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Randomised, placebo-controlled, double blind study on the clinical efficacy of a cream containing 5% a-lipoic acid related to photoaging of facial skin.

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Περίληψη της κλινικής μελέτης:

«Randomised, placebo-controlled, double blind study on the clinical efficacy of a cream containing 5% a-lipoic acid related to photoaging of facial skin.»

Ο σκοπός της μελέτης ήταν να διερευνηθεί η αποτελεσματικότητα μιας κρέμας προσώπου που περιέχει 5% λιποϊκό οξύ κατά της γήρανσης και της φωτογήρανσης σε σχέση με μια άλλη που δεν περιέχει λιποϊκό οξύ.

Η γήρανση και η φωτογήρανση εμφανίζεται με ρυτίδες, χρωματισμένες κηλίδες, επιδερμική δυσπλασία, καταστροφή ελαστικού ιστού, απώλεια κολλαγόνου, και εύθραυστη όψη που οφείλονται κυρίως σε κακή λειτουργία των μιτοχονδρίων, αύξηση των ελευθέρων ριζών και βλάβες στα νουκλεϊκά οξέα, πρωτεΐνες και λιπίδια. Οι βλάβες αυτές στη λειτουργία των κυττάρων αυξάνουν με το πέρασμα του χρόνου.

Η μελέτη απέδειξε ότι το α-λιποϊκό οξύ σε ποσοστό 5% παίζει πολύ σημαντικό ρόλο στην αντιγηραντική δράση της κρέμας που περιέχει 5% α-λιποϊκό οξύ, 0.3% συνένζυμο Q10 και 0.003% ακέτυλο-L-καρνιτίνη και μας δίνει την νέα, μοναδική πατέντα Lipodermix QA100.

Το α-λιποϊκό οξύ έχει αντιοξειδωτική δράση καθώς μπορεί να εγκλωβίσει τις ελεύθερες ρίζες υδροξυλίων, υπεροξειδίων, ατομικού οξυγόνου και οξειδίου του αζώτου. Ακόμα, έχει αντιφλεγμονώδη δράση, παίζει το ρόλο των βιταμινών C+ E, βελτιώνει τη λειτουργία των μιτοχονδρίων και αυξάνει τις ενδοκυτταρικές ποσότητες των πρωτεϊνών και νουκλεϊκών οξέων.

Το συνένζυμο Q10 είναι γνωστό για την αντιοξειδωτική του δράση ενώ η ακέτυλο-L-καρνιτίνη συντελεί στη βιοσύνθεση των λιποϊκών οξέων.

Τα αποτελέσματα της μελέτης αποδεικνύουν ότι το σταθεροποιημένο σε μια κρέμα 5% λιποϊκό οξύ μειώνει κατά 50% το βάθος των ρυτίδων και τις αλλαγές του δέρματος που οφείλονται στην επίδραση του φωτός, ενώ η σύνθεση της κρέμας αποτελεί πρωτοποριακή θεραπεία του δέρματος για προβλήματα που έχουν σχέση με τη γήρανση.

Η φαρμακευτική δράση του δραστικού συστατικού της κρέμας και τα αποτελέσματα της ως άνω μελέτης την έκαναν δεκτή από το επιστημονικό συμβούλιο του περιοδικού British Journal of Dermatology, όπου και δημοσιεύθηκε.

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Key words: α-lipoic acid, photoageing, intrinsic aging, antioxidant

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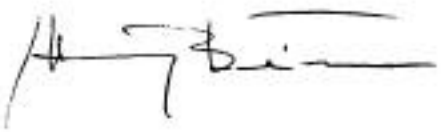

Abstract

Background: α-lipoic acid (LA) or the reduced form dihydrolipoate (DHLA) is a potent scavenger with anti-inflammatory properties. Previous uncontrolled studies with topical treatment of 5% LA containing creams indicate a beneficial effect on photoageing skin.

Object: The purpose of this study was to investigate whether a cream containing 5% LA showed any advantages concerning a number of the criteria associated with aging of the facial skin, compared to an identical cream lacking LA.

Material and methods: 33 women, mean age 54.4 years were included in this controlled study. After randomisation half the face was treated twice daily for 12 weeks with the LA cream and the other half with the control cream. The following methods of assessment were used: self evaluation by the test subjects, clinical evaluation, photographic evaluation and laser profilometry. The later performed before start of treatment and at the end.

Results: All four methods of assessment showed a statistically significant improvement on the LA-treated half of the face. Laser profilometry as the most objective method used showed an average decrease in skin roughness of 50,8 % (44.9 – 54.0) on the LA treated side, versus 40.7% (32.4 – 48.7) on the placebo-treated half of the face $p<0.001$ (Wilcoxon matched pairs test).

Conclusion: It is indicated that 12 weeks of treatment with a cream containing 5% LA improves clinical characteristics related to photoageing of facial skin.

Ageing of skin consists of a combination of intrinsic and photoageing. Intrinsic or chronological ageing is mainly a result of genetically predisposed factors resulting in a thinner epidermis, increased fragility, a decrease in dermal thickness and vascularity, a reduction in the number of dermal fibroblasts and in their synthetic ability, and a decreased response to growth factors. No topical treatment exists that significantly affects intrinsic aging. Photoageing results in melanocytic clumping, elastosis and atrophy of the dermis with loss of collagen. The corresponding clinical manifestations are mottled hyper pigmentation, wrinkles, change of the superficial texture resulting in a coarseness of the skin and formation of comedones. Photoageing can be modified by retinoic acid in combination with effective sun protective measures (1).

α-lipoic acid (LA) was isolated in 1951 by Reed and co-workers (2). LA, or the reduced form dihydrolipoate (DHLA), is a potent scavenger of hydroxyl radicals, superoxide radicals, peroxyl radicals, singlet oxygen and nitric oxide. LA also plays an important role in the mitochondrial dehydrogenase processes and as a modulator of the inflammatory response. LA is insoluble in water, but soluble in organic solvents. The small molecule weight 206.3 in combination with the solubility characteristics suggests the possibility of LA being absorbed by the skin and, in the skin, exercising pharmacological activities (3). Penetration of the skin has been shown in hairless mice. Kinetics of cutaneous and subcutaneous distribution after topical application of LA on hairless mice demonstrates a swift penetration through the epidermis and, after four hours, LA is distributed in the dermis and the subcutaneous tissue (4). The effect of LA on a cellular level indicated at first that this could be considered to be a vitamin. However, both animals and humans can synthesize LA, although the exact mechanism is not yet fully understood (5). Thus, LA is at present considered to be a co-enzyme in the citric acid cycle of the mitochondria. Ketoglutararte dehydrogenase and pyruvate dehydrogenase contain LA (6). Oxidative damage of the DNA, particularly the

DNA of the mitochondria (mtDNA) accumulates with increasing age. It has been shown that age related decay of mitochondria function can be improved by the addition of LA (7,8).

Other compounds in the tested creams that may exercise a pharmacological effect are Coenzyme Q10 (Q10) and Acetyl-l-Carnitine (AC). Q10 is synthesized both in animals and humans (9). Most of Q10 is absorbed in the stratum corneum, but in an ethanol solution 20% is absorbed in the basal layers of the epidermis and 2% in the papillary dermis (10). Q10 is, in its reduced form, ubikinol, an antioxidant present in all biological membranes.

AC has a very important function in the citric acid process by enhancing the uptake of AcetylCoA in the reduction of fatty acids. Whether skin penetration occurs is not known, but the binding of AC to fatty acids is a characteristic that might facilitate skin penetration. It has been shown that AC penetrates the cornea in calf eyes (11). AC is usually administrated orally, 1 – 3 g/day, or intravenously, 1.5 – 2 g/day. No serious adverse events have been reported.

The purpose of this study was to investigate whether a cream containing 5% LA showed any advantages concerning a number of criteria associated with aging of the facial skin, compared to the same cream lacking LA.

Material and methods

33 females, age 40 - 75, mean age 54.4 years, were included in the study. In order to standardize conditions during the test period they were asked to replace the different kinds of soaps in use with Lactacyd®, a mild lactic acid soap (pH 3.5; SmithKline Beecham). The test subjects were also asked to avoid getting a sun tan. However, all were equipped with and instructed how to use Coppertone® (Schering-Plough) lotion, sun protection factor 15, on a daily basis in the case of visits to countries with a sunny climate. Regarding make-up, the test

subjects were advised to continue their daily routines, with the exception being on days scheduled for test controls, on which the use of cosmetics was restricted.

Test procedure

The test procedure was done according to good clinical practice (GCP). The study consisted of four parts: self evaluation by the test subjects on four occasions, handed to the study nurse before the clinical evaluation, five clinical evaluations by the same physician, an evaluation based on standardized photographs and laser profilometry before and after treatment. The clinical evaluation took place at inclusion and after 2, 4, 8 and 12 weeks of treatment. At each control the following clinical characteristics were evaluated; fine lines, deep lines, pigmentation, bags under the eyes, telangiectasia, pore size, skin colour, visible dryness/scaling, elevated uneven structures – tactile roughness, degree of elasticity/flaccidity and thickness of skin. The clinical evaluation included protocols for assessment by the clinician according to an eleven grade scale, ranging from –1 (worse), 0 (no change) to 9 (very pronounced improvement). Also an assessment of adverse events was performed. At inclusion and after 12 weeks of treatment standardized photo and silicon prints for laser profilometry were performed.

Test tubes

Creams contained identical vehicle, 0.3% coenzyme Q_{10} and 0.03% acetyl-l-carnitine. 5% LA was added to the active cream, which otherwise was identical in colour, smell and consistency to the control cream. Two coded 50g tubes, marked right and left respectively, for use on each half of the face, twice daily during the 12-week treatment period, were distributed at inclusion and the first visit. At the second and third visits the number of tubes handed to the subjects were doubled. Whether the right or left side should receive active treatment was chosen at

random according to a prepared coded list in order to assure that the test was blind. At each control used tubes were collected in order to allow calculation of the amount of cream used per month of treatment.

Photography

All test subjects were photographed by the same photographer in the same place, using identical equipment and film before and after treatment to ensure maximal standardization. Each subject had a frontal, left and right profile taken on each occasion. The two sets of photos were evaluated independently of each other. The investigator used a Nikon magnifying-glass with 8x enlargement at a standard distance of 4.7 cm and on the same light board. Lines, pigment disorders, other colour changes in the skin, telangiectasia, skin texture and pouches under the eyes were evaluated using an eleven grade scale ranging from –1 (worse) to 9 (very pronounced improvement).

Laser profilometry

The periorbal region was cleansed with alcohol before application of adhesive rings (Dermatest, Denmark) and silicone impression material (Orbis Denatal, Germany). Precise application of the adhesive replica locating rings was aided with a ruler graded in two directions to ensure consistent distances from reference points of the lateral orbital cantus and superior auricular tragus. The center spot of the adhesive rings was marked with a marker pen. The orientation of the ring tap was inward facing, toward the eye.

With the subject in a supine position, a thin layer of the silicon impression material was applied over the bounded area of the ring and allowed to polymerise over a 3 to 4 minute period, after which the ring was lifted from the skin, together with the replica. Each specimen was labelled with the date and the subject's identification number, along with the side of the

face. The specimens were stored in individual Petri dishes until analyzed by laser profilometry. Precise instructions on how to accomplish this and an evaluation of the reproducibility of the method have been described elsewhere and the method is certified according to DIN-standard 4768 ff. (12).

Statistical method and considerations

The power analysis was based on an estimate of the proportion of subjects showing improvement on the active side. Using a chi-square test for proportions in a group of 28 subjects a power of 80% is achieved to detect the difference between the null hypotheses p=0.5 (active side preferred) and a hypothetical improvement p=0.75 for the active side. A statistically significant difference in efficacy is achieved if the difference from the null hypothesis (no difference between active and control side) reaches $p<0.05$. $P<0.1$ indicates a significant difference, but is not conclusive. All clinical variables were compared before and after 12 weeks of treatment. The difference between the active and placebo side was statistically analysed using the Wilcoxon matched pairs rank test (WT).

Files were closed 27th May 2001.

Ethical considerations

All subjects included in the study were recruited through an advertisement in a local newspaper. They were informed both in writing and verbally. Subjects who met the conditions for inclusion signed a written consent form before being allowed to enter the study. The study was approved by the ethical committee of the Karolinska Hospital.

Results

Of the intention to treat population, 32 out of 33 subjects completed the 12-week treatment period according to the clinical protocol. One subject, for unknown reasons, did not show up for the first clinical control. None had to leave the study due to adverse events or serious side effects. 81% (n=26) belonged to skin type III, 13% (n=4) to skin type II and 6% (n=2) to skin type I. Side effects were reported by the test subjects and mainly occurred during the first 4 weeks of treatment (Table I). The most common side effects reported were burning and warmth in the skin. This occurred immediately upon application of the cream and lasted a few minutes. These symptoms eventually decreased and, in most cases disappeared during the treatment period.

Two subjects initially reported development of a rash in connection with the application of the cream. The rash disappeared soon after application and was never observed at the clinical control. No allergic reactions were documented during the test period.

An indirect estimate of compliance was achieved by weighing the remains of the cream left in the tubes collected at each control. The mean use was 31.8 g /month on the active side and 32.1 g/month on the placebo half of the face.

In the clinical overall assessment the eleven characteristics in table I were evaluated according to the scale presented in the same table. Slight improvement was defined as a higher point on the scale in at least three different variables. Improvement, as higher points in five variables and much improvement in seven or more variables. The half of the face treated with 5% LA showed an improvement and, when tested with WT, the difference was statistically significant, p=0.033 (Fig.1). Furthermore, in the clinical evaluation a significant improvement of fine lines, p=0.011 analysed with WT, was observed on the LA-treated side (Fig. 2).

In the photographic evaluation the following clinical characteristics were excluded:

dryness, elevated uneven structures of the face identified by touch, degree of elasticity and evaluation of skin thickness. Slight improvement was defined as an increased grading in the eleven grade scale of two variables, improvement in three variables and much improvement in four or more variables. The improvement demonstrated on the active half of the face was statistically significant $p=0.025$ (Fig. 3). Besides improvement of fine lines, $p<0.031$, the photographic evaluation also showed decreased pigmentation, $p<0.007$ and indications of decreased under-eye bags and puffiness, $p<0.088$, and decreased pore size, $p<0.078$.

In the self assessment by the subjects included in the study 78% claimed the active side (25/32) showed different degrees of improvement, while 32% claimed the placebo treated side (10/32) had improved. The difference tested with WT was statistically significant, $p=0.0015$ (Fig. 4).

The laser profilometry, measuring skin roughness lateral of the periorbital area, predominately the depth of fine lines, demonstrated a significant improvement on the LA treated side. After three months the median improvement on the LA side was 50.8 % (44.9 – 54.0) and 40.7 % (32.4 – 48.7) on the placebo treated half of the face, $p<0.001$ (Fig.5). The results are based on measurements from 62 silicon impressions. Due to technical difficulties, two specimens from one test subject, were lost from follow up. Age versus the results from the laser profilometry indicated a weak correlation between degree of improvement on the active side and increasing age. However, this association was not statistically significant.

Discussion

In recent years there has been increased interest in LA, related to its sometimes dramatic protective effect in tissues under extreme oxidative stress created under conditions of critical ischemia (13). DHLA has been shown to suppress UVB erythema when applied topically straight after UV-exposure (14). In a non-controlled study, after 12 weeks of treatment with

5% LA cream a 50% reduction in the depth of medium vertical lines on the upper lip and a significant reduction of fine lines in the periorbital region was reported (15). In that study the evaluation was done only by assessment of photographs.

Thus, the results of this controlled study support earlier observations that 5% LA might be effective in reducing photo induced changes in skin. Possible mechanisms causing this effect can be the antioxidant properties of LA and its acting as a modulator of the inflammatory reaction. Oxidative damage on DNA, cells and tissue increases with age. In particular damage on mtDNA occurs with an increased frequency . It has been demonstrated that addition of LA systemically to older rats improves the function of mitochondria (16,17,18). Administration of LA to older rats significantly increases the intracellular amount of nucleic acids and protein (16). This increase in intracellular proteins may enhance the production of enzymes necessary to transform retinols to retinoic acid. It has been shown that cellular reactive oxygen intermediates may affect fibroblast proliferation and collagen gene expression (19). A recent report demonstrated that topically applied vitamin C enhances the mRNA level of collagens I and III and their processing enzymes and tissue inhibitors of matrix metalloproteinase 1 in human dermis. In the same study the level of accumulated solar damage estimated in the placebo treated side of the test subjects did not correlate with responsiveness to the topically applied vitamin C. This suggested that a reduced biosynthetic activity related to chronological aging and/or a low tissue concentration of the vitamin are the likely targets of topical treatment (20). LA can replace both vitamins C and E (21). DHLA has the capacity to reshape ascorbic acid from dihydro-ascorbic acid and α-tocopherol (22). Strong evidence indicates that antioxidants including LA can act as an anti-inflammatory agent by reducing the production of transcription factors such as nuclear factor-κB and indirectly affect the gene expression of inflammatory cytokines such as TNF-α, IL-1, IL-2, IL-6 and IL-8 (23). The

tested creams probably also have epidermal moisturising affects. Results indicate that addition of LA further improves properties related to skin roughness (Fig. 5).

It must be noted that in most biochemical systems feedback mechanisms occur. Thus, a continuous supply might induce mechanisms reducing further beneficial effects of the treatment. Accordingly, the long term effect of topically adding a compound such as LA is at the moment unclear. The length of treatment necessary to ensure maximum improvement is still being investigated. At present we do not know which is the ideal treatment period. In order to investigate whether additional improvement in skin texture occurs, a six-month follow-up study is in progress. Since photo exposure is an ongoing event, it has to be anticipated that repeated treatment courses are necessary in order to maintain the results obtained by the LA treatment.

The 5% concentration of LA cream used in this study is mainly based on empirical data. As no serious side effects occurred and none of the subjects withdrew due to inconveniences caused by the treatment, 5% LA seems to be a suitable therapeutic agent. Whether this concentration is optimal regarding clinical effect in relation to risks still has to be determined. From a toxicological point of view topical application of 5 % LA is safe. The LD_{50} for LA in rats are 1g/kg (20), in dogs 400 – 500 mg/kg (24). In systemic treatment of humans the most common dose range is 200 – 600 mg/day, equivalent to 3 – 9 mg/kg/day . The median amount of the 5% LA cream used by the test subjects in this study was approximately 1 g on half the face/day, corresponding to1,5 mg/kg/day of LA for the whole face. With an average weight of 65 kg, this represents a dose of approximately 100 mg/day of LA. Thus, full face of topical treatment with a 5% LA cream applied b.i.d does not reach the lower range of doses used for systemic treatment. Concerning clinical safety, allergic skin reactions are among the few side effects previously reported (25) after systemic administration. In this study we have noticed that local irritation on application of 5% LA is common during the first weeks of treatment,

but eventually reduces and disappears in the vast majority of cases (*Table I*). However, side effects commonly seen in patients treated with retinoic acid, such as a scaly erythema combined with swelling of the skin seem to be a rare event in topical LA-treated subjects.

In this study we have used four different assessment methods to document the effect of topical LA treatment on the skin. Two of these methods are subjective, the photographic evaluation has to be considered as a semi-objective and the laser profilometry as an objective method. The results obtained, independently of the method used, show a similar pattern in the global assessment.

In this study no age-dependent improvement pattern was statistically detected. This is probably due to the relatively few subjects in each age group.

In conclusion, 12 weeks of 5% LA in the tested cream vehicle seems to improve several clinical characteristics related to *photoageing* of the facial skin. Further studies to elucidate possible mechanisms, optimal dosage and treatment periods are warranted.

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Table I.

Protocol of side effects, recorded on the active side (left) and vehicle side (right) by the subjects included in the trial. A test subject could report more than one side effect.

Side effects reported by test subjects								
	2 weeks		**4 weeks**		**8 weeks**		**12 weeks**	
A. No side effect	4	27	12	30	16	29	22	29
B. Causes a feeling of warmth in the skin	11	2	6	0	4	1	2	0
C. Causes burning	13	0	9	0	5	1	4	0
D. Causes stinging	13	1	10	2	6	1	5	1
E. Causes redness	4	1	1	0	2	0	0	1
F. Causes desquamation	1	0	0	0	2	1	1	0
G. Causes dryness	2	1	2	0	3	1	2	1
I. Causes itching	1	0	1	0	1	0	1	0
J. Causes a rash	2	0	2	0	1	1	1	1

Legends to figures

1. The result of the overall clinical assessment after three months of treatment. Slight improvement was defined as a higher point on the scale in at least three different variables. Improvement, as higher points in five variables and much improvement in seven or more variables.

2. The clinical evaluation showed a significant improvement of fine lines, $p=0.011$. Worse (= -1), no change (= 0), slight improvement (= 1), improvement (= 2) and much improvement (= 3).

3. Slight improvement in the overall photographic evaluation was defined as an increased grading in the eleven grade scale of two variables, improvement in three variables and much improvement in four or more variables. The improvement demonstrated on the active half of the face was statistically significant.

4. In the self assessment by the subjects included in the study 78% claimed the active side (25/32) to show different degrees of improvement, while 32% claimed the placebo treated side (10/32) had improved. None reported a deterioration of the treated skin.

5. Each ring represents a test subject and indicates in % the difference between the laser profilometry measurements before start of treatment and after tree months. At the end of the study period the median improvement on the LA side was 50.8 % (44.9 – 54.0) and 38.7 % (32.4 – 48.7) on the vehicle treated half of the face, $p<0.001$.

6 a. Test subject, with moderate to severe signs of photoaging. A generalized mottling of skin pigment combined with an increase in discrete solar lentigines. The skin appears yellow, coarse with deep wrinkles.

6 b. After 12 weeks of treatment with the active cream a change of the overall appearance of the skin is seen.

7 a. Close up of the eye region in a test subject with light to moderate signs of photoageing before treatment.

7 b. Corresponding region after 12 weeks of treatment. Observe change in lentigines, appearance of under the eye bag and reduction in fine lines.

Fig 1.

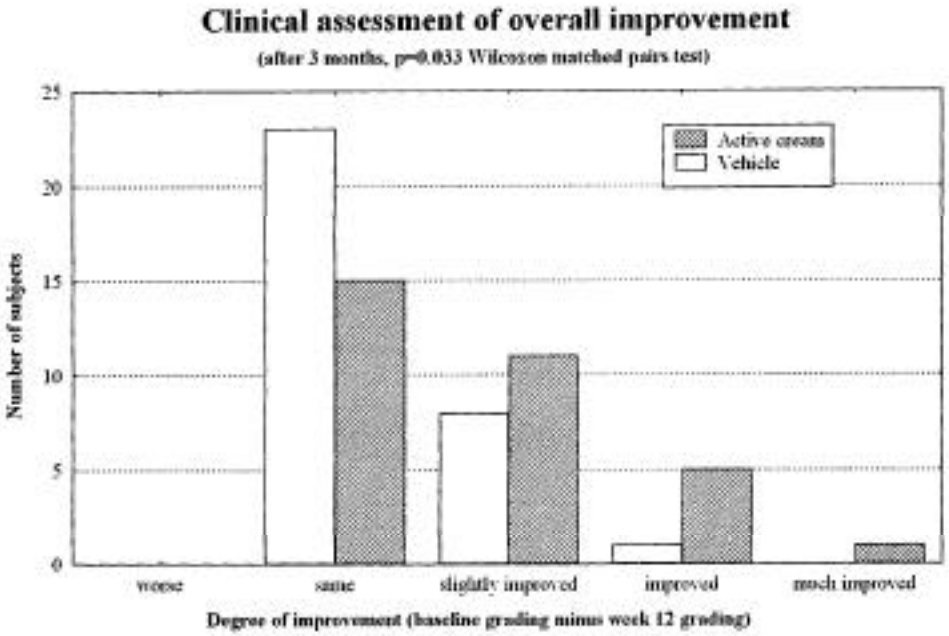

Clinical assessment of overall improvement
(after 3 months, p=0.033 Wilcoxon matched pairs test)
Active cream
Vehicle
Number of subjects
25
20
15
10
5
0
worse
same
slightly improved
improved
much improved
Degree of improvement (baseline grading minus week 12 grading)

Fig 2.

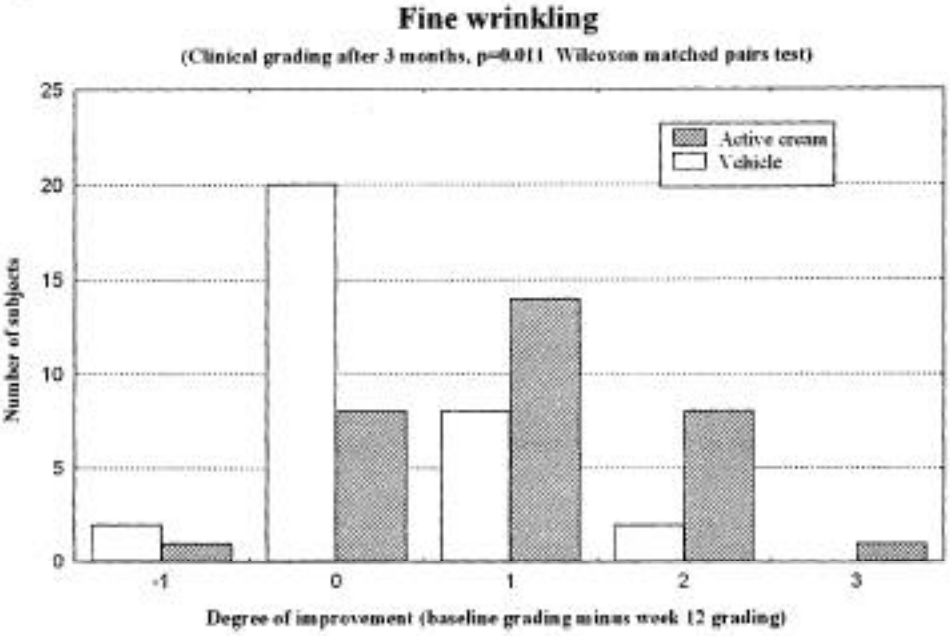

Fine wrinkling
(Clinical grading after 3 months, p=0.011 Wilcoxon matched pairs test)
Active cream
Vehicle
Number of subjects
25
20
15
10
5
0
-1
0
1
2
3
Degree of improvement (baseline grading minus week 12 grading)

Fig 3.

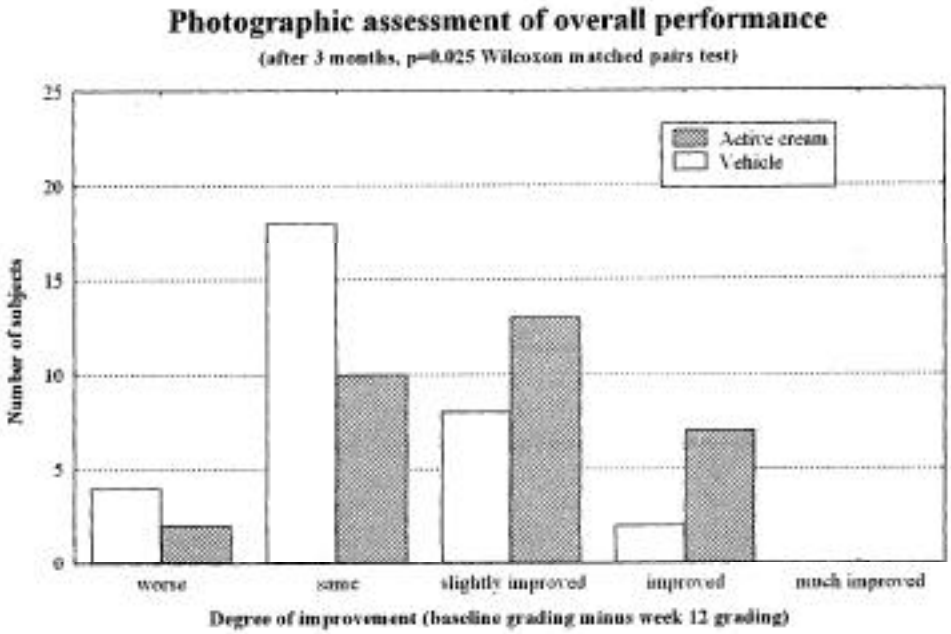

Photographic assessment of overall performance
(after 3 months, p=0.025 Wilcoxon matched pairs test)
Active cream
Vehicle
Number of subjects
0
5
10
15
20
25
worse
same
slightly improved
improved
much improved
Degree of improvement (baseline grading minus week 12 grading)

Fig 4.

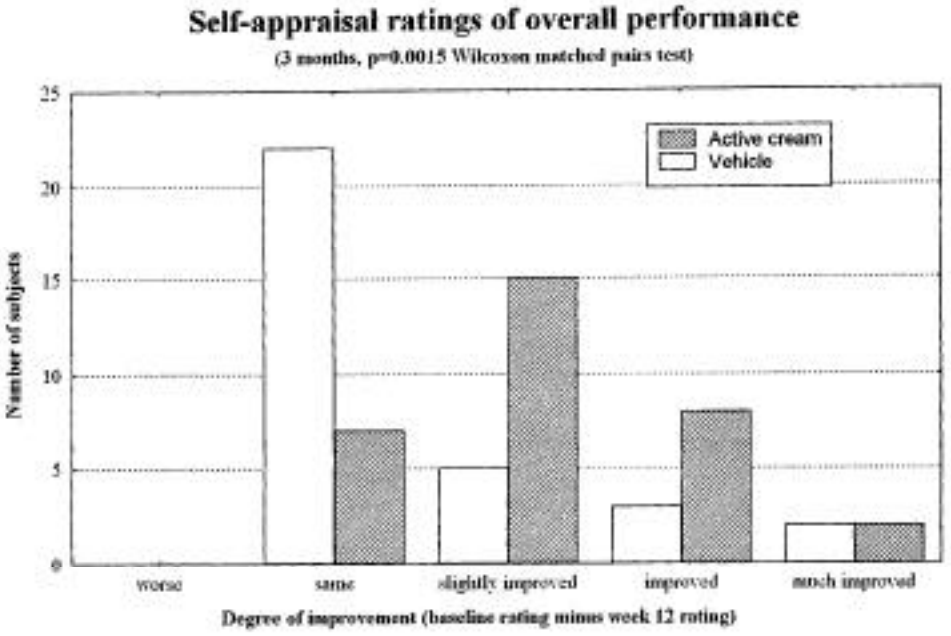
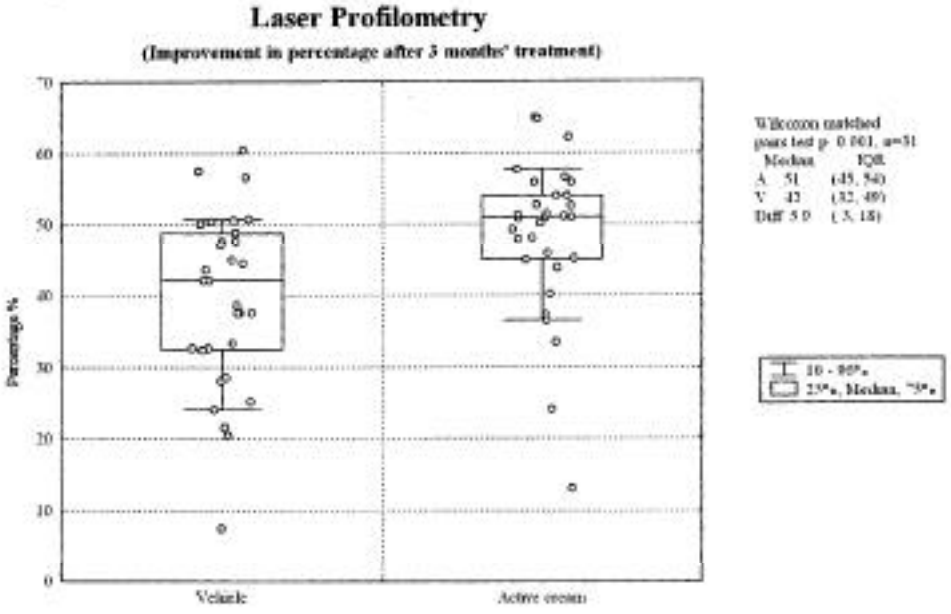

Self-appraisal ratings of overall performance
(3 months, p=0.0015 Wilcoxon matched pairs test)
Active cream
Vehicle
Number of subjects
0
5
10
15
20
25
worse
same
slightly improved
improved
much improved
Degree of improvement (baseline rating minus week 12 rating)

Fig 5.


Laser Profilometry
(Improvement in percentage after 3 months' treatment)
Percentage %
70
60
50
40
30
20
10
0
Vehicle
Active cream
Wilcoxon matched pairs test p 0 001, n=31
Median IQR
A 51 (45, 54)
V 42 (32, 49)
Diff 5 0 (3, 18)
10 - 90%
25%, Median, 75%

Jabu'she

Το μοναδικό κοσμετολογικό προϊόν με απόλυτα φαρμακευτική δράση

DfL

Dermatological Functional Lipoic

Jabu'she

Το μοναδικό κοσμετολογικό προϊόν με απόλυτα φαρμακευτική δράση

UNITED CARE
SCANDINAVIA AB

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