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JPD

JOURNAL of PLASTIC *and Pathology* DERMATOLOGY

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EDITOR in CHIEF
Antonino Di Pietro

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a new approach aimed at restructuring extracellular matrix of deeper layers of the skin.
Efficacy and safety of a new specific formula
(part 1)
Adele Sparavigna

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GIULIANI RICERCA E INNOVAZIONE IN DERMATOLOGIA

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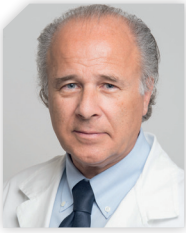

Cari amici, cari soci,
Come avete potuto notare con il cambio del nuovo editore del Journal of Plastic and Pathology Dermatology è cambiata anche la grafica.
Un nuova versione blu molto più elegante e professionale.
Finalmente i numeri in uscita saranno posizionati sul sito Isplad (www.isplad.org) così come i reprint.
Nei prossimo mesi inseriremo il maggior numero di pubblicazioni, in modo che i nostri soci e lettori saranno aggiornati anche on line.
Si avvicina lo storico appuntamento delle EADV, finalmente in Italia a Milano a Settembre.
Un momento straordinario per confrontarsi con i nostri colleghi Dermatologi europei e non solo.
Un programma scientifico di altissimo livello (troverete all'interno del JPD la locandina con i collegamenti per l'iscrizione)
Sul sito www.isplad.org troverete, già ,il programma preliminare del nostro congresso di Dicembre finalmente in presenza.
Quello definitivo sarà comunicato brevissimo e vi aspetto numerosi per salutarvi personalmente e per goderci questo momento di confronto che purtroppo manca da un po' di tempo.
Un caro saluto a tutti e buona lettura.

Dear friends, dear members,
As you have noticed, with the change of the new editor of the Journal of Plastic and Pathology Dermatology, the graphics have also changed.
A new blue version that is much more elegant and professional.
Finally, the upcoming issues will be placed on the Isplad website (www.isplad.org) as well as the reprints.
In the next months we will insert as many publications as possible, so that our members and readers will also be updated online.
The historic EADV appointment is approaching, finally in Italy in Milan in September.
An extraordinary moment to discuss with our fellow dermatologists from Europe and beyond.
A scientific program of the highest level (you will find the poster with the links for registration in the JPD)
On the website www.isplad.org you will already find the preliminary program of our December congress finally in attendance.
The final one will be communicated very shortly and I am waiting for you to greet you personally and to enjoy this moment of confrontation which unfortunately has been missing for some time.
Greetings to all and happy reading.

Antonino Di Pietro
Editor in Chief

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Un solare non basta a proteggere la **PELLE FOTO-DANNEGGIATA**

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CONTENTS

pag. 65 ***Injective treatment of the so-called cellulite: a new approach aimed at restructuring extracellular matrix of deeper layers of the skin. Efficacy and safety of a new specific formula (part 1)***
Adele Sparavigna

pag. 70 ***Injective treatment of the so-called cellulite: a new approach aimed at restructuring extracellular matrix of deeper layers of the skin. Efficacy and safety of a new specific formula (part 2)***
Adele Sparavigna

pag. 79 ***Observational study for the clinical evaluation of the effectiveness and tolerability of a neurosensinetm based cream in the therapy of eczematous dermatitis of the face***
O. De Pità, M. D'Ambrosi, F. Lupi, S. Voltolini, A. Musarra

pag. 87 ***Psoriasis? Crusted scabies!***
Italo Francesco Aromolo, Stefano Veraldi

pag. 91 ***Alopecia androgenetica maschile con forte componente infiammatoria***
Intervista a Paolo Gigli

pag. 98 ***Four years of publication***
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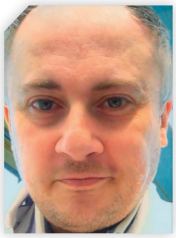

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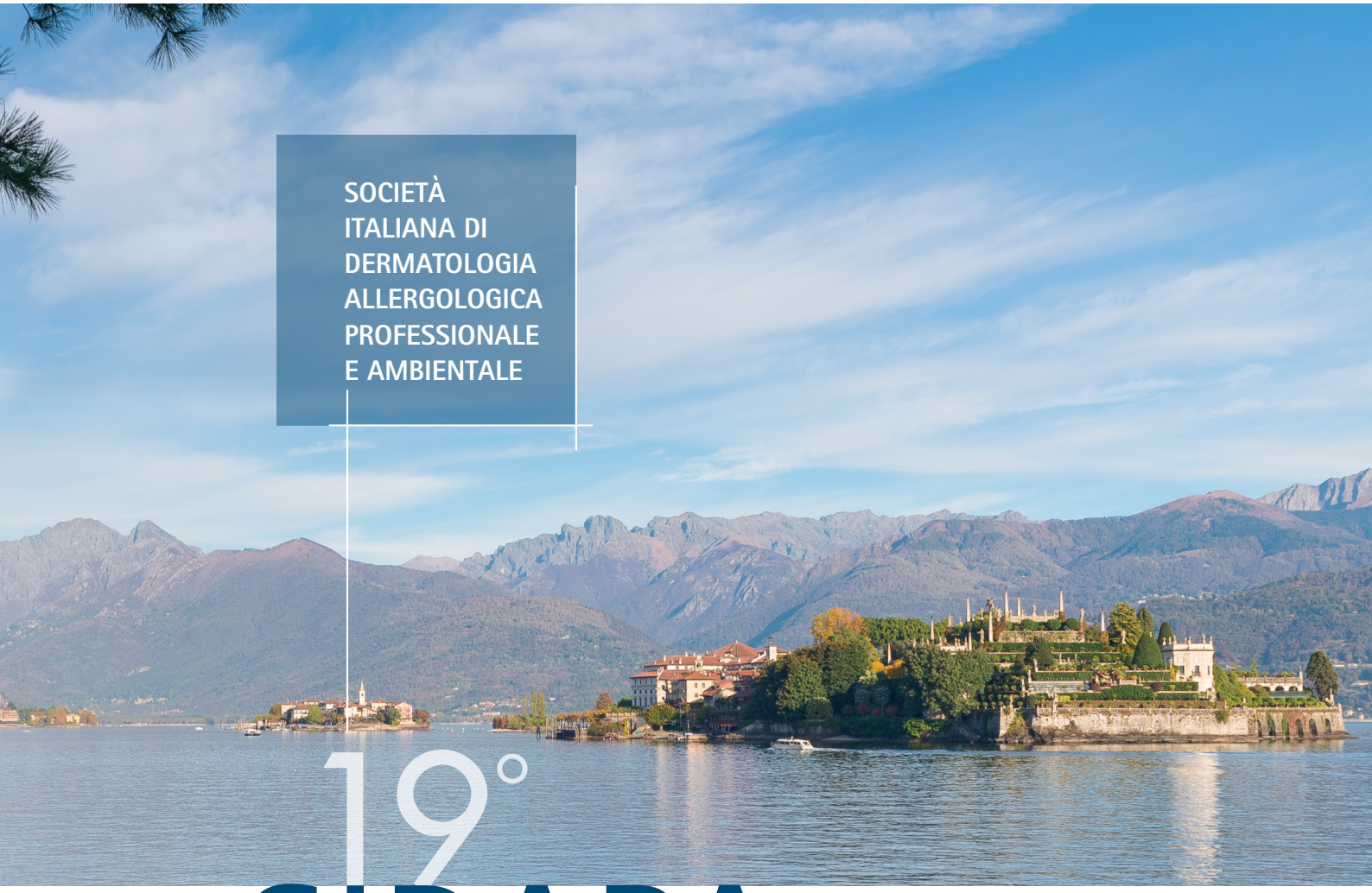

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Injective treatment of the so-called cellulite: a new approach aimed at restructuring extracellular matrix of deeper layers of theskin. Efficacy and safety of a new specific formula (part 1)

ADELE SPARAVIGNA

• Adele Sparavignai[1]

SUMMARY

Background: An innovative injectable solution containing low molecular weight hyaluronic acid (HA), a specific Amino Acids mixture and a carbonate plus bicarbonate solution was formulated to counteract moderate edematous – fibrosclerotic lipodystrophy (PEFS) on the thighs.

Objective: The aim of this open clinical trial was to evaluate the efficacy and tolerance of the injectable product under study, on the main signs of cellulite. Methods: A single Italian center treated 25 female subjects aged 35-55 years, informed and consenting. The study treatment foresaw 6 injective sessions at intervals of 10 days, by blunt tip cannula. The study had to be interrupted prematurely because of the COVID-19 pandemic and auto-isolation procedure of participating subjects. A minimally representative number of clinical observations was reached even after only 2 injection sessions.

Results: data highlighted a reduction of cellulite visual aspect of at least 1 degree in 20% of subjects vs T0 (not statistically significant), according to reference photographic scales and a mean reduction of clinical degree of cellulite of 0,3. Interestingly, a statistically significant reduction of mean circumferences of the thighs occurred:-0,8 cm at T3i. While the injected product was tolerated very well, light bruises occurred in 45% of subjects.

Conclusions: Although two injection sessions represented only one third of the foreseen complete treatment, the data obtained already confirms the tolerance and a partial aesthetic performance of the injectable solution on the main signs of cellulite. In particular on the visual aspect and the circumferences of the treated areas. Nevertheless, too many light bruises occurred, because of the use of blunt tip cannula. The Author argues that improving the injection technique could result in better clinical results on P.E.F.S.

KEYWORDS
Cellulite, Hyaluronic Acid, Carbonates, Bicarbonates, Acidosis, Amino Acids

INTRODUCTION

Cellulite is a major concern for women at every age. This condition, better defined as panniculosis, or edhematous fibrosclerotic panniculosis (P.E.F.S.), leads progressively to a degenerative disease of adipose pannicula, also involving more superficial layers of the skin. The result is a profound structural and functional alteration of the skin in sites such as the buttocks, thighs, knees and even the inner surface of the arms. Basically, at the forefront of advanced research on extracellular

1 Derming Clinical Research Institute, Milan

matrix (ECM), injection treatments can exert a therapeutic effect. In spite of the techniques currently in use, which involve the destruction of the altered adipose panniculus and the fibrous shoots typical of the most advanced stages of cellulite, the proposed treatment represents an attempt to remodel the biochemical and architectural structure of the deep and superficial components of the skin. In recent years, scientific research has made it possible to develop a solution of low molecular weight hyaluronic acid (HA) and collagen and elastin amino acids (AA) capable of specifically stimulating the synthesis of the main components of the extracellular matrix. A previous version of this solution is currently used with success in skin rejuvenation and redensification protocols. The product "Sunekos Cell" (SC), proposed for the study, contains a patented platform of six structural amino acids fundamentally and specifically dosed for an optimal neo-synthesis of collagen and elastin in the dermis. It has already been demonstrated, in vitro, that its functional cluster of amino acids is suitable for promoting in loco the synthesis of collagen and elastin.

Local injection of this formulation can be a powerful tool in expert hands because chemotaxis induced by the presence in the dermis of specific amino acids for the production of collagen and elastin is known to be the strongest force in nature that drives life: living things are attracted to food. In fact, we are sending a very strong biological message to the fibroblasts. Feeding the fibroblasts with the right food (the right amino acids) can reactivate them and also restore a normal structure of the dermal architecture.

Moreover, the natural low molecular weight hyaluronic acid (HA) (200,000 daltons) synergistically present in the Sunekos Cell formula exerts a targeted stimulating action on the fibroblasts through the binding to the specific receptors for the HA fragments.

A bicarbonate/carbonate buffer has been added to the standard formula in order to have a pH 8.2 for specific use in panniculosis. The bicarbonate and carbonate solution buffers local acidosis due to the state of latent inflammation that characterizes both the early and late stages of the disease.

Materials and methods

Aim of this pilot study was to evaluate by clinical, morphometric and non invasive instrumental evaluations the efficacy of an injective treatment on cellulite sign and symptoms.

The tested product, a mixture of HA, aminoacids and carbonates solution, was administered by the injection technique, on healthy female volunteers with moderate oedematous – fibrosclerotic lipodystrophy (PEFS) on the thighs. An additional aim of this study was to evaluate the treatment tolerance. The treatment foresaw 6 injective sessions at intervals of 10 days according by blunt tip cannula (25G, 50mm).

The study had obtained the approval of an Independent Ethical Committee.

Inclusion criteria were: healthy female Caucasian subjects, age ranges: 35-65 yrs. with moderate oedematous – fibrosclerotic lipodystrophy on the thighs (3rd superior). Exclusion criteria were pregnancy, lactation, general or local disease, smoking, alcohol and drug abuse. Sample population: 25 volunteers to be included. The volunteers had to accept to respect the rules fixed in the list of recruitment criteria and not to deviate from their normal life habits; particular attention was paid to alimentary and drug assumption habits, as well as to cosmetic product(s) and cleansing for the body.

During the entire period of treatment, the exposure to strong UV irradiation (UV session, or sun bathing) was to be avoided. Evaluations were carried out mono-laterally on the right or left thigh (3rd superior), according to a subjects' randomization list defined by the investigator before the subjects' inclusion.

Clinical evaluations **(Fig.1)** was performed according to the following visual score:

➜ **Cellulitis visual aspect (clinical score according to a reference photographic scale)**

- no cellulitis **0**
- slight dimpling on skin surface **1**
- dimpling and skin depressions **2**
- dimpling and depressed striations **3**
- nodules and depressed striations **4**

➜ **Product tolerance was evaluated considering:**

- local expected events/reactions induced by the injection procedure (tardive swelling, pain, erythema, bruise);
- any other adverse event/reaction, also of systemic source occurring during the study.

Morphometric evaluation
Circumference measurements

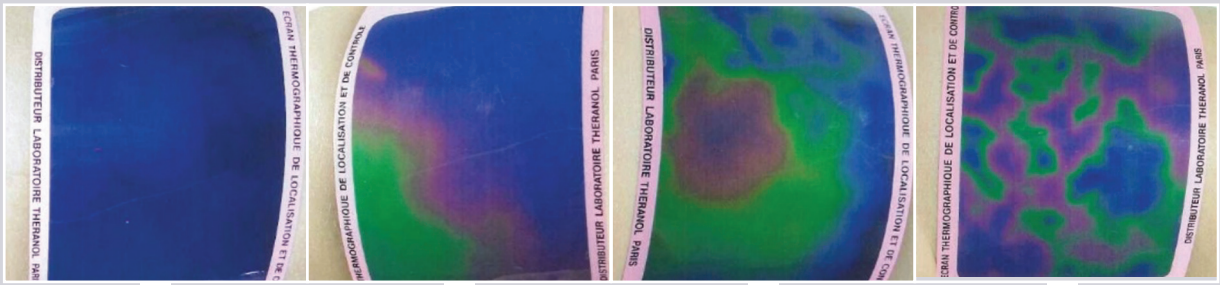
All the measures were performed in standard conditions at the thigh level (middle thigh and under gluteus), thanks to a specific electro-optical system able to fix the volunteer's position.

Fig. 1

0 1 2 3 4

Visual grading of cellulite

Fig. 2



1 2 3 4

Visual grading of contact thermography

Contact thermography

Contact thermography permits visualizing, through colors, the temperatures of the areas being examined by using encapsulated liquid crystals plates. It is therefore much helpful in pointing out skin temperature alterations. Each color of the liquid crystal corresponds to a different temperature following a standard chromatic scale from 21°C to 27°C: higher temperatures are shown by dark blue, while lower temperatures by green, yellow and black-red.

The thermography with liquid crystal allows to detect information about cutaneous microcirculation in normal conditions, after functional stimuli or vasoactive treatments: skin temperature grows in case of vasodilation, increase of blood vessels, increase local metabolism and reduced in case of vasoconstriction, pathological decrease of blood vessels, decrease of local metabolism, oedema and increase of adipose tissue. A characteristic thermography aspect of legs' oedematous – fibrosclerotic lipodystrophy is represented by the typical leopard skin with large hypothermic zones **(Fig.2)**.

➜ **Panniculopatia evaluation of the external thigh (3rd superior) follows next classification:**

- **0** = uniform hyperthermal image
- **1** = shaded spots thermal image (hyperthermal images)
- **2** = leopard spots (numerous hyperthermal images)
- **3** = hypothermal black holes
- **4** = uniform hypothermal image

Results

The study was started on 25 female healthy adult subjects, age range: 35-55 (mean age: 50 yrs.), whose written consent had been obtained. Unfortunately, the study had to be interrupted prematurely because of COVID-19 pandemic and auto-isolation procedure of participating subjects. A minimally representative number of clinical observations was only reached for T0, T2i, T3i. T2i is the time relating to the result of the first injection session (in fact the evaluation was performed immediately before the second injection session) and time T3i is relative to the result of the second.

Data processing and statistical analysis were performed in accordance to our internal procedures (de-

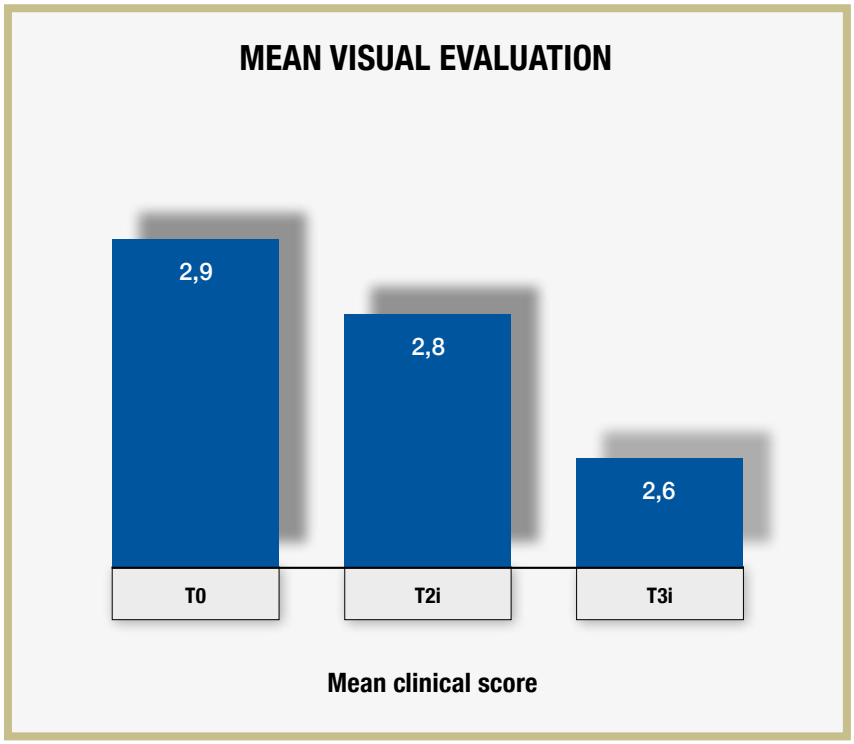


Fig. 3

scriptive and inferential analysis) as follows:

Friedman test followed, in case of statistically significant result, by Holm-Sidak Adjusted test.

Clinical assessment

Obtained results highlighted: a reduction of cellulite visual aspect of at least 1 degree in 20% of subjects vs T0 (not statistically significant), according to DERMING reference photographic scales and a mean reduction of clinical degree of cellulite of 0,2 at T2i and 0,3 at T3i **(Fig.3)**

Morphometric evaluation

All circumference measurements were performed in standard conditions thanks to a specific electro-optical system able to fix the volunteer's position.

At T2i the reduction corresponded to 0,4cm and at T3i to 0,8 cm. The last result was clinically/statistically significant, when compared to baseline **(Fig.4)** (Holm-Sidak Adjusted t test $p<0.05$ vs T0).

Tolerance evaluation

Although no important adverse event/reaction occurred during the trial, bruises occurred in 45% of cases. The average duration of the bruises was 12 days.

Contact thermography

Contact thermography mean score resulted reduced of 0.1 for both evaluation times, although this was not statistically significant (**Fig.5**).

Discussion and conclusions

Although the study was interrupted prematurely, some initial conclusions can be observed about the activity of injected formula and injection techniques. The formula in itself has demonstrated to exert a relevant restructuring activity on altered ECM at the level of P.E.F.S. In fact, already after only two injection sessions, a visible reduction of cellulite signs was obtained and, interestingly, a statistically significant reduction of thigh mean circumferences was obtained. In particular, this reduction was not expected, since the injected formula was not designed to have a slimming activity. Probably, mean circumference was due to a "panty" activity determined by an improvement of skin tone and consistency. On the contrary, while the formula itself was very well tolerated, the occurrence of bruises after the use of the blunt tip cannula was very high and probably not useful for a treatment aimed at reconstructing ECM of dermis and hypodermis. Based on this result, a less invasive needle technique should be designed. Previous studies on the use of the HA-6AA formula on the face demonstrated the superiority of Interstitial Fluid Technique (IFT) on intradermic random technique. In fact, IFT was demonstrated to combine injection and lymph-drainage by pushing interstitial fluids towards local lymph-nodes. Since in early stages of P.E.F.S. oedema and stasis are the main characteristics of the conditions, intradermal IFT towards inguino-crural lymphatic stations could be useful to reduce stasis at the level of thighs. On the other side, in advanced P.E.F.S. local fibrosis at the level hypodermis prevails.

In this case, a thin needle could reach deeper levels in order to put the product directly into the fibrosis. A new study for the evaluation of efficacy and tolerability of SC should therefore be designed in order to obtain the best from the treatment.

Fig. 4

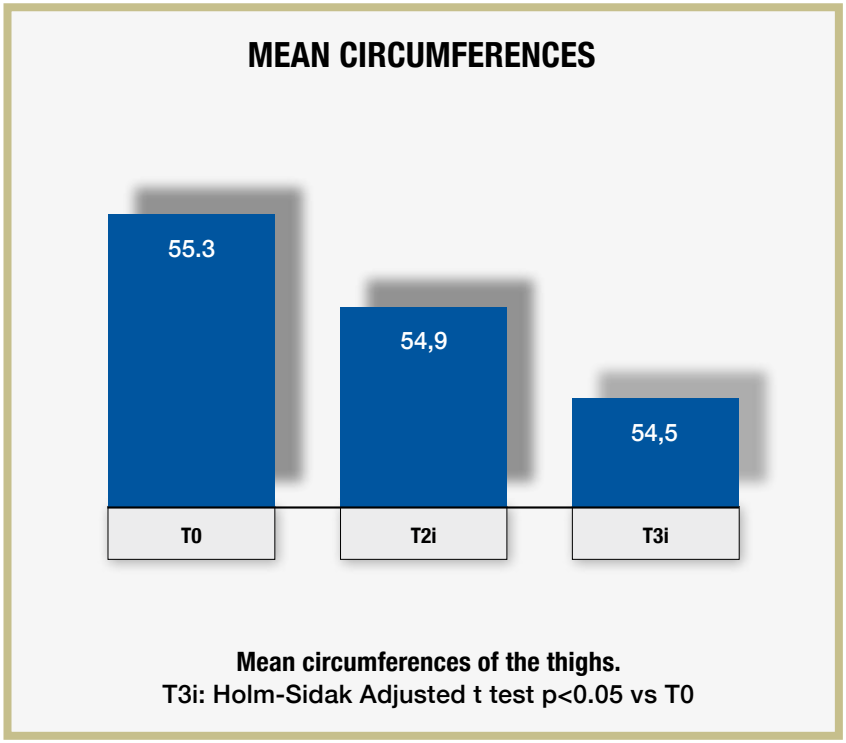
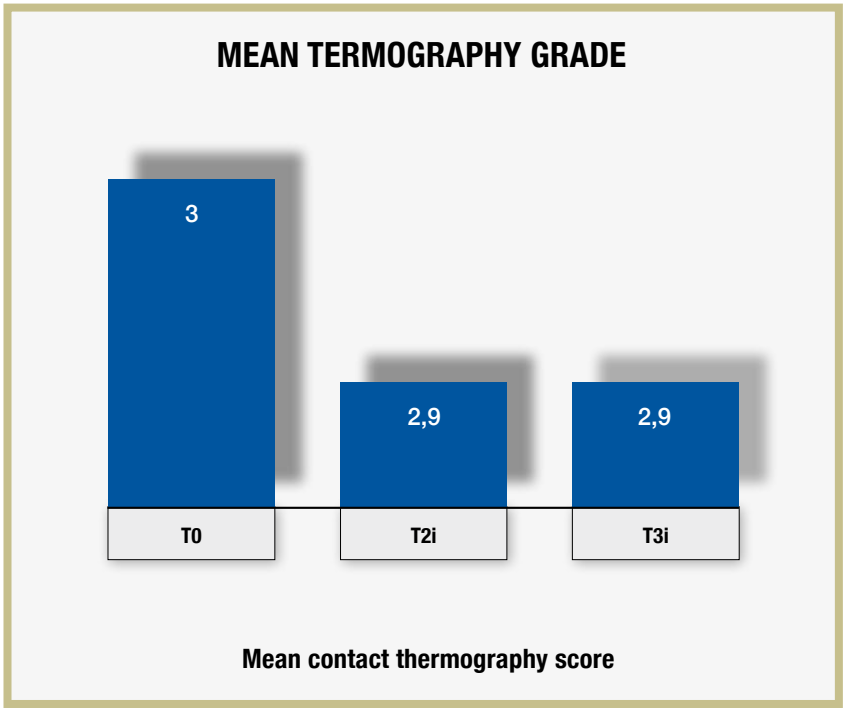

MEAN CIRCUMFERENCES
55.3
54,9
54,5
T0
T2i
T3i
Mean circumferences of the thighs.
T3i: Holm-Sidak Adjusted t test p<0.05 vs T0

Fig.5


MEAN TERMOGRAPHY GRADE
3
2,9
2,9
T0
T2i
T3i
Mean contact thermography score

Injective treatment of the so-called cellulite: a new approach aimed at restructuring extracellular matrix of deeper layers of the skin. Efficacy and safety of a new specific formula (part 2)

ADELE SPARAVIGNA

SUMMARY

Background: an innovative injectable solution containing low molecular weight hyaluronic acid (HA), a specific Amino Acids mixture and a carbonate plus bicarbonate solution was formulated to counteract moderate edematous – fibrosclerotic lipodystrophy (PEFS) on the thighs.

Objective: The aim of this open clinical trial was to evaluate efficacy and tolerance of the injectable product under study, on the main signs of cellulite. Methods: The study was conducted on 25 female adult subjects, age range: 33-60, whose written consent had been obtained. The patients were divided into 2 groups during the basal visit: - Group A (early stage): patients with grade 1-2 as per visual aspect grade : 11 patients

Group B (late stage): patients with grade 3-4 as per visual aspect grade: 14 patients

The study treatment foresaw 2 injective sessions at intervals of 10 days, according to a brand new injection method in the treatment of cellulite: IFT (for Group A) or Matelassé technique (for Group B) depending on the cellulite's stage. The study foresaw four observational visits over a four months period with the first and second injections at an interval of 10 days.

Results: data highlighted a reduction of cellulite visual aspect of at least 1 degree in 92% of all subjects (group A + group B) vs T0 (Holm-Sidak Adjusted Wilcoxon signed rank test p<0.05 T1M and T4M vs T0) according to reference photographic scales and a mean reduction of clinical degree of cellulite of of 0,88 at T1 and 0,95 at T4 for Group B and 0,9 at T1 and 0,6 at T4 per Group A 0,3. Interestingly, Morphometric evaluations underlined the "panty" activity of the treatment; in fact, already at T1M and at T4M the mean value of thigh and circumferences resulted clinically/ statistically reduced, when compared to baseline in both groups (-1,04 cm at T1 and -1,78 cm at T4 for Group B and –0,87 cm at T1 and -1,39 cm for Group A) (Holm-Sidak Adjusted t test p<0.05 vs T0). Obtained results were respectively of -4% for group A and -13,5% for group B at T1 and of -8,6% and -11,6% at T4, corresponding to a clinically and statistically significant reduction of the pannicula thickness vs T0, index of a lipo-reducing efficacy of the tested product

Conclusions: *Sunekos Cell was able to counteract the dermal damage which seems to be the most important triggering of the condition and acidosis at local level. The injection techniques should be less invasive as possible and take into account the phase of the disease.*

INTRODUCTION

Injection therapy has always been considered one of the most viable solutions for the treatment of cellulite. Obviously, it is very important to identify the most suitable product for the case, having clearly in mind the mechanism of action and the expected results, but also the most suitable injection technique to be used. Treatment of the ECM is certainly the primary goal. As we have seen, the alterations at this level play a fundamental role in the genesis of the so-called cellulite.

It has been demonstrated that, on histological samples of animal models it was possible to evaluate that physiological elastinogenesis and collagenogenesis, induced in a specific dermal district, have been shown to be capable of reducing skin laxity, mainly correlated to the manifestations of cellulite.

The product "Sunekos Cell" (SC), proposed for the study ,contains a patented platform of six structural amino acids fundamentally and specially dosed for an optimal neo-synthesis of collagen and elastin in the dermis. It has already been demonstrated that a functional cluster of amino acids is suitable for promoting in loco the synthesis of collagen and elastin.

Local injection of this formulation can be a powerful tool in expert hands because chemotaxis induced by the presence in the dermis of specific amino acids for the production of collagen and elastin is known to be the strongest force in nature that drives life: living things are attracted to food. In fact, we are sending a very strong biological message to the fibroblasts. Feeding the fibroblasts with the right food (the right amino acids) also means restoring a normal structure of the dermal architecture.

Moreover, a natural low molecular weight hyaluronic acid (HA) (200,000 daltons) is also synergistically present in the Sunekos Cell formula, exerting a targeted stimulating action on the fibroblasts even through the binding the specific receptors for the HA fragments.

A bicarbonate/carbonate buffer was added to the standard formula of Sunekos to Sunekos Cell in order to have a pH 8.2 for specific use in panniculosis. The bicarbonate and carbonate solution buffers local acidosis due to the state of latent inflammation that characterizes both the early and late stages of the disease.

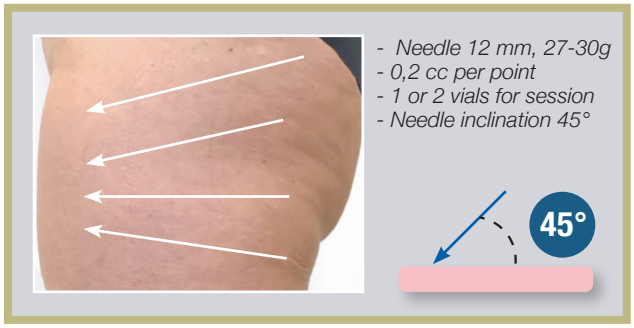
The disruption of the extracellular matrix of the dermis and hypodermis can be treated effectively, depending on the level and injection technique used. In the early stages, as we have seen, it is first of all important to treat the deep dermis, for an action on the interstitial fluids, in order to restore the physiological interstitial fluid movement towards the lymphatic circulation. In the advanced stage, the aim will be to rearrange the structural and architectural disorder of the fibrous septa of the hypodermis and injecting treatment with Sunekos Cell should therefore be exercised at a deeper level, in the fat adipose tissue. To summarize, when the process is initial and mainly involves the dermis, the injection technique will be at the level of the deep dermis, however taking into account the fact that the product, thanks to its low viscosity characteristics, will however spread optimally throughout the surrounding area. If, however, we are facing an advanced stage, the treatment will be at the level of the more superficial hypodermis, so as to exert a non-invasive action. Contrary to what is often stated by other authors, it is not necessary to violently disrupt fibrous branches, which is commonly done with large-caliber cannulas and often even with a "bayonet" cutting tip. The traumatic action of breaking the fibrous branches, in addition to systematically provoking at this level the formation of large bruises and hematomas (which often remain in unsightly hemosiderinic hyperpigmentations) greatly distances the objective of "restitutio ad integrum". Better then, reach the hypodermis with a smaller gauge needle and inject an adequate amount of the SC product, which will punctually manage to spread alone in a large surrounding area. In more detail, in the initial phase it will be possible to use the method we already know as Interstitial Fluid Technique (IFT), that is, making sure that the injecting treatment is at the same time able to push the movement of the interstitial fluids towards the local lymph node stations, realizing a real lymphatic drainage thanks to the push of the injected product. The injection is then followed by a light manual massage in the same direction. Since, in the early stages of panniculosis, the problem of stagnation of interstitial fluids, together with alterations of the micro-vascular-tissue exchange and the acidosis typical of the state of latent inflammation of the disease, is able to trigger the process of disruption of the 'ECM, it is very important to contrast the problem in its entirety, thanks to the specific formula SC, with a targeted injection technique. For IFT, it is advisable to use a 27-30G needle, 12 mm long, with an inclination of 45 ° with respect to the skin surface, made to penetrate for half of the length into the skin. Then inject 0.2-0.3 cc per point, with the

points arranged along radial lines converging from the lateral surface to the medial surface of the thigh, in the direction of the inguinal lymph nodes anteriorly and inguinal-crural posteriorly. The number of points (at a distance of about 2 cm from each other) and lines, will obviously vary depending on the extent of the edema and the orange peel skin **(Fig.1)**.

As for the more advanced stages, in order to obtain a rearrangement of the fibrous septae in the least traumatic way possible, the same type of needle will be used, 27-30G, mm12 in length, but this time inserted perpendicularly to the skin surface made to penetrate for its entire length and injecting 0.3-0.5 cc of product per point (Matelassé technique). Each point will be on lines drawn in the deepest depressions of the skin surface (mattress skin) at a distance of about 1.5 cm from each other **(Fig. 2)**.

To draw the areas to be treated, the patient must be examined in an orthostatic position, preferably in lighting conditions from above and slightly to the side, in order to accentuate the imperfections to be treated, tracing the lines most suitable for the case in question.

Fig. 1
IFT – Interstitial Fluid Technique



Study objective

The aim of this pilot study was to evaluate by clinical, morphometric and non invasive instrumental evaluations the efficacy of an injective treatment on "cellulite" signs and symptoms. A mixture of SUNEKOS® Cell a medical device composed of a small 10 ml bottle containing 210 mg of hyaluronic acid and 50 mg of aminoacids (glycine, proline, lysine ,leucine, valine and alanine) and 3 ml a solution of carbonates and bicarbonates was administered by injection technique, on healthy female volunteers with moderate oedematous – fibrosclerotic lipodystrophy (PEFS) on the thighs.

An additional aim of this study was to evaluate the treatment tolerance.

This study had obtained the approval of an Independent Ethical Committee on 16 January 2020.

10 ml of SUNEKOS® Cell (1 small bottle of aminoacids and sodium hyaluronate in 7 ml of distilled water) and carbonates (3 ml ampoules) in solution was injected by needle (27-30G length 13mm); the needle was inserted into the medium-deep dermis (45°) at level of the trochanteric region, following the IFT pattern in case of light cellulite (orange peel appearance, following a fan shaped pattern across the thigh area converging towards inguinal lymph-nodes) and perpendicularly to the skin (90°) in the max deepness of furrows in case of moderate cellulite (mattress appearance). The distance between injection points was 1,5 cm.

Treatment

The study was conducted on 25 female adult subjects, age range: 33-60 (mean age: 48 yrs.), whose written consent had been obtained. The patients were divided into 2 groups during the basal visit:

Group A (early stage): patients with grade 1-2 as per visual aspect grade : 11 patients

Group B (late stage): patients with grade 3-4 as per visual aspect grade: 14 patients

The study treatment foresaw 2 injective sessions at intervals of 10 days according to IFT (for Group A) or Matelassé technique (for Group B) depending on the cellulite's stage.

4 visits were performed during the study (Fig. 3):

- T0+T1i: basal assessments, followed by the 1st injection procedure
- T2i: preliminary assessment and 2nd injection procedure
- T1M (1 month after the last injection procedure: evaluations foreseen by the study protocol (Follow-up phase)
- T4M (4 months after the last injection procedure)

Data processing and statistical analysis were performed as follows: Friedman test followed, in case of statistically significant result, by Holm-Sidak Adjusted test.

The inclusion criteria were the following: volunteers aged 35-65 years, with moderate oedematous – fibrosclerotic lipodystrophy on the thighs (3rd superior), with regular menstrual cycle (28-32 days), no Body Mass Index (BMI) variation (± 1) during the last month preceding the study inclusion, available and

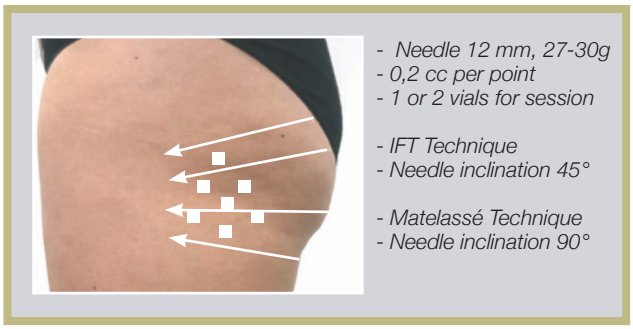


Fig. 2
Matelassé Technique

able to return to the study site for the treatment phase and post-procedural follow-up examinations, accepting not to change their habits regarding food, physical activity, cosmetic and cleansing products for the body, accepting not to expose their body to strong UV irradiation (UV session and/or sun bathes) during the entire duration of the study, accepting to sign the informed consent form.

The exclusion criteria were: pregnancy (only for female subjects not in menopause), lactation (only for female subjects not in menopause), smokers, alcohol abuse and/or drug use, female subjects not in menopause, who do not accept to perform the pregnancy test at T0 and T1M, female subjects not in menopause, who do not use adequate contraceptive precautions in order to avoid pregnancies during the study, oral contraceptive/replacement therapy started less than 1 year ago, change in the normal habits regarding food and physical activity during the month preceding the test and during the study period, use of any anti-cellulite/weight-loss treatment (manual or instrumental massage) on skin test areas during the three months, use of any drug able to cause a weight body variation, Body Mass Index (BMI) variation (± 1) during the study period, presence of clinically important vascular disorders, sensitivity to the test product or its ingredients, including delayed hypersensitivity to hyaluronic acid and granulomatous reactions (to be assessed by the investigator during the baseline), subjects whose insufficient adhesion to the study protocol was foreseeable, participation in a similar study currently or during the previous 6 months.

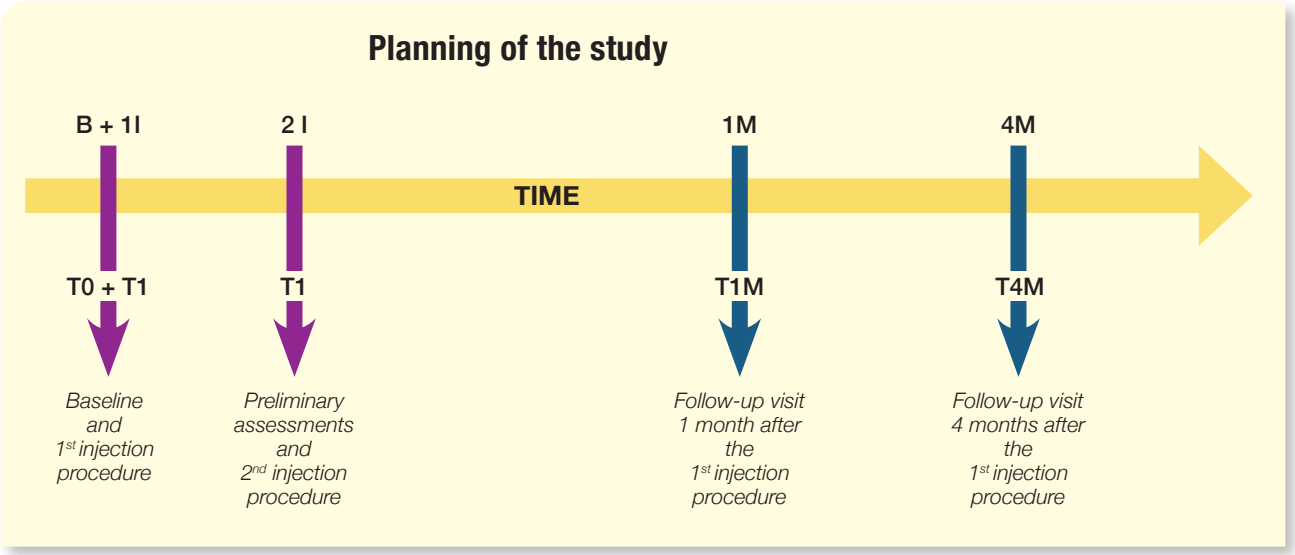
All evaluations were carried out mono-laterally on the right or left thigh (3rd superior), according to a subjects' randomization list defined by the investigator before the subjects' inclusion. At T2i, T1M and T3M clinical, morphometric and instrumental assessment were performed before the injection procedure.

Clinical evaluations were performed according to the following visual score:

➜ **Cellulite visual aspect (clinical score according to a reference photographic scale)**

- no cellulite **0**
- slight dimpling on skin surface **1**
- dimpling and skin depressions **2**
- dimpling and depressed striations **3**
- nodules and depressed striations **4**

Fig. 3



Photographic documentation

At T0, T1M and T4M, 2D pictures of the thigh treated areas (left or right side randomly) for all included volunteers were taken.

Circumference measurements

All the measures were performed in standard conditions at the thigh level (middle thigh and under gluteus), thanks to a specific electro-optical system able to fix the volunteer's position.

To reduce the intra-individual variability, circumferences measurement were performed 3 times for each level.

Ultrasonographic evaluations

Ultrasonographic measurement of adipose panniculum thickness (mm) were performed at level of the 3rd superior (external side), through the instrument Body Metrix™ BX 2000 (Genex).

The BX 2000 generates an ultrasound signal (5 MHz) that propagates through tissue and then records the reflected signal.

Results

Clinical assessment

Obtained results highlighted a reduction of cellulite visual aspect of at least 1 degree in 92% of all subjects (group A + group B) vs T0 (Holm-Sidak Adjusted Wilcoxon signed rank test $p<0.05$ T1M and T4M vs T0), according to DERMING reference photographic scales and a mean reduction of clinical degree of cellulite of 0,88 at T1 and 0,95 at T4 for Group B and 0,9 at T1 and 0,6 at T4 per Group A **(Fig. 4)**.

Morphometric evaluation

All circumferences measurements were performed in standard conditions thanks to a specific electro-optical system able to fix the volunteer's position (see procedure).

Morphometric evaluations underlined the "panty" activity of the treatment; in fact, already at T1M and at T4M the mean value of thigh and circumferences resulted clinically/statistically reduced, when compared to baseline in both groups (-1,04 cm at T1 and -1,78 cm at T4 for Group B and –0,87 cm at T1 and -1,39 cm for Group A) (Holm-Sidak Adjusted t test $p<0.05$ vs T0) **(Fig. 5)**.

Ultrasound assessment

Ultrasonographic measurement of adipose pannicula was performed through the instrument Body Metrix™ BX 2000 (Genex). Obtained results were respectively of -4% for group A and -13,5% for group B at T1 and of -8,6% and -11,6% at T4, corresponding to a clinically and statistically significant reduction of the pannicula thickness vs T0, index of a lipo-reducing efficacy of the tested product **(Fig 6)**.

Tolerance evaluation

No adverse event/reaction (nor those expected, such as pain, discomfort and bruises) occurred during the trial. The very high tolerance (100%) was confirmed by the investigator at the end of the treatment period.

In order to highlight the results obtained not only numerically, the photographs of two patients, one of the early group and one of the late group, at time T0 and time T4M, are shown below **(Figg. 7 and 8)**

Discussion and conclusions

The so-called "cellulite" (needless to say, this term does not correspond to the exact medical definition of the condition) afflicts at least 90% of female population in the post-pubertal age almost all over the world and also male population is not entirely exempt from it. To date, there are scientific bases, now well documented, as they are based on histological, biochemical and ultrastructural observations that highlight the pathological aspects. Furthermore, the comorbidities (obesity, overweight, venous pathology of the lower limbs), the subjective symptomatology and the clinical signs that accompany its course, certify the clear deviation from the physiology of the skin. Certainly, the histological aspects that well represent the complexity of the pathogenesis of this disease are characterized by three essential events: alterations of the adipose tissue, hyper-polymerization of the connective tissue matrix and profound alterations of the microcirculation.

Female sex hormones play a significant role in the development of cellulite, in fact this pathology occurs almost exclusively in the female gender.

The main pathogenetic mechanism of cellulite is the altered capillary-venular permeability, with a slowing of the speed and volume of blood flow (vasomotion) at the local micro-circulatory level. The particular conformation of the micro-vascular-tissue unit justifies the fact that the defects in microcirculation of panniculopathy are often associated with alterations in the blood flow that extend to the skin and regional muscles, causing clinical effects such as hyperkeratosis (orange peel skin), tenderness and, in the more advanced stages, profound subversion of the loco-regional aesthetic (mattress skin). The presence of estrogen receptors in endothelial cells and smooth muscle explains the functional differences of female microcirculation, especially in relation to vascular tone and permeability and, therefore, the greater susceptibility of the female sex to the so-called cellulite.

The most recent studies inform us

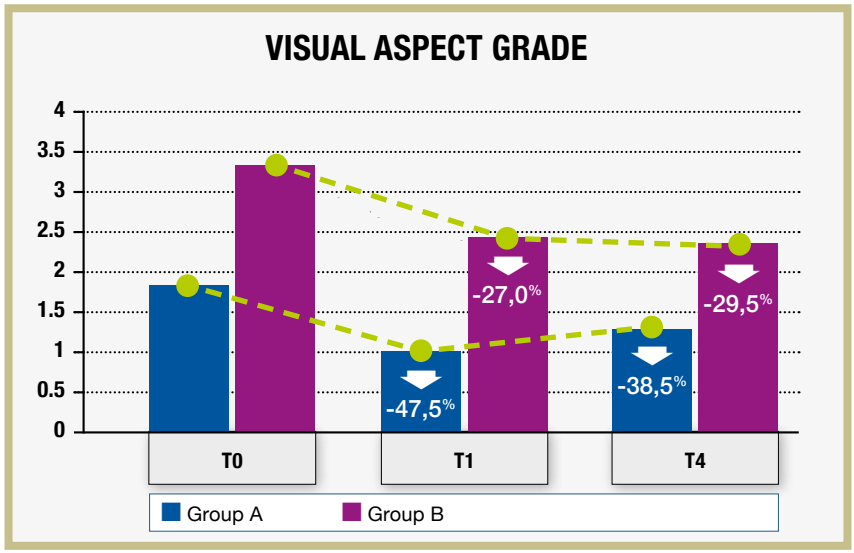


Fig. 4

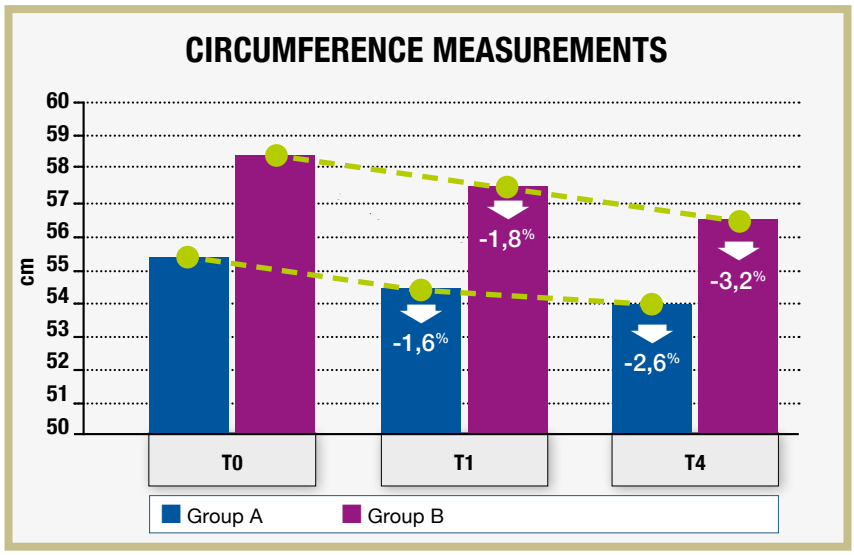


Fig. 5

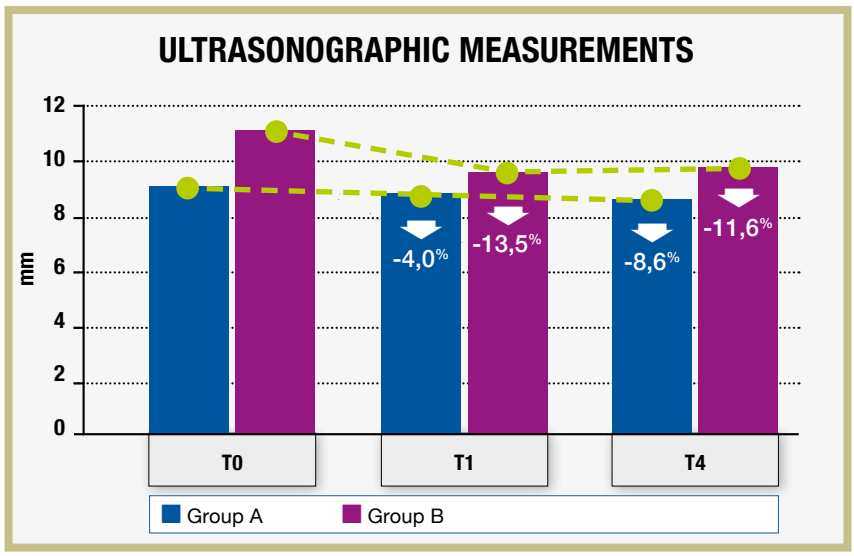


Fig. 6

Fig. 7
Early stage Cellulite

Fig.8
Late stage Cellulite

that, at the level of cellulite, among the functional alterations encountered by adipocytes, there is an increase in the release of phlogistic cytokines. Therefore, adiposity involves the activation, at regional level, of biochemical-cellular mechanisms of an inflammatory nature.

This notation is absolutely consistent with the estrogenic activity on the development of cellulite, which has been widely described and has been further ascertained with the observation of the tissue of women undergoing hormonal therapies and monitored by imaging techniques such as ultrasound and computerized axial tomography.

Once the process is triggered, over time it develops, due to the inflammatory processes described above, on the one hand the neo-synthesis of collagen that leads to the formation of fibrous branches, on the other the reduction of the compactness of the tissues around the fibrous branches. This increase in skin laxity seems in some ways similar to the manifestations of skin aging, also characterized by a degradation of the dermo-epidermal fibrous matrix. Sunekos Cell was able to counteract the dermal damage which seems to be the most important triggering of the condition and acidosis at local level. The injection techniques had an important influence on the results and was planned according to the phase of the disease: in early phases the Interstitial Fluid Technique was the most suitable in late stages the Matelassé Technique demonstrated to be amazingly effective.

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Observational study for the clinical evaluation of the effectiveness and tolerability of a neurosensinetm based cream in the therapy of eczematous dermatitis of the face

O. DE PITTÀ

Studio osservazionale per la valutazione clinica di efficacia etollerabilita' di una crema a base di neurosensinatm nella terapiadella dermatite eczematosa del volto

• O. De Pità*1 • M. D'Ambrosi*1 • F. Lupi *1 • S. Voltolini *2 • A. Musarra*2

ABSTRACT

Dermatitis on the face represents one of the most common reasons for frequent dermatologists and/or allergologists examination because it generally affects people at young age. Besides, the face is one of the dermatological sites with the greatest impact on the emotions related to the personal image and social relationships.

In recent years, medical studies led to the formulation of some dermocosmetic products with therapeutical properties and high tolerability. A study has been conducted on 36 patients with eczematous dermatitis on the face to assess a secure and tolerable product which is deemed to reduce skin sensitivity and reactivity and to increase the tolerance threshold.

KEYWORDS
Neurosensine, Eczematous Dermatitis, Face, Clinical Evaluation, Effectiveness, Tolerability

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**2 AAIITO – Associazione Allergologi Immunologi Italiani Territoriali e Ospedalieri*

INTRODUZIONE

Le dermatiti localizzate al volto rappresentano un motivo di frequente consultazione dello specialista dermatologo e/o allergologo sia perché interessano con maggiore frequenza soggetti in giovane età, sia perché la localizzazione al volto rappresenta una delle forme dermatologiche con maggiore impatto sull'emotività correlata all'immagine personale e ai rapporti relazionali.

Ciò può infatti costituire motivo di importante alterazione della qualità di vita dei pazienti e rappresenta lo stimolo maggiore alla richiesta di intervento diagnostico-terapeutico specialistico.

Tra le varie forme dermatologiche con possibile localizzazione al volto, quelle di tipo eczematoso rappresentano forse le più frequenti ed interessano in particolare la dermatologia allergologica data l'etiologia correlabile in molti casi ad allergia da contatto (irritativa o allergica) o a forme di eczema atopico. Il trattamento di tali manifestazioni, che spesso tendono a cronicizzare, prevede l'utilizzo di prodotti dermocosmetici e farmacologici che devono essere dotati di proprietà antinfiammatorie, emollienti e protettive senza effetti collaterali nell'uso a lungo termine. La possibilità di evitare l'utilizzo di cortisonici topici nelle localizzazioni palpebrali, periorali, al volto in generale, rappresenta pertanto un obiettivo significativo 1-2.

Negli ultimi anni la ricerca ha portato a sintetizzare alcuni prodotti dermocosmetici dotati di proprietà terapeutiche dermatologiche e di tollerabilità. Il prodotto a base di NeurosensinaTM (Nacetyl-Tyr-Arg-hexadecylester) (0,04%) grazie alla formulazione, comprendente un numero limitato di componenti attivi e priva di alcool e sostanze allergizzanti (profumi, conservanti, coloranti, lanolina) in una confezione ermetica, quindi priva di possibili contaminazioni, ha dimostrato in alcuni studi di ridurre sensibilità e reattività cutanea e aumentare la soglia di tolleranza, associando assoluta sicurezza e tollerabilità. La formula attiva comprende acqua termale ad azione decongestionante (10%), glicerina (6%) come idratante, burro di karitè (7%) con azione sulla barriera cutanea e un ingrediente attivo di sintesi originale, la NeurosensinaTM.

Essa ha dimostrato una azione di stimolo sui cheratinociti inducendoli alla produzione di endorfine ed encefaline con il risultato di creare uno scudo protettivo delle terminazioni nervose e di bloccare i circuiti percorsi dai segnali dolorosi 3-4. In questo modo, oltre alla attività antinfiammatoria e protettiva, appare in grado di ridurre rapidamente le sensazioni di bruciore e dolore, aumentando la soglia di tolleranza della cute affetta da dermatite eczematosa in maniera persistente nel tempo. Ciò con conseguente miglioramento della qualità di vita dei pazienti con cute sensibile 5.

Fino ad oggi il prodotto non è stato paragonato con farmaci per uso topico quali i cortisonici nel trattamento di dermatiti eczematose6.

Scopo dello studo

Questo studio è stato effettuato per valutare clinicamente l'efficacia del prodotto topico contenente NeurosensinaTM in associazione ad acqua termale e burro di karité in soggetti adulti con dermatiti del volto paragonando l'efficacia ad un trattamento di associazione con idrocortisone topico seguito da crema base idratante.

Lo studio è stato effettuato con modalità osservazionale in aperto.

Materiali e metodi

Lo studio è stato effettuato su 36 pazienti, 14 maschi e 22 femmine, di età compresa tra i 19 e i 61 anni (età media di 39,33) affetti da dermatite del volto di grado lieve-medio di tipo irritativo (DIC), da contatto (DAC) associata in alcuni dei casi trattati a dermatite atopica (DA) i quali sono stati valutati idonei alla partecipazione allo studio e non af-

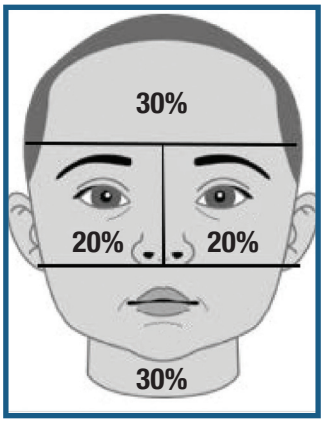


Figura 1.

INTENSITA' DELLE LESIONISEGNI CUTANEI
Eritema
Edema
Lesioni crostose
Vescicolazioni-essudazione
Desquamazione
Secchezza
0: assente
1: lieve
2: moderato
3: severo

Tabella 1.

SINTOMI SOGGETTIVI (PAZIENTI)
Prurito
Bruciore
Disagio relazionale
Punteggio attribuito ai singoli sintomi da 0 a 10

Tabella 2.

fetti da altre lesioni sulle aree della pelle da sottoporre a trattamento e dai quali è stato ottenuto il consenso informato al trattamento Sono stati esclusi, invece, i pazienti in trattamento sistemico con antistaminici, cortisone e altre terapie sistemiche immunosoppressive, mentre per i pazienti che facevano uso cronico di steroidi topici è stato previsto un wash out di 3 settimane. Durante l'arruolamento è stata valutata la presenza di allergie o ipersensibilità al prodotto o ad un componente dell formulazione e nei soggetti con DAC sono stati eseguiti patch test serie Sidapa. Le attività lavorative principali svolte dai pazienti arruolati nello studio erano le seguenti: operatore sanitario, cuoco, impiegato, casalinga, operaio, studente. 21 pazienti presentavano DIC ,11 DAC, 4 DIC/DAC +DA.

- I pazienti sono stati ridistribuiti in due gruppi: il gruppo A composto da 11 pazienti e il gruppo B composto da 25 pazienti
- Trattamento del gruppo A: terapia a base di idrocortisone topico per 7 giorni 1 volta al dì, per i restanti 21 giorni applicazione di una crema base 2 volte al dì;
- Trattamento del gruppo B: il solo prodotto studiato per 28 giorni, con 2 applicazioni al giorno.

Parametri di valutazione

È stato effettuato un esame clinico accurato dei pazienti per la valutazione delle lesioni cutanee e dei segni clinici al momento dell'inclusione nello studio e durante il trattamento dividendo empiricamente il volto in quattro quadranti, a cui è stata attribuita la seguente percentuale di estensione: 30% per la fronte, 30% per il mento, 20% per gli occhi-zigomo destro, 20 % per gli occhi-zigomo sinistro **(Figura 1)**, e particolare interesse è stato attribuito al miglioramento dei sintomi soggettivi. Inoltre, è stato chiesto ai pazienti di autovalutare la tollerabilità e il gradimento del prodotto.

➜ **Efficacia:**

1. Valutazione della estensione e intensità dei segni clinici (eritema, desquamazione, vescicolazione-essudazione, edema, lesioni crostose, secchezza) mediante SCORE a T0, T7 gg, T28gg. **(Tabella 1)**

2. Valutazione dei sintomi soggettivi da parte del paziente (prurito, bruciore cutaneo, disagio
nelle relazioni) **(Tabella 2)**

➜ **Gradevolezza/tollerabilita':**

1. Valutazione attraverso un questionario di autovalutazione (molto soddisfatto, soddisfatto, poco soddisfatto, per niente soddisfatto) dei seguenti parametri: facilità di applicazione, effetti collaterali all'applicazione, sensazione pelle morbida/idratata, benessere globale. **(Tabella 3)**

2. Valutazione dei pazienti in drop out. Questionario telefonico per indagine sulla ragione dell'abbandono del trattamento.

➜ **Periodo di studio:** 6 mesi

Risultati

Sono stati arruolati 36 pazienti, 22 femmine e 14 maschi, affetti da dermatite da contatto del volto di grado lieve-medio. 21 pazienti affetti da DIC, 11 pazienti da DAC e 4 da DIC/DAC +DA (3 DIC e 1 DAC).

Due pazienti, uno per ciascun gruppo, hanno interrotto la terapia per motivi personali di conseguenza la valutazione al termine dello studio includeva 10 pazienti nel gruppo A e 24 pazienti nel Gruppo B.

Nessun effetto collaterale importante è stato riportato dai pazienti nel periodo del trattamento.

Le forme lievi con estensione delle lesioni del 30% erano 17, tutte DIC, in particolare 9 con coinvolgimento della zona perilabiale e 8 con coinvolgimento della zona perioculare. È stata rilevata una sola DIC di forma moderata ed estensione delle manifestazioni del 60% e 2 DIC di forma grave con estensione del 100% .

Le DAC presentavano estensione in 4 casi del 60% e in 8 casi del 100%.

3 pazienti presentavano la combinazione DIC + DA di forma medio- grave ed estensione delle lesioni del 100%, mentre 1 solo paziente presentava DAC+DA sempre di forma medio- grave ed estensione del 100%.

I 2 pazienti usciti dallo studio erano affetti uno da DAC e uno da DIC ed entrambi presentavano estensione ed intensità del 60% di lesioni al volto

I Patch Test eseguiti su 12 pazienti hanno presentato le seguenti positività 5 per il Nichel, 4 per i Parabeni, 3 per Lyral, 2 per Diffusi Mix, 5 per profumi mix, tutti allergeni che possono dare anche manifestazioni a livello del volto

Le attività lavorative dei soggetti arruolati evidenziano che le forme più gravi si legavano ai lavori dove l'esposizione agli allergeni e più frequente (operatore sanitario, cuoco, operaio)

I pazienti di entrambi i gruppi hanno presentato un miglioramento evidente delle manifestazioni e dei sintomi dopo la prima settimana, miglioramenti che si sono confermati e progressivamente resi più evidenti a 28 giorni dall'inizio dei trattamenti.

Considerando i due tipi di terapia topica applicata e raffrontando i risultati nei due gruppi si evidenzia che: i pazienti del gruppo A in terapia cortisonica topica nei primi 7 giorni hanno ridotto i valori globali di intensità delle lesioni in maniera raffrontabile ai pazienti del gruppo B e successivamente al termine del periodo di osservazione di 28 giorni si evidenzia un miglioramento globale simile nei 2 gruppi.

In particolare, il valore dell'intensità delle lesioni valutata secondo quanto descritto in **Tab. 1** con la misurazione di 6 segni cutanei (eritema ,edema ,lesioni crostose ,vescicolazione-essudazione, desquamazione, secchezza) e distribuzione del grado di severità da 0 a 3 è nel gruppo A erano 11,5 a tempo zero, 6,3 dopo 7 giorni di terapia e 2,9 (UA=Unità Arbitrarie) dopo 28 giorni e nel gruppo B 8,8 al tempo zero,4,8 dopo 7 giorni e 1,6 a 28 giorni **(Tab. A1, A2, A3, A4, A5, A6, A7)** dimostrando una riduzione di intensità di manifestazioni simili nei due gruppi.

GRADEVOLEZZA/TOLLERABILITA'
Facilità applicazione
Effetti collaterali all'applicazione
Sensazione pelle morbida/idratata
Benessere globale
molto soddisfatto
soddsfatto
poco soddisfatto
per niente soddisfatto

Tabella 3.

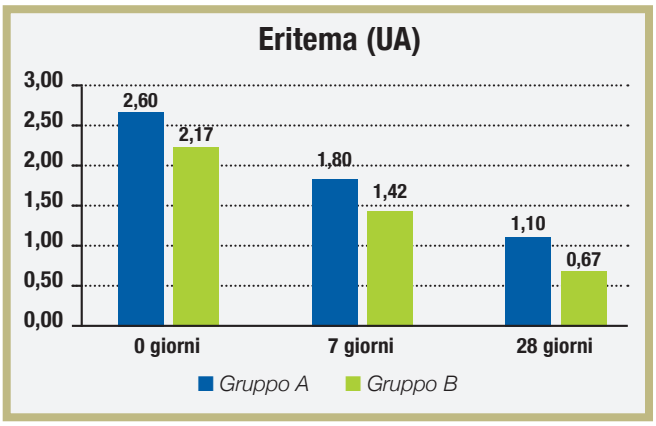
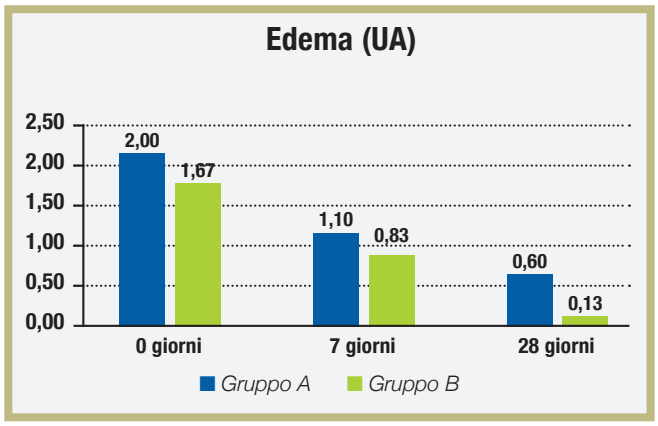


Tabella A1



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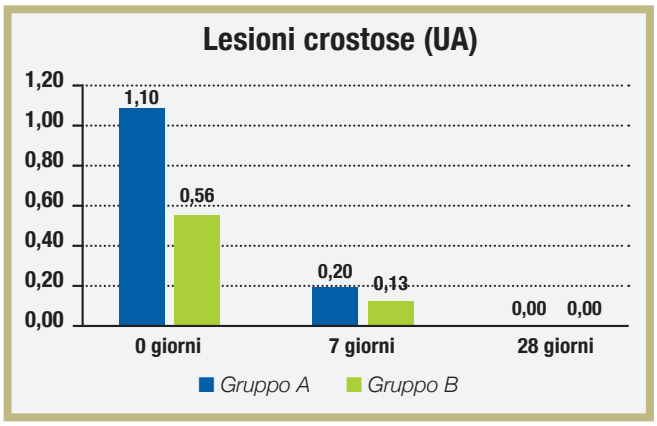

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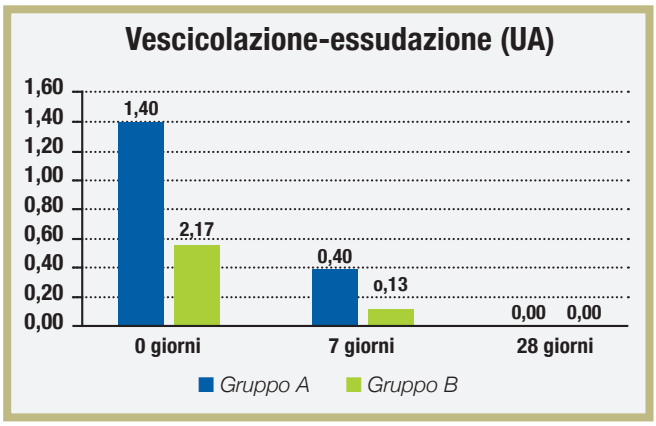

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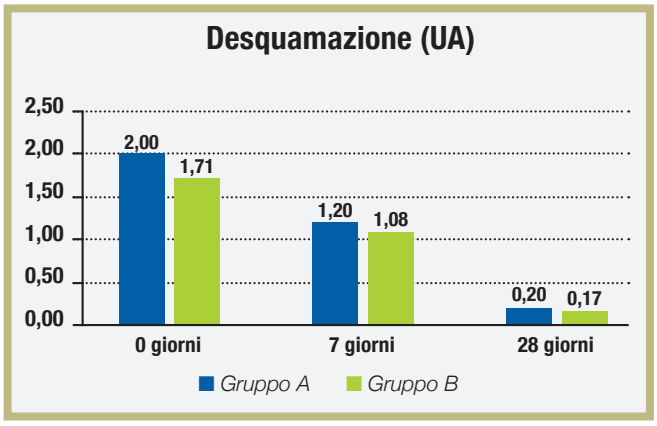

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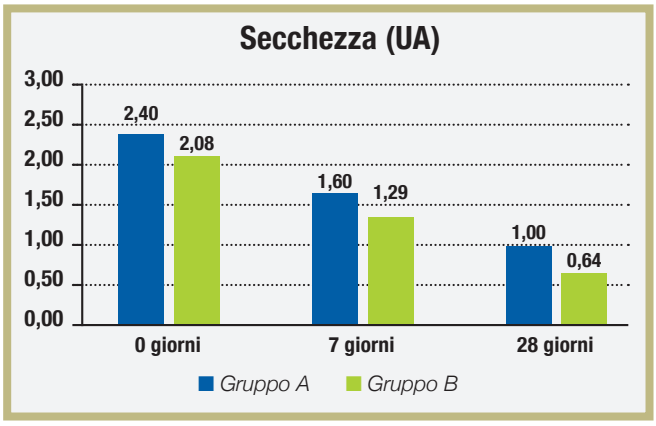

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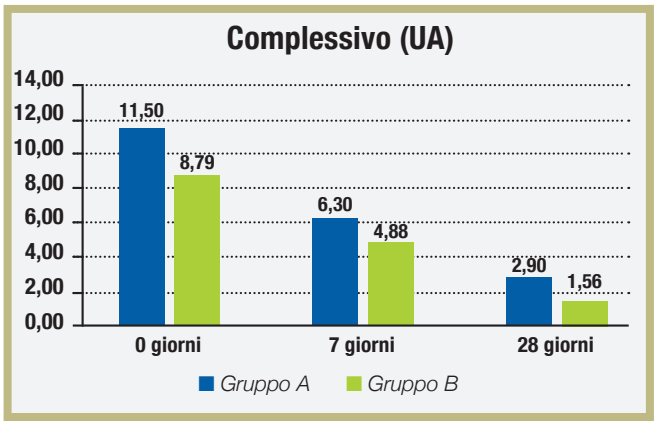

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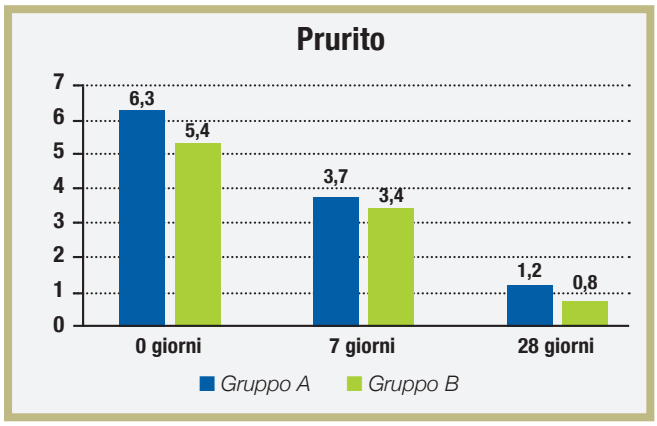
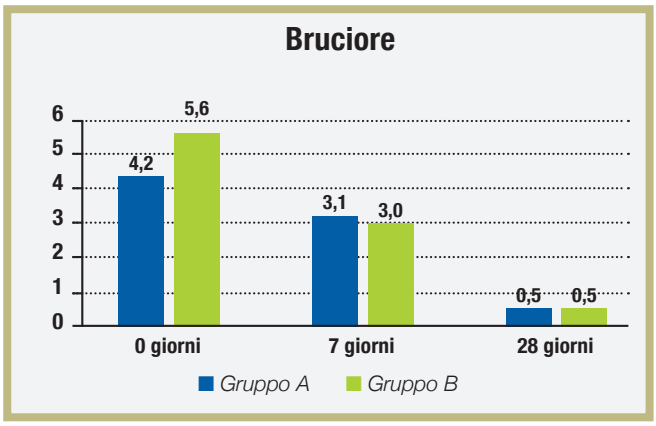
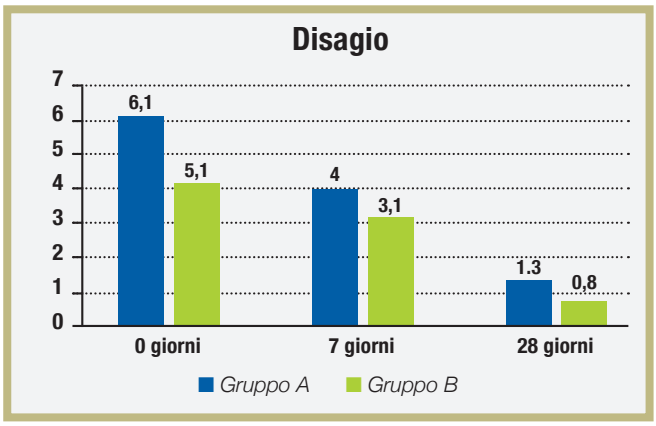


Tab. B1



Tab. B2



Tab. B3

I sintomi soggettivi espressi dai pazienti (prurito, bruciore e disagio relazionale)espressi con grado di severità da 0 a 10 **(Tab. B)** evidenziano come il bruciore sia più intenso nel gruppo b perché' legato alla forma di DIC che generalmente si caratterizza con sensazione di bruciore nei pazienti affetti a differenza di quanto avviene nelle DAC e nella DA in cui il prurito è il sintomo più importante .

Il bruciore che nel gruppo B dei pazienti si presenta a tempo 0 con valori più elevati (5,6 vs 4,2 UA) successivamente a 7 e 28 giorni si riduce e i valori si presentano pressoché uniformi a quelli del gruppo A

Il prurito si presenta tempo 0 più intenso nel gruppo A rispetto al gruppo B (6,3 vs 5,4 UA) e il dato è giustificato dal fatto che i pazienti afferenti al Gruppo A erano per la maggior parte affetti da dermatite allergica da contatto e dermatite atopica

Infine la valutazione sulla gradevolezza e tollerabilità espresse dai pazienti dimostrano una maggiore facilità di applicazione una sensazione di pelle morbida e di facilità di applicazione migliore nel gruppo B rispetto al gruppo A **(Tab. 3)**

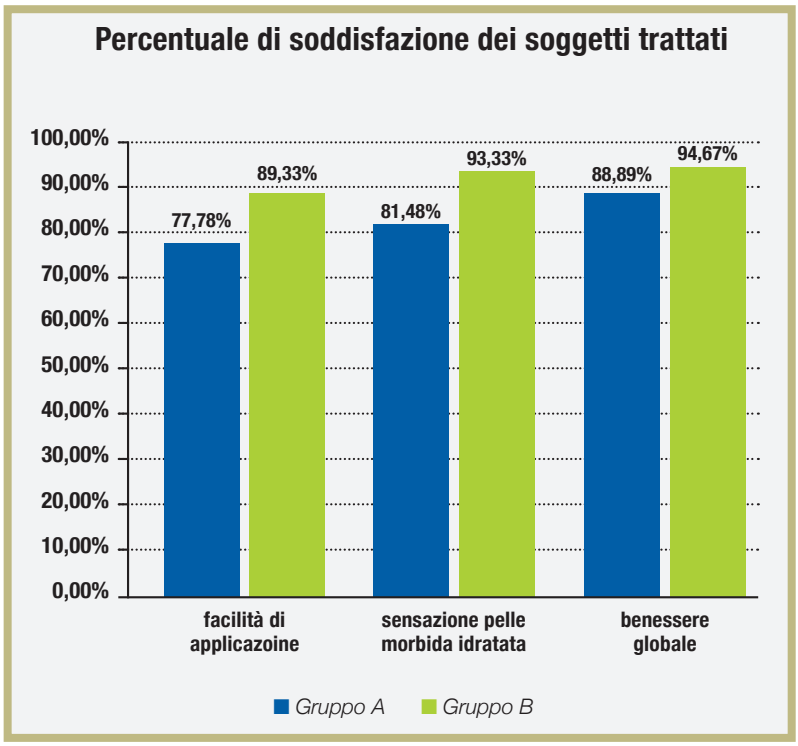
Conclusioni:

Le dermatiti localizzate al volto rappresentano un motivo di frequente consultazione dello specialista dermatologo e/o allergologo sia perché interessano con maggiore frequenza soggetti in giovane età, sia perché la localizzazione al volto rappresenta una delle forme dermatologiche con maggiore impatto sull'emotività correlata all'immagine personale e ai rapporti relazionali. Ciò può infatti costituire motivo di importante alterazione della qualità di vita dei pazienti e rappresenta lo stimolo maggiore alla richiesta di intervento diagnosticoterapeutico specialistico

Negli ultimi anni la ricerca ha portato a sintetizzare alcuni prodotti dermocosmetici dotati di proprietà terapeutiche dermatologiche e di tollerabilità. Il prodotto a base di NeurosensinaTM

(N-acetyl-Tyr-Arg-hexadecylester) (0,04%) grazie alla formulazione, comprendente un numero limitato di componenti attivi e priva di alcool e sostanze allergizzanti (profumi, conservanti, coloranti, lanolina) in una confezione ermetica, quindi priva di possibili contaminazioni, ha dimostrato in alcuni studi di ridurre sensibilità e reattività cutanea e aumentare la soglia di tolleranza, associando assoluta sicurezza e tollerabilità

Fino ad oggi il prodotto non è stato paragonato con farmaci per uso topico quali i cortisonici nel trattamento di dermatiti eczematose.



Tab. 3

Questo lavoro confronta due tipi diversi di trattamento , il primo con un idrocortisone topico applicato per un periodo di 7 giorni e seguito dall'applicazione di una crema idratante per 14 giorni il secondo con una crema a base di NeurosensinaTM in associazione ad acqua termale e burro di karitè che ha dimostrato una azione di protezione sulla cute e di blocco sui circuiti percorsi dai segnali dolorosi come dimostrano studi in vitro ed in vivo. In particolare gli stimoli dolorosi legati al bruciore caratteristico della dermatite irritativa risultavano migliorati con indici di soddisfazione evidente nei soggetti trattati con il topico a base di NeurosensinaTM.

Il rapido miglioramento delle manifestazioni, la riduzione dei sintomi caratteristici di queste patologie e la soddisfazione dei pazienti nell'applicazione supportano la scelta di un prodotto non farmacologico con caratteristiche specifiche atto a ridurre sensazioni come il bruciore e il prurito nel trattamento di dermatiti del volto di grado lieve medio con la possibilita' di allungare i tempi di trattamento e ridurre le recidive .

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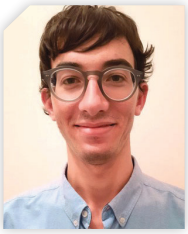
Psoriasis? Crusted scabies!



ITALO FRANCESCO AROMOLO

• Italo Francesco Aromolo • Stefano Veraldi

SUMMARY

In an adult male, with a 7-year history of psoriasis treated with topical and oral corticosteroids, methotrexate, cyclosporin, infliximab and other biological drugs, crusted scabies was diagnosed. The patient was successful treated with three courses of oral ivermectin. This case teaches us that we should never trust diagnoses made by others, even if they are important and famous dermatologists.

KEYWORDS
Psoriasis, scabies, crusted scabies

Department of Pathophysiology and Transplantation, Università degli Studi, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

A 37-year-old Caucasian man was admitted with a clinical diagnosis of psoriasis. The patient stated that the disease appeared approximately seven years earlier and that it was unsuccessfully treated at other dermatological centers with topical and oral corticosteroids, methotrexate, cyclosporin, infliximab and other biological drugs. He also declared that the disease worsened in the summertime. The patient complained of pruritus. Dermatological examination revealed widespread, mildly erythematous, scales and crusts. The scalp, face **(Figure 1)**, hands and scrotum **(Figure 2)** were in particular involved. General physical examination did not reveal anything pathological.

Laboratory tests showed leucocytosis (10.100 white blood cells/mm3), eosinophilia (8%) and increase in erythrocyte sedimentation rate (35 mm at the 1st hour). A clinical diagnosis of crusted scabies (CS) was made. Microscopical examinations confirmed the presence of numerous adults and eggs of Sarcoptes scabiei var. hominis. The patient was treated with ivermectin (15 mg/day) and cetirizine (20 mg/day). A cream containing Prunus amygdalus dulcis oil and Capparis spinosa fruit extract was also prescribed. Three courses of ivermectin were necessary. The therapy was well tolerated, except for worsening of pruritus during the first days and mild tremors. Recovery was confirmed by negative microscopical examinations. Follow up (8 months) was negative. CS, previously named Danielssen-Boeck disease and norwegian scabies, occurs in patients with severe neurological or psychiatric diseases (backwardness, oligophrenia, Down's syndrome, Alzheimer's disease, neuropathies with hypo-anaesthesia), AIDS and cachexy. CS is the final clinical result of a scabies that was never treated or it was badly treated or it was caused by the chronic use of topical and/or systemic corticosteroids. CS is rare in children. Microscopical examina

tions reveal hundreds of mites/mm2. CS is characterized clinically by mildly erythematous, squamous-crusted, hyperkeratotic lesions: they may be located on specific areas, such as the scalp, elbows, hands, knees and feet, or may be widespread. Pruritus is absent or mild. Onychodystrophies caused by hyperkeratosis of the nail bed are common. Lymphadenopathy is also common. Bacterial superinfections and erythroderma (erythrodermic scabies or scabious erythroderma) are the most frequent complications. Differential diagnosis includes psoriasis and chronic eczemas.1

It is possible that in this patient CS developed because of the chronic use of topical and oral corticosteroids and immunosuppressive drugs, such as methotrexate. As previously mentioned, this patient was previously treated at other dermatological centers with several drugs. Unfortunately, he was not treated with acitretin. This because it was demonstrated that oral retinoids increase the desquamation and inhibit the differentiation of keratinocytes. A reduction in filaggrin expression was observed in mouse keratinocyte cultures treated with retinoids.2 Human keratinocyte cultures grown in the presence of retinoids at concentrations that inhibit differentiation, contain neither filaggrin nor profilaggrin.2 Retinoids can alter filaggrin expression at the level of profilaggrin synthesis and/or at the level of post-translational processing of profilaggrin to filaggrin.2 Filaggrin is very important for mite survival because it was demonstrated that it is the main "food" for mite.3 It is possible that acitretin is active thanks to its keratolytic action, but also thanks to its inhibitory action on filaggrin synthesis. Furthermore, it is known that some arthropods have retinoid receptors, such as the retinoid X receptor.4 Acitretin and tretinoin showed to be effective in some anecdotical cases.5,6.

What does this case teach us? It teaches us that we should never trust diagnoses made by others, even if they are important and famous dermatologists.

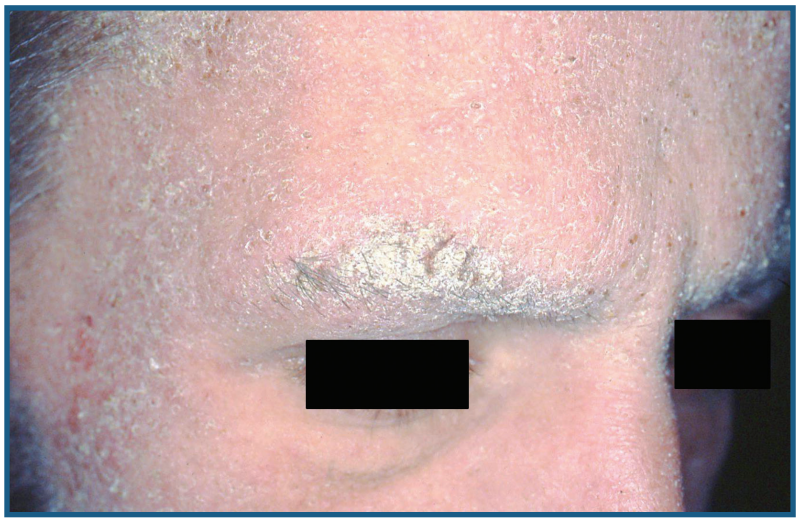


Figure 1.
Widespread squamous lesions on the face.

Figure 2.
Scales and erosions: the latter caused by chronic scratching.

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Alopecia androgenetica maschile con forte componente infiammatoria

• Intervista a Paolo Gigli[1]

PAOLO GIGLI

Guarda il video dell'intervista!

Nella patogenesi della quasi totalità delle patologie tricologiche, esiste un minimo comune denominatore patogenetico che è l'infiammazione. Questo tipo di meccanismo lo ritroviamo non solo nell'alopecia androgenetica ma anche nell'Alopecia Areata e nel Telogen Effluvium. Per cui è basilare nell'economia della cura prescritta al paziente, agire contrastando i fenomeni infiammatori.

Da un punto di vista clinico, l'infiammazione al cuoio capelluto si manifesta con sintomi quali dolore al cuoio capelluto (tricodinia), bruciore e prurito. Alla tricoscopia si identificano delle aree giallastre che circondano i follicoli piliferi, chiamati Yellow Dots e che sono il corrispettivo dermatoscopico dell'infiammazione.

Per trattare un'alopecia androgenetica bisogna sia bloccare gli effetti del diidrotestosterone sul follicolo pilifero sia modulare l'infiammazione e bloccarla. Quest'ultima tende a creare **fenomeni di fibrosi** che pian piano fanno superficializzare il follicolo, riducendo la profondità follicolare e la fase Anagen. Negli scenari peggiori si può arrivare ad atrofizzazione del follicolo.

Per trattare questa infiammazione è possibile intervenire sia con terapie farmacologiche, prevalentemente corticosteroidi di bassa potenza in lozione, sia con nutraceutici specifici e mirati per via sistemica.

Quindi è possibile intervenire con anti-infiammatori che non siano farmacologici, ma naturali ovvero da fitoestratti. Questi esercitano la loro azione in maniera mirata: un principio attivo che può essere impiegato è l'EPILOBIO che rappresenta una novità tra i fitocomplessi, in quanto si tratta di un antinfiammatorio naturale ancora non utilizzato in tricologia.

Si tratta di un antinfiammatorio naturale che ha anche proprietà sedative, decongestionanti e lenitive. Deve le sue caratteristiche a delle componenti che si chiamano **ellagitannini**. L'Epilobio riduce la liberazione di mediatori dell'infiammazione acuta, fra cui LOX e COX, riduce la liberazione del TNF-alfa ed esercita un'azione seboregolatrice come inibitore della 5-alfa-reduttasi. L'Epilobio trova la sua massima espressione terapeutica se viene usato in associazione

1 Medico specialista in Dermatologia e Venereologia, Professore a contratto in Scienze Tricologiche Mediche e Chirurgiche presso l'Università degli Studi di Firenze, Socio fondatore della Società Italiana di Tricologia, Vice direttore Scientifico del Giornale Italiano di Tricologia

alla terapia classica, ad esempio con attivatori dell'attività mitotica come Minoxidil o inibitori della 5-alfa-reduttasi come la Serenoa Repens in soft gel (olio al 92%) o la Finasteride, associato agli antiossidanti. L'approccio terapeutico ottimale è gestire i meccanismi ormonali dell'alopecia androgenetica da un lato e dall'altro gestire l'infiammazione.

L'epilobio si usa con un dosaggio di circa 350mg al giorno, è ben tollerato, esercita un effetto seboregolatore e quindi è un ausilio sistemico molto utile in queste situazioni.

Gli inibitori della 5-alfa-reduttasi, quindi, rappresentano un'ottima associazione all'**Epilobio** stesso, poiché bloccano l'azione del diidrotestosterone sul follicolo pilifero. Soprattutto, dobbiamo ricordare che gli anti-infiammatori somministrati devono essere tollerabili per lungo tempo, quindi non devono presentare eccessivi effetti collaterali e devono dimostrarsi adatti a terapie lunghe, come possono essere quelle tricologiche che durano anche anni consecutivi.

Solitamente nelle cure tricologiche dell'alopecia androgenetica, la prima visita di controllo avviene dopo sei mesi, con i primi risultati e si raggiunge il plateau del risultato dopo un anno o un anno e mezzo di cura. Successivamente c'è un periodo di mantenimento.

L'infiammazione è uno dei trigger che scatenano la calvizie e nello specifico all'alopecia androgenetica maschile. Intervenire in maniera mirata sull'infiammazione è fondamentale per agire efficacemente sulla causa che porta a tale patologia.

Oggi la ricerca scientifica ci mette a disposizione degli strumenti terapeutici evoluti di ultima generazione che vanno a completare e migliorare quanto è già presente.

➜ Epilobio ENOTProst®

Epilobium Angustifolium (estratto brevettato) è una pianta nota in Europa per le sue proprietà antinfiammatorie e antiossidanti, legate all'attività sinergica dei suoi numerosi componenti, tra cui principalmente gli ellagitannini, in particolare l'Enoteina B.

Comunemente l'Epilobio, applicato localmente o assunto come infuso, è stato utilizzato nella medicina tradizionale per il trattamento di ferite cutanee traumatiche, ustioni, sintomi delle vie urinarie in virtù dei suoi effetti antiinfiammatori, analgesici, antibatterici. Gli estratti di epilobio sono da tempo utilizzati anche in diverse patologie prostatiche, quali l'ipertrofia prostatica benigna e le prostatiti, per il loro effetto antinfiammatorio, anti-proliferativo e **anti-androgenico** dato il **blocco fisiologico sulla 5-alfareduttasi.**

La composizione fitochimica degli estratti di Epilobio vede la presenza di acidi grassi (caproico, linoleico, linolenico, ecc.), acidi aromatici (ellagico, gallico, ecc.), steroli (campestrolo, β-sitosterolo, ecc.), flavonoidi (guaiaverina, quercetina, ecc.), ellagitannini (enoteina A e B, ecc.).

Studi sperimentali in vitro ne hanno dimostrato proprietà analgesiche, anti-proliferative (effetto citotossico e ad un'interferenza nella progressione del ciclo cellulare), antinfiammatorie (inibizione della LOX e delle COX, riduzione di TNF-α), immunomodulanti (induzione dell'endo-peptidasi neutra, aumento della risposta immunitaria mediata dall'attivazione di macrofagi), **anti-androgeniche (inibizione dell'aromatasi e della 5α-riduttasi**), antimicrobiche (effetto battericida ad ampio spettro), antiossidanti (aumento dei livelli di SOD1), **radical-scavenger** (inibizione della perossidazione lipidica di membrana), anti-aging e foto-protettivi (inibizione di collagenasi, ialuronidasi, metalloproteasi della matrice). Studi su animali di laboratorio ne hanno confermato l'**attività antinfiammatoria, anti-androgenica**, analgesica con un buon margine di sicurezza.

ENOTProst® è un estratto secco standardizzato e brevettato di Epilobio contenente acidi organici e fenolici, tannini, flavonoidi ed ellagitanni, di cui il 15% dei Enoteina B. ENOTProst® si è mostrato efficace nel ridurre i sintomi urinari correlati all'ipertrofia prostatica benigna in uno studio clinico controllato in doppio cieco.

Molti composti impiegati con successo nell'ipertrofia prostatica hanno dimostrato la loro efficacia anche nell'alopecia androgenetica. Grazie alle sue proprietà antinfiammatorie, antiossidanti, radical-scavenger ed anti-androgenetiche, quindi l'estratto di Epilobio costituisce un valido aiuto nell'alopecia androgenetica con componente infiammatoria, in sinergia con gli altri principi attivi.

Infine, l'estratto di Epilobio in vitro sembra **ridurre la produzione di sebo da parte dei sebociti** e regolare l'immunità innata a livello cutaneo, tramite l'espressione di **De-**

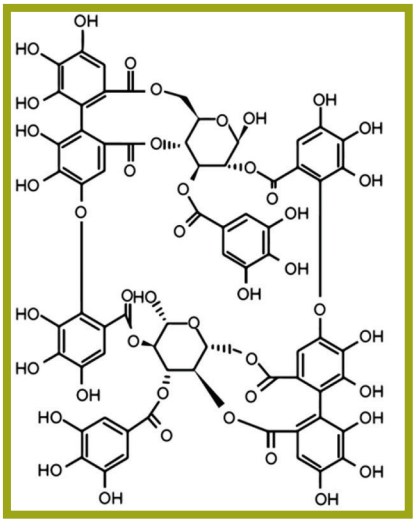

Figura 1.
Fitocomplesso dell'EPILOBIO

fensine e TLR-2, con un potenziale ruolo nella sebo-regolazione e nella riduzione della colonizzazione da parte di Malassezia furfur. Questi dati sono stati confermati in uno studio clinico che ha mostrato una riduzione della desquamazione e della seborrea in pazienti affetti da dermatite seborroica, condizione spesso associata all'alopecia androgenetica.

➜ Fitosteroli (β-SITOSTEROLO)

I fitosteroli sono steroli di origine vegetale in particolare, il β-sitosterolo in particolare è il fitocomplesso attivo della **Serenoa Repens** e si trova in concentrazioni elevate soprattutto negli estratti oleosi (soft-gel) piuttosto che negli estratti secchi.

Il β-Sitosterolo ha dimostrato di avere effetto antiandrogeno sia a livello prostatico che del follicolo pilifero, probabilmente per una riduzione della biodisponibilità del colesterolo nel microambiente locale, con una riduzione della biosintesi del testosterone e dell'attività della 5α-reduttasi. Il β-sitosterolo si è dimostrato efficace nel migliorare la qualità dei capelli in pazienti affetti da alopecia androgenetica e sembrerebbe in grado di inibire l'espressione di geni coinvolti nei processi infiammatori a livello dei cheratinociti.

Antiossidanti utili in tricologia

Astaxantina: carotenoide di origine vegetale estratto dall'alga verde Haematococcus pluvialis è noto per l'elevato potere antiossidante e antinfiammatorio.

PAC: Proantocianidine sono una classe di polifenoli presenti in numerose varietà di specie botaniche tra cui la corteccia di pino, con proprietà antiossidanti, ipoglicemizzanti e ipolipemizzanti. Inoltre, le proantocianidine oligomeriche contribuiscono a rinforzare l'elasticità e la funzionalità del letto capillare favorendo una miglior irrorazione sanguigna dei tessuti.

Conclusioni

Concludendo, la combinazione, in associazione precostituita per via orale di Epilobio, β-Sitosterolo, Astaxantina e Proantociadine costituisce un ottimo razionale terapeutico per un approccio mirato all'alopecia androgenetica maschile con forte componente infiammatoria, in associazione a terapie topiche e/o sistemiche farmacologiche.

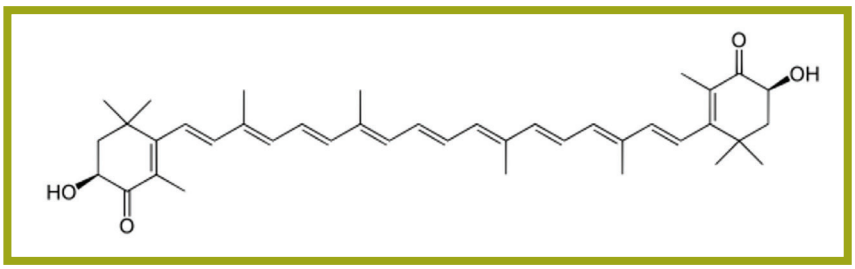

Figura 2.
Astaxantina

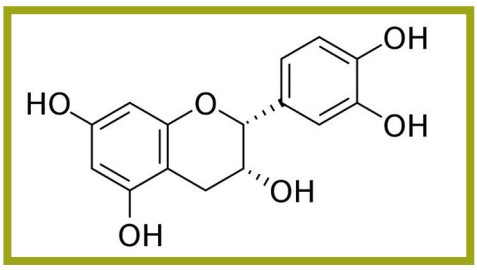

Figura 3.
Proantocianidine

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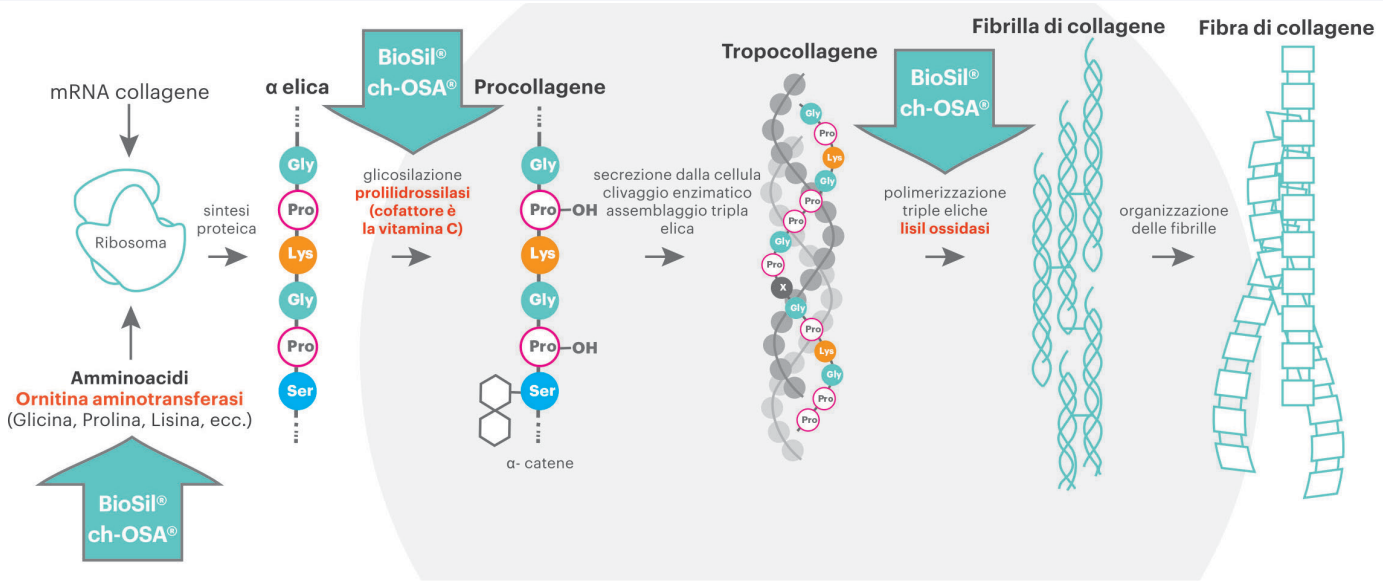

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Volume 14, n3

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- **Aesthetic outcome of laparoscopically harvested omental flap versus glandular flap in breast conservative surgery** *Waleed Y. El- Sherpiny, Mohamed A. Mlees, Ayman A. Elnemr, Ahmed A. Darwish*

2019

➜ Volume 15, n. 1

- **How does face age? A retrospective observational study and meta-analysis** *Adele Sparavigna*
- **Erbium laser treatment for facial acne scars and skin regeneration** *Bruno Mandalari, Antonino Di Pietro*
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- **Anti IL23 biologic therapy in the treatment of psoriasis** *Martina Silvestri, Luigi Bennardo, Maria Passante, Francesco Rizzuto, Giusy Schipani, Stefano Dastoli, Federica Tamburi, Steven Paul Nisticò*
- **The sun makes you happy but it also hurts you: the right strategy to prevent damage** *Stefania Bizzarri*
- **New therapeutic opportunity in acne treatment: daylight photodynamic therapy** *Francesca Romano*
- **Eye and ear disorders in vitiligo** *Claudio Comacchi*
- **Multidisciplinary Psoriatic Disese Unit: our experience** *Luisa Di Costanzo, Maria Grazia Ferrucci*
- **Different modalities of eyebrow reconstruction: retrospective study** *Mohamed Radwan El-Hadidy, Ahmed AM Khalil, Basem Esam Elfiky*

➜ Volume 15, n. 2

- **Efficacy of a novel emollient plus cream in atopic dermatitis: a randomised, vehicle-controlled, double-blind study** *Adele Sparavigna, Beatrice Tenconi, Laura La Penna*
- **Evaluation of the effect of a hair cosmetic treatment through a clinical test** *Evelyn Falconi Klein, Massimo Perrone, Claudio Angelinetta, Antonino Di Pietro*
- **Chemo-Exfoliation with Glycolic Acid, Chitosan, N-acetyl-cysteine, L-carnitine hydrochloride. Therapeutic Protocols for a Highly Socially Presentable Treatment in the Management of Skin Aging, Melasma and Acne** *Marina Romagnoli, Carlotta Pastorino*
- **Acne and sun exposure,** *Giuseppe Alessandrini*
- **Folliculitis caused by argan oil** *Michela Brena, Diego Tosi, Rossana Schianchi, Mauro Barbareschi, Stefano Veraldi*
- **Use of homologous skin and dermal allografts in hard to heal wounds: an integrated surgical approach,** *Linda Tognetti, Ernesto De Piano, Chiara Cencetti, Giulio Cortonesi, Roberto Perotti, Guido Lorenzini, Claudia Panzano, Giancarlo Palasciano, Francesca Ierardi, Elisa Pianigiani, Pietro Rubegni*
- **Drug induced pemphigus** *Maria Passante, Martina Silvestri, Luigi Bennardo, Francesco Rizzuto, Giusy Schipani, Stefano Dastoli, Federica Tamburi, Steven Paul Nisticò*

➜ Volume 15, n. 3

- **Effectiveness of microwaves in the treatment of cellulite: a preliminary study** *Antonino Di Pietro, Simona Ferri, Paolo Bonan, Alice Verdelli, Silvia Stevan, Chiara Tartaglia, Elisabetta Perosino*
- **Evaluation of the balneotherapy treatment of psoriasis with water "Terme di Sorano": efficacy in terms of clinical quality of life** *Gianni Baldi, Stefano Perlini*
- **The Off Label Dermal Biorigeneration with Macromolecular Free Hyaluronic Acid use, through a review of the literature, a retrospective study and case report** *Fabiano Svolacchia, Lorenzo Svolacchia*
- **Dermatological diseases of the lower limbs: the nails** *Elisabetta Sorbellini*

➜ Volume 15, n. 4

- **Postbiotics and Paraprobiotics: the new frontier of the microbiome in dermatology** *Fabio Rinaldi, Daniela Pinto*
- **Promobarrel Pilot Study** *Delia Colombo, Matteo Benedet, Basso Di Pasquale, Antonino Di Pietro*
- **Plexiform fibroistiocytoma in an 8-year old patient: description of a clinical case** *Michele Pezza, Filomena Barbato, Maria Elena Errico, Valentina Carlomagno, Enrico Pezza, Roberto Calandriello, Gerardo Casucci, Orsola Ametrano, Elena Sammarco*
- **Autologous Plasma in Aesthetic & Regenerative Medicine and the role of PRP and PPP. Regeneration, Fibrosis or only Matrix? A Retrospective Study** *Fabiano Svolacchia, Lorenzo Svolacchia*

- **Vitiligo and scalp** *Claudio Comacchi*
- **Malleability of thoracodorsal artery perforator flaps for axilla reconstruction** *Ahmed Mahmoud El-Shebly, Mohammed Hassan El Fahar, Ahmed Mohammed Bahaa Eldin, Samy Ahmed Shehabeldin, Mohamed Radwan El-Hadidy*
- **Temporalis galea and periosteal extension Transfer as Part of a Comprehensive Approach to Facial Reanimation** *Ahmed Kamal, Eman H. El-Hakeimm*
- **Boswellic acids: a shining perspective to treat skin and articular inflammation and skin aging signs** *Andrea Fratter*

2020

➜ Volume 16, n. 1

- **The exosomes of Adipose Tissue in Regenerative Medicine. The results of our protocol in a clinical study of Anti Aging** *Fabiano Svolacchia, Lorenzo Svolacchia*
- **Hydrochlorothiazide based therapy and non-melanoma skin cancer: our experience** *Mariano Saviano, Flora De Natale, Carla Ceddia, Francesco D'Alessandro, Gennaro Castaldo, Gabriella Rametta*
- **Case reports: Scabies in an arm wrestler** *Stefano Veraldi, Alice Monestier*
- **Photodynamic therapy and alopecia areata** *Claudio Comacchi*
- **Oxygen-ozone therapy and dermis** *Ruben Oddenino*
- **Probiotics and atopic dermatitis: charming promise or clinical truth?** *Andrea Fratter*
- **The role of extracorporeal septoplasty in management of crooked nose** *Mohamed R. Elhadidy, Amr M. E. Khater*

➜ Volume 16, n. 2

- **Action of topic aminoacid mixtures in chronic pressure sore repair in spinal-cord injured patients** *Carla Pezzuto, A. Frenello, S. Levetti, C. Castagnoli, B. Giacumbo, D. Alotto, I. Cambieri*
- **Clinical and radiological assessment about the effectiveness of collagen and hyaluronic acid supplement** *Giuseppe Colombo, Ruben Oddenino, Vittorio Ruvolo, Alessandro Garlaschi*
- **Haberland syndrome: case report** *Flora De Natale, Elena Sammarco, Filomena Barbato, Arcangelo Menna, Patrizia Forgione*
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- **Cat scratch disease: case report** *Michele Pezza, Valentina Carlomagno, Roberto Calandriello, Innocenzo Pengue, Gerardo Casucci*
- **Intraglandular flap as an oncoplastic technique for the treatment of breast cancer located in the upper outer quadrant** *Waleed Y. El-Sherpiny, Mohamed A. Mlees*

➜ Volume 16, n. 3

- **Open multi-centre study on the use of a novel emollient plus cream (EC) for maintaining eczema regression after pimecrolimus therapy in atopic dermatitis** *Adele Sparavigna, Antonino Trischitta*
- **Bacterial infections in acne patients previously treated with oral antibiotics** *Stefano Veraldi, Rossana Schianchi, Andrea Beretta, Mauro Barbareschi*
- **Diffuse generalized Granuloma Anulare after a morbilliform eruption: a case report** *Giuseppe Donato, Luca Donato, Luigi Bennardo, Martina Romano, Lorenzo Donato, Claudia Sicilia, Steven Paul Nisticò*
- **Coronavirus and teledermatology** *Michele Pezza, Valentina Carlomagno, Antonino Trischitta*
- **Secukinumab in the treatment of Acrodermatitis continua of Hallopeau: a case series** *Luca Gargano, Luigi Bennardo, Claudia Sicilia, Stefano Dastoli, Nicola Gargano, Steven Paul Nisticò*
- **Use of Low-Dose Insulin in Aesthetic Medicine in a Systematic Review and Meta-Analysis in Literature** *Fabiano Svolacchia, Lorenzo Svolacchia*
- **The importance of the cutaneous Microbiota** *Bruno Mandalari*

➜ Volume 16, n. 4

- **An open observational trial of a novel peptide and hyaluronic acid based lip cosmetic** *Neil Fisher*
- **COVID-19 infection and autoimmune bullous diseases: results of a short survey in Italy** *Giuseppe Cianchini, Carola Pulvirenti, Giovanna Gemmato, Alessandra Scarabello, Ornella De Pità*
- **Case Report: Remote diagnosis to differentiate between Melanoma and Sebhorreic Keratosis in a patient travelling on a sailing boat in the Caribbean Sea during Covid-19 lockdown: clinical and psychological features** *Emiliano Sordi, Silvia Toma, Giovanni Imbriani, Alessandro Miani, Prisco Piscitelli*
- **Clinical efficacy study of a new supplement containing Curcuma Longa and Piper Nigrum in 60 patients with generalized vitiligo** *Claudio Comacchi*
- **Clinical-Observational Study on the Chrono and Photoaging to the Face** *Corinna Rigoni, Annalisa Barba, Cristiana Belloli, Alessandra M. Cantù, Patrizia Cecchetti, Annachiara Corazzol, Maria Pia De Padova, Sandra Lorenzi, Maria Mariano, Marisa Praticò, Norma Cameli*
- **The PDRN (PolyDeoxyRiboNucleotide) in aesthetic medicine: biological introduction and meta-analysis of literature** *Fabiano Svolacchia, Lorenzo Svolacchia*

2021

➜ Volume 17, n. 1

- **Extracellular matrix targeting and new injection techniques towards the personalization of antiaging care. Treatment of thin hollow faces** *Adele Sparavigna*
- **N-Acetylcysteine in trichology. Evaluation of its efficacy in the prevention of autumnal seasonal telogen effluvium, study in 20 patients** *Claudio Comacchi*
- **Nanoparticles: potential, skin toxicity and environmental impact** *Mariano Saviano, Gabriella Rametta*
- **Air Pollution and Skin** *Alessandro Miani, Prisco Piscitelli, Maria Concetta Pucci Romano*
- **Use of myoinositol in androgen-dependent dermatological diseases: observational study** *Michele Pezza, Valentina Carlomagno, Amalia Vitiello, Elena Fiorentini, Elvira Masturzo, Elena Sammarco, Mariano Saviano, Francesca Gaudiello, Antonino Trischitta*
- **Asymmetric Periflexural Exanthem of Childhood: Case report** *Antonino Trischitta*

➜ Volume 17, n. 2

- **Randomized clinical study of a tablet supplement and shampoo in healthy male volunteers for the treatment of Telogen Effluvium associated with mild to moderate androgenetic alopecia. Evaluation of efficacy and tolerability** *Bianca Maria Piraccini, Francesca Bruni, Aurora Alessandrini, Michela Starace*
- **Technological tests for the inclusion of pharmacological active ingredients within a polymeric hydrogel: comparing molecular structures** *Tiziana Ciardiello*
- **Atopic dermatitis - A particular location** *Francesco Rizzuto, Maria Passante, Luigi Bennardo, Steven Paul Nisticò*
- **Skin manifestations associated with SARS-CoV-2 infection: USCA ASL BN 1 experience** *Michele Pezza, Luca Sorice, Lidia Festa, Aurelio Di Palma, Angela Simone, Verdiana Zollo, Giovanni Izzo, Gianluca Giaquinto, Mario De Vita, Caterina Mazzone, Michele Basile, Maria Luisa Salerno, Pellegrino Longo, Alessandro Martone, Maria Concetta Conte, Gennaro Volpe, Tommaso Zerella, Annarita Citarella*
- **Efficacy and tolerability of a topical formulation on stretch marks and xerosis: a confocal and ultrasound evaluation** *Caterina Mazzella, Mariateresa Cantelli, Maria Ferrillo, Gabriella Fabbrocini*
- **Ten-year revision of breast augmentation with preoperative imaging diagnostics** *Giuseppe Colombo, Vittorio Ruvolo, Massimo Calabrese, Irene Valente, Alessandro Garlaschi*

➜ Volume 17, n. 3

- **Efficacy and tolerance evaluation of a probiotic food supplement in subjects with sebum production alterations** *Adele Sparavigna*
- **Melatonin, vitamin C (LAA15%) and resveratrol the gold treatment for psoriasis and skin desease** *Giuseppe Tutino, Saverio Croce, Laura Tutino, Vincenzo Savona, Matteo Tutino*
- **Treatment of the Nasolacrimal sulcus and Dark-Circle with adipose tissue to different sizes: 500-micron micrograft for Deep volumetric correction and dermo-epidermal regeneration with 50-micron micrograft. A case report** *Fabiano Svolacchia, Lorenzo Svolacchia*
- **Dermatofibrosarcoma protuberans: description of a clinical case** *Michele Pezza, Valentina Carlomagno, Gerardo Casucci, Umberto Ferbo, Elisabeth Raphaela Picciotti*
- **Chronic pruritus in COVID-19-recovered patients** *Stefano Veraldi, Cristina Spigariolo*
- **Trichilemmal cysts: history, diagnosis and therapy** *Antonio Di Bartolomeo*

➜ Volume 17, n. 4

- **Objective study using Vitiligo Activity Index (V.A.I.) on the clinical efficacy of a therapeutic combination of a new supplement containing Curcuma Longa and Piper Nigrum and a new cream based on Resveratrol and Piper Nigrum in 60 patients suffering from generalized vitiligo** *Claudio Comacchi*
- **Skin reactions to anti SARS-CoV-2 vaccines: ADECA experience** *Michele Pezza, Bruno Brunetti, Valentina Carlomagno, Carla Ceddia, Fabrizio Ciarletta, Gabriella De Marco, Flora De Natale, Francesca Gaudiello, Annino Pepe, Elio Pezzullo, Umberto Raulo, Giovanni Sarracco, Antonella Tammaro, Pieralba Todaro, Antonino Trischitta*
- **Clinical study on the efficacy of an anti-dandruff shampoo containing climbazole, zinc lactate and salicylic acid for seborrhea of t he scalp in 15 male patients** *Claudio Comacchi*
- **Mapping Melanoma with Google – a record breaking summer and insights into public awareness using Google Trends** *Mohammad Mohammad, Saul Crandon, Rowan Pritchard-Jones*
- **Actinic keratosis of the ear? Cutaneous leishmaniasis!** *Eleonora Quattri, Pier Luca Mandolini, Stefano Veraldi*

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