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Modern approaches to the correction of age-related skin changes in women

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The article is devoted to the literature review on the correction of age-related skin changes in women. Skin aging is a physiological process that is caused by the constant action of unmodified factors, for example, endocrine disorders, shortening of telomeres, etc., in combination with periodic influence of modified (exposomal) factors.
Ultraviolet radiation takes first place among external factors affecting the progression of degenerative changes in skin, however, in women, involutional changes in skin are primarily associated with a fading of synthetic function of ovaries. During the first five years from the onset of menopause, content of collagen fibers I and III types is reduced by 30% in combination with a further reduction of 2% annually for the next 15 years.
Involutive transformations occur in all layers of skin and are visually characterized by the presence of wrinkles, roughness of the epidermal surface (with photoaging) or a decrease in its thickness (with chronic aging), dryness, pigmentation disorders in the form of uneven hyperpigmented spots, telangiectasias, oval deformations.
Today, there are many methods of aesthetic correction of age-related skin changes. In the arsenal of a cosmetologist there are both invasive (PRP-therapy, microneedling, microneedle radio wave lifting, administration of preparations based on calcium hydroxyapatite, polylactic and hyaluronic acid, etc.) and minimally invasive (administration of botulinum neuroprotein, application of chemical acid peelings, IPL-therapy and laser polishing, photodynamic therapy) methods. Patients prefer minimally traumatic procedures due to the fact that they almost do not disturb the processes of socialization, however, each of these methods has both advantages and disadvantages.
Modification of a woman life quality in peri- and menopause in form of changes in lifestyle and eating behavior, increasing physical activity, quitting smoking and limiting the use of alcoholic beverages is an integral part of therapeutic care. However, the appointment of menopausal hormonal therapy, including the use of estrogens, progestogens and combined hormonal drugs, allows to achieve a stable and long-lasting effect from cosmetology procedures and home care.
Keywords: *women, age-related skin changes, aging, menopausal disorders, correction.*

Сучасні підходи до корекції вікових змін шкіри у жінок

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Стаття присвячена огляду літератури щодо корекції вікових змін шкіри у жінок. Старіння шкіри є фізіологічним процесом, який зумовлений постійною дією немодифікованих факторів, наприклад ендокринних порушень, скороченням теломер тощо у комбінації з періодичним впливом модифікованих (експосомальних) чинників.
Серед зовнішніх факторів впливу на прогресування дегенеративних змін шкіри перше місце посідає ультрафіолетове опромінення, однак у жінок інволютивні зміни шкіри перш за все пов'язані зі згасанням синтетичної функції яєчників. Протягом перших п'яти років від настання менопаузи вміст колагенових волокон I та III типів знижується на 30% у комбінації з подальшим зниженням на 2% щорічно протягом наступних 15 років.
Інволютивні перетворення відбуваються у всіх шарах шкіри та візуально характеризуються наявністю зморшок, шорсткості поверхні епідермісу (при фотостарінні) чи зниженням його товщини (при хроностарінні), сухістю, порушенням пігментації у вигляді нерівномірних гіперпігментних плям, телеангіоектазій, деформацій овалу.
Сьогодні існує багато методів естетичної корекції вікових змін шкіри. В арсеналі лікаря-косметолога є як інвазивні (PRP-терапія, мікронідлінг, мікроголковий радіохвильовий ліфтинг, уведення препаратів на основі гідроксіапатиту кальцію, полімолочної та гіалуронової кислот тощо), так і малоінвазивні (уведення ботулінічного нейропротеїну, застосування хімічних кислотних пілінгів, IPL-терапії та лазерного шліфування, фотодинамічної терапії) методики. Пацієнтки віддають перевагу саме малотравматичним процедурам через те, що вони майже не порушують процеси соціалізації, однак кожен з цих методів має як переваги, так і недоліки.
Модифікація якості життя жінки у пері- та менопаузі у формі змін способу життя та харчової поведінки, підвищення фізичної активності, відмови від куріння та обмеження вживання алкогольних напоїв є невід'ємною частиною терапевтичної допомоги. Однак призначення менопаузальної гормональної терапії, включаючи застосування естрогенів, прогестагенів та комбінованих гормональних препаратів, дозволяє досягти стійкого і тривалого ефекту від косметологічних процедур та домашнього догляду.
Ключові слова: *жінки, вікові зміни шкіри, старіння, менопаузальні порушення, корекція*.

Aging is a regular biological natural process, the speed and progression of which depends on a combination of permanent (genetic disorders, shortening of telomeres, impaired resistance of cellular structures to oxidative damage, endocrine disorders, immunosenescence) and modified (ultraviolet radiation, environmental pollution, smoking, stress, diet), insufficient sleep, cosmetic products) factors [1–3].

Degenerative processes occur in all organs and systems, but age-related changes in the skin, which we can see with the naked eye, have the greatest impact on the psycho-

emotional state and socialization of every subject of society. Skin is the largest integral organ of the human body, the area of which is on average 1.5–2.1 m^2, which provides the main protection of a body against external damage and is important for maintaining general homeostasis [4, 5].

Complex anatomical division of skin into epidermis, dermis, and hypodermis makes it possible to perform a number of vital functions, such as: protection against ultraviolet (UV) radiation and various chemical and mechanical irritants, thermoregulation, immunological protection [6]. At the same time, skin is inevitably prone to involutional transformations with loss of functional capabilities. The most significant exogenous factor is UV radiation. With excessive exposure to UV, direct damage to deoxyribonucleic acid (DNA) of a cell apparatus is observed. In addition, the generation and accumulation of reactive oxygen species (ROS) is manifested as a mechanism of indirect effect of cell damage, as well as induction of inflammation, destruction of collagen and elastin fibers [7].

Increased collagen fiber degradation is caused by UV induction of activation of matrix metalloproteinases-1, 3 and 9. A decrease in expression of type I procollagen is observed due to the blocking of type II Transforming growth factor-beta receptors [3]. When there is an imbalance between ROS and antioxidant protection with a shift towards increasing the concentration of ROS, pro-inflammatory cytokines (IL-2, IL-6, TNF-α (Tumor necrosis factor-alpha)) are activated, and there is also a deficiency of the Klotho protein [8]. The formation of ROS seems to play an important role in age-related skin changes [5]. That is why involutive skin changes are combined with inflammatory dermatological diseases.

In addition to photoaging, as one of predictors of age-related changes in skin, endocrine disorders, which are associated with the fading of the synthetic function of the ovaries in women, should also be considered. Menopause, as a physiological period of every woman's life, begins between the ages of 45 and 55 and affects the functioning of a body both in a short and in a long term [9].

Climacterium is a physiological transition period in a woman's life, during which, against the background of age-related body changes, involutional processes in the reproductive system dominate, characterized by a decrease in reproductive and menstrual function due to the genetically programmed fading and cessation of ovarian function. To clarify the stages of reproductive aging, it is advisable to use the criteria of the Working Group on determining the stages of reproductive aging of women (STRAW +10). According to the criteria of STRAW+10 (Stages of Reproductive Aging Workshop) 4 periods of menopause are distinguished: the period of menopausal transition, menopause, perimenopause and postmenopause [10–12].

With the onset of perimenopausal period, new socio-economic, general medical and psychological problems, related to the adaptation of women to the neuroendocrine reorganization of the body, arise. Morbidity, disability and mortality in this age period are significantly higher than in other age groups [13].

During menopause symptoms occur as a result of physiological changes in a woman's body and are associated with a decrease in the production of estrogen hormones (sex hormones in women) [10, 11]. Estrogens significantly alter skin physiology by affecting keratinocytes, fibroblasts, melanocytes, hair follicles, and sebaceous glands and enhance angiogenesis, wound healing, the immune response. Estrogen deficiency reduces protection against oxidative stress [14].

A decrease in a level of sex steroids in blood serum accelerates biological aging of body tissues. Physiological changes after menopause are especially visible in skin, which loses its structural architecture and becomes prone to damage [15]. Estrogens significantly modulate functioning of all systems of a female body. A decrease in the concentration of 17β-estradiol in blood serum leads to many long-term consequences for a female body (osteoporosis, cardiovascular and metabolic disorders, vasomotor symptoms). However, skin is the first to respond to estrogen dysfunction [16].

Dryness of skin can be observed at the beginning of perimenopause, but initially it can be somewhat compensated by the hypertrophy of the sebaceous glands. Later in menopause, when production of sebum is significantly reduced, skin becomes increasingly dry and itchy and this leads to its atrophy in future [17]. During the first 5 years from the onset of menopause, the content of collagen fibers of types I and III decreases by 30%, and further decrease of 2% is observed annually during the next 15 years [18].

Skin aging is a complex multifaceted process that covers all its components. In the epidermis proliferation of basal keratinocytes decreases, there is a thickening of epidermis due to the stratum corneum during photodamage, while when the effect of UV radiation is excluded, the thickness of epidermis, on the contrary, decreases [19, 20], the epidermal-dermal junction flattens. The thickness and density of the dermis also decrease, the expression collagen types IV and VII – due to a reduction in a thickness of collagen fibers in both papillary and reticular dermis [20].

There is a large number of bundles of fragmented collagen, a decrease in the concentration of hyaluronic acid and fibrillin, defects in the organization of elastin [5]. Visually, age-related changes in women's skin are manifested by xerosis, roughness, sagging, a decrease in tone and turgor, ptosis, static wrinkles, uneven hyperpigmentation and other color changes, telangiectasias [5]. These disturbances are accompanied not only by aesthetic changes, but also by additional psycho-emotional disorders that complicate socialization of a woman in her personal and professional life and reduce its quality [21, 22].

Thanks to the discoveries in modern medicine, not only life expectancy has increased, but also its quality, therefore the interest of patients in aesthetic correction of age-related skin changes is increasing. According to the statistics of the American Society of Plastic Surgeons for 2020, the number of performed cosmetic procedures aimed at improving the quality of skin amounted to 15,595,955 manipulations, among all patients who applied for aesthetic correction (surgical and cosmetic), 92% were women [23].

Today there is a fairly large number of aesthetic medicine procedures that are used to prevent and cor-

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rect age-related skin changes in women. According to the statistical selections of the American Society of Plastic Surgeons and The Aesthetic Society for 2020 and 2021, respectively, the most common cosmetic procedures are: neurotoxin injections, chemical peels, intense pulsed light (IPL), laser skin resurfacing, fillers based on hyaluronic acid [23, 24].

As you know, one of the most effective methods of prolonging youth of women of specified age is menopausal hormone therapy (MHT), which is indicated not only for treatment of menopausal symptoms, but also for improving the condition of skin and hair, and this should be taken into account when discussing it separately with each patient. Improvements in skin surface texture, hydration, dermal collagen content and elasticity have been demonstrated in women treated with MHT/estrogen (oral and transdermal) [16, 17, 25–27].

MHT remains the most effective treatment for vasomotor symptoms and genitourinary syndrome during menopause and has been shown to prevent bone loss and fracture development [10, 28–30]. It is also necessary to individualize and adapt MHT according to symptoms, personal and family history, research results, wishes and expectations of a woman. The duration of therapy is not limited to a specific period and is determined individually depending on the goals of treatment, its effectiveness and tolerability by the patient during an annual benefit/risk assessment [16, 29].

At the same time, women with external changes during menopause are looking for cosmetic and medical procedures that can improve their self-perception and slow down skin aging, especially on exposed areas (face, neck, and hands) [31]. Today, preference is given to minimally invasive methods of aesthetic correction, namely: the introduction of botulinum neuroprotein, the use of chemical peels, IPL therapy and laser grinding, photodynamic therapy.

Among the variety of procedures, clinical trials regarding neurotoxins continue – with the aim of determining new indications for use, increasing the duration of the effects of injections. Botulinum toxin is a neurotoxin produced by C. Botulinum and divided into 7 serotypes (A to G). Only A and B are allowed for therapeutic use [32]. The neuroprotein type A molecule consists of a light chain (50 kDa) and a heavy chain (100 kDa), and the mechanism of action is based on the cleavage and deactivation of the target protein SNAP-25, which, in turn, blocks the release of neurotransmitters (acetylcholine) from vesicles of the presynaptic membrane neuromuscular synapse and leads to reverse paralysis of muscle contraction [33].

The FDA (Food and Drug Administration, USA) has approved for use four types of neuroprotein type A: onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA, prabotulinumtoxinA-xvfs and one type B – rimabotulinumtoxinB [34]. However, botulinum toxin type A is used in cosmetology practice the average duration of the effect of injection of which is 12 weeks [32, 35]. The registered indications are: blepharospasm, glabellar wrinkles, lateral periorbital wrinkles, hyperhidrosis of the armpits, strabismus, dynamic equinus foot deformity of spastic genesis in children over 2 years old with cerebral palsy, spastic torticollis, etc. [35].

A new version of botulinum toxin purified from complexing proteins – DaxibotulinumtoxinA is at the stage of clinical trials, the basis of which is a neurotoxin with a molecular weight of 150 kDa and a stabilizing peptide RTP-004 obtained from human immunodeficiency virus type 1. The declared average duration of the effect is 24 weeks [36]. Indications for cosmetology therapy are hyperactivity of a muscular apparatus of face and neck, the goal is to prevent the formation or deepening of static wrinkles, such as glabellar, lateral periorbital and horizontal forehead wrinkles, smoker's wrinkles (puppets), Venus' rings (horizontal neck wrinkles). They also use toxin injection for masticatory muscle hypertonicity [37].

Postprocedural reactions are usually limited to erythema, pain, swelling and bruising at injection sites. When using this type of correction of age changes, there are also undesirable side effects. For example, hypersensitivity reactions, blepharoptosis, drooping eyebrows, asymmetry and abnormal shape of eyebrows or smiles, drooping of a mouth corner, lagophthalmos, diplopia, dry eye syndrome and xerostomia [38–40]. The complications listed above are temporary (limited by the time of blocking the release of acetylcholine), however, they limit the use of this technique. There is also insufficient data on the impact on other age-related stigmas, so it is better to combine this type of technique with others.

Chemical acid peeling is a controlled damage and inflammation of skin with subsequent exfoliation of its layers, one of the most popular procedures used to correct age-related changes in face and body skin [41]. According to the statistics of the American Association of Plastic Surgeons for 2019, chemical peels rank 3rd among the most used aesthetic procedures (1,387,607 manipulations were performed) [42]. Due to the depth of acid penetration and induction of inflammation, peels (even superficial variations) are able to stimulate neocollagenesis, especially types I, III and IV. Depending on the acid concentration and pH level, peelings are divided into superficial, middle and deep [41, 43, 44].

Such acids as lactic (10-30%), pyruvic (up to 50%), mandelic (up to 40%), glycolic in low concentration (up to 50%) and salicylic (up to 30%), Jessner's solution are used for the surface version. Damage occurs at the epidermal level (to the basement membrane), complete recovery takes 7–10 days [41, 43]. Glycolic acid is used in medium and high concentration (50–70%) with a primer in a form of combined Jessner solution, trichloroacetic acid (30–50%) for the middle option. Penetration of acids extends beyond basement membrane, to the level of papillary dermis, aepithelialization occurs due to the proliferation of follicular epithelium.

Exfoliation is completed 10–14 days after the procedure [41, 43, 45–47]. Trichloroacetic acid (> 50%), phenol (50-55%) and its combination in the form of Baker-Gordon solution (the concentration of phenol reaches 88%) is used for deep peels. Skin damage extends to the entire epidermis, papillary dermis and reaches the middle part of reticular dermis, healing occurs due to follicular epithelium [41, 43, 45–47].

Despite a large number of procedures, there are certain limitations and side effects that encourage patients to refuse acid peeling. In general, serious adverse complications occur with the use of medium and deep peels. Limitations are due to a long pre-peeling preparation at least for 3 weeks, the use of systemic retinoids and a withdrawal period of 6 months, post-peeling rehabilitation in the form of peeling, swelling, erythema.

Such factors disturb the social adaptation of patients and their daily behavior. Undesirable side effects such as cardiotoxicity of phenol in the form of the development of arrhythmias (observed in 34–50% of patients), nephro- and hepatotoxicity, persistent hypopigmentation, post-inflammatory hyperpigmentation, delayed re-epithelialization, cicatricial skin changes and cicatricial contractures, joining of secondary bacterial and fungal infection, exacerbation of herpes virus infection [41, 45, 46], can be observed mainly with deep peelings.

Intense pulsed light is used for hyperpigmentation, vascular pathology of skin (including telangiectasia), age-related skin changes, and acne. IPL is based on a source of polychromatic incoherent light in wavelength range from 420 to 1200 nm. With the help of special adapter filters, the doctor can limit the range of waves used to optimize exposure parameters (wavelength, duration and pulse energy). The mechanism of action is based on selective photothermolysis. The main chromophores of this method are hemoglobin and melanin [48, 49]. To achieve a sustainable result a certain course of procedures is needed. The postoperative period is accompanied by edema and erythema. Complications in the form of burns, increased hyperpigmentation (in case of violation of postoperative care), hypopigmentation [50] can be present.

Depending on the indications and needs, ablative and non-ablative laser fractional or continuous laser skin resurfacing methods are used today [51, 52]. The chromophore for this type of radiation is water. Mechanism of action of ablative lasers is based on absorption of laser energy by water molecules in skin structures, a vaporization process occurs with the subsequent release of thermal energy and the formation of a damaged zone (epidermis and dermis) or an ablative crater. There is an alternation of coagulation zones with intact skin with the fractional method, and with the continuous method total damage is observed. Non-ablative methods leave the epidermis intact due to selective photothermolysis of dermal layer of skin [53].

In cosmetology practice, both ablative lasers – CO2 (wavelength 10600 nm), Er:YAG (2940 and 2790 nm), and non-ablative lasers – Nd:YAG (1450 nm), PPTP (1032 and 1064 nm) are used [54]. Fragmentation of collagen fiber with further restructuring of collagen types I and III, activation of fibroblasts occurs after exposure to laser energy. This leads to a decrease in a depth of wrinkles, a tightening of the dermis, and an increase in hydration [55–57]. Laser polishing requires special care before and after procedure. Cosmetic agents that affect the blocking of melanogenesis links are introduced for a month before, surface chemical acid peelings are possible. Post-procedural care forces you to abandon daily rituals of care during rehabilitation.

It is recommended to clean the skin only with water without additional products for up to 1 week instead, with the subsequent transition to mild forms of cleansing products without fragrances, use additional moisturizing (sometimes with the addition of glucocorticosteroid drugs), SPF – creams with repeated application every 2 hours [58]. Complications from the procedure: exacerbation of acne or herpes, secondary bacterial or fungal infection, persistent erythema, hyperpigmentation, hypopigmentation, formation of crusts, skin scarring [59].

One of the promising topical non-invasive methods of aesthetic correction is photodynamic therapy (PDT). This method containes a local application of photosensitizer on skin followed by exposure to visible spectrum of light with a certain wavelength [60]. Light sources with a wavelength from 400 to 1200 nm are used. Red spectrum of light (630–700 nm) is used for remodeling dermal collagen due to the depth of penetration and activation of fibroblasts [61]. The depth of action of waves from 550 to 650 nm is from 3000 to 5000 μm [62].

Mechanism of action is based on the application under occlusion of a photosensitizer molecule, the accumulation of PpIX in mitochondria of cells, followed by its activation by a certain wavelength light source, as a result of which unstable forms of singlet oxygen and free radicals are generated, which cause redox reactions in the environment and selective cytotoxic effect. PpIX has its absorption peaks at 405 nm, 510 nm, 545 nm, 580 nm and 635 nm, however, it is precisely the red spectrum of light that is used due to greater penetration depth [63, 64]. Programmed cell death (apoptosis) is activated, which is disrupted by skin aging when using low doses of PDT.

5-aminolevulinic acid (5-ALA) and its methylene ester (MAL) are widely used in dermatological practice. An increase in the production of type I collagen is observed, and remodeling occurs through stimulation of TGF-β1 after the use of PDT for the purpose of photorejuvenation (strength of recommendation A, level of evidence I). Among the post-procedural reactions, erythema and swelling can be distinguished, which can persist for 4–7 days. At high doses, pain, hypo- and hyperpigmentation is observed [65].

Thus, in the context of an overall strategy to support peri- and postmenopausal women's health, which includes recommendations for lifestyle, diet, exercise, smoking cessation and safe levels of alcohol consumption, using this term to refer to various types of treatment, MHT considers as one of key methods, including the use of estrogens, progestogens and combined hormonal drugs, and the main condition for the effectiveness and safety of treatment is the timeliness of their appointment [66]. For the purpose of aesthetic correction of external age changes, it is possible to develop and use skin care programs, taking into account the modern possibilities of aesthetic medicine and individual characteristics of each woman. Thus, cosmetic care is definitely, first of all, a medical problem and the result of interdisciplinary work of obstetrician-gynecologists and dermatovenerologists.

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