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GIULIANI RICERCA E INNOVAZIONE IN DERMATOLOGIA

Vol. 18
n. 4
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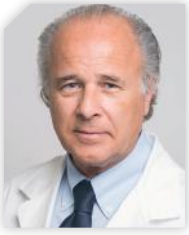
International-Italian Society of Plastic-Regenerative and Oncologic Dermatology

Merry Christmas and Happy new Year



Dear friends, dear colleagues
It was a less difficult year than the previous rich one important events fo our profession.
The EADV of Milan, the Isplad congress, the Isplad courses and all the initiatives promoted by the companies that support the *JPD*.
I don't want to dwell on the easier rhetoric. We come from the very hard times of Covid, a challenge that we are still fighting, with all our strength, not least by living with it, the war that is putting a strain on the Ukrainian people and indirectly also on Europe, creating crisis and uncertainty.
But I want to be positive. No war, no abuse, no violence, no crisis will distract us from our work. Ensure health, commitment, professionalism to people who turn to us for the health of their skin.
For this we took an oath! I thank Isplad, all the scientific societies that have joined the *JPD*, their Presidents, their scientific boards and last but not least, all the companies that have supported Isplad initiatives and those of the other scientific societies.

To all of you, and to our readers, we wish you a Merry Christmas.

Cari amici, cari colleghi
È stato un anno meno difficile del precedente ricco di eventi importanti per la nostra professione.
Le EADV di Milano, il congresso Isplad, i corsi Isplad e tutte le iniziative promosse dalle società che supportano il JPD.
Non voglio soffermarmi nella retorica più facile. Veniamo dai tempi durissimi del Covid, una sfida che ancora stiamo combattendo, con tutte le nostre forze non ultima convivendoci, la guerra che sta mettendo a dura prova il popolo Ucraino e indirettamente anche l'Europa creando crisi e incertezza.
Ma voglio essere positivo. Nessuna guerra, nessun sopruso, nessuna violenza, nessuna crisi ci distoglierà dal nostro lavoro. Garantire salute, impegno, professionalità alle persone che si rivolgono a noi per la salute della loro cute.
Per questo abbiamo fatto un giuramento! Ringrazio Isplad, tutte le società scientifiche che hanno aderito al JPD, *i loro Presidenti, i loro board scientifici e non ultime, tutte le aziende che hanno supportato le iniziative Isplad e quelli delle altre società scientifiche.*

A tutti voi, e ai nostri lettori vanno i nostri Auguri di un sereno Natale.

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Long Term Efficacy And Tolerance Of High-And Low-Molecular-Weight Hyaluronans (Profhilo®) intradermal injections

ADELE SPARAVIGNA

• Adele Sparavigna[1] • Marco Cicerone[2] • Andrea Maria Giori[2] • Gilberto Bellia[2]

SUMMARY

The use of hyaluronic acid (HA) based products spread widely and proved to be efficacious in ameliorating skin deterioration, particularly in the facial area. Here we analyzed the long-term safety and efficacy of high and low molecular weight hyaluronans (Profhilo®, IBSA Farmaceutici Srl). The study included 7 sessions of injection of Profhilo® and this long-term safety evaluation till month 12th from the first injection. Investigator-based evaluation using standard scale determination (i.e FVLS-Facial Volume Loss Scale- and WSRS-Wrinkle Severity Rating Scale-) was used for efficacy analysis. Safety was assessed by the Investigator at each visit together with a final self-evaluation of the volunteers. The results confirmed the efficacy of the studied medical device in reducing both FVLS and WSRS in all the subjects participating in the study; these results were maintained up to the last evaluation. Besides the expected side effects related to the injection procedures, that were limited, rapidly resolved and reported by 65% of the volunteers; approximately 20% of the subjects did not show any injection-related and expected side effects. None of the study volunteers developed unexpected side effects and the volunteers self-evaluation showed optimal or very good the tolerance of this procedure. The study highlights the efficacy and safety of long-term application of Profhilo® in subjects with signs of facial ageing.

KEYWORDS

Hybrid Cooperative Complex; Hyaluronic Acid; Skin ageing; Skin laxity

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

INTRODUCTION

Hyaluronic acid (HA) based products are widely used in aesthetic medicine for correction of wrinkles, skin ageing and skin laxity in several body areas (1–4). Many positive attributes of HA, such as high biocompatibility, low antigenicity and tolerance, facilitated its applications (5–10). Several HA formulations differing in HA content, molecular weight, are available and have shown efficacy on facial wrinkles A particular injectable formulation of hybrid complexes of low and high HA molecular weight has been reported to be safe and efficacious for the correction of skin defects (11–13).

The majority of the studies reporting the activity of different HA formulations, including Profhilo®, generally show the activity and tolerance within a short time frame. Although, as already discussed, the properties of HA suggest no tolerance issues in long lasting treatments, specific studies evaluating the long-term effects of HA-based fillers are indeed warranted. Limited number of studies reporting the efficacy and toler-

ability of HA formulations injected for at least six months have been published (14–16). However, it is pivotal to collect these long-term informations, since with long lasting treatments the different HA formulations could give distinct results.

Based on these considerations, the present study aimed at evaluating long-term efficacy and tolerance of this medical device, that was injected in seven session and evaluated for a period of 12 months.

Material and methods

➜ Study Design

This was an open, controlled clinical trial conducted in a single site on 30 healthy volunteers under the control of a dermatologist.

The product studied (Profhilo®, produced and distributed by IBSA Farmaceutici Italia Srl, Lodi, Italy) is a medical device containing a blend of high- and low-molecular-weight HA (H-HA and L-HA) packed in prefilled glass disposable syringes (32 mg of high molecular weight HA and 32 mg of low molecular weight HA dissolved in 2 ml of buffered saline) for intradermal use. This product contains a highly purified sodium salt of HA, obtained without any chemical modification through a patented technology based on stable hybrid cooperative complexes of H-HA and L-HA (NAHYCO™ technology).

The treatments were performed bilaterally in the face in five different areas as illustrated in **Figure 1**, according to IFU of the medical device (BioAestheticPoint (BAP) technique). For each half-side of the face, a total of 1 ml of the product was injected, 0.2 ml for each injection point. The first injections were performed at basal visit, after evaluation of the eligibility of the subjects as described in the subsequent subchapters. The second treatment was performed after 4 weeks. The subsequent five injections were performed every 2 months for a total of 7 injections. The final visit was performed 4 weeks after the last injection (1 year after study initiation). Subjects underwent clinical assessment, photographic documentation and record of any possible adverse event every scheduled injection visit (including basal visit) and at the last visit 4 weeks after the last injection **(Figure 2)**. The study was approved by an Independent Ethic Committee and was conducted in accordance with the Declaration of Helsinki. Each subject signed an informed consent before study participation.

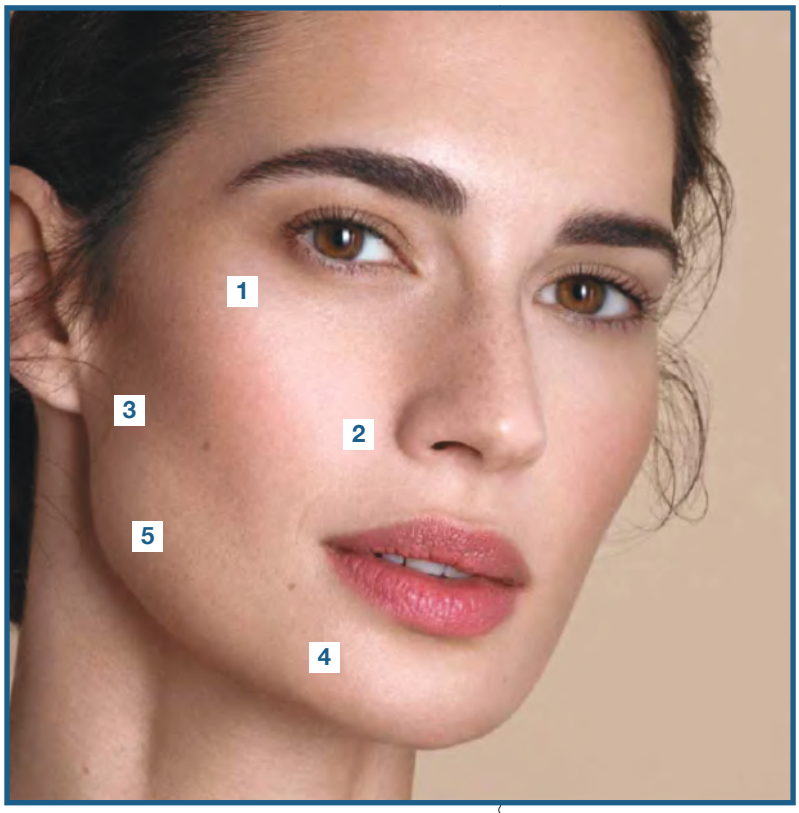

Figure 1.
Schematic representation of the sites of injections.

1. *Zygomatic protrusion at least 2 cm away from the lateral canthus of the eye.*
2. *1.5 cm away from the nasal base: at the intersection between the pupil line and the horizontal line starting from the nasal base.*
3. *1.5 cm anterior to the inferior margin of tragus.*
4. *1.5 cm away from the middle of the chin.*
5. *1.5 cm above the mandibular angle.*

➜ Study Subjects

The study was opened to adult women volunteer with at least initial signs of ageing, keen to perform the entire study including the follow-up, avoiding make-up during the visits, maintaining throughout the duration of the study normal habits relative to food, physical activity, face cosmetic and make-up, use of cleaning products, avoid UV irradiation (UV session or sunbathes) during the study without appropriate sun protection, accepting to sign the informed consent. Exclusion criteria for study subjects are outlined in the **Table 1**.

Figure 2.
Schematic representation of the study procedure. The arrows indicate the time at which injections were performed. M indicates months. Pregnant test was performed only for women not in menopause.

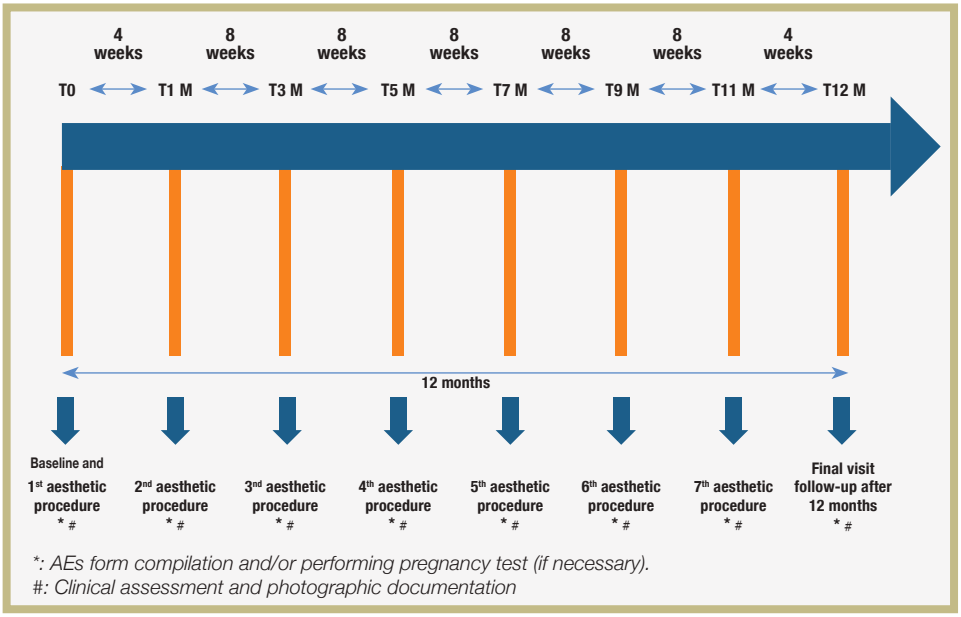

Table 1.

EXCLUSION CRITERIA

Dependent on the volunteers' characteristics

- Pregnancy, lactation
- Subjects not in menopause with no adequate contraceptive precautions
- Use of other skin treatments for aesthetic correction in the area of interest in the 12 month prior to study start
- Use of permanent fillers in the past
- Sensitivity to the product or its ingredients
- Participation to similar studies in the past three months

Dependent on clinical conditions

<u>Dermatological disease</u>

- Presence of cutaneous disease on the tested area
- Recurrent herpes in the facial of labial areas
- Clinical and significant skin condition in the test area (dermatitis, psoriasis, active eczema)

<u>General disease</u>

- Diabetes, endocrine disease
- Hepatic, renal, cardiac or pulmonary disease
- Cancer
- Neurological or psychological disease
- Inflammatory/immunosuppressive disease
- Drug allergy

Dependent on pharmacological treatment

- Use of anti-inflammatory, anti-histaminic, topic and systemic corticosteroids, narcotics, antidepressant, immunosuppressive drugs
- Assumption of drugs able to influence test results in the opinion of the Investigator
- Other drugs not mentioned above, can be authorized by the Investigator and must be reported

➜ Efficacy Assessments

Each subject was carefully clinically evaluated at first visit (T0, basal conditions) to check her compliance with the inclusion/exclusion criteria. Clinical assessments were then performed at T1, T3, T5, T7, T9, T11 and T12 months.

Nasolabial folds and marionette lines were rated according to the Wrinkle Severity Rating Scale (WSRS) (17) **(Table 2)** while cheek ptosis was rated according to the Facial Volume Loss Scale (FVLS) photographic scale **(Table 3)**.

Photographic documentation was recorded at each study time for all the subjects, using a digital camera. The pictures were taken with standardized methods to ensure reproducibility, both from dx and sx side with an angle of 45°, at the same distance from the subject and with the same intensity of illumination. The volunteers were asked to keep still, with open eyes and relaxed facial muscles.

➜ Safety Assessments

Tolerance of the product was assessed by evaluating local expected reactions induced by the injection procedures and by checking for the presence of adverse events throughout the study.

For this specific study, Adverse Events (AE), Serious Adverse Events (SAE), Adverse Device Effects (ADE) and Serious Adverse Device Effects (SADE) were considered. All adverse events (if any) had to be reported in the case report form (CRF) and the Investigator had the responsibility to proper document these eventual AEs (any kind) and had the power to decide whether continue or interrupt (temporary or definitively) the treatment.

WSRS SCALE

Grade	Definition
1 (absent)	no visible nasolabial fold; continuous skin line
2 (mild)	shallow but visible nasolabial fold with a slight indentation; minor facial feature
3 (moderate)	moderately deep nasolabial folds; clear facial feature visible at normal appearance but not when stretched
4 (severe)	very long and deep nasolabial folds; prominent facial feature; <2mm visible fold when stretched
5 (very severe)	extremely deep and long nasolabial fold, detrimental to facial appearance; 2-4 mm visible V-shaped fold when stretched

Table 2

FVLS SCALE

Grade	Definition
1	Mild flattening or shadowing of one or more facial regions (including the cheek, temple, preauricolar and periorbital areas). No prominent bony landmarks. No visibility of underlying musculature
2	An intermediate point between grade 1 and grade 3
3	Moderate concavity of one or more facial regions (including the cheek, temple, preauricolar and eriorbital areas. Prominence of bony landmarks. May have visibility of underlying musculature
4	An intermediate point between grade 3 and grade 5
5	Severe indentation of one or more facial regions (including the cheek, temple, preauricolar and periorbital areas). Severe prominence of bony landmarks. Clear visibility of underlying musculature

Table 3

Results

Thirty healthy female volunteers entered the study. Of these, 7 did not complete the study for personal reasons not related to the treatment. All the data from these 7 subjects were excluded from the analysis. The 23 subjects included in the analysis ranged in age from 50 to 73 years, with a mean of 63 years. For all the subjects an improvement of at least 1 grade was achieved in the WSRS or FVLS scales. Specifically, the results obtained relative to the WSRS scale are reported in **Figure 3**. This figure reports the mean value for all the subjects, indicating that at Visit at T5 there is the evidence of amelioration, then maintained throughout the entire period up to the last visit

SAFETY ANALYSIS

	N of subjects	% of total events
No events	4	17.4
Expected	15	65.2
Small bump	4	17.4
Unexpected	0	0
Serious Adverse Event (SAE) and/or Adverse Device Event (ADE) and/or Serious Adverse Device Event (SADE)	0	0

No events: no reported side effect
Expected refers to light ecchymosis lasting 5-7 days
Small bump was lasting 7-10 days
Unexpected refers to any other side effects not related to injection

Table 4

at T12. Importantly, this significant amelioration is achieved independently from the initial severity in the scale, as shown in panel B of the same Figure, reporting the results at T0 and at T12.

Similarly, the FVLS data reported in **Figure 4** indicate a pattern similar to the one obtained for WSRS. In this case, the improvement was anticipated and already at T3.

The clinical and instrumental evaluation of the efficacy was also reported in the self-evaluation performed by the volunteers. In fact, at T12, 95% and 99% of the subjects indicated an amelioration

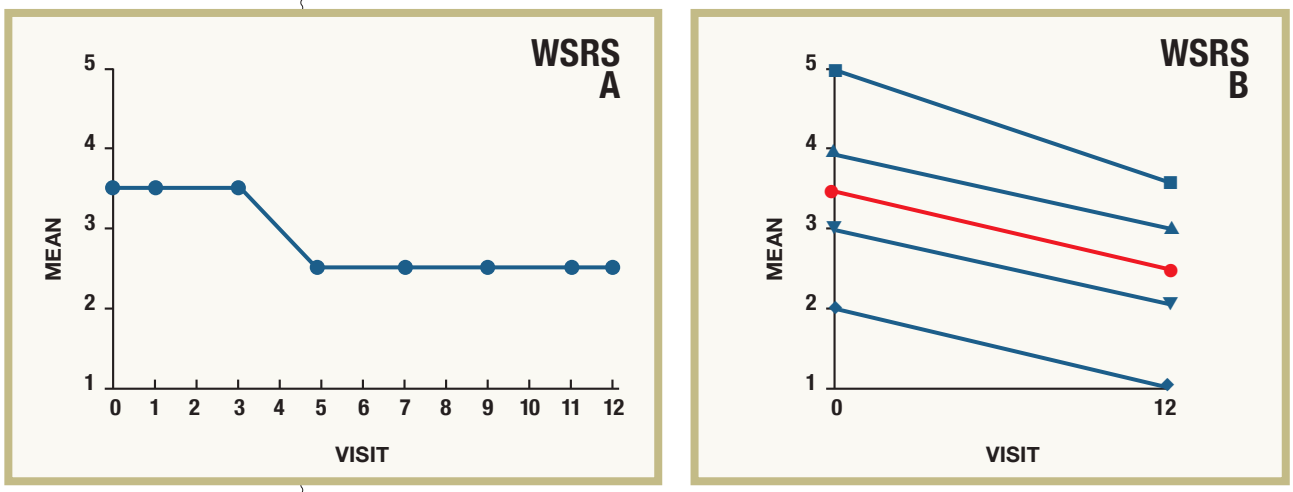

Figure 3.
Mean WSRS values. Panel A: Mean WSRS values at each visit (from T0 to T12). Panel B: mean values relative to the initial severity scale value. The curve in red represents the mean values independent from the initial severity scale value.

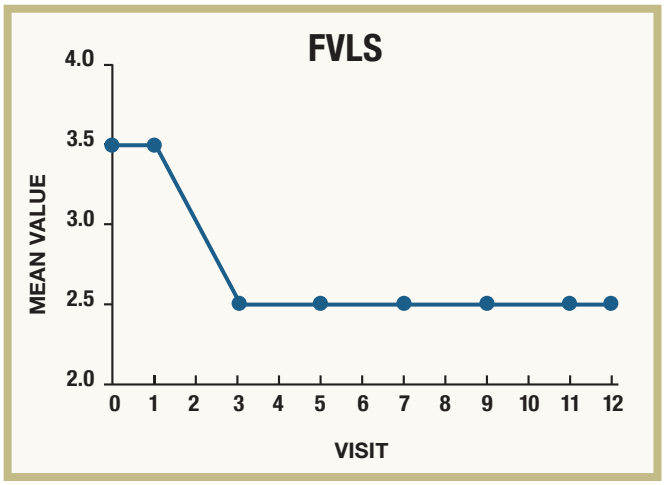

Figure 4.
Mean FVLS values at each visit (from T0 to T12) relative to all the participating subjects.

for WSRS and FVLS, respectively, in line with the objective data shown before.

No adverse events were reported during the entire study, besides the ones expected and imputable to the injection procedures that rapidly disappeared and did not cause any stop or delay in the subsequent treatments. **Table 4** reports the data evaluated by the Investigator proving that none of the volunteers reported unexpected/serious adverse events. Approximately 20% of subjects did not show any side effect (even those related to injection procedure) and the majority had light ecchymosis lasting 5-7 days due to injection procedure. Finally, only 4 out of 23 subjects had small bumps lasting 7-10 days again due to injection procedure. The objective evaluation of the safety was also corroborated by the volunteers, who at the end of the study considered the tolerance optimal and/or very good.

Discussion

This study aimed at evaluating the long-lasting tolerance and efficacy of a well characterized and efficacious HA-based injectable. Intradermal injection of the same formulation, was in fact reported to be effective in several reports with a very good safety profile (11–13). Here we provide evidence on the ability of the formulation not only to maintain efficacy when tested for longer period, but also, and perhaps more importantly, to maintain the very good safety profile shown in short term evaluations. The subjects enrolled in the present study had at the initial visit different level of skin deterioration, ranging from a value of 2 (mild effects) in the WSRS scale to 5 that is the highest possible value for this scale. Even in the presence of very severe damage to the facial skin, the injections of the studied medical device were able to modify the skin deterioration with at least one grade scale improvement at the end of the observation period. This means that the studied product not only can show benefit for mild skin deterioration, but its effects could be appreciated also in very severe skin deterioration conditions. The beneficial effects were observed quite early in the treatment (at 3 or 5 months according to WSRS and FLVS scales respectively). This positive effect was maintained up to the last evaluation done at 12 months. One of the potential limitations of repeated injections of HA based products is tolerance and safety. The discomforts due to the injection procedures resolved rapidly. During the entire period of the study no serious adverse events were recorded by the Investigators and the judgement of the volunteers was extremely positive, also regarding the tolerance of the product. This is an important point considering that safety was one of the main objective of the study.

Conclusions

In conclusion, this study not only reached the primary aim that was proving the safety of long-term treatments of high and low molecular weight hyaluronans, but also confirmed its efficacy and tolerance in ameliorating facial wrinkles. This is an important result that open the way for longer yet safe treatments, at least for facial skin ageing, although the data reported could be potentially extended to other body areas.

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Topical testosterone cream: dosing, safety, efficacy and rationale of use

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SUMMARY

Testosterone is an androgen hormone, produced by the ovaries, the adrenals and the adipose tissue, that reaches high plasma levels in childbearing age. All major organs have testosterone receptors. The testosterone-receptor interaction induces androgen-mediated somatic (brain, muscle, bone), sexual and reproductive functions. Androgens reach their plasma peak around 20 years, then present an age-dependent decline. At 50, the woman has lost about 50% of testosterone. After bilateral ovariectomy testosterone is reduced by 80%. This reduction, worsened by estrogen deficiency, contributes to systemic and genital aging, and to the "low grade inflammation" typical of post-menopause. The genitourinary syndrome of menopause (GSM) includes vaginal (dryness, burning, itching, leucorrhea); sexual (vaginal dryness, coital pain/dyspareunia, sexual dysfunctions) and urinary (urgency, dysuria, cystitis) symptoms and underlies a chronic and destructive inflammatory process involving the full thickness genitourinary structures. The vestibular-vaginal application of testosterone allows for the enhancement of a powerful local, anti-inflammatory, and reconstructive action, mediated by the activation of androgen receptors (AR), which are maximally expressed in the vestibular area and in the labia minora. To date, there is no cream drug, approved by AIFA and EMA, based on testosterone; therefore, it must be made through the pharmaceutical compounding. The goal of this work is first to analyze the criteria for prescribing a topical testosterone-based galenic drug, focusing on dosing and efficacy. Second, to discuss why testosterone can optimize therapeutic choices for the genitourinary syndrome of menopause. A special focus is dedicated to: 1) the topical application of testosterone in cream; 2) the criteria to select the appropriate doses within the physiological range; 3) the standardization of the dosage through special dispensers; 4) safety and advantages of local genital therapies. The compounding testosterone of vegetable origin in cream plays a precise and non-replaceable role in women's health, especially after menopause where testosterone deficiency causes vulvar, vestibular, vaginal, and sexual symptoms secondary to the androgenic insufficiency.

KEYWORDS

androgens, testosterone, genitourinary syndrome of the menopause (GSM).

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LIST OF ABBREVIATIONS

AIFA	Italian Medicines Agency
AIS	Androgen Insufficiency Syndrome
AR	Androgen Receptor (Androgenic Receptor)
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
EMA	European Medicines Agency
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
GSM	Genitourinary Syndrome of the Menopause
HSDD	Hypoactive Sexual Desire Disorder
LPS	Lipopolysaccharide
NBP	Good Preparation Standards (of Medicines in Pharmacy)
VVA	Vulvar and Vaginal Atrophy

INTRODUCTION

Why is the topical application of testosterone compounding cream a valid aid for women after menopause in the therapy of genitourinary syndrome of menopause (GSM)? What is the bio-evidence supporting this treatment option? Why does the doctor need compounding preparations? What are the dosage and efficacy criteria for prescribing a topical testosterone compounding drug?

This work examines all these aspects, relevant to good clinical practice, to make a rigorous contribution to doctors and patients, and to be a reference point for the use of testosterone-based compounding drugs.

Androgens, especially testosterone, are essential sex hormones for women's health and well-being. These hormones, however, are still underappreciated in their potential therapeutic role, especially after menopause [1,2].

Androgen receptors were detected throughout the genitourinary tract by western blot, immunohistochemistry, ligand binding and gene expression. They are well present in all vulvar tissues: in the large and small labia, in the clitoris, in the vestibule, as well as in the three layers of the vaginal mucosa (epithelium, lamina propria and muscular). Androgen receptors appear to be particularly abundant in epidermal keratinocytes and dermal fibroblasts. They are also abundant in the dermis of the labia minora and vestibule, where they are more numerous than in the vagina. In addition, androgen receptors have also been found in Bartholin's glands. [3]

Genitourinary Syndrome of the Menopause (GSM) [4] includes vulvovaginal symptoms (dryness, burning, itching, leucorrhoea); sexual (vaginal dryness, coital pain/dyspareunia, sexual dysfunction) and urinary (urgency, dysuria, cystitis) symptoms **(Fig. 1)**.

This symptomatic comorbidity is underpinned by a chronic and destructive inflammatory process that involves full-thickness genitourinary anatomical structures. GSM includes vulvovaginal atrophy (VVA) and parallel involution of urethral, bladder and corpora cavernosa structures, as well as muscle-connective structures of the pelvic floor [5].

The 2019 Global Consensus [6] highlights a significant change compared to the 2014 Consensus [7] where experts had sided "against" both testosterone therapy and, and even more, compounding preparations due to the absence of safety data.

The current language choice ("wording") states that "therapy with "biodentic" testosterone compounds cannot be recommended for the therapy of HSDD, i.e. for the lapse of desire, due to the lack of data on safety and efficacy, "unless an authorized equivalent preparation is not available" (Expert opinion). In this case, the compounding drug must be prepared by the pharmacist according to the Good Manufacturing Practice (GMP), which in Italy is equivalent to saying prepared in the pharmacy according to the Good Preparation Standards (NBP) of medicines. Furthermore, dosages "should be limited to reaching plasma levels within physiological limits for premenopause" [6].

Therefore, the use of testosterone-based compounding preparations is appropriate and in line with the 2019 Global Consensus, especially when intended for the treatment of GSM, to reduce the genital biological components that are important etiological factors both in the decline of post-menopausal libido (HSDD) and in the reduction of genital arousal, pleasure, and orgasmic intensity. A therapeutic choice that can offer patients even more significant and appreciated results if used in synergy with systemic hormone replacement therapy, in a personalized way.

The aim of this work is to analyze why testosterone has a crucial

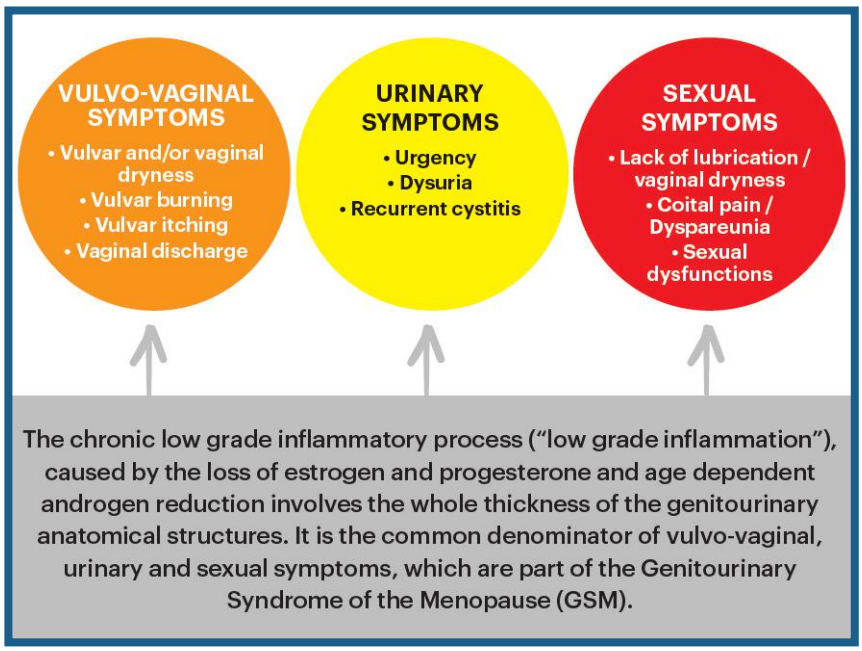

Figure 1.
Genitourinary Syndrome of the Menopause (GSM) and anatomical-functional consequences

Hormone	Concentration (pg/mL)		
	Childbearing age	Natural menopause	Induced menopause
Estradiol	100-150	10-15	10
Testosterone	400	290	110
Androstenedione	1900	1000	700
DHEA	5000	2000	1800
DHEAS	3.000.000	1.000.000	1.000.000

Table 1.
Average hormone levels in women. Values converted to pg/mL. Androgens are much more present in a woman's body than estrogen, except for pregnancy. Courtesy of Professor Rogerio Lobo, 1999

role in the therapy of GSM, thanks to its trophic, anti-inflammatory, sexual and reconstructive effect on the vulva, vulvar vestibule, and vagina, with clinically interesting effects also at the urethral level. An in-depth analysis will be conducted on the topical application of testosterone cream and on the criteria to guarantee the doctor and the patient effective doses within the physiological ranges, with particular attention to safety data and the advantages of local therapies.

Rationale for the use of testosterone cream in menopausal women

Androgens have four main functions: trophic, sexual, anti-inflammatory and reconstructive [8,9].

Testosterone has a pro-hormone role. Together with its metabolite dihydrotestosterone (DHT), it is the most potent endogenous androgen receptor (AR) ligand [10]. It is produced, in women of childbearing age, for about a quarter by the ovary, a quarter by the adrenal gland and the remaining part in peripheral tissues starting from various precursors [11].

Androgens reach their peak in plasma at age 20 and decrease with age. During menopause, decreased ovarian activity leads to a reduction in endocrine function, which also affects Leydig cells located in the hilum of the ovaries and secreting testosterone. The woman at age 50 has lost about 50% of testosterone and 60-70% of DHEA. The gradual age-related decline of androgens:

- contributes to systemic and genital aging and, in parallel to post-ovarian exhaustion estrogen deficiency;
- participates in low-grade systemic inflammation typical of post-menopause and in the parallel involution of the urogenital organs and pelvic floor muscles [12].

The reduction of plasma testosterone concentration has been confirmed by chromatographic and spectrometric analysis methods [13-18].

Bilateral oophorectomy also reduces testosterone, whose plasma value can drop by 80%.

Anatomical, physiological, endocrinological and pathological bio-evidence indicates that androgens:

- reach high plasma levels in childbearing age, higher than estradiol levels **(Table 1)**, with the exception of pregnancy, in which at term estrogens reach very high levels, between 30,000 and 40,000 pg mL;
- have cell receptors in major organs [3];
- interact with their own receptor by inducing somatic androgen-mediated functions (among which brain, muscle and bone functions stand out), sexual and reproductive functions [19,20]. Recent studies indicate that the immunomodulatory effects of testosterone during the menstrual cycle are closely related to the reproductive environment [21,22];
- when they are deficient in the body they cause precise signs and symptoms of androgen deficiency (androgen insufficiency syndrome or Androgen Insufficiency Syndrome – AIS) [23] **(Box 1)**.

Mechanisms of action of testosterone

Testosterone acts by three mechanisms:

- such as testosterone, on muscle, bone and brain dopaminergic pathways, mediating extraversion, appetite and pleasure pathways ("seeking-appetitive-lust system"), motor skills and muscle trophism; has a peculiar role in the modulation of ovulation and apoptosis of non-dominant follicles, with different effects depending on plasma and intraovarian levels [22,23];
- converted to estradiol, thanks to the aromatase enzyme, it also acts on neurons and glia, and promotes the construction of bone tissue;
- activated by dihydrotestosterone (DHT) by the enzyme 5-alpha-re-

SIGNS AND SYMPTOMS OF ANDROGEN DEFICIENCY

The genital and extragenital signs and symptoms of androgen deficiency most frequently reported after menopause to consider at least local androgen therapy include:

SYMPTOMS UNDERLYING ANATOMICAL AND FUNCTIONAL CHANGES IN UROGENITAL STRUCTURES

- Generalized hypoactive sexual desire, in the component underlying the genitourinary syndrome of menopause
- Less excitability
- Lower sexual responsiveness
- Vaginal dryness
- Coital pain/superficial dyspareunia
- Orgasm disorders, with difficulty reaching it
- Cystitis after intercourse

SYSTEMIC SYMPTOMS

- Asthenia
- Reduced energy and vitality
- Reduced assertiveness
- Hypotonic ("slumped") posture
- Anxiety and depression
- Loss of strength, muscle mass and competence, underlying inflammation and destruction of muscle tissue (sarcopenia)

GENITAL SIGNS

- **Vulvar:**
  - ➜ vulvar dystrophy
  - ➜ clitoral and/or vulvar hypotrophy
  - ➜ vulvar lichen sclerosus
- **Related to the elevator muscle:**
  - ➜ hypotonia of the elevator muscle, with depletion of the muscular component, accentuated in women who have had vaginal deliveries
- **Vaginal signs, in etiological synergy with estrogen deficiency:**
  - ➜ high vaginal pH (6.5 – 7)
  - ➜ signs of vaginal dystrophy/atrophy: pale colour, mucosal thickness very reduced with ease to the petechiae, dystrophy of the vaginal mucosa

Box 1.
Signs and symptoms of androgen deficiency

ductase, it has a role of particular interest for the gynecologist, thanks to the powerful anti-inflammatory action, well demonstrated at the vaginal level [24], in addition to the trophic action, sexual and reconstructive at the vaginal, vulvar, cavernous bodies and pelvic floor muscle structures.

Applications of topical testosterone cream

In general, topical testosterone cream is recommended for women with GSM who report genital sexual symptoms (vulvar and vaginal dryness, pain during intercourse, difficulty reaching orgasm, post-coital cystitis, and related lapse of desire) as a particularly important component of postmenopausal urogenital dystrophy, at the individual and couple level. Women with early, spontaneous or iatrogenic menopause, from bilateral oophorectomy, for example for endometriosis, or after chemotherapy or radiotherapy (pelvic or total body) for non-hormone-dependent neoplasms, such as leukemia or lymphomas, or cer-

vical squamous carcinomas due to papillomavirus can benefit even more [25]. It remains contraindicated in women who have had hormone-dependent breast, endometrial or ovarian cancer.

Testosterone is therefore a powerful biological anti-inflammatory and reconstructive architect. Its use at the vaginal level was brilliantly considered by Maseroli and collaborators, in an excellent study [24]. The authors emphasize that GSM is underlying chronic tissue inflammation and have evaluated, in vitro, on vaginal smooth muscle cells of women the anti-inflammatory and immunomodulatory effect of DHT (activated form of testosterone and more powerful agonist of androgen receptor).

DHT applied in vitro to vaginal smooth muscle cells pretreated with a strong inflammatory stimulus, lipopolysaccharide (LPS), has been shown to significantly reduce the synthesis of both messenger RNA and corresponding inflammatory biomarkers, including IL-1RA, IL-2, IL-5, IL-15, FGF, VEGF and TNFα, and increases the synthesis of anti-inflammatory cytokines, thus confirming the tissue anti-inflammatory role of testosterone in women.

A laboratory evidence well correlated with the clinical experience of over forty years of use of local testosterone at the genital level to treat vulvovaginal atrophy and related symptoms (formerly VVA, now GSM) in post-menopause, by the author of this article (AG).

It is interesting the clinical annotation, by particularly attentive partners, who have reported an unexpected and welcome "invisible plus", after two-three months of application of testosterone cream on the vulva by the partner: the return of genital sexual perfume lost with menopause. Observation that correlates with the well-known effect induced by testosterone on the secretion of sebum and pheromones at the vulvar level, with consequent increase in olfactory and gustatory allure.

Thanks to this powerful anti-inflammatory and cellular reconstructive action of testosterone, future synergies with pelvic floor physiotherapy, laser, radiofrequency, and oxygen therapy are highlighted.

Efficacy and safety of testosterone therapy

Since 1946, evidence has accumulated that androgens, particularly testosterone, are beneficial to the health of postmenopausal women [1, 26,27]. A recent major systematic review and meta-analysis shows that testosterone administered non-orally (e.g. via transdermal patches or cream) effectively improves sexual function in natural and surgical postmenopausal women with low sex drive regardless of whether they are simultaneously using estrogen and without causing adverse effects on the lipid profile [28]. It is widely used in the form of compounding preparation, especially in the United States, but has met strong resistance in the academic and scientific community with the greatest negativity highlighted in the Endocrine Society document of 2014 [7], where the key word was "against", against all use. An authoritative work indicates that there are two limiting factors to the development of a testosterone-based drug for women [29]:

- "unproven concerns" means undocumented concerns, the result of hormonephobia rather than a rigorous and calm assessment;
- "Inconsistent regulatory barriers and challenges": inconsistent regulatory barriers which significantly hinder the development and proper evaluation of relevant clinical trials on testosterone.

The 2019 Global Consensus [6] states instead that systemic therapy with testosterone at doses close to premenopausal physiological doses:

- does not increase mammography density (Level 1, grade A);
- does not impact the risk of breast cancer (assessment of short-term transdermal testosterone patch therapy) (Level 1, grade A);
- is not associated with major adverse events (Level 1, grade A), with safety assessments available for up to 24 months of use (Level 1, Grade A).

If systemic testosterone therapies have excellent safety profiles for up to 24 months, it is reasonable and appropriate to assume that local therapy at low doses is even safer.

Despite substantial evidence regarding safety, efficacy and clinical use, access to testosterone therapy for the treatment of HSDD in women remains a significant unmet need [30]. To date, there is no medicinal specialty in testosterone cream, for genital use, approved by AIFA and EMA (with the exception of the Intrinsa® patch, which was subsequently withdrawn for lack of prescriptions and use). The only testosterone-based drug approved for women is AndroFeme®1, a cream registered in 2020 in Australia and used to treat postmenopausal women with hypoactive sexual desire dysfunction.

Therefore, pharmaceutical galenic is an important tool for doctor and patient to meet this "unmet need".

Compounding preparations in cream based on testosterone propionate or vegetal origin testosterone

Topical compounding preparations of testosterone have been widely used for decades in outpatient settings, with considerable satisfaction from women and couples, but have received little attention in the

scientific literature. Only recently has new attention been paid to the role of testosterone in women's health, especially after menopause [31].

Testosterone is administered for therapeutic purposes in two forms:

- **ester:** Testosterone esters are considered pro-drugs of the hormone itself but have different chemical and pharmacokinetic characteristics. They are produced synthetically, and their administration aims to lengthen the plasma half-life of testosterone, reducing the dosage frequency. The half-life increases proportionally to the length of the carbon chain of the acid used for the esterification reaction. The propionate ester, for example, has a half-life of about 20 hours and an elimination time of more than 4 days, while the half-life of enanthate is 108 hours and that of undecanoate of over 500 hours [32];
- **bioidentical:** it is obtained by semisynthesis from a plant matrix containing steroid-based molecules (for example, diosgenin from Dioscorea villosa); it has a plasma half-life of less than 12 hours and is totally eliminated from the body within 24 hours.

Since there is a lack of testosterone-based medicinal specialties that can be prescribed for women, the only way to obtain them today is through the pharmaceutical compounding preparation, whose prescription is limited to the endocrinologist, urologist, andrologist, gynecologist and oncologist as reported in AIFA determination no. 199 of 5 February 2016.

The prescription of testosterone cream is legitimized by two testosterone-based medicinal products (Testovis® and Enant®) on the basis of Article 5 of Law no. 94, 8 April 1998, according to which, in paragraph 1, doctors may prescribe compounding preparations exclusively based on active ingredients described in the pharmacopoeias of the countries of the European Union or contained in industrially produced medicines whose trade is authorized in Italy or in another country of the European Union. The same article defines, in paragraph 5, that the provisions relating to paragraphs 3 and 4 (including the obligation of informed consent, the indication in the prescription of the special needs justifying the use of the extemporaneous prescription and the name of the patient by means of an alpha-numeric code) shall not apply where the medicinal product is prescribed for therapeutic indications corresponding to those of authorised industrial medicinal products based on the same active substance.

The compounding preparations of testosterone for vulvovaginal use currently most used in Italy are two.

Vegetal origin Testosterone

It is commonly formulated in Pentravan® transdermal cream, at a dosage of 2.8 mg per day, the same as the Intrinsa® patch with indication for hypoactive sexual desire disorder (HSDD). The patch contained 8.4 mg of testosterone and was replaced every three days, releasing 300 mcg of testosterone in 24 hours. The intake of testosterone administered as Pentravan® cream at a dose of 3 mg per day to menopausal women via vulvovaginal application is completely eliminated within 24 hours [18]. The daily application dosage of testosterone cream can be reduced up to 10 times, to arrive at the application of 0.3 mg (i.e. 300 mcg) of testosterone per day canceling the share of systemic absorption of the hormone [33].

The optimization and standardization of the galenic drug takes place through the use of a cream base (Pentravan®) that favors the transdermal penetration of testosterone through mono- and double-layer liposomes [34]. Pentravan® is a liposomal matrix vehicle ideal for the application of sex hormones at vulvar, vestibular, and vaginal level; it is free of petrolatum, petroleum jelly, propylene glycol, parabens and allows the hydration of the mucosa thanks to vegetable liposomes and pH 4-5.5.

The compounding preparation, consisting of bioidentical hormones within these bases, is administered thanks to specific Topi-CLICK® pharmaceutical dispensers, which allow a standardized delivery of the formulation. Topi-CLICK® consists of a transparent pharmaceutical polymer, approved by FDA, able to completely block UVA and UVB rays. The device reduces the risk of contamination, as it has two caps, one perforated for the dispensing of the cream and one that acts as a lid. The dispensing of the preparation takes place by a rotation of the colored base which, during movement, stops by emitting a click. Topi-CLICK® is available in different formats:

- 5 mL, which delivers 0.05 mL per rotation;
- 35 mL, which delivers 0.25 mL per rotation;
- 140 mL, which delivers 0.5 mL per rotation.

Testosterone propionate

The 1% or 2% compounding formulation, in stringy vaseline just enough at one hundred grams (therefore 10 or 20 mg per gram of cream), is consolidated in the practice of galenic formulations of clinical use in gynecology for more than 50 years.

Given the long half-life of testosterone in the ester form, this ointment should usually be applied in "minimal amounts", to minimize absorption and possible systemic effects. The ointment should be taken with the fingertip of the index finger, in the amount of about one centimeter wide by a millimeter thick, and then applied to the vulva and vestibule. Pre-

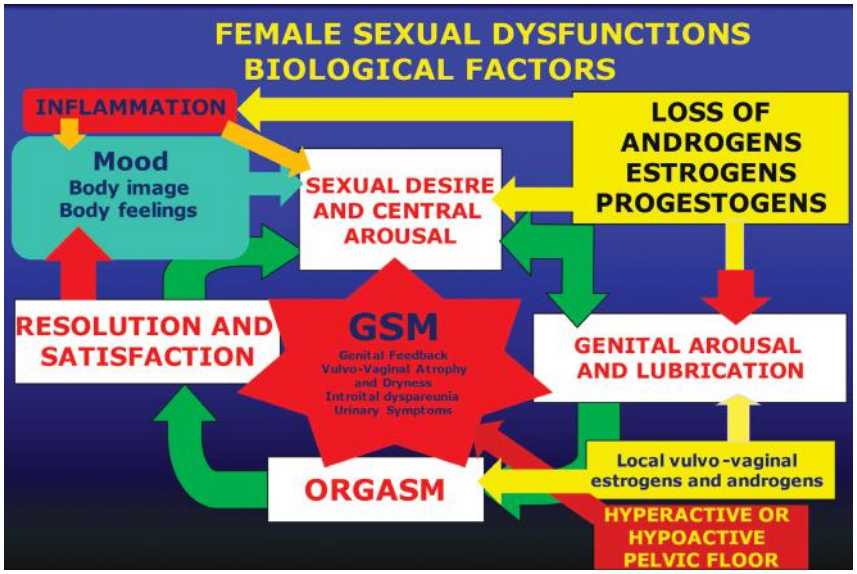

Figure 2.
Female sexual circuit and main biological factors. Favorable effects of local, vulvovaginal, androgenic therapies to reduce chronic-tissue inflammation associated with GSM (Genitourinary Syndrome of the Menopause) consequently acting favorably on the entire physical-sexual response.

cisely because of the long half-life, after the attack phase of about 15 days, a vulvo-vaginal application twice a week was recommended, to avoid summing effects and side effects such as acne, oily skin and hair and, more rarely, hypertrichosis or hirsutism. However, since the estimate of the "minimum amount" is subjective, the variability on the amount of ointment actually administered per day and absorbed is very wide.

When and how to administer testosterone compounding cream

The physiological production of testosterone occurs in women, as well as in men, with a circadian rhythm and decreases with age from the age of 20. According to the U.S. National Institutes of Health, women over the age of 60 have a baseline total testosterone level of 35 ng/dL.

The plasma concentration of testosterone in women presents a single acrophase in the very early hours of the morning and then maintains a baseline level throughout the rest of the day [35]. It is therefore optimal, based on this data, to consider a morning administration for both products. In good clinical practice, it is good to suggest to the patient to test the drug, applying a click of cream with the finger at the level of the pubis, once a day, for a week. If no adverse reactions appear, continue by applying a first click on the labia, half by side (not on the clitoris, unless you have to treat a severe atrophy, to avoid unwanted increases in volume), and a second click at the vaginal entrance and, with the finger, on the anterior vaginal wall, to optimize the effectiveness also at the urethral level.

After three months of treatment, the patient should be re-examined. The maintenance dose is one application twice a week, for example on Mondays and Thursdays, or three, to be varied according to the judgment of the treating gynecologist.

Directions

According to the Global Consensus 2019 [6], the main indication for systemic testosterone therapy remains hypoactive sexual desire (HSDD), when severe personal distress occurs. The recommended dose approaches physiological plasma concentrations of testosterone in pre-menopausal women, as demonstrated with the testosterone patch. It has beneficial effects not only on desire, but on all other aspects of sexual function [6]. However, GSM is the anatomical factor that most contributes to the suppression of desire, due to negative genital feedback **(Fig. 2)**, and the disappointing sexual response that many postmenopausal women complain about. GSM affects the entire reproductive biological component of the sexual response. Given these premises of bio-evidence, according to the author (AG) it is appropriate to consider GSM as the main indication for testosterone therapy at least locally, at vulvar, vestibular, and vaginal level.

The compounding drug based on testosterone, propionate or of vegetable origin, can therefore be indicated for the treatment of GSM, especially when the patient complains of a dominant sexual component, which affects sexual identity, in its genital dimension (the patient complains of no longer feeling woman), the entire circuit of sexual function (drastic decrease in desire , difficulty of physical arousal, low intensity of orgasm which is also more difficult to achieve) and the same sexual relationship of the couple (sexual difficulties with the partner).

The application of the hormone on the vaginal vestibule allows a powerful local, anti-inflammatory and reconstructive action, mediated by the activation of androgen receptors (AR) maximally expressed in the clitoral area, vestibular, in the labia minora [3, 36] and on the anterior vaginal wall.

Finally, the vulvar and vaginal administration of testosterone may be beneficial for the potential systemic release of the drug, always depending on the dose used. It should there-

fore be carefully considered, for the dual aspects:

- positive, in case of loss of sexual desire, which can be improved in its biological component by testosterone;
- negative, in case of sensitivity of skin and hair appendages to the androgenic effects of testosterone, with seborrhea, acne, hypertrichosis or initial hirsutism, and more fragile and thin hair.

Anatomical conditions that favor absorption include a large contact surface with the drug, a rich network of arterial and venous vessels, and a high level of permeability due to the absence of the stratum corneum in the mucosa [37], especially in the first treatment period if the vaginal mucosa is very atrophic. Systemic absorption is reduced with improvement of mucosal trophism.

Examinations and diagnostic insights

Also according to the 2019 Consensus, approved by the major scientific societies worldwide, it is appropriate to measure total plasma testosterone, with great accuracy and reproducibility, using liquid/gas chromatography or mass spectrometry (grade B) [6]. It is advisable to dose testosterone both before treatment, to exclude elevated levels at baseline, and during treatment to exclude supraphysiological levels (Expert Opinion).

For GSM, vaginal pH is an easy element of evaluation, measurable and repeatable, to evaluate both the basal state of trophism, and the progress of therapy on trophism itself. Its measurement is independent operator. Colpocytological examination, at baseline and follow-up, can evaluate the percentage of basal, parabasal and superficial cells, at time zero and 6 months after the start of therapy.

The Female Sexual Function Index [38] is the most recognized test worldwide to assess sexual function at time zero, in which GSM is diagnosed; to be repeated, in the opinion of the clinician, after 3-6 months of androgen therapy on the vulva and vagina.

Benefits of using vegetal origin testosterone

The greater possibility of dosing a drug with local action also allows to better evaluate both the personalization of use, and the short and long-term effects. For plant-based testosterone, the use of an approved dispenser allows to evaluate doses and clinical impact on the individual patient much better.

Free testosterone, together with its metabolite DHT, is the most potent endogenous ligand for androgen receptor (AR) [15] and is effective at low doses; the elimination time within 24 hours allows daily administration without risk of overdose. The peak of maximum concentration at 3 hours after administration allows to reproduce the physiological circadian curve of the hormone, whose acrophase is detected in the early hours of the morning [11]. Discontinuation of therapy coincides with the cessation of drug administration. The plant origin is a guarantee of bioidentity, as the carbon of steroid structures in plants has the same isotopic composition as that which we introduce into our body through food [39,40].

In general, the bioidentical testosterone cream (more manageable and with softer action, compared to the ester) has an excellent appreciation, by the woman and the partner, also thanks to its invisibility and discretion. At clinical follow-up, the majority of ladies report an appreciated improvement in the softness of the tissues at the level of both the vulva and the vagina, the quality and quantity of lubrication, the quality of orgasm, and a return of desire, provided that there were no couple problems due to other factors and provided that finding a good physical intimacy was a personal desire of the woman, as well as the couple.

Some physiotherapists have reported a better response to rehabilitation therapy of the pelvic floor muscles, probably due to the trophic action on the striated muscles of the elevator of the anus, mediated by the great richness of androgenic receptors contained in that muscle [3,12].

As already pointed out, the most attentive partners have also reported a gradual and unexpected return of the genital "scent of woman", due to the probable reactivation of pheromone production by the vulvar sebaceous glands.

Side effects and contraindications

The side effects that can lead to discontinuation of the drug, in about 1% of patients, concern the feeling of "excessive swelling", of "discomfort", of unwanted excitability, sometimes of burning.

The woman may present acne, seborrhea, thinning / hair loss, hirsutism in case of excessive doses and / or high absorption.

Testosterone cream, vulvar and / or vaginal, remains contraindicated in case of hormone-dependent tumors (breast and adenocarcinoma of the uterus and ovary).

As a precaution, it is contraindicated in case of androgenetic alopecia or in the presence of other signs of previous hyperandrogenism, for example severe acne with "priming" of the androgenic skin receptor in childbearing age.

Conclusions

Androgens reach high plasma levels in childbearing age, higher than those of estradiol, and have cellular receptors in the main organs. The hormone-receptor interaction mediates somatic androgen-mediated functions (especially cerebral, muscular, bone), sexual and reproductive. Androgen deficiency causes definite symptoms. A growing body of scientific evidence explains their four main actions: nutritional, sexual, anti-inflammatory, and restructuring.

Testosterone compounding cream (propionate or vegetable extraction) offers numerous therapeutic advantages in GSM, with an effective and articulated trophic effect, at full thickness:

- on all tissue components of the vulva, well evident even to the naked eye after 3-6 months of local therapy;
- on the urethra and bladder, with improvement in urge incontinence;
- on the pelvic floor muscles, with enhancement of the benefits obtainable with physiotherapy.

There is also a significant improvement in sexual function, primarily in its vulvo-vaginal dimension.

The vulvovaginal administration of testosterone cream allows the gynecologist to personalize the therapy of genitourinary syndrome of menopause. These pharmacological interventions lead to great therapeutic results that are increasingly appreciated in the clinical field and that, for this reason, deserve to be substantiated definitively in controlled studies to be prescribed with conviction, for their effectiveness and safety, with full serenity and satisfaction of the woman and the couple.

Conflicts of interest

The author has collaborated with Alfasigma, Bayer, Fagron, Gedeon-Richter, Lolipharm, Shionogi, Theramex, Uriach as a speaker and / or consultant, in the two-year period 2021-2022.

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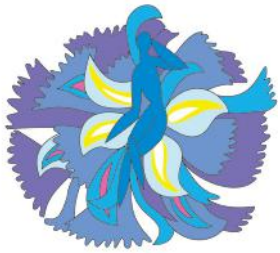
Topical agents for adequate skincare pre-post dermatological treatments: a review of the literature



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Agenti topici per un'adeguata skincare pre-post trattamenti dermatologici: una revisione della letteratura

• Norma Cameli[1] • Corinna Rigoni[2] • Alessandra M. Cantù[2] • Martina Silvestri[1] • Enzo Berardesca[3]

SUMMARY

In this article we review the role of some topical agents that can be used in the pre and post treatment phases in order to improve aesthetic outcomes, accelerate wound healing processes and reduce the onset of adverse effects, such as erythema and pigmentation changes.

A literature search was performed on MEDLINE / PubMed, EMBASE and Google Scholar to identify studies evaluating the effectiveness of the following active ingredients: hyaluronic acid, soluble collagen, niacinamide, saccharide isomerate, schisandra chinensis, bacterial lysates.

KEYWORDS
hyaluronic acid, soluble collagen, niacinamide, products for cosmetics

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INTRODUCTION

Aesthetic treatments that aim to reduce the signs of skin aging, improve texture, pigmentation or scarring, including chemical peels, lasers and therapeutic lights, are increasingly used and requested by patients all over the world. . Due to their reduced invasiveness, these methods are generally preferred by patients over invasive cosmetic surgery. These procedures act by causing controlled damage to the skin which subsequently leads to the activation of regeneration processes with the development of new tissue (epidermal and dermal) and improvement of the aesthetic appearance of the skin (1). Proper management of the pre-post treatment phases can reduce healing times and improve the outcome of aesthetic procedures (2). Generally, pre-post treatment skin care and the choice of the related topical agents is based on the professional's personal experience.

Pre-post operative skin care strategies aim to prepare the skin for the treatment it will receive, optimize the degree of hydration, control microbial growth, and protect the healing skin barrier. Generally, formulations in creams, ointments, serums or gels are used, which provide the skin with important factors that stimulate cell proliferation, migration and protein synthesis (3).

Maintaining a moist microenvironment is necessary for optimal skin healing; emollient and humectant agents retain moisture in the stratum corneum, maintain skin hydration and preserve skin barrier function, thus reducing itching and discomfort associated with wound healing processes.

INTRODUZIONE

I trattamenti estetici che hanno come scopo la riduzione dei segni dell'invecchiamento cutaneo, il miglioramento della texture, della pigmentazione o degli esiti cicatriziali, tra cui peeling chimici, laser e luci terapeutiche, sono sempre più utilizzati e richiesti dai pazienti in tutto il mondo. A causa della loro ridotta invasività, queste metodiche sono generalmente preferite dai pazienti rispetto agli interventi chirurgici estetici invasivi. Queste procedure agiscono determinando un danno controllato alla cute che comporta successivamente l'attivazione dei processi di rigenerazione con sviluppo di nuovo tessuto (epidermico e dermico) e miglioramento dell'aspetto estetico della pelle (1). Un'adeguata gestione delle fasi pre-post trattamento può ridurre i tempi di guarigione e migliorare l'esito delle procedure estetiche (2). Generalmente, la cura della pelle pre-post trattamento e la scelta dei relativi agenti topici, si basa sull'esperienza personale del professionista.

Le strategie di cura della pelle pre-post operatorie hanno l'obiettivo di preparare la cute al trattamento che dovrà ricevere, ottimizzare il grado di idratazione, controllare la crescita microbica, e proteggere la barriera cutanea in guarigione. In genere ci si avvale di formulazioni in creme, unguenti, sieri o gel, che forniscono alla pelle importanti fattori che stimolano la proliferazione cellulare, la migrazione e la sintesi proteica (3).

Mantenere un microambiente umido è necessario per una guarigione ottimale della cute; gli agenti emollienti e umettanti trattengono l'umidità nello strato corneo, mantengono l'idratazione della pelle e preservano la funzione di barriera cutanea, riducendo così il prurito e il disagio associati ai processi di guarigione delle ferite.

Methods

A computerized literature search was performed to identify studies evaluating the efficacy of the following active ingredients: hyaluronic acid, soluble collagen, niacinamide, saccharide isomerate, Schisandra chinensis, topical postbiotics. The search was conducted on MEDLINE/PubMed, EMBASE and Google Scholar.

Results

Hyaluronic acid. Hyaluronic acid (HA) is a glycosaminoglycan made up of two disaccharides and involved in various biological processes, such as cell differentiation, inflammation, wound healing, etc. The molecular weight of HA influences its penetration into the skin and its biological activity. Through a passive mechanism, HA which is highly hydrophilic, attracts water molecules and allows tissue hydration, contributing to osmotic balance and stabilizing the structure of the extra cellular matrix. Hyaluronic acid is one of the most effective and safe ingredients used in cosmetics. The properties of HA can be improved by the presence of other bioactive ingredients (eg plant extracts, vitamins, amino acids, peptides, proteins, minerals, saccharides, postbiotics, etc.). Cosmetic products, such as creams or lotions, which contain HA allow the skin to hydrate and improve elasticity, thus decreasing the depth of wrinkles (4). The application of formulations containing HA on the surface of the skin causes the formation of an occlusive layer, which by retaining the water molecules, hydrates the skin; moreover, the occlusive properties of HA can allow biologically active substances present in cosmetics to persist in the skin layers and facilitate their penetration into the epidermis. Studies have shown the effectiveness of some HA-based cosmetic products in protecting the skin from UV rays and in maintaining firmer skin, thanks to the potential antioxidant effect of HA (5). Many studies have shown the important role of HA in the epidermis and in particular in the dermis, in remodeling, tissue repair and healing processes. The characteristics of HA therefore make the cosmetics that contain it highly suitable for pre- and post-treatment skincare, ensuring an adequate level of skin hydration and facilitating healing processes.

Metodi

È stata eseguita una ricerca bibliografica computerizzata per identificare gli studi che valutano l'efficacia dei seguenti principi attivi: acido ialuronico, collagene solubile, niacinamide, saccaride isomerato, Schisandra chinensis, postbiotici topici. La ricerca è stata condotta su MEDLINE/PubMed, EMBASE e Google Scholar.

Risultati

Acido ialuronico. L'acido ialuronico (HA) è un glicosaminoglicano costituito da due disaccaridi e coinvolto in diversi processi biologici, come il differenziamento cellulare, l'infiammazione, la guarigione delle ferite, ecc. Il peso molecolare dell'HA influenza la sua penetrazione nella pelle e la sua attività biologica. Attraverso un meccanismo passivo, l'HA che è altamente idrofilo, attira le molecole d'acqua e permette l'idratazione dei tessuti, contribuendo all'equilibrio osmotico e stabilizzando la struttura della matrice extra cellulare. L'acido ialuronico è uno degli ingredienti più efficaci e sicuri utilizzati nei cosmetici. Le proprietà dell'HA possono essere migliorate dalla presenza di altri ingredienti bioattivi (es. estratti vegetali, vitamine, aminoacidi, peptidi, proteine, minerali, saccaridi, postbiotici, ecc.). I prodotti cosmetici, come creme o lozioni, che contengono HA permettono l'idratazione della pelle e il miglioramento dell'elasticità, diminuendo così la profondità delle rughe (4). L'applicazione di formulazioni contenenti HA sulla superficie della pelle determina la formazione di uno strato occlusivo, che trattenendo le molecole di acqua, idrata la pelle; inoltre, le proprietà occlusive dell'HA possono consentire alle sostanze biologicamente attive presenti nei cosmetici di persistere negli strati cutanei e facilitare la loro penetrazione nell'epidermide. Studi hanno dimostrato l'efficacia di alcuni prodotti cosmetici a base di HA nel proteggere la pelle dai raggi UV e nel mantenere una pelle più soda, grazie al potenziale effetto antiossidante dell'HA (5). Molti studi hanno mostrato il ruolo importante dell'HA nell'epidermide e in particolare nel derma, nel rimodellamento, nella riparazione dei tessuti e nei processi di guarigione. Le caratteristiche dell'HA, rendono pertanto i cosmetici che lo contengono, alta-

➜ **Soluble collagen.** Collagen is the main structural protein of connective tissues such as skin, tendons, ligaments and bones, and is the most common component of the extracellular matrix (ECM). It can have different origins, in the industrial sector generally collagen of bovine and porcine origin is used. Collagen has always been used in various cosmetic formulations as a natural moisturizing and humectant component for the skin; in fact, thanks to its high molecular weight, it cannot be absorbed by the horny layer of the skin and remains on the surface, thus keeping the skin hydrated (6). Studies have highlighted the anti-inflammatory and anti-aging properties of the hydrolyzed collagen tripeptide which, when applied topically, resulted in significant improvements in wrinkles, elasticity and skin density with a reduction in the skin accumulation of advanced glycated end products (AGE) at the week 4. In vitro studies revealed a preventive effect of topical collagen on AGE accumulation, denatured collagen production and reactive oxygen species in dermal fibroblasts. Furthermore, treatment with hydrolyzed collagen tripeptide demonstrated a reduction in the induction of matrix metalloproteinases by increasing the level of collagen 1 (7). Percutaneous administration of collagen resulted in increased histological deposition of collagen and elastin, with approximately 40% thickening of the epidermis, mainly of the spinous layer, 1 year after treatment (8).

➜ **Niacinamide.** Niacinamide, amide of vitamin B3 (niacin), has antipruritic, antimicrobial, vasoactive, photoprotective, sebostatic and lightening effects depending on its concentration. It is a component of important coenzymes involved in hydrogen transfer. Niacinamide is a well-tolerated and safe substance, widely used in cosmetics: the topical application of niacinamide has a stabilizing effect on the epidermal barrier function, which leads to a reduction in transepidermal water loss and an improvement in hydration (9). Niacinamide causes an increase in protein synthesis, has a stimulating effect on the synthesis of ceramides, accelerates the differentiation of keratinocytes and increases the levels of intracellular NADP. In skin aging, topical application of niacinamide improves skin texture, smoothes wrinkles and inhibits photocarcinogenesis. Studies have shown anti-inmente indicati nella skincare pre- e post-trattamento, assicurando un adeguato livello di idratazione cutanea e facilitando i processi di guarigione.

➜ **Collagene solubile.** Il collagene è la principale proteina strutturale dei tessuti connettivi come pelle, tendini, legamenti e ossa, e risulta il componente più diffuso della matrice extracellulare (ECM). Può avere diverse origini, in ambito industriale generalmente si utilizza collagene di origine bovina e suina. Il collagene è da sempre utilizzato in diverse formulazioni cosmetiche come componente idratante e umettante naturale per la pelle; infatti, grazie al suo elevato peso molecolare, non può essere assorbito dallo strato corneo della pelle e rimane in superficie, mantenendo così la pelle idratata (6). Studi hanno evidenziato le proprietà antinfiammatorie e antietà del tripeptide di collagene idrolizzato il quale, applicato topicamente, ha determinato miglioramenti significativi delle rughe, dell'elasticità e della densità della pelle con una riduzione dell'accumulo cutaneo dei prodotti finali glicati avanzati (AGE) alla settimana 4. Studi in vitro hanno rivelato un effetto preventivo del collagene topico sull'accumulo di AGE, sulla produzione di collagene denaturato e delle specie reattive dell'ossigeno nei fibroblasti dermici. Inoltre, il trattamento con il tripeptide di collagene idrolizzato ha dimostrato una riduzione nell'induzione delle metalloproteinasi della matrice aumentando il livello di collagene 1 (7). La somministrazione percutanea di collagene ha determinato un aumento della deposizione di collagene ed elastina a livello istologico, con circa il 40% di ispessimento dell'epidermide, principalmente dello strato spinoso, 1 anno dopo il trattamento (8).

➜ **Niacinamide.** La niacinamide, ammide della vitamina B3 (niacina), ha effetti antipruriginosi, antimicrobici, vasoattivi, fotoprotettivi, sebostatici e schiarenti a seconda della sua concentrazione. È un componente di importanti coenzimi coinvolti nel trasferimento dell'idrogeno. La niacinamide è una sostanza ben tollerata e sicura, molto utilizzata nei cosmetici: l'applicazione topica di niacinamide ha un effetto stabilizzante sulla funzione di barriera epidermica, che comporta una riduzione della perdita di acqua transepidermica e un miglioramento dell'idratazione (9). La niacinamide determina un aumento della sintesi proteica, ha un

flammatory effects in acne and rosacea patients. Due to its beneficial effects, niacinamide is a useful component in cosmetic products intended for the treatment of disorders of the epidermal barrier function, skin aging, pigmentation changes, inflammatory diseases such as acne, and in skin care that she underwent dermo-aesthetic treatments (10).

➜ **Saccharide isomerate.** Saccharide isomerate (SI) is a complex of mucopolysaccharide carbohydrates similar to that found in the stratum corneum of the skin and acts as an occlusive and humectant component. This active principle forms hyaluronic acid in the epidermis, causing an increase in the water content in the stratum corneum. SI binds strongly to the stratum corneum and can only be released through the peeling process, so it is very effective in moisturizing the skin, making it even smoother and reducing itchy symptoms (11). SI increases the water content in the stratum corneum and maintains the level of skin hydration even in conditions of low air humidity. A recent study evaluated the effects of SI on the scalp skin, highlighting an improvement in transepidermal water loss (TEWL), sebaceous secretion and desquamation (12). SI can bind to the skin even in very low pH conditions, so it is ideal when used in conjunction with moisturizers that contain alpha hydroxy acids (AHAs). The results of the studies showed that the use of moisturizers containing SI effectively reduced the value of TEWL in patients with eczema.

➜ **Schisandra chinensis.** Schisandra chinensis is a well-known climbing plant in Traditional Chinese Medicine and in Modern Chinese Medicine. Its fruit was used in the treatment of various diseases of the gastrointestinal tract, respiratory insufficiency, cardiovascular diseases, in states of fatigue and body weakness, excessive sweating and insomnia (13). The aqueous extract of Sc. Chinensis (SCE) is characterized by the presence of polysaccharides (11.98%), flavonoids (9.03%) and lignans (8%). SCE can be used in cosmetic products, as a preservative due to its antibacterial activity (14). S. chinensis fruit extracts and their active compounds are powerful antioxidants that exert anti-inflammatory, antiviral, antitumor and anti-aging effects. Flavonoids, phenolic acids, vitamin C, vitamin E, phytosterols, dibenzocyclooctadiene lignans

effetto stimolante sulla sintesi delle ceramidi, accelera la differenziazione dei cheratinociti e aumenta i livelli di NADP intracellulare. Nell'invecchiamento cutaneo, l'applicazione topica di niacinamide migliora la texture cutanea, leviga le rughe e inibisce la fotocarcinogenesi. Studi hanno dimostrato effetti antinfiammatori nei pazienti affetti da acne e rosacea. Per i suoi effetti benefici la niacinamide rappresenta un componente utile nei prodotti cosmetici destinati al trattamento dei disturbi della funzione di barriera epidermica, dell'invecchiamento della pelle, delle alterazioni della pigmentazione, in patologie infiammatorie come l'acne, e nella cura della pelle che è stata sottoposta a trattamenti dermoestetici (10).

➜ **Saccaride isomerato.** Il saccaride isomerato (SI) è un complesso di carboidrati mucopolisaccaridi simile a quello che si trova nello strato corneo della pelle e agisce da componente occlusivo e umettante. Tale principio attivo forma nell'epidermide acido ialuronico, determinando un aumento del contenuto di acqua nello strato corneo. Il SI va a legarsi fortemente allo strato corneo e può essere rilasciato solo attraverso il processo di desquamazione, quindi è molto efficace nell'idratare la pelle, rendendola anche più liscia e riducendo la sintomatologia pruriginosa (11). Il SI aumenta il contenuto di acqua nello strato corneo e mantiene il livello di idratazione cutanea anche in condizioni di bassa umidità dell'aria. Un recente studio ha valutato gli effetti del SI a livello della cute dello scalpo evidenziando un miglioramento della perdita di acqua transepidermica (TEWL), della secrezione sebacea e della desquamazione (12). Il SI può legarsi alla cute anche in condizioni di pH molto basso, quindi è ideale se usato insieme a creme idratanti che contengono alfa idrossiacidi (AHA). I risultati degli studi hanno mostrato che l'uso di creme idratanti contenenti SI ha ridotto efficacemente il valore della TEWL in pazienti affetti da eczema.

➜ **Schisandra chinensis.** La Schisandra chinensis è una pianta rampicante molto nota nella Medicina Tradizionale Cinese e nella medicina cinese moderna. Il suo frutto veniva utilizzato nella cura di svariate malattie del tratto gastrointestinale, insufficienza respiratoria, malattie cardiovascolari, negli stati di affaticamento e debolezza corporea, sudorazione eccessiva e insonnia (13). L'estratto acquoso di Sc. chi-

are responsible for the antioxidant activity of S. chinensis (15). S. chinensis bioactive compounds inhibit pro-oxidant signaling pathways: cyclooxygenase 1 and 2 (COX-1 and 2), nitric oxide production and gene expression of pro-inflammatory cytokines (16). The bioactive compounds of S. chinensis have a powerful protective action on the skin. Their anti-aging and revitalizing actions are carried out through an improvement in hydration, tone and skin healing processes by reducing the dilation of blood vessels and restoring the skin barrier (17).

➜ **Postbiotics**. Probiotics can be defined as "live microorganisms which, when administered in adequate quantities, confer a health benefit to the host". However, for reasons of stability, their use in cosmetic formulas is subject to debate, therefore, it is preferable to use postbiotic elements.

The imbalance of the skin microbiome can alter skin homeostasis and cause various inflammatory conditions.

Postbiotics have been shown to block the release of inflammatory cytokines and thus help reduce skin inflammation. Postbiotics accelerate the recovery of the skin barrier function and inhibit skin inflammation. The ability of some postbiotic strains to improve the function of the epidermal barrier has been highlighted by various studies (18). Lysates are cells whose outer membrane has been broken down due to chemical or physical processes, and are used in medical practice as immunomodulators, as they are able to upregulate the immune response of host cells. There are a number of studies that provide evidence of the benefits of specific postbiotic strains on skin health (19). Some postbiotic strains can help regulate pH, reduce oxidative stress, protect against photoaging and improve skin barrier function, having a direct effect at the application site. Recent research has evaluated the antioxidant and anti-aging action of some postbiotics, finding a significant improvement in the depth of wrinkles and facial hyperpigmentation in patients who had received high topical concentrations of postbiotics (20). Topical postbiotics represent a very promising therapeutic approach for the treatment of skin disorders and, thanks to their ability to maintain skin homeostasis, they are also indicated in post-surgery skin care.

nensis (SCE) è caratterizzato dalla presenza di polisaccaridi (11,98%), flavonoidi (9,03%) e lignani (8%). SCE può essere utilizzato nei prodotti cosmetici, come conservante grazie alla sua attività antibatterica (14). Gli estratti dei frutti di S. chinensis e i loro composti attivi sono potenti antiossidanti che esercitano effetti antinfiammatori, antivirali, antitumorali e antietà. I flavonoidi, acidi fenolici, vitamina C, vitamina E, fitosteroli, dibenzocicloottadiene lignani sono responsabili dell'attività antiossidanti di S. chinensis (15). I composti bioattivi di S. chinensis inibiscono le vie di segnalazione pro-ossidanti: ciclossigenasi 1 e 2 (COX-1 e 2), produzione di ossido nitrico ed espressione genica di citochine pro-infiammatorie (16). I composti bioattivi di S. chinensis svolgono una potente azione protettiva a livello della pelle. Le loro azioni antietà e rivitalizzanti si esplicano attraverso un miglioramento dell'idratazione, del tono, dei processi cicatrizzanti della cute riducendo la dilatazione dei vasi sanguigni e ripristinando la barriera cutanea (17).

➜ **Postbiotici.** I probiotici possono essere definiti come "microrganismi vivi che, se somministrati in quantità adeguate, conferiscono un beneficio per la salute dell'ospite". Tuttavia, per ragioni di stabilità, il loro impiego in formule cosmetiche è oggetto di dibattito, pertanto, si preferisce utilizzare elementi postbiotici.

Lo squilibrio del microbioma cutaneo può alterare l'omeostasi cutanea e causare diverse condizioni infiammatorie.

È stato dimostrato che i postbiotici siano in grado di bloccare il rilascio di citochine infiammatorie e quindi di aiutare a ridurre l'infiammazione cutanea. I postbiotici accelerano il recupero della funzione di barriera cutanea e inibiscono l'infiammazione cutanea. È stata evidenziata da varie ricerche la capacità di alcuni ceppi postbiotici di migliorare la funzione della barriera epidermica (18). I lisati sono cellule la cui membrana esterna è stata scomposta a causa di processi chimici o fisici, e sono utilizzati nella pratica medica come immunomodulatori, in quanto riescono a sovraregolare la risposta immunitaria delle cellule ospiti. Esistono numerosi studi che forniscono prove dei benefici di ceppi postbiotici specifici sulla la salute della pelle (19). Alcuni ceppi postbiotici possono aiutare a regolare il pH, ridurre lo stress ossidativo, proteggere dal fotoinvecchiamento e migliorare la funzione di barriera

Conclusions

A correct clinical classification of the imperfections on which to intervene and the skin type of the face is of essential importance for the choice of the corrective dermoaesthetic procedure to be adopted. The association of a topical, home and outpatient therapeutic protocol before, during and after these interventions, is fundamental and supportive for the specialist, as it allows to optimize the therapeutic effectiveness of his work. The recent cosmetological innovations also allow not only to exploit the effect of active ingredients, whose qualities are known, but to associate multiple molecules in pools conveyed in serum, gel and cream, favoring their penetration, amplifying their responses, increasing compliance. of the patient and to maximize the effectiveness and safety of aesthetic procedures, such as chemical peels, lasers and therapeutic lights, needling, etc. The topical agents reviewed in this article are effective in supporting skin healing processes, reducing post-surgery recovery times and improving the results of both physical and cosmetological dermatological treatments. The opportunity to carry out a complete daily routine of the face, from cleansing to photoprotection, dedicated to correcting the signs of skin aging and imperfections, such as discoloration, acne outcomes, etc., based on the different types of skin (xerotic skin, sensitive, normal and seborrheic), allows a global approach with long-lasting benefits.

cutanea, avendo un effetto diretto a livello del sito di applicazione. Recenti ricerche hanno valutato l'azione antiossidante e anti-aging di alcuni postbiotici, riscontrando un miglioramento significativo della profondità delle rughe, delle iperpigmentazioni del volto nei pazienti che avevano ricevuto elevate concentrazioni topiche di postbiotici (20). I postbiotici topici rappresentano un approccio terapeutico molto promettente per il trattamento dei disturbi della pelle e inoltre, grazie alla capacità di mantenere l'omeostasi cutanea sono indicati nella cura della pelle post-intervento.

Conclusioni

Un corretto inquadramento clinico degli inestetismi su cui intervenire e della tipologia cutanea del volto è di importanza essenziale per la scelta della procedura dermoestetica correttiva da adottare. L'associazione di un protocollo terapeutico topico, domiciliare e ambulatoriale, prima, durante e dopo tali interventi, risulta fondamentale e di supporto allo specialista, poiché consente di ottimizzare l'efficacia terapeutica del suo operato. Le recenti innovazioni cosmetologiche consentono inoltre non solo di sfruttare l'effetto di principi attivi, le cui qualità sono note, ma di associare più molecole in pool veicolati in siero, gel e crema, favorendo la loro penetrazione, amplificandone le risposte, aumentando la compliance della/del paziente e per massimizzare l'efficacia e la sicurezza delle procedure estetiche, come peeling chimici, laser e luci terapeutiche, needling, etc. Gli agenti topici revisionati in questo articolo risultano efficaci nel supportare i processi di guarigione cutanea, nel ridurre i tempi di recupero post-intervento e nel migliorare i risultati dei trattamenti dermatologici, sia fisici che cosmetologici. L'opportunità di poter effettuare una routine quotidiana completa del viso, dalla detersione alla fotoprotezione, dedicata alla correzione dei segni dell'invecchiamento cutaneo e delle imperfezioni, come discromie, esiti acneici, ecc., in base alle diverse tipologie della pelle (cute xerotica, sensibile, normale e seborroica), consente un approccio globale con benefici che si prolungano nel tempo.

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Comparison of the improvement effect in periocular area with lipofilling versus adipose micrografts at 500 and 50 microns. A clinical study

FABIANO SVOLACCHIA

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SUMMARY

Aim

The purpose of this study was to demonstrate that through a technique of superficial and deep correction of the periocular area with the adipose tissue extracted with a needle and microfiltered during the same surgery session, we could have clinically better results in terms of wrinkles and volume over time to a classic lipofilling.

Background

The area around the eyes has the characteristic of being covered with a very thin tissue. The skin of the eyelids is among the thinnest in the human body (<1mm), it is very delicate and during aging it can lose elasticity and turgor to the point of atrophying. In its lower anatomical portion that continues with the valley of tears it can very quickly undergo aging phenomena.

Method

This retrospective study began in December 2019 and the only criterion for enrollment in the study was the presence of wrinkles in the periocular area and volume defects that accentuated the nasolacrimal sulcus. One half of patients underwent exclusively the classic technique of the volumetric correction of the periocular area through a lipofilling, while the other half underwent a double treatment with adipose tissue, a 500 micron microfiltered that was injected in depth to correct volume defects and a 50 micron microfiltered micron for surface regeneration.

Results

From the analysis of the results obtained, although it was possible to obtain good results with both methods highlighted in the Modified Vancouver Scale, we were able to observe a better result over time with the combined technique compared to that of the classic lipofilling technique.

Conclusion

This retrospective clinical evaluation through the VAS and Berardesca scales allowed us to observe that the superficial and deep correction technique in the same surgery session and with the adipose tissue extracted with a needle and microfiltered gave better results for the clinical result of wrinkles and volume of the periocular area.

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KEYWORDS
Lipofilling, Microfiltration, ADSCa, Progenitors, Tissue regeneration

INTRODUCTION

The area around the eyes has the characteristic of being covered with a very thin tissue. The skin of the eyelids is among the thinnest in the human body (<1mm), it is very delicate and during aging it can lose elasticity and turgor to the point of atrophying. In its lower anatomical portion that continues with the valley of tears it can very quickly undergo evident aging phenomena. They are linked both to a physiological aging process caused by ROS but also to ultraviolet (UV) radiation responsible for the so-called photo-aging. This phenomenon occurs physiologically with the passage of time in all individuals, inducing changes in the proportions between the different anatomical structures with an increase in tissue laxity and periocular wrinkles. Although the eye cannot sink beyond a certain limit, the nasal portion of the lower eyelid makes evident the transition with the skin of the cheek below with folds and wrinkles. To improve that anatomical area, multiple therapeutic approaches can be adopted including autologous adipose tissue transplantation. The aim of our study was to observe the improvement of the periocular area over time by comparing the classic technique of lipofilling, with adipose tissue extracted with a multi-hole cannula compared to a lipofilling with adipose tissue extracted by means of a needle , microfiltered at different sizes and providing for a treatment combined superficial and deep. The evaluation of the differences was expressed through the VAS, Berardesca and Vancouver scales. Modified to verify if there had been a difference in the result over time. For the physician who adopts regenerative therapy techniques by means of tissue progenitors, adipose tissue is the most accessible and richest source. Lipoaspirate contains multipotent cells and represents a source of stem cells with which to improve texture defects and also correct volumetric defects. The presence of adipose tissue in all individuals and the self-renewal capacity of the Progenitors allows to improve the recipient area as they possess a high capacity of differentiation (1). The adipose tissue can be obtained through aspiration with a multi-hole cannula or with a needle of sufficient size mounted on a Luerlock® syringe and the tissue provides a colony of cells similar to fibroblasts in culture. These cells can be maintained in vitro for long periods with stable population doubling and low levels of senescence. Immunofluorescence and flow cytometry show that most cells are of mesodermal or mesenchymal origin (2). Stem cells derived from adipose tissue (ADSc) are able to induce the production of a new extracellular matrix (ECM), the deposition of a physiological collagen and an early neovasculogenesis (3). Adult mesenchymal stem cells when transferred to a recipient tissue participate in the homeostatic regulation of tissues as they are mediators of tissue trophism. In the tissues they participate in the attenuation of inflammation, in the reprogramming of immune cells and wild fibroblasts to promote tissue regeneration and inhibit the formation of fibrotic tissue (4). Clinical activity shows that adipose tissue and the stem cells contained in it can replace fillers in restoring the volumes and texture of facial tissues (5). Adipose tissue is easily accessible, is a source of progenitors with surface markers typical of adult stem cells and they can differentiate along numerous lineages (6). In regenerative medicine, supplementation of tissue progenitors derived from adipose tissue allows to counteract the effects of aging caused by the decrease in stem cell niches

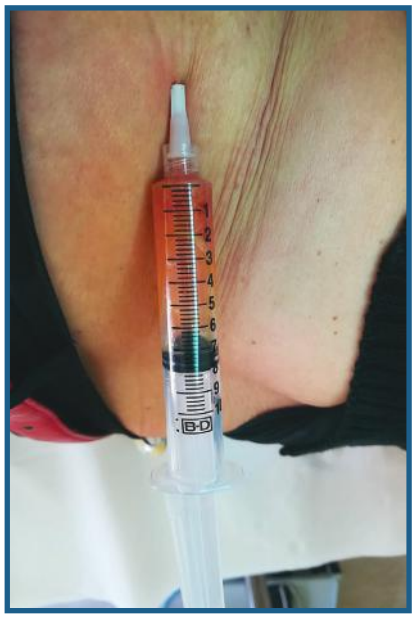


Figure 1.
Liposuction performed with a 16 G needle after anesthesia with Klein solution.

(7) and can be a valid therapeutic approach for the problems of depression and wrinkles. By adopting the technique of adipose tissue transfer procedures there is a long-term tissue improvement for cell mediation and tissue regeneration (8). Adipose tissue is a very rich source of multipotent mesenchymal stem cells and when transferred to recipient tissues they promote a paracrine effect with improvement of tissue homeostasis (9). Mesenchymal stem cells of adipose origin initiate and maintain the key factors of the regenerative process in the tissues (10). They are adherent cells, so they are easy to isolate and show contact inhibition making the procedure safe (11). Adipose tissue contains at least 100 times more adult mesenchymal stem cells than marrow and these cells have great proliferative potential (12) through a well-orchestrated cascade of biological and molecular processes involving cell migration, proliferation, extracellular matrix deposition and remodeling (13). In addition to being multipotent, mesenchymal stem cells possess immunomodulatory functions that have been studied as potential treatments in various immune disorders. Mesenchymal stem cells can physio-

Figure 2.
Deep volumetric correction with cannula.

Figure 3.
500 Micron Microfiltration.

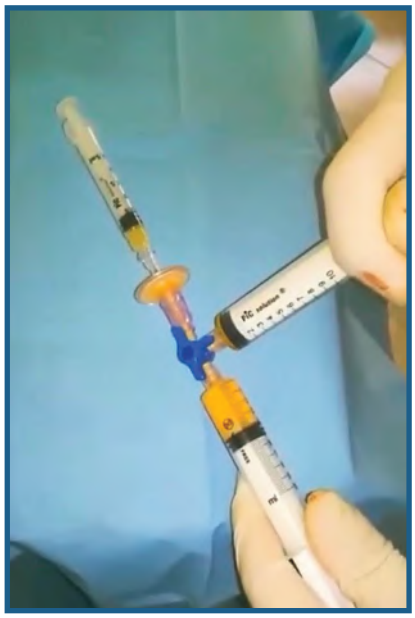


Figure 4.
50 Micron Microfiltration

logically interact with the cells of the innate and adaptive immune system, both through direct cell-to-cell contact and through their secretome (14). The techniques for using an adipose disaggregate are constantly evolving and the possibility of a use that provides for the exclusion of the inflammatory portion such as fibrous shoots and cellular debris capable of activating the Toll-Like system has improved the clinically objective results in a long period.

Patients and Methods

This retrospective study started in December 2019 and involved 28 female patients divided into two study groups. All 28 volunteer patients (aged between 34 and 62 years) attended the clinic between 2019 and 2022. The only criterion for entry into the study was the presence of wrinkles in the periocular area and volume defects. that accentuated the nasolacrimal sulcus. One half of patients underwent exclusively the classic technique of volumetric correction of the periocular area through lipofilling, while the other half underwent a double treatment with adipose tissue, a 500 micron microfiltered that it was injected deeply to correct volume defects and a 50 micron microfiltered that was injected more superficially. The aim was to verify over time the improvement of that anatomical area and any differences between the two groups. The study was performed following the standards of the local ethics committee and in accordance with the Declaration of Helsinki (2000). All patients were female and had no specific dermal or other systemic pathologies. In the first group the adipose tissue was extracted by means of a Notrox 2.5x150 multiholes cannula mounted on a 10 ml Luerlock® syringe. In the second group we used a 10 ml Luerlock® syringe to which a 16 G needle was applied **(figure 1)**. The use of the needle allows the progenitors a greater survival and a better vitality (15). Furthermore, using a needle we have an overlap in the amount of viable cells extracted compared to extraction with a liposuction cannula (16, 3). Before extraction, local anesthesia with Klein's solution was performed on the donor area. We extracted about 9 cc of lipoaspirate and let it settle to eliminate the anesthesia fluids for 15 minutes from which we obtained about 6 ml of adipose tissue. In the first group of patients, the lipoaspirate was injected immediately after being decanted with a Notrox 0.7-1.2x70 cannula until the volumetric defects were completely corrected **(figure 2)**. In the second group the adipose tissue obtained was filtered at 500 microns **(figure 3)** from which we obtained about 5.5 ml of final lipoaspirate. We took 4 ml from this and used it with a Notrox 0.7-1.2x70 cannula until the volumetric defects were completely corrected. According to Tonnard 2013, we disintegrated a quantity of tissue equal to 1.5 ml and filtered at 50 microns to better preserve the Side Population (17) **(figure 4)**. We obtained 0.8 ml of final suspension (photo 5) and we injected it superficially **(figure 6)**. Although during the disintegration according to Tonnard 2013 and the subsequent filtration there is a loss of vital elements (18), their therapeutic potential is higher (19) because the fibrous shoots and cellular debris are eliminated (20) **(figure 5)**. Filtration at various sizes has also allowed us to better safeguard the receiving areas as the fibrous shoots and cellular de-

Figure 6.
Surface injection after filtration at 50 microns with 30 G Needle.

Figure 5.
Fibrous shoots and cell debris after fragmentation captured by the filter. 50 Micron Microfiltration.

Table 1.

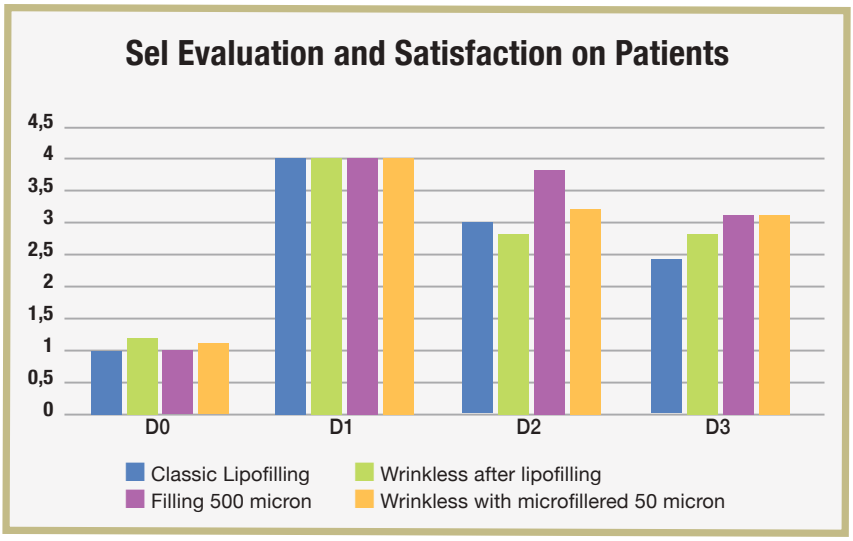
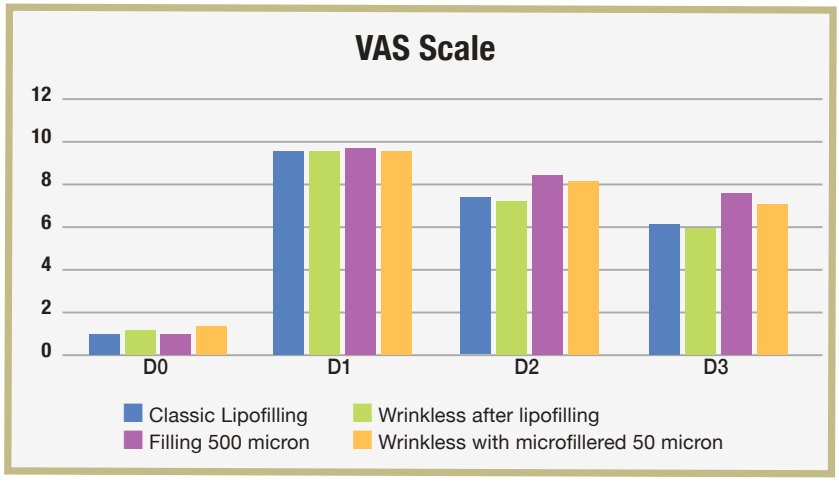


Table 2.



bris are responsible for the activation of an inflammatory state through the Toll-Like system (3). The possibility of exploiting a nanofat according to Tonnard 2013 deprived of inflammatory elements through microfiltration at 50 microns to supplement the superficial area of the periocular area with tissue Progenitors and correct the deep part with a microfiltered at 500 microns for the volumetric improvement have led us to enroll a sufficient number of patients and to study them for a suitable time in order to be able to express a retrospective clinical evaluation in vivo and the differences over time with the only volumetric correction with classic lipofilling. Both procedures kept us busy with overlapping times that we quantified in 90 minutes.

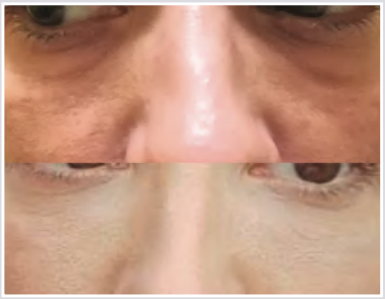
Results

Both the use of the classic lipofilling technique and the use of the combined technique by means of filtration at different sizes of the adipose tissue in order to correct the periocular area allows to obtain excellent results of volume correction and texture improvement even with a single treatment. However, from the analysis of the results obtained, we obtained a better result over time with the combined technique compared to that of the classic lipofilling technique.

The patients of both groups reported an improvement in periocular wrinkles even after 180 days as shown by the Berardesca VAS and Vancouver Modified scales. After the first and second month, with a follow-up at the sixth month the subjects evaluated their satisfaction or dissatisfaction by giving scores on filling and wrinkle, using a scale of 0–4 for each criterion (0 = unsatisfactory; 4 = satisfactory), as per Berar-

Figure 7.

Volumetric correction to 500 microns in depth and regeneration with microfiltered at 50 microns result after 30 days



Volumetric correction to 500 microns in depth and regeneration with microfiltered at 50 microns result after 180 days

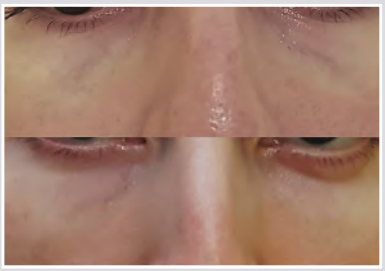
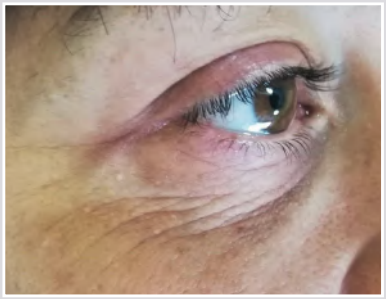
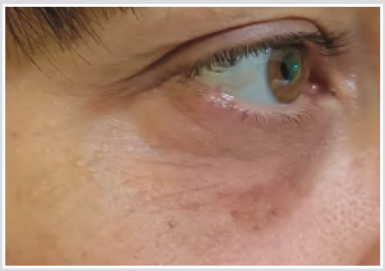


Figure 8.

Lipofilling of the periocular area with classical technique result after 30 days





desca et al. (21) with a difference in favor of treatment with a combined technique. In **table 1** we have reported the results obtained.

Individual signs of periocular wrinkles and the degree of correction obtained for each treatment and each area were objectively evaluated using a 10-0 visual analog scale with separate scores for each site (10 = no correction; 5 = satisfactory correction; 0 = correction total) with a difference in favor of treatment with a combined technique. In **table 2** we have reported the results obtained.

The periocular skin tissue was also evaluated with the Modified Vancouver scale and in both methods led to the same results. In **table 3** we have reported the results obtained.

The different results are shown with some photographic examples **(figure 7 and figure 8)**.

Discussion

Adipose tissue is a valid substitute for fillers in restoring volumes with the advantage of improving the texture of the tissues of the anatomical area relating to the implant. This phenomenon is mediated by the stem cells it contains (5). This occurs due to the ability to reintegrate part of the niches of mesenchymal stem cells into the tissues, counteracting the effects of aging caused by their decrease, especially after the first third of life (7), through the triggering and maintenance of key factors for the initiation of tissue regeneration (10). They can differentiate along many lineages (6), they can reprogram wild fibroblasts (4), they can induce the production of a new extracellular matrix (ECM) with physiological collagen deposition and early neovasculogenesis (3).

The awareness of obtaining better results by using a technique that involves the filtration of the adipose tis-

Table 3.

VANCOUVER MODIFIED SCALE

Baseline				Follow up 180 Days
Vascularity :	Red	Purple	Grey	Normal
Pigmentation :	Hyperpigmentation	Hypopigmentation		Normal
Pliability :	Firm	Ropes		Normal/Supple

sue at two different sizes and injected at different depths in the different planes, or by combining in a single operating session both the volumetric approach and the regenerative approach of a difficult anatomical area such as the periocular one (22) led us to compare this technique versus the classic approach of lipofilling with the results reported in the tables.

Conclusion

This retrospective clinical evaluation allowed us to observe that the superficial and deep correction technique in the same surgery session and with the adipose tissue extracted with a needle and microfiltered gave better results for the clinical result of wrinkles and volume of the periocular area. This phenomenon can be explained by a better positioning in the different anatomical planes of the Progenitors as well as having a more selected tissue. In fact, the filtration at 500 microns in the volumetric treatment allows to eliminate a part of the fibrous shoots and cellular debris responsible for the activation of an inflammatory state through the Toll-Like system, safeguarding the adipocytes (3) and obtaining better results in the filling over time. The injection of the microfiltered at 50 microns more superficially produces a better regulation of the phenomenon of Plasticity through the autocrine and paracrine signaling pathways (10,13) and an attenuation of ROS in the ECM (8,9) safeguarding the tissue Progenitors (3). Moreover, this technique will provide a physiological increase in the formation of natural niches in which the adult mesenchymal stem cells are included in every anatomical plane, providing them with a protective action (23) with a consequent longer stay in the injection site.

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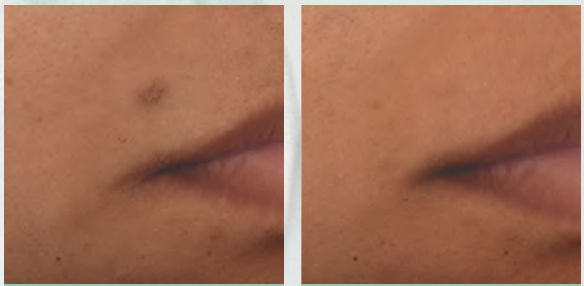

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