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Review

Updates on corneal collagen cross-linking: Indications, techniques and clinical outcomes

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Abstract

Purpose: To review the historical background and basic principles of collagen cross-linking, to bring together the data regarding the outcomes and complications of collagen cross-linking and finally to explore the efficacy and safety of new variations of this technique.
Methods: A literature review was performed using PubMed and Scopus. The following keywords were used for literature search: cross linking, crosslinking, cross-linking, keratoconus, keratectasia.
Results: In contrast to traditional treatment modalities for keratoconus (KCN), this new technique addresses the progression of the disease. Several clinical studies have been conducted to assess the efficacy of corneal collagen cross-linking (CXL) in the last decade. The results were promising as collagen cross-linking showed significant improvement in visual acuity and keratometric values. Moreover, initial results show that it is a safe procedure with few reported complications.
Conclusion: CXL is an emerging treatment method in ophthalmology that offers the possibility to effectively treat progressive KCN.

Keywords: Corneal collagen cross-linking; Keratoconus; Safety and efficacy

Introduction

Keratoconus (KCN) is a progressive corneal ectatic disorder characterized by bilateral inferior steepening of the cornea. The alteration in matrix collagen production causes an irregular protrusion of the cornea. The specific cause that initiates this disease in not well understood, but it is long known that collagen fibrils play a major role in determining the shape and biomechanical properties of the cornea. Treatment options for patients with KCN include the use of spectacles and contact lenses. For patients who cannot tolerate contact lens wear or do not achieve good vision with contact lenses, the implantation of an intracorneal ring segment (ICRS) may be considered. This improves visual rehabilitation and facilitates the use of contact lenses.[1] In advanced stages however, with corneal scarring or severe thinning, the above-mentioned methods cannot restore good vision, and corneal transplantation like penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK) may be the only treatment options.[2] Unfortunately, none of the mentioned traditional treatments can alter the natural history of KCN. It was at the late decades of the twentieth century that collagen cross-linking was reported to be of great benefit for stiffening the cornea.[3,4] This new treatment modality offered new hopes to stop the progression of KCN. In this paper we aim to review the most recent publications regarding the application of corneal collagen cross-linking (CXL) in KCN.

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Literature search

The literature review was performed using PubMed and Scopus databases on abstracts of articles from 2003 to 2017. The following keywords were used: cross linking, cross-linking, cross-linking, keratoconus, keratectasia. The electronic references were initially scrutinized based on the titles and abstracts. Full text articles were then screened based on their relevance to the subject. Only English written papers were included in this study.

History

CXL is widely used for several applications such as tissue fixation and prosthetic heart valve stiffening.[5,6] Photosensitized oxidation in biologic systems was first introduced in 1968 by Foote et al.[7] Then Fujimori et al. explained the photo oxidation of collagen and its cross-linking by either ozone or ultra violet (UV) light.[8] In cornea, cross-linking was introduced in 1998 in Germany by Sporl et al., in porcine eyes.[9] Their results showed the efficacy of riboflavin and UV (365 nm), Glutaraldehyde (0.1%, 10 min) and Karnovsky's solution (0.1%, 10 min) on increased stiffness of the cornea.[3] Later, these three agents were studied in vivo in rabbit eyes and riboflavin − UVA was suggested for studies in human.[10] Wollensak et al. conducted pilot study on humans using riboflavin UVA in 2003.[11] In the United States, the FDA approved CXL in 2016 according to the results of three 12-month clinical trials for treating progression of KCN and post-LASIK ectasia.[12,13] However, a 2015 Cochrane review by Sykakis et al. reported the insufficiency of collected data by published papers to clarify the beneficial utilization of CXL in KCN.[14]

Basic principles of corneal collagen cross-linking

Collagen plays a supportive role in various human tissues. Inter molecular cross-links between collagen monomers help to strengthen the structure of collagen. Cross-linking happen as a normal process in human cornea as well as during ageing or as a result of diseases such as diabetes. In human cornea, collagen cross linking process occurs in 3 ways: enzymatic, glycation, and oxidation. The enzymatic cross-linking is part of normal maturation of collagen fibrils.[15] The end of the collagen fibril is not in helical form and contains lysin or hydroxylysine amino acids. Enzyme lysin oxidase would catalyze these residues into aldehyde groups which then reacts with lysine/hydroxylysine residues inside the triple helix structure.[16] The result is binding head to tail through bivalent bond formation which will be converted into trivalent bonds later.[17]

Glycation is a non-enzymatic mechanism with bonding between sugar (advanced glycation end product such as pentosidine) and the amino group of a protein.[15] This was called Maillard or Browning reaction.[18] Pentosidin is an advanced glycation end product which is able to form covalent bonds between arginine and lysine residues.[15] This mechanism occurs significantly in diabetes mellitus and to a lesser extent in aging process. Corneal stiffness in older people and slower progression of KCN in diabetes mellitus type 2 has been attributed to this mechanism.[19–21]

CXL takes advantage of oxidation reactions to form bonds between collagen fibrils in the treatment of KCN.[7] Reactive oxygen species (ROS) is generated by UV light and then mediates the process of converting monomers into cross-linked polymers.[15] Oxygen needs to be present in the tissue to participate in this reaction. Richoz and colleagues[22] found that the biomechanical effect of CXL is oxygen dependent and low oxygen tension might reduce the effect of CXL. Kreuger et al.[23] observed that the oxygen is depleted rapidly during CXL, concluding that oxygen and ROS may play an important role in polymerization process.

The technique of cross-linking for keratoconus treatment

Many protocols have been suggested for collagen cross-linking up to now, but the mainstay of all is the same as demonstrated by Wollensak.[11] In sterile settings, after anesthetizing the eye, the central 8–9 mm of the corneal epithelium will be removed and a 0.1% riboflavin solution, consisting of 10 mg riboflavin-5-phosphate in 10 ml dextran 20%, will be instilled for about 30 min (2 drops every 2 min) to the cornea. Riboflavin acts as a photosensitizer and increases UVA absorption by the cornea. After 30 min of instillation, irradiation with UVA of 370 nm and 5.4 J/cm2 is applied for 30 min. During irradiation, riboflavin instillation (1 drop every 2 min) will be continued in addition to balanced salt solution (every 6 min to moisten the cornea).[11,24] It must be noted that irradiation dose should be individualized for every patient to reassure prevention of any harm. De-epithelialization is performed to provide a facilitated homogenous diffusion of riboflavin inside the cornea.[24] In human studies, the penetrance of riboflavin was limited to the anterior 300 μ even with longer application time and more concentrations.[25]

Other protocols include CXL without de-epithelialization,[26] CXL with riboflavin in a femtosecond laser-created pocket,[27] excimer laser epithelial removal and mechanical full thickness epithelial removal.[28]

Indications for CXL

CXL is meant to stop the progression of KCN. Therefore, the best candidates for this treatment are patients who are suffering from progressive corneal ectasia. Several parameters are proposed to define the progression of corneal ectasia, but in most studies, progression was defined as an increase of 1.00 diopter (D) or more in the steepest keratometry measurement, an increase of 1.00 or more in manifest cylinder, an increase of 0.50 or more in manifest refraction spherical equivalent (MRSE) in one year, reduction of central corneal thickness $\geq$ 5% in three consecutive tomographies in 6 months.[29,30]

History of corneal surgery, known sensitivity against ingredients used during the procedure, corneal pachymetry less

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