REVIEWS

CURRENT STATE OF METHODS OF CORRECTION OF INVOLUTIONAL CHANGES OF SKIN AND THE PLACE OF PHOTODYNAMIC THERAPY AMONG THEM

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Abstract

This work is a review of modern scientific data on the process of aging, as well as the prospect of using photodynamic therapy for correction of involutional skin changes in the age cohorts, cohorts with a burdened medical history, including cancerous and precancerous skin neoplasms. The data on the predicted increase in life expectancy and, as a consequence, the potential risk of pathologies, including those with skin localization, progression of malignancy processes, as well as the formation of *de novo* elements, is presented. The increase in life expectancy also demonstrates the socialization of the elderly population, along with the increasing need for correction of involutional skin changes. However, considering the risks associated with the chronic diseases and increased malignancy in this cohort, methods have to be carefully selected. One such technique is photodynamic therapy (PDT). PDT is actively used in oncology, and recently has been increasingly showing its aesthetic effectiveness. It can be predictably used not only on cancer patients, but also in an age cohort.

Keywords: photodynamic therapy, correction of involutional changes, actinic keratosis.

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СОВРЕМЕННОЕ СОСТОЯНИЕ МЕТОДОВ КОРРЕКЦИИ ИНВОЛЮЦИОННЫХ ИЗМЕНЕНИЙ КОЖИ И МЕСТО ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ СРЕДИ НИХ

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Резюме

Данная работа представляет собой обзор современных научных данных о процессах старения кожи, а также о перспективе использования метода фотодинамической терапии для коррекции инволюционных изменений кожи у возрастного населения. Приводятся данные прогнозируемого увеличения продолжительности жизни и, как следствие, потенциального риска возникновения патологий, в том числе кожной локализации. Увеличение продолжительности жизни также демонстрирует и социализацию пожилого населения, вместе с тем возрастающую потребность в преображении и коррекции инволюционных изменений кожи, но, учитывая риски в связи с наличием хронических заболеваний и возрастающей малигнизации данной когорты, следует тщательно подбирать методики, учитывая вышеперечисленные особенности. Одним из таких методов является фотодинамическая терапия. Фотодинамическая терапия активно применяется в онкологии, а в последнее время все чаще показывает свою эффективность в эстетическом направлении, соответственно прогнозируемо может использоваться не только у онкологических больных, но и возрастной когорты.

Ключевые слова: фотодинамическая терапия, коррекция инволюционных изменений, актинический кератоз.

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Medicine has been developing rapidly in many areas recently, and cutaneous science is no exception. Thanks to the OMICS revolution, researchers have come to understand that the skin is one of the main links of the key neuro-immune-endocrine axes of the body. Stratification of skin diseases and individual skin conditions allows for the implementation of targeted and effective treatment methods. Close attention to skin conditions is due to a significant increase in the average life expectancy of a person, as well as an alarming increase in the number of patients with such diagnoses as diabetes, skin cancer and other chronic diseases. At the same time, demographic trends observed all over the world make it more important to find clinical solutions for numerous age-related (involution-type) skin disorders caused by external and internal factors. In the context of a deep study of human skin aging, it is emphasized that maintaining functional activity in this complex multicellular organ is key to maintaining the quality of life in old age [1].

The recent advances in the study of age-related skin changes have led to the development of classifications of types of aging. In particular, one of them was proposed in 2014 by Zh. Yu. Yusova and is presented below:

1. *Aging of the wrinkled type* is more often observed in people with dry, dehydrated skin, and the signs of aging are observed before the age of 40, with the spread of wrinkles throughout the face. In this type, the skin has gray color, and the dominant involution signs are wrinkles. Characteristic features: pronounced "crow's feet" in the periorbital area, wrinkling of the upper and lower eyelids, "corrugation" in the upper lip and chin area. Some atrophic changes are observed, as well as blood circulation disorders in the dermis. Ultrasound examination reveals a set of linear structures in the epidermis, many areas with a high degree of the dermis fraying, thinning and the reduction of its acoustic density.

2. *Deformational type aging* is more often observed in people with oily skin prone to greasiness, which is characterized by a decrease in elasticity, turgor and the formation of a tired-looking face. The external signs of this type of aging are pitting edema, a pronounced nasolabial fold, and later the corners of the mouth become drooping. Other characteristics observed are couperosis and rosacea, smoothing of the face oval, sagging cheeks, double chin, folds on the neck. Wrinkles for this type of aging are less pronounced and are not the leading sign of the process. In this type of aging, poor microcirculation is also observed, but due to a decrease in venous blood flow and the formation of edema in the tissues. The ultrasound picture is characterized by an inhomogeneous hypoechoic structure, a dense epidermis, and the inclusion of intercellular fluid.

3. *Mixed-type aging* refers to aging which is a combination of the two types described above. It is possible to distinguish a special type, which features a combination of both wrinkles and pastiness, but in people with a mixed type of skin aging, hyperkeratosis and pigmentation are observed, and skin thinning and complex microcirculation disorders are present: both blood flow to the dermis and venous outflow are abnormal. In some areas, ultrasound reveals the acoustic characteristics of the first and second types of skin aging: before the cosmetic correction, the chin and cheeks feature heterogeneous, hypoechogenic structure with a dense epidermis and areas of fraying, a subepidermal hypoechogenic band in the periorbital area, dermis thinning, with the decrease in its the density [2].

The classification of the skin aging mechanisms, combined with the understanding of the process, helps to make a correction plan for the improvement of the appearance of mature and senior individuals. Most studies focus on the influence of solar radiation as the main inducer of aging, but in older people, many additional factors that go beyond environmental conditions should be considered. Lifestyle factors such as diet, sleep, and smoking are currently undergoing thorough analysis, as are the general age-related conditions (menopause, diabetes, and heart and lung diseases). All these factors can accelerate the natural deterioration of skin structure and function, which can affect the effectiveness of involution changes treatment. The search for new approaches to managing skin aging is becoming more and more relevant [3].

New scientific evidence has been obtained recently to support the long-debated assumption that air pollution is also one of the causes of premature skin aging. This conclusion is based on epidemiological and mechanistic data. In particular, exposure to the corresponding particulate matter and nitrogen dioxide (NO_2) is associated with an increased risk of developing facial pigmentation. In addition, genetic studies indicate modification of gene penetration under environmental influence: women carrying certain genetic variants of the aryl-carbohydrate receptor signaling pathway have a higher risk of developing facial pigmentation spots in response to exposure to fine particulate matter of a certain size. Mechanistic studies prove a causal relationship, since local exposure of human skin *ex vivo* or *in vivo* to non-toxic concentrations of standardized diesel exhaust mixture increases skin pigmentation, causing *de novo* synthesis of melanin through an oxidative stress reaction. Therefore, the use of anti-pollution cosmetics containing antioxidants, as well as aryl hydrocarbon receptor antagonists, is effective for preventing or reducing the development of skin pigmentation. In a real-life situation, human skin is affected by both environmental factors simultaneously, i. e., solar radiation and mechanical irritation. Relevant epidemiological studies show that solid particles present in the troposphere and solar ultraviolet radiation interact with each other. This makes it possible to discuss environmentally caused skin aging [4].

Taking into account the speed of adverse changes in the environmental situation, it is necessary to recognize the fact that facial aging is one of the most popular topics of modern "cutaneous science". Changes in the human face inevitably progress over time; however, there are many methods, both surgical and non-surgical, that can reduce the stigma of aging and provide patients with a desired appearance [5].

The shifting attitude to age-related changes in the skin within the healthy lifestyle trend has been reflected in the establishment of public health programs in a number of countries. Since facial wrinkles can be seen as a marker of internal aging, there is an incentive to motivate people to adopt a number of healthy behaviors in senior age [6].

The mechanisms of skin aging include the action of reactive oxygen intermediates (ROI), mitochondrial DNA mutations and telomere shortening, as well as hormonal changes [1]. The variable that determines the rate of aging of the skin or tissue as a whole is the predominance of tissue degeneration over tissue regeneration. One distinguishes between the mechanisms of internal and external aging (photoaging). Special emphasis is placed on the influence of ultraviolet (UV) exposure on the visual signs of skin aging and the variability of UV effect depending on the geographic location of a particular person and their skin type. UV radiation has a direct photochemical impact on the DNA, RNA, proteins and vitamin D. At the same time, it is shown that skin aging processes are initiated and often spread not only under the influence of UV, but also as a result of oxidative phenomena, despite the recently recognized adaptive responses to oxidative stress [7].

The increase in the average age of men and women initiated the formation of the foundations of the so-called "successful aging", the founders of which are considered to be P. B. Baltes and M. M. Baltes, who proposed a model of selective optimization with compensation [8]. It included the maintenance of health and the achievement of apparent well-being. E. Kahana and B. Kahana focused on social and psychological resources of a human being, preventive and corrective adaptations, psychological, existential and social well-being [9, 10]. The theory of "successful aging" was further advanced by C. A. Depp and D. V. Jeste, who showed that even in the presence of disability, it is possible to maintain physical and cognitive functioning and life satisfaction in general [11, 12].

Active longevity is currently promoted by Russian researchers, but it is foreign scientists who first produced an evidence-based prediction of increased life expectancy. It is expected that in the near future life expectancy will increase in 35 developed countries, with a probability of at least 65% for women and 85% for men. There is a 90% probability that life expectancy at birth among South Korean women in 2030 will exceed 86.7 years, which corresponds to the world's highest life expectancy in 2012, and 57% probability for this indicator to reach 90 years. The projected life expectancy of women in South Korea follows that of France, Spain and Japan. There is a more than 95% probability that life expectancy at birth among men in South Korea, Australia, and Switzerland will exceed 80 years in 2030, and a more than 27% probability that it will exceed 85 years. More than half of the projected increase in life expectancy at birth for women will be due to an increase in life expectancy over the age of 65. Thus, researchers point to a constant increase in life expectancy, as well as the need for careful planning of health care, social services and pensions [13-15].

The improvement of the quality of life due to the growth of therapeutic possibilities for the treatment of chronic diseases is one of the factors that promote the development of correction treatments against involutional skin changes. The prospects for further expansion of the range of health, i. e., a period free from age-related disability and diseases, are evaluated critically. Understanding human aging is a major challenge for the physiological sciences. This is becoming an increasingly urgent issue because of the increasing proportion of people who live to old age, and because of changes in the main reasons for the continued increase in life expectancy. The previous increase was almost entirely due to the prevention of mortality in childhood and middle age. This process has been so successful that there is little room for significant further increases from the achieved level in the developed countries. The recent increase in life expectancy is due to a new reason. As a rule, we reach old age with better health, and now the mortality rate in old age is lower. At the same time, biologic science has established that there is almost certainly no fixed program of aging that is caused by the accumulation of damage throughout life. It becomes obvious that the aging process is much more malleable than we used to think. This leads researchers to look for factors that regulate this malleability, and to identify relationships between, on the one hand, the internal biological processes that cause many chronic diseases and disorders, among which age is by far the largest risk factor, and, on the other hand, social factors and lifestyle that affect our individual health pathways in old age [16].

Most researchers believe that one of the key directions in the development of anti-aging technologies should be the enhancement of socialization among people of senior age. In this aspect, non-invasive methods of correction of involution-type skin changes are the most promising field of dermatology and cosmetology, as evidenced by the variety of methods proposed for correcting age-related skin changes.

The main noninvasive methods of correction of involution changes in the skin of the face

1. *CO_2 laser (λ10.6 μm)*

A CO_2 laser is a laser that operates on gas mixtures. The radiation of this laser is absorbed by water molecules of tissues and cells, which leads to vaporization (evaporation), and, as a result, the emission of tissue structures with the formation of a damage zone (ablation crater). The disadvantage of the CO_2 laser is the release of thermal energy in the tissue around the ablation site. If the power increases, tissue removal accelerates, while the depth of thermal exposure is reduced. The wavelength (λ) of 10.6 microns pertains to long-wave radiation, and its use allows to penetrate to a considerable depth, unlike with other lasers [17].

There are 2 modes:

1. Fractional: a) rejuvenation, b) correction of scarring or stretch marks of the skin
2. Continuous: a) removal of skin neoplasms, b) surgery.

2. *Er:YAG laser (λ 2.94 μm)*

Er:YAG refers to solid-state lasers, and their working medium is erbium and yttrium aluminium garnet. It is characterized by high absorption of water molecules. Its wavelength is 2940 nm. It has a smaller area and depth of penetration, in contrast to the CO_2 laser, which results in a faster healing of the surface which was treated. [18]

A more superficial effect in contrast to a CO_2 laser:

– rejuvenation (laser peeling)
– correction of scarring and stretch marks of the skin.

3. *Er:glass laser (λ 1.54 μm)*

Er:glass laser on erbium glass. Chromophores are water-containing components of the dermis, which allows the thermal effect to act directly without damaging the epidermis, with the activation of neocollagenesis and reparative processes. The wavelength of 1540 (1550 nm), which affects the infrared range of radiation, is used for ablative fractional photothermolysis [19].

Applications:

– correction of involution changes of the skin
– correction of scarring and stretch marks of the skin
– dentistry
– ophthalmology

4. *Intense pulsed light (IPL)*

Intense pulsed light (IPL) is produced by a source of electromagnetic radiation with a wide range of wavelengths, i. e., polychromatic light (from 420 nm to the mid-infrared spectrum) and is delivered in the form of flashes (pulses) rather than as constant light. As a rule, IPL technology involves the use of filters in order to work with certain chromophores. The main chromophores are melanin and oxyhemoglobin. Blue and green light produce an effect on the surface layers, while orange and yellow spectra act on the middle layers of the skin, and infrared light influences the deep ones. Green light reaches the level of the papillary dermis and has an effect on the vessels in this layer [20, 21].

The red spectrum is used for epilation of dark hair, while the green spectrum is for vascular malformations and correction of hyperpigmentation.

5. *Exposure to high frequency radio waves*

Morphological changes caused by exposition to high-frequency radio waves occur in the deep layers of the dermis and the adjacent fat tissue. At the same time, remodeling of the extracellular matrix of the dermis causes the expansion of its deep layers with the accumulation of collagens of the 1st and 3rd types and maintaining the ratio between them in favor of type 1 collagen. Activation of neoangiogenesis in the dermis can be considered a key anti-aging factor of radio wave exposure, which occurs gradually, reaching its maximum 12 months after a single exposure [22]. The correction of involution changes of the skin includes RF-microneedling and RF-lifting.

6. *Photodynamic therapy (PDT)*

PDT is a two-component treatment method: one of the components is a photosensitizer (PS), the other is the light of a low-energy laser, the wavelength of which corresponds to the peak of the PS absorption. PDT is essentially selective destruction of pathological tissue, which is achieved due to the difference in the concentration of PS in pathological and normal tissues, as well as due to the local application of a light source.

PDT is used in various areas of modern dermatology and cosmetology. Some see this technique as a new opportunity for the treatment of microbial infections complicated by microbial resistance. Clinical experience with PDT in the field of dermatology for the treatment of infections is mainly related to the use of 5-aminolevulinic acid (5-ALA) and the use of phenothiazine modifications in dentistry. It is expected that in the coming years, PDT will be introduced for the treatment of complex infections, and will be administered with the use of modern antimicrobial PSs targeted at microbial cells [23]. Treatment of papillomatoses with a combination of surgery and PDT is recognized as effective and safe: with a relapse rate of 25%, the level of satisfaction with treatment in patients was 95% three months after treatment and 100% six months after treatment [24].

The prospects and results of PDT application receive increasing attention at various international conferences, where the issue is discussed by medical cosmetology experts. PDT can help correct pigmentation, reduce skin roughness, eliminate fine lines and improve the complexion, as well as reduce actinic elastosis. The anti-aging effect of various PDT methods used in different modes with different PSs is documented in research publications. In particular, it is proved that topical PDT "stops" some signs of skin aging: the severity of fine wrinkles, spotty hyperpigmentation, tactile irregularity and yellow color decrease. It has been confirmed by immunohistochemistry methods that PDT normalizes collagen production and increases epidermal proliferation. An indirect stimulation of neocollagenesis occurs under the influence of cytokine production [25]. Due to the effect of PDT on the skin, its texture improves, its elasticity increases, the number of small wrinkles decreases, and deeper ones become less pronounced and increase skin elasticity [26]. In support of the above, the results of a number of studies are provided in the following part.

The most commonly used PSs in cosmetology are 5-aminolevulinic acid (5-ALA) and its methyl esther (MAL). Their use significantly increases the efficiency of PDT, both in its classic version with the use of activating light sources and with daylight. Just two sessions of PDT of the facial skin with MAL using red light (37 J/cm^2) resulted in a significant increase in collagen deposition and a decrease in of solar elastosis signs. An immunohistochemical study confirmed an increase in the expression of procollagen-I and matrix metalloproteinase 9 genes [27]. The effectiveness of MAL as a PS in combination with the therapeutic effect of red color was also evaluated in a double-blind randomized placebo-controlled study of the treatment of photoaging of face skin. In this study, half of the participant's face was exposed to PDT, with a second course 2-3 weeks later, and the other half of the face was irradiated with red light without the use of PS (placebo). The primary result was the assessment of the total photo damage 1 month after the second session. Secondary control points were a comparative assessment of the skin condition in terms of the presence of fine wrinkles, pigmentation, tactile roughness, yellowness, erythema and telangiectasia 1 month after the second session. The use of MAL showed significantly higher effectiveness of facial skin photoaging treatment compared to placebo. This therapy was found to be effective for all other specific secondary indicators, except for telangiectasis [28, 29].

As for the frequency of procedures with MAL, cosmetologists usually recommend 2 or 3 procedures with an interval of 3-6 months before clinically and aesthetically visible results of the therapy are achieved. The choice of the interval between PDT courses depends, first of all, on the initial clinical indicators and the individual reparative potential of the patient, which are revealed after the first PDT procedure. However, an interval of 4 weeks, or even longer, should be observed between treatments in the case of additional intermediate effects on the skin (any of the types) [30].

It is believed that one of the ways to improve the effectiveness of PDT against actinic keratosis is to use it in combination with drug therapy. For example, researchers have examined the effectiveness of a combination of PDT amd Imiquimod and 5-Fluorouracil creams, Ingenol mebutat gels, Tazarotene and Calcipotriol ointment. Patients receiving combined treatment showed a higher clearance rate of actinic keratosis (HR 1.63; 95% CI 1.15-2.33; P = 0.007). Similarly, the clearance of actinic keratosis in PDT with topical applications was higher compared to monotherapy (HR 1.48; 95% CI 1.04-2.11; P = 0.03). A subgroup analysis was performed for PDT in combination with Imiquimod, revealing an increased total clearance rate compared to monotherapy (HR 1.57, 95% CI 1.09-2.25, P = 0.02). No PDT-induced pain or registration of local skin reactions after treatment were reported. The combination of PDT with other local medicinal effects actually improves the clearance rates of actinic keratosis compared to any monotherapy. This study highlights that the sequential use of two treatment methods provides an effective therapy in patients with multiple foci of actinic keratosis [31].

In addition to the combination with medications, the authors also report that the combination of PDT with various physical techniques, such as microdermabrasion, microneedle exposure, and laser therapy, improves the clinical effectiveness and cosmetic results of treatment of actinic keratosis [32].

Taking into account the impairment of the environment and its role in the aging process, the increasing share of elderly people in the society, as well as the accumulation of cancer and precancerous skin pathologies, it is possible to talk about the prospects of PDT methods for cosmetic correction in persons with a burdened history.

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