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PRACA POGLĄDOWA
REVIEW

Cross-linking – review of therapy options

Cross-linking – przegląd metod terapeutycznych

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ABSTRACT

INTRODUCTION: In recent years, keratoconus has become an increasingly prevalent eye disease, characterized by progressive thinning of the central or paracentral cornea. The primary treatment is corneal cross-linking (CXL), which offers a wide range of therapeutic techniques. The main aim of this review is to compile and present the most commonly used CXL treatment methods in a manner that will help clinicians create the most appropriate treatment plan based on each patient's unique needs.

REVIEW METHODS: This review is based on 42 articles meticulously selected through open-access sources, utilizing the PubMed and Google Scholar databases. The search encompassed therapeutic approaches to CXL for both adults and children. The literature review covers publications from 2003 to 2024.

STATE OF KNOWLEDGE: CXL is considered a primary therapeutic strategy for the management of keratoconus. Numerous studies suggest that this treatment modality exhibits superior efficacy in patients suffering from this condition.

CONCLUSIONS: This review evaluates various CXL. The transepithelial cross-linking (TE-CXL) approach retains the epithelial layer, which reduces postoperative complications and enables treatment for thinner corneas and advanced keratoconus. Although the aforementioned method is safer, less painful, and promotes faster recovery, its effectiveness may be compromised by inadequate riboflavin penetration. Conversely, epithelium-off (epi-off) CXL, especially the Dresden protocol, remains the gold standard, though it poses risks of complications such as pain. The study emphasizes the need to balance safety and efficacy when choosing CXL methods, while recognizing that all the methods are effective in managing keratoconus progression.

KEYWORDS

keratoconus, cross-linking, transepithelial cross-linking method, contact lens-assisted cross-linking, epithelium-off CXL, pediatric CXL

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STRESZCZENIE

WPROWADZENIE: W ostatnich latach stożek rogówki stał się często diagnozowanym schorzeniem okulistycznym, charakteryzującym się postępującym ścieńczeniem obszaru centralnego lub paracentralnego rogówki. Standardową metodą terapeutyczną jest cross-linking rogówki (CXL), który oferuje różnorodne techniki leczenia dostosowane do zaawansowania choroby. Celem niniejszego przeglądu jest zebranie i omówienie najczęściej stosowanych metod CXL w sposób, który ułatwi lekarzom dobór najbardziej odpowiedniego planu terapeutycznego, uwzględniającego indywidualne potrzeby pacjenta.
METODY PRZEGLĄDU: Niniejszy przegląd opiera się na 42 artykułach starannie wybranych z ogólnodostępnych źródeł, z wykorzystaniem baz danych PubMed i Google Scholar. Wyszukiwanie obejmowało postępowanie terapeutyczne w CXL zarówno u dorosłych, jak i u dzieci. Przegląd literatury obejmuje publikacje z lat 2003–2024.
STAN WIEDZY: CXL jest uważany za podstawową strategię terapeutyczną w leczeniu stożka rogówki. Liczne badania wskazują, że metoda ta jest bardzo skuteczna u pacjentów cierpiących na to schorzenie.
WNIOSKI: Przegląd ocenia różne metody CXL. W metodzie przeznabłonkowego CXL (*transepithelial cross-linking* – TE-CXL) zachowuje się warstwę nabłonka, co zmniejsza ryzyko powikłań pooperacyjnych i umożliwia leczenie cieńszych rogówek oraz zaawansowanego stożka rogówki. Chociaż wspomniana metoda jest bezpieczniejsza, mniej bolesna i sprzyja szybszemu powrotowi do zdrowia, jej skuteczność może być ograniczona przez niewystarczającą penetrację ryboflawiny. Z kolei CXL z usunięciem nabłonka (*epithelium-off* – epi-off), zwłaszcza protokół drezdeński, pozostaje złotym standardem, choć niesie za sobą ryzyko powikłań, takich jak ból. Praca podkreśla potrzebę równoważenia bezpieczeństwa i skuteczności przy wyborze metod CXL, przy jednoczesnym uznaniu, że wszystkie metody są skuteczne w hamowaniu postępu stożka rogówki.

SŁOWA KLUCZOWE

stożek rogówki, cross-linking, przeznabłonkowy cross-linking, cross-linking wspomagany soczewką kontaktową, CXL z usunięciem nabłonka, CXL w pediatrii

INTRODUCTION

Keratoconus is a progressive eye disorder where the cornea becomes thinner and bulges outward, forming a cone-like shape. This change leads to irregular astigmatism, reduced visual sharpness, swelling, and scarring, significantly affecting vision, especially in younger people. The condition often involves both eyes but can progress unevenly between them, typically beginning in adolescence and worsening over the next 15 years [1]. However, it can also start earlier in childhood or later in adulthood. Its prevalence is estimated to be about 1.38 per 1,000 people (95% confidence interval: 1.14–1.62 per 1,000), with a higher incidence among people aged 20 to 30 and those of Middle Eastern and Asian heritage [2].

As keratoconus progresses, patients often experience changes in their vision that necessitate a transition from glasses to rigid gas-permeable contact lenses. The precise cause of the condition remains unknown, although it is believed to be influenced by a combination of genetic factors, though no specific gene has been identified. Structural changes in the corneal stroma, including disruptions in the arrangement of collagen fibers, are frequently observed. Keratoconus is also commonly associated with conditions such as asthma, eczema, Down syndrome, and various connective tissue disorders. Additionally, frequent eye rubbing, often due to chronic allergies, can contribute to alterations in the corneal shape and pressure, leading to a reduction in corneal cells, known as keratocytes. While keratoconus is not classified as an inflammatory disease, recent research suggests that proteolytic enzymes, cytokines, and free radicals – specifically matrix metalloproteinase 9 (MMP-9), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α) – play a role in its development, even in the subclinical stages. This indicates that the condition may have certain inflammatory-like characteristics [1].

Histological studies reveal the key features of keratoconus, such as thinning of the corneal stroma, damage to the anterior limiting membrane, and localized bulging of the cornea. Early detection can be challenging, with corneal topography serving as a primary diagnostic tool, supplemented by measurements of corneal thickness and other advanced assessments to ensure a thorough evaluation. The severity and progression of keratoconus are categorized based on specific clinical signs, morphological characteristics, and standardized indices. The treatment options vary based on the stage of the condition. In the initial stages of keratoconus, glasses and contact lenses can help improve vision. Nevertheless, as the condition worsens, surgical interventions may become necessary. These procedures include penetrating keratoplasty, deep anterior lamellar keratoplasty, and the implantation of intracorneal ring segments [2].

In the last 25 years, corneal cross-linking (CXL) has been recognized as a non-invasive approach to treat keratoconus and has become integral to clinical practice. This method employs riboflavin-based solutions in combination with ultraviolet A (UVA) light. Riboflavin serves as a photosensitizer, facilitating

the creation of covalent bonds among collagen fibers when exposed to UVA radiation. This photochemical reaction enhances the cornea's stiffness, increases collagen fiber thickness, and improves resistance to enzymatic degradation, particularly in the anterior stroma. Since the late 1990s, various peer-reviewed studies have reported encouraging outcomes for CXL in the treatment of progressive keratoconus [1,2]. Findings suggest that CXL can boost corneal stiffness by more than 300%, increase the collagen fiber diameter by 12.2%, and promote the formation of cross-linked bonds within the collagen structure [1]. This procedure has shown success in slowing the progression of keratoconus with minimal risks and side effects.

The primary aim of this review is to examine the current knowledge on keratoconus treatments, focusing on the benefits and limitations of standard and surgical interventions. It also explores the roles of various treatment methods, outlining their advantages and potential challenges.

REVIEW METHODS

This review is grounded in a comprehensive analysis of 42 studies meticulously selected from open-access sources, utilizing the PubMed and Google Scholar databases. The search strategy focused on therapeutic approaches to CXL for both adults and children, ensuring a broad representation of the topic. The literature reviewed encompasses publications from 2003 to 2024, allowing in-depth exploration of advancements and trends in CXL treatments over two decades. Previously published articles were excluded unless they presented historical perspectives or important findings, owing to ongoing changes in treatment approaches.

STATE OF KNOWLEDGE

Transepithelial CXL method

The development of transepithelial cross-linking (TE-CXL) in 2004 was a response to the high incidence of postoperative complications caused by epithelial debridement, such as keratitis and abnormal wound healing. As a result, significant research efforts were made to create TE-CXL [3,4]. The primary difficulty associated with this method is the restricted ability of riboflavin to penetrate the lipophilic cornea and the tight junctions of the epithelium [5]. Fortunately, there are several techniques available to enhance the diffusion of riboflavin into the stroma. To increase its absorption, the preoperative application of drops containing preservatives such as benzalkonium chloride (BAC) and tetracaine can be used to break down tight junctions [6]. Alternatively, an epithelial trauma can be induced on the eye without completely detaching the epithelium [7]. Additionally, altering the physiochemical properties of the epithelium may increase its permeability, which can facilitate the creation of an epithelial flap or pocket [5].

In order to perform the classic TE-CXL procedure, a 0.1% riboflavin, 15% dextran solution is applied for corneal inhibition, which is further enhanced with tris-hydroxymethyl aminomethane and sodium EDTA. The aforementioned solution is applied every 5 minutes for a duration of 30 minutes, by administering 2 drops each time. One drop of 1% pilocarpine is applied 30 minutes before the start of surgery. 20 minutes before UV radiation, 4% lidocaine is administered onto the cornea. A blepharostat is used to increase the penetration of riboflavin. During the procedure, Ricolin TE is administered every 5 minutes and a slit-lamp examination is conducted in order to assess the presence of a proper amount of riboflavin in the corneal stroma. Following this, Vega, a UVA light source, is applied at the rate of 3 mW/cm^2 for a duration of 30 minutes. Upon completion, the eye is treated with ofloxacin antibiotic and an Acuvue bandage for 3 days [4].

Prior to and post-surgery, various tests should be performed, including uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), corneal topography, pachymetry, and in vivo confocal microscopy. Patients are monitored every three months during the first year after the procedure. Complications, such as corneal edema, stromal hyperdensity, hyperemia, and photophobia can be recorded [8].

In the clinical review written by Chan and Snibson [7] several studies were discussed. One of them was the study of Chan et al. [9], which utilized intracorneal ring segments with or without collagen cross-linking to treat keratoconus. The cornea was soaked in a riboflavin solution diluted with carboxymethylcellulose instead of dextran for five minutes, followed by 30 minutes of UVA. The findings revealed improvement in the manifest cylinder of the cross-linked group, the average K, and steepest K keratoconus measurements. Additionally, Baiocchi et al. [10] suggested that increasing the dose of UV energy may be necessary to achieve the same effect when the epithelium remains intact. Subasinghe et al. [11] mentioned that according to Bottós et al. [12], UVA transmittance is not the reason for the decreased stromal concentration by riboflavin. What is more, the presence of an intact epithelium may impede oxygen diffusion into the stroma, which could weaken the CXL effect [13]. Additionally, the duration of application and the concentration of riboflavin have a minimal effect on the diffusion of riboflavin into the stroma [11]. The Fard et al. [14] meta-analysis revealed that at the end of the follow-up period, there was no improvement in

the keratometry readings following TE-CXL. Nevertheless, paradoxically, there was an improvement in the average K and steep K.

In summary, it has been highlighted that TE-CXL is a safe and effective therapy, resulting in a reduction in corneal astigmatism, spherical equivalent (SE), and maximum keratometry (Kmax), as well as improvement in Snellen's visual acuity [15].

Epithelium-off CXL

The standard technique for CXL has emerged as the preferred treatment to impede or decelerate the advancement of corneal ectatic disorders, yielding favorable long-term results. Following the removal of the epithelium, it is recommended that the stromal thickness be a minimum of 400 μm [16]. This precaution is essential to safeguard the corneal endothelium and other intraocular tissues from irreversible adverse effects associated with UV irradiation, as substantiated by both experimental and clinical research [16]. There are two types of epithelium-off (epi-off) techniques: the Dresden protocol and the accelerated or modified protocols.

The Dresden protocol is also known as the conventional protocol for corneal collagen cross-linking (C-CXL). Subsequent prospective and retrospective studies have affirmed the effectiveness of C-CXL in arresting the progression of keratoconus. This technique involves removing the epithelium in the central 8–9 mm zone, followed by immersing the cornea in a 0.1% riboflavin solution for 30 minutes. Subsequently, the cornea is exposed to 370 nm UVA light (3 mW/cm^2 for 30 minutes), achieving a surface dose of 5.4 J/cm^2 [4,17]. There are various methods that can be employed to remove the corneal epithelium (alcohol, an Amoils brush, transepithelial phototherapeutic keratectomy (PTK), a hockey knife) [17]. The elimination of the hydrophobic corneal epithelium enhances riboflavin penetration into the stroma, facilitating effective UVA induced photochemical reactions and subsequent CXL. Studies on corneal biomechanics have demonstrated the stiffening effect of CXL on corneas. C-CXL has been found to enhance corneal curvature, reducing steepening and improving visual acuity [5,17]. Corneal thinning is observed up to 3 months post-surgery, gradually recovering by 1 year. Currently regarded as the standard for CXL, this procedure is commonly conducted in outpatient settings. Generally, CXL proves more effective in the early stages of keratoconus compared to advanced cases [17]. Additionally, innovative approaches like Epi-Flap CXL have also been introduced, showing associations with less postoperative pain and anterior stromal haze when compared to conventional epi-off CXL [17].

Accelerated or modified protocols: accelerated cross--linking (ACXL) protocols capitalize on the principles of the Bunson-Roscoe law [11]. In contrast, the conventional cross-linking (CCXL) protocol, also referred to as the Dresden protocol, employs a lower irradiation intensity of 3 mW/cm^2 and an irradiation time of 30 minutes [18]. Nevertheless, advanced settings with high-energy levels, reaching up to 43 mW/cm^2 [5], and in ex vivo studies even 45 mW/cm^2, have been developed [19]. This results in a reduction in the irradiation time to 2 and 1 minute, respectively, and a shortened soak time for the riboflavin solution [20]. Accelerated protocols present advantages such as a shorter treatment duration, reduced patient discomfort, a decreased risk of postoperative complications, infections, and enhanced cost-effectiveness; the clinical benefits are still under discussion in various studies [5,17]. It is shown that it is not only beneficial for adult patients but also for pediatric patients [17].

Epithelium on vs. off

One of the initial steps in the conventional Dresden protocol is the removal of the central 7 mm of epithelium of the cornea using a blunt knife [18]. This epithelial debridement, however, carries a risk of various short-term and long-term postoperative complications. Aside from transient, reversible side effects, there have been reported cases of complications such as corneal haze and scarring, reduced uncorrected and best spectacle-corrected visual acuity, infectious and non-infectious keratitis, stromal melting, and treatment failure leading to the progression of ectasia [21]. While CXL treatment has been utilized in infectious keratitis, it also leads to a variety of complications itself, including secondary keratitis. Numerous studies have reported these phenomena in patients with non-infectious corneal disorders [22,23]. Other microbiological causes of postoperative infections or ulcers may include *Streptococcus salivarius*, *Streptococcus oralis*, coagulase-negative *Staphylococcus* sp., *Staphylococcus epidermidis*, herpes simplex virus, and severe keratitis caused by *Pseudomonas aeruginosa* [24]. Nonetheless, severe complications after CXL treatment remain rare [25].

Postoperative pain is a common complaint associated with cross-linking procedures as the removal of the epithelium often causes significant discomfort during the procedure and in the days following, leading to a delay in returning to daily activities [19,21]. However, the risk of these aforementioned complications can be reduced by employing techniques that do not require removal of the epithelium, known as the "epithelium on" method.

Research has found that dextran-enriched riboflavin cannot penetrate the intact epithelium, prompting the development of various methods to enhance the penetration of riboflavin into the corneal stroma, such as adjunctives that weaken the epithelial tight junctions. These include a tetra-acetic acid (EDTA) enriched

riboflavin solution, which has not proven to be effective in the long-term, and benzalkonium chloride (BAC) [26].

In a study conducted by Rossi et al. [27], the efficacy of two treatments was evaluated in two groups: one treated with the standard epi-off CXL and the other with a transepithelial approach (epi-on). At the 12-month follow-up, the authors found no significant differences in the age and baseline pachymetric and keratometric parameters between the two groups, while uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) were higher in the epi-off CXL group. Both procedures were found to be efficient and useful in halting the progression of keratoconus, but a limitation of the study might have been the small group size of only 20 patients. Furthermore, the risk of infection and pain in the epi-on CXL group was significantly lower than in the epi-off CXL group.

A study by Badawi [28] demonstrated that the transepithelial approach (epi-on) led to a better and earlier recovery from corneal haze compared to the standard approach (epi-off). The reduced keratocyte damage in the transepithelial approach may explain the less pronounced post-CXL corneal haze. Another contributing factor is the riboflavin absorption behavior, which differs between the two approaches. The hypo-osmolar riboflavin used in transepithelial CXL has a shorter break-up time (90 s) and lower absorption efficiency compared to the isotonic riboflavin used in standard CXL (22 min).

In contrast, a study conducted by Razmjoo et al. [29] did not find significant differences in corneal haze between the two groups, where one group received conventional CXL with a fully removed epithelium and the other group received partial removal of the epithelium. Thus, neither approach was deemed more desirable for the reduction of corneal haziness. Nevertheless, the group treated with the partially removed epithelium showed better improvement in corrected vision, whereas the total epi-off technique resulted in better improvement of Kmax and the Q value.

Ouyang et al. [6] conducted a comparative study involving two groups, each consisting of 30 patients, who underwent ACXL treatment. One group underwent the conventional method with epithelial removal, while the other group underwent transepithelial CXL. At the baseline, both groups were comparable and did not exhibit significant differences in the keratometry values following treatment and during the 6-month follow-up period. However, the group that underwent epithelium removal (epi-off) demonstrated overall better corneal biomechanical strength compared to the transepithelial CXL group. This was indicated by higher values of A1L (the first applanation length), lower values of A1V (the first applanation velocity), and A2L (the second applanation length). Furthermore, differences in corneal endothelial function were observed, revealing that the effects of corneal edema and UV irradiation were more pronounced in the epi-off group. These findings, combined with the lower irradiation intensity in transepithelial CXL, suggest a greater level of safety for endothelial function, particularly for individuals with thin corneas and poor corneal endothelial function [4]. Other authors have also suggested the potential benefits of transepithelial CXL for patients with the aforementioned conditions [30], despite its relatively limited efficacy in halting the progression of keratoconus [31].

A recent meta-analysis conducted by Fard et al. [14] compared the outcomes of CXL and TE-CXL specifically in pediatric patients. The findings of the study suggested that the transepithelial approach was safe, but it exhibited lower efficacy compared to C-CXL. During the 12- to 24-month follow-up period for the transepithelial group, only the uncorrected distance visual acuity demonstrated significant improvement. On the other hand, the values of steep K and average K showed a non-significant trend towards worsening over the course of the follow-up period.

These findings corroborate the conclusions drawn in a previous meta-analysis conducted by Kobashi et al. [32], which discouraged the use of TE-CXL for the purpose of slowing down the progression of keratoconus in pediatric patients due to its insufficient efficacy. The parameters of Kmax (maximum keratometry) and visual acuity did not exhibit significant changes following CXL, regardless of whether the transepithelial or accelerated transepithelial approach was utilized. The observed disparity in the findings could potentially be attributed to variances in the biomechanical properties of the cornea among different age group.

Contact lens-assisted CXL

Chen et al. [33] referred to the study conducted by Jacob et al. [34] who introduced the contact lens--assisted CXL (CACXL) technique. When the intraoperative pachymetry is > 400 microns, UVA irradiance of 3.0 mW/cm^2 is applied for 30 minutes [33]. A solution of riboflavin in dextran T500 is reapplied every 3 minutes during UVA radiation [35] in order to maintain corneal saturation and to attain a uniform pre-corneal and pre-contact lens film [33]. Simultaneously, a disposable, daily contact lens of 0.9 mm in thickness, 14 mm in diameter and an 8.6 mm basal curvature is soaked in 0.1% iso-osmolar riboflavin in dextran for 30 minutes before being applied onto the de-epithelized, riboflavin-saturated cornea [35]. Upon completion of the procedure, a type of protective bandage contact lens is applied. Patients

are advised to use 0.5% moxifloxacin eye drops 4 times a day until the epithelium regenerates, followed by a gradual decrease in the dose of 1% fluorometholone drops over 2 weeks in addition to tear substitutes [35].
Amidst the 14 eyes being treated with CACXL, the doctors observed an increase in the minimum corneal thickness of 108 μm when taking into account the inclusion of the contact lens and riboflavin film [33]. After the follow-up period of 6.1 ± 0.3 months, the mean depth of the stromal demarcation line was measured at 252.9 μm. No endothelial loss or signs of postoperative endothelial damage were observed. Although no significant alterations were observed in the corrected visual acuity or the mean maximum keratometric value postoperatively, a reduction of 1 D in the maximum keratometric value was observed in 4 eyes (28.5%) [33].
The advantage of CACXL lies in its independence from the cornea's swelling characteristics, ensuring that edema does not impact the cornea, preventing issues like Descemet membrane [33] folds and potential endothelial damage. The contact lens soaked in riboflavin hinders oxygen diffusion, which has been proven to be vital in the CXL method and absorbs UVA radiation, resulting in a 40–50% decrease in the surface irradiance level [36].

Pediatric CXL

Keratoconus is a disease that rather manifests in the second decade of life. Nonetheless, there have been cases reported in young children (below the age of 18). The occurrence of the disease in childhood has been associated with unfavorable progression statistics [37,38], often leading to corneal transplant surgery [8]. It is vital to note that while data proves corneal transplantation as successful, CXL has provided an alternative treatment, aiming at delaying or preventing the need for transplant surgery [7]. Protocols other than ACXL are more effective than the accelerated one for corneal flattening, especially in advanced keratoconus cases, while a higher preoperative corneal curvature (Kmax) correlates positively with improved outcomes, emphasizing the heightened effect of CXL in more severe disease states [39]. A recent study by Khalil [40] on ACXL for pediatric keratoconus further confirms the potential of modified protocols in reducing the adverse effects while maintaining efficacy. Accelerated CXL showed significant improvement in visual acuity and the stabilization of keratoconus progression over a three-year period. It was associated with minimal adverse effects, such as transient haze in some cases, and no significant long-term changes in corneal thickness beyond the second postoperative year.
Studies comparing the efficacy and post-operative outcomes of the TE-CXL and epi-off CXL methods have been conducted. According to the study by Magli et al. [8], TE-CXL has demonstrated itself as a safer alternative to the epi-off method. Patients undergoing epi-off CXL exhibited transient corneal edema and experienced glare disability, which was effectively managed by applying topical steroids. Nevertheless, such inconveniences were absent in the TE-CXL patients, likely due to the reduced exposure of the corneal endothelium to UV damage subsequent to epithelium removal. Furthermore, the epi-off method resulted in higher pain levels, particularly in the initial three days post-procedure. It has been suggested that there is an inverse correlation between pain and the patient's age. Additionally, there is an inverse correlation between corneal sensitivity and age, possibly related to the reduced activity of nerves in the sensory periphery with aging, affecting the signal of transmission to the central nervous system. In summary, while the effectiveness of both methods is comparable, the side effects differ.
It is important to note that numerous studies tend to advocate the standard technique as the preferred method. Both the standard approach and ACXL exhibit significant efficacy, leading to notable improvements in patients' visual acuity, while the standard approach seems to provide greater changes in visual and pachymetric outcomes than accelerated transepithelial CXL [41]. They reveal consistent enhancements in eyesight, even though studies employing the accelerated method typically have shorter follow-up periods. The goal in current medical practice is to develop an optimal method that ensures the highest levels of safety and efficacy, yielding the best possible outcomes. As a result, there is no clear consensus on the most suitable technique, particularly for children [42]. Various factors, including the application of riboflavin or excessive UVA energy radiation, may significantly impact the surgical outcome [32,38].
A summary of the cross-linking methods discussed in the review is presented in Table I.

Table I. Summary of cross-linking methods

Transepithelial cross-linking	Method designed to preserve natural shape of cornea by avoiding removal of epithelial layer. This method not only leads to less painful recovery period for patients but also makes it possible to effectively treat thinner corneas and advanced keratoconus.
Epithelium-off cross-linking	Method involving removal of epithelium. There are two main types of epithelium-off techniques in corneal cross-linking: the Dresden protocol and accelerated or modified protocols. These protocols may vary in terms of total procedure time, ultraviolet A light intensity, and duration of riboflavin application.
Contact lens-assisted cross-linking	It is a technique designed for corneas of thickness ranging from 359 to 400 microns subsequent to removal of epithelial layer.
Pediatric cross-linking	Keratoconus and its treatment in minors are not yet fully explored or scientifically explored. Given the multitude of cross-linking methods available, it can be concluded that all these techniques effectively contribute to slowing down progression of keratoconus disease. The main difference among those methods is side effects that may arise following surgery.

CONCLUSIONS

This review explores CXL therapies for keratoconus, a progressive eye condition marked by thinning and a conical distortion of the cornea. It emphasizes the benefits and challenges linked to various treatment methods and techniques.

TE-CXL, introduced in 2004 to reduce complications linked to epithelial removal, focuses on enhancing riboflavin absorption through different techniques, such as using preservatives or inducing minor epithelial trauma. However, the intact epithelium often limits oxygen diffusion, affecting the treatment's efficacy. In contrast, epi-off CXL techniques like the Dresden protocol involve removing the corneal epithelium to improve riboflavin penetration and have shown long--term effectiveness, especially in the early stages of keratoconus.

Alternative methods, such as accelerated protocols and CACXL, offer shorter treatment times and specific benefits for patients with thinner corneas. Studies have also compared the epi-on and epi-off methods, with epi-off showing higher biomechanical strength but also more complications like corneal haze and scarring. TE-CXL, though less effective in some aspects, presents a safer option with reduced postoperative issues, especially in pediatric cases where keratoconus progression is often aggressive.

In conclusion, the epi-on method is highly valued for its reduced incidence of complications associated with epithelial debridement, such as scarring, infections, or delayed healing. Nevertheless, it is acknowledged that the epi-off procedure is more efficacious in achieving the desired outcomes.

Overall, while the standard epi-off approach remains the most effective in halting keratoconus progression, emerging techniques continue to refine safety and efficacy, with ongoing research to determine the optimal treatment for various patient groups, particularly children.

Conflict of interest statement

The authors report no conflicts of interest in this work.

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Ethics

The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.

Authors' contribution

Study design – N. Papachristoforou, A. Ueno
Data collection – N. Papachristoforou, A. Ueno, K. Ledwos
Manuscript preparation – N. Papachristoforou, A. Ueno, K. Ledwos, J. Bartuś
Literature research – N. Papachristoforou, A. Ueno, K. Ledwos, J. Bartuś
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