Advances in Ophthalmology and Optometry 2 (2017) 367–383

ADVANCES IN OPHTHALMOLOGY AND OPTOMETRY

Corneal Collagen Crosslinking

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Keywords

• Corneal collagen crosslinking • Keratoconus • Post-LASIK ectasia
• Accelerated crosslinking • Transepithelial crosslinking • Infectious keratitis

Key points

- Corneal ectasias are a group of diseases that cause progressive steepening, protrusion of the cornea, and loss of best corrected visual acuity.
- Corneal collagen crosslinking using riboflavin and ultraviolet-A irradiation is a procedure proven to strengthen the cornea and retard or halt the pathologic process of corneal ectasia.
- Various techniques have been tested including the standard (epithelium-off) protocol, transepithelial crosslinking, and accelerated crosslinking in an effort to improve efficacy and reduce risks.
- Infectious keratitis not responsive to antimicrobial therapy is another condition in which corneal crosslinking has proven helpful.
- Future areas of investigation may include combining crosslinking with currently accepted refractive procedures, like post laser in situ keratomileusis and photorefractive keratectomy, or using crosslinking as an independent refractive procedure.

INTRODUCTION

Corneal collagen crosslinking (CXL) is the process by which covalent bonds are created between adjacent collagen fibrils within the corneal stroma. Approximately 90% of the cornea consists of stroma, which is composed of approximately 300 lamellae or layers of collagen fibers. Collagen type 1 is primarily present, but types III, V, and VI also can be found [1]. Crosslinking of these fibers can occur naturally via nonenzymatic glycation, which is an age-related process that can be accelerated in hyperglycemic environments like

Disclosure Statement: The author has nothing to disclose.

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http://dx.doi.org/10.1016/j.yaoo.2017.03.021

that of diabetes mellitus [1]. It has been postulated that the age-related strengthening of the cornea is a result of this process [2]. Additional methods of collagen crosslinking include exposure to aldehydes as well as ultraviolet radiation [3]. Before the investigation of corneal applications of this technology, crosslinking was applied in other areas of medicine with regard to prosthetic biomaterials for implantation. These bioprostheses experienced reduced biodegradation after treatment. Extrapolation to corneal tissue was then theorized and applied in animal models for the purpose of treating keratoconus [3].

Keratoconus is a type of noninflammatory ectasia in which the cornea undergoes gradual thinning and protrusion, resulting in a cone shape. The pathophysiology responsible for the weakening, thinning, and protrusion of the cornea is not completely clear. It is possible that focal or diffuse changes in collagen fibrils are responsible for this ectasia. Collagen fibrils are of normal size. However, lower numbers of collagen fibrils have been identified in the conical portion of the keratoconus cornea compared with the peripheral portion [1]. The natural instability of the interlamellar inferior and central cornea may also contribute to the ectatic process [4].

Until the advent of corneal collagen crosslinking, the treatment of keratoconus was limited to overcoming topographic abnormalities by way of rigid gas-permeable, hybrid, or scleral contact lenses, reshaping the cornea using intrastromal corneal ring segments, or removing and replacing diseased tissue through penetrating and lamellar keratoplasties. Corneal crosslinking allows for potential preservation of host tissue as well as improvement in visual acuity and topographic abnormalities [5]. In addition to keratoconus, corneal crosslinking can be used to treat other disease processes, such as post laser in situ keratomileusis (LASIK) ectasia and infectious keratitis not responsive to traditional antimicrobial therapies [6,7]. CXL may even serve as a type of refractive surgery itself. This article serves as a review of the numerous variations in corneal crosslinking technique as well as potential future applications.

SIGNIFICANCE

Preclinical studies

Before human studies, the theory of improved corneal strength by means of crosslinking was tested using porcine corneas. Age-related nonenzymatic crosslinking of collagen had been identified as a naturally occurring process, as well as one accelerated by diabetes [8]. Spoerl and colleagues [3] noted the effects of various forms of tissue crosslinking on the production of biomaterials composed of collagen. This included meniscal allografts, dural substitutes, and porcine heart valves [3]. The methods of crosslinking included exposure to glutaraldehyde, formaldehyde, and irradiation. Crosslinked implants were noted to experience less tissue breakdown and antibody induction [9]. As a result, an in vitro investigation of the effects of crosslinking on porcine corneas using various wavelengths of light and photosensitizing solutions was performed. The combination of a photosensitizing agent, riboflavin, and ultraviolet irradiation at a wavelength of 365 nm resulted in significant stiffening of the