NON-THERMAL ATMOSPHERIC-PRESSURE PLASMA IN THE ANTI-AGE THERAPY OF FACIAL SKIN

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Traditionally, anti-age therapies employ ultraviolet radiation and exposure to ozone, nitric oxide and electromagnetic fields. Non-thermal atmospheric-pressure plasma (NTAPP) combines the effects of all those techniques. The aim of our study was to assess the feasibility of low-dose NTAPP application in anti-age facial skin therapy. Ten female patients aged 50 to 55 years were examined and three facial zones were chosen for the experiment: the T-zone (the central part of the forehead) and the "crow's feet" areas on the right and left sides of the face. Ultrasonography was performed on the DUB SkinScaner before the treatment course and 24 hours after the last treatment. Cleansed skin was exposed to a low-energy NTAPP helium jet generated by the HELIOS system (Plasma Research and Production, Russia). Exposure time was 5 min per zone. Each participant received 10 NTAPP procedures on alternate days. Before therapy, the skin condition in all participants fitted into morphotype 3. Ultrasonography of the studied zones revealed a considerable deformation of the skin surface, a thickening of the epidermis with a distinct border between the epidermis and the dermis, a slight thinning of the dermis, its relatively homogenous echogenicity, and a blurred border between the dermis and the hypodermis. After the course was completed, all patients demonstrated an evener skin surface, reduced epidermal thickness and reduced acoustic density of the epidermis and the dermis; the dermis tended to have above average thickness. The most significant changes were observed for the wrinkles: they became less pronounced in the "crow's feet" area. Exposure to NTAPP caused the epidermal corneum to diminish in thickness; it also stimulated microcirculation and improved the condition of the hydrolipidic film, all of which ultimately led to the effacement of wrinkles. Treatment produced no adverse effects on the skin or its appendages.

Keywords: skin aging, non-thermal atmospheric-pressure plasma, wrinkles

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НИЗКОТЕМПЕРАТУРНАЯ АТМОСФЕРНАЯ ПЛАЗМА В КОРРЕКЦИИ ВОЗРАСТНЫХ ИЗМЕНЕНИЙ КОЖИ ЛИЦА

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В антивозрастной терапии кожи лица стандартно используют ультрафиолетовое облучение, обработку поверхности кожи озоном и оксидом азота и воздействие электромагнитным полем. Низкотемпературная атмосферная плазма (НТП) способна оказать все эти воздействия. Целью работы было оценить эффективность НТП низкой интенсивности в качестве антивозрастной терапии кожи лица. Десяти пациенткам в возрасте 50–55 лет проводили исследование состояния кожи лица (Т-зону (центр лба), области «гусиных лапок» справа и слева) на аппарате DUB SkinScaner до начала применения НТП и через сутки после 10 процедур. После очищения кожи ее обработали НТП низкой интенсивности, которую генерировали в среде гелия в виде плазменного факела на приборе «ГЕЛИОС» («НПЦ Плазма», Россия). Время экспозиции НТП составило 5 мин на каждую зону, процедуры проводили через день. До лечения состояние кожи лица всех участниц соответствовало третьему морфотипу инволюционных изменений. Ультразвуковое исследование (УЗИ) всех зон показало значительную деформацию микрорельефа, утолщение эпидермиса при сохранении четкой границы эпидермиса и дермы, некоторое снижение толщины дермы с однородной эхоструктурой, смазанное отграничение дермы от гиподермы. После завершения курса у всех пациенток отмечено уменьшение деформации микрорельефа, средней толщины эпидермиса и ультразвуковой плотности эпидермиса и дермы, тенденция к увеличению средней толщины дермы. Наибольшие изменения коснулись морщин: наблюдалось их сглаживание в области «гусиных лапок». Таким образом, использование НТП вызвало уменьшение толщины рогового слоя эпидермиса, улучшение микроциркуляции и улучшение качества гидролипидной мантии кожи, что сопровождалось сглаживанием морщин. Нежелательных явлений со стороны кожного покрова и придатков кожи не было отмечено.

Ключевые слова: возрастные изменения кожи, низкотемпературная атмосферная плазма, морщины

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Skin aging is the first visible sign of changes occurring in the body as it grows old. There are two types of aging: chronological (intrinsic) and sun-induced (extrinsic, also called photoaging) [1]. Typical features of chronological aging include a 10% to 50% loss of the epidermal thickness, atrophy of the prickle cell layer, shrinking and flattening of basal cells, decreased mitotic activity of basal keratinocytes, slow lipid renewal, flattening of the dermal-epidermal junction, and progressive loss of melanocytes, Langerhans cells and melanocyte heterogeneity. Dermal fibroblasts of the aging skin become less abundant, the extracellular matrix atrophies, collagen and elastic fibers degrade and shrink, and amyloids deposit. Such involution causes skin deformation and wrinkles. The second type of aging, photoaging, is an inevitable result of skin exposure to the hostile environment that causes skin withering. Its symptoms can be noticed long before the first wrinkles appear. Morphological and functional signs of photoaging are traditionally categorized into dermal and epidermal. Visible manifestations of photoaging include telangiectasias and pigment spots (lentigines).

The main differences between photoaging and intrinsic aging include epidermal thickening caused by the thickening of the stratum corneum and accumulation of atypical amorphous elastin in the dermal extracellular matrix. However, in photoaging the dermis retains its ability to synthesize collagen and other components of the extracellular matrix; therefore, some of its manifestations can be reversed.

Visible signs of aging vary and can be grouped into five morphological types [2]:

• morphotype 1 referred to as “the tired face”; the face looks puffy, with drooping mouth corners;

• morphotype 2 known as “the wrinkled face”; it is characterized by the pronounced wrinkles around the eyes (“crow’s feet”) and on the upper and lower eyelids; vertical upper lip wrinkles are also visible;

• morphotype 3, which refers to age-related facial and neck deformities, namely excess skin on the upper and lower eyelids, sagging cheeks, and a double chin;

• morphotype 4 is the combined type; it brings together the age-related changes mentioned above, lack of skin firmness, deep wrinkles, and overall skin deformation;

• morphotype 5 is the muscular type characterized by the folds on the lower and upper eyelids, pronounced expression wrinkles, and loss of facial contours; this type is most often seen in Asian and Japanese people who have well developed facial muscles and not so much subcutaneous fat.

As we grow older, our skin becomes thinner and paler, loses its elasticity and firmness, and the texture of its surface changes. Age affects all skin layers, including the epidermis, the dermis, and the subcutis. In young people these layers are visually distinct; dermal papillae create a very clear pattern showing on the epidermis, the dermis is firm, the subcutaneous tissue is well-pronounced [2]. As we age, the skin thins out and loses its well-defined structure [2]. The pattern on the skin surface fades out and the interface contact between the epidermis and the dermis shrinks in size [2]. The fibrous support of the dermis becomes lax, the signs of edema are observed [2]. Wrinkles start to show. The subcutaneous tissue looks fibrotic and the border between the subcutis and the dermis becomes very blurred.

Skin aging is an issue for many patients and a challenge for a cosmetic dermatologist. Treatments invented to combat skin aging are abounding and based on the use of special cosmetic products, chemical peeling and other non-surgical procedures used alone or in combination [3–5]. All of them serve to restore the hydrolipidic film of the skin, maintain adequate water content in the epidermis and dermis, and improve microcirculation in all skin layers, promoting synthesis of collagen fibers [3]. However, these therapies often have unpleasant or even severe adverse effects. Treatments for the aging face, neck or décolleté area may provoke allergies [5]; chemical peelings can cause skin flaking, edema and/or pigmentation of the treated areas [5]; laser treatments, electrical stimulation or the like may result in demarcation lines, hyper- or hypopigmentation, scarring, thermal burns, pain, loss of skin tone, or electric injury [6]. Therefore, the search for effective and safe treatments against skin aging is still ongoing. So far, a number of experiments have shown that low-dose non-thermal atmospheric-pressure plasma (NTAPP) can improve tissue nutrition and the ability of skin to rejuvenate [7–10].

NTAPP is a novel noninvasive method that combines the effects of ultraviolet light and exposure to ozone, nitric oxide, and the electromagnetic field [8–12]. In its essence, plasma is a partially or fully ionized gas, the so-called fourth state of matter. NTAPP is generated when the electromagnetic field is applied to the gas at atmospheric pressure. When the field is strong enough, gas molecules start releasing electrons, turning into gas ions. Free electrons are accelerated by the electromagnetic field and move to the anode colliding with gas molecules, generating more gas ions and more free electrons (ionization by collision). The process goes on and on, resulting in the generation of plasma. Plasma properties are determined not only by the electromagnetic field, but also by gas pressure, gas type and the radiation source geometry [12, 13]. Conveniently, NTAPP lacks the main drawback of other therapies: high concentrations of toxic chemicals.

The main components of NTAPP are electrons, ions, free radicals, and light [13]. Free radicals are particularly important for cell and tissue physiology. Reactive oxygen and nitrogen species have a crucial role in cellular health and pathology [14–16]. In the recent decade new devices have been invented for NTAPP production [17, 18]. NTAPP’s direct effects on lipids, proteins, and nucleic acids of living cells, as well as its indirect impact on signaling pathways, are well studied [15, 19].

Recently, NTAPP has been introduced into regenerative medicine. Low-dose NTAPP stimulates cell growth and proliferation, while high-dose NTAPP is capable of inducing apoptosis or necrosis, confirming the dose-dependent effect of oxidative stress [13, 20, 22]. Studies of the effects of different NTAPP energies applied to mammalian cells have demonstrated that low doses (under 0.2 J/cm^2) stimulate cell proliferation, medium doses (0.2 to 0.6 J/cm^2) do not have any effect on mammalian cells, whereas high doses (over 0.6 J/ cm^2) induce apoptosis [19, 22]. Multiple *ex vivo* and *in vivo* experiments described in the literature prove antiseptic [22–28] and wound-healing [9, 10, 29, 30] effects of NTAPP. High-dose NTAPP has found its application in cancer treatment [20, 31] and is employed to fight pathogens [21–28]. Low-dose NTAPP is used in regenerative medicine [9, 10, 20, 29, 30].

In the present work we study the feasibility of low-dose NTAPP for improving the condition of aging facial skin.

METHODS

The study was conducted in September through November 2017 at the Department of Dermatology and Venerology (Pirogov Russian National Medical Research University) in 10 healthy female volunteers aged 50 to 55 years who gave informed consent to participate. The study was approved by the independent ethics committee (Protocol 2 dated February 8, 2017) and the Academic Council of the Research

and Medical Center of Dermatology and Cosmetology of the Department of Healthcare, Moscow (Protocol 3 dated March 2, 2017). The study included only females between 50 and 55 years of age without facial inflammation or infection and normal sugar levels. Females who had facial inflammation or infection, diabetes mellitus, chronic kidney or liver diseases, vasculitis or decompensated cardiovascular diseases and those who had undergone a previous anti-age therapy less than 3 months before the study were excluded.

All study participants had their facial skin examined; 3 facial zones were selected for the experiment: zone 1, or the T-zone, covered the central part of the forehead; zone 2 included the "crow's feet" area on the right side of the face; zone 3, "crow's feet" on the left. We used the DUB SkinScaner (Digital Ultraschall Bildisystem, Germany) equipped with two 22 MHz and 75 MHz applicators with an axial resolution of 72 μm and 21 μm, respectively; the applicator with 75 MHz center frequency (frequency range of 65 MHz to 85 MHz) was used. The participants were examined twice: before NTAPP therapy was started and 24 hours after the last treatment. A standard ultrasound conductive gel was used for ultrasound examinations. The obtained data were interpreted and analyzed using the original software for the DUB SkinScaner according to the manufacturer's guidelines. Ultrasound examinations were performed at room temperature, with the patients lying in the supine position. We measured the average thickness of the epidermis and the dermis, the acoustic density of the epidermis and the dermis, assessed the microtopography of the skin (length of the epidermal external surface contour), calculated the index of epidermal deformation and the coefficient of acoustic density distribution in the dermis (ADDD), i.e. the ratio of the acoustic density of lower dermal layers to the acoustic density of upper dermal layers; the reference interval for the coefficient ranged from 0.75 to 1.70 units [33, 34].

After cleansing the face was exposed to the non-thermal atmospheric pressure helium plasma jet (HELIOS, Plasma Research and Production, Russia; see Fig. 1). Helium, the inert gas, was released from the tank at 1.5 l/min on the rotameter scale at moderate jet intensity. Exposure time was 10 min for the "crow's feet" areas and 5 min for the T-zone (the region of the procerus muscle). Every participant received 10 procedures in total with a one-day interval between successive procedures.

RESULTS

Before the experiment all participants were ascribed to morphotype 3 based on their skin condition (puffy face, drooping mouth corners, pronounced "crow's feet", wrinkles on the upper and lower eyelids, vertical lip wrinkles, excess skin on the upper and lower eyelids); one participant had a deep furrow between the brows. Figures 2A and 3A show photos of the participants with typical signs of skin aging.

The ultrasound examination (Table 1) revealed a considerable deformation of the skin surface in all participants, a thickening of the epidermis with a distinct border between the epidermis and the dermis, a slight thinning of the dermis, its relatively homogenous echogenicity, and a blurred border between the dermis and the hypodermis. In one case (a 50-year-old female) a deep wrinkle was observed in the T-zone (width of 2, 867 μm, depth of 250 μm; see Fig. 2A).

After completing the procedures, we observed improvements of skin condition in all participants (Table 1, Fig. 2B and 3B). Epidermal deformation decreased by 35% in the T-zone, by 58% and 30% in the "crow's feet" area on the right and left sides of the face, respectively. Average thickness of the epidermis decreased by 13.3%, 5.0% and 6.3%, respectively. The acoustic density of the epidermis was 20% in the T-zone, 46.6% and 35.6%, respectively, in the "crow's feet" areas on the right and left sides of the face, demonstrating improved epidermal nutrition. Positive changes were also observed for the dermis. Its average thickness increased in the T-zone by 6%, in the "crow's feet" area by 1.2% and 2.7% on the right and left sides, respectively. The acoustic density of the dermis decreased by 37.7%, 20.6% and 52.2%, respectively. The observed changes indicate better nutrition and better tissue hydration. On the whole, the skin structure in the studied zones became considerably healthier, which was confirmed by the increase in the ADDD value by 27.1%, 11.9% and 30.3%, respectively. The deep wrinkle between the eyebrows in one of the participants became narrower, though its depth remained unchanged (Fig. 2B).

The most pronounced changes were observed for the microtopography of the skin surface in the "crow's feet" area: the skin became smother, and the wrinkles shallower.

DISCUSSION

It is known that exposure to NTAPP induces production of reactive oxygen and nitrogen species, UV-protons, electrons and ions [32]. Experiments have demonstrated improved skin microcirculation and, therefore, better hydration and activation of collagen synthesis after exposure to low-dose NTAPP [33–35]. In another study conducted in healthy male and female volunteers over 18 years of age, changes in microcirculation and the lowering of skin pH depended on the duration of exposure to NTAPP [36]. It has been shown that nitric oxide generated by low-dose NTAPP triggers β-catenin activation by epidermal cells, stimulating the renewal of the epidermis [37].

For normal epidermal function, proliferation of keratinocytes and their apoptosis (programmed cell death) need to be well balanced. Repeated exposure to NTAPP helps to achieve normal epidermal thickness and better regeneration [37]. At present NTAPP is used for microbial decontamination; it is also employed to promote wound or venous ulcer healing. Currently, the feasibility of NTAPP application in regenerative medicine is being explored. Our study proves that NTAPP is safe for the skin. We have shown that after 10 procedures of facial skin exposure to NTAPP, epidermal acoustic density decreases significantly, suggesting the loss of excess corneum thickness, better microcirculation and improved quality of the hydrolipidic film. Our findings are consistent with the published experimental data [7, 12, 17, 33, 34]. Decreased acoustic density of the dermis can be the result of good hydration of deep

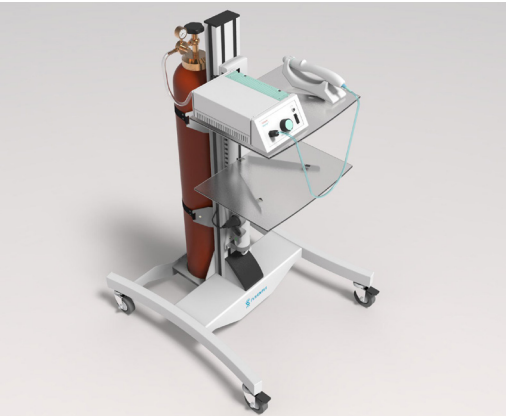

Fig. 1. Low-dose non-thermal atmospheric-pressure helium plasma jet generator (HELIOS, Plasma Research and Production, Russia)

Table 1. Ultrasonography of different facial skin zones before and after exposure to NTAPP (M±σ)

Parameter	Before exposure to NTAPP			After exposure to NTAPP		
	Zone 1	Zone 2	Zone 3	Zone 1	Zone 2	Zone 3
Microtopography, mm	13.2 ± 0.1	13.2 ± 0.3	13.1 ± 0.2	13.1 ± 0.1	12.9 ± 0.08	13.02 ± 0.13
Epidermal deformation, un.	0.416 ± 0.07	0.43 ± 0.26	0.33 ± 0.18	0.27 ± 0.09*	0.18 ± 0.08*	0.23 ± 0.13*
Epidermal thickness, μm	72.9 ± 12.3	64.3 ± 10.0	65.1 ± 7.8	63.3 ± 8.2*	61.1 ± 8.7*	61.0 ± 9.8*
Acoustic density of the epidermis, un.	142.1 ± 12.8	106.6 ± 7.2	125.6 ± 28.7	113.7 ± 24.0*	56.9 ± 21.0*	82.1 ± 33.7*
Dermal thickness, μm	1521.6 ± 249.8	1313.4 ± 121.1	1292.4 ± 106.1	1612.4 ± 168.0*	1329.1 ± 136.4*	1326.4 ± 92.4*
Acoustic density of the dermis, un.	11.4 ± 6.7	19.9 ± 14.6	20.7 ± 10.8	7.1 ± 4.7	15.8 ± 14.8	9.9 ± 5.1
ADDD	0.70 ± 0.11	1.09 ± 0.16	0.944 ± 0.191	0.89 ± 0.14*	1.22 ± 0.18*	1.23 ± 0.28*

Note: ADDD is distribution of acoustic density in the dermis; * shows statistically significant differences between the parameters before and after exposure to NTAPP ($p < 0.05$).

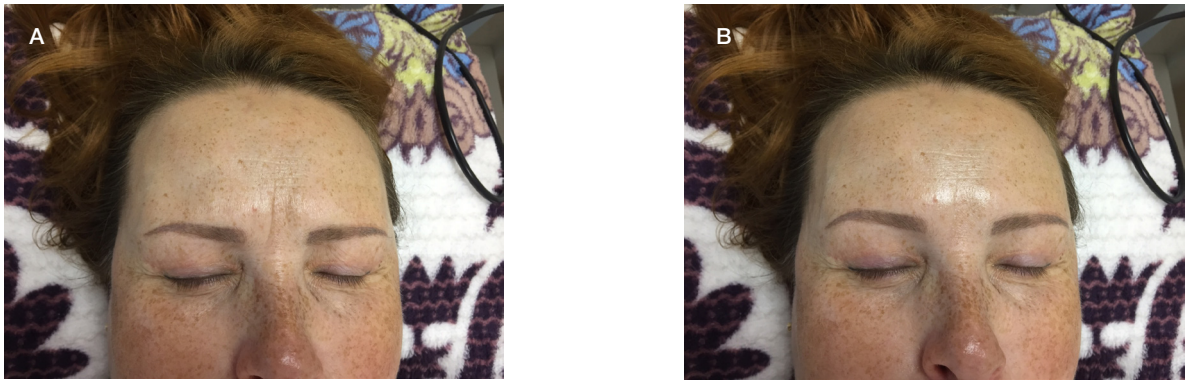

Fig. 2. The area between the eyebrows before (**A**) and after 10 procedures of exposure to NTAPP (**B**)

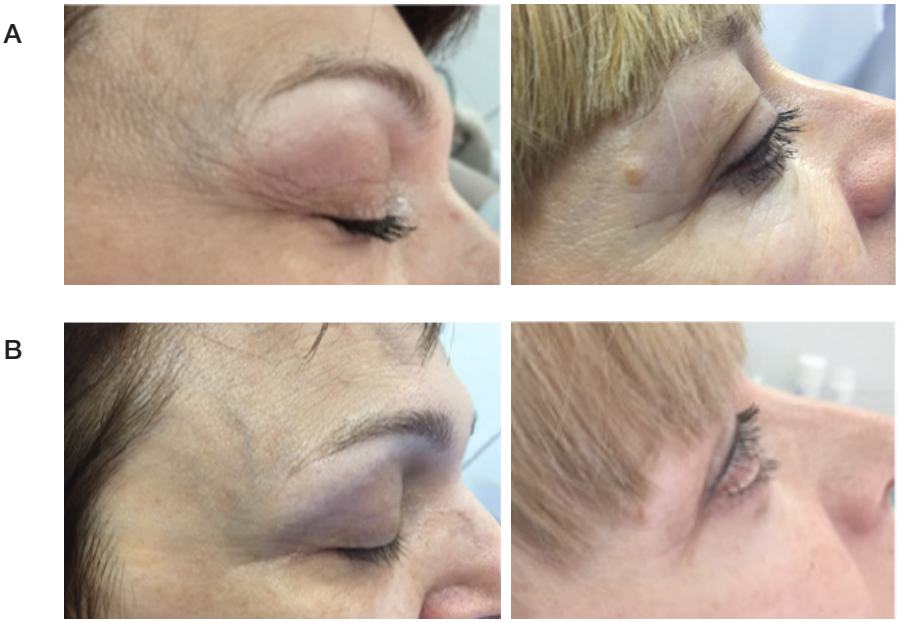

Fig. 3. The "crow's feet" area before (**A**) and after 10 procedures of exposure to NTAPP (**B**)

skin structures. The structural changes in the skin following the treatment course demonstrate the anti-age effect of NTAPP. All study participants noticed changes in their skin appearance (fewer and shallower wrinkles in the areas of interest). It is still unclear, though, how many procedures need to be performed and at what interval in order to achieve the best possible effect. Perhaps, structural improvements would have been more pronounced if the number of exposures had been higher. This question requires further investigation.

CONCLUSION

Exposure to low-dose NTAPP can significantly improve the condition of the epidermis, smoothing out the wrinkles that negatively affect women's emotional state. No adverse effects on the skin or its appendages have been observed. Further clinical studies of NTAPP application in cosmetology are necessary to perfect the technique and define the optimal duration of the treatment course for the best anti-age effect.

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