C regulates keratinocyte viability, epidermal barrier, and basement membrane in vitro, and reduces wound contraction after grafting of cultured skin substitutes. *J Invest Dermatol.* 2002 Apr;118 (4):565-72. PMID: 11918700 [PubMed -indexed for MEDLINE]
37. Fitzpatrick RE, Rostan EF. Doubleblind, half-face study comparing topical vitamin C and vehicle for rejuvenation of photodamage. *Dermatol Surg.* 2002 Mar;28(3):231- 6. PMID: 11896774 [PubMed - indexed