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HISTOLOGICAL EVALUATION OF SYSTEMIC ISOTRETINOIN'S EFFECT ON THE SKIN

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The presented literature review contains data on histomorphological changes in the dermis when using isotretinoin. The systematic search was conducted for the results of scientific studies published between January 1980 and January 2026. The analysis included original researches, clinical and morphological work, experimental studies and review publications on morphological changes in the skin during systemic isotretinoin therapy. The result of the relevant search turned out to be 409 articles, of which, after the initial study, 25 articles were selected for final analysis: 19 articles were devoted to the anti-acne effect, the remaining 6 articles – to the involution of signs of photoaging against the background of the use of isotretinoin. Based on the literature analysis, data were collected on histological changes in the skin during the systemic use of isotretinoin from both the sebaceous glands and the dermis.

Systemic use of isotretinoin caused a number of changes in the skin, confirmed clinically and histologically. In particular, sebaceous glands were significantly reduced (up to 90%), and sebocyte differentiation was inhibited. The structure of the glands became elongated, «cellular» with a small number of sebocytes remaining in the center, on the basal plate. The amount of cytoplasm decreased by 35% compared to the size of the nucleus. There was a noticeable decrease in the number of immature cells and there was no mitotic numbers. The number of partially differentiated cells was very small, most of the cells were mature and full of lipid droplets. Desmosome destruction and disruption of links between keratinized keratinocytes were recorded, therefore, microcomedones regressed, and sebaceous filaments significantly decreased clinically. Follicular keratinization decreased by 55-70%. The amount of sebum and bacteria in comedones decreased markedly.

In the context of the effect of isotretinoin on photoaging, the following histological changes were identified: the significant increase in epidermal thickness, the decrease in elastosis, the decrease in epidermal p53, the straightening of the papillae of the dermis, the trophism improvement, the decrease in inflammatory infiltrate and in the degree of basophil degeneration of collagen, the increase in its density and concentration. There was the decrease in the number and changes in elastic fibers: elastic fibers were more tangled and fragmented before treatment, and more fibrillar and whole after treatment.

Key words: acne, isotretinoin, retinoids, skin biopsy, sebaceous glands, epidermis, sebocytes, keratinocytes

INTRODUCTION

Systemic use of isotretinoin is by far the most effective method of acne treatment [1]. Isotretinoin (13-cis-retinoic acid) differs from other drugs for systemic acne therapy in its ability to influence all major factors in the pathogenesis of the disease, which is a unique property. The history of the use of systemic retinoids in the treatment of acne begins in 1909 with the discovery of vitamin A. It was soon proved that vi-

tamin A is necessary to maintain vision, reproductive function, growth process, immune status and homeostasis, as well as to stimulate cell differentiation [2]. In the 1940s, the effect of vitamin A on acne was first documented, and in 1947, the first synthetic retinol was obtained. In 1962, trans-retinoic acid (tretinoin) was discovered. The task of reducing the toxicity of therapeutic (effective) dosages of the first systemic retinoids was solved together with the discovery of

13-cis-retinoic acid (isotretinoin) in 1969, which reduced the therapeutic index by 2.5 times compared with the use of fully trans-retinoic acid. The first large clinical trial led by G. Plevig with the participation of 19 dermatological centers and 136 patients was conducted in 1981. Isotretinoin itself was registered for the treatment of severe forms of acne in the USA in 1982, in Europe in 1983, which was a major breakthrough in treatment and gave hope to patients against whom medicine had been powerless until that moment [3].

The widespread use of isotretinoin in world practice began in the 80s of the 20th century, in the CIS countries – only since the late 90s, and in Kazakhstan the first steps in the use of isotretinoin began only in the 21st century (the first isotretinoin was registered in the territory of the Republic of Kazakhstan on November 25, 2016). Despite the extensive experience of foreign colleagues and the official registration of the drug, the prescriptions were modest and were accompanied by phobias of side effects on the part of both patients and doctors. Fortunately, in recent years, doctors have become much bolder and patients more aware of systemic retinoids, which has significantly increased the frequency of use of this modern and effective therapy.

The aim of the study was to analyze and systematize the available data on histomorphological changes in the epidermis, dermis and appendages of the skin during systemic therapy with isotretinoin.

MATERIALS AND METHODS

The systematic search was conducted for the results of scientific research in the international and national electronic databases PubMed, Scopus, Web of Science, Embase, Cochrane Library, eLibrary and Google Scholar, published from January 1980 to January 2026. The analysis included original research, clinical and morphological work, experimental studies, and review publications on morphological changes in the skin during systemic isotretinoin therapy. The following search queries were used: isotretinoin, 13-cis-retinoic acid, histology, biopsy, acne. The inclusion criteria were as follows: original articles with data on histological examination of the skin against the background of the use of isotretinoin. The exclusion criteria were considered to be the absence of histological data, animal studies and *in vitro* cultures. The result of the relevant search turned out to be 409 articles, of which, after the initial study, 25 articles were selected for final analysis: 19 articles were devoted to the anti-acne effect, the remaining 6 articles – to the involution of signs of photoaging against the background of the use of isotretinoin.

The object of the study was scientific publications devoted to the study of morphohistological changes in the skin against the background of the use of systemic isotretinoin.

RESULTS

In 1982, J. A. Goldstein published the first study of isotretinoin on 7 male patients, during which he revealed noticeable histological changes in all patients in the form of changes in the structure of the sebaceous glands: before the start of treatment, the sebaceous glands were well developed with typical lobules and cells of the sebaceous glands. After 16 weeks of therapy, there was the absence or marked atrophy of the sebaceous glands. On average, the decrease was up to 90%, and the amount of cytoplasm decreased by 35% compared to the size of the nucleus. Clinically, this was expressed in the significant decrease in sebum production (by 88.4%) [4].

G. L. Peck et al. confirmed the significant reduction in the size of sebaceous glands and an obvious inhibition of sebocyte differentiation, however, histological examination was performed in only 3 out of 33 subjects [5]. K. Dalziel, T. Kingston and R. Marks noted that the glands became elongated and «cellular» with a small number of sebocytes, remaining in the center. The authors did not confirm the theory of isotretinoin's anti-inflammatory properties, although this effect was later proven. In the publication by the same group of scientists 3 years later, in addition to monitoring the size of sebocytes, emphasis was placed on studying changes in enzymatic activity, but no significant changes were detected [6]. A. S. Zelickson (1986) stated that, in addition to the decrease in the size of the sebaceous glands, there was the noticeable decrease in the number of immature cells and no mitotic numbers on the basal plate during treatment with isotretinoin. The number of partially differentiated cells was very small, most of the cells were mature and full of lipid droplets. This work is valuable because it considered different daily and therefore cumulative dosages of the drug. Thus, it was confirmed that with low daily dosages (0.1 mg/kg), the restoration of the structure and activity of sebocytes occurred faster than with high dosages (1 mg/kg) [7]. There was also the perceptible decrease in sebum and bacteria in the gums. The destruction of desmosomes was recorded, therefore, the connection between the keratinized cells was disrupted [8].

G. Plevig investigated combination therapy with topical tretinoin and systemic isotretinoin in different dosages. During the observation of morphological changes in the skin of patients with conglobate and papulopustular acne (16 cases), G. Plevig recorded the decrease in the area and circumference of sebaceous glands by 35-58%, follicular keratinization – by 55-70%, the decrease in the density of active sebaceous glands – by 1 cm², as well as the complete regression of microcomedones and the significant decrease in sebaceous filaments [9].

The search for a less toxic impact of isotretinoin led to the search for an answer to the question

Table 1 – Data from publications studying the effect of isotretinoin on acne skin

Authors	Title	Year of issue	Number of patients	Frequency and time of tissue sampling	Morphological changes
Goldstein J. A. et al.	Isotretinoin in the Treatment of Acne. Histologic Changes, Sebum Production, and Clinical Observations	1982	7	Before treatment, at week 16 of treatment	The significant decrease in the size of sebaceous glands, the decrease in sebum production ($\approx 88\%$) after 16 weeks of treatment. Partial restoration of sebaceous glands 32 weeks after the end of therapy; classic evidence of SG atrophy under the action of isotretinoin
Goldstein J. A. et al.	The effects of isotretinoin on follicular and sebaceous cell differentiation	1982	3 biopsies, 33 patients in total	Before treatment, after 6 months, during the repeat course	The noticeable decrease in the size of the sebaceous glands and the clear suppression of sebaceous gland differentiation: the increase in the number of peripheral sebaceous cells, which lack typical cytoplasmic droplets
Dalziel K. et al.	The effects of isotretinoin on follicular and sebaceous cell differentiation	1987	17	Before treatment, at week 4, at week 8 of treatment	The significant decrease in the volume of sebaceous glands in the dermis at both weeks 4 and 8, the glands become elongated and «cellular» with a small number of sebocytes remaining in the center
Zelickson A. S. et al.	Ultrastructural Changes in Sebaceous Glands. Following Treatment of Cystic Acne with Isotretinoin	1986	15	Before, after 20 weeks, and 2 months after the end of treatment	The noticeable decrease in the number of immature cells and no mitotic numbers. The number of partially differentiated cells was very small, most of the cells were mature and full of lipid droplets. A noticeable decrease in the amount of sebum and bacteria was recorded in comedones. Desmosome destruction was noted – the connection between the keratinized cells was disrupted
Plewig G. et al.	Low dose isotretinoin combined with tretinoin is effective to correct abnormalities of acne	2004	16	Before treatment and at the end of the 6-month therapy	The decrease in the size (area) and circumference of sebaceous glands, the decrease in the number of active sebaceous glands per 1 cm ² , the complete regression of microcomedones and the significant decrease in sebaceous filaments
Tschan T., Steffen H., Supersaxo A.	Sebaceous-gland deposition of isotretinoin after topical application: an in vitro study using human facial skin	1997	Model <i>in vitro</i> from the skin of the women parotid zone	Before and 16 hours after application	The concentration of isotretinoin in the sebaceous glands ranged from 0.17 to 1.57 ng/mg of tissue
Vahlquist A. Rollman O., Holland D. B. Cunliffe W. J.	Isotretinoin treatment of severe acne affects the endogenous concentrations of vitamin A in sebaceous glands	1990	22	Before treatment, after 2, 4 and 7 – 11 months of treatment	Sebaceous glands contain higher amounts of both retinol and dihydroretinol than the epidermis and dermis
Amanda G., Nelson M., Zhao W., Gilliland K. L.	Isotretinoin temporally regulates distinct sets of genes in patient skin	2009	8	Before and 8 weeks after the start of treatment	The size of the sebaceous glands decreased by 76% (4.17 times) compared to the baseline level ($P=0.009$). After a week, the size of the glands decreased by about 49%

of why topical forms are not effective in severe forms. The answer to it was given by T. Tschan, H. Steffen, and A. Supersaxo in 1997 [10]. Histological examination revealed that the concentration of isotretinoin in the sebaceous glands ranged from 0.17 to 1.57 ng/mg of tissue. Autoradiography and *in vitro* fluorescence microscopy have shown that when applied topically, a significant amount of isotretinoin enters the sebaceous glands via the follicular pathway, while the effectiveness of the ethanol gel is not inferior to that of liposomal or mixed micellar gel. In comparison with the data of A. Vahlquist, O. Rollman, D. B. Holland, and W. J. Cunliffe, [11] who measured the concentration of isotretinoin in the sebaceous glands with oral administration and obtained values of 0.28-0.44 ng/mg, depending on the duration of treatment, the results were comparable or even higher, which is at odds with the clinical effects. The authors explain this discrepancy by the difference in vascular clearance in the model *in vitro*, nuances in the calculation of isotretinoin isomers, and the fact that the distribution of isotretinoin in the sebaceous glands remains in the lipophilic center of the sebaceous glands during topical use and is not transferred to basal sebocytes (target cells), which are actively affected by systemic isotretinoin, penetrating through the microcirculation system.

In 2009, G. Amanda, M. Nelson, W. Zhao, and K. L. Gilliland studied the regulation of the activity of individual groups of genes in the patient's skin with isotretinoin and confirmed the change in the size of the sebaceous glands: it decreased by 76% (4.17 times) compared with the baseline level ($p=0.009$). After a week, the size of the glands decreased by about 49% [12].

The described above data are summarized in table 1.

The occurred changes are recorded by observing histological changes in the skin, while molecular biology helps to understand the processes. Indeed, despite its undeniable effectiveness in acne and seborrhea, the molecular basis of the unique sebostatic activity of this compound is still not fully understood. Thus, in the works of R. K. Randolph and M. Simon, the ability of dermal fibroblasts to metabolize exogenous retinoic acid was proved, thereby regulating its concentration in the skin. At the same time, fibroblasts practically do not metabolize retinol itself, which indicates a difference in the processing pathways of different forms of retinoids. These studies mean that there is a local mechanism in the dermis to control the activity of retinoic acid, which can limit or modulate its biological effects [13].

J. M. Baron, R. Heise, and W. S. Blaner analyzed the functional activity of fully trans-, 9-cis-, and 13-cis-retinoic acid and their 4-oxo metabolites in normal human epidermal keratinocytes and dermal fibroblasts using gene and protein expression profiling methods. The study showed that retinol 4-oxometab-

olites have strong and isomer-specific regulatory activity in relation to transcription, and do not represent only inert end products of catabolism, as previously thought. Microarray and proteomic analysis have identified a number of new genes and gene products that are affected by retinol treatment of keratinocytes or fibroblasts, including genes for enzymes that catalyze the biotransformation of retinoids, corticosteroids and antioxidants, as well as genes for structural and transport proteins that are known to be necessary for maintaining homeostasis. The results of the study showed the significant decrease in the expression of keratins 1, 10, 14 and 17, as well as matrix metalloproteinase-10, vascular endothelial growth factor C, thrombospondin-1, plasminogen activator inhibitor-2, cyclooxygenase-2, psoriasis-associated fatty acid binding protein, filaggrin. Incubation of dermal fibroblasts with retinoic acid isomers for 24 hours revealed more significant changes than those observed with NHEK, including the decrease in the activity of p-450-dependent enzymes involved in xenobiotic/endogenous biotransformation, including cytochrome P450 (CYP)2D, CYP3A7, CYP4A1, corticosteroid 11b dehydrogenase, prostaglandin-endoperoxide synthase-1, phosphatase-11 with dual specificity, glutathione S-transferase M1, and transport proteins such as solute transporter family 16 member 1 (SLC16A1) [14].

A. M. Nelson and K. L. Gilliland confirmed *in vitro* the previously described antiproliferative effect of isotretinoin on human sebocytes. These authors attributed part of this decrease to cell cycle arrest and found sebocyte apoptosis, which was not reproduced by alitretinoin or tretinoin. These events were specific to sebocytes because isotretinoin failed to induce apoptosis in keratinocytes. Isotretinoin-induced apoptosis was shown to be a mechanism that was independent of RAR [15]. In 2009, the same group of authors conducted a transcription analysis and found that the lipocaine 2 gene (involved in innate immunity) is among the genes whose expression is most strongly increased by exposure to 13-cis-retinoic acid, and also confirmed sebaceous gland apoptosis by TUNEL staining [16].

Isotretinoin affected the expression of many other genes, which can be roughly divided into three categories: tumor suppressor genes, genes involved in protein synthesis, and genes involved in the transfer or binding of ions, amino acids, lipids, or retinoids. In addition to genes, the role of dissolved substance carrier proteins is also important in skin biology. The study revealed the increase in the expression of proteins of the S100 family, which regulate cell differentiation, energy metabolism, interaction of the cytoskeleton with the membrane, and the cell cycle. The increased activity of S100 proteins is induced by oxidative or inflammatory stress, which suggests that the initial activation of S100 13-cis proteins is respon-

Table 2 – Data from publications studying the effect of isotretinoin on the skin at the cellular, gene, and molecular levels

Authors	Title	Year of issue	Material	Morphological changes
Randolph R. K., Simon M.	Dermal Fibroblasts Actively Metabolize Retinoic Acid but not Retinol.	1988	Fibroblast culture	Dermal fibroblasts metabolize exogenous retinoic acid, thereby regulating its concentration in the skin.
Baron J. M., Heise R., Blaner W. S.	Retinoic Acid and its 4-Oxo Metabolites are Functionally Active in Human Skin Cells In Vitro	2005	Culture of human epidermal keratinocytes (NHEK) and dermal fibroblasts	The significant decrease in the expression of keratins, matrix metalloproteinase-10, vascular endothelial growth factor-C, thrombospondin-1, plasminogen activator inhibitor-2, cyclooxygenase-2, psoriasis-associated fatty acid binding protein, filaggrin.
Nelson A. M., Gilliland K. L., Cong Z., Thiboutot D. M.	13-cis-retinoic acid induces apoptosis and cell cycle arrest in human SEB-1 sebocytes	2006	Sebocyte culture	13-cis-retinoic acid causes cell cycle arrest and apoptosis in SEB-1 sebocytes by a mechanism independent of RAR, which corresponds to sebosuppression
Schroeder M., Zouboulis C. C.	All-trans-retinoic acid and 13-cis-retinoic acid: pharmacokinetics and biological activity in different cell culture models of human keratinocytes	2007	Keratinocyte culture with high and low density	Retinoic acid isomers enhanced proliferation At low cell density, but at high density, they showed an antiproliferative effect in normal keratinocytes, and stimulating effect in HaCaT keratinocytes.
Amanda G., Nelson M., Zhao W., Gilliland K. L., Zaenglein A. L.	Neutrophil gelatinase-associated lipocalin mediates 13-cis retinoic acid-induced apoptosis of human sebaceous gland cells	2008	Sebocyte culture	Increased levels of lipocalin 2, which encodes the protein lipocalin associated with neutrophilic gelatinase (NGAL).
Amanda G., Nelson M., Zhao W., Gilliland K. L., et al.	Early gene changes induced by isotretinoin in the skin provide clues to its mechanism of action	2009	7 patients before and one week after the start of therapy	Increased expression of S100 family proteins.
Amanda G., Nelson M., Zhao W., Gilliland K. L.	Temporal changes in gene expression in the skin of patients treated with isotretinoin provide insight into its mechanism of action.	2009	8 patients before and 8 weeks after	197 genes were significantly activated, 587 were significantly suppressed.
Lumsden K. R., Nelson A. M., Dispenza M. C., Gilliland K. L., et al.	Isotretinoin increases skin-surface levels of neutrophil gelatinase-associated lipocalin in patients treated for severe acne.	2011	15 patients with acne and 15 people in the control group (1-4-8 weeks)	The level of NGAL protein increased, which triggered apoptosis in sebocytes, but did not directly affect <i>P. acnes</i>
Dispenza M. C., Wolpert E. B., Gilliland K. L.	Systemic isotretinoin therapy normalizes exaggerated TLR-2-mediated innate immune responses in acne patients	2012	27 subjects, the control group (23 persons). Blood before treatment and at 1-4-8-20 weeks, as well as 6 months after the end of treatment	Isotretinoin caused acne remission by normalizing the innate immune response to the commensal bacterium <i>Propionibacterium acnes</i> by reducing TLR-2 expression in monocytes
Agamia N. F., Hussein O. M., Abdelmaksoud R. E., Abdalla D. M., et al.	Effect of oral isotretinoin on the nucleo-cytoplasmic distribution of FoxO1 and FoxO3 proteins in sebaceous glands of patients with acne vulgaris	2018	14 patients, control group (10 persons). Puncture biopsy before and after 6 weeks	FoxO expression was activated by isotretinoin.
Agamia N. F., El Mulla K. F., Alsayed N. M., Ghazala R. M., et al.	Isotretinoin treatment upregulates the expression of p53 in the skin and sebaceous glands of patients with acne vulgaris	2023	25 patients, control group (15 persons). Biopsy with immunohistochemistry, ELISA and PCR	Increased nuclear expression of p53 in sebaceous glands

sible for the «acne outbreak» reaction observed in some patients receiving oral or topical retinoids for the treatment of acne [17].

After the initial start of apoptosis and the cell cycle stops in the sebaceous glands, genes characteristic of wound healing are expressed in the skin, followed by significant regeneration and remodeling, as evidenced by increased expression of extracellular matrix proteins. A total of 197 genes were significantly activated, 587 genes were significantly suppressed. Most of the genes whose activity decreased after 8 weeks are associated with the metabolism of steroids, cholesterol, and fatty acids, which is consistent with the well-known fact that sebum production decreases under the influence of 13-cis-retinoic acid. The genes activated at week 8 encode structural proteins such as collagens and fibronectin, which is consistent with the known effect of retinoids on extracellular matrix repair [18].

The level of NGAL protein in the skin of patients taking isotretinoin increases, and this increase precedes a decrease in sebum production and the amount of *Propionibacterium acnes* (*P. acnes*). These data indicate a temporal relationship in which an increase in NGAL triggers apoptosis in sebocytes, which leads to a decrease in sebum production and *P. acnes* levels. However, the antibacterial effect of NGAL against *P. acnes* has not been confirmed. Consequently, *P. acnes* decrease a second time during isotretinoin treatment after a decrease in sebum secretion, which is a source of nutrients for *P. acnes* [19].

M. C. Dispenza et al. demonstrated the decrease in TLR-2 expression in monocytes and the subsequent inflammatory response to *P. acnes* after a week of isotretinoin therapy. This effect persisted for 6 months after discontinuation of therapy, indicating that TLR-2 modulation may be associated with the long-term therapeutic effect of isotretinoin. This proves that isotretinoin has an immunomodulatory effect on patients [20].

N. F. Agamia et al. analyzed the distribution of proapoptotic transcription factors FoxO1 and FoxO3 in the nuclear and cytoplasmic compartments of human sebocytes *in vivo* before and during acne treatment with isotretinoin (6 weeks after initiation of isotretinoin therapy). The results showed a significant increase in the nuclear-cytoplasmic ratio of nonphosphorylated FoxO1 and FoxO3 in the treatment of acne with isotretinoin, which is involved in proapoptotic signaling, caused by isotretinoin in sebocytes and confirms the scientific hypothesis of activation of FoxO expression under the action of isotretinoin [21].

Against the background of isotretinoin treatment, the expression of the protein and the p53 gene in the skin significantly increased. The amount of p53 expression was inversely correlated with the severity of acne and body mass index. In clinical settings, isotretinoin stimulated the expression of p53, which

controls many transcription factors involved in the pathogenesis of acne vulgaris, including FoxO1, the androgen receptor, and critical genes involved in the induction of autophagy and apoptosis. The enhancement of the p53-FoxO1 signaling pathway caused by systemic isotretinoin administration explains the underlying transcript changes that lead to suppression of sebum production, as well as side effects associated with systemic isotretinoin therapy [22].

M. Schroeder and C. C. Zouboulis studied the effect of retinoic acid isomers on keratinocyte proliferation at low and high densities (imitation of hyperkeratotic diseases and age-related skin or skin exposed to steroids). The results of the study proved that at low cell density, retinoic acid isomers enhanced proliferation, but at high density, they showed an antiproliferative effect in normal keratinocytes, and stimulating effect in HaCaT keratinocytes. The absence of the effect of retinoids on cell proliferation at a high seeding density of normal keratinocytes may indicate that the normalizing effect of retinoids in hyperkeratotic diseases such as acne or psoriasis is most likely due to the modulation of cell differentiation rather than their growth. On the other hand, induced keratinocyte proliferation at low seeding density may serve as an explanation for acanthosis caused by topical application of retinoids to age-related and steroid-damaged skin [23].

The described above data from publications studying the effect of isotretinoin on the skin at the cellular, gene, and molecular levels are summarized in table 2.

The active use of isotretinoin continued, and in addition to its sebostatic and anti-acne effects on the skin, dermatologists observed other changes. So, in 2000, S. Maddin et al. published the study on the effect of topical isotretinoin on the signs of photoaging. The study involved 20 dermatology centers with a total sample of 800 patients. Histological examination was performed among 120 patients and revealed the significant increase in the thickness of the epidermis. There were no obvious changes in skin elastosis, dermis thickness, melanin content in the epidermis, fibroblast count, melanocyte dysplasia, or keratinocyte atypia. At the same time, the absence of significant histological changes in the dermis did not exclude the possibility of remodeling of its fine structure. It is worth noting that the clinical changes were more expressed and manifested themselves in improving the appearance of the photo-damaged skin. Significant reduction of fine and coarse wrinkles, improvement of texture and pronounced pigmentation were observed after 12 weeks of daily use of isotretinoin. And within 36 weeks, the effect of the treatment was further enhanced [24].

C. L. Kalil investigated the effect of systemic isotretinoin in the treatment of photoaging. 50 women aged 40-60 years received 20 mg of isotretinoin 3 times a week for 3 months. The decrease in the signs of photoaging was recorded: straightening of

Table 3 – Data from publications studying the effect of isotretinoin on skin at photoaging

Authors	Year of issue	Title	Number of patients	Frequency and time of tissue sampling	Morphological changes
Maddin S. et al.	2000	Isotretinoin improves the appearance of photodamaged skin: Results of a 36-week, multicenter, double-blind, placebo-controlled trial	120 biopsies from 800 patients	Before therapy and after 36 weeks	Reduction of signs of photoaging, thickening of the epidermis
Kalil C. L. et al.	2008	Use of Oral Isotretinoin in Photoaging Therapy	30	Before therapy, a week after the end	Straightening of the papillae of the dermis, improvement of trophism and reduction of collagen degeneration
Rabello-Fonseca R. M. et al.	2009	Oral isotretinoin in photoaging: clinical and histopathological evidence of efficacy of an off-label indication	30	Before and after 3 months of therapy	The decrease in inflammatory infiltrate, the decrease in the degree of basophilic collagen degeneration, the decrease in the number of elastic fibers. Elastic fibers were more tangled and fragmented before treatment, and more fibrillar and whole after treatment. The concentration of collagen has increased significantly
Bagatin E. et al.	2014	Low-dose oral isotretinoin versus topical retinoic acid for photoaging: a randomized, comparative study	22 completed observations out of 24	Before and after 6 months of therapy	The increase in the thickness of the epidermis, the decrease in elastosis and the decrease in epidermal p53, the increase in the amount of type 1 surface dermal collagen
Bravo B. S. et al.	2015	Oral isotretinoin in photoaging: objective histological evidence of efficacy and durability*	20	Before therapy, at the end of the 12-week therapy, and after 12 weeks of therapy	Increased density of collagen and elastic fibers, matrix remodeling
Weiss J. S., Ellis C. N., Headington J. T.	1988	Topical tretinoin improves photoaged skin. A double-blind vehicle-controlled study	30	Before and after 16-week therapy	The epidermis thickened by 273%, the granular layer became homogeneous and more dense by 118%, the number of mitotic figures increased, hypertrophy and hyperplasia of melanocytes decreased

the papillae of the dermis, improvement of trophic tissue and reduction of collagen degeneration in 20 patients. The condition of 10 patients has not changed. It should be noted that clinical improvement was noted in 79.99% of the subjects. The question remains whether a longer intake will lead to more pronounced changes [25].

R. M. Rabello-Fonseca et al. observed 30 patients with signs of photoaging and registered the following morphological changes against the background of oral isotretinoin intake: the decrease in inflammatory infiltrate and the decrease in the degree of basophilic degeneration of collagen, the decrease in the number of elastic fibers and elastic material. Elastic fibers were more tangled and fragmented before treatment, and more fibrillar and whole after treatment, and there was the significant increase in collagen concentration [26].

E. Bagatin compared topical and systemic retinol in the context of effects on photoaging. Histological analysis revealed the statistically significant increase in epidermal thickness, the decrease in elastosis and the decrease in epidermal p53, and the increase in the amount of type 1 surface dermal collagen in both groups. No significant differences were found between the groups [27].

B. S. Bravo studied 20 patients with signs of photoaging using systemic isotretinoin at the dosage of 20 mg/day 3 days a week. In 65% of patients, there was the change in the distribution and thickness of elastic fibers, which can be interpreted as the improvement in skin condition. The increase in collagen density was recorded in 60% of patients from 51.2 to 57.4% ($p=0.004$). By the end of the 12-week follow-up period, collagen density decreased to 54.7% ($p=0.050$). The density of elastic fibers increased from 26.5 to 31.3% ($p=0.02$), and decreased to 27.5% by the end of the 12-week follow-up period [28].

In 1988, J. S. Weiss, C. N. Ellis, and J. T. Headington conducted the study on the impact of topical tretinoin on photoaging symptoms and found the following changes. The mean thickness of the epidermis rose by 273%, while the mean thickness of the granular layer in patients using tretinoin increased by 118%. The count of mitotic figures in seven adjacent high-power fields was notably higher on the skin of patients treated with tretinoin. The stratum corneum appeared denser and more uniform, with an enhanced appearance of the shiny layer, reduced hypertrophy and hyperplasia of melanocytes, and less severe epidermal atypia and dysplasia compared to before therapy. The papillary layer of the dermis exhibited wider vascular lumens relative to biopsies from untreated areas. However, the thickness of the papillary layer of the dermis did not show a significant increase [29].

Data on morphological changes in the skin during photoaging with the use of isotretinoin are shown in Table 3.

DISCUSSION

Observations of morphological changes in tissues are very scarce: the number of studies is small, and the samples average 20-30 subjects. Perhaps this is due to the high injury rate during the sampling of the material for the study, followed by the formation of a skin defect, which is especially difficult for patients with acne. Another factor that reduces the need for histological data is that only observation (with the naked eye) and photo documentation are sufficient to verify the effectiveness of therapy. Nevertheless, research in this direction continues. However, the format has changed in recent years. Scientists are moving from classical histological observations, which were carried out in the 1970-2000s, to the *in vitro* cell biology stage on cultures of sebocytes, keratinocytes and immune cells (1990-2010), and in the last decade they have been actively moving to the genomic and transcriptomic stage. Modern discoveries and opportunities allow switching to the molecular level, while it is worth noting that the work is mainly carried out outside the human body, in *in vitro* conditions. This is very important for understanding the therapeutic mechanisms of isotretinoin. However, the issue of variability of daily and cumulative dosages in different population groups, long-term morphological changes years after completion of treatment, correlation of different dosages and duration of morphological changes in tissues remains equally important.

CONCLUSION

The use of isotretinoin systemically causes a number of changes in the skin, confirmed clinically and histologically. In particular, sebaceous glands are significantly reduced (up to 90%), and sebocyte differentiation is inhibited. The structure of the glands becomes elongated, «cellular» with a small number of sebocytes remaining in the center, on the basal plate. The amount of cytoplasm decreases by 35% compared to the size of the nucleus, there was the noticeable decrease in the number of immature cells and there was no mitotic numbers. The number of partially differentiated cells was very small; most of the cells were mature and full of lipid droplets. Desmosome destruction and disruption of communication between keratinized keratinocytes were recorded, therefore, microcomedones regressed, and sebaceous filaments significantly decreased. Follicular keratinization decreased by 55-70%. The amount of sebum and bacteria in comedones decreased markedly. It has been confirmed that when using low daily dosages (0.1 mg/kg), the restoration of the structure and activity of sebocytes after the end of treatment occurs faster than when using high dosages (1 mg/kg).

The following histological changes were identified in the context of the effect on photo-aging: the significant increase in the thickness of the epidermis, the decrease in elastosis, the decrease in epidermal p53,

straightening of the papillae of the dermis, improvement of trophism, less inflammatory infiltrate and the decrease in the degree of basophil degeneration of collagen, an increase in its density and concentration. There was the decrease in the number and changes in elastic fibers: elastic fibers were more tangled and fragmented before treatment, and more fibrillar and whole after treatment.

Histological changes in the skin when using systemic isotretinoin are a clear and indicative criterion of the effectiveness of therapy. Given the tendency to increase cumulative dosages in recent years, monitoring histological changes *in vivo* against the background of isotretinoin use is a promising and necessary vector for drug research in particular and acne therapy in general.

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X. D. Besplemyannaya, M. K. Panova – research concept and design.

X. D. Besplemyannaya, R. Zh. Nygyzbayeva – data collection and processing.

X. D. Besplemyannaya – text writing.

L. M. Stabayeva, O. V. Edi – editing.

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The authors declare no conflict of interest.

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ГИСТОЛОГИЧЕСКАЯ ОЦЕНКА ВЛИЯНИЯ СИСТЕМНОГО ИЗОТРЕТИНОИНА НА КОЖУ

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В представленном обзоре собраны данные о гистоморфологических изменениях дермы на фоне применения изотретиноина. Проведен систематизированный поиск научных публикаций в период с января 1980 по январь 2026 г. В анализ включались оригинальные исследования, клинико-морфологические работы, экспериментальные исследования и обзорные публикации, посвященные морфологическим изменениям кожи при системной терапии изотретиноином. Релевантный поиск выдал 409 статьи, после первичного изучения для итогового анализа было отобрано 25 статей, 19 из которых направлены на изучение анти-акне эффекта и еще 6 наблюдали инволюцию признаков фотостарения на фоне применения изотретиноина. На основании анализа литературы собраны данные о гистологических изменениях кожи на фоне применения системного изотретиноина как со стороны сальных желез, так и со стороны дермы. Данные упорядочены и оформлены в единую таблицу.

Применение изотретиноина системно вызывает целый ряд изменений в коже, подтвержденных клинически и гистологически. В частности, сальные железы значительно редуцируются (до 90 %), происходит ингибирование дифференциации себоцитов. Структура желез становится удлинённой, «ячеистой» с небольшим количеством себоцитов, остающихся в центре, на базальной пластинке. Количество цитоплазмы по сравнению с размерами ядра уменьшается на 35 %, наблюдается заметное уменьшение количества незрелых клеток и никаких митотических цифр. Количество частично дифференцированных клеток очень малое, а большинство клеток зрелые и полные липидных капель. Было зафиксировано разрушение десмосом, нарушение связи между ороговевшими кератиноцитами, следовательно, микрокомедоны регрессировали, а сальные нити значительно уменьшались клинически. Фолликулярная кератинизация снизилась на 55-70 %. В комедонах заметно уменьшалось количество кожного сала и бактерий.

В контексте влияния на фотостарение были выявлены следующие гистологические изменения: значительное увеличение толщины эпидермиса, уменьшение эластога, снижение эпидермального p53, выпрямление сосочков дермы, улучшение трофики, уменьшение воспалительного инфильтрата и снижение степени базофильной дегенерации коллагена, увеличение его плотности и концентрации. Уменьшение количества и изменения эластичных волокон: эластические волокна до лечения были более спутанными и фрагментированными, после – более фибриллярными и цельными.

Ключевые слова: акне; изотретиноин; ретиноиды; биопсия кожи; сальные железы; эпидермис; себоциты; кератиноциты

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ЖҮЙЕЛІК ИЗОТРЕТИНОИННЫҢ ТЕРІГЕ ӘСЕРІН ГИСТОЛОГИЯЛЫҚ БАҒАЛАУ

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Ұсынылған әдеби шолу изотретиноинді қолдану кезінде дермадағы гистоморфологиялық өзгерістер туралы деректерді қамтиды. Жүйелі іздеу 1980 жылғы қаңтардан 2026 жылғы қаңтарға дейін жарияланған ғылыми зерттеулер нәтижелері бойынша жүргізілді. Талдауға жүйелік изотретиноин терапиясы кезінде терідегі морфологиялық өзгерістерге арналған түпнұсқа зерттеулер, клиникалық-морфологиялық жұмыстар, эксперименттік зерттеулер және шолу мақалалар енгізілді. Іздеу нәтижесінде 409 мақала анықталды, олардың ішінен бастапқы іріктеуден кейін соңғы талдауға 25 мақала алынды: олардың 19-еуі безеуге қарсы әсерге, қалған 6-еуі – изотретиноин қолдану аясында фотокартаю белгілерінің кері дамуына арналды. Әдебиеттерді талдау негізінде жүйелік изотретиноинді қолдану кезінде май бездері мен дерма тарапынан терідегі гистологиялық өзгерістер туралы деректер жинақталды.

Жүйелік изотретиноинді қолдану теріде клиникалық және гистологиялық тұрғыдан дәлелденген бірқатар өзгерістерге әкеледі. Атап айтқанда, май бездері айтарлықтай кішірейді (90%-ға дейін), ал себоциттердің дифференциациясы тежеледі. Бездердің құрылымы созылық, «жасушалық» сипатқа ие болып, ортасында базальды пластинада орналасқан аздаған себоциттер ғана сақталады. Цитоплазма мөлшері ядро көлемімен салыстырғанда 35%-ға азаяды. Жетілмеген жасушалар саны айқын төмендейді, митоздар байқалмайды. Жартылай дифференцияланған жасушалар өте аз, жасушалардың көпшілігі жетілген және липид тамшыларымен толы болады. Десмосомалардың бұзылуы және кератинденген кератиноциттер арасындағы байланыстардың әлсіреуі тіркеледі, соның нәтижесінде микрокомедондар регрессияға ұшырайды, ал май жіпшелері клиникалық тұрғыдан айқын азаяды. Фолликулярлық кератинизация 55-70%-ға төмендейді. Комедондардағы тері шел майы мен бактериялар мөлшері айтарлықтай азаяды.

Изотретиноиннің фотокартаюға әсері тұрғысынан келесі гистологиялық өзгерістер анықталды: эпидермис қалыңдығының едәуір артуы, эластоздың азаюы, эпидермальды р53 деңгейінің төмендеуі, дерманың емізікшелерінің тегістелуі, трофиканың жақсаруы, қабыну инфильтратының және коллагеннің базофильді дегенерация дәрежесінің азаюы, оның тығыздығы мен концентрациясының артуы. Сонымен қатар, эластикалық талшықтардың саны азайып, құрылымы өзгерді: емге дейін олар шатасқан және фрагменттелген болса, емнен кейін неғұрлым фибриллярлы және тұтас күйге келген.

Кілт сөздер: безеу; изотретиноин; ретиноидтар; тері биопсиясы; май бездері; эпидермис; себоциттер; кератиноциттер