Original Research Article

New possibilities of refractive modeling of the cornea by the radiation of an argon-fluorine excimer laser

Abstract

Purpose: To consider new possibilities of refractive modeling of the cornea by the radiation of an argon-fluorine excimer laser in ablative and subablative modes after saturation of the stroma with riboflavin.

Material and methods: Experimental (20 pork, 90 rabbit eyes) and clinical studies on photorefractive and phototherapeutic operations with saturation of the corneal stroma with riboflavin (610 operations) were analyzed. To activate riboflavin, secondary radiation induced by exposure to ablative and subablative energy densities was used. A quick transition to energy densities below the ablation threshold without additional calibrations was carried out using a "Microscan Visum-500" excimer laser (Optosystems, Russia). An objective assessment of the refractive keratomodelling effect and visual results was carried out according to the data of complex optometric studies.

Results: Experimental and clinical studies have shown the advantages of refractive keratomodeling by the radiation of an argon-fluorine excimer laser in ablative and subablative modes after saturation of the stroma with riboflavin. Isotonic 0.25% riboflavin solution did not affect the accuracy of refractive ablation and blocked the negative effect of induced secondary radiation on keratocytes and corneal nerves. This reduced the aseptic inflammatory response and the risk of developing an irreversible form of fibroplasia. Ablation with riboflavin initiated a damped crosslinking effect, which increased the photoprotective and strength properties of the thinned cornea. A refractive keratomodelling effect was found when energy densities were applied below the stromal ablation threshold. The magnitude of this refractive effect depended on the total radiation dose and the topography of the affected area. This approach made it possible to implement laser-induced refractive keratomodeling without ablation of the corneal stroma.

Conclusion: Refractive modeling of the cornea by the radiation of an argon-fluorine excimer laser in ablative and subablative modes after saturation of the stroma with riboflavin opens up new possibilities in laser correction of ametropia.

Key words: argon-fluorine excimer laser, refractive modeling of the cornea, riboflavin, photoprotection, crosslinking.

Introduction. The range of refractive modeling of the cornea by laser radiation of various spectral ranges is expanding every year. Historically, laser refractive keratomodeling was originally used to correct hyperopia and hyperopic astigmatism. For this, laser thermokeratoplasty was performed by applying coagulates with infrared laser radiation (1.54-2.09 microns). Unfortunately, with such laser keratomodeling it was not always possible to achieve the desired stability and accuracy of the refractive effect. In addition, as a result of laser refractive thermokeratoplasty, opacities of various intensities of a rounded shape were formed in the corneal stroma. In some cases, induced irregular astigmatism and optical side effects developed [1-3].

A qualitatively new direction in the correction of ametropia was refractive keratomodeling by radiation of an argon-fluorine excimer laser. High submicron accuracy of layer-by-layer evaporation of the corneal stroma made it possible to form almost any refractive profile of the cornea [4].

In recent years, excimer laser refractive surgery has been contrasted with femtolaser refractive surgery with intrastromal removal of the lenticule [5]. Nevertheless, to this day, photorefractive keratoablation by excimer laser radiation with a wavelength of 193 nm occupies a leading position in refractive laser surgery in terms of the accuracy of corneal re-profiling.

With all types of laser refractive surgery on the cornea, a number of problems arose associated with denervation and regenerative processes in the stroma. Ablative thinning of the stroma was accompanied by a weakening of the strength properties and a violation of the photoprotective function of the cornea to protect the intraocular structures from external UV radiation. With a large volume of stromal ablation, the risk of postoperative keratoectasia and earlier development of cataracts was increased [6].

From the standpoint of the above, the idea of laser refractive keratomodeling without coagulation and ablation of the corneal stroma was very attractive. In 1989-2004, the possibility of such an approach was experimentally confirmed for infrared and ultraviolet laser radiation [7-11]. In 2009, the idea of laser-induced refractive keratomodeling was theoretically substantiated for radiation of a femtosecond laser using energy parameters below the threshold of plasma-mediated photodestruction [12,13]. In recent years, publications have appeared on the possibility of using crosslinking for refractive modeling [16-24]. In experimental studies, the effect of corneal crosslinking was obtained by irradiation with subthreshold modes of femtolaser radiation without saturation of the stroma with riboflavin. At the same time, a refractive keratomodelling effect was revealed, which indicated the possibility of such a method for correcting weak degrees of ametropia [14,15].

However, all these approaches were significantly inferior to refractive keratoablation by radiation of an argon-fluorine excimer laser in terms of the accuracy and range of refractive corneal profiling.

Purpose. To consider new possibilities of refractive modeling of the cornea by radiation of an argon-fluorine excimer laser in ablative and subablative modes after saturation of the stroma with riboflavin.

Material and methods. Experimental (20 pork, 90 rabbit eyes) and clinical studies on photorefractive and phototherapeutic operations with saturation of the corneal stroma with riboflavin (610 operations) were analyzed. All studies were carried out in compliance with the principles of the Declaration of Helsinki and with the permission of the ethical committee of the FSBI "National Medical and Surgical Center named after V.I. N.I. Pirogov "of the Ministry of Health of Russia. Written informed consent was obtained from all patients and approved by the local ethics committee. To activate riboflavin, secondary radiation was used, induced by exposure to ablative and subablative radiation energy densities of an argon-fluorine excimer laser. Particular emphasis was placed on the clinical evaluation of corneal crosslinking using subablative pulse energy densities. Operations using radiation below the ablation threshold were performed using the Russian excimer laser "Microscan Visum-500" (Opto systems, Russia). This laser was the first to use an original technical solution for a quick transition from ablative to subablative energy densities, without any additional calibrations. In experimental studies, biomechanical testing of cornea samples, light and electron microscopy were used to assess the state of the cornea after photorefractive and phototherapeutic ablation with preliminary saturation of the stroma with 0.25% isotonic riboflavin solution. In the clinic, the assessment of the visual and refractive keratomodelling effect and visual results was carried out according to the data of complex optometric studies. The effect of crosslinking in photoablation with riboflavin was assessed according to the data of spectral optical coherence tomography (OCT), keratotopography, and corneal densitometry. Corneal OCT was performed using RTVue 100 and RTVue XR100 devices (Optovue, USA). Keratotopographic and densitometric studies were performed using a TMS-5 device (Topcon, Japan). The terms of clinical observations, complex optometric and special instrumental studies ranged from 1 month to 7 years.

Results. Experimental studies on photokeratoablation with stroma saturation with 0.25% isotonic riboflavin solution revealed the effect of crosslinking and an increase in the strength characteristics of thinned corneal ablation. In biomechanical testing, an increase in tensile strength and maximum tensile strength was noted (Fig. 1-3). According to the data of transmission microscopy, in the stromal layers adjacent to the ablation zone, the compactness of the packing of collagen fibrils and fibers was noted due to an increase in the number of cross-links (Fig. 4, arrows). Their concentration per unit area was approximately twice as high [25]. Photorefractive keratomodeling with riboflavin by the crosslinking effect was sufficient to compensate for the weakening of the strength properties of the thinned ablation of the cornea. With this technology, riboflavin-saturated layers of the corneal stroma worked like spectral filters, protecting keratocytes

Comment [M1]: How could it be? There were at most 220 eyes.

Comment [M2]: Porks and rabbits??? Were they literate?!

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Comment [M3]: What was the primary radiation? What protocol was used for riboflavin saturation?

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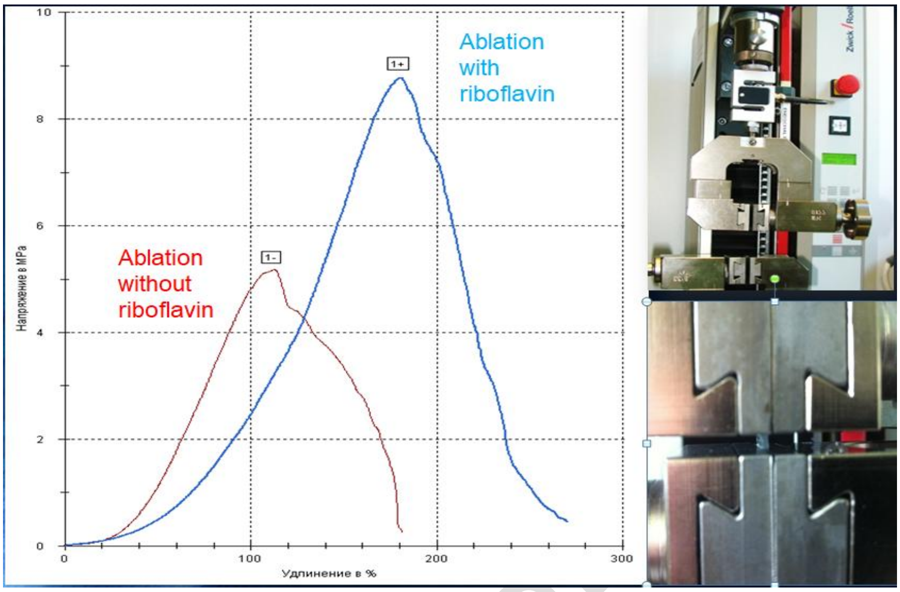

Fig. 1. Curves of biomechanical testing of thinned cornea samples after photoablation (without and with riboflavin). Tensiometric device Zwick / Roell BZ 2.5 / TN1S (Germany) and a corneal-scleral flap installed in the clamps.

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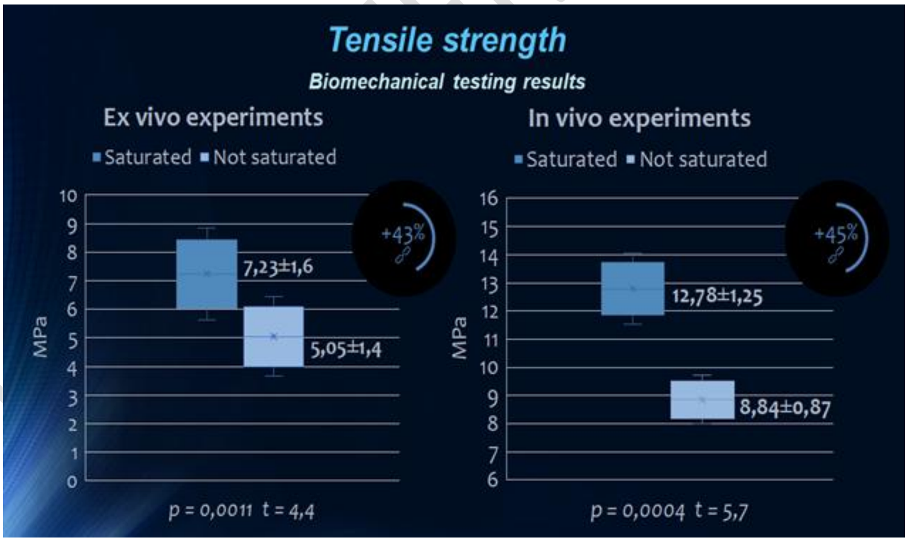

Fig. 2. Comparative evaluation of the increase in tensile strength of thinned cornea samples during photoablation with riboflavin in ex vivo andin vivo.

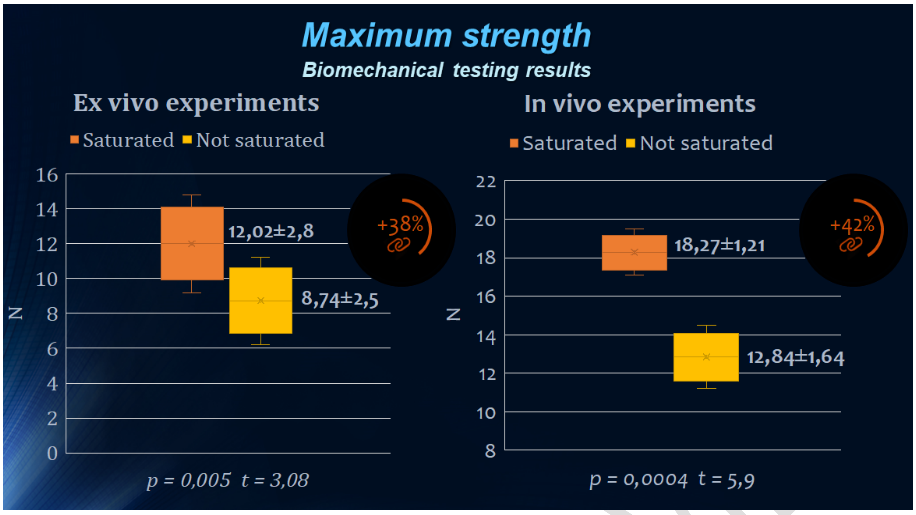

Fig. 3. Comparative evaluation of the increase in the maximum tensile force of thinned cornea specimens during photoablation with riboflavin in ex vivo and in vivo experiments.

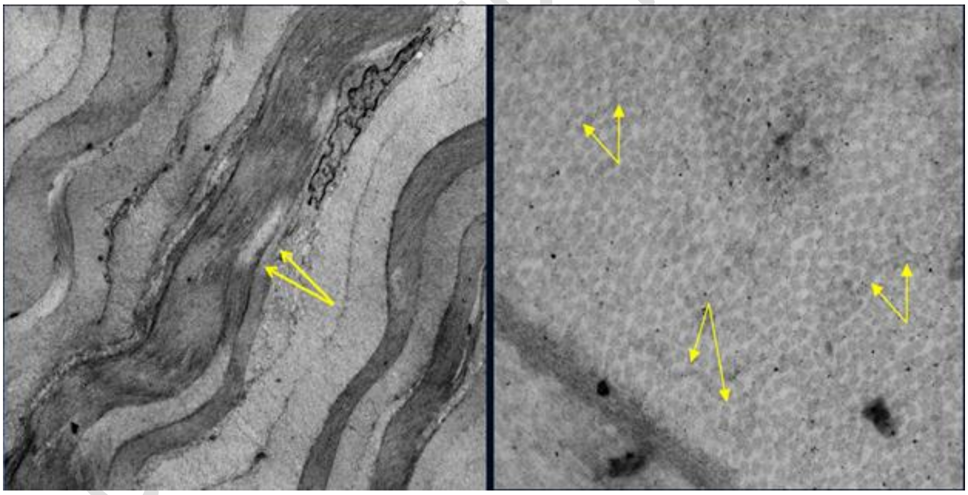

Fig. 4 Additional cross-links in collagen structures of thinned corneal stroma after ablation with riboflavin according to transmission electron microscopy.

and nerves in the layers of the emaciated cornea from ablation-induced secondary radiation. Upon completion of ablation, crosslinking effect carrying a decaying character was initiated in the adjacent layers of the stroma. During photokeratoablation with riboflavin, a thin Bowman-like membrane structure was formed on the ablative surface. This structure was revealed only in those cases when its thickness exceeded 5 µm, which corresponded to the resolution of the device. In addition, according to OCT and densitometric studies, a decaying effect of an increase in optical density in the stromal layers adjacent to the ablation zone was noted. The results of photorefractive ablation with riboflavin are described in more detail in previously published works [26-30].

To enhance the effect of cross-linking and the formation of a Bowman-like membrane structure of greater thickness on the ablative surface, a special technology of additional irradiation was used at energy densities in the pulse below the ablation threshold (Fig. 5).

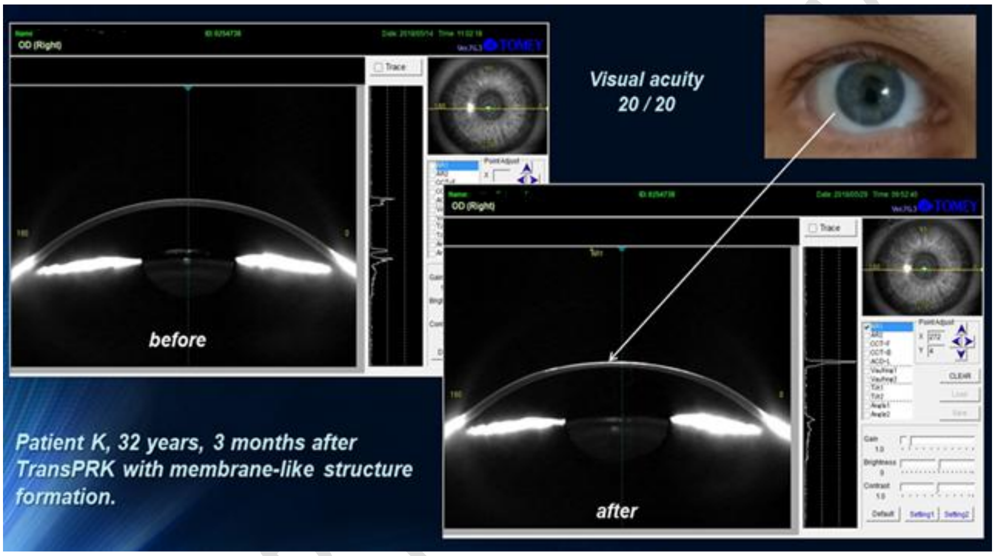

Fig. 5. Densitokeratograms before and after photorefractive ablation with riboflavin and a formed membrane structure under additional irradiation with an energy density in a pulse below the ablation threshold.

Comment [M8]: It seems to be a human eye

The use of subablative radiation energy densities of an argon-fluorine excimer laser predetermined the development of new technologies for therapeutic laser-induced crosslinking in keratoconus, secondary keratoectasias and other corneal pathologies of various etiologies [31-41]. These technologies consisted of ablation of the epithelium, saturation of the stroma with riboflavin and its activation by secondary radiation of an argon-fluorine excimer laser at pulse energy densities below the ablation threshold. With such technologies of corneal crosslinking, all the classic signs of traditional crosslinking were revealed. Corneal OCT and densitometry showed an increase in optical density in the corneal stroma in the first days after laser-induced crosslinking(Fig. 6). After 3-4 weeks, a demarcation line was formed in the stroma, which was subsequently subjected to complete resorption. According to differential keratotopography one month after laser-induced crosslinking there was noted with varying degrees of severity a keratomodelling refractive effect Its value depended on the total radiation dose, shape and size of the affected area. In a number of cases,

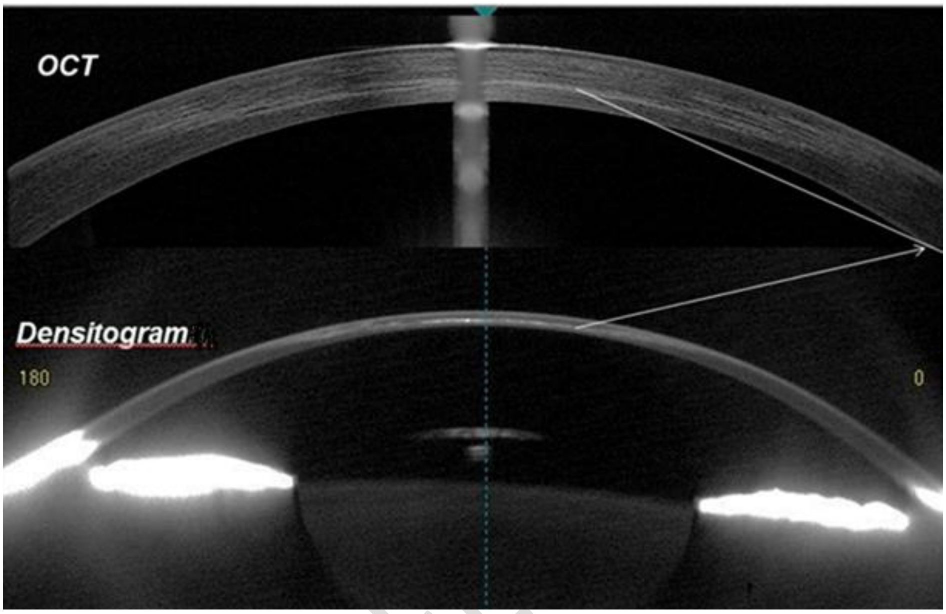

Fig. 6. Corneal OCT and densitogramone month after crosslinking by radiation of an argon-fluorine excimer laser for progressive II stage keratoconus.

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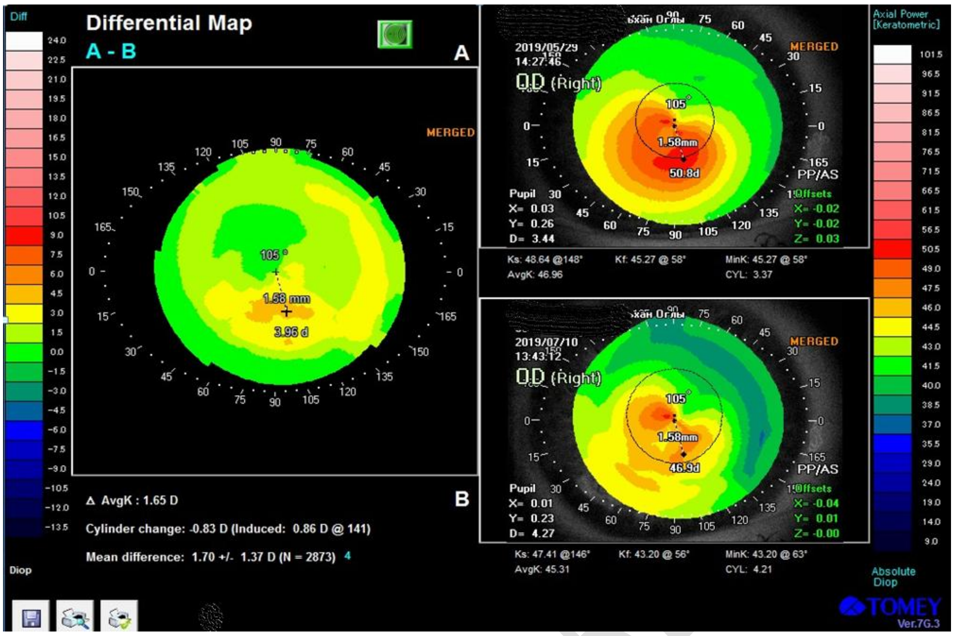

Fig. 7. Refractive keratomodelling effect according to differential keratotopography one month after crosslinking by radiation of an argon-fluorine excimer laser for progressive II stage keratoconus.

Comment [M10]: Please explain how did you do the measurements.

an increase in visual acuity was noted, which could not be explained by the data of objective refractometry and computed keratotopography. This visual effect may have been associated with changes in the refractive index and orientation of collagen structures in the crosslinked areas of the stroma. This indicated new possibilities for refractive modeling of the cornea without stromal ablation. Investigations in this direction are continued by us with an assessment of the refractive effect according to the data of two-wave optical scanning of the cornea [38].

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The data obtained on the possibility of non-ablative refractive modeling of the cornea and the results of previously conducted experimental studies and clinical observations predetermined new approaches to the continuation of scientific research in this direction. These studies should provide various options for refractive modeling based on the effects of polymerization (cross-linking) and depolymerization (swelling) in the corneal stroma under the influence of excimer and femto-laser photons (Fig. 8).

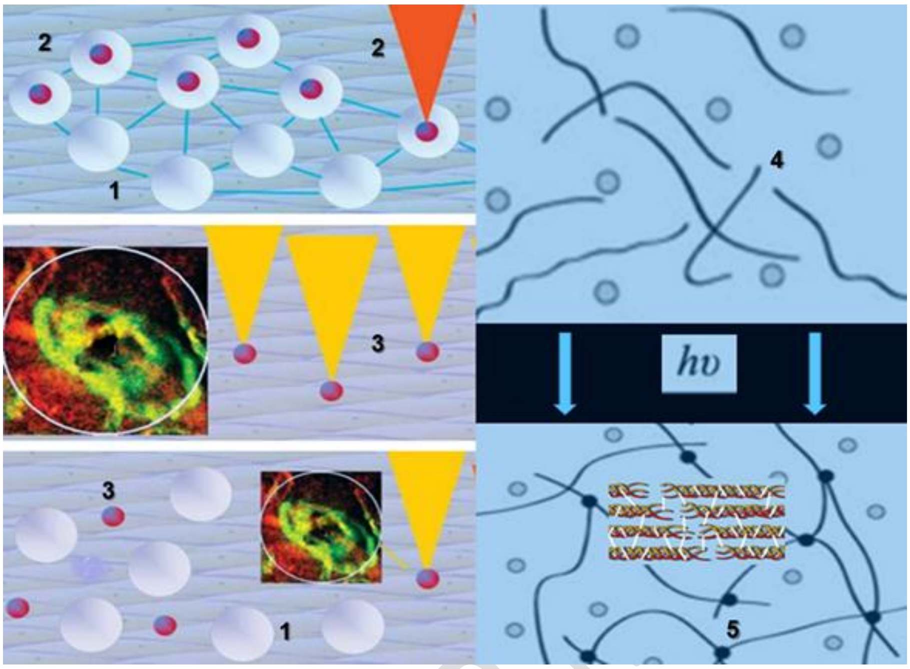

Fig. 8. Schemes of various variants of excimer laser and femtolaser polymerization (crosslinking) and depolymerization (swelling) for refractive modeling of the cornea without ablation and photodestruction of the stroma.
1 - plasma-mediated femtophotodestruction with the formation of a gas bubble; 2 - femtophotochemical effect with the perifocal zone of the gas bubble; 3 - femphotochemical effect without the formation of a gas bubble; 4 - the effect of laser-induced swelling;
5- effect of laser-induced ultraviolet (UV) crosslinking and infrared (IR) radiation below the ablation threshold and the plasma-mediated thresholdphotodestruction.

To perform non-invasive technologies of laser refractive modeling of the cornea, various effects of laser interaction with the corneal stroma can be applied (Fig. 8). The effect of photopolymerization due to the formation of additional crosslinks in the polymer-colloidal complex. The effect of photodepolymerization, called swelling, in which inter- and intramolecular bonds are broken. The effect of microphotodestruction with the formation of micron-sized plasma bubbles. The effect of photochemical interaction without thermal or thermo-mechanical effects on the corneal stroma. With certain radiation parameters, such a photochemical effect can occur without and with the perifocal zone of the gas bubble. Various combined versions of the above effects are also possible for the implementation of laser refractive keratomodeling without coagulation and ablation of the corneal stroma. These options, depending on the energy parameters of laser radiation, can be implemented without and with the use of various photoactivators (riboflavin, Bengal rosea, etc.).

Discussion. The refractive keratomodelling effect after corneal crosslinking has been identified in the studies of many authors [16-24, 31-41]. However, as shown by clinical studies, the very fact of additional UV irradiation of the cornea after photorefractive ablation inevitably increased oxidative stress in the stroma. This influenced the intensity and duration of postoperative aseptic inflammatory and regenerative reactions. These reactions increased the risk of developing fibroplasia and influenced the final refractive effect. Moreover, with the combined use of photorefractive keratoablation with accelerated crosslinking technology, the cornea became unnecessarily rigid. This inevitably disrupted the corneal smoothing of IOP oscillations during accommodative-convergent loads. The latter are known to play an important role in the development and progression of myopia.

Experimental and clinical studies have revealed a number of advantages of laser-induced crosslinking for refractive keratomodeling using ablative and subablative modes of pulsed radiation of an argon-fluorine excimer laser. First of all, this concerned the rejection of additional UV irradiation of the cornea. Moreover, a wide spectrum of induced secondary radiation overlapped all peaks of maximum absorption by riboflavin, which increased the efficiency of the formation of crosslinks in the corneal stroma [39]. Moreover, when scanning with a small spot, oxygenation in the stroma was less disturbed.An indisputable advantage of excimer laser crosslinking is the possibility of a wide range of local effects, including personalized crosslinkingaccording to keratotopography data [38-40]. The latter made it possible to move on to the development of new technologies for ablative refractive modeling of the cornea in ametropia.

Laser refractive modeling of the cornea without coagulation and ablation of the stroma has a theoretical explanation. According to modern concepts, the corneal stroma can be represented as a hydrophilic cross-linked biopolymer, which is capable of forming an insoluble volumetric network. The volumetric structure of this network is the result of cross-linking in collagen, proteoglycans and glycoproteins. Normally, the network remains in equilibrium with free and bound water and at the same time there is a balance of elastic forces of cross-linked biopolymers of the corneal stroma with the osmotic forces of its tissue fluid. The density of cross-links in hydrocolloid structures affects the volume of the corneal stroma. Depending on how these characteristics change in a particular layer and section of the corneal stroma under the influence of laser photons irradiation, an increase or decrease in their volume will be observed with a change in the refractive profile of the anterior surface of the cornea. Depending on the place of exposure, its refractive power in the optical zone will be enhanced or weakened. With this approach, refractive modeling of the cornea with laser radiation of various spectral ranges can be implemented without coagulation, ablation, or photodestruction of the stroma. The continuation of experimental and clinical research in this direction is of undoubted scientific interest and is of great practical importance.

Conclusion. Refractive modeling of the cornea by the radiation of an argon-fluorine excimer laser in ablative and subablative modes after saturation of the stroma with riboflavin opens up new possibilities in laser correction of ametropia.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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