

# Long-term Follow-up of Intacs in Keratoconus

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- **PURPOSE:** To evaluate long-term follow-up of Intacs microthin prescription inserts (Addition Technology, Inc, Fremont, California, USA) for the management of keratoconus.
- **DESIGN:** A long-term (five years) retrospective, follow-up study.
- **METHODS:** Seventeen eyes of 15 patients with keratoconus ages 24 to 52 years (mean age  $\pm$  standard deviation [SD], 34.0  $\pm$  10.5 years) who had completed five years of follow-up (mean follow-up  $\pm$  SD, 67.2  $\pm$  7.5 months; range, 58 to 78 months) were included. Two Intacs segments of 0.45-mm thickness were inserted in the cornea of each eye, aiming at embracing the keratoconus area to try to achieve maximal flattening.
- **RESULTS:** No late postoperative complications occurred in this series of patients. At five years, the spherical equivalent error was statistically significantly reduced (pre-Intacs, mean  $\pm$  SD  $-5.54 \pm 5.02$  diopters [D]; range,  $-12.50$  to  $3.63$  D;  $-3.02 \pm 2.65$  D; range,  $-8.25$  to  $1.88$  D) ( $P = .01$ ). Pre-Intacs uncorrected visual acuity (UCVA) was 20/50 or worse in all eyes (range, counting fingers to 20/50), whereas, at the last follow-up examination, 10 (59%) of 17 eyes had UCVA of 20/50 or better (range, counting fingers to 20/32). Six eyes (35%) maintained the pre-Intacs best spectacle-corrected visual acuity (BSCVA) and one eye lost 3 lines of BSCVA, whereas the rest of the 10 eyes (59%) experienced a gain of one up to 8 lines.
- **CONCLUSIONS:** After five years, intracorneal ring segments implantation improved UCVA, BSCVA, and refraction in the majority of the keratoconus patients. There was no evidence of progressive sight-threatening complications in this study. (Am J Ophthalmol 2007; 143:236–244. © 2007 by Elsevier Inc. All rights reserved.)

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**K**ERATOCONUS IS A BILATERAL, NONINFLAMMATORY disease characterized by progressive corneal steepening. The cornea assumes an irregular conical shape, which leads to a decrease in visual acuity secondary to high irregular astigmatism. In early stages, treatment consists of spectacles or rigid contact lenses. In more advanced stages, in which these treatment options are no longer effective, surgical treatment with penetrating keratoplasty (PK) is required.<sup>1–4</sup>

Intacs (Addition Technology, Fremont, California, USA) were designed to correct low myopia. Several studies have demonstrated the efficacy and the reversibility of Intacs in correcting myopia,<sup>5–7</sup> whereas in keratoconic eyes, Intacs implantation has resulted in an increase in topographic regularity and in uncorrected visual acuity (UCVA).<sup>8–17</sup>

There are only a few articles in the literature with limited follow-up (up to three years) regarding the management of keratoconic patients with Intacs microthin prescription inserts.<sup>14–17</sup> Despite the promising results that previous studies presented, the possibility of chronic stromal remodeling, unstable corneal biomechanics, and late regression still remains, especially in such unstable, by definition, corneas. To investigate further long-term refractive and mechanical stability and late sequelae after Intacs implantation in keratoconic corneas, we conducted the current study in which all eyes had a minimum follow-up of five years.

## METHODS

ETHICAL COMMITTEE APPROVAL WAS OBTAINED FOR THE original trial, and patients were asked to sign an informed consent form (in accordance with Institutional guidelines and to the Declaration of Helsinki) before treatment and for further follow-up examinations. The information for this clinical trial is available to the public through the National Institutes of Health database (<http://www.clinicaltrials.gov>).

- **SUBJECTS:** Twenty-eight patients (36 eyes) had initially participated in a clinical trial for the safety and efficacy of Intacs implantation in keratoconic patients. In

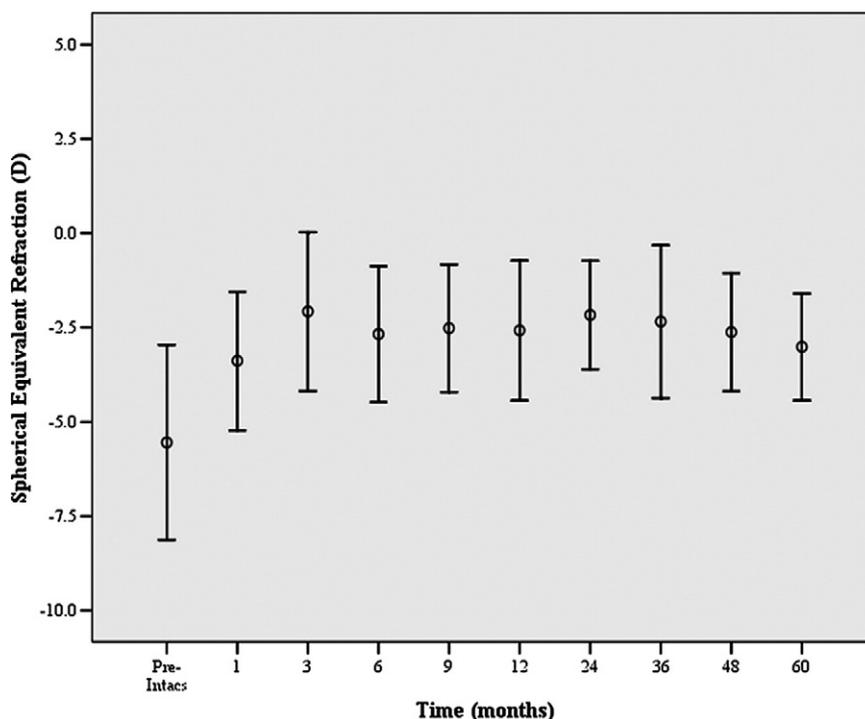


FIGURE 1. Mean change in refraction. Mean spherical equivalent refraction (MSER) in diopters (D) after Intacs implantation.

five patients (seven eyes), Intacs segments were removed three to 12 months after implantation because of patients' dissatisfaction (lack of improvement of the patients' data) without any late postoperative complication (all of them underwent uneventful PK). From the remaining 23 patients (29 eyes), eight patients (12 eyes) were unable to attend follow-up appointments because of work and family commitments and were, therefore, excluded from the present study. The remaining, 15 patients (65%), 17 eyes (59%), and eight males and seven females ages 24 to 52 years (mean  $\pm$  standard deviation [SD],  $34.0 \pm 10.5$  years) completed five years of follow-up (follow-up ranged from 58 to 78 months [mean  $\pm$  SD,  $67.2 \pm 7.5$  months]).

All patients had clear central corneas and contact lens intolerance (rigid gas-permeable contact lenses intolerance, frequent contact lens displacement, unsatisfactory visual acuity with contact lenses). Patients were excluded if any of the following criteria applied after the preoperative examination; history of herpes keratitis, diagnosed autoimmune disease, and systemic connective tissue disease.

A complete ophthalmologic examination was performed preoperatively to exclude other ocular diseases, and the preoperative and postoperative follow-up evaluations included UCVA, best spectacle-corrected visual acuity (BSCVA), manifest refraction, biomicroscopy, and corneal topography.

• **SURGICAL PROCEDURE:** The surgical procedure was done under topical anesthesia. Two Intacs segments of 0.45-mm thickness were inserted to embrace the steepest

keratoconus meridian, according to the topographic image, aiming at maximal flattening.

There were 11 eyes (65%) with topographically inferior ectasia and six eyes (35%) with central corneal ectasia. In the first group, two Intacs segments (0.45 mm) were inserted superoinferiorly (embracing the steep axis), whereas, in eyes with central keratoconus, Intacs (0.45 mm) were inserted in the location used for low myopia procedure (nasotemporally).

The corneal thickness was measured intraoperatively at the incision site and peripherally in the cornea along the ring placement markings with ultrasonic pachymetry (Sonogage, Cleveland, Ohio, USA). Using a diamond knife, set at 70% of the thinnest corneal measurement, a 0.9-mm radial incision was formed, and corneal pockets were created using two Sinsky hooks and a Suarez spreader. Two corneal tunnels were then formed using clockwise and counterclockwise dissectors under suction created by a vacuum-centering guide. The two polymethyl methacrylate segments (0.45-mm thickness) were implanted in the respective corneal tunnels, maintaining a space of approximately 2.0 mm between their ends and 1.5 mm between the opposite edge of each segment and the edge of the incision. The incision site was sutured using a single 10/0 nylon stitch. All procedures were uneventful.

• **POSTOPERATIVE EVALUATION:** Postoperatively, all eyes received antibiotic/steroid combination eye drops four times per day for two weeks. In addition, all patients were instructed to use preservative-free artificial tears frequently.

The sutures were removed two weeks after surgery. Postoperative follow-up occurred at two weeks, one month, three months, six months, nine months, one year, and every 12 months thereafter. At each visit, refraction, slit-lamp, and topographic examination (EyeSys Technologies, Houston, Texas, USA, and TechnoMed C-Scan/TechnoMed GmbH; Technomed, Baesweiler, Germany) were performed.

• **CONFOCAL MICROSCOPY:** Confocal microscopy was performed with a modified confocal scanning laser ophthalmoscope (HRT II; Heidelberg Engineering GmbH, Dossenheim, Germany) in 10 of 17 eyes at the last postoperative follow-up examination. With the addition of the Rostock cornea module, the HRT II was converted into a confocal corneal microscope that allowed the acquisition of two-dimensional images of the various layers of the cornea by sequentially scanning a 670-nm laser beam over the cornea. After the instillation of local anesthetic (one drop of sodium chloride proxymetacaine; Alcaine, ALCON Lab, Hellas AEBE) and eye high viscosity gel (carbomer 3.0 mg/g, Thilogel; ALCON Lab, Athens, Hellas), the patients were asked to fixate using an external fixation target. The instrument objective was then brought into optical contact with the cornea tissue by a disposable sterile polymethyl methacrylate cup and a high viscosity gel (Thilogel). Depth scans across the whole cornea were performed manually while an external electronic unit kept track of the focal plane. Images of the various layers of the cornea were acquired at the optical center of the cornea as well as off-center and adjacent to the implants. The acquired images consisted of  $384 \times 384$  pixels over a  $300 \times 300$  micron field of view with a transversal resolution of about 2 microns and a longitudinal resolution of approximately 4 microns. Qualitative evaluation of the images was performed with special interest at the boundaries of the segments.

• **QUESTIONNAIRE:** A questionnaire was specifically designed to assess overall satisfaction (subjective assessment of their visual outcome including UCVA, BSCVA, night vision, daytime and night driving). In each case, an analog scale (1 to 5) was used, with 1 meaning very dissatisfied and 5 indicating extreme satisfaction.

• **STATISTICAL ANALYSIS:** Group differences for continuous variables were tested using the paired Student *t* tests. The change in manifest refraction spherical equivalent and topographic *k* values and topographic astigmatism were plotted over time to determine long-term stability. The difference as a function of time was analyzed using paired two-tailed *t* tests (at time intervals of preoperative to one month, one to three months, three to six months, six to 12 months, and every year of the follow-up period). Results are presented as means  $\pm$  SD. A *P* value less than .05 was regarded as statistically significant.

## RESULTS

• **REFRACTIVE OUTCOME STABILITY:** At five years, spherical equivalent error was statistically significantly reduced (pre-Intacs, mean  $\pm$  SD:  $-5.54 \pm 5.02$  diopters [D]; range,  $-12.50$  to  $3.63$  D, to  $-3.02 \pm 2.65$  D; range,  $-8.25$  to  $1.88$  D) (*P* = .01). At the sixth postoperative month, refractive stability was obtained and remained stable during the follow-up period with no significant changes between the interval meantime (sixth month post-Intacs: range,  $-2.68 \pm 2.83$  to  $-3.02 \pm 2.65$  at the fifth year post-Intacs, *P* = .52) (Figure 1).

• **UCVA AND BSCVA:** UCVA and BSCVA were measured using Snellen scale charts. Uncorrected visual acuity was improved in 13 eyes (77%) compared with preoperative levels. Pre-Intacs uncorrected visual acuity was 20/50 or worse in all eyes (range, counting fingers to 20/50), whereas at the last follow-up examination, 10 (59%) of 17 eyes had uncorrected visual acuity of 20/50 or better (range counting fingers to 20/32). The mean difference between preoperative and postoperative UCVA was a gain of 2.8 lines (range, unchanged UCVA to gain of 9 lines).

BSCVA was maintained to the pre-Intacs level; its level in six eyes was (35%), whereas 10 eyes were 59%. BSCVA experienced a gain of one up to 8 lines at the last follow-up examination. Only in one eye with advanced keratoconus (mean keratometric astigmatism 8.14 D) was a decrease of 3 lines found. Despite this deterioration in BSCVA, the patient did not want to remove the Intacs segments. The mean difference between preoperative and postoperative BSCVA was a gain of 1.4 lines (range, lost of 3 lines to gain of 8 lines).

• **TOPOGRAPHIC FINDINGS (KERATOMETRIC VALUES):** A significant reduction in keratometric values was found at the post-Intacs follow-up examinations (Figure 2). Mean preoperative keratometry was  $49.59 \pm 5.10$  D (range, 41.66 to 57.77 D) and significantly changed to  $48.02 \pm 4.99$  D (range, 39.04 to 56.93 D) (*P* = .009) at the last follow-up, with a mean reduction of  $1.57 \pm 2.18$  D (range,  $-5.61$  to  $1.47$  D). Similarly, mean preoperative keratometric astigmatism was  $4.46 \pm 2.74$  D (range, 0.20 to 8.14 D) and significantly changed to  $3.48 \pm 2.23$  D (range, 1.13 to 8.72 D) (*P* = .03) at the last follow-up, with a mean reduction of  $0.98 \pm 1.79$  D (range,  $-4.10$  to  $2.44$  D).

Between the sixth month and the fifth postoperative year, mean keratometric values and topographic astigmatism stability were obtained and remained stable during the follow-up period (Figure 3). Mean *k* values at the sixth month were  $45.20 \pm 4.62$  D vs mean *k* values at the fifth year, which were  $48.02 \pm 4.99$  D, *P* = .28. Mean keratometric astigmatism at the sixth month was  $3.77 \pm 2.75$  D vs mean keratometric astigmatism at the fifth year, which was  $3.48 \pm 2.23$  D, *P* = .55 (Figure 3). Furthermore, in patients with low keratometric values (less than 47 D, five eyes), topographic

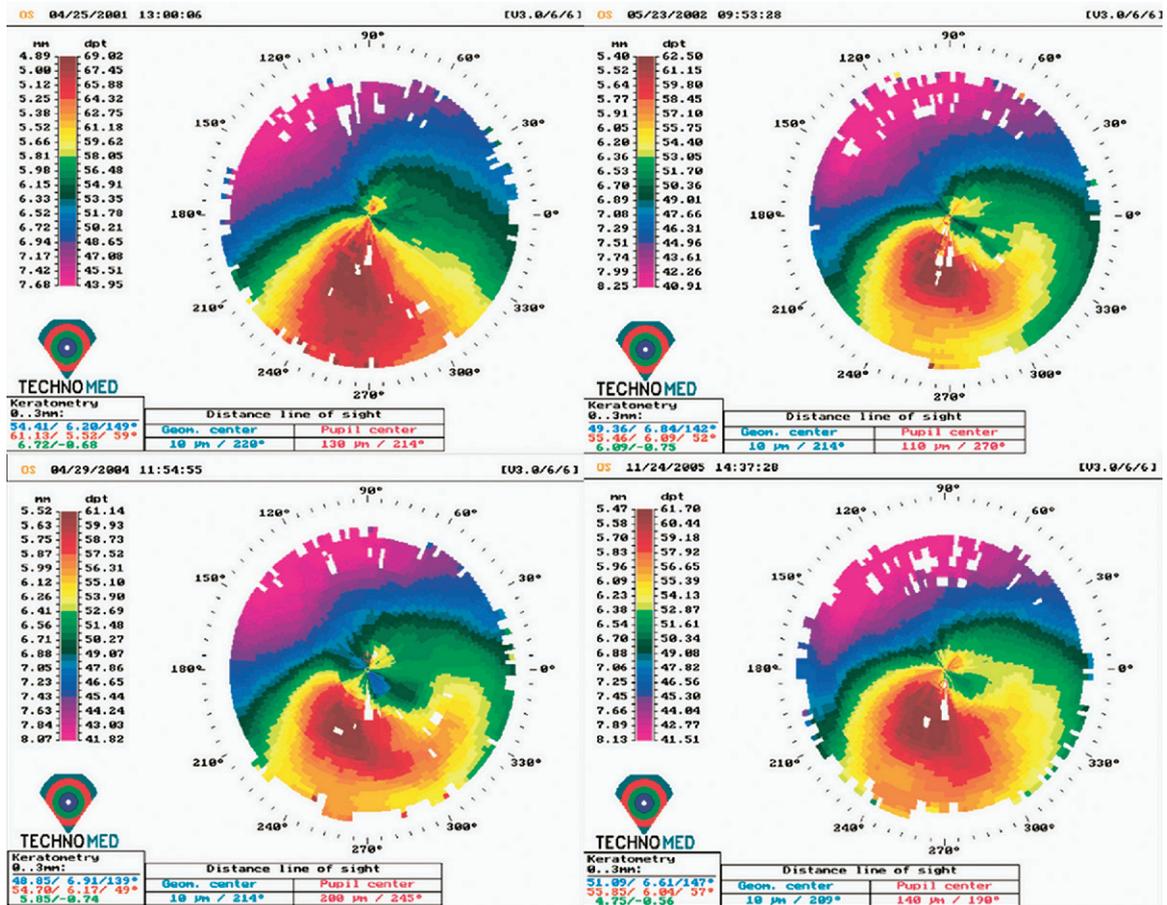


FIGURE 2. Preoperative (Top left), and postoperative topographies at one year (Top right), three years (Bottom left), and five years (Bottom right) after Intacs implantation.

stability was obtained and maintained after the first postoperative month without any statistically significant changes during the interval time (Figure 4, Top and Bottom), whereas similar results were not observed in patients with more advanced stages of keratoconus ( $k$  values more than 47 D, 12 eyes).

In six (35%) of the 17 eyes, rigid gas-permeable contact lens tolerance without displacements and satisfactory visual acuity was found after Intacs implantation.

• **CONFOCAL MICROSCOPY:** Most patients exhibited normal central corneal images in all layers with normal epithelial cells, subepithelial nerve plexus, keratocyte scattering, and endothelial morphology. Nonetheless, needle-shaped keratocytes (Figure 5, Top left) and tortuous subbasal nerves were observed within the stroma in one patient. Moreover, microdeposits, stretched keratocytes, and mild fibrosis were observed at or close to the anterior channel of all patients (Figure 5, Top right). At the plane of the implant, oval-shaped deposits of increased size as compared with the microdeposits at the anterior site of the channel were observed (Figure 5, Bottom left), whereas one patient exhibited increased fibrosis or collagen disrup-

tion a few microns away from the ring segment (Figure 5, Bottom right).

• **QUESTIONNAIRE:** On a scale of 1 to 5 for current overall satisfaction, 14 patients (82%) were considered to be happy with the results (score 5). The rest of the patients (three eyes, 18%), who all had an advanced stage of keratoconus, were considered unhappy (score 2 to 3).

• **ADVERSE EFFECTS AND POSTOPERATIVE COMPLICATIONS:** No intraoperative or late postoperative serious complications occurred in this series of patients. At five years, superficial wound site neovascularization and channel deposits were found in the majority of the eyes (12 of 17 eyes), which remained stable during the follow-up period (Figure 6). These findings were clinically insignificant with no loss of BSCVA.

## DISCUSSION

THE ETIOLOGY AND THE BIOMECHANICAL CHANGES THAT induce keratoconus have not been clearly established, but

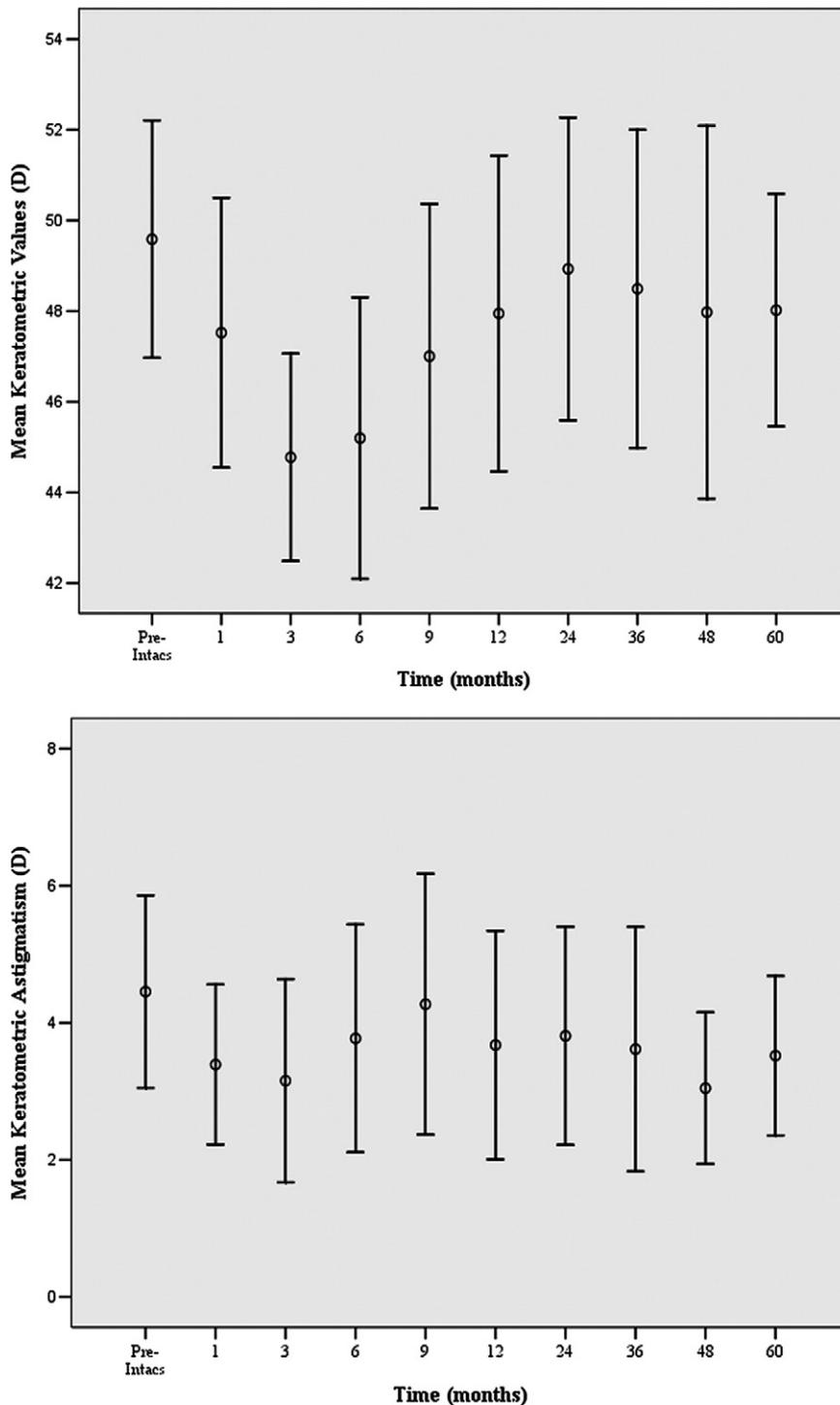


FIGURE 3. Mean keratometric values (Top) and topographic astigmatism (Bottom) after Intacs implantation during the follow-up period. D = diopters.

corneal collagen abnormalities have been reported.<sup>18,19</sup> Patients have a progressive deterioration in UCVA and BSCVA resulting from the irregular astigmatism induced by the corneal irregular shape. The cornea begins to thin, and when the resultant irregular astigmatism cannot be

corrected with gas-permeable contact lenses, PK is necessary for visual rehabilitation.

Several possible alternatives to manage keratoconic corneas are reported in the literature, including scleral fitted gas-permeable contact lenses, deep lamellar kerato-

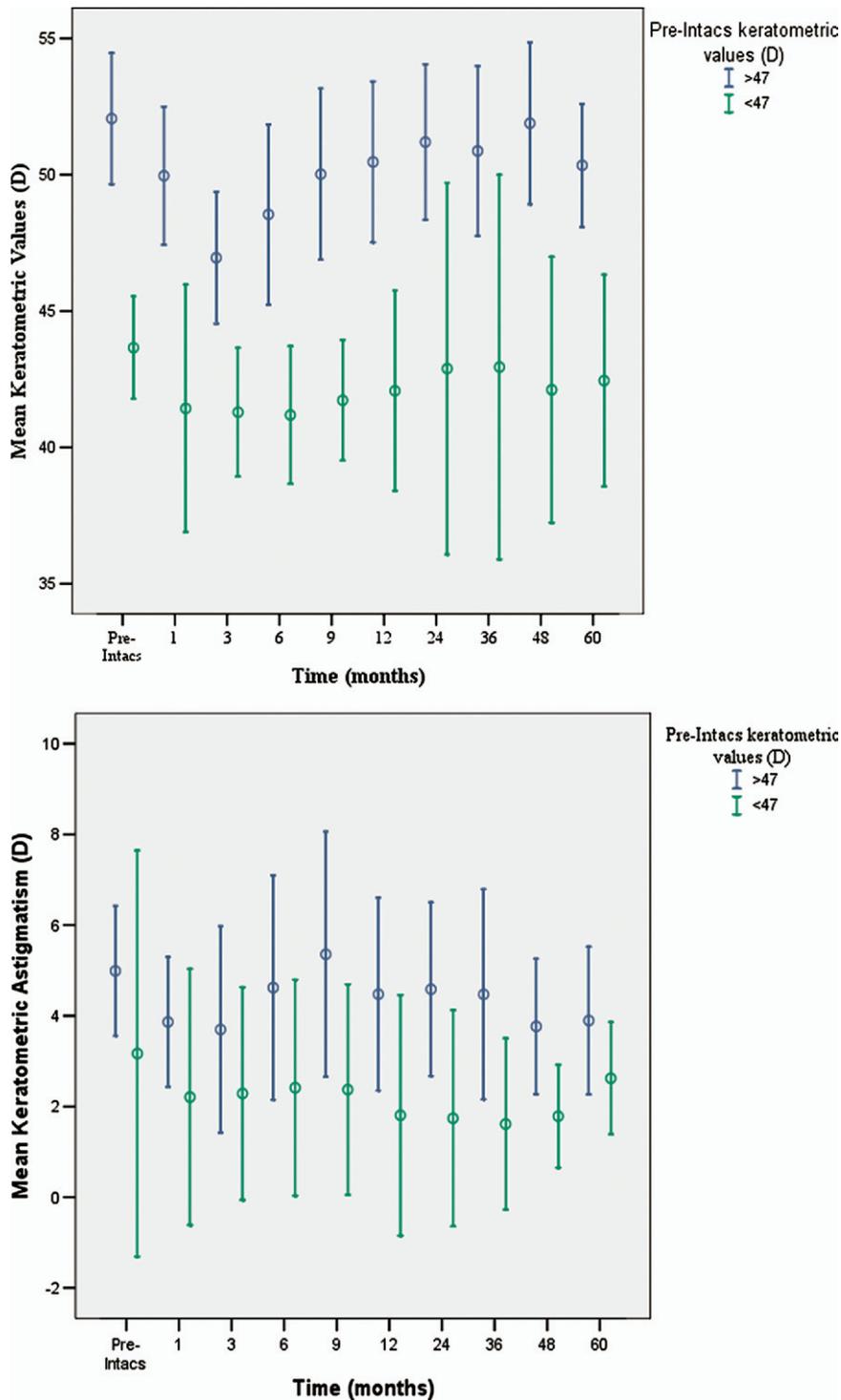
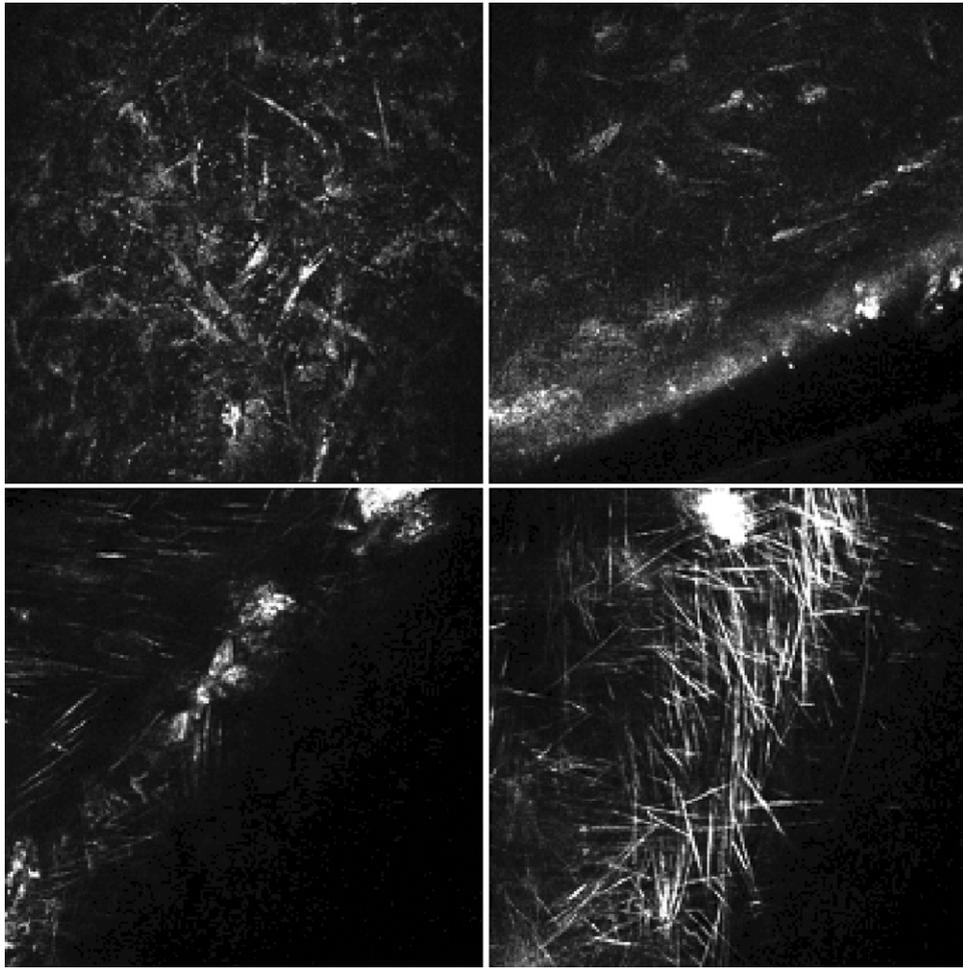


FIGURE 4. Mean keratometric values (Top) and topographic astigmatism (Bottom) changes after Intacs implantation during the follow-up period in patients with low (less than 47 diopters [D]) and high (more than 47 D) preoperative keratometric values.

plasty, and, recently, collagen cross-linking with riboflavin/ultraviolet A.<sup>1-4,20</sup> Intrastromal corneal ring segments (KeraVision, Inc, Fremont, California, USA) were designed to achieve a refractive adjustment by flattening the central corneal curvature while maintaining clarity in the central optical zone; they were first used in patients with low myopia.

Because of the removable and tissue-saving character of this technique, its application expanded to patients with thinning disorders, such as post-laser in situ keratomileusis (LASIK) corneal ectasia<sup>21-24</sup> and keratoconus.<sup>8-17</sup>

In this study, despite the small sample of eyes (17 eyes), it seems that the major changes in refraction and topo-



**FIGURE 5.** Corneal confocal images of keratoconic patients after Intacs implantation. Needle-shaped keratocytes and mild fibrosis (Top left), microdeposits on top of ring segment and morphologically elongated keratocytes (Top right), deposits adjacent to the ring segment and mild structural collagen changes (Bottom left), and significant fibrosis or collagen disruption adjacent to the inner aspect of the ring (Bottom right).

graphic findings took place during the early postoperative period (the first six postoperative months), whereas a trend for stable results was observed after this period. These results are in accordance with the results of Intacs implantation in low myopia patients,<sup>5-7</sup> patients with keratoconus,<sup>8-12,14-17</sup> and patients with post-LASIK ectasia,<sup>21-24</sup> where stability in refraction and visual acuity after the sixth month were observed. There was no incidence of delayed complications (except the superficial wound site neovascularization that remains stable during the follow-up and could potentially increase the risk of graft rejection in future corneal transplantation), and no significant evidence of ectasia—even though there were some time-progressive alterations (statistically insignificant) in keratometric values and keratometric astigmatism. It seems that, despite the improvement in visual acuity and refraction after Intacs implantation, the possibility of chronic corneal stroma remodeling from keratoconus progression is still an issue. Furthermore, in patients with low keratometric values (less than 47 D) and early stage of keratoconus,

mean keratometric and topographic astigmatism values remained stable after the first post-Intacs implantation month with no significant changes during the interval meantime. Similar results were not observed in patients with more advanced stages of keratoconus.

In confocal microscopic analysis, central corneal images exhibited normal epithelial cells, regular subbasal and subepithelial nerve plexus, bright keratocyte nuclei against the darker background of the acellular part in the stroma, and normal endothelial cells, all being characteristics of a normal cornea.<sup>25</sup> However, images of disrupted corneal morphology with respect to keratocyte shape and subbasal nerves' tortuosity appeared in one of the subjects. Even though similar findings were not observed in the rest of the subjects, these images are indicative of a keratoconic cornea and are very site-specific.<sup>26</sup> A more thorough examination of the various sites of the cornea of all patients would might have revealed similar images. With respect to the implants, microdeposits of various sizes were observed, depending on the plane of focus along with

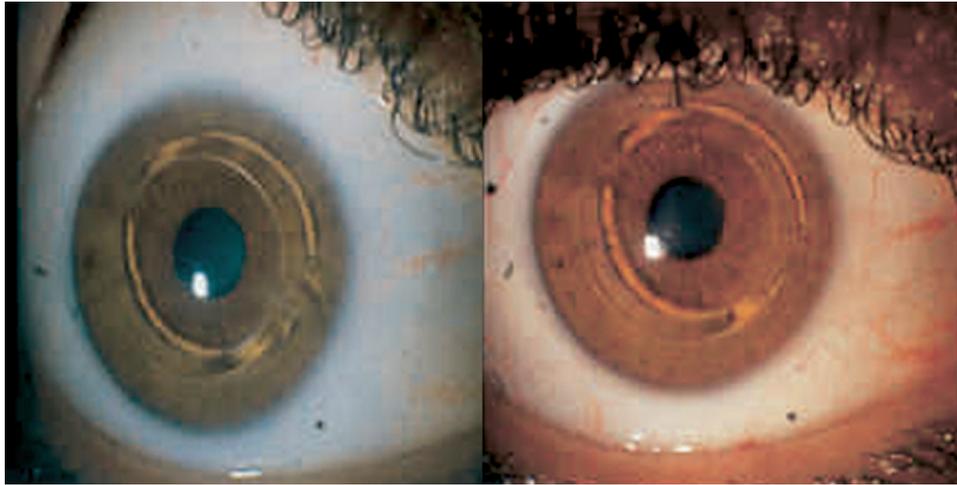


FIGURE 6. Slit-lamp examination of an eye with keratoconus one month and five years after Intacs implantation.

elongated keratocytes adjacent to the implants. Clinical characterization of channel deposits has indicated an increase up to 18 months and a small decrease thereafter up to 24 months, at which time it seems to reach a plateau.<sup>27</sup> Although the exact composition of these deposits has been a controversy, recent histologic evaluation of tissue from adult New Zealand rabbits<sup>28</sup> and a human cornea<sup>29</sup> implanted with intrastromal corneal ring segments support the notion that these deposits primarily consist of intracellular lipid accumulations and new collagen formation. In addition, the elongated appearance of keratocytes might be related to keratocyte with accumulation of cytoplasmic lipid droplets and deformed nuclei that have been described in the case report.<sup>29</sup> Finally, one patient had an increased occurrence of fibrosis or collagen disruption that appeared as needles within the cornea, as it has been described by previous studies.<sup>30</sup>

A few potential limitations are apparent in this study, with the small sample of studied eyes and the absence of control group of patients being the major reservations concerning the conclusiveness of the results. Another major issue is whether Intacs contributes to corneal stability and inhibition of keratoconus progression. It is possible that the stability in refraction and visual acuity after Intacs implantation is due to slow progression of keratoconus during the follow-up period (because progression was not documented pre-Intacs) and not from the Intacs implantation. (Intacs do not affect collagen strength, so these patients probably had stable keratoconus pre-Intacs). Future prospective comparative randomized studies, including more patients, are needed to clarify these crucial limitations of the current study.

In conclusion, despite the small sample of patients, we have shown that refractive stability was maintained for up to five years in keratoconic patients after Intacs implantation. There was no evidence of progressive time-dependent complications in this study. Intacs seem to offer a mini-

mally invasive alternative treatment for patients with keratoconus. Because long-term stability is a critical issue for any surgical intervention in these patients, it will be important to evaluate how Intacs affect corneal ectasia over a more extended follow-up period. Further follow-up and additional cases must be reviewed to draw final conclusions about the efficacy of this surgical technique in keratoconic eyes.

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### **Biosketch**

George Kymionis, MD, PhD, was born in Piraeus, Greece, in 1969. He graduated from the Medical School of the University of Athens, and three years later he finished his first PhD (apoptosis in human carotid atheroma) at the same university. Dr Kymionis worked as a research fellow in Ophthalmology at Vardinoyiannion Eye Institute of Crete for several years in which he finished his second PhD (ocular rigidity in AMD patients). Currently, Dr Kymionis is doing his residence in Ophthalmology in University Hospital of Crete. He participates in several research protocols and publications in medical journals, and he is a reviewer in several ophthalmic journals.