

# An innovative approach to the treatment of keratoconus: Corneal Cross-Linking

Keratoconus is a **non-inflammatory degenerative disease of the cornea** characterized by its progressive thinning and stretching. The incidence is approximately 1 case in every 2000 people and, in general, subjects affected by this pathology are aged between 10 and 25. Very rarely is a single eye affected, while bilaterality is reported in more than 90% of cases. The progression varies from subject to subject: the seriousness of the condition cannot, in fact, be correlated with the age at which it manifests or the acuity of sight on diagnosis. In general the first eye affected will develop the greatest deformation. In some patients, the disease progresses rapidly in a few months and then stabilizes for years, while in others a continual worsening is observed.

At the beginning, an irregular curvature develops, modifying the refractive power of the cornea, producing distorted images, blurred vision at both short and long range and sensitivity to light. Patients also complain of worsening eyesight, above all at distance. The sight continues to deteriorate irreversibly and this entails frequent changes of spectacles. In the initial stage, symptoms may be attributed to **myopia** associated with **astigmatism**.

In these patients, owing to its structural weakness, the cornea tends to stretch progressively and to become thinner towards the apex. An irregular curvature of the cornea thus develops, as it loses its typical shape and assumes the characteristic conical shape.

Biomicroscopic examination of the cornea reveals a considerable decrease in its thickness from the base of the cone towards the apex (up to 80% of the normal thickness). In time the summit of the cone becomes opaque owing to the local metabolic alteration.

Staging of keratoconus takes account of various factors, such as anamnestic data, clinical history, diagnostic examinations (topography, pachymetry, etc.).

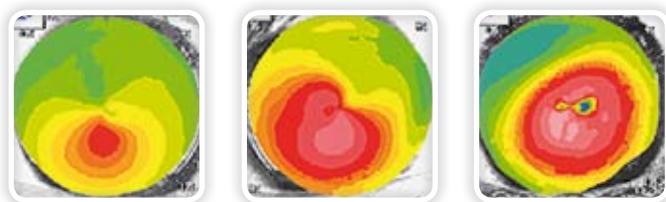
KRUMEICH STAGING				
KC	STAGE 1	STAGE 2	STAGE 3	STAGE 4
Myopia and astigmatism	< 5 D	>5D to <8D	>8 D <10D	Not measurable
K readings	< 48 D	< 53 D	> 53 D	> 55 D
Corneal Opacity	Vogt's striae + - - Absence of scars	Vogt's striae + + - Absence of scars	Vogt's striae + + + Absence of scars	Scars
Pachymetry	Normal	> 400 µm	> 200 µm < 400 µm	< 200µm

If the disease is neglected, the corneal apex ulcerates with consequent perforation. Patients experience **pain, lachrymation** and **blepharospasm**. These changes in the cornea produce an alteration in the arrangement of the corneal proteins, causing micro-scars which distort images further and in some cases can reduce the passage of light.

As mentioned above, to correct the sight it becomes necessary to change spectacles frequently. When the deformation progresses and the astigmatism becomes so irregular that it makes spectacles incapable of ensuring good sight, the use of contact lenses becomes necessary. There is no single type of contact lens which suits all patients affected by keratoconus; instead each individual situation has to be assessed carefully to find the lens that offers the best combination of visual acuity and comfort. In the design and manufacture of contact lenses suitable for the purpose it is very useful to perform Corneal Topography accompanied by simulation software for the application of contact lenses. When the cornea becomes too thin or there is scarring following lacerations of the corneal surface, **keratoplastic** surgery becomes necessary.

## DIAGNOSTIC TECHNIQUES

**Corneal topography** is an irreplaceable technique for the diagnosis and study of the progression of keratoconus. The Placido disc topograph with reflection (currently the most widely-used) projects on to the cornea a series of rings with different diameters and, using special algorithms, returns an image of the corneal surface by attributing a different colour to the different values measured. Each colour, for a given scale (absolute, relative, personalized, etc.), corresponds to a dioptric range. Conventionally, “colder” colours (blue, black) are attributed to the flattest corneal areas, while “warm” colours (red, pink) represent the most curved areas. These coloured (topographic) maps are extremely precise and capable of analysing accurately (with a resolution of a few microns) the shape and regularity of the corneal surface. The topographic picture of a patient affected by keratoconus is characterized by an increase in corneal curvature (warm hues in which generally the reddest part corresponds to the apex of the cone), generally localized in the infero-temporal or, more rarely, in the central sector.



*Topographies of patients affected by keratoconus at different stages*

**Tomography** (or slit-lamp topography) also provides data on the back surface of the cornea (often the zone first altered in keratoconus). It enables a pachymetric map to be prepared with point-to-point measurements of the corneal thickness.

**Pachymetry** is an ecographic instrumental examination which enables measurement of the corneal thickness in several sectors. It is indispensable for staging of keratoconus, assessment of its progression and definition of whether a CL operation is indicated.

**Confocal microscopy** with Confoscan is particularly suited to the in-vivo study of all the cellular and tissue layers of the cornea. It enables assessment of the specific alterations of the cornea which evolve with the advancement of the pathology, revealing the presence of areas of increased reflectivity, anomalous structures near the Bowman's membrane, and the presence of Vogt's striae. These assessments can provide valid clinical support for the correct therapeutic strategy such as, for example, determination of the tolerance of the corneal surface to CLs or the choice of surgical technique among those available (lamellar keratoplastic, perforating, ICR implant, cross-linking).

## THERAPEUTIC INTERVENTION

### ■ Spectacles and CLs

In the early stages of keratoconus (the refractive stage) there is sufficiently regular astigmatism, sometimes associated with slight myopia, and the ametropia can be corrected with spectacles; if the astigmatism becomes more irregular and the ametropia increases, correction with spectacles is no longer possible and it becomes necessary to resort to the use of contact lenses.

### ■ ICRs (Intrastromal Corneal Rings)

ICRs (Intrastromal Corneal Rings) consist of two semi-circular rings of transparent synthetic material which are inserted behind the cornea after dissection to 70% of the depth of the corneal stroma, leaving a gap of at least 1 mm from the limbus. It is a way used to improve visual acuity approved in 2004 by the FDA for the reduction of myopia and irregular astigmatism in keratoconus.

### ■ Cornea transplant

In the advanced stages of keratoconus, in which corneal alterations (thickness, structure of the tissue, etc.) become serious, lamellar or perforating keratoplastic surgery becomes inevitable.

### ■ Corneal Cross-Linking

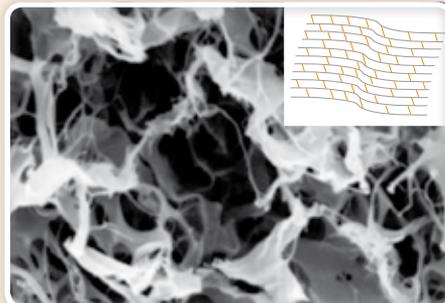
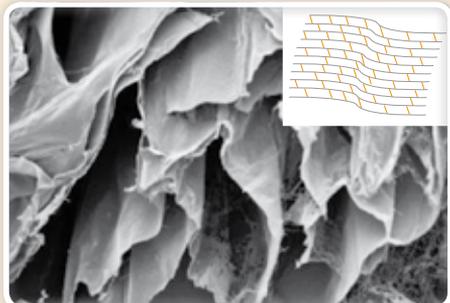
Corneal cross-linking is a treatment, carried out at a Day Hospital, which uses a combination of ultraviolet light of type A emitted by a dedicated instrument (VEGA®) and vitamin B2 (RIBOFLAVIN, RICROLIN®) eye drops. This treatment enables the formation of new links between the corneal collagen fibres (cross-linking), leading to increased biochemical rigidity of the corneal structure. The studies conducted have demonstrated that this technique is capable of reducing astigmatism and arresting the progression of keratoconus, thus avoiding a corneal transplant.



#### Treatment procedure

- Instillation of 2% PILOCARPINE
- Local anaesthesia
- Abrasion of the epithelium (Ø 8-9 mm)
- Introduction of Riboflavin phosphate dropsevery 1-2 minutes in the imbibition stage and during the 30 minutes of irradiation (6 steps of 5 minutes each) with 370 nm UV-A rays emitted by a special device (VEGA®)
- Intraoperative medication and positioning of the therapeutic CL

### Cross-Linking of the collagen fibrils



### Post-surgical therapy

The post-surgical therapy involves the administration of:

- AMINOFTAL tablets, 2 tabs twice a day for 10 days
- OFLOXACIN eye drops, 1-2 drops 4 times a day for 20 days
- FLURBIPROFEN eye drops, 1-2 drops 4 times a day for 20 days
- TRIUM eye drops, 1-2 drops 4 times a day for 3 months

## CONCLUSIONS

- **The treatment of corneal collagen with Riboflavin/UV-A modifies the biochemical and biomechanical characteristics of the cornea.**
- **Above all in the forward part of the cornea (200-250  $\mu\text{m}$ ), treatment with riboflavin phosphate + UV-A radiation causes an increase in the rigidity and compactness of the stromal tissue (due to a 12% increase in the diameter in nm of the collagen fibres).**
- **The sensitive structures of the eye (endothelium, retina, crystalline lens) are not damaged.**
- **The progression of keratoconus is arrested and the sight is stabilized or improved.**

## Bibliography

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Parasurgical therapy for keratoconus by riboflavin–ultraviolet type A rays induced cross-linking of corneal collagen. Preliminary refractive results in an Italian study. Aldo Caporossi, MD, Stefano Baiocchi, MD, Cosimo Mazzotta, MD, Claudio Traversi, MD, Tomaso Caporossi, M J. Cataract Refract Surg 2006; 32: 837-845.