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Major review

Corneal cross-linking

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ABSTRACT

Since its inception in the late 1990s, corneal cross-linking has grown from an interesting concept to a primary treatment for corneal ectatic disease worldwide. Using a combination of ultraviolet-A light and a chromophore (vitamin B2, riboflavin), the cornea can be stiffened, usually with a single application, and progressive thinning diseases such as keratoconus arrested. Despite being in clinical use for many years, some of the underlying processes, such as the role of oxygen and the optimal treatment times, are still being worked out. More than a treatment technique, corneal cross-links represent a physiological principle of connective tissue, which may explain the enormous versatility of the method. We highlight the history of corneal cross-linking, the scientific underpinnings of current techniques, evolving clinical treatment parameters, and the use of cross-linking in combination with refractive surgery and for the treatment of infectious keratitis.

1. Introduction

Corneal cross-linking represents a physiologic principle of tissue biomechanical alteration that may affect every facet of corneal disease, from ectatic corneas and cornea-based refractive surgical procedures to corneal transplantation, infectious keratitis management, corneal edema management, resistance to collagenase activity, and beyond. Cross-linking represents a testament to translational science, and this rigorous basic science foundation has allowed the cross-linking principle to permeate our treatment regimens and inspire novel approaches.

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1.1. History

The theory that induction of cross-links in cornea tissue could result in stiffening and strengthening of ectatic cornea tissue sparked the development of cornea cross-linking in the late 1990s.[140] Observational studies demonstrating decreased rates of keratoconus in patients with diabetes revealed that natural cross-linking occurs in these patients from the nonenzymatic glycosylation of proteins, which results in the formation of advanced glycosylation end products.[135] This, combined with Theo Seiler's inspiration to use ultraviolet (UV) light to stimulate cross-linking in the cornea, similar to the manner in which dentists use cross-linking to strengthen gums, led to the advent of this revolutionary treatment (Theo Seiler, personal communication, 2014).

Initial treatment in porcine eyes showed up to 70% increase in cornea rigidity compared to controls[140] that was repeated in other studies using porcine,[143,166] rabbit,[144] and human cadaver eyes.[144,166] In these models, the safety of cross-linking was related to cornea thickness to avoid damage to the cornea endothelium and other ocular structures.[167]

Wollensak and colleagues treated 23 eyes with progressive keratoconus, resulting in halting progression in all eyes and corneal flattening in up to 70%.[165] Further clinical studies showed similar promising results in patients with ectasia after refractive surgery.[48]

2. Fundamental concepts in corneal cross-linking

The basic requirements for corneal cross-linking include a photoinducer, a light source with adequate intensity but safe parameters, and a photochemical reaction that induces free radicals while creating a chemical bond between collagen fibrils.[36]

2.1. Riboflavin

Riboflavin (vitamin B2) is the standard photoinducer in cross-linking, as its alkylisoalloxazine structure allows for absorption over a wide range of the light spectrum, including an absorption peak in UV-A range.[30] All flavins are thermostable, yet photosensitive, which allows for molecular changes in a short amount of time.[62] Riboflavin is safe for systemic absorption, readily available in fortified foods and food coloring, but is water insoluble; therefore, the more soluble riboflavin-5 phosphate is commonly used in cross-linking protocols.

Adequate absorption of riboflavin is required for effective cross-linking; however, corneal epithelial tight junctions limit the penetration of its large molecules (molecular weight 376 g/mol). To allow for sufficient riboflavin concentration in the corneal stroma, epithelial debridement is required in standard protocols.[7] Variations in riboflavin soak time[62] and the role of the riboflavin in tear film[164] have the goal of providing adequate penetration to allow for effective stromal cross-linking treatment.

2.2. UV light

UV light is the second necessary component for cross-linking, with important safety parameters that depend on wavelength,[119] irradiance, and time of irradiation.[51] The absorption peak of riboflavin at 370 nm (E. Spoerl, personal communication, 2014) is ideal for the effectiveness of cross-linking and the protection of other ocular structures.[141] Because of the limited availability of light-emitting diodes at that specific wavelength, the first devices used a wavelength of 365 nm (Fig. 1). Variations to the intensity and duration of UV exposure in preclinical studies led to the development of the original standard Dresden protocol, which was found to provide maximum efficacy of tissue stiffening using 3 mW/cm^2 of energy for 30 minutes, which corresponds to a total energy dose (fluence) of 5.4 J/cm^2.

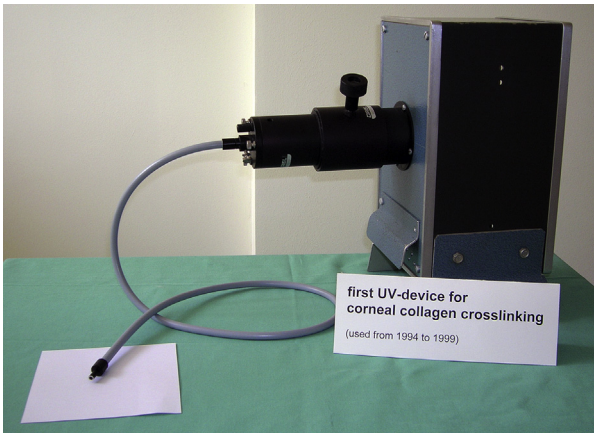

Fig. 1 – The first ultraviolet (UV) light–emitting device used for collagen cross-linking. Image courtesy of Eberhad Spoerl.

In attempts to accelerate the treatment, variations on these parameters promoted use shorter treatment times at higher intensities. The Bunsen-Roscoe law of reciprocity states that a photochemical effect should be similar as long as total fluence remains constant. Laboratory studies showed that the Bunsen-Roscoe law may apply over a limited range in the cornea. At intensities higher than 45 mW/cm^2, the increase in biomechanical stiffness may drop significantly.[54,160] Alteration of the protocol timing, termed accelerated cross-linking, is discussed in more detail in Section 7.3.

2.3. The cross-linking photochemical reaction

The photosensitizer riboflavin absorbs UV-A energy and excites into a triplet state that can undergo 2 types of reactions: aerobic type 2 and, to a limited extent, anaerobic type 1. Both create reactive oxygen species that induce covalent bonds between collagen molecules and also between proteoglycans and collagen.[171] Clinically, the extent of this effect can be seen as a demarcation line, initially observed at the slit lamp[134] and later confirmed with confocal microscopy[104] and anterior segment ocular coherence tomography.[29,88,168] This line typically presents at 300–350 μm depth after cross-linking with the standard protocol and might be produced by changes in the reflectivity of the cross-linked part of the corneal stroma. Although this has not been definitively established, many clinicians believe that the demarcation line indicates the depth or extent of cross-linking treatment.