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AIDA Associazione Italiana Dermatologi Ambulatoriali
ADECA
SINut Società Italiana di Nutraceutica
SIMA Società Italiana di Medicina Ambientale
SIFNUT Società Italiana Formulatori in Nutraceutica
ASSECE European Association of Aesthetic Surgery

KERÀ CHERATOSI ATTINICA

KERÀ mucose

AK piane

AK ipercheratosiche

Affezioni della mucosa labiale

DISPOSITIVI MEDICI CE 0051

Leggere attentamente le avvertenze o le istruzioni per l'uso

GIULIANI

RICERCA E INNOVAZIONE IN DERMATOLOGIA

VOL. 19
n. 1
2023

ISPLAD
International-Italian Society of Plastic-Regenerative and Oncologic Dermatology

LA DOSE

La dose si può definire come la giusta quantità utile per mantenere il corretto equilibrio o l'armonia. La dose è una legge che regola gran parte della nostra vita, dei nostri atti quotidiani e delle nostre abitudini, è una regola a cui tutti cercano dì attenersi. La dose è un dogma e per certi versi un tabù. La dose è il contrario dell'anarchia. La dose è ordine. La dose è il punto di riferimento, si può trasgredire col sottodosaggio o con il sovradosaggio ma non si può ignorare la dose.
Ma chi decide la dose? Chi decide il giusto, il poco o il troppo?
Al ristorante è lo chef che riempie con la giusta dose i piatti.
Il self-service senza la dose spesso ci fa avanzare il cibo e crea spreco.
Per un medico la dose è scienza, ricerca, sicurezza, arma appuntita per combattere la malattia, il legame più forte con il paziente, il patto di alleanza per la sopravvivenza.
La dose regola la cattiveria e la bontà, difatti non ci sarebbe la percezione dell'una e dell'altra senza una dose piccola o grande di entrambe.
La dose è alla base della buona politica e le leggi sono i limiti in cui la dose deve essere rispettata.
La dose potrebbe annullare il libero arbitrio e impedire il progresso delle cose ma in ognuno di noi c'è sempre una giusta dose di trasgressione che permette i cambiamenti e l'evoluzione.
Anche la vita di ogni uomo è una dose: una dose di tempo che qualcuno ha deciso debba durare più o meno un centinaio di anni, almeno fino a quando dovrà cambiare per l'armonia di qualcosa che la nostra dose di intelligenza non ci permette di capire.

Antonino Di Pietro
Founding president ISPLAD

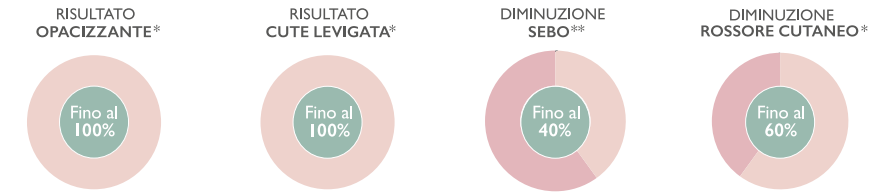
ALUSAC®

La prima MASCHERA DERMATOLOGICA con ARGILLA VERDE e ALUSIL per gli inestetismi della pelle impura, mista, grassa e a tendenza acneica

Per VISO e CORPO

DERMOCOSMETICO DERMATOLOGICO CONTRO L'ACNE GIOVANILE e ADULTA

RISULTATI DOPO LA PRIMA APPLICAZIONE



DOPO 14 GIORNI

COMPLESSO ALUSIL

MICROSPUGNE DI ARGENTO azione antimicrobica

ALUKINA *complesso brevettato*

- **Allume di potassio** azione sebo normalizzante dalle proprietà antisettiche
- **Acido Glicirretico** azione lenitiva
- **Vitamina A** favorisce il ricambio cellulare

COMPLETANO LA FORMULA:

ARGILLA VERDE di origine minerale, con proprietà dermopurificanti, detossinanti e adsorbenti il sebo

MORINGA OLEIFERA pianta tropicale con proprietà purificanti, l'estratto dei semi ha mostrato in vitro attività antimicrobica

MENTA PIPERITA con proprietà rinfrescanti, dermopurificanti, seboregolatrici, in grado di contribuire a ridurre le irritazioni cutanee tipiche delle pelli acneiche

ADATTA TUTTO L'ANNO

* Test clinico eseguito su volontari di età compresa tra i 18 e i 40 anni

** Test di efficacia strumentale eseguito su volontari di età compresa tra i 18 e i 40 anni

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Efficacy and tolerance of the Hyaluronic acid-based, lips re-volumizing filler Aliaxin® Lip Volume

Adele Sparavigna

Adele Sparavigna[1], Franco Grimolizzi[2], Marco Cicerone[2], Gilberto Bellia[2]

SUMMARY

Lips volumization represents a common aesthetic request for women, particularly for aging women whose lips structure changes with time. Hyaluronic acid (HA)-based filler are commonly used in aesthetic medicine to try to regenerate normal lips appearance or to increase their volume. In this study, the efficacy and tolerability of Aliaxin® Lip Volume, a specific crosslinked HA-based lips filler, has been tested in female volunteers requiring lips re-volumization. The studied medical device, mixed with lidocaine to reduce potential distress due to the injection, was injected into the mucosa using a linear retrograde technique. Clinical and instrumental evaluations were performed at baseline, after 3-4 weeks, after 2 and 6 months after the injection. A single injection of the studied medical device was able to induce a statistically significant increase in lip volume detectable both clinically and through photographic documentation. At T1 visit (3-4 weeks after first injection procedure) a touch-up treatment was evaluated and eventually performed with very small dosage of product to correct any possible asymmetries. The positive results of the injection were achieved in the absence of significant adverse events. In conclusion, this study demonstrated the efficacy and tolerability of Aliaxin® Lip Volume as lip volumizer.

KEYWORDS
lip filler, hyaluronic acid, aesthetic treatment.

INTRODUCTION

The process of aging is accompanied by changes in exterior aspect that could impact on self-confidence, as well as on relations with other people (1–6). Facial aging is considered particularly detrimental, being this part of our body the most exposed to other people. The changes in face are mostly due to loss of volume, decrease of subcutaneous adipose tissue, thinning of skin, and elastosis (3,7–10). Similar considerations can be done for lips, an important component of whole facial appearance. In fact, with time, lips status changes as a consequence of aging process (4,7,11,12). It must be considered that lips represent, for several people, one of the major factor contributing in facial attractiveness and for this reason when they are plump and properly curved are associated with beauty and youthfulness (12–16).

Youthful appearance is more and more demanded and aesthetic treatments are gaining increasing popularity not only for women but also for men (2, 17–19). Proper lips volume and shape remain so far a woman specific request. Lip volumization is a very popular medical aesthetic procedure giving fuller and plumper lips. Many types of dermal filler can be injected into the lips and/or around the mouth (15, 20–23). The most common fillers are those containing hyaluronic acid (HA). HA is considered one of the most powerful component in aesthetic medicine because of its particularly favorable properties (24–28). In fact, it is not only able to restore elasticity and good appearance to the skin, but has also low contraindications, being well tolerated and poorly allergenic.

1 DERMING S.r.l., Milano, Italy.
2 IBSA Farmaceutici Italia, Lodi, Italy

This is mostly due to the fact that HA is very abundant in our organism, present in several tissues and in the spaces between cells in the tissues and therefore not recognized as an external component. There are many filler preparations containing HA in different concentrations, molecular weight or combined with other components (24,29–35). Aliaxin® LV Lip Volume is a cross-linked HA-based filler particularly designed to increase the volume and contours of the lips.

The particular rheology of the gel (G': 107Pa; tanδ: 0.21) with 2 different HA cross-linked molecular weights (1.000 KDa and 2.000 KDa) guarantees a high resistance to mechanical stress and an excellent diffusion in the labial tissues (36).

In this study, the efficacy and tolerability of the studied medical device has been determined in 25 healthy female volunteers with indication for lips volumization.

Material and methods

Study design and procedures

The study was designed as an open clinical trial, aimed at evaluating the efficacy of one micro-injection session of the lip filler "Aliaxin® LV (IBSA Farmaceutici Italia Srl)" performed in 25 female volunteers subjects with indications for lips volumization, ranging in age between 45 and 67 years (Mean: 55,0), although 2 of 25 subjects interrupted earlier the study due to personal reasons, and they were excluded from data analysis.

The primary endpoint was the average improvement of at least 1 grade of the lip volume/thickness clinical score, according to a reference photographic scale (37).

Together with the photographic evaluation, a self-assessment questionnaire was administered to the volunteers to have their efficacy evaluation.

An additional aim of this study was to assess the tolerance of the medical device determined both by the subjects participating and by the investigator.

The study has been approved by an Independent Ethical Committee and was conducted in accordance with the Declaration of Helsinki and with the International Conference on Harmonisation following the guidelines on Good Clinical Practice. An informed consent has been obtained at the basal visit from each volunteer.

The subjects, before enrolling, had to fulfil several inclusion criteria. In particular they had: to be female adults; to be non-smokers; to have at least in one of the lips (inferior or superior) a lip volume/thickness grade of 1-3 (according to a clinical reference scale (37)); willing to have lip volumization; to be keen in following the study on site for the entire duration including the post-procedural follow-up examinations; to accept to maintain normal habits in terms of food, physical activity, cosmetic and make-up products for the lips, as well as detergents for the face/lips; to avoid exposure to strong UV irradiation. In addition, several exclusion criteria (listed in Table 1) were considered before allowing the participation to the study of the Subjects. The study plan is schematically represented in **Figure 1.**

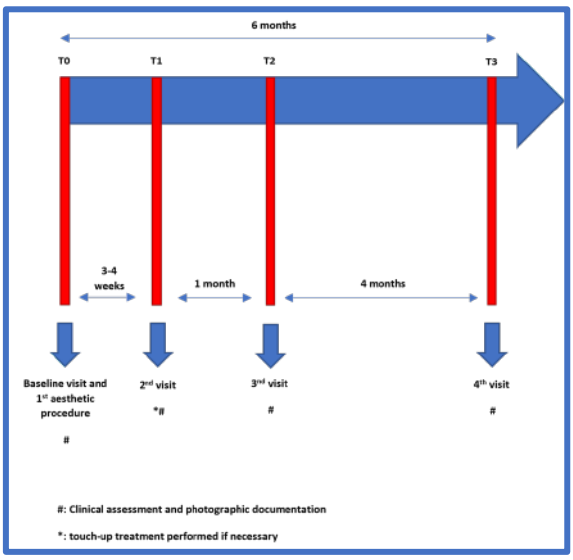


Fig. 1 *Schematic representation of the study plan;*
Timepoints: *T0: baseline and first injection procedure; T1: visit 3-4 weeks after injection and possible touch-up treatment; T2: visit 2 months after first injection; T3: visit 6 months after first injection;*

Table 1.

EXCLUSION CRITERIA
Volunteers' characteristics
Pregnancy; Lactation; Smokers; alcohol abuse and/or drug use; subjects not in menopause who do not use adequate contraceptive precautions in order to avoid pregnancies during the study; Body Mass Index (BMI) variation (± 1) during the study period; having performed skin treatments for lip aesthetic correction (biomaterials implants, lip lifting, laser, chemical peeling) in the 6 months prior to the beginning of the study; having used permanent filler in the past; change in the normal habits regarding food, physical activity, cosmetic/make-up product for the lips and detergents for the face/lip during the month preceding the test; having used permanent filler in the past; sensitivity to the test product or its ingredients; subjects whose insufficient adhesion to the study protocol is foreseeable; participation in a similar study currently or during the previous 9 months;
Clinical Conditions
Dermatitis; presence of cutaneous disease on the tested area, as lesions, scars, malformations; recurrent facial/labial herpes clinical and significant skin condition on the test area (including active eczema, psoriasis, severe rosacea, scleroderma, local infections and severe acne); Diabetes, endocrine disease, hepatic and renal disorder; Cardiac or pulmonary disease; Cancer; neurological or psychological disease; inflammatory/immunosuppressive disease; drug allergies;
Pharmacological treatment
Anticoagulants and antiplatelet drugs, anti-histaminic, topic and systemic corticosteroids, narcotic, antidepressant, immunosuppressive drugs (with the except of contraceptive or hormonal treatment started more than 1 year before); use of drugs able to influence the test results in the investigator's opinion; The use of other drugs, not mentioned above, could be authorized and reported by the Investigator;

At T0, the subjects were submitted to a careful clinical examination to verify their adherence to the inclusion criteria. At this initial visit, a photographic record of the lips was taken (using a 3D-VECTRA H1 imaging system). This Vectra Analysis Module (VAM) merges and compares the 3D pictures taken at two different times and automatically calculates the volume difference using a colour distance map. A careful standardization of the procedure was followed to avoid inconsistencies between the images.

In particular, attention was paid to the distance from subject, the intensity of the illumination source as well as the position of the volunteer (still, with open eyes and relaxed face muscles).

A clinical evaluation of both superior and inferior lip volume/thickness was also recorded by the Investigator using a visual score (37) that goes from 1 (very thin lip) to 5 (very full lip).

If all the criteria were fulfilled, the subjects received the injection of the studied medical device. 1 ml of Aliaxin® LV" was mixed with 0.3ml of lidocaine (10 mg/1ml) to reduce discomfort or pain sensation during the procedure. Up to a maximum of 1.3 ml of the mixture were injected into the middle-deep dermis by a 27G needle using a linear retrograde technique; the needle was inserted along the vermilion border and the filler was slowly and continuously deposited along the length of the lip border during the needle extraction.

At T1 (3-4 weeks after the 1st injection) there was a first clinical evaluation and photographic documentation for lip volume image analysis. At this time point a second injection, to correct eventual asymmetries (touch-up), was eventually performed. Two additional follow-up times were performed collecting both clinical and photographic documentation: T2 (2 months from the first injection) and T3 (6 months from the first injection). Eventual undesired events were monitored during the study by the Investigator, who could eventually decide to withdraw the subject from the study.

Statistical analysis

The statistical evaluations of clinical and instrumental data (adjusted means and standard deviation) and relative graphs were performed at the times required by the protocol.

The statistical analysis was carried out with not parametric tests for the clinical data (Wilcoxon test). For the data obtained by instrumental evaluation (lip volume image analysis), the analysis of the parameters (arithmetic mean, standard deviation) and their relative graphs were carried out by non-parametric tests (Wilcoxon test) when the normality hypothesis was rejected by the Shapiro-Wilk test at the threshold inferior to 5%, while a parametric test (Paired-t-test) was adopted when the normality hypothesis was confirmed by Shapiro-Wilk test.

The evaluation at each time point of the study was compared with that obtained at basal level (T0).

Results

In view of the above, full analysis (Clinical Evaluation and VECTRA H1 image analysis) were conducted on 23 subjects considering T3 as last time point.

For clinical evaluation, a statistically significant increase in clinical score (mean value) was reported for each timepoint compared to baseline, for both superior and inferior lips (Wilcoxon test, $p<0.05$) **(Figure 2, panel A) (Figure 3, panel A).** The aforementioned increase in superior and inferior lips clinical score, was reported in 91,3% of the subjects, according to a reference scale (37).

In details, for the superior lip **(Figure 2, panel B)** an increase of 1 grade was observed in 47,8% of subjects, 2 grades in 34,8% and 3 grades in 8,7%. In addition, data obtained for the inferior lip **(Figure 3, panel B)** showed an amelioration of 1,2 or 3 grades observed in 60,9%, 26,1% and 4,3% of cases, respectively. The increase in volume for both superior and inferior lips was statistically significant comparing the baseline with the last known follow up time for each participant ($p<0,05$ Paired t test) **(Figure 4).**

The clinical evaluation was corroborated by the photographic records; indeed, **Figure 5 (Panels A, B, C)** shows representative 3D pictures of three volunteers taken at baseline (T0) and at T1, T2 and T3.

Evaluation for local tolerance at injection sites show light bruises in 10 out of 23 (43%) volunteers which totally disappeared within 5-10 days. Since all these light effects represent expected events imputable to the injection procedure, the investigator judged the product tolerance good-excellent in all the subjects participating in the study.

Discussion

HA-based fillers have been extensively used in aesthetic medicine to ameliorate age-induced changes in facial appearance (24, 38, 39). One of the major determinant of facial appearance are considered the lips, which, as for the rest of the face, undergo changes with time, losing their curved aspect and volume (4,7,12). There is an increasing request of aesthetic treatments, including those able to restore lips volume and shape and several techniques and products are available (11, 13–15).

In this study we evaluated the efficacy and tolerability of a new crosslinked HA-based filler which demonstrated a positive effect after a single injection in female volunteer requiring lip volumization. The positive effects were demonstrated both by a clinical evaluation and by photographic changes occurring after 1, 2 and 6 months after the injection. In a substantial percentage of subjects there was a two or three scale grades amelioration. Interestingly, all the subjects showed an increase in terms of volume and all of them were satisfied of the results achieved. No adverse events were registered, and those slight distresses were associated to the injection procedure rather than to the product itself. Although the study was proven extremely positive in terms of efficacy and tolerability, a limitation is represented by the premature

termination of the study due to the Covid-19 pandemic. Despite data longer than 6 months are lacking, the constant increase in lip volume observed over time suggest that the volume effect could have been visible longer that 6 months from the treatment. In addition, the rapid relief from distress after injection suggest that no additional toxicity would potentially arise with time.

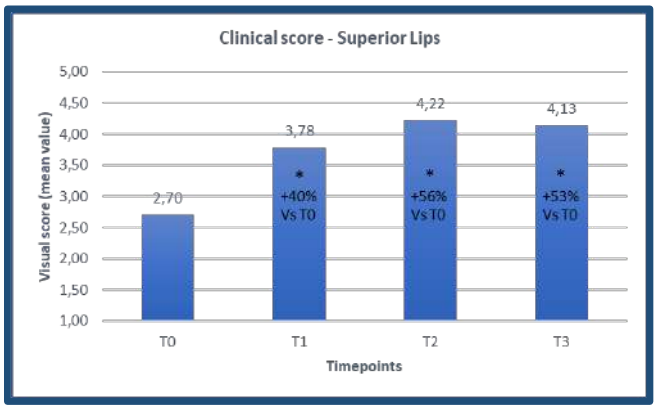


Fig. 2 Panel A : Clinical score (mean value) for the superior lips at the different timepoints (T0, T1, T2, T3)(*p<0,05 Wilcoxon test).

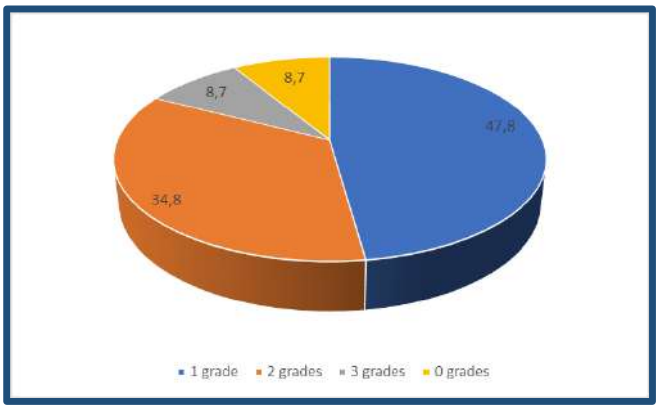


Fig. 2 Panel B: Improvement in clinical score for superior lips of 1 grade, 2 grades, 3 grades or 0 grade (no change) at T3 (as % of total subjects).

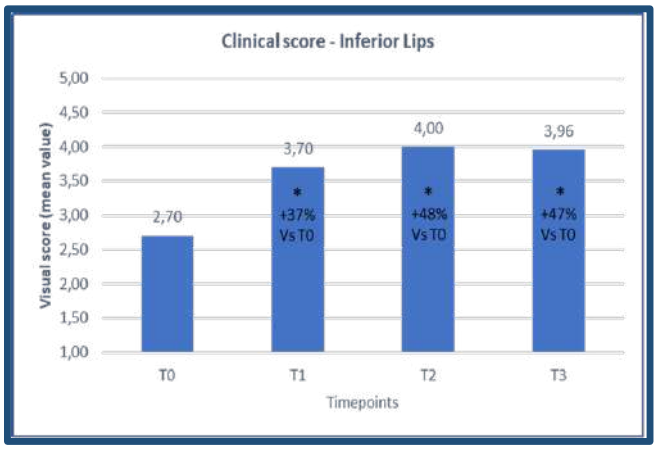


Fig. 3 Panel A: Clinical score (mean value) for the inferior lips at the different timepoints (T0, T1, T2, T3)(*p<0,05 Wilcoxon test).

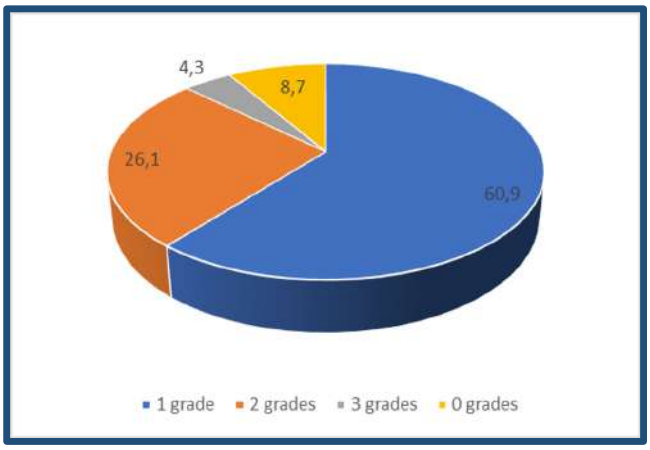


Fig. 3 Panel B: Improvement in clinical score for inferior lips of 1 grade, 2 grades, 3 grades or 0 grade (no change) at T3 (as % of total subjects).

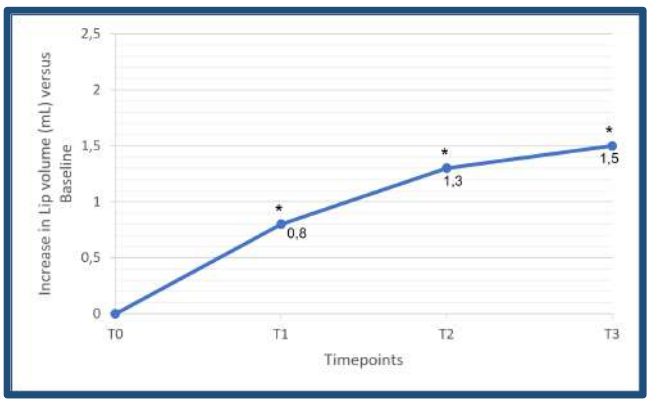


Fig. 4 Mean increment of lip volume at different time points (T1, T2, T3) compared to baseline (T0) (*p<0,05 Paired t test).

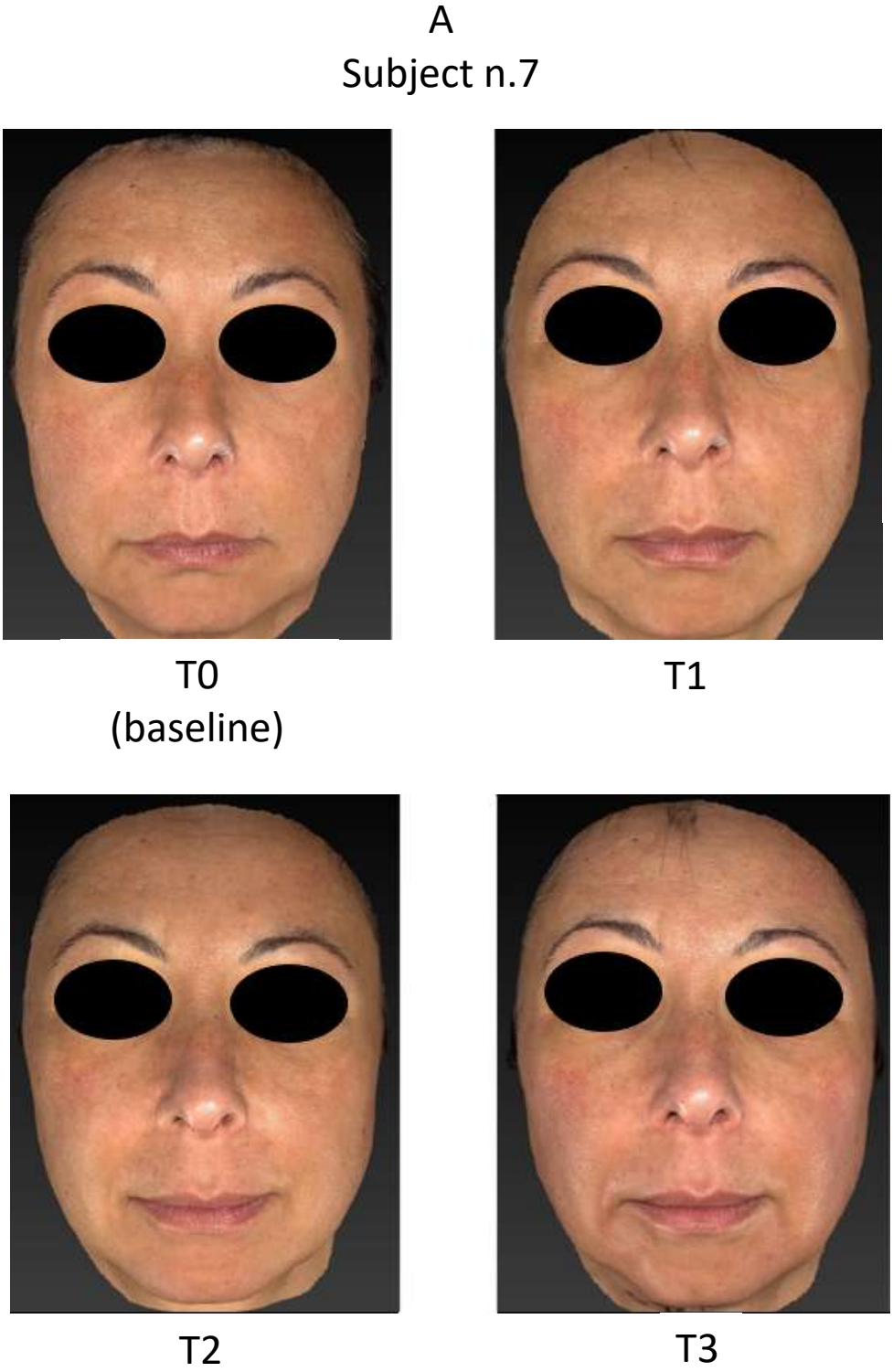
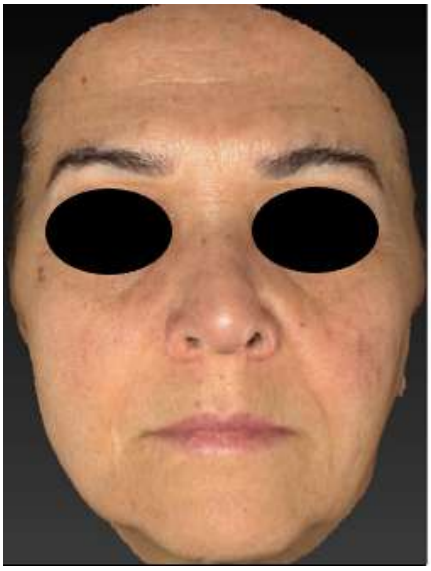
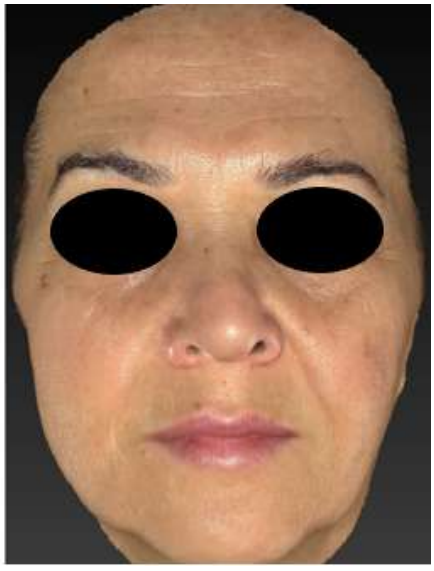


Fig.5
Representative 3D photographs of 3 volunteers (A-Subject n°7, B- Subject n°8, C-Subject n°18) taken at T0 (baseline visit), T1, T2 and T3 (follow-up visits after 3-4 weeks, 2 months and 6 months after first injection procedure, respectively).

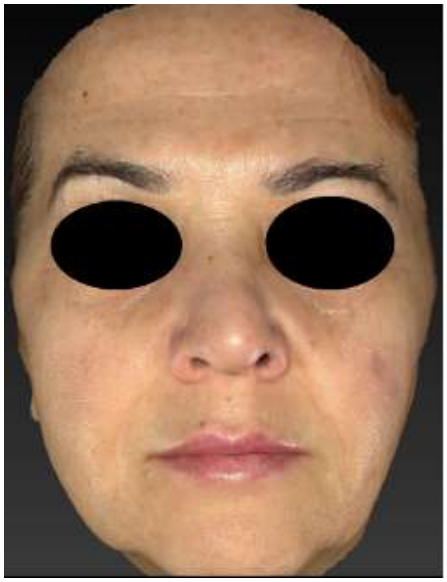
B
Subject n. 8



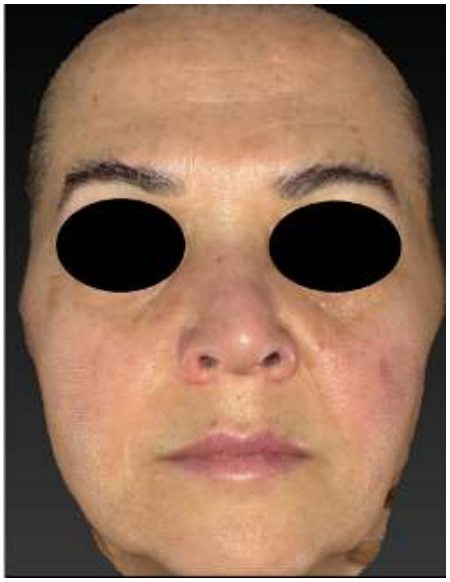
T0
(baseline)



T1

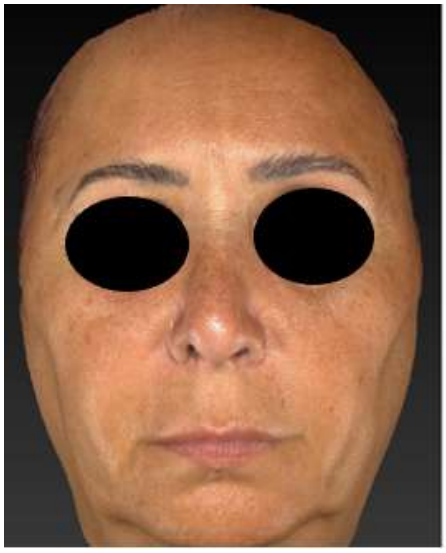


T2

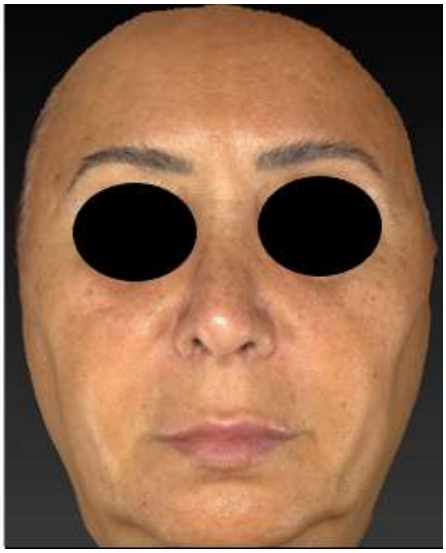


T3

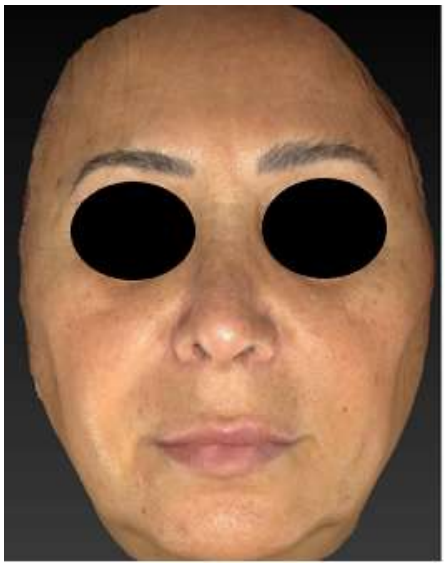
C
Subject n.18



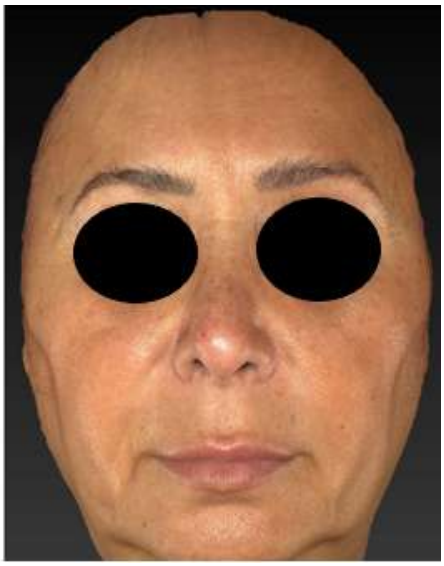
T0
(baseline)



T1



T2



T3

Conclusions

In conclusion, this study shows that the HA-based filler, Aliaxin® Lip Volume, was able to induce a statistically significant improvement both clinically (clinical score according to the photographic reference scale (37)) and instrumentally (increase in lip volume), without any adverse events.
Long-term follow-up (after 6 months) of patients was not feasible as the study was prematurely stopped due to COVID-19 outbreak and lockdown.

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Conflict of interests

FG, MC & GB are employees of IBSA Farmaceutici Italia Srl; the authors report no other conflicts of interest in this work.

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Choline-stabilized orthosilicic acid, applications of an oral supplement in dermatology


Maria Rosa Gaviglio


Mario Remi Calomme

Maria Rosa Gaviglio, Mario Remi Calomme

SUMMARY

Several clinical trials have investigated the use of choline-stabilized orthosilicic acid as an oral supplement to improve the quality of skin, hair and nails. This specific complex of orthosilicic acid and choline was shown to stimulate collagen synthesis and protect the collagen network in connective tissue. Women with photoaged skin, who took choline-stabilized orthosilicic acid were found to have improved skin microrelief and elasticity. But also, nail brittleness and tensile properties of hair have been shown to improve after the use of choline-stabilized orthosilicic acid. Other benefits of choline-stabilized orthosilicic acid have been reported in clinical trials that are related to bone, joint and gum health.

KEYWORDS
collagen, choline-stabilized orthosilicic acid, aging, skin, hair, nails, bone, joints, gum.

Maria Rosa Gaviglio
Studio Dermatologico Gaviglio
20121 Milan ITALY

Mario Remi Calomme
Bio Minerals N.V.
Research & Development
B-9070 Destelbergen
BELGIUM

INTRODUCTION

Choline-stabilized orthosilicic acid (tradename ch-OSA®) is a specific complex of choline with orthosilicic acid which is used in dietary supplements. The health benefits of ch-OSA® have been documented in clinical trials and are supported by animal studies.

These studies show that the ch-OSA® complex activates biological pathways that generate and protect collagen. Collagen is a fibrous protein, essential for the structural integrity and biomechanical properties of connective tissue and is present in high amounts in skin, bone, and joints. Starting at age 21, collagen in skin decreases linearly with 1% per year (1) resulting in a decline of skin thickness and elasticity (2).

Post-menopausal changes are even more dramatic with a loss of 30% skin collagen in the first 5 years (3) and an annual decline in skin elasticity of 0.55% (4).

Elasticity is correlated with the depth of wrinkles, suggesting that the formation of wrinkles primarily results from the loss of elasticity (5). Importantly, the postmenopausal decrease in skin collagen correlates with the age-related decrease in bone mineral density (6).

The present article discusses the potential use of ch-OSA® as an oral supplement in dermatology, its mechanisms of action and other health benefits outside the field of dermatology.

Application of ch-OSA® in dermatology

Several clinical studies report positive anti-aging effects of ch-OSA® on skin, hair and nails when administered as an oral supplement **(table 1).**

Skin

A clinical trial was undertaken by the University of Brussels in Belgium (7) to evaluate the effect of ch-OSA® on photo-aged skin. Photo-aging is the result of chronic exposure to ultraviolet radiation (e.g., sun, sunbeds) superimposed on chronobiological (intrinsic) ageing. Photo-aged skin is characterized by major changes in the dermis i.e., a marked decrease in collagen, glycosaminoglycans and proteoglycans combined with a degeneration of elastic fibers (elastosis) resulting in a rough leathery skin surface with many fine and coarse wrinkles. Typically, decreased elasticity is found in photo-aged skin because of the degraded mesh of collagen and elastin fibers in the dermis. Over time these changes also occur in normal, chronobiogical ageing, therefore photo-aging is a valuable model to study anti-aging products. In the clinical trial, fifty healthy women, aged between 40 and 65 years, with clear signs of photo-aging were randomized in a ch-OSA® and a placebo group. Participants were instructed not to change their daily dietary and cosmetic regimen during the study. In addition, any dermatological or anti-aging therapy was prohibited.

Non-invasive, validated methods were used to evaluate skin roughness with skin replicas (Visiometer, Courage-Khazaka, Germany) and skin elasticity by measuring mechanical anisotropy (Reviscometer, Courage-Khazaka, Germany). Quantifying skin microrelief is a standard method to measure the depth of fine lines and wrinkles and include typical parameters such as maximum roughness (Rm) i.e., the depth of the main wrinkle (8).

Mechanical anisotropy of skin is an indirect parameter of skin elasticity (9). The participants also scored the severity of hair and nail brittleness on a 4-point numeric scale. After 20 weeks, the depth of the main wrinkle improved significantly in the ch-OSA® group by 19% but continued to decline in the placebo group by 11%, resulting in an overall improvement of 30% **(figure 1a).** Skin microrelief in young skin is characterized by a multi-directional pattern of lines. When skin ages, the lines become both deeper and more oriented in a dominant, single direction (8). These changes in microrelief reflect the ongoing deterioration with age of the underlying collagen framework in the dermis. Women who took ch-OSA® were found to have after 20 weeks a more multidirectional pattern of skin lines compared to the start of the study (baseline), resembling "younger" skin because of a denser collagen framework in the dermis **(figure 2).**

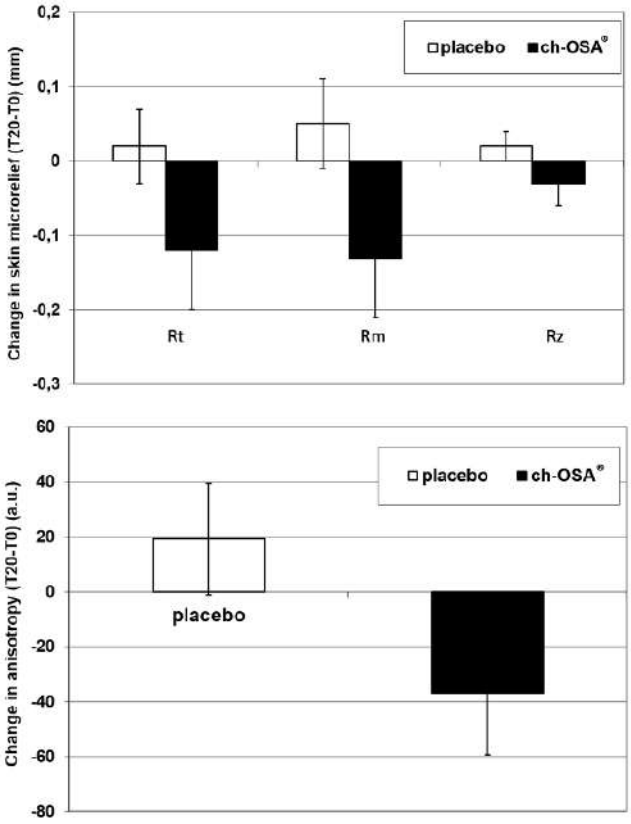
Skin elasticity, measured as mechanical amiso-tropy, increased significantly in the ch-OSA® group compared to the placebo group i.e., 89% improvement was observed in the ch-OSA® group over placebo **(figure 1b).**

The investigators explained the reduction in fine lines and the improvement in skin elasticity as a regeneration or de novo synthesis of collagen fibers i.e., the activation of collagen pathways by ch-OSA® resulting in a denser collagen framework in the dermis and better skin quality. Supporting evidence is found in an animal study from the University of Antwerp, Belgium (10). Young animals were given ch-OSA® or a placebo in their diet and randomly chosen skin biopsies were analyzed for the hydroxyproline content.

Hydroxyproline is a specific component of collagen i.e., it can be used as a marker of collagen content.

A significant 12.5% higher hydroxyproline content was found in skin of animals on the ch-OSA® diet compared to skin of placebo controls.

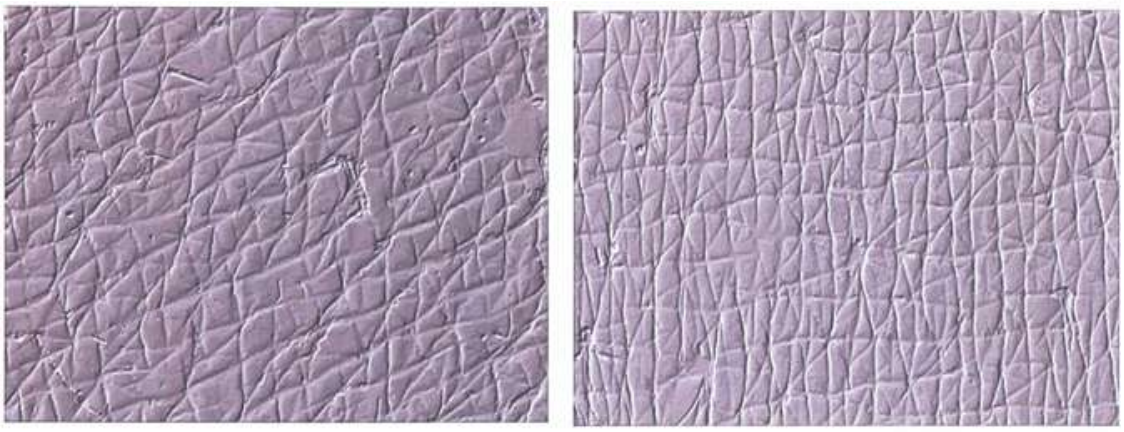
Figure 1
The effect of ch-OSA®, an oral supplement, on skin microrelief and skin elasticity in women with photoaged skin (7).



1 A
Change in depth of roughness (Rt, -24% vs. placebo), maximum roughness (Rm, -30% vs. placebo), and mean depth of roughness (Rz, -12% vs. placebo) after 20 weeks supplementation (mean values ± SE are shown).

1 B
Change in mechanical skin anisotropy, an indirect measurement of elasticity, after 20 weeks supplementation (-89% vs. placebo). Improvement in skin elasticity is observed as a decrease in anisotropy.
(Mean values ± SE are shown, T0: baseline, T20: after 20 weeks) (SE: standard error)

Figure 2
Skin microrelief of a patient with photoaged skin, at baseline (left) and after 20 weeks supplementation with ch-OSA® (right): a more multidirectional pattern of shallow lines resembling younger skin is observed after 20 weeks compared to placebo because of a denser collagen network in the dermis (7).



Additionally, physiological concentrations of orthosilicic acid were also reported to stimulate the synthesis of collagen type I in human skin fibroblast cell cultures (11).

In an open label, single arm study which was conducted in India, women with photodamaged skin (12) took ch-OSA® for 5 months. The patients were followed up for additional 3 months. Compared to baseline, skin hydration improved significantly already after 2 months, whereas both dyschromia and skin roughness improved significantly after 5 months.

Nails

The study of Barel et al. (7) in women with photoaged facial skin, also investigated brittleness of nails. It was found that brittleness decreased significantly in the ch-OSA® group whereas no significant change was observed for women in the placebo group.

More recently, a team led by professor Piraccini, presented a study (13) on nail fragility.

Ten female patients aged 52-65 years (mean age: 59,2 y) took for 6 months ch-OSA®, and nail quality was evaluated by clinical pictures and a video-dermatoscope at baseline, and after 3- and 6- months study. Both the patients and the investigators rated the change in the quality of nails on a 4-point, numeric scale. At baseline all patients had rough nails, 70% had longitudinal ridges of the nail plate, and 30% had onychoschizia.

The investigators scored after 6 months study that 44% of the patients had completely normal nails, i.e., full recovery of the nail disorder, and in 56% of the patients the quality of the nails showed good improvement. In fact, the clinical pictures showed an improvement in roughness of the nail plate and onychoschizia in all patients, as well as an improvement in longitudinal ridges in 83% of the patients.

Dermatoscopic results, confirmed these findings as nail plate characteristics after 6 months study improved in all patients.

Evaluation by the patients indicated in 78% of the cases a full recovery and in 22% a slight improvement.

In a small open label study in India (12), 10 women between 40-65 years with brittle nails on both hands and feet took for 5 months ch-OSA® and were followed up for an additional 3 months. Nail roughness improved significantly after 2 months study, whereas the percentage of broken nails (baseline 53%) and discolored (yellow) nails (baseline 50%) completely normalized after 3 and 8 months of study respectively.

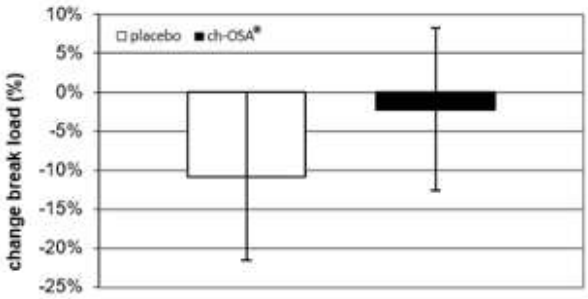
Hair

The effect of ch-OSA® on hair quality was investigated in a collaborative study led by Professor Randy Wickett of the University of Cincinnati and the Dr. Schrader Institute (Germany) (14). Forty-eight women aged between 18 and 65 years, with thin, fine hair were randomized in a ch-OSA® and a placebo group. Hair morphology and tensile properties were evaluated with validated methods. Investigated tensile properties included the elasticity of the hair (elastic gradient, elastic modulus) and the force needed to break hair fibers (break load, break stress). After 36 weeks the hair elasticity decreased significantly in the placebo group but remained unchanged in women who took ch-OSA®.

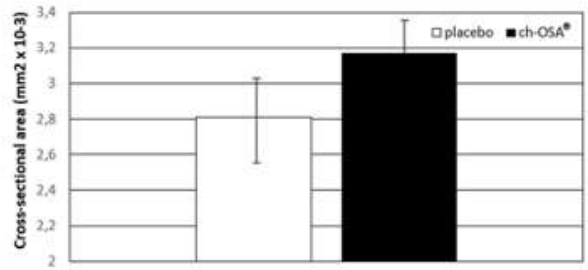
The break load was found 13.1% higher in women taking ch-OSA® compared to women in the placebo group. With respect to hair morphology, women who took for 36 weeks ch-OSA® had a 12.8% bigger cross-sectional area of hair fibers compared to women taking placebo.

Several mechanisms of action were suggested by the investigators to explain these results. A direct interaction with keratin-associated proteins is possible considering that silanol groups in ch-OSA® form complexes with amino acids and peptides.

Figure 3
The effect of ch-OSA®, an oral supplement, on hair quality in women with fine, thin hair (14).



3 A Change in tensile strength measured as break load, after 36 weeks study remained stable in patients who took ch-OSA®, whereas a significant decrease was observed in the placebo group (net difference of 13.1% between groups).



3 B Hair morphology measured as the cross-sectional area, was found significantly higher in patients who took ch-OSA® compared to the placebo group (net difference of 12.8% between groups).(Mean values ± SD are shown, T0: baseline, T20: after 20 weeks) (SD: standard deviation)

Such an interaction could change the biomechanical properties of hair since keratin is the major constituent of hair. The increase in cross-sectional area suggests that ch-OSA® has a structural influence on keratin fibers or on the hair follicle. Since the hair follicle is embedded in a collagen rich matrix and serviced by collagen rich blood vessels, stimulation of collagen synthesis by ch-OSA® will improve the flow of nutrients to the hair follicle resulting in more keratin formation. While most of the hair structure arises from epidermal keratinocytes, a specialized population of fibroblasts called the dermal papilla controls hair growth and hair volume. Increased collagen synthesis by ch-OSA® in fibroblasts of the dermal papilla, will increase the volume of the dermal papilla resulting in a bigger cross-sectional area of the newly formed hair shaft.

These same factors could also explain the significative reduction of hair brittleness after 20 weeks measured by self report VAS scores.

An open label, pilot trial was done in the Philippines (15), to investigate the effect of ch-OSA® on abnormal hair loss. In total 19 patients were included between 17-54 years (10 men and 9 women). Eight patients with male pattern hair loss (stages 2-5) and 11 patients with alopecia (2 men, 9 women) took for 6 months ch-OSA®. Semi-quantitative rating scales and clinical pictures were used to evaluate the treatment. After 6 months study, the scores for hair regrowth and hair loss significantly improved.

The investigator observed an improvement in 89% of the patients of which in 28% a slight improvement, 55% moderate and in 5% of the patients a marked improvement. Most of the patients (95%) observed an improvement in hair loss, of which 33% a marked improvement.

Similar results were observed in another pilot trial in India (12). Nine alopecia patients between 17-54 years (5 men, 4 women) took for 5 months ch-OSA®, and the hair density measured with a non-invasive trichoscopic device (Medicam 1000,

FotoFinder Systems GmbH) improved significantly compared to baseline.
The study of Barel et al. (7) in women with photoaged facial skin, also investigated brittleness of hair. It was found that brittleness decreased significantly in the ch-OSA® group whereas no significant change was observed for women in the placebo group.
Interestingly, in a review article of the Memorial Sloan-Kettering Cancer Center on side effects by cancer treatments and nursing care (16), the dietary supplement Biosil® which contains ch-OSA® is recommended together with other supplements to help ameliorate nail changes and hair loss, during or after anticancer treatment. In dermatological practices similar recommendations have been made for the use of ch-OSA® in patients who experience nail brittleness and hair loss following or during anticancer treatment (17).

Health benefits of ch-OSA® outside the field of dermatology

The effect of ch-OSA® on other collagen-depending tissues such as bone, cartilage, and gums, has also been investigated in clinical trials **(table 2).**

Bone

The effect of the ch-OSA® on markers of bone turnover and bone mineral density was investigated in a clinical trial at the St Thomas Hospital in London (18). One hundred and eighty-four osteopenic and osteoporotic, but otherwise healthy women with a T-score at the lumbar spine of < -1.5 were randomized in ch-OSA® and placebo groups. All the subjects took 1000 mg calcium and 20 mcg cholecalciferol daily. Biochemical markers of bone formation and bone resorption were measured, and bone mineral density (BMD) was assessed by Dual-Energy X-Ray Absorptiometry.
Overall, there was a trend for ch-OSA® to have a positive effect on bone formation markers. In particular, the procollagen marker PINP (procollagen type I N-terminal propeptide) increased significantly after 12 months in women who took ch-OSA® compared to women in the placebo group. PINP is known as the most sensitive marker for bone collagen formation and an early marker of bone formation. Women on ch-OSA® who were osteopenic for both the lumbar spine and the hip were found to have a 2% higher BMD at the critical hip region compared to women in the placebo group. This difference in BMD was not only statistically significant but also clinically relevant since 1% differences with placebo is generally accepted as the threshold for clinical relevance. Supporting evidence that ch-OSA® promotes bone health can be found in two animal studies. In an animal model for postmenopausal osteoporosis (19) it was found that ch-OSA® increased the femoral BMD with 3 to 7% in ovariectomized animals with a high bone turnover. Ovariectomy causes estrogen deficiency comparable to what happens in postmenopausal women. This condition will dramatically increase bone resorption and result in bone loss. This animal study demonstrates that ch-OSA® helps to prevent post-menopausal bone loss. In another experiment, it was shown in young, developing birds that ch-OSA® increased femoral BMD by almost 6% and marginally improved the biomechanical properties of the femur (20).
The fact that ch-OSA® increases bone collagen formation means that it can help improve bone quality. In fact, the soft framework of bone collagen fibers is essential for bone flexibility and fixation of calcium phosphate in the bone. This combination of collagen and calcium makes bone both flexible and strong, which in turn helps bone to withstand stress (21).

Table 1
Dermatological applications of choline-stabilized orthosilicic acid (ch-OSA®), reported in clinical trials. ch-OSA® was administered as an oral supplement, i.e., twice daily one capsule containing 5 mg of silicon and 100 mg choline as ch-OSA® (Bio Minerals NV, Belgium).

	Author, study design	Study population	Observations
Skin	Barel et al. (7) Placebo-controlled, randomized, double-blind.	50 women with photoaged skin. (Age: 40-65 years)	Decreased roughness (-30% vs. placebo, and increased elasticity (+89% ch-OSA® group versus placebo group) after 20 weeks.
	Chandrashekar et al. (12) Open label, single-arm.	10 women with photodamaged skin. (Age: 40-65 years)	Improved hydration, dyschromia, and roughness (versus baseline) after 5 months.
Hair	Wickett et al. (14) Placebo-controlled, randomized, double-blind.	48 women with fine hair. (Age: 18-65 years)	Improved tensile strength (+13,1%, versus placebo) and increased hair cross-sectional area (+12,8% ch-OSA® group versus placebo group) after 36 weeks.
	Chan (15) Open label, single-arm.	8 patients with male pattern hair loss and 11 patients with alopecia. (2 men, 9 women) (Age: 17-54 years)	Improved hair re-growth and reduced hair loss (versus baseline) after 6 months.
	Chandrashekar et al. (12) Open label, single-arm.	9 alopecia patients (5 men, 4 women) (Age: 17-54 years)	Increased hair density (versus baseline) after 5 months.
Nails	Barel et al. (7) Placebo-controlled, randomized, double-blind.	50 women with photoaged skin (Age: 40-65 years)	Decreased nail and hair brittleness (versus baseline) after 20 weeks.
	Bruni et al. (13) Open label, single-arm.	10 women with fragile nails (hand). (Age: 18-65 years)	Improvement in nail roughness, onychoschizia, and longitudinal ridges (versus baseline) after 6 months.
	Chandrashekar et al. (12) Open label, single-arm.	10 women with brittle nails both on hands and feet. (Age: 40-65 years)	Improvement in nail roughness, the number of broken and discolored nails (versus baseline) after 5 months.

Table 2
Other health benefits of ch-OSA®, reported in clinical trials. ch-OSA® was administered as an oral supplement, i.e. twice daily one capsule containing 5 mg of silicon and 100 mg choline as ch-OSA® (Bio Minerals NV, Belgium) or ch-OSA® containing drops (once daily 6 drops containing 6 mg of silicon and 120 mg choline as ch-OSA®).

	Author, study design	Study population	Observations
Bones	Spector et al. (18) Placebo-controlled, randomized, double-blind.	184 osteopenic women. (Age: 18-79 years)	Improvement of bone formation biomarkers, e.g. increased bone collagen formation (+1%) increased bone mineral density in the hip (+2%) (ch-OSA® /calcium/vitamin D3 group versus calcium/vitamin D3) after 1 year.
Joints	Geusens et al. (22,23) Placebo-controlled, randomized, double-blind.	166 patients (46 men and 120 women) with knee osteoarthritis. (Age: 34-77 years)	Improvement in symptoms (pain, stiffness, mobility) and biomarkers of cartilage degradation (CTX-II, COMP) in men (ch-OSA® group versus placebo group) after 12 weeks.
Dental	Teughels et al. (26) Placebo-controlled, randomized, double-blind.	73 patients (34 men and 39 women) with severe periodontitis. (Age: 20-67 years)	Improved pocket depth of teeth with a pre-stage of periodontitis, and less bleeding of gums (ch-OSA® group versus placebo group) after 6 months.
	Teughels et al. (27) Pilot, placebo-controlled, randomized, double-blind.	21 peri-implantitis patients (10 men and 11 women). (Age: 32-68 years)	Improved gum recession and stabilization of bone loss at per-implantitis sites (ch-OSA® group versus placebo group) after 12 months.

Joints

The effect of ch-OSA® on joint health was investigated in a multicenter, randomized, double-blind, placebo-controlled, single joint study in patients with painful knee osteoarthritis (OA) (22, 23). Over 12 weeks, one hundred sixty-six patients with documented knee OA (K&L grade II and III) and a baseline knee pain score of moderate or moderately severe on a 5-point Likert scale, completed the study. The patients were randomized in a ch-OSA® group and a placebo group. The mean age of the patients was 61.9 years and 72% were women of which 98% were post-menopausal. Patients were allowed to take rescue medication (paracetamol) up to 48 hours prior to each clinical investigation.

Symptoms of OA were evaluated in the target knee with the validated WOMAC questionnaire which measures joint pain, joint stiffness, and physical function.

Patient Global Assessment was measured on a 100 mm scale. Biochemical markers of cartilage degradation i.e., C-telopeptide fragments of type II collagen (CTX-II) and cartilage oligomeric matrix protein (COMP) were analyzed respectively in urine and serum.

The investigators found no differences between the two groups in the total study population but did found a significant improvement in men taking ch-OSA® compared to men in the placebo group after 12 weeks, respectively for total WOMAC (ch-OSA®: -43% vs. placebo: -17%), WOMAC pain (ch-OSA®: -48% vs. placebo -22%), WOMAC stiffness (ch-OSA®: -48% vs. placebo: -13%) and WOMAC physical function (ch-OSA®: -41% vs. placebo: -16%).

A similar trend was observed in patient global assessment (ch-OSA®: -50% vs. placebo: -34%).

The change in biochemical markers for cartilage degradation was also significantly different in men for both CTX-II (ch-OSA®: +20% vs. placebo: +45%) and COMP (ch-OSA®: -2% vs. placebo: +17%), i.e., significantly less cartilage degradation was found in patients who took ch-OSA® compared to placebo. Baseline levels of CTX-II were higher in women compared to men indicating more cartilage breakdown in women at the start of the study. Patients (women and men) with moderate baseline knee pain and K&L grade II, showed a significant improvement in WOMAC after 6 weeks supplementation (ch-OSA®: -55 % vs. placebo: -22 %).

This study demonstrated that ch-OSA® reduces joint pain and stiffness and improves physical function of the knee joint already after 12 weeks of supplementation in men with painful knee OA. This clinical improvement was associated with decreased cartilage degradation as demonstrated by reduced levels of biochemical markers in both serum and urine.

The difference in response to ch-OSA® supplementation between men and women was explained by previously reported gender differences in the incidence and severity of knee OA (24) including higher levels of cartilage degradation products (25) in women compared to men. The investigators therefore suggested that longer ch-OSA® supplementation may be needed in women to obtain a similar clinical improvement as is observed in men.

Dental

Recently two clinical studies have been presented, which investigate a potential role of ch-OSA® in dental health. In fact, the oral cavity is characterized by collagen-rich gingiva, but also the alveolar bone in which both natural teeth and dental implants are integrated is dependent on an optimal collagen network for adequate biomechanical strength. In a first randomized, placebo-controlled double-blind study, 72 patients with severe, generalized periodontitis completed a 6-month study (26). Periodontitis starts with an inflammatory condition of gums resulting in the formation of so called "pockets" around the affected teeth.

This inflammation results in swollen, painful, bleeding gums and may lead to bone loss and

ultimately loss of teeth. The investigators found that for teeth with a pre-stage of periodontitis, observed as "shallow" pockets, the pockets became less deep, and the gums had less bleeding in patients who took ch-OSA® compared to the placebo group. In a second study 21 patients with peri-implantitis were randomized in ch-OSA® or placebo groups and followed for 1 year (27). Peri-implantitis, starts also with inflammation of gums, resulting in swollen, painful gums and leads to receding gums, bone loss and ultimately loss of the implant. The investigators observed after 1 year a decrease of receding gums and a stabilization of the alveolar bone loss in patients who took ch-OSA® compared to patients taking placebo.

Mechanism of action of ch-OSA®, its impact on collagen biosynthesis.

Collagen synthesis is a complicated biochemical process that comprises several chronological steps and various enzymes **(table 3).**

Choline-stabilized orthosilicic acid was suggested to have an impact on the activity of four enzymes, that are required in different steps of collagen biosynthesis.

The impact on these enzymes is in part related to (a) ch-OSA's silicon component orthosilicic acid, (b) from its choline component, and (c) from the complex as a whole.

Experiments in animals have shown that insufficient dietary intake of bioavailable silicon (e.g., orthosilicic acid) result in connective tissue abnormalities including bone defects and lowered concentration of collagen. Low dietary intake of bioavailable silicon has been found to reduce the activity of the enzyme ornithine aminotransferase which catalyzes the biochemical production of proline from ornithine (28). Proline is together with glycine and lysine, a major amino acid in the primary structure of collagen.

Prolyl hydroxylase is the enzyme which converts proline in the collagen peptide into hydroxyproline, a collagen specific amino acid. In fact, two types are known for postranslation prolyl hydroxyalation in collagen synthesis, i.e. prolyl 4-hydroxylase and prolyl 3-hydroxylase (29). The in-vitro activity of prolyl hydroxylase in bone explants of chick embryos was found to be dependent on the concentration of silicon in the culture medium (30). In vivo, young animals which were supplemented with ch-OSA® in their diet, were found to have 12.5% higher hydroxyproline content in the dermis compared to controls without ch-OSA® supplementation (10). Physiological concentration of orthosilicic acid were found in cell cultures of human fibroblasts, to increase m-RNA and protein expression of lysyl hydroxylase, the enzyme which converts lysine in the collagen peptide into hydroxylysine (31). A significant increase in the procollagen marker PINP (procollagen type I N-terminal propeptide), an early marker of bone formation was reported for osteopenic women who took ch-OSA® compared to women in the placebo group (17), which directly illustrates that ch-OSA® stimulates collagen formation in man.

Proper cross-linking is critical for normal collagen structure and optimal mechanical properties of the connective tissue in which the collagen fibers are embedded (32). Beside lysyl oxidase, at least 9 different enzymes are involved in the maturation process of collagen which also includes non-enzymatic reactions. Proper cross links formed by lysyl oxidase shouldn't be confused with the distriputive cross links that collagen molecules are susceptible over time by the undesirable reactions of reducing sugars, particularly glucose ("glycation") and lipid oxidation products resulting in "aged" collagen fibers which result in connective tissue with poor mechanical properties.

Lysyl oxidase is also responsible for the formation of cross-links in elastin, the second

most important fibrous protein in connective tissue. Collagen and elastin together determine the biomechanical properties of skin.

Accumulation of homocysteine was found to have a negative impact on collagen metabolism, as it was reported to interfere with lysyl oxidase's synthesis and its enzymatic activity **(table 4).**

In animals and man, hyperhomocysteinemia has been shown to correlate with poor quality of bone collagen (33) and altered bone morphology. In man, blood levels of homocysteine correlate with the collagen cross-links ratio in bone forming areas (34). Recently, a meta-analysis and systematic review of the literature demonstrated that homocysteine significantly increased the risk of fracture (35).

Choline, a component of ch-OSA®, functions as a precursor of betaine, a compound which is used as a methyl donor in the biochemical conversion of homocysteine to methionine by the enzyme betaine-homocysteine methyltransferase. The dietary choline intake is inversely associated with plasma homocysteine i.e., a high choline intake correlates with low plasma homocysteine levels and choline depletion tends to increase the homocysteine level in blood. In addition, human intervention studies show that choline supplementation results in a significant decrease of plasma homocysteine levels. The European Food Safety Authority (EFSA) has confirmed (36) that a cause-and-effect relationship is established between the consumption of choline and contribution to normal homocysteine metabolism which resulted in the authorization of the health claim "choline contributes to normal homocysteine metabolism". Homocysteine can also be trans-sulphurated to cysteine, which requires vitamin B6 as a co-factor.

Cysteine is an important sulfur-containing amino acid used in the production of keratin, the structural protein of hair and nails, and is used by the body to make glutathione, a powerful antioxidant that protects cellular components against oxidative damage via the glutathione peroxidase pathway.

The above illustrates that a balanced homocysteine metabolism is important for optimal health i.e., relatively low levels of homocysteine are needed since it is used as a precursor for other amino acids (methionine, cysteine) but accumulation will cause connective tissue related health problems such as cardiovascular, skin and bone defects due to the negative impact on collagen metabolism.

The intake of the choline containing ch-OSA® complex, contributes to a healthy homocysteine metabolism and protects collagen against homocysteine mediated denaturation.

Table 3
The different steps in the biosynthesis of collagen. ch-OSA® has a positive impact on key enzymes that are needed in collagen biosynthesis: ornithine transferase and 3 post-translation enzymes, i.e., prolyl hydroxylase, lysyl hydroxylase, and lysyl oxidase.

1 - Amino acid synthesis	**Ornithine transferase converts ornithine into proline, a major amino acid in collagen.**
2 - Transcription	**Genes (DNA) encoding the collagen molecule must be turned on and transcribed into messenger RNA.**
3 - Translation	**Messenger RNA leaves the nucleus and is translated by ribosomes in a pro-peptide which is basically a chain of amino acids.**
4 – Post-translation	▪ **Several modifications such as hydroxylation of lysine and proline residues in the pro-peptide by the enzymes lysyl hydroxylase and prolyl hydroxylase.** ▪ **Association of three pro-peptides into a triple helix (procollagen).** ▪ **Peptidase enzymes cleave the N- and C- terminal pro-peptides, which then assemble into a tropocollagen triple helix.** ▪ **The enzyme lysyl oxidase is responsible for the formation of cross-links between tropocollagen molecules which then generates collagen fibrils.** ▪ **Additional cross-linking occurs between different fibrils to form strong collagen fibers.**

Table 4
Hyperhomocysteinemia negatively impacts collagen metabolism by several mechanisms. Choline, which is present in ch-OSA®, contributes to a normal homocysteine metabolism i.e. it helps prevent hyperhomocysteinemia.

Inhibits lysyl oxidase	**Homocysteine thiolactone, a derivative and by product of homocysteine metabolism inhibits lysyl oxidase activity directly (37). An inverse correlation was found between the homocysteine concentration and the lysyl oxidase activity in vitreous specimens of patients with proliferative diabetic retinopathy (38).**
Down regulation transcription	**Homocysteine interferes indirectly by down-regulation the expression of lysyl-oxidase's messenger RNA and other genes involved in collagen cross-linking (39).**
Interacts with cross-linking	**Homocysteine reacts chemically with collagen thereby interfering with collagen cross-linking. In bone samples of orthopedic patients, about 50 % of the bone homocysteine is bound to collagen plus an association was found between altered bone morphology and bone homocysteine concentration (40).**

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Profhilo Body® for tackling skin roughness and laxity of inner arm, abdomen and knees.

Adele Sparavigna

Adele Sparavigna[1], Franco Grimolizzi[2], Clara Cigni[2], Roberto Lualdi[1], Gilberto Bellia[2]

ABSTRACT

Hyaluronic acid (HA) is well known for its potential benefits in ameliorating skin defects produced by ageing, UV exposure, environmental factors and it can be delivered in different formulation depending on its molecular weight, composition or components. The use of HA is nowadays particularly interesting for the treatment of skin aesthetic defects of both face and body. In this context, Profhilo Body®, composed by hybrid cooperative complexes (HCC) of high and low molecular weight HA at the concentration of 32 mg/ml, is a unique formulation and the only product currently available which is indicated for the treatment of skin laxity in the body. The present study aimed at evaluating the efficacy and safety of Profhilo Body® for the treatment of skin roughness and laxity. The study included 50 female volunteers with mild to moderate skin roughness and laxity signs into inner arm, abdomen and knees body areas. Subjects received two injections of Profhilo Body® using BAP technique (Bio Aesthetic Points) at one month distance. Efficacy and safety were evaluated one and four months after treatment. Both clinical and instrumental assessment indicate a strong statistically significant improvement after completion of the treatment with Profhilo Body® kit. The efficacy was also confirmed by a self-assessment of the volunteers. The clinical and instrumental improvements were obtained in the absence of adverse events, further supporting the use of Profhilo Body® for the treatment of skin laxity in different body areas.

KEYWORDS

Hyaluronic acid, skin laxity, roughness, inner arm, abdomen, knees

1 DERMING S.r.l., Clinical Research and Bioengineering Institute Milano, Italy.
2 IBSA Farmaceutici Italia, Lodi, Italy

INTRODUCTION

Ageing and exposure to environmental factors such as ultraviolet (UV) light are some of the known causes of loss of skin elasticity[1-7] therefore leading to increased skin roughness and laxity. Nowadays, clinicians have often considered these effects on skin quality primarily in the facial area, which is considered the most exposed body area to the environmental factors. Moreover, face and neck are also considered by both patients and clinicians the most visible body areas and hence relevant in terms of social behavior[8-10]. Despite the evidence, skin laxity and roughness involve other body districts such as arms, knees, abdomen, neck, décolleté and hands; these body areas, are particularly sensitive to changes due to both endogenous and external factors, including genetics, aging, rapid changes in body weight (diet, pregnancy), sun exposure and lifestyle[11-14]. Skin roughness and laxity can also range from very mild to severe and severe cases usually require surgical intervention. For mild to moderate loss in skin elasticity, there are alternative treatments not involving surgical procedures such as energy-based devices, (lasers, radiofrequency or ultrasonic devices). However, they are usually quite expensive, both for physicians and patients, require several

procedures and restrictions (e.g. no sun exposure among treatments) to obtain the expected results and include some disadvantages like pain, burns and damages. For these reasons, the use of hyaluronic acid (HA) based products for body treatments is nowadays particularly interesting considering evidence linking the loss of extracellular matrix components in the connective tissues to skin roughness and laxity[15-18].

In particular, HA-based fillers are very efficacious due to the ability of HA to maintain a sufficient degree of hydration, turgidity, viscosity and plasticity of connective tissue[18-24]. In this context, skin hydration is maintained thanks to HA ability to bind and retain water. In addition, HA bio-stimulatory effect can promote new collagen formation. Furthermore, HA has a very low allergenic potential, resulting in the ideal product for skin rejuvenation treatments. Currently, HA exists in different formulations which have been proven to be effective in different application. Thanks to the use of patented NAHYCO® technology, Profhilo Body® is an innovative formulation composed by hybrid cooperative complexes (HCC) of low and high molecular weight HA, which allows to deliver high concentration (96 mg into 3 ml) of HA to different body areas. This product has shown high skin remodeling efficacy, improving skin elasticity and homeostasis, and very good tolerability either for short or long period of times[25-28]. Moreover, Profhilo Body® proved its efficacy to counteract signs of skin laxity and roughness in a previous study performed on inner arm and abdomen[29] and therefore represents the only injectable treatment for body with the specific indication for the treatment of skin laxity. In this regard, the aim of this study was to evaluate efficacy and tolerability of Profhilo Body® for the treatment of mild to moderate skin roughness and laxity of abdomen, inner arm and knees using a new Bio Aesthetic Point technique (BAP) of injection.

Material and methods

Characteristics of the subjects

Single center study has been performed under the supervision of a dermatologist and enrolled female volunteers (age range: 35 - 65) with mild to moderate signs of roughness and skin laxity at inner arm, abdomen and knees. In particular, inner arm skin laxity was evaluated equal to grade 3 and 4 according to IBSA inner arm reference scale[30].

Exclusion criteria, valid for the entire duration of the study, are pregnancy or lactation, use of smoke, alcohol or drugs or the performance of surgical procedures in the skin treatment area. Moreover, subjects were excluded in presence of dermatitis and cutaneous disease or in presence of other pathologies as diabetes, hepatic, renal, cardiac or pulmonary disorders. Other exclusion criteria were allergies or know sensitivity to test products as well as the assumption of anticoagulant, anti-histaminic, corticosteroids, immunosuppressive and any drugs judged by the investigator that could potentially affect the results of the study.

Based on the results from a similar previous study[29], a sample size of 45 subjects was calculated to provide a power of 80% ($\beta = 0,20$) to detect an improvement of at least one point in the clinical assessment in the 15% of participants, with $\alpha = 0,05$[31-32]. Assuming a 10% drop rate, 50 subjects were enrolled in the study.

The study was submitted and approved by the local Ethical Committee.

Study design

Two injections of Profhilo Body® were performed at different timepoints: first injection was performed after initial clinical and instrumental evaluation (baseline) and the second one after 1 month. The injections consisted in 3 mL of Profhilo Body® for each brachial zone, 3 mL for abdomen and 3 mL for each superior part of the knees injected with 29G needle into the middle-deep dermis using a bolus technique called "BAP" (Bio Aesthetic Point technique)[28].

This technique involves a series of 10 micro-wheals (300 microliters per injection point) on 3 horizontal-levels for each tested areas (3-4-3 injection points respectively for the 1st, the 2nd and the 3rd horizontal-level, as schematically shown in **Figure 1.** The 10 points identify the 10 anatomically receptive areas of the abdomen, inner arm and knees where the absence of large vessels and nerve branches allows to minimize the risks and to maximize the diffusion of the product in the treated areas.

Clinical and instrument evaluation

Both clinical and instrumental evaluation were performed at each visit, at baseline (T0), after 1 month (T1) and 4 months (T2). Clinical evaluation was performed using IBSA photographic scale for inner arm and a visual score for abdominal skin roughness and laxity ranging from 1 (no roughness and laxity) to 5 (very severe roughness and laxity). Standardized 2D pictures of inner arm, abdomen and knee were taken and recorded for each volunteer.

Non-invasive instrumental evaluations were performed using three different measurements: tissue dielectric constant and skin density or profilometry.

Tissue dielectric constant of skin layers at 0,5 mm and 1,5 mm was measured using MoistureMeterD instrument, which applied high frequency, low power electromagnetic wave, measuring changes in the total water content of the skin.

Skin density was measured pinching a little skin area of about 7 cm^2 (2.5x2.8 cm) at level of inner arm in standardized conditions. After pinching, the skin profile changes depending on cutaneous density; on the other hand, when the skin is slack the "pinch" forms a lot of wrinkles.

The profilometric parameters Ra (mean roughness, represents the average roughness of the skin profile) and Rv (maximum depth of the skin profile) were measured using Primos compact portable device (GFMesstechnik).

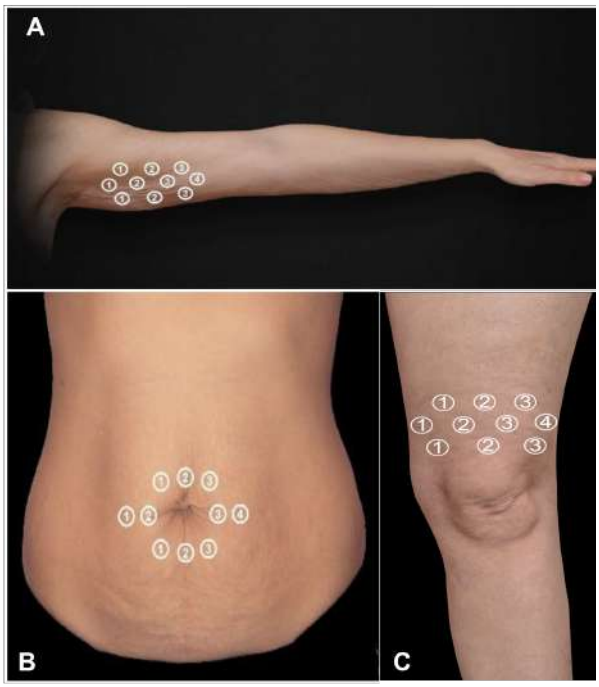


Figure 1. *Schematic representation of the BAP injection procedure utilized in the study for inner arm (A), abdomen (B) and knees (C).*

All the evaluations were performed under standard environmental conditions (Temperature=22+\-2°C; Relative Humidity<60%) and the volunteer was asked to acclimatize under relax conditions for at least 10-15 min before each visit.

Safety and subject self-evaluation

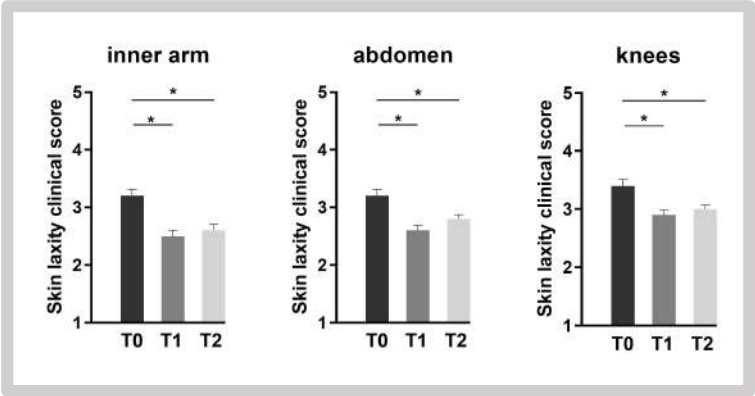
Each volunteer filled a questionnaire at the end of the study to evaluate the treatment efficacy on skin roughness and laxity suppleness, smoothness, hydration, lifting and contour redefinition/remodeling. Finally, they also evaluate treatment tolerance (score: bad; poor; good; excellent).

Moreover, adverse events such as local expected reactions induced by the injection procedure (tardive swelling, pain, erythema, bruise) or any other adverse event/reaction, also of systemic source, were evaluated during the entire duration of the study.

Statistical analysis

For clinical data evaluation, a non-parametric Friedman test was calculated followed by the Holm-Sidak Adjusted test in case of statistically significant result.
For instrumental data evaluation, Shapiro-Wilk normality test (threshold at 5%) was performed followed by Friedman test when the normality hypothesis was rejected or followed by a Anova parametric test, when the normality hypothesis was confirmed. In case of statistically significant results, Holm-Sidak Adjusted test was also calculated.

Figure 2.
Clinical evaluation of skin laxity in the inner arm, abdomen and knees at baseline visit (T0) and 1 (T1) or 4 months (T2) after beginning of the treatment. (* p<0.05 versus T0, Holm-Sidak Adjusted Wilcoxon signed ran



Results

For this single center study, fifty subjects (age from 35-65) were enrolled and no dropouts occurred at the end of the study. To evaluate the efficacy of the treatment, clinical evaluation was performed at different timepoints (T0, T1 and T2).
Subjects showed a significant improvement in the skin laxity clinical score for each anatomically area analyzed (inner arm, abdomen and knees). In particular, the majority of the subjects had an improvement of at least 1 grade in the evaluation scale at T1 and T2 relative to T0 in all the areas investigated **(Figure 2).**
These clinical evaluations were supported by photographic documentation that confirmed the general improvement induced by the treatment for all the anatomical body areas, including inner arm and abdomen **(Figure 3)** and knees **(Figure 4).**

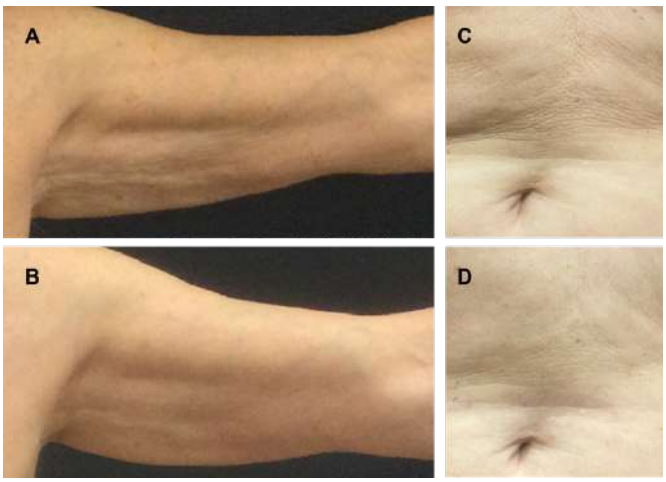


Figure 3.
Photographic documentation for inner arm and abdomen taken at baseline visit (A and C) and 4 months after the beginning of the treatment (B and D).

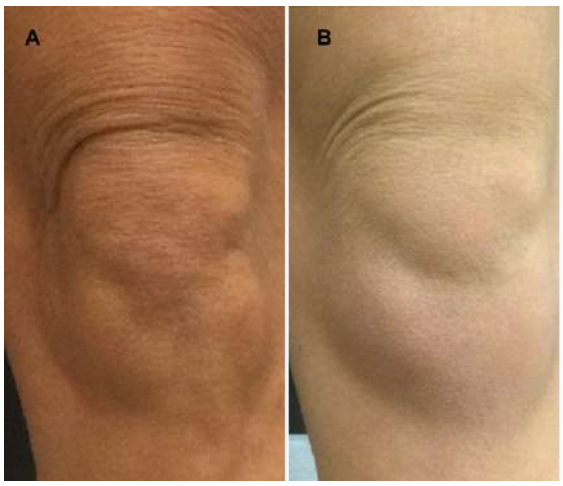


Figure 4.
Photographic documentation for knees taken at baseline visit (A) and 4 months after the beginning of the treatment (B).

Amelioration of clinical score was also confirmed by non-invasive instrumental evaluations. In this regard, skin hydration measurements at 0,5 mm showed a statistically significant improvement at T1 and T2 for both inner arm and abdomen, while statistically significant differences were only obtained at T1 when knees were evaluated **(Figure 5A).** Although skin hydration measurements at 1,5 mm showed a statistically significant improvement at T2 for only inner arm, a positive trend can be also observed for abdomen and knees areas of treatment **(Figure 5B).**

Skin density was also evaluated performing profilometric measurements for the entire duration of the study. Two different parameters for the evaluation of skin density were evaluated: Ra and Rv, representing the average roughness and maximum depth of the skin profile, respectively. Accordingly to previous results, a significant improvement for Ra was detected, especially for inner arm and abdomen at T1 and T2, while significant results for knees were only obtained at T2 **(Figure 6A).** Significant results have also been obtained for Rv parameter for inner arm at both the time points and abdomen at T2, while a positive trend but not statistically significant result was obtained after knees treatment **(Figure 6B).**

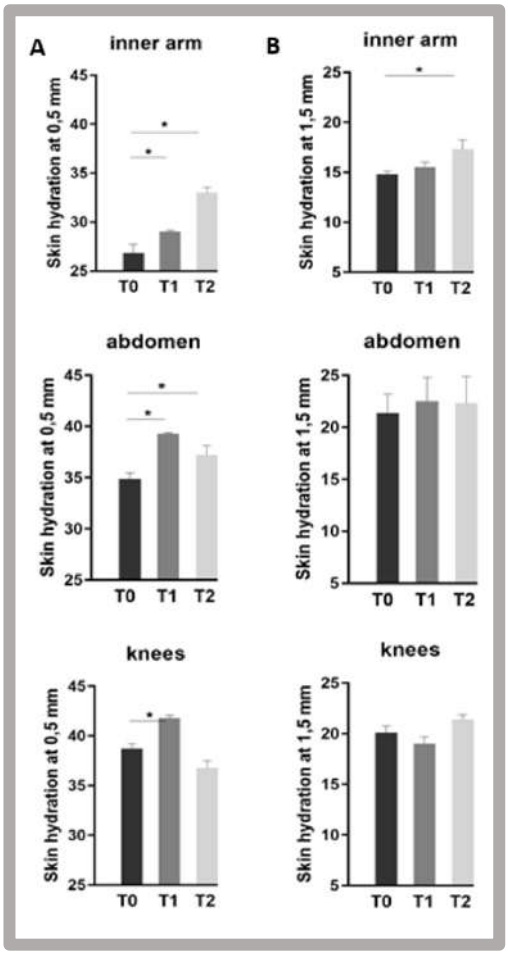


Figure 5. Skin hydration measurement at 0,5 mm (Panel A) and 1,5 mm (Panel B) for inner arm, abdomen and knees determined by measurement with Moisture MeterD at baseline visit (T0) and 1 (T1) or 4 months (T2) after beginning of the treatment. (* p<0.05 versus T0, Holm-Sidak Adjusted Wilcoxon signed rank test).

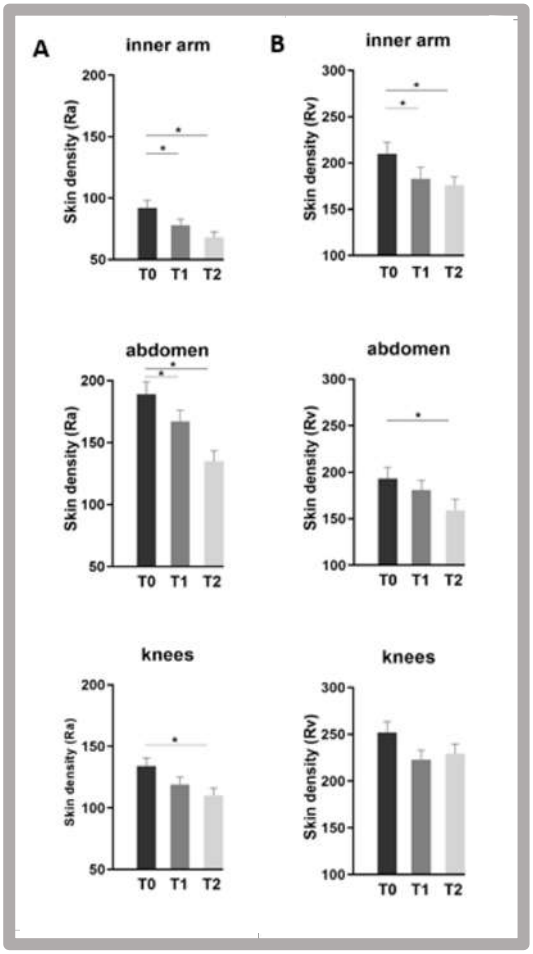


Figure 6. Skin density determined by profilometry. The graphs report the Ra parameter (Panel A) and the Rv parameter (Panel B) for the inner arm, abdomen and knees determined at baseline visit (T0) and 1 (T1) or 4 months (T2) after beginning of the treatment. (* p<0.05 versus T0, Holm-Sidak Adjusted Wilcoxon signed rank test).

Finally, positive results obtained after clinical and instrumental evaluations were supported by the positive judgement of the volunteers obtained at the end of the study **(Figure 7).** In this context, approximately 90% or more of the subjects reported an improvement after the two injections. More importantly, positive results were achieved for all the parameters indicated in the questionnaire and extremely positive judgements (94% and 92% for inner arm and abdomen/knees, respectively) have been obtained for skin laxity improvement.
Profhilo® Body did not also produce any side effect and tolerance was judged from good to excellent by the Investigator for all the volunteers. In this context, when subjects experienced a light bruise at the injection points, this effect disappeared in few days and was not attributable to the product.

Discussion

The results obtained in the present study, involving 50 volunteers with mild to moderate skin laxity and roughness, confirm the usefulness of HCC as bioremodelling agent. The particular formulation used for Profhilo Body®, consisting of HCC of high and low molecular weight HA, strengthen the positive results already obtained with this formulation for the treatment of facial skin deterioration[25-27]. Importantly, when abdomen and inner arm were treated, a strong and statistically improvement can be observed in all the parameters analyzed, either clinically or instrumentally. This evidence further supports the use of Profhilo Body® specific formulation for the treatment of skin laxity and roughness of skin body areas which are losing the initial fitness of young skin, due to ageing, environment exposures, changes in body weight or other conditions.

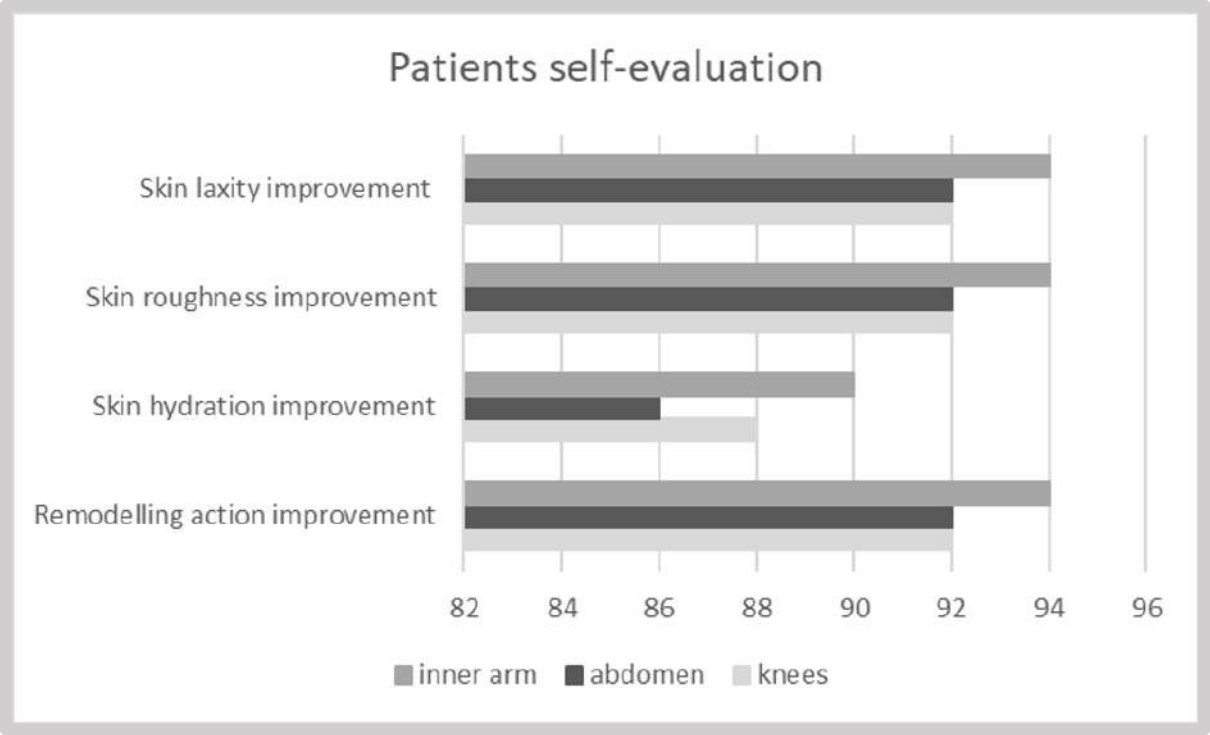


Figure 7. Efficacy evaluation evaluated by patients 3 months after the end of the treatment. Percentages sum of positive judgements (lightly, medium and markedly improved) are represented in the graph.

Moreover, this study also demonstrated that clinical evaluations for other anatomical area of treatment rather than inner arm and abdomen, like knees, are also promising. Indeed, a clear improvement trend was visible for the knees for all the parameters evaluated even at the beginning of the treatment, while clinical significance is also reached at the end of the treatment. In this context, fundamental importance should be given to selection of patients to maximize the efficacy of the treatment with Profhilo Body®. Indeed, patients with clear signs of skin laxity and roughness and without or few ptosis of the muscle and adipose tissue should be selected.

Importantly, Profhilo Body® was also extremely tolerable as resulted from both investigator and volunteers' judgement. In this context, only a light and procedure dependent bruise was reported by the volunteers. This event, reversible in few days and not attributable to the product, does not limit the potential use of Profhilo Body® for the treatment of skin defects.

Interestingly, it is also possible to observe a further improvement at the end of the treatment compared to the evaluation performed after the first injection. This observation would be in line with the hypothesis that HA-based products, including Profhilo Body®, possess a bio-stimulating activity on the connective tissue. This activity is able to promote collagen formation and in turn helps in increasing skin tonicity[24,33-36].

This bio-stimulating activity can also be more relevant when longer application of HA-based products is considered. In this context, a recent report performed with the same formulation of Profhilo® for facial skin treatment showed a strong efficacy of the product but, more importantly, a good safety and lack of adverse events even after 7 treatments in one year[37]. Taken together, these data strongly support the efficacy of Profhilo® Body and the possibility to extend their use in other body district for which skin deterioration is an important concern.

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Nuovi approcci terapeutici dell'alopecia androgenetica maschile

Gaia Fasano

Gaia Fasano[1], Steven Paul Nisticò[1]

ABSTRACT

Background: Androgenic alopecia (AGA) is a frequently dermatological condition that impacts the patient quality of life. Topical minoxidil and oral finasteride are well-established treatment for men with AGA. Several new pharmacological and non-pharmacological options have been proposed during the last few years for AGA treatment.
Objective: This article assesses the pharmacology and current therapeutic strategies for AGA and new therapeutic approach.
Results: A topical finasteride formulation has been developed for AGA treatment with the aims to minimize systemic exposure and adverse events caused by oral administration and to act specifically on hair follicles. Multiple studies on topical finasteride showed positive results with a favorable safety profile. The use of oral minoxidil in androgenic alopecia has not been approved by Food and Drug Administration (FDA), however several clinical studies have shown that it is an effective treatment option but hypertrichosis, the main adverse effect, limits its use. Platelet-rich plasma is a non-pharmacological option that induce an improvement in hair count in male with AGA, but, due to the heterogeneity of the procedure, it's difficult to standardize and compare the efficacy of the results. Other topical options, with some initial promising results, are: pyrilutamide, GT20029 and cetirizine. Several natural products may be used in conjunction with conventional therapy to enhance clinical outcomes.
Conclusions: Androgenetic alopecia therapy remains challenging. The pathogenesis is not fully understood, therefore, once the underlying biological mechanisms have been established new targeted treatments may emerge. However, more randomized controlled trials are needed to further investigate and confirm the efficacy of these new treatments.

KEYWORDS
Androgenetic alopecia, minoxidil, topical finasteride, PRP, treatment outcome, new therapy

[1]Department of Health Sciences, Magna Graecia University, 88100 Catanzaro, Italy

ARTICLE

L'alopecia androgenetica (AGA) è una condizione caratterizzata dalla progressiva perdita di capelli che interessa più comunemente le regioni fronto-parietali e il vertice dello scalpo. Interessa più frequentemente gli uomini, a partire dalla pubertà, con una prevalenza che può variare tra le diverse nazioni in base alla razza o all'etnia (1). La frequenza della AGA aumenta con l'età: a 30 anni interessa il 30% degli uomini, a 50 anni il 50%, a 70 anni l'80%. Diversi fattori eziopatogenetici contribuiscono all'insorgenza della patologia, tra cui la predisposizione genetica e l'influenza ormonale. L'interazione tra questi fattori e gli altri meccanismi, che contribuiscono alla miniaturizzazione follicolare, è ancora oggetto di studio.

L'alopecia androgenetica è considerata una patologia ereditaria a trasmissione poligenica multifattoriale, questo è dimostrato da numerosi studi dove viene evidenziato un aumento del rischio di cinque volte di sviluppare AGA nei pazienti i cui genitori presentavano la stessa patologia (2).

Tale modalità di trasmissione giustifica i diversi pattern di alopecia androgenetica che possono coesistere in una stessa famiglia.

Sono stati identificati diversi loci di suscettibilità come, ad esempio, il locus per il recettore degli androgeni (AR)/EDAR2 sul cromosoma X, il locus PAX1/FOXA2 sul cromosoma 20, il gene HDAC9 sul cromosoma 7 ed altri (3).

L'aumento della produzione degli androgeni durante la pubertà è coinvolto nell'induzione e nella promozione dell'alopecia androgenetica. Il Diidrotestosterone (DHT) è un metabolita del testosterone che ha un'elevata affinità per i recettori degli androgeni.

L'enzima 5-alfa-reduttasi, mediatore della conversione del testosterone in DHT, è presente in due isoforme a livello del cuoio capelluto: tipo 1 e tipo 2. Sebbene entrambe le isoforme siano coinvolte nella patogenesi della AGA, il ruolo del tipo due è più importante (4). I giovani pazienti affetti da AGA presentano a livello del cuoio capelluto livelli più elevati dell'enzima 5-alfa-reduttasi e una quantità maggiore di recettori per gli androgeni; le concentrazioni ematiche di testosterone, al contrario, sono simili a quelle dei pazienti non affetti da AGA (5).

Il DHT, legando il recettore degli androgeni e formando il complesso ormone-recettore, determina l'attivazione dei geni responsabili dell'induzione di una fase anagen ridotta. Questo processo, denominato miniaturizzazione follicolare, porta trasformazione dei follicoli terminali in follicoli più piccoli e produzione di piccoli peli "vello" che determinando un progressivo decremento del volume dei capelli e alla percezione della "perdita" (6).

La progressiva riduzione del calibro e della lunghezza dei capelli può essere valutata utilizzando la scala di Hamilton-Norwood (7). Questa scala, suddividendo i diversi stadi clinici in sette gradi, offre una rappresentazione visiva delle fasi sequenziali dell'alopecia. È riportato che una percentuale di pazienti, circa il 10%, presenta un pattern di caduta diverso da quello comune riportato da Hamilton-Norwood (8).

Alla tricoscopia possiamo notare, già nelle fasi iniziali della AGA, il fenomeno dell'anisotrichia caratterizzato dalla presenza contemporanea di capelli terminali, intermedi e miniaturizzati, quest'ultimi devono essere presenti in una percentuale maggiore del 20% per poter porre diagnosi. È possibile, inoltre, osservare la presenza di un alone perifollicolare roseo-giallastro indice di flogosi (9). Progressivamente si nota una riduzione del numero di capelli per unità follicolare fino alla scomparsa delle unità follicolari con comparsa di follicoli vuoti (yellow dots). La riduzione della densità capillare espone il cuoio capelluto ad un danno attinico che determina la comparsa di un reticolo pigmentato (10).

Il minoxidil topico e la finasteride orale sono gli agenti terapeutici più studiati ed utilizzati per il trattamento dell'alopecia androgenetica maschile; sono approvati dalla Food and Drug Administrayion (FDA) e dall'European Medicines Agency (EMA) per il trattamento della AGA. Entrambi i farmaci hanno dimostrato efficacia ed elevata tollerabilità in numerosi trials randomizzati controllati pertanto sono considerati terapia di prima linea (11). Più recentemente è stata introdotta in commercio una nuova formulazione di finasteride topica che ha modificato radicalmente la gestione terapeutica dei pazienti (12).

Il minoxidil topico promuove la crescita dei capelli attraverso l'aumento della durata della fase anagen del ciclo del capello e riducendo la fase telogen. L'esatto meccanismo attraverso il quale il minoxidil influenza il ciclo follicolare e le strutture del follicolo è ancora oggetto di approfondimento (13).

Il minoxidil è un agente vasodilatatore, l'induzione dell'espressione del fattore di crescita dell'endotelio vascolare (vascular endothelial growth factor – VEGF) è un meccanismo attraverso il quale il minoxidil aiuta a mantenere la vascolarizzazione delle papille dermiche. L'aumento di dimensioni delle papille dermiche correla e contribuisce all'aumento di dimensioni del capello emergente dal follicolo (14). In aggiunta, il minoxidil è un regolatore dei canali del potassio, funzione che contribuisce agli effetti benefici del farmaco (15).

Il minoxidil topico è presente in soluzioni al 2% e al 5%, numerosi trial randomizzati riportano una maggiore efficacia della formulazione al 5% determinando una più rapida risposta, un aumento del numero di capelli non-vello ed una minore percezione soggettiva di perdita di capelli (16). L'utilizzo del minoxidil è raccomandato per un tempo indefinito, in quanto i benefici ottenuti svaniscono nelle settimane/mesi successive alla sospensione. Gli effetti indesiderati sono infrequenti, i più comuni sono le dermatiti da contatto irritative e le dermatiti allergiche da contatto (17). Non sono riportate alterazioni della pressione arteriosa o della frequenza cardiaca. È possibile un'ipertricosi del volto (18). La finasteride è un inibitore dell'enzima 5-alfa-reduttasi di tipo due, pertanto, inibisce la conversione di testosterone in diidrotestosterone (DHT).

Al dosaggio di 1 mg/die determina una riduzione di più del 60% dei livelli di DHT nel siero e a livello dello scalpo. La finasteride non ha affinità per i recettori degli androgeni, pertanto, non interferisce con l'azione del testosterone (19). L'efficacia dopo 6-12 mesi di trattamento è stata dimostrata da trials randomizzati controllati (20). Il farmaco agisce determinando un aumento del numero, dello spessore, della lunghezza e della pigmentazione dei capelli; questi fattori contribuiscono ad una maggiore percezione di copertura dello scalpo (21). Le disfunzioni sessuali, tra cui riduzione della libido, disfunzione erettile, alterazioni dell'eiaculazione e riduzione della conta spermatica, sono effetti collaterali occasionali, che aumentano con l'aumentare dell'età del paziente (22). Nella maggior parte dei casi gli eventi avversi si risolvono dopo l'interruzione della terapia, anche se alcuni studi riportano in una percentuale di pazienti la persistenza dei sintomi nei mesi/anni successivi la terapia (23). Sono necessari ulteriori studi per valutare la reale frequenza di questi eventi.

Eventi avversi più rari sono la comparsa di ginecomastia e dolore testicolare, più comuni quando la finasteride viene utilizzata ad un dosaggio di 5 mg per il trattamento dell'ipertrofia prostatica. La finasteride è teratogena (24).

La presenza di questi effetti collaterali limita l'utilizzo a lungo termine del farmaco.

Pertanto, per minimizzare gli effetti collaterali della finasteride orale, è stata elaborata una formulazione topica in spray allo 0.25% (1-4 spray/die), che applicata a livello del cuoio capelluto, agisce in modo diretto sui follicoli piliferi evitando gli effetti sistemici del farmaco.

Piraccini et all. (12) hanno valutato l'efficacia e la sicurezza della finasteride topica in spray nel trattamento dell'alopecia androgenetica maschile con un trial randomizzato di fase 3 di confronto tra finasteride spray, finasteride orale e placebo.

Lo studio, condotto per 24 settimane su 458 pazienti, ha dimostrato un aumento del numero dei capelli, maggiore rispetto al placebo e paragonabile a quello ottenuto con la formulazione orale. Non sono stati riportati eventi avversi e altri motivi di interruzione del trattamento nel braccio trattato con finasteride topica e placebo. Poiché la concentrazione plasmatica di finasteride è 100 volte inferiore e la riduzione della concentrazione di DHT nel siero è minore (34.5 vs 55.6%) rispetto al trattamento con finasteride orale, la probabilità di eventi avversi a carattere sessuale si riduce notevolmente. I livelli ematici di testosterone non risultano essere modificati.

L'effetto della finasteride topica è simile a quello della finasteride orale ma con un'esposizione sistemica al farmaco molto inferiore e una considerevole riduzione dell'impatto sulle concentrazioni sieriche di DH. Questa terapia rappresenta, pertanto, una scelta terapeutica alternativa alla finasteride orale (25).

I risultati degli studi preliminari sono ancora limitati ma incoraggianti, sono necessari ulteriori studi per individuare la concentrazione ideale, la frequenza di applicazione ottimale e valutare la comparsa di eventuali altri eventi avversi (26).

La combinazione di minoxidil topico e finasteride topico potrebbe amplificare l'effetto di entrambi i farmaci (27).

Recentemente, nuovi studi hanno dimostrato l'efficacia dell'utilizzo del minoxidil con somministrazione orale nei pazienti affetti da alopecia androgenetica maschile (28).

È stata dimostrata un'associazione dose-dipendente tra l'uso del minoxidil orale, gli effetti a livello dei capelli e la comparsa di effetti collaterali (29). L'aumento nel diametro e nella densità dei capelli è collegato al rischio di ipertricosi, sensazione di capogiri, edemi degli arti inferiori e alla comparsa di eventi avversi cardiovascolari come ipotensione arteriosa, pericardite, effusione pericardica fino all'anasarca (30)

Pertanto, l'utilizzo di basse dosi (2.5 mg/die per gli uomini) consente di ridurre gli effetti collaterali ed ottenere un risultato promettente per il trattamento della AGA.

Tra le opzioni terapeutiche non farmacologiche per il trattamento dell'alopecia androgenetica maschile, diversi trials hanno dimostrato l'efficacia dell'utilizzo del plasma ricco di piastrine (PRP) (31). Il PRP è una preparazione di plasma autologo che contiene un numero elevate di piastrine a cui è associata la presenza di molteplici fattori di crescita come EGF, IGF-1 e VEGF. Questi fattori giocano un ruolo importante nella regolazione del ciclo di crescita del follicolo pilifero (32). Tuttavia, esiste un importante variabilità nei protocolli di preparazione e di somministrazione del PRP, per cui risulta difficile standardizzare la procedura e comparare i risultati ottenuti.

Il regime più utilizzato prevede un trattamento ogni 4 settimane per i primi 3 mesi a cui seguirà uno specifico follow-up in base alla risposta individuale (33).

Nuove formulazioni topiche sono attualmente oggetto di studio. Alcuni studi hanno fornito risultati incoraggianti con l'utilizzo del pyrilutamide e del GT20029 come antagonisti dei recettori degli androgeni (34). Ottimi risultati sono stati, inoltre, ottenuti utilizzando la cetirizina in formulazione topica all'1%; per comprendere appieno il meccanismo d'azione e il ruolo della cetirizina nell'alopecia androgenetica sono necessari studi clinici randomizzati e controllati (35).

Numerose altre sostanze naturali sono state proposte per il trattamento dell'alopecia androgenetica tra cui caffeina, melatonina, estratti marini, olio di rosmarino, procianidina, olio di semi di zucca e olio di cannabidiolo (36).

Tuttavia, sono necessari più studi randomizzati controllati per approfondire e confermare l'efficacia di questi nuovi trattamenti.

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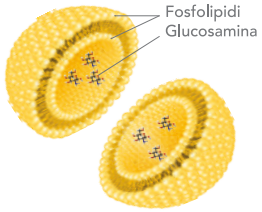
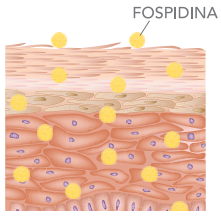
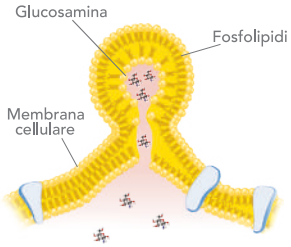


I fosfolipidi si dispongono in doppio strato a costituire una sfera cava (liposoma) all'interno della quale si posizionano le molecole di glucosamina.



Il liposoma penetra negli strati più profondi trasportando la glucosamina, che favorirà la produzione di nuovo acido ialuronico e la fisiologica rigenerazione cellulare.



Il liposoma, che è costituito da fosfolipidi come le membrane cellulari, si integra facilmente con la membrana cellulare creando un canale attraverso cui passa la glucosamina.

Fonte: B. Mandalari e D. Tedeschi, Journal of Plastic Dermatology joined with Update in Plastic Surgery, vol 12, 2, 2016 Fosfolipidi, glucosamina, fitoestrogeni e rigenerazione cutanea

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Fonte: A. Di Pietro e I. Luppino, Journal of Plastic Dermatology, vol 10, 1, 2014
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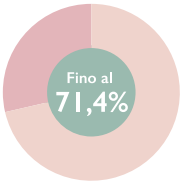

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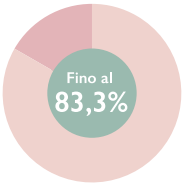

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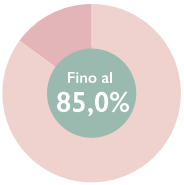

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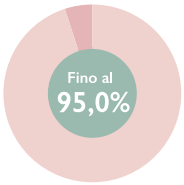

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