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PUBLICATION INFORMATION:

Lotfi M, Khani M, Shokri B. A Review of Cold Atmospheric Plasma Applications in Dermatology and Aesthetics. Plasma Medicine, Volume 13, Issue 1, 2023, pp. 39-63. DOI: 10.1615/PlasmaMed.2023049359.

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As with any procedure, individual results may vary. As with all energy devices there are inherent risks associated with its use, refer to the IFU for further information.

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Plasma Medicine, 13(1):39–63 (2023)

A Review of Cold Atmospheric Plasma Applications in Dermatology and Aesthetics

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ABSTRACT: Nowadays, there is a growing use of plasma technology, especially in medicine and aesthetics. Plasma medicine is an innovative, multidisciplinary science combining plasma physics and technology with medicine and life sciences. Billions of dollars are spent annually in the United States to rejuvenate and reduce signs of aging. For this reason, several methods have been created to perform such operations. Methods with different degrees of invasiveness, from cosmetic surgery, like forehead lifts and blepharoplasty, to noninvasive, such as high-intensity focused ultrasound and nonablative lasers, have been used in the field of aesthetics and skin rejuvenation. Plasma can also be used as a noninvasive, minimally invasive, or even invasive method in cosmetic applications such as removing wrinkles and strengthening the skin, that can somewhat replace cosmetic procedures such as blepharoplasty and rhytidectomy. By using various active species, plasma affects biological activities and increases the proliferation and transfer of skin cells. With local application of heat and an increase in proliferation and activity of fibroblasts, the production of type III collagen and elastin density in the skin increases. Plasma can be used to sublimate the skin and remove excess tissue. This article summarizes the most recent studies and clinical trials in dermatology and skin rejuvenation, in which different cold plasma sources (jet and spark) have been used, and examines their results.

KEY WORDS: plasma medicine, skin, rejuvenation, cold atmospheric plasma

I. INTRODUCTION

Skin is the largest body organ and can be considered the body's environmental sensor. However, it is not limited to this function but has many applications that can be understood in the literature, such as "What is true function of skin?"[1] Aging in humans is an inevitable process. Loss of skin elasticity and wrinkling due to old age, pregnancy, and menopause in women or to working under direct sunlight, and the effect of ultraviolet rays on the skin in men are widespread problems in society. They occur due to the destructive effects of nicotine and constant muscle movements in some areas, and their effects occur even at young ages.[2] The skin is also known as one of the most vulnerable organs of the body; because it is the outermost part, it is in danger of all kinds of wounds and pathogens. Every year in developed countries, about 100 million scars occur, which lead to 55 million elective surgeries and 25 million post-accident surgeries to treat them. Notably, 70% of cases occur only in children. A scar is the final stage of cellular repair of mammalian tissue; it is the ideal type of tissue repair, with the new skin looking exactly look like the undamaged tissue. It is assumed that over thousands of years, the human body has evolved to repair wounds in unhygienic conditions in such a way as to prevent them from becoming infected. This is why the high rate of proliferation and migration of cells sometimes causes the creation of extra tissue (hypertrophy), or the body does not have the ability to repair the tissue completely and so it appears as a scar with tissue retraction (atrophy).[3]

The primary and most crucial point in this field is the willingness of people in society to perform aesthetics procedures such as facelifts, blepharoplasty, and neck lifts to eliminate the effects of aging on the skin. For example, according to the statistics provided by the Society of Plastic Surgeons in America (2020), the number of blepharoplasty surgeries in 2016 was 209 thousand, reaching 325 thousand surgeries in 2020. In this case, the number of facelift or rhytidectomy in 2016 was 131 thousand surgeries. However, in 2020 this number increased to 234 thousand surgeries, with a turnover of 1 billion and 390 million dollars for blepharoplasty and 1 billion and 850 million dollars for rhytidectomy.[4] According to Zamani and Fazilatpour, one of the reasons for the popularity of cosmetic surgery is its positive psychological effect, especially on self-esteem, although the most important factor is to reduce patients' negative perception of themselves.[5] Studies show that people who go to clinics and plastic surgeons for cosmetic surgery do not necessarily have self-esteem problems but their self-esteem and positive view of themselves increase after cosmetic surgery.[6]

II. PLASMA

In the 1830s, while Michael Faraday was working on electric discharge tubes, he accidentally came across a new phenomenon (later named glow discharge). However, he was unaware of his findings, and his experiments only aimed to investigate the electrons' trajectory in a vacuum tube. In 1879, William Crooks produced an ionized gas for the first time with his invention, the Crooks lamp, which led to the discovery of plasma. However, he did not precisely define plasma or even name it. In the 1920s, Irving Langmuir, researching the electric discharge tube, called it plasma due to the similarity of the ionized gas properties in the tube with blood plasma.[7] Experimental results on the positive column in the discharge tube show that the electric field in this region is weak (about 1 V/cm) and only sufficient to maintain a constant ionization. The charged species density in this region is about 10^{15}–10^{16}/cm^3 and exhibits the property of quasi-neutrality, which may have helped Langmuir come up with a definition of plasma.[8]

Plasma medicine can be considered a relatively new science; however, the first applications of plasma in medicine were in the 19th century. The use of ozone in the 1850s, by Siemens, was as dielectric barrier discharges to clean biologically contaminated water was followed by carbon arc lamps to treat high blood pressure and electrotherapeutic devices such as violet ray machines. These were the first experimental approaches to therapeutic plasma applications (without describing it as plasma medicine).[9]

Plasma is the fourth state of matter that makes up almost 99% of the visible world around us. However, we live in precisely 1% of this world, where it is not found naturally.[10] Plasma is the result of a phase change from a gas state that occurs due to energy transfer. For example, by giving energy to a solid, that solid can be turned into a liquid; by providing energy to the liquid, that liquid can be turned into a gas and then to plasma. Plasma is an ionized gas that consists of electrons, positive and negative ions, electronically excited species (e.g., singlet oxygen, triplet oxygen), as well as active and reactive species of elements such as oxygen and nitrogen (depending on the gas used in the electric discharge) and electric field and ultraviolet radiations.

Artificial plasma at low or atmospheric pressure results from applying energy to a gas such as argon or helium.[11] Plasma can be classified as thermal and nonthermal regarding the kinetic energy of its constituent particles. In the nonthermal type (also called the nonequilibrium type), some of the gas is only partially ionized. The temperature of such plasmas is low and usually near room temperature. In this case, because the electrons have a lower mass, they have a higher speed (temperature) than the ions; also, because of the low mass, they cannot transfer energy to heavy ions.[12]

One of the fundamental characteristics of nonthermal plasmas is their selective properties.[13] Here we describe the basic concepts of plasma physics, production techniques, and plasma parameters. Several books and monographs describe all topics in detail.[14–19]

The formation of nonequilibrium plasmas and gas discharges is based on the formation of electron avalanches. Cosmic rays, radioactivity, or residual charges from previous discharge activities provide the very first free electrons that initiate discharge. The main ionization mechanism in most gases is direct electron impact ionization by free electrons accelerated in the applied electric field, E. Especially at low pressure, the positive ions generated drift to the cathode, resulting in a secondary emission of electrons. This subsequent supply of free electrons seeds new avalanches, which are the main aspect of the Townsend breakdown mechanism, leading to a self-sustaining gas discharge. The process can be viewed as successive avalanches crossing the discharge gap without the build-up of space charge.

The voltage at which a self-sustaining discharge is achieved is described by Paschen's law and is a function of the scaling parameter pd (Torr-cm). While the Townsend criterion (Paschen's law) provides the starting voltage for the Townsend mechanism, the Meek criterion (sometimes called the Raether criterion) describes the conditions for streamer initiation. The streamer formation conditions are related to the charge number density in the primary avalanche required for a significant space charge field perturbation—namely, exp [eff d] = 10^8, where eff = effective first Townsend ionization coefficient. This criterion is typically met in the air at pd values above 1,000 Torr-cm.

Streamers can be viewed as the initial stage of the electrical breakdown of any un-ionized medium (gas, liquid, and solid). They can precede sparks and provide the path for lightning, and they are responsible for the filamentous discharge structure in many nonequilibrium plasmas at atmospheric pressure. Although both cathode- and anode-directed streamers have been observed, cathode-directed (or positive) streamers are more pronounced, and anode-directed (negative) streamers are obtained only in the case of high overpotentials and sufficiently large discharge gaps. Both types of streamers can have branches and thus quite complex spatial structures. Nonequilibrium atmospheric-pressure plasmas operate in a very different parameter space than their low-pressure counterparts, offering new possibilities and presenting their own limitations.

Arguably the most important property of low-pressure nonequilibrium plasmas is their ability to propel ions toward a target substrate anisotropically. This anisotropic bombardment is possible because at low pressure the mean free path of the ions is greater than the width of the plasma sheath. The energy of the ions striking a substrate decreases rapidly with increasing pressure. Mean free paths of ions at atmospheric pressure are on the order of 1 μm and are therefore 100 times smaller than typical sheath widths.

Although physical bombardment is critical to the success of many low-pressure plasma processes, the high collision efficiency encountered at atmospheric pressure prevents the collision-free passage of ions through the sheath. As a result, the ions reach the surface with very low kinetic energy. Although magnetic confinement in low-pressure plasmas has been exploited to improve plasma efficiency, the numerous collisions electrons undergo in a cyclotron period disrupt any effective confinement at atmospheric pressure.

Since, as discussed above, physical ion bombardment in atmospheric pressure plasmas is not very energetic due to ion-neutral collisions in the sheath, most atmospheric pressure treatments rely on plasma chemistry. Here, too, the increased background density brings differences to the processes observed in low-pressure plasmas, and 3-body collisions in particular become important. In atmospheric pressure plasmas, the collision rates of 3-body processes are four to six orders of magnitude higher than in conventional low-pressure plasmas. As a result, atmospheric pressure discharges of atomic noble gases exhibit significant concentrations of dimer ions and molecules, including excimers, leading to the production of VUV radiation.[20,21] The 3-body collisions also result in the formation of chemical species such as O_3 and H_2O_2, which can only be generated by surface reactions at low pressure. Furthermore, in the presence of water molecules, positive and negative ions are hydrated in atmospheric pressure plasmas, with larger water clusters forming at higher water contents. This hydration can significantly affect ion mobility and affect overall plasma dynamics.

The ability to produce cold plasma under atmospheric pressure conditions has been the basis for the rapid growth of plasma-related applications in biomedicine. For example, anti-itch, antimicrobial, anti-inflammatory, tissue-stimulating, blood flow–enhancing, and proapoptotic effects were demonstrated in *in vivo* and *in vitro* experiments, and until now no resistance of pathogens against plasma treatment was observed.[22] As mentioned earlier, plasma is suitable for dermatology and rejuvenation applications.

III. SKIN

Skin is a quasi-solid compound consisting of three main layers: dermis, epidermis, and hypodermis. All three layers have nonhomogeneous composition and structure. The first task of the skin is to protect the internal organs and muscles against physical, chemical, and biological damage in the surrounding environment, but it also ensures homeostasis by limiting phenomena such as water evaporation. Skin is a sensitive organ containing thermal, mechanical, and pain receptors. Also, since it is visible in some areas of the body in all conditions (such as the face area) and at the same time has an aesthetic value, it is exceptionally important. However, after the third decade of life, the skin's structure changes.[23] Skin aging is a progressive process that environmental factors can influence in certain conditions; that is why it falls into two categories: intrinsic and extrinsic.[24,25]

Intrinsic, or chronological, aging occurs due to the passage of time. Usually, it begins in the middle of the third decade of life; when collagen production decreases, elastin is not as elastic as before and dead cells are replaced at a lower rate. Although this process starts in the third decade, its effects are visible only a long time after that.[24]

Extrinsic aging can have various causes that, unlike intrinsic aging, have nothing to do with time. The most crucial reason for abnormal aging is exposure to ultraviolet radiation (e.g., the sun). This is most common in people whose life style forces them to be active in the open air or sunny areas. Aging caused by light is a multistep process that affects the skin and skin support systems. In people exposed to sunlight for a long time, the density of melanocytes is almost twice that of an average person. At the same time, permanent telangiectasia can cause erythema and prevent hydration of the stratum corneum layer. Other causes of abnormal aging include nicotine addiction, constant movements of facial muscles in some areas, sleeping positions, and even gravity and air pollution.[26–29] Conditions in the atmosphere can also be considered a reason for skin damage and aging, even among young people. One factor can be active oxygen species in the earth's atmosphere (e.g., ozone), which cause oxidation processes in the constituent parts of the skin, such as lipids and proteins. This set of reactions causes chronic damage that eventually results in signs of aging such as wrinkles.[30,31]

The aforementioned are skin aging factors that can occur even at young ages due to extrinsic aging. The most common effects of skin aging are primarily observed in the face area, which has constant movements of some muscles and is exposed to sunlight more than other body areas. These signs of aging can be seen as wrinkles in the forehead area, around the eyes, and the lips.[32]

Due to society's increasing desire to be young and beautiful, various approaches have been developed to eliminate this problem, each with advantages and disadvantages.

IV. SKIN REJUVENATION METHODS

A. Cosmetic Surgery

Cosmetic surgeries, while effective, have disadvantages such as a lengthy recovery period. One of the most common side effects patients complain of is pain. After surgery, the scar remains. At the same time, the possible risks cannot be ignored. The face has a high number of nerves compared to other body parts. These nerves can sometimes be at risk; for example, in rhytidectomy, the zygomaticofacial, greater auricular, and auriculotemporal nerves are at high risk of damage. In blepharoplasty, supraorbital, supratrochlear, and infratrochlear nerves are at risk.[33] Other problems, such as seroma, infection, necrosis, hematoma, and wound issues, are also possible.[34,35]

B. Laser

Laser is also one of the methods that can be used to remove spots, wrinkles, and scars from acne. Lasers can be divided into ablative and nonablative. Although nonablative lasers are less effective than ablative lasers, their recovery time is shorter.[36] Laser applications in aesthetics have been much studied. One of the main problems in ablative lasers—which have the highest level of effectiveness due to complete ablation of the treated tissue—post-processing care is a complicated and lengthy procedure, particularly in the first two weeks. Sometimes problems such as dermatitis and hyperpigmentation occur due to skin processing with ablative lasers. It should be mentioned that the statistics on these problems are lower for fractional lasers.[37] Also, lasers are expensive, requiring relatively high maintenance and repair. Due to safety and care points for operators and patients, lasers are not appropriate for all areas of the body (such as around the eyes).[38]

V. PLASMA IN MEDICINE

At the beginning of the 21st century, studies started to show that low doses of atmospheric pressure cold plasma could improve phagocytosis and accelerate the proliferation of fibroblast cells. Also, such plasmas could isolate cells without causing necrosis, which in some cases and conditions caused apoptosis.[39,40] Although the use of plasma in medicine has a vibrant history, its use in dermatology goes back to the beginning of the 20th century. Darsonvalization has been one of the most common and straightforward electrical treatments, which, like today's plasmas, is a high-frequency treatment method. The French physiologist Jacques-Arsène d'Arsonval (1851–1940) discovered the possibility of influencing the human body with high frequencies created by his device and by creating electrical tension.[41] Nowadays d'Arsonval devices usually use a simple step-up transformer (1:l30) which obtains a maximum voltage of 12 KV and a maximum current of 5 mA. Plasma medicine involves using cold atmospheric plasma (CAP) directly on or in the body for aesthetics or therapeutic purposes.[42] Reports so far indicate plasma's effectiveness and usefulness in medicine, food safety, environmental health, and aesthetics.[43] In dermatology, the main applications of CAP are sterilization, increasing growth factors, inducing cell migration, and creating apoptosis and angiogenesis.[44,45] These functions are related to the active components of plasma, such as reactive oxygen and nitrogen species, electric fields, charged species (e.g., ions and ultraviolet radiation), and controllable local heat.[46] CAP is one of the best choices for clinical applications due to its electrical and chemical adjustability.[47]

Cold plasma produces a multitude of different types of reactive species (e.g., RONS),[48,49] which activate critical cellular signal transduction processes[50] resulting in redox signaling in many cellular processes involved in, and often described as the basis of, plasma effects.[51] However, plasma treatment's molecular and functional consequences on the skin and its barrier-like function remain unclear. These processes are essential because excessive oxidative stress disrupts skin homeostasis.[52] Different mechanisms can create cold plasma to be used for purposes of dermatology such as described in the following sections.

A. Spark

Spark discharges are created in the gaps between two electrodes with a high potential difference (Fig. 1). In the middle of the 18th century, Benjamin Franklin proved that lightning and sparks created in laboratories have the same phenomenal basis.[53] Spark plasma is used in various therapeutic-aesthetics fields. According to histological studies, it can sublimate the epidermis without passing through the basal layer. Spark plasma can cause contraction in elastic fibers and produce type III collagen without causing unwanted skin lesions (by local heat generation).[54]

Collagen is a family of proteins found in all vertebrates, although their function and tissue distribution vary.[55] All collagen family members have the characteristic triple helix structure consisting of 3 α chains.[56] Although type III collagen only makes up about 15% of the extracellular matrix,[57] studies show that this member of the collagen family plays an essential role in cell attachment, growth promotion, and differentiation.[58] According to the mentioned mechanism, we can create correction in fibrosis and granulation and other medical lesions such as xanthelasma, skin hemangioma, dermatochalasis, papilloma, skin fibroma, and benign tumors.[59] Also, studies using confocal microscopes show the effect of plasma spark in reconstructing collagens that have changed shape due to aging.[60] For these reasons, one of medicine's most practical plasma devices today is the Spark device. A high-voltage power supply in these devices can create a potential difference between the device's needle and the skin's surface and cause an electrical breakdown in this area. To break down each millimeter of air gas electrically at a pressure of one atmosphere, a potential difference of about 3,000 volts must be created

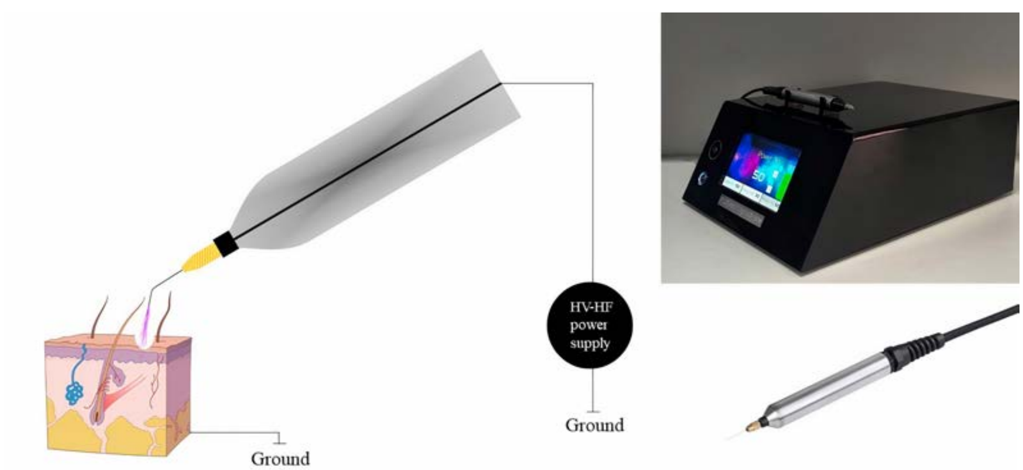

FIG. 1: Schematic of spark plasma device

between the needle of the device and the skin.[61] Various devices with AC and DC power sources are used.

B. Plasma Jets

By creating a controlled gas flow between two electrodes, the charged and active particles can be transformed into a jet stream of plasma (Fig. 2), which can have many applications in various fields of surface processing or medicine.[62] The structural architecture of plasma jets can be in different forms, consisting of one nozzle for the jet or an array of several nozzles, which can optimize them for accurately processing surfaces of large areas.[63,64]

Studies in the animal phase show that the plasma jet using argon gas can stimulate the activity of fibroblasts and create collagen. Although the cellular-molecular details are still unclear, these studies report the positive effect of plasma processing for 15 seconds in the activation of fibroblasts and its negative impact for 30 seconds in mammalian cells.[65]

Comprehensive investigations on plasma interaction and tissue were carried out by Weiss et al. The result showed no tissue-harming effect caused by the plasma but dose-dependent cell growth in the G1 phase of the cell cycle.[66] Another study demonstrated that exposure to plasma was not genotoxic to human cells *in vitro*.[67] Fibroblasts synthesize collagen, the main component of the extracellular matrix and connective tissue. Fibroblasts are mainly responsible for synthesizing type I collagen (85%–90%) and type III collagen (10%–15%), which help tissue repair.[68]

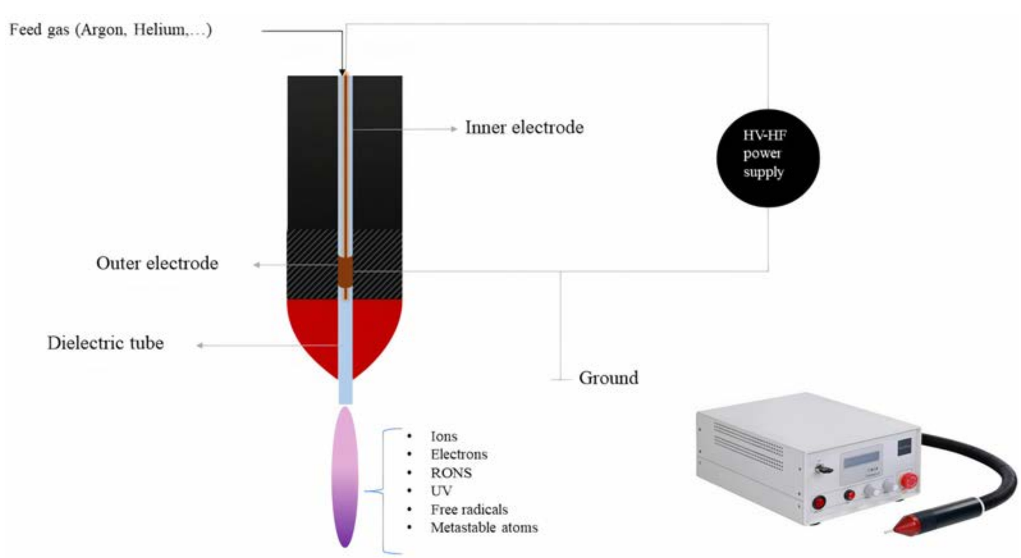

FIG. 2: Schematic of APPJ

Studies on the processing of human cells using cold atmospheric plasma show the effect of plasma produced with helium gas in increased cell proliferation and migration in primary cells such as fibroblasts.[69,70] Some studies have been dedicated to characterizing a plasma jet's physical and chemical properties, which calculate the metastable atom density, electron temperature, electric field, patient current leakage, voltage, and density of chemical compounds present in the plasma medium (section 2).[71–83]

A comprehensive study of the plasma jet developed for medical applications was carried out by Nastuta et al., who gave the physical properties of the discharge as follows: current up to 4.2 mA with a duration of about 6 s and a second discharge current of 4.5 mA with a duration of 3 to 6 s in argon; 2-mA amplitudes and a discharge duration of 12 s in helium. The estimated electric power for Ar averaged 0.7–1 W, while He was reported to be 0.4 to 0.96 W.[75] KinPen, Cinogy PlasmaDerm, and Adtec Steriplas are among the most famous devices in this field having the mentioned applications.[84,85]

VI. SPARK PLASMA'S AESTHETIC APPLICATIONS

Plasma medicine is an interdisciplinary subfield in plasma physics, medicine, and human biology. Applications in medicine and beauty have been investigated, with some studies turning out to be milestones. In this article we review some of these studies with the goal of rejuvenation (see Table 1).

A. Wrinkles and Signs of Aging

Dermatochalasis is a part of the aging process of the eyelid (which appears in the form of extra, loose skin), often improved by blepharoplasty. Many studies have investigated the ability of spark plasma to sublimate excessive tissue. During an experiment, 17 individuals (16 women and 1 man) aged between 46 and 75 years with an average age of 61.1 years suffering from moderate and severe dermatochalasis were treated in the upper eyelid area by spark plasma. The degree of severity of the condition was between 0 and 4. The results were that 7 out of 17 patients (41%) showed 2 degrees of improvement and 10 out of 17 (59%) showed 1 degree.[86]

In another, similar experiment, 60 individuals (9 men and 51 women) were treated on the upper eyelid (blepharoplasty) by spark plasma using the Plexr Plus (GMV, Italy). All patients were examined at intervals of 6, 12, and 18 months to gauge the long-term effects of plasma along with client satisfaction. During treatment, pain was described as very little by 60% of patients, and most expressed minimal discomfort. Scabs after treatment were immediately visible and disappeared in 5–14 days. Patients were directed to use antibiotic ointments in the first days after treatment, so no cases of infection were recorded. They were also asked not to expose themselves to direct sunlight for one month without the necessary measures to prevent hyperpigmentation. Eyelid swelling was common, but disappeared 3 to 5 days after the procedure. Among patients, 66.6% (40) had 100% satisfaction, 25% (15) had 80% satisfaction, and 8.3% (5) had

TABLE 1: Milestones of plasma spark applications in medicine and skin rejuvenation

Year	Description	Title	Ref.
2012	First article on spark plasma in improving wrinkles published in reputable journal	"Treatment of Perioral Rhytides with Voltaic Arc Dermoabrasion"	86
2012	First article on spark plasma in treatment of xanthelasma	"Treatment of Xanthelasma palpebrarum with Voltaic Arc Dermoabrasion"	87
2014	First article on spark plasma in blepharoplasty	"Plexr: The Revolution in Blepharoplasty"	88
2014	Comparison between surgery and spark plasma in blepharoplasty	"Noninvasive Upper Blepharoplasty in Relation to Surgical Blepharoplasty"	89
2015	First article on spark plasma in treatment of acne	"Plexr in Acne Treatment"	90
2015	First histological study of spark plasma	"Clinical and Histological Presentation after Plexr Application, Needle Shaping (Vibrance) and OFF"	59
2016	Widespread use of spark plasma in treatment of wrinkles, moles, post-acne scars, etc.	"Applications of Plasma Exeresis in Dermatology"	91
2017 & 2018	Complementary histological studies of spark plasma in clinical and applied cases	"The Gas Ionization by Plasma Technology for Noninvasive Techniques in Oculoplastic"	92
		"Noninvasive Blepharoplasty with Plasma Exeresis (Plexr) Pre/Post Treatments"	93
2020	Comparative study of surgery and spark plasma in blepharoplasty on two eyelids	"Conventional vs. Noninvasive Upper Lid Blepharoplasty in Upper Lid Dermatochalasis: A Comparative Case Series Study"	94
2022	First quantitative study of spark plasma on skin characteristics	"The Quantitative Investigation of Spark Plasma on Skin Parameters: Skin Elasticity, Thickness, Density, and Biometric Characteristics"	95

60% satisfaction at 6-month follow up, and at 12 and 18 months 100% satisfaction was recorded for 58.3% (35 people), 80% for 33.3% (20) and 60% for 8.3% (5).[87]

In other studies, the level of client satisfaction with the Firebolt plasma device (Mersateb, Iran) was recorded. Fifty-eight individuals participated (56 women and 2 men; results for the men were not discussed due to their small number). The power of the device was 8 J/s. Of the patients, 58.9% (33) were satisfied, 23.2% (13) were completely satisfied, and 17.9% (10) were dissatisfied. As for side effects, 73.5% (41) had none; 10.7% (6) had swelling and erythema, 6 had only erythema and 3 had swelling although complete recovery was observed after one week.[88] Regarding facial wrinkles, 135 individuals (127 women and 8 men) were subjected to spark plasma treatment to remove crow's feet around the eyes; of these 12 were addicted to nicotine. The average age of the patients was 59.1 years (51–67 years).

Pain recorded in this experiment was 3.45 ± 1.64 (out of 10). No pain was reported at 1 week, 1 month, and 1 year. Patients reported almost no discomfort after the end of the procedure, and only 14% reported a feeling of warmth with mild irritation. In the first week after treatment, only two patients experienced swelling; at 1 month, no swelling was reported. Satisfaction in the first month was 4.15 ± 0.6, and the average surgeon satisfaction was 4.68 ± 0.5 (out of 5). However, at one year, patient satisfaction was 3.25 ± 0.5 and average surgeon satisfaction was 4.1 ± 0.3.[89]

In similar research, 80 individuals with preauricular wrinkles (56 women and 24 men) were treated. Post-treatment edema was reported by 24 patients in the first week. Swelling was reported by 10, but it improved after three days. Patient satisfaction was 8.1, and physician satisfaction was 8.5 (out of 10).[90] Hassan et al. conducted experiments on 40 individuals to eliminate dermatochalasis. Each client was treated with the Derma Plax (Dermica Laboratoires, Zurich, Switzerland) plasma device 3 times at 1-month intervals. The final results were recorded 3 months after the treatment period and in the final follow-up. The results for FLR (facial laxity rating) were compared, and showed positive changes in 36 patients (90%) and no change in 4 (10%). The numerical evaluation of improvement in excess eyelid tissue was reported as 2 patients with 4 degrees of improvement, 16 with 3 degrees, 14 with 2 degrees, and 4 with 1 degree. Four were reported without improvement (0 degrees).[91]

Scarano et al. performed tests to eliminate wrinkles around the lips using the Plexr device. Fifteen participants (11 women and 4 men) between 30 and 65 years of age participated. In the first week post-treatment, 9 cases of swelling were reported, and at 30 days 7 cases were observed. In terms of the effect of treatment after 1 month, 50%–75% improvement was reported in 9 cases, and 25%–50% improvement was reported in 5 cases. No hyperpigmentation, hypopigmentation, infection, transmission of diseases such as herpes, or other problems like erythema, pain, burning, or itching were reported.[92]

The effect of plasma in combination with other rejuvenation methods is one of the most attractive areas of research. Paganelli et al. investigated the impact of spark plasma and hyaluronic acid injection for neck skin rejuvenation in 10 patients aged between 45 and 63. Improvement was reported in all 10, and client satisfaction was even higher than researcher satisfaction. GAIS (Global Aesthetic Improvement Scale) scores of 1 and 2 were reported by 90% of patients, and only 1 patient reported a score of 3. The horizontal lines of the neck were almost entirely improved in all patients. The pain VAS score among patients was 2.4 out of 10 (average).[93]

Rossi et al. investigated the effectiveness of the Plexr device for noninvasive blepharoplasty. In this research, 10 patients (all women) aged 40 to 72 were subjected to eyelid surgery using the Spark device. According to clinical evaluations, 4 had moderate dermatochalasis, and 6 had severe dermatochalasis. At the end of the tests, improvement was observed in all patients: 7 with 3 degrees of improvement, 2 with 2 degrees, and 1 with 1 degree. No severe side effects were observed. Slight swelling was observed in all patients. The resulting micro-burns healed between 3 and 7 days, and the erythema improved between 25 and 40 days. No hyper/hypopigmentation was reported.[60]

In a study using a dermal ablation surgery (DAS) device, experiments were conducted to determine the effectiveness of this method in noninvasive blepharoplasty in 10 individuals (7 women and 3 men) aged between 40 and 72 years. Each was treated at intervals of 30 days. All patients tolerated the treatment during and after without any problems, and no pain was reported. No hyper- or hypopigmentation was reported, and visual average scale (VAS) improvement was above 8 (out of 10).[94] One study investigated the effect of the Plexr device on 250 individual of which 75.2% (188) were women and 24.8% (62) were men aged between 12 and 80 years. This experiment treated different problems using a Plexr device; details are provided in Table 2.

Regarding eyelid treatment, slight swelling was observed which healed after 24 to 72 hours. Burns resulting from skin sublimation by the device healed between 3 and 7 days in the case of single-point treatment and between 7 and 14 days for continuous treatment, such as mole removal. After healing, the skin at the burn site appeared somewhat pink and the resulting erythema improved between 20 and 45 days. The healing of sublimated tissue took 2 to 9 days for the single-point treatment and 3 to 14 days for the continuous treatment. All patients healed without scarring, but 2 cases of

TABLE 2: Details of Plexr treatment

Condition	Method	Power (W)	No. sessions	No. patients
Dermatochalasis	Dot	0.7	3–6	45
Perioral rhytids	Dot	1	1–2	25
Glabellar wrinkles	Dot	1	1	10
Solar lentigo	Continuous	0.7 and 1	1	47
Seborrheic keratosis	Continuous	1 and 2	1	53
Skin moles	Continuous	1 and 2	1	44
Active acne	Dot	1	3–6	9
Post-acne scars	Dot	1	2	8
Wound scars	Continuous	0.7 and 1	1	9

hyperpigmentation (both women) were reported, the first on the eyelid and the second on the upper lip; both were completely healed at 3 months.[95]

Sotiris et al. compared noninvasive treatment using the Plexr device and blepharoplasty. Fifty individuals were tested, of which 10 were treated surgically and 40 were treated with the Plexr. The results indicated that every repetition of plasma treatment improved dermatochalasis by 30%. The surgical recovery period (stitches) was 5 days, and the plasma recovery (scab healing) was 7 days. However, more care and maintenance were required after surgery. The superiority of the plasma device was illustrated by the need for less care, the absence of any possibility of asymmetry in the eyelids, the short treatment duration, and the repetition of treatment as many times as desired.[96]

B. Other Skin Conditions

Plasma can also be used to eliminate active skin acne. In this regard, Stamatina et al. conducted experiments on 30 cases (10 men and 20 women) aged between 14 and 45. Ten patients were treated three times using the plasma device. No adverse side effects, such as scars and hyperpigmentation, were observed, and 100% of the desired results were obtained without clinical treatment.[97] In another study, the Plexr device was used to treat active acne in two patients. Treatment was once every 2 weeks for 2 months (4 treatments total). No hyper/hypopigmentation, infection, erythema, or swelling were reported after the treatment period, and no scars were reported at follow-up.[98]

In today's world, plasma is advancing quickly in aesthetics, and its use is not limited to creating regional heat and increasing collagen production. It can also be used to remove benign moles. Scarano et al. researched the application of spark plasma in 45 individuals (26 women and 19 men). In no patient was erythema, itching, or outbreak of herpes and bleeding reported. Rather, it was proven that spark plasma can be an effective method for benign mole removal.[99]

Spark plasma can improve the negative results of other aesthetics procedures. Sioumas et al. reported on the treatment of negative impacts of filler injection in the upper lip area been ongoing for 15 years. Spark plasma was used to successfully mitigate these impacts with no adverse effects reported.[100]

Favre-Racouchot syndrome is a solar elastotic disease from numerous open comedones in skin damaged by solar radiation. Lesions usually appear around the eyes and temples. The main risk factors are smoking and excessive exposure to ultraviolet rays. Histological studies show atrophy in the epidermis tissue. One study conducted on a 65-year-old man investigated the effects of Plexr in treating Favre-Racouchot syndrome, with the device operated in continuous mode (spray). The treatment session was reported to be efficient, and all resulting wastes were treated. At 10 months, no recurrence of lesions was noted.[101] Comprehensive cases have also been registered in skin aesthetics using ablative spark plasma. Various skin lesions and signs of aging were treated including moles, excessive tissue, boils, xanthelasma, and the like.[102]

Freckles are concentrations of melanin in a specific location on the skin caused by sunlight and genetics among other factors. The Plasmage (Brera Medical Technologies, Italy) plasma device's performance in removing freckles on the face was investigated via tests on 7 women. Improvement was reported to be better at 6 months than at 2 and 4 months.[103]

Xanthelasma (fat under the skin of the eyelid) is often seen as soft or semi-solid lesions. They are benign on the eyelids and generally harmless, although they can significantly reduce the aesthetics of appearance. Fifteen patients with xanthelasma were treated with the Plexr device for a total of 27 lesions. Twelve patients had xanthelasma in both eyelids; and 3 had them in only one. All complications disappeared with one session. Immediately after treatment, a brown burn mark was seen at the treatment site which healed in 7 to 14 days. No adverse post-treatment effects were observed, and no cases of relapse or recurrence were reported at 12 months.[104] In another study, 20 individuals (14 women and 5 men) were treated with a plasma device for xanthelasma. The energy setting for all patients was set to 0.6 J. According to need, the treatment was repeated 3 or 4 times at 1-month intervals. To prevent hyperpigmentation, patients avoided direct exposure to sunlight for 5 months without the necessary protection.[105]

Darwin's tubercle (DT) is a congenital outer ear deformity characterized by a posterior thickening of the auricular helix. It is more common in some ethnic groups than in others. In one study, a 28-year-old female underwent treatment with the Plexr device, and healing was evaluated up to 6 months after the first treatment session. At the end of the treatment period, the patient reported her status as very improved.[106]

Nasal telangiectasias are small, superficial vessels in the nasal fold with different origins. They can create discomfort and frustration. Micro-sclerotherapy, electrosurgery, various types of laser therapy, needle electrocoagulation, and TRASER therapy have been used to treat this condition.[107] In a study of 23 individuals, a Spark device was used to treat this condition. The power supply settings were to 3 kV and 2 W. During the treatment, clients reported moderate pain, which disappeared after the treatment was completed. Swelling and erythema was reported to improve within 4 to 6 days. After treatment, the skin was gray-black due to residual carbon compounds, but recovered within 6 days. Improvement according to aesthetic criteria was observed at 6 days (after wound healing).[108]

C. Scars

Individuals often seek medical advice with the expectation—conditioned by the media—that their scars can be removed entirely. It is essential to inform them that scars cannot be completely eradicated but there may be potential for improvement[109] with spark plasma, an effective and low-risk approach. Ting Lan et al. used Micro-Plasma Pixel RF (Pixel RF, Micro-Plasma, Alma Laser, Israel) to treat 95 individuals for atrophy scars caused by acne for 1 to 9 years. All of them underwent 3 treatments in 2 months. Eighty-six (53 men and 33 women) completed their follow-up period (1, 3, and 6 months). Three dermatologists evaluated post-treatment and improvement rates, and the results were reported as 15, excellent; 46, good; 24, moderate; and 1, poor. Client satisfaction was 38, very satisfied; 48, satisfied; and 0, dissatisfied.[110] Baroni and Verolino investigated the effectiveness of ablative spark plasma in eliminating scars on 10 individuals (6 women and 4 men) using the DAS device. At the end of treatment, all patients reported higher than 8 on the VAS scale.[36] As reported by Baroni in another study, the DAS device was used to remove a scar from the upper lip of a 45-year-old woman resulting from surgery. The treatment consisted of 2 sessions using plasma at 0.6 J and 30-day intervals. The woman avoided direct sunlight for 5 months, and applied an antibiotic ointment for several days. Excellent clinical improvement was reported.[111]

D. Hybrid Lifting Homologous (HLH) Method

According to the basic principles of facial anatomy and lifting surgery, the HLH method was created for aesthetics and rejuvenation. An alternative to surgery with the least invasiveness is the lifting method using thread along with plasma. Sotirios reported that improvement in wrinkles and facial changes were clearly evident after the first session, with no adverse results or negative side effects. After the first session, patients expressed satisfaction with the stretching and strengthening of their skin.

Plasma treatment, as proven by histological examination, causes the production of type III collagen. Also, it causes sublimation of both the topmost layer of the epidermis (stratum corneum) and dead keratinocytes. Elastic fibers in the face become shorter and thicker by changing their direction and quality. At the same time, histology re-examinations show that after 28 days, new elastic fibers are formed in the tissue. Extra tissue on the skin is sublimated by plasma.[112]

VII. ATMOSPHERIC PRESSURE PLASMA JET

In plasma skin regeneration, energy is transferred to the skin by plasma instead of laser, light, or electrodes. Selwyn et al. were probably the first to use the atmospheric pressure plasma device, calling it the atmospheric pressure plasma jet (APPJ).[113,114] Before starting plasma aesthetics/therapeutic procedures, there must be appropriate review of protocols and standards. APPJ with argon as the feed gas (KinPen9), Lademann et al. observed that no wavelength was lower than 300 nm, and that the stratum corneum completely absorbed ultraviolet radiation with a wavelength of 310 nm. A layer of keratinocyte cells can absorb 25% of ultraviolet rays, whereas the stratum corneum consists of 15 to 25 cell layers. Also, Lademann et al.’s recorded values indicated that the radiation released from the plasma jet was one-tenth of the radiation from the sun falling on the Earth’s surface.[115] Other standards have been registered by the German Standards Agency to determine criteria for using a plasma device (DIN SPEC 9131). Standards, such as for pre-treatment, patient selection, and treatment and patterns, have been the subject of some research.[116,117] In the following we investigate the effect of different feeding gases for plasma on skin regeneration.

A. Nitrogen

The FDA-approved Portrait PSR (Rhytec, USA) is one of the most practical APPJs, having variable energy settings and single- and multi-pass processing. It transfers energy to the nitrogen gas flow inside the its handpiece and turns it into plasma. Nitrogen is a gas source because it can remove oxygen from the skin's surface, minimize the risk of unpredictable hot spots, and prevent scarring and burns. As the plasma hits the skin, the energy is quickly transferred to the skin's surface, causing instant heating in a uniform and controlled manner without an explosive effect on the skin and removal of epidermal tissue. In research conducted on Portrait PSR in single-pass treatment at 1–4 J and in multi-pass treatment at 1– 2 J on the skin at the side of the ear (postauricular skin), it was shown that the thermal effects were no deeper than the epidermal layer and the epidermal junction. They penetrated the papillary dermis when the energy was increased to 3–4 J for multi-pass treatment.[114]

PSR devices with nitrogen-feeding gas can be considered a competitor of CO_2 lasers. The effects left by the CO_2 laser and by the PSR device were compared during histological studies on three miniature pigs. The effectiveness of these devices in rejuvenating and improving the appearance of the skin was then investigated. The results indicated that destruction of the epidermis caused by the PSR device was less than that caused by the laser, and that the PSR had a more significant effect.[118] In another study, a nitrogen plasma jet device was used to investigate APPJ's performance in removing scars caused by a CO_2 laser. Four wounds were created on each of five patients (4 men, 1 woman; 20 wounds) using a CO_2 laser device. The wounds were subjected to short-term, long-term, and repeated plasma treatment, with one sample designated the control. It should first be mentioned that all cases were monitored for 12 months and no adverse effects, such as growth of cancer cells, were observed. It turns out that plasma therapy supported the inflammation necessary for tissue healing, and that, at later stages and in mature scars, it would probably have better results than those for the control group in avoiding various post-traumatic skin disorders. Treatment in different time-related doses exhibited superior aesthetic properties from the beginning to the end of scar formation.[119]

In another study, 8 patients underwent complete face treatment using the Portrait device to confirm its skin rejuvenating properties. Each patient was subjected to three complete face treatments at intervals of 3 weeks. Energy settings of 1.5–1.8 J were used on the forehead, cheeks, and upper lip, and settings of 1.2–1.4 J were used on more delicate parts such as the eyelids. The lowest pain reported was during treatment, and all patients reported improvement.[120]

PSR affects two general areas of the skin structure: the thermal damage area and the thermal modification area. The amount of thermal damage is such that cells are not able to continue their vital activities. However, in thermal modification either cells are not damaged or the severity of the damage is such that they can continue their vital activities. Even so, increasing the energy or the number of treatment sessions increases the area of thermal damage. In tests on 24 patients who were treated with the Portrait device for skin rejuvenation, all 24 tolerated the process. The amount of pain patients reported had an expected value of 4.3 (out of 10). The average time of each treatment was 14.3 minutes. Swelling and erythema were observed in patients after treatment, but there was no trace of destruction of the epidermis. At 24 to 48 hours, it was reported that recovery time would be around 7 days (an average of 7.89 days). Swelling at 7 days and erythema at 30 days disappeared completely.[121]

Studies have shown that skin healing can be enhanced by ointments with active ingredients such as botulin.[122] During 28 months, 272 cosmetic procedures were performed on 95 patients by Holcomb et al. to investigate the effects of nitrogen plasma as well as common cosmetic surgeries such as blepharoplasty, rhytidectomy, and elimination of sagging cheeks. These processes improved results with no reported increase in problems.[123] Other researchers have investigated the combination of helium plasma devices and standard surgical methods.[124]

The uncontrolled proliferation of fibrous tissue causes keloids. Several treatment strategies that may be effective for this complication have been reported, including steroid injections, surgical resection, laser therapy, and radiation therapy, but few studies have focused on the performance of plasma skin regeneration (PSR) in keloid treatment. In one study to evaluate the effectiveness of PSR combined with radiation therapy for keloids on different body parts, 71 patients with 98 keloid scars participated. Colloids with a thickness of less than 4 mm were treated by PSR, while those with a thickness greater than 4 mm were injected with betamethasone compound before treatment. Radiation therapy was also performed at 24 hours and 7 days after PSR. Twenty-three cases of keloids were reported on the face, 26 on the chest, 16 on the shoulders, 16 on the waist and back, and 17 on the legs. Sixty-two patients reported how their keloids were created. Twenty-nine developed after wound formation, such as from surgery, and 33 were hereditary. It was observed that face, chest, and back keloids experienced better improvement compared to those on the shoulders and legs. The return rate was reported to be 15.3%, and all returns were mild.[125]

PSR technology can eliminate the effects of injury and acne as well as their scars. In an experiment by Kono et al., tests were performed using a plasma device on 20 patients with post-injury scars. These tests were performed 3 times at 1-month intervals at 2–3 J. Pain was reported as 5.8 (out of 10). Approximately 7 days after treatment, the lost epidermal tissue was replaced by epithelial cells. No signs of infection were reported, nor were any signs of worsening of scars.[126] Research in the animal phase also showed the effects of nonthermal plasma in preventing the formation of scars and scar marks after wounds created on the skin of the head.[127]

Higashimori et al. investigated the effects of a PSR device on skin scars grafted with mesh in post-traumatic scar healing. Four patients were treated at 3–4 J, and care was taken to ensure that the treatment areas were distinct. The amount of pain reported was 6.9 ± 1.2 (out of 10). All patients tolerated the pain well. After treatment, hypopigmentation was reported in 2 patients, gradually improving by the 6th month. Improvement above 50% was reported in all clients.[128] Other studies have examined plasma's effectiveness in healing scars, removing benign moles, and eliminating problems such as rhinophyma.[129]

B. Helium and Argon

In a study by Holcomb et al.,[130] 55 patients were treated with atmospheric pressure helium plasma at a power of 20% to reduce wrinkles and increase skin elasticity. Most of the patients were given complete face treatment and the results were evaluated using the Fitzpatrick Wrinkle and Elasticity Scale (FWS). Improvement of more than 1 degree was recorded for 63%–64% of patients by observers who were unaware of the treatment. However, improvement of more than 1 degree for 54–55 patients (99%) was reported by the researchers and by observers who were aware of the treatment. This set of studies recorded improvement for 90% of clients by GAIS.[130] In a 2022 study conducted by the group mentioned earlier as a continuation of their research, helium plasma with a power of 40% was used to treat the skin of patients. According to the researchers, an earlier study showed that 20% power could not highlight all the potential of this technology. In the 2022 study, 55 patients underwent full face treatment using this device (J-Plasma, Apyx Medical, USA). It was reported that all patients had an amelioration grade of more than 1 according to the FWS. Also, according to GAIS criteria 96.4% showed improvement in their wrinkles at 90 days.[131] Doolabh et al. conducted experiments on the effect of cold atmospheric plasma on restoring elasticity to sagging neck skin in 15 patients. Helium was used as the feed gas, and the FDA-approved Renuvion (Apyx, USA) was used as the gas's excitation source. Two cases of adverse effects were reported. On average, a 37.29% improvement in the angle and area of sagging skin was observed.[132]

In studies conducted in 2019, 40 women were treated with the BIOplasma (PhotoBioCare, Nonthaburi, Thailand) jet device in the facial area to evaluate the device's performance in removing wrinkles and changing facial parameters. Each subject was treated for 20 minutes at 4 J for the whole face, once a week for 5 consecutive sessions. According to the researchers, most subjects had quartile grading scale improvement of 51%–75% at 4 and 12 weeks. Greater than 75% improvement in dyspigmentation, wrinkles, and elasticity was reported in 60%, 50%, and 57.5% of patients, respectively.[133]

Grigoras et al. studied the performance of cold atmospheric plasma in increasing the speed of tissue healing and epithelial cell migration in 12 Wistar rats. Using an atmospheric pressure plasma jet device with helium as the feed gas, burn wounds on the rats were treated and the results compared with the results for controls. Histological tests were performed on the treated and control rats at 3, 8, 14, and 21 days. The results indicated an increase in the reproduction rate of epithelial cells on the tissue of the treated rats.[134]

It has also been proven that cold atmospheric plasma with argon as the feeding gas can increase anti-aging genes without damaging skin cells.[135] And various studies have shown that such devices can create antiseptic properties and benefit clinical applications.[18,136,137] Plasma production devices can be used to speed up the proliferation of fibroblast cells and wound healing[138] without creating any risk while reducing the bacterial load of the wound.[139,140]

VIII. CONCLUSION

Plasma technology is finding a solid place in medicine and engineering among other fields. Specifically, various plasma production systems, such as argon, nitrogen jets, and spark devices, are used in aesthetics. According to the findings of the studies discussed here, plasma can be seen as one of the best options for aesthetics procedures involving eyebrows, eyelids, and facelifts.

Although there is no doubt that cosmetic surgery has many positive effects, its risks cannot be ignored. Plasma, as a low or noninvasive method, can be used in various aesthetics processes without patients worrying about their physical health. It is worth mentioning that, although the results of initial plasma treatments may be weak compared with the results of surgical procedures, their low cost and low risk mean that they can be performed repeatedly, with shorter recovery periods.

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