



# Ferrara ring and the nomogram as the main strategy for correcting keratoconus: a systematic review of clinical findings

Malú Inês Perez Moura<sup>1</sup>, Isabelle Dalloul Daher<sup>1</sup>, Rafaella Scalabrini Ferrari<sup>1</sup>, Ana Cristyna Saad Murad<sup>1</sup>, Eneidia Batista Neiva<sup>1</sup>, Pablo Nori de Souza<sup>1</sup>, Raul Pereira Galvão Dourado<sup>1</sup>, Ana Laura Martins Todesco<sup>1</sup>, Fernanda Soubhia Liedtke<sup>1\*</sup>

<sup>1</sup> Unioftal - Ophthalmology And Eye Plastic, São José do Rio Preto, São Paulo, Brazil.

\*Corresponding author: Dr. Fernanda Soubhia Liedtke,  
Unioftal - Ophthalmology And Eye Plastic, São José do  
Rio Preto, São Paulo, Brazil.  
Email: drafernandaliedtke@unioftal.com.br

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## Abstract

**Introduction:** In the setting of corneal ectasias, keratoconus (KC) is a bilateral and asymmetrical disease that results in progressive thinning and tilting of the cornea, leading to irregular astigmatism and decreased visual acuity. The condition affects all ethnicities and both sexes. KC prevalence and incidence rates are close to between 0.2 and 4790 per 100,000 people and 1.5 and 25 cases per 100,000 person-years, respectively. For surgeons who implant Ferrara rings, the manufacturer has developed an online nomogram aimed at optimizing patient outcomes. **Objective:** The present study carried out a systematic review to present the main clinical outcomes of keratoconus treatment using the Ferrara ring. **Methods:** The systematic review rules of the PRISMA Platform were followed. The literature search was carried out from January to February 2023 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Scientific articles from the last 15 years were selected. The quality of the studies was based on the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 60 articles were found, of which only 21 were part of this systematic review, after an eligibility analysis. It was concluded that the insertion of Ferrara rings in keratoconic eyes with previous cross-linking history using the company's nomogram results in significant improvements in visual, refractive, and tomographic results. Corneal densitometry in the anterior layer of the cornea decreases after the implantation of intrastromal corneal ring segments and correlates with corneal keratometry. Over 5 years, Ferrara-type intrastromal corneal ring

segment implantation is a safe, effective, and stable procedure for restoring vision in pediatric patients with keratoconus old.

**Keywords:** Corneal ectasia. Keratoconus. Intrastromal ring. Ferrara rings. Clinical studies.

## Introduction

In the setting of corneal ectasias, keratoconus (KC) is a bilateral and asymmetrical disease that results in progressive thinning and tilting of the cornea, leading to irregular astigmatism and decreased visual acuity. KC develops in the second and third decades of life and progresses into the fourth decade. The condition affects all ethnicities and both sexes. KC prevalence and incidence rates are close to between 0.2 and 4790 per 100,000 people and 1.5 and 25 cases per 100,000 person-years, respectively, with higher rates typically occurring in people aged 20 to 30 [1].

Still in this context, a family history of KC, itchy eyes, eczema, asthma, and allergies are risk factors for its development. Detecting KC in its early stages remains a challenge. Corneal topography is the main diagnostic tool for detecting KC, as well as corneal pachymetry and higher-order aberration data. KC treatment varies depending on the severity and progression of the disease. Mild cases are typically treated with eyeglasses, moderate cases with contact lenses, and severe cases that cannot be treated with scleral contact lenses may require corneal surgery [1].

In this sense, surgical options for KC include corneal transplantation, topography-guided photorefractive keratectomy (PRK), phototherapeutic

transepithelial keratectomy (PTK), phakic intraocular lenses, intrastromal corneal ring segments (ICRS) or a combination of the above [2]. Corneal intrastromal ring segments are made of polymethyl methacrylate (PMMA) and are inserted into the corneal stroma to flatten and smooth the cornea [3,4]. There are several types of corneal intrastromal ring segments. These include Ferrara Rings (AJL Ophthalmics, Miñano, Spain), INTACS (Addition Technology, Inc., Fremont, CA, USA), KeraRings (Mediphacos, Belo Horizonte, Brazil), Corneal Ring (Visiotech, Belo Horizonte, Brazil) and Myorings (Dioptex GmbH, Linz, Austria) [5]. They vary according to their diameter, thickness, arc length, and cross-sectional shape [6].

In this regard, several nomograms have been developed to guide surgeons in choosing the ICRS. These nomograms aim to induce a specific change in the corneal profile based on preoperative parameters [7-10]. Still, others have based their choice of ICRS on the degree of corneal astigmatism [11]. For surgeons who implant Ferrara rings, the manufacturer has developed an online nomogram aimed at optimizing patient outcomes such as power and axis of flat and steep keratometry (K1 and K2), the corneal thickness of the thinnest point of the tracking ring (5 mm in diameter), corneal thickness on the inclined axis in a 5 mm zone, and a description of the shape of the cornea as an oval cone, a nipple cone, or pellucid marginal degeneration. Thus, the nomogram then recommends to the surgeon how many rings and the thickness, arch length, and depth at which the rings should be inserted [12-14].

Therefore, the present study carried out a systematic review to present the main clinical outcomes of keratoconus treatment using the Ferrara ring.

## Methods

### Study Design

The rules of a systematic review of the PRISMA Platform (Transparent reporting of systematic review and meta-analysis-[HTTP://www.prisma-statement.org/](http://www.prisma-statement.org/)) were followed.

### Data Sources And Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "Corneal ectasia. Keratoconus. Intrastromal ring. Ferrara rings. Clinical studies". The search literature was carried out from January to February 2023 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Scientific articles from the last 15 years were selected. In addition, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator were used to target scientific articles of interest.

### Study quality and risk of bias

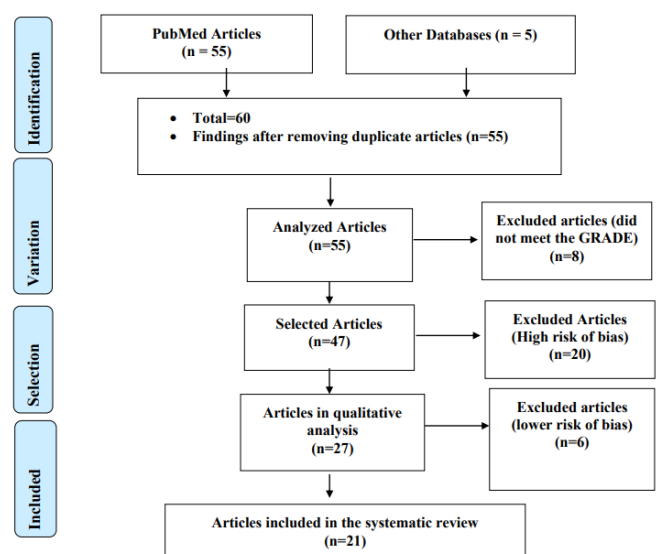
The quality of the studies was based on the GRADE instrument. The highest ratings were for controlled clinical studies with a sample size with statistical significance. The risk of bias was analyzed using the Cochrane instrument, based on the effect size of each study versus the sample size.

## Results and Discussion

### Major Findings

A total of 60 articles were found. Initially, article duplication was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the topic of this article, resulting in 35 articles. A total of 27 articles were included in this study, of which 21 articles were from the main current clinical studies on the use of intraocular lenses (**Figure 1**). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 8 studies that did not meet the GRADE that was removed. Figure 1. Flowchart showing the article selection process

**Figure 1.** Flowchart showing the article selection process.



### Major Clinical Findings - Keratoconus and Ferrara Ring

A clinical study carried out by the author McIntock et al. 2021 reported the visual, refractive, and tomographic results after implantation of corneal intrastromal ring segments (ICRS, Ferrara rings) in eyes with a history of KC and corneal crosslinking using the Ferrara ring nomogram. A total of 21 eyes of 19 patients with a history of KCe and corneal collagen cross-linking had Ferrara intrastromal corneal ring segments implanted. Mean uncorrected visual acuity (UDVA)

improved from 0.88 to 0.52 logMAR ( $p < 0.001$ ). Mean corrected visual acuity (CDVA) improved from 0.47 to 0.36 logMAR ( $p = 0.046$ ). The percentage of eyes achieving 20/40 UDVA and CDVA increased from 5% to 38% and from 38% to 67%, respectively. Of the eyes, 52.3% gained at least two lines of CDVA. The spherical equivalent improved from -7.51D to -3.76D ( $p < 0.001$ ) and the magnitude of refractive astigmatism improved from 5.14D to 2.76D ( $p = 0.004$ ). There were significant improvements in corneal tomography with mean keratometry (KM) improving from 50.40D (3.53) to 48.24D (3.00) ( $p = 0.01$ ) and magnitude of keratometric astigmatism improving from 5.14D (2.91) to 2.76D (1.67) ( $p = 0.004$ ) [15].

Also, a retrospective clinical study prepared by the author Rodrigues et al. 2021 evaluated changes in central corneal densitometry after implantation of the Ferrara ring segment in patients with keratoconus, especially the correlation between corneal densitometry and keratometry. The study sample consisted of 43 eyes of 36 patients. Mean corrected visual acuity improved from 0.82 LogMAR preoperatively ( $SD \pm 0.33$ ) to 0.19 LogMAR ( $SD \pm 0.13$ ) postoperatively. The mean spherical equivalent ranged from -4.63 ( $SD \pm 3.94$ ) preoperatively to -2.16 ( $SD \pm 2.63$ ) postoperatively. Asphericity ranged from -0.69 ( $SD \pm 0.32$ ) preoperatively to -0.27 ( $SD \pm 0.31$ ) postoperatively. The mean maximum K was 54.01D ( $SD \pm 3.38$ ) preoperatively and 51.50D ( $SD \pm 2.90$ ) postoperatively. The mean anterior densitometric value was 18.26 ( $SD \pm 2.03$ ) preoperatively and 17.66 ( $SD \pm 1.84$ ) postoperatively [16].

In previous years, a study evaluated the morphological, optical, and visual properties of the cornea before and after implantation of Ferrara intracorneal ring segments (ICRS) and compared them with normal values. A total of 37 keratoconic eyes were implanted with Ferrara ICRS and compared pre- and postoperatively with 38 nonkeratoconic (normal) eyes. Considering the correlations, the 3 mm central cornea was considered responsible for the low-quality vision in KC ( $p < 0.01$ ). After the implantation of the Ferrara ICRS, all keratometric parameters improved significantly. The optical path difference has also improved. Except for slope and other lower-order Zernike coefficients, higher-order aberrations, PSF and MTF did not change. The flattening effect is greater in the central 3 mm, but paracentral changes are responsible for residual defects [17].

Furthermore, a retrospective clinical study developed by Moscovici et al. 2021 investigated the role of ICRS in stopping the progression of KC in a large sample of patients. The medical records of 123 operated eyes with follow-up ranging from 3 to 16 years (mean

of  $5.3 \pm 3.6$  years) were analyzed. Corrected distance visual acuity, keratometry, and topographic astigmatism improved in most cases, with statistical significance. In 42 eyes (53.8%) there was an increase in K1 or K2 and 36 (46.2%) there was a reduction or maintenance of K1. Considering a difference greater than 1 D, between 3 months postoperatively and the final visit (group 3), 32 eyes (41%) showed an increase and 46 eyes (59%) ended up equal to or below this value. Therefore, ICRS may be effective in delaying disease progression, especially in older patients [18].

Also, a 2-year follow-up study evaluated visual, refractive, topographical, and aberrometry outcomes after ICRS in adolescent patients with keratoconus. A retrospective longitudinal study was carried out with a total of 61 eyes of 47 patients with keratoconus, aged between 13 and 18 years, implanted with ICRS-type Ferrara. Uncorrected distance visual acuity (UDVA) exhibited a statistically significant increase at all time points from 1 month to 2 years after surgery ( $p < 0.001$ ), while corrected distance visual acuity (CDVA) showed a statistically significant improvement in 1 month, 6 months and 2 years ( $p < 0.002$ ), but dropped in significance at 1 year postoperatively ( $p = 0.097$ ). The refractive error analysis did not show statistically significant variation in the sphere ( $p = 0.712$ ) after 2 years. The cylinder showed a statistically significant decrease in diopters at all time points from preoperatively to 2 years postoperatively ( $p < 0.007$ ). The steepest keratometry manifested a statistically significant decrease in slope at all time points after surgery ( $p < 0.001$ ), while the flattest keratometry lost significance at 1 year ( $p = 0.298$ ) and 2 years ( $p = 0.053$ ) after surgery. There was no statistically significant change in spherical aberration at any of the measured times. The vertical coma was only significantly different at 2 years postoperatively. Therefore, ICRS implantation is a safe and effective treatment to improve the visual and morphological parameters of the cornea, as demonstrated in 2 years of follow-up in adolescent patients with KC [19].

Still, the authors Alfonso et al. 2019 analyzed the efficacy, safety, and stability of the Ferrara-type ICRS for visual rehabilitation in pediatric patients with KC with a 5-year follow-up. The study included KC patients aged 18 years and younger who received a Ferrara-type ICRS implant. A total of 118 eyes of 88 patients (mean age 16.1) were studied. Mean uncorrected distance visual acuity changed from  $0.67 \pm 0.37$  preoperatively to  $0.37 \pm 0.30$  6 months after ICRS implantation. Mean corrected distance visual acuity increased from  $0.19 \pm 0.15$  to  $0.10 \pm 0.12$  ( $p < 0.0001$ ). The percentage of eyes with a refractive cylinder  $\leq 2.00$  D increased from 30.5% before surgery to 70.3% 6 months later, and the root

mean square for corneal coma-like aberration showed a statistically significant decrease ( $p < 0.001$ ). At follow-up visits, refractive and visual values remained stable compared to the 6-month visit. Therefore, over 5 years Ferrara-type ICRS implantation is a safe, effective, and stable procedure to restore vision in pediatric patients with KC [20].

Another 5-year follow-up and retrospective cohort study evaluated the efficacy, safety, and long-term stability of Ferrara-type corneal intrastromal ring (ICRS) segments via manual surgery in patients with keratoconus. A total of 124 eyes that had ICRS implantation using the manual technique were included. Mean UDVA and CDVA improved significantly ( $p < 0.0001$ ) from a preoperative value of  $0.91 \pm 0.36$  to  $0.46 \pm 0.32$  logMAR and  $0.40 \pm 0.27$  to  $0.22 \pm 0.20$  logMAR, respectively. Spherical equivalent, refractive cylinder, and all topography values decreased significantly postoperatively ( $p < 0.0001$ ). No regression was observed in any visual or topographic parameter during the entire follow-up. Regarding the subgroup analysis, both younger and older patients demonstrated similar and stable results from preoperative to the 5-year visit, except for the minimal change in pachymetry value over time [21].

Ultimately, the biggest challenge faced by surgeons when implanting corneal ring segments is determining which ICRS will induce the desired change in corneal shape in a given eye. This has led to the development of several nomograms that are intended to assist surgeons in selecting the correct ring segment for a given eye. The Ferrara nomogram is one such tool.

## Conclusion

It was concluded that the insertion of Ferrara rings in keratoconic eyes with previous cross-linking history using the company's nomogram results in significant improvements in visual, refractive, and tomographic results. Corneal densitometry in the anterior layer of the cornea decreases after the implantation of intrastromal corneal ring segments and correlates with corneal keratometry. Over 5 years, Ferrara-type intrastromal corneal ring segment implantation is a safe, effective, and stable procedure for restoring vision in pediatric patients with keratoconus old.

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## Ethics approval

Not applicable.

## Informed consent

Not applicable.

## Data sharing statement

No additional data are available.

## Conflict of interest

The authors declare no conflict of interest.

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