JOURNAL OF EDUCATION, HEALTH AND SPORT
eISSN 2391-8306 · Open Access · Peer-reviewed
apcz.umk.pl/JEHS · Nicolaus Copernicus University in Toruń

Cite as: GĄSIOREK, Natalie, GRUCHOT, Hanna, KUŹNAR, Anna, BAJOREK, Julia and ŻABICKI, Michał. The impact of Hyaluronic Acid Fillers on skin ageing: a clinical, histological and psychosocial analysis. Journal of Education, Health and Sport. 2026;94:72951. https://doi.org/10.12775/JEHS.2026.94.72951

ARTICLE TIMELINE
Received: 02.06.2026 Revised: 10.07.2026
Accepted: 10.07.2026 Published: 17.07.2026

INDEXING & EVALUATION
MEiN points: 40 Unique ID: 201159
Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The impact of Hyaluronic Acid Fillers on skin ageing: a clinical, histological and psychosocial analysis

Natalie Gąsiorek[1], ORCID: https://orcid.org/0009-0005-0035-7186
Email: natalie.gasiorek.edu@gmail.com
Kazimierz Pulaski University of Radom, Poland

Hanna Gruchot[2] , ORCID: https://orcid.org/0009-0002-9380-3410
Email: hanna.gruchot.edu@gmail.com
Kazimierz Pulaski University of Radom, Poland

Anna Kuźnar[3] , ORCID: https://orcid.org/0009-0003-8630-2199
Email: anna.kuznar.edu@gmail.com
Kazimierz Pulaski University of Radom, Poland

Julia Bajorek[4], ORCID: https://orcid.org/0009-0008-7686-6333
Email: jula.ola2@gmail.com
Medical University of Lublin, Poland

Michał Żabicki[5], ORCID: https://orcid.org/0009-0008-0949-2466
Email: michal-zabicki99@wp.pl
Medical University of Lublin, Poland

Corresponding Author
Natalie Gąsiorek, E-mail: natalie.gasiorek.edu@gmail.com

Abstract:

Introduction: Hyaluronic acid, a fundamental component of the extracellular matrix, plays an essential role in preserving skin elasticity, hydration, and structural cohesion.

The clinical component of the analysis reviews the effectiveness of HA-based injectable formulations commonly used in aesthetic dermatology. The histological discussion focuses on tissue-level changes following HA administration, including stimulated collagen production, fibroblast activation, and remodelling of the extracellular environment. On the psychosocial level, the study evaluates how such procedures affect patients' quality of life, self-image, emotional well-being, and overall self-worth.

Aim of the study: This study aims to comprehensively explore the influence of hyaluronic acid (HA) fillers on the multifaceted process of skin ageing, incorporating clinical, histological, and psychosocial perspectives.

Materials and methods: A review of the literature available in the PubMed database was conducted using selected keywords related to hyaluronic acid fillers, skin ageing, histological changes, and psychosocial outcomes.

Conclusions: Current literature supports the conclusion that hyaluronic acid fillers effectively counteract visible signs of skin ageing. The benefits are reflected not only in improved physiological parameters but also in enhanced self-perception and mental well-being.

Key words:

hyaluronic acid, aesthetic medicine, skin ageing, dermal fillers

Introduction

Skin ageing is a multifactorial biological process involving numerous morphological and physiological changes in the skin's structure. These changes result from both internal factors and environmental influences. Ultraviolet radiation has a particular impact on skin ageing [2]. With age, there is a decline in fibroblast activity and a reduction in the production of collagen, elastin and hyaluronic acid (HA), resulting in a loss of skin firmness, elasticity and volume [2,4].

To help patients maintain a youthful appearance for as long as possible, as well as improve their self-esteem, aesthetic medicine is developing a range of strategies designed to counteract the signs of ageing. One of the most commonly used solutions is dermal fillers based on cross-linked hyaluronic acid [14].

HA is a glycosaminoglycan (GAG) found in the skin's extracellular matrix (ECM) [12]. It has a unique ability to bind water molecules and maintain tissue homeostasis [5,12].

In addition to its mechanical effect (immediate filling of tissue defects), increasing attention is being paid to its biostimulating action. The administration of HA stimulates fibroblasts and may lead to the synthesis of collagen and elastin. It may also influence ECM remodelling, resulting in an improvement in skin quality at the histological level [6,8].

This study attempts a multidimensional analysis of the impact of hyaluronic acid-based fillers on the skin ageing process. It encompasses not only a review of the literature on the clinical and histological effects of HA use, but also the psychological and social aspects associated with aesthetic procedures. This provides a comprehensive overview of the phenomenon of skin ageing and its modification using modern therapeutic methods.

Theoretical foundations of skin ageing

1.1. Anatomy and physiology of the skin

The skin is considered one of the largest organs of the human body [24]. Its surface area can be as large as 2.0 m^2in an adult, and its thickness ranges from 0.5 to 1.0 mm. It performs protective, thermoregulatory and secretory functions, and is the site of synthesis for certain

compounds, such as vitamin D. It also participates in the immune response and conducts sensory stimuli [1]. It also acts as a sensory organ [24].

It is composed of three layers: the epidermis, the dermis and the subcutaneous tissue. It also contains sweat and sebaceous glands, hair, nails, blood and lymphatic vessels, and nerve endings [1].

The epidermis is the outermost layer of the skin, composed of keratinocytes. It comprises four layers: the basal, spinous, granular and stratum corneum [24]. Its primary function is to form a protective barrier [1].

The dermis consists of two layers: the reticular and papillary layers, both of which are composed of connective tissue. The reticular layer accounts for 80% of the skin's thickness. It is composed of collagen fibres (made up of type I and II collagen), elastin fibres (made up of elastin with high tensile strength) and reticulin fibres (made up of type III collagen). This layer also contains histiocytes, mast cells and lymphocytes [1].

Subcutaneous tissue (hypodermis): this consists of collagen, proteoglycan gel and fat cells. It has a cushioning and insulating function [1].

1.2. Biological mechanisms of ageing (intrinsic and extrinsic)

Skin ageing affects all three layers of the skin, as well as the muscles and bone structures. With age, the production of sebum, sweat and vitamin D decreases. As a result of the reduction in the number of fibroblasts, there is a decrease in the synthesis of collagen fibres, particularly types I and III [2].

Changes begin to become visible, particularly around the eyes and mouth. Ageing is divided into endogenous and exogenous ageing [2].

1. **Endogenous ageing**: This is a physiological process, linked to the passage of time and genetically determined. It is also influenced by hormonal changes. It is characterised by atrophic and atrophic changes, dryness of the epidermis, loss of firmness and thinning of the skin, as well as the formation of wrinkles [2].

We divide these into:

- chronological – age-related. This is a highly individual concept, and chronological age (based on date of birth) can very often differ from biological age. With age, the amount of adipose tissue decreases. This is particularly noticeable in the face, neck and back of the hands [2].
- hormonal – particularly affecting postmenopausal women [2]. This results from changes in oestrogen activity, which plays a key role in cellular function. Oestrogens influence the skin's elasticity and resilience, its proper pigmentation, and its ability to retain water. As a result of the decrease in oestrogen levels, the skin becomes thin, atrophic and less elastic, and wrinkles appear on its surface. The amount of hyaluronic acid produced also decreases [17].
- expression lines – changes resulting from the expression of emotions, associated with facial expressions [18]. This causes constant contraction and relaxation of the epidermis and dermis. Most commonly, these changes are visible around the eyes, nose and mouth, and on the forehead [19].

2. **Exogenous ageing**: results from the action of environmental factors and is considered non-physiological. It is influenced by climatic conditions, diet, smoking or other stimulants, stress, or excessive exposure to ultraviolet (UV) radiation. It is regarded as a chronic inflammatory process, which differs from endogenous ageing in histological terms [20].

These two mechanisms often occur simultaneously, which exacerbates the effects of skin ageing.

1.3. UV radiation as a factor exacerbating skin ageing

Photoageing is the result of excessive exposure of the skin to ultraviolet radiation, both natural and from artificial UV irradiation. The changes that occur resemble a process of gradual skin scarring [2]. UV radiation is a factor that penetrates connective tissue and is responsible for 80% of degenerative changes in the epidermis and dermis. It is also

responsible for the formation of free radicals and toxic and allergic processes in the skin [2,3,4].

Ultraviolet radiation can be divided into three types, based on wavelength [3]:

- **UVA** – with a wavelength of 320–400 nm. It penetrates deepest into the skin. In addition to the dermal cells it affects, it also has a harmful effect on melanocytes, keratinocytes and epidermal stem cells. It also exhibits carcinogenic and mutagenic properties.
- **UVB** – with a wavelength of 290–320 nm. It causes sunburn and erythema, as well as disrupting the function of Langerhans cells. It also has mutagenic properties.
- **UVC** – with a wavelength of 200–290 nm. It causes DNA damage and severe erythema.

The development of skin lesions depends largely on the duration of exposure and individual factors, including skin phototype. People with skin phototypes I (very fair skin) and II (fair skin) are particularly at risk [21].

In 1997, skin damage was classified into four stages: [34]

- stage I (20–30 years) – these are the initial signs of skin ageing. Fine lines and slight discolouration appear
- stage II (35–50 years) – the appearance of expression lines, particularly around the corners of the eyes and around the mouth. The early signs of actinic keratosis also appear
- stage III (>50 years) – pronounced wrinkles, pigmentation disorders and actinic keratosis
- stage IV – advanced ageing process, with numerous deep furrows, loss of elasticity, dry skin and a yellowish tinge.

In addition to the changes listed above, ageing also leads to sebaceous gland hyperplasia, telangiectasia and the appearance of discolouration, pseudo-scars, lentigines and stellate spots. Lentigines arise as a result of the interaction and clustering of melanocytes and keratinocytes [3].

1.4. Clinical and histological picture of ageing skin

The first noticeable changes, visible without the need for specialist equipment, are wrinkles. These are divided into superficial wrinkles, which do not extend deeper than 0.05 mm, and deep wrinkles. Superficial wrinkles include the common but undesirable ‘crow’s feet’ around the eyes. Deep wrinkles, on the other hand, appear as vertical or horizontal furrows, particularly on the cheeks, forehead, lower face and neck [4].

A characteristic of ageing skin is its dryness and the formation of areas with a high degree of flaking. The reason for this is the loss of lipids and water in the epidermis [4].

After the age of 40, ceramides, which belong to the group of natural lipids, cease to be produced. As a result, there is increased water loss and dryness of the skin, as ceramides act as intercellular cement, preventing dehydration and protecting the skin from harmful factors [4].

Loss of lipids is responsible for skin laxity. Fat tissue is reduced particularly in the periorbital, temporal and subzygomatic regions. Excess fat, in turn, appears on the chin, jawline and cheeks [4].

Pigmentary changes also occur, caused by melanocytes – their increase, decrease or complete disappearance. This leads to hypopigmentation or hyperpigmentation [4].

Skin ageing is associated with a range of histological changes [1,2,4]:

- **Epidermis**: it becomes thinner as a result of the atrophy of the granular and spinous layers. Keratinocyte proliferation is disrupted. The basal layer flattens and its proliferative activity decreases. Sebum secretion decreases, which significantly contributes to skin dryness. The dermo-epidermal junction flattens, leading to a reduction in the exchange of nutrients between the skin layers [2]. Susceptibility to irritation increases, and due to slowed regenerative processes, wound healing is impeded [22].
- **Dermis**: the size and number of fibroblasts decrease, thereby reducing collagen synthesis. The activity of metalloproteinases (MMPs), which break down collagen,

also increases, causing the collagen fibres to become thicker and irregular. Collagenase (MMP-1) is considered one of the main factors causing skin ageing, as it contributes to damage within collagen fibres [4].

Additionally, elastin fibres become thinned out (in the papillary layer they may disappear completely). However, in the reticular layer these fibres become hypertrophied, which may result in senile elastosis. This is the most common histological change associated with UV-induced damage [2,4].

In the papillary layer, vascular loops also disappear, resulting in a reduced supply of nutrients to the skin.

As a result of impaired fibroblast function, the amount of hyaluronic acid produced by them decreases; this acid is responsible for maintaining water and electrolyte balance [4].

The activity and density of melanocytes also decrease, resulting in a pale complexion and the appearance of pigmented spots [23].

- **Subcutaneous tissue**: a reduction in adipocytes and a change in their distribution are observed, which affects the facial contour [37].

Structure of hyaluronic acid

Hyaluronic acid belongs to the group of glycosaminoglycans (GAGs). It is a polysaccharide composed of repeating disaccharide units. It consists of a D-glucuronic acid molecule and an N-acetylglucosamine molecule, linked alternately by β-(1-4) and β-(1-3) glycosidic bonds [5,11]. Unlike other GAGs, it lacks sulphate residues and consequently does not form proteoglycans [12].

HA has a homogeneous structure. The molecular weight of the disaccharide subunits in this acid is approximately 400 daltons; however, HA may consist of a large number of subunits, meaning that the molecular weight can be as high as 4×10^{6} daltons (Da) [10,12].

Hyaluronic acid has the ability to bind large amounts of water, which is possible due to the anionic structure of the acid [5]. It thus affects the volume and compressibility of the skin. According to data, it has the ability to bind water up to 1,000 times its own molecular weight [6,9].

It is synthesised in the cell membrane, and the greatest amount is found in the ECM of connective tissues. Its estimated concentration in the dermis is approximately 200–500 μg/ml, and in the epidermis 100 μg/ml [5]. However, this concentration is not constant. Elevated levels can be observed during inflammatory processes, proliferation, regeneration or repair processes. Its concentration is also increased in the tissue surrounding a wound [9,6].

As we age, there is a reduction in the total amount of GAGs in the skin, including HA. This process begins as early as the age of 25, and between the ages of 25 and 50, the amount is reduced by as much as half [6].

The biological functions of HA depend on the length of its fragments and their molecular weight [6,7]:

- HMWHA – high molecular weight hyaluronan. It has anti-angiogenic, anti-inflammatory and immunosuppressive effects
- LMWHA – low-molecular-weight hyaluronan. It has antioxidant, anti-tumour and angiogenic properties

LMWHA has greater penetration capabilities than HMWHA, due to its small size [6,7].

Hyaluronic acid-based dermal fillers.

Hyaluronic acid molecules are hygroscopic, flexible and elastic, which offers a wide range of therapeutic applications. It is commonly used as a moisturising agent [8].

3.1 Hyaluronic acid in cosmetology

In cosmetic preparations, HA is present in the form of hyaluronic acid, sodium hyaluronate and potassium hyaluronate. It is used in concentrations of up to 2% in lotions, creams, serums

and cleansing gels. As a cosmetic ingredient, due to its high molecular weight, it does not penetrate the dermis but remains only on the surface of the epidermis (penetration through the epidermis is limited when the molecular weight exceeds 100 kDa). It moisturises and smooths by forming an occlusive layer, thereby reducing transepidermal water loss [9,10].

According to scientific reports in the Journal of Drugs in Dermatology, 0.1% HA present in cosmetics significantly affects skin hydration. A study was conducted on 76 women aged between 30 and 60 who used preparations with different molecular weights – 50, 130, 300, 800 and 2000 kDa. It was shown that the most effective in reducing wrinkles was the acid with a low molecular weight – 50 and 130 kDa. The use of high-molecular-weight acid protects the skin against external factors [12].

3.2 Hyaluronic acid in aesthetic medicine

Year on year, an increasing number of people, particularly women, are undergoing aesthetic medicine treatments [25].

In 2017, the most common procedures involved the use of botulinum toxin (29%), with procedures using dermal fillers coming in second place, just 1% behind [11].

Dermal fillers are tissues or synthetic substances that have the ability to fill in defects and contour the body. Dermal fillers must meet specific requirements in order to be used. These include, amongst others, high tolerability by the body, no induction of inflammation, long-lasting results, and the possibility of rapid removal [8,27].

HA is currently the most popular and most widely used filler. It stimulates collagen production and ensures adequate skin hydration, thereby helping to restore its natural volume [26]. When administered into the dermis via subcutaneous injection, it provides longer-lasting effects than when used as an ingredient in cosmetics [11].

The correct concentration of hyaluronic acid prevents the formation of wrinkles and other adverse changes. With age and exposure to UV radiation, the HA content in the skin decreases, resulting in a reduction in water content and a weakening of regenerative processes. Collagen fibres lose their elasticity and their number decreases, leading to the formation of wrinkles [27].

Hyaluronic acid used to correct wrinkles takes the form of an elastic gel, which functions similarly to the building blocks of tissue. The molecules are tailored to match the size of the tissue structure in the specific skin layer. This ensures the best possible aesthetic result, as the type of treatment is individually selected based on the type and depth of the wrinkles [11].

Dense fillers are used to correct nasolabial folds, frown lines, improve lip contour and marionette lines. In contrast, liquid HA is used to correct shallow wrinkles around the mouth and eyes. Lip correction requires fillers with a homogeneous structure and high fluidity, which allows the lips to be plumped and properly hydrated [27].

Hyaluronic acid has a short half-life (approximately 12 hours), so when administered subcutaneously, it degrades within a few days. To prevent this and prolong its effect, chemical modifications and cross-linking are used. Cross-linking methods using epoxides, aldehydes and divinyl sulfones are employed [12]. The most commonly used cross-linking agent is BDDE (1,4-butanediol diglycidyl ether) [28]. This increases viscosity and maintains the filling effects until the HA has completely degraded, a process which takes approximately one year [14].

After injection of a BDDE-crosslinked HA preparation into the body, it undergoes two main degradation processes. The first is oxidative degradation, which is caused by free radicals formed as a result of tissue damage caused by the needle during injection. Free radicals are small in size, which allows them to move into the pores between the filler particles and break down its structure. The second process is enzymatic degradation involving hyaluronidases (enzymes that degrade HA). However, due to its large molecular size, it can only act on the surface of the filler [29].

HA fillers undergo two degradation processes and are metabolised, so there is no concern regarding their elimination from the body. BDDE, as a cross-linking agent, is in turn removed via hydrolytic degradation [14].

Due to the widespread use of cross-linking agents, including BDDE, a maximum of 20 ml of HA filler per year is recommended for a person weighing 60 kg [14].

3.3 Histological changes in tissues following the use of hyaluronic acid fillers

At the site of filler injection into the body, the tissue reacts to the foreign substance. Inflammation and swelling occur. Biostimulation and foreign body reactions also take place. Initially, when the foreign substance enters the body, plasma proteins begin to adhere to the surface of the material. Monocytes and macrophages are activated, and they begin to fuse to form giant cells. A dense collagen capsule also forms, completely surrounding the foreign material – a reaction to the foreign body [14].

In the early stages of wound healing, changes occur in type III collagen. Four weeks after injection, it accounts for approximately 14% of the filler's volume and gradually increases until around week 32, when it accounts for approximately 21.5% [30,31].

Studies confirm that fillers injected into the body are partially replaced by autologous tissue. Consequently, there are cases where the effect lasts for over 2 years, due to the formation of a thick capsule around the filler mass, thanks to collagen regeneration. This prevents the degradation of HA by hyaluronidase, which can only act on the surface [32,33].

Currently, patients report satisfaction with the long-lasting effects of the injections, sometimes even without additional touch-ups [14].

3.4 Clinical aspects of hyaluronic acid injections

HA fillers are viscous and elastic substances. They are introduced into the body via thin tubes, such as needles and cannulas [14].

These injections have two main purposes. The first is to correct depressions in the dermis, which results in wrinkle correction. The second is to increase the volume of the facial skin and soft tissues to restore volume. Currently, the clinic uses a wider range of fillers designed to increase facial volume [14].

As HA is hydrophilic in nature, the filler reaches a peak of approximately 1.8 times its initial volume after 4 weeks. Thereafter, this volume decreases and remains relatively stable between 16 and 64 weeks following injection [30].

Clinically, both low-elasticity fillers, which easily form the desired shape but do not hold it well under pressure, and harder fillers with high viscosity and elasticity are used. The latter are more difficult to inject and shape, but retain their shape better. They are preferred for use in deeper layers of the skin, but patients must be aware of possible side effects, such as a

foreign body sensation or impaired circulation resulting from pressure on adjacent tissues [14].

Fillers used for wrinkle correction or skin smoothing are administered into more superficial layers, which undergo horizontal stretching and contraction as a result of facial muscle movement. Soft fillers with low viscosity and elasticity are used here. This is required for proper and even distribution, particularly around the eyes [35,36].

In conclusion, the appropriate type of hyaluronic acid-based filler should be selected individually based on the injection site, the patient's skin condition and the desired outcomes.

3.5 Contraindications for the use of hyaluronic acid-based fillers

HA is a natural polymer, so it causes fewer reactions compared to synthetic polymers [9].

Nevertheless, injection treatments using hyaluronic acid are contraindicated in cases of active autoimmune disease, uncontrolled diabetes, infection at the injection site, or herpes. Pregnant or breastfeeding women should also refrain from undergoing aesthetic medicine procedures. An obvious contraindication is also an allergy or anaphylactic reaction to any component of the filler [9].

Side effects associated with the use of fillers also include: redness, swelling, minor bruising and slight bleeding. Occasionally, HA migration occurs, resulting in scarring and inflammation at the injection site. Swelling may be caused by HA's water-retaining effect. The procedure should not be repeated too soon, as this may lead to overcorrection [9].

Delayed and chronic reactions, involving the formation of granulomas, are associated with delayed-type immune reactions (type IV hypersensitivity) [6].

The occurrence of adverse effects depends to a large extent on the patient's individual immune sensitivity, the technique used, and the material injected. Most of these effects are mild and transient; however, it is essential to inform the patient of all possible effects [13].

The impact of hyaluronic acid treatments on patients' mental well-being – a psychosocial analysis

As the years go by, signs of ageing begin to appear on the skin. People may start to be perceived as less attractive or tired, which not everyone can come to terms with. Facial expressions may also mistakenly convey emotions. Wrinkles between the eyebrows are mistaken for anger, and drooping corners of the mouth for sadness. Some people may experience social prejudice and associated emotional distress.

Correcting the signs of unwanted facial expressions is often the primary aim of treatments using HA fillers. The right volume and facial contours contribute to a more attractive and friendly appearance [16].

The MD Codes™ method is frequently used in the treatment of signs of ageing. This is an approach to aesthetic treatments that takes emotional expressions into account. It is based on four negative facial expressions: tired, sad, drooping and angry; and four positive ones: looking attractive, younger, more athletic and possessing certain gender-specific traits. After the injections have been administered and the intended goal achieved, patients describe themselves as more optimistic, friendly and energetic [16].

Between January and August 2022, a study [Aesthetic Surgery Journal Open Forum] was conducted among patients who had come forward for treatments using HA fillers. The study was approved by the Research Ethics Committee of the Institut du Savoir Montfort (study no. 21-22-11-027).

Twenty-eight individuals (26 women and 2 men) who had registered at a private aesthetic clinic in Ottawa were selected for the study. Patients met specific criteria: aged 30–65 years, BMI <30, no previous surgery in the face and neck area, no body dysmorphic disorder, no allergies or other contraindications, no use of chemical peels, and no filler treatments within the last year [15].

Outcomes were measured using three scales (data collected before and after treatment): psychological functioning, body dissatisfaction, and social functioning. The questions covered satisfaction with facial appearance, feelings of happiness and attractiveness, as well as self-confidence and behaviour in social and group situations. The results confirm that treatments using HA fillers were associated with a significant improvement in patients' psychological and social functioning and significantly reduced appearance-related stress [15].

It should also be noted that hyaluronic acid is used to accelerate the reversal of acne-related changes, which are characterised by the formation of spots, discolouration or uneven skin texture. This helps patients increase their sense of self-acceptance. Acne is a condition that largely affects young people, so appearance-related issues have a significant negative impact on these patients' mental well-being [12].

Summary:

Ageing is a process that occurs in every organism over time. The use of hyaluronic acid fillers is an effective and relatively safe method of counteracting the effects of skin ageing. A review of the literature and the analysis conducted confirm the multifaceted impact of HA on both the external appearance and the mental well-being of patients. Mechanical filling of skin spaces not only temporarily improves appearance but also contributes to the synthesis of collagen and elastin, which translates into long-term improvement in skin condition. Improved appearance significantly affects self-acceptance and interpersonal relationships; however, this also carries certain risks. Patients may have unrealistic expectations regarding the results, and the risk of potential addiction to correcting imperfections is high.

Disclosures:

Author's Contribution:

Conceptualization: Natalie Gąsiorek, Hanna Gruchot, Anna Kuźnar

Methodology: Natalie Gąsiorek, Hanna Gruchot, Anna Kuźnar, Julia Bajorek, Michał Żabicki

Investigation: Natalie Gąsiorek, Hanna Gruchot, Anna Kuźnar, Julia Bajorek, Michał Żabicki

Writing-rough preparation: Anna Kuźnar, Julia Bajorek, Michał Żabicki

Writing-review and editing: Natalie Gąsiorek, Hanna Gruchot, Anna Kuźnar, Julia Bajorek, Michał Żabicki

Project administration: Natalie Gąsiorek

All authors have read and agreed to the published version of the manuscript.

Funding:
This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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