Corneal Collagen Cross Linking

Mazen M. Sinjab
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Sight is possibly man's greatest blessing. This book is dedicated to patients around the world that are suffering with keratoconus while dreaming of a better way and to their physicians that spend their time, energy, and resources trying to make that dream come true.

Foreword

Keratoconus is a corneal ectasia that has historically been a diagnostic and therapeutic challenge. Forme fruste keratoconus and early keratoconus belie the fact that the prevalence of keratoconus may be underestimated. To further confound estimates of prevalence, the advent of advanced diagnostic technologies has led to earlier diagnosis and perhaps increased rates of diagnosis. Three decades ago, prior to the introduction of corneal topography into clinical practice, early diagnosis was virtually impossible.

The age-old adage "I have a diagnosis, now what" is especially pertinent in treating keratoconus. Ophthalmologists are generally faced with try to maintain functional vision for the patient, using the paradigm of spectacles then contact lens and eventually some form of surgery. The "now what" is a constant reminder that this progressive disease requires progressive treatments. Interestingly, two decades ago, rigid gas permeable lenses and penetrating keratoplasty were the main options; currently they are the least desirable.

The advent of corneal cross linking and implantable corneal ring segments have perhaps addressed the "now what" question more definitively for early and moderate keratoconus. With appropriate patient selection and treatment protocols, the progression of keratoconus can be halted and functional vision can be maintained. For stable keratoconus, implantation of phakic intraocular lenses can maintain patient vision.

Corneal cross linking is steadily becoming part of routine care for early and moderate keratoconus. Hence, procedures are now being developed to address the residual refractive error and treatment of more advanced keratoconus. These procedures include combining corneal cross linking with other refractive modalities. However, some combination therapies such as excimer laser ablation and corneal cross linking remain controversial. Additionally, the indications for customized ablation and corneal cross linking remain unclear. The caveat remains that corneal cross linking is a relatively new procedure that still requires extensive research and long-term follow-up. The near future of corneal cross linking is promising, and there are studies aimed at predicting the refractive change after corneal cross linking allowing more appropriate selection of combination treatments. Combined with

current diagnostic technology, the question may be "…now when" is the treatment being delivered and will it be a combined or staggered treatment.

This timely book on corneal cross linking addresses many of these questions. Current diagnostic criteria for keratoconus and corneal ectasia are presented by some of the world's foremost authorities. Expert surgeons present their therapeutic regimens and decision-making criteria for corneal cross linking and the appropriate use of combination therapies. Controversies are addressed including pediatric treatments. The editors of this book have ensured that it will serve as a reference text on corneal cross linking for many years.

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Preface

Corneal cross linking (CXL) is a revolution in the field of keratoconus (KC) management and ectatic corneal disease. Before 1998, when the first patient was treated with CXL, many patients had been left to face their inevitable fate of disease progression and keratoplastic surgery. Professor Theo Seiler and his team brought this treatment to light after their preliminary investigations and conducted the first clinical study, which extended from 1999 to 2003, in the University of Dresden in Germany. After that, in December 2005, the CXL device and Riboflavin solution were introduced to the commercial market, and the 1st International Corneal Cross Linking Congress took place in Zurich in Switzerland.

Although the Dresden protocol of CXL treatment proved to be the most efficient over time, many protocols were and are still being developed in clinical trials to reduce the time of treatment and to make it more comfortable for the patient with fewer side effects. Moreover, more applications of CXL have arisen since then, such as an augmented treatment of infectious keratitis, corneal detergence for bullous keratopathy, scleral CXL, CXL of lens capsule and amniotic membrane, and others. Nevertheless, CXL entered the field of KC in the pediatric population, and it is being introduced as a refractive procedure in the adult population. One can be sure that this is not the end but rather the beginning, and the future looks promising.

In this book, we put this science within the hands of readers. There are other books in the market, but what are different here are both clinical and scientific experience and the academic approach. Over twenty, high-caliber, international experts have contributed to this work, which extended over almost three years to be produced as an evidence-based, up-to-date, classified, and well-illustrated material. A systematic methodology was followed in order to present the material in a seamless, harmonic, and easy-to-reach method.

Chapter one discusses diagnostic tools in corneal ectatic diseases, to be an introduction to chapter two, which presents all the patterns found in – and the classifications of – these diseases. Chapter three focuses on the infrastructure of CXL, starting with the history of CXL, the CXL procedure itself, and highlighting the role of scientists in creating an optimum treatment. Chapter four is the core of the book. It starts with the parameters that affect decision making in KC management in general

and CXL in particular. Thereafter, it presents all modalities of CXL as well as the combination between CXL and other modalities of KC management, going through Epi-On, Epi-Off, accelerated and customized techniques, and the combination with laser refractive surgery, thermal procedures, lens procedures, and orthokeratology. After this in-depth evidence-based presentation of variations, chapter five comes to put these into clinical practice, studying nine cases as clinical examples to build up a decision-making approach. Chapter six presents detailed results of CXL, specifically highlighting intraoperative results, results in iatrogenic ectasia, results of iontophoresis, and the role of age in the outcomes of CXL. CXL is not risk free, thus chapter seven is devoted to discuss the complications of CXL. Since KC is being diagnosed more frequently in the pediatric population due to advanced technology, CXL is becoming more common in this population. The cornea in this population cannot be dealt with in the same way as in the adult population, therefore a separate chapter, chapter 8, is devoted to address this topic in detail. As in every field of science, man is still on the edge of the ocean, on the beach as it were, looking forward to the future. Chapter 9 opens the door for the future. Based on the present, and taking advantage of the past, chapter nine extends the scope of CXL to new applications, techniques, and devices.

There are sure to be some errors in this book and as the ophthalmology editors, we take full responsibility for these and look forward to being further educated by your feedback and comments.

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Chapter 1
Diagnostic Tools for Ectatic Corneal Diseases

Gustavo Guerra, Fernando Faria Correia, Daniel G. Dawson, Lia Florim Patrão, Ivan Dias Ferreira, and Renato Ambrósio Junior

Abstract Refractive surgery allowed great advances in understanding the pathophysiology, diagnosis, and treatment of corneal ectatic diseases. Identification of mild cases with normal spectacle-corrected distance visual acuity (CDVA) and minimal or no biomicroscopic signs represent a challenge faced by refractive surgeons in daily practice. In fact, the different situations that highlight this importance range from screening the candidates for laser vision correction (LVC) for ectasia risk to the impact of refractive surgery technologies on treatment. This is also fundamental to detect cases that will benefit from therapeutic surgery such as collagen cross linking (CXL). Diagnostic techniques should also be effective for staging, prognosis, and follow up of ectatic corneal diseases, as well as to enhance the efficiency of refractive LVC. Corneal ectasia is a condition of the cornea characterized by chronic biomechanical failure that leads to thinning and tissue protrusion without an acute inflammatory sign. Keratoconus (KC) is the most common disease of this group of corneal disorders. This chapter overviews the clinical diagnosis and characterization, including ancillary and advanced tests that have a role on the diagnosis and management of corneal ectatic diseases, especially KC.

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Introduction

Corneal ectatic diseases have been widely studied for over 150 years [1, 2]. However, the advent of refractive surgery enabled great advances in understanding the pathophysiology, diagnosis, and treatment of such diseases. The different associations that highlight this importance range from the need of early diagnosis in the screening process of selecting candidates for LVC to the impact of new technologies related to refractive surgery in the treatment of these diseases [3, 4]. Corneal ectatic diseases are generally diagnosed or suspected during general ophthalmological examination, but supplemental testing plays a major role in the diagnosis, staging, and follow-up of these conditions [1].

Corneal Ectatic Diseases

Corneal ectasia is characterized by chronic biomechanical failure that leads to thinning and protrusion without an acute inflammatory reaction [5]. The changes are progressive and cause astigmatism and irregularities (high order aberrations), which may or may not be associated with myopia. Accordingly to the thinning pattern, corneal ectatic diseases can be classified into three primary disease types: keratoconus (KC), pellucid marginal degeneration (PMD), or keratoglobus (KG) [2]. Secondary types of corneal ectatic diseases are also found, usually from previous corneal trauma or corneal surgery.

Keratoconus is a Greek word (kerato: Cornea; konos: Cone) meaning cone-shaped protrusion of the cornea. It is the most common ectatic disorder, and its incidence is classically described as one patient for every 2000 inhabitants [1, 2, 6]. However, some studies indicate a higher incidence of the disease. For example, such a condition is identified in about 1–5 % of candidates that come in for refractive surgery screening examinations, which is certainly related to a process of self-selection, as each patient with KC is more likely to seek help because of their visual impairments [3, 7]. The disease tends to progress during the adolescence and, sometimes, even into the mid-20s and 30s, although progression can occur at any time. It typically is a bilateral disease, but can be quite asymmetric. KC may be associated to systemic diseases, such as Down syndrome, retinitis pigmentosa, Leber congenital amaurosis, mitral valve prolapse, Ehlers-Danlos syndrome, and Marfan syndrome. One of the most important associations is related to ocular allergic disorders like atopic dermatitis and vernal keratoconjunctivitis [1, 2, 6].

PMD and KG ARE less common corneal ectatic diseases. The PMD has a thinning "band" in the inferior peripheral cornea near the limbus, which induces flattening of the vertical meridian and against-the-rule astigmatism [1, 2]. The term "pellucid" means transparent, referring to an avascular condition free of acute inflammation or lipid deposits, which differentiates PMD from other diseases, such as Terrien's marginal degeneration and Mooren's ulcer [1, 2, 8]. Both of the latter two conditions are not ectatic diseases. KG is defined by diffuse thinning of the cornea and severe diffuse protrusion, with a significant increase of the anterior chamber depth [1]. Therefore, the differentiation between KC, PMD, and KG is possible only through the pattern of thinning topographically on the cornea [2, 9].

Ectasia progression with thinning and tissue protrusion may also occur after trauma or surgical procedures. Such situations can lead to chronic biomechanical failure of corneal stroma and consequent ectasia. It is vital to recognize that ectasia can occur after refractive corneal surgery performed through different techniques, such as radial keratotomy (RK), laser assisted in situ keratomilleusis (LASIK), or photorefractive keratectomy (PRK) [10–12].

In this chapter, we are going to focus especially on KC, since it is the most common disorder of this group of corneal diseases.

Clinical Findings and Biomicroscopy in Keratoconus

Clinical evaluation of corneal ectasia patients should include a complete ophthalmologic workup with supplemental testing being ordered when helpful. Clinical history is an important step in order to identify and clarify the visual symptoms, which may vary according to the stage of the disease. KC patient's most common symptoms or complaints are progressive visual blur and distortion, which is typically secondary to myopia and high astigmatism [1, 2, 6]. One important clinical sign that we have to take into account is the refractive instability in these patients in which they complain of frequent changes of the prescribed refractive error. Photophobia, glare, and monocular diplopia can be other presenting symptoms [1, 2, 6]. Searching for symptoms related to ocular allergy, such as itchy discomfort and irritation, is essential. Eye rubbing has a great impact on the corneal "biomechanical stress" applied to the cornea and is strongly associated with the development and progression of KC [13].

Regarding family history, it is important to identify close relatives with the disease. Even though that etiology is multifactorial, a genetic inheritance has been demonstrated along with environmental influences in twin studies [14]. In addition, different studies have shown variability in the association of KC to the degree of positivity of family history [15, 16].

Visual acuity assessment is an important step to evaluate, document, and follow the impact of this disorder. In initial stages, the condition typically allows for good uncorrected visual acuity (UDVA), but there might be mild symptoms related to visual quality [6, 17]. In moderate cases, variable degrees of visual impairment are usually present and the use of glasses and/or contact lenses is a solution for achieving adequate

best corrected distance visual acuity (CDVA) [6, 18]. Visual acuity evaluation should be considered for selecting the best therapeutic approach for the patients with contact lens intolerance. Interestingly, visual acuity measurements with the pinhole or the potential acuity meter should be considered in order to establish a visual prognosis. We found that wavefront analysis is also relevant in order to facilitate the refraction in KC patients as it improves the CDVA in cases with contact lens intolerance. The wavefront data can also be used as the basis for subjective refraction, providing data to customize soft contact lenses with correction for higher-order aberrations [19].

Depending on the stage of the disease, different clinical signs may be present during ophthalmological examination. A scissoring reflex during retinoscopy is a very early sign [6]. Slit lamp examination may reveal an area of central or paracentral thinning of the stroma, most commonly inferior or inferotemporal, and sometimes this area is also shown as a cone of protrusion due to the steepening of the cornea (Fig. 1.1) [6]. A common slit-lamp finding is the increased visibility of corneal nerves (Fig. 1.2). In 1919, Vogt postulated that this finding results from the stress on the corneal nerve resulting from protrusion and thinning of the ectatic cornea. Another biomicroscopic finding is Rizzutti sign (Fig. 1.3), which is a conical reflection on the nasal cornea when a penlight is shone from the temporal side. Iron deposits are often present within the epithelium around the base of the cone [6]. This represents Fleischer ring (Fig. 1.4), which is brown in color and is best seen with the cobalt blue filter using a broad and oblique beam [6]. Vogt striae (Fig. 1.5) are vertical lamellar folds observed in the posterior stroma and can be seen as fine and roughly parallel striations or stress lines, although in some cases they may be oriented according to the protrusion axis. The striae disappear when gentle digital pressure is applied to the ocular globe [6]. In cases with severe disease, it is possible to notice Munson sign. This finding consists in a protrusion of the lower lid upon downgaze [6]. Another sign that appears during slit-lamp evaluation is the haziness of the second Purkinje image at the posterior surface of the cornea when the illumination is performed in an oblique and lateral way. We think that this signal is due to the presence of stromal lamellae irregularities with subsequent changes in corneal optics.

Hydrops and scarring may also occur. Corneal hydrops occurs due a rupture in Descemet's membrane, resulting in the sudden development of corneal edema. The break in the posterior cornea usually heals in 6–12 weeks, leading to stromal scarring, which may be beneficial in some cases. The final CDVA following the resolution of hydrops depends largely on the extent and location of the resulting corneal scar [6].

The following sections describe different corneal imaging approaches for KC assessment.

Corneal Topography

"Topography" derives from Greek words "to place" (topo) and "to write" (graphein), which means to describe a place. The term "corneal topography" has been classically used for the reconstruction of the front (anterior) corneal surface [20]. In the mid-1980s, Stephen D. Klyce, Ph.D., is recognized for first having

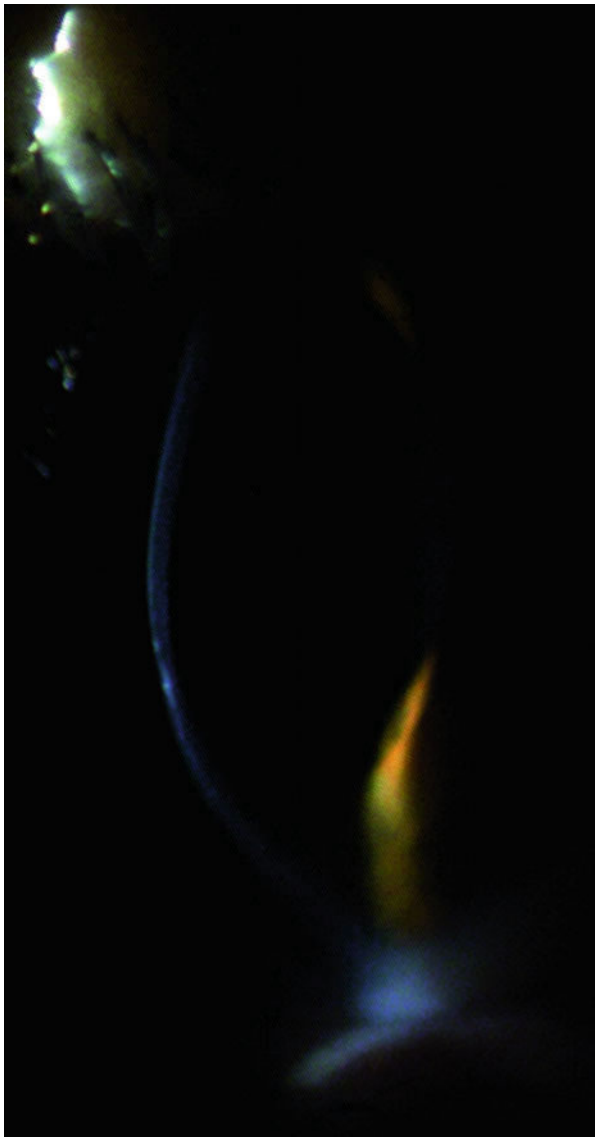

Fig. 1.1 Paracentral thinning of the cornea

developed algorithms for surface reconstruction of the acquired reflection image from Placido-based videokeratoscopy, allowing color-coded maps and quantitative data of the front surface of the cornea [21]. Corneal topography represented a true revolution in the diagnosis and management of corneal disease [20]. It has been found to be sensitive for detecting subclinical changes of KC prior to loss of CDVA and the development of typical slit lamp biomicroscopy findings [17]. The need for detecting these cases early in the disease process represents an unquestionable argument for topography to be considered as an essential test

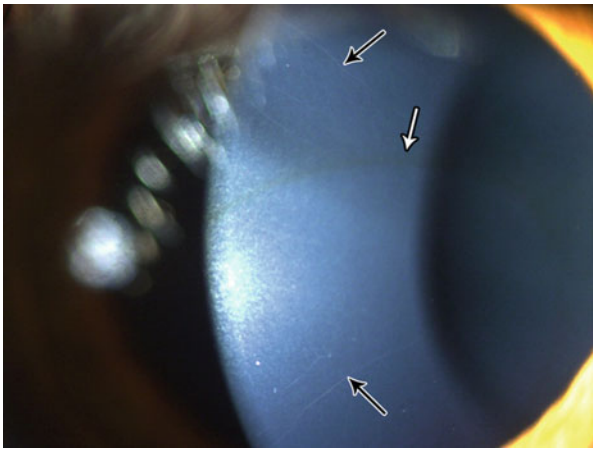

Fig. 1.2 Fleischer ring (*white arrow*) and enlargement of corneal nerves (*black arrow*)

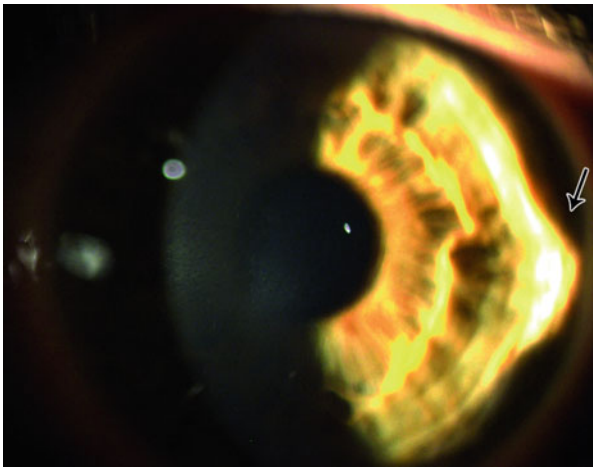

Fig. 1.3 Rizzuti sign

prior to laser vision correction (LVC) procedures since screening for such conditions is mandatory for avoiding major complication of keratectasia [3].

Like we already mentioned above, KC is classically defined as the topographic pattern of inferior steepening, but different patterns are also identifiable [22, 23] (Fig. 1.6). In general, higher corneal curvature values over 47.2 D are suspected cases of KC [22–24]. Additionally, the asymmetry between the values in the 3 mm radius in the upper and lower regions (or between the nasal and temporal regions) is suspected cases of KC when greater than 1.4 D. Such parameters are integrated in the calculation of the KISA index, described by Rabinowitz and Rasheed [25].

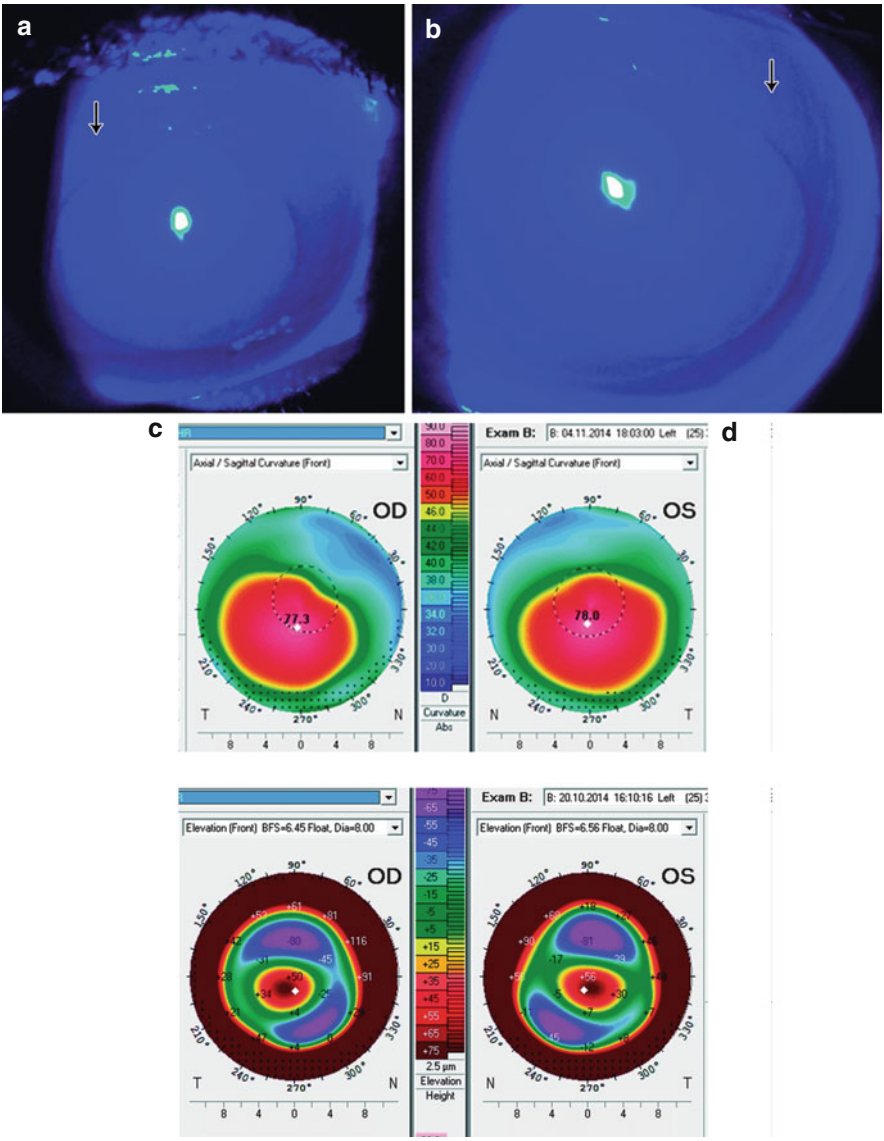

Fig. 1.4 Fleischer ring (*arrows*) seen with cobalt blue light (**a**, **b**). Note the correlation between Fleischer with axial curvature (**c**, **d**) and elevation maps (**e**, **f**) from the front surface

Corneal Tomography

The term "tomography" also derives from the Greek, as the combination of "to cut or section" (*tomos*) and "to write" (*graphein*). It is related to the three-dimensional (3-D) reconstruction of the cornea characterizing the elevation of the front and back

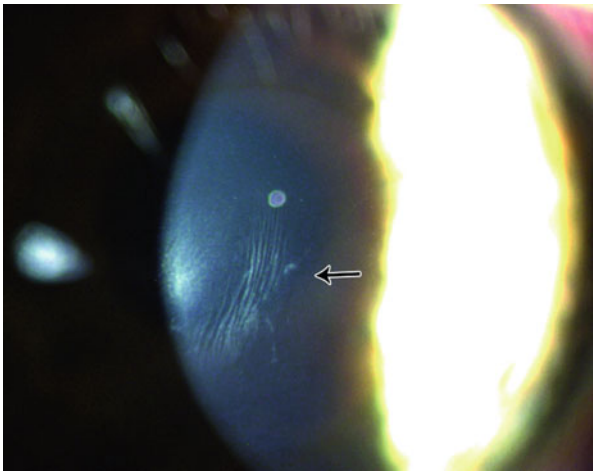

Fig. 1.5 Vogt striae (*arrow*)

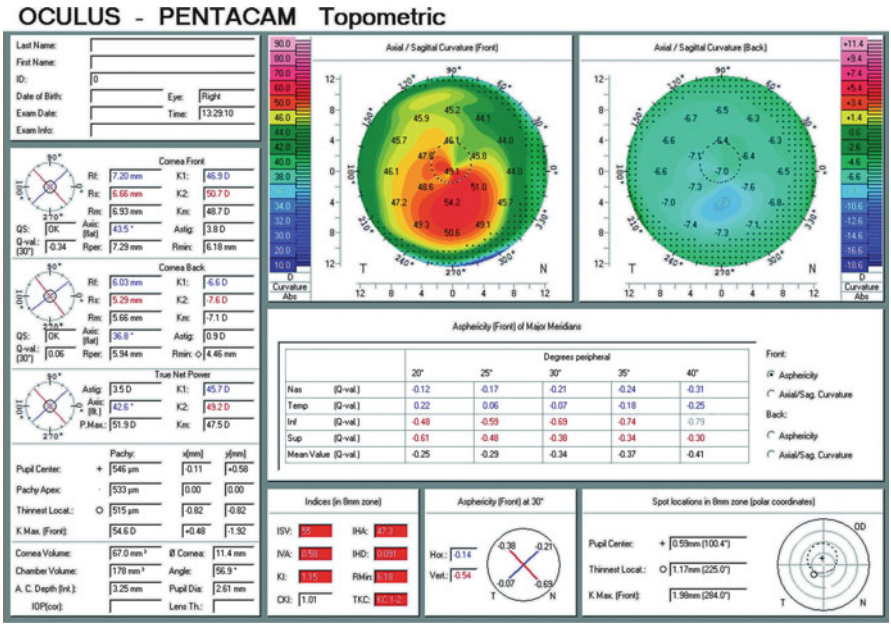

Fig. 1.6 Curvature patterns in KC

surfaces of the cornea along with pachymetric mapping. Different technologies, such as horizontal slit scanning, rotational Scheimpflug, very-high frequency ultrasound, and optical coherence tomography (OCT) are available in many commercial instruments [20].

Elevation maps represent the difference from the examined corneal surface (anterior or posterior) compared to a chosen reference surface. Typically, the reference is calculated to have more coincident points (best-fit) with the examined surface [4, 26]. For ectasia screening purposes, our preference is to fix to the central 8 mm zone for calculating the best-fit sphere (BFS), since this zone is available for the majority of examined eyes. Concerning the elevation maps, different geometric bodies can be used as reference. The clinician should understand the impact of selecting different geometric bodies along with the zone diameter to calculate the best-fit [4]. For example, the BFS allows for the identification of astigmatism, while the best-fit toric ellipsoid (BFTE) facilitates the evaluation of irregular astigmatism. Interestingly, one study reported similar performances for the elevation values at the thinnest point of the posterior surface using BFS and BFTE (8 mm zone) [4].

The evaluation of the pachymetric distribution allows an understanding of the structural stability of the cornea. Since there is an increase in thickness from the center to the periphery, this gradual thickening ratio has a normal range. The ectatic cornea has changes in this pattern of pachymetric spatial distribution with a steeper increase of the thinned area to the periphery [27, 28].

The Belin-Ambrósio enhance ectasia display (BAD) is a comprehensive display that enables a global view of the tomographic structure of the cornea and is available on the Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany). Deviation of normality values was implemented for the front (df) and back (db) enhanced elevations, thinnest value, pachymetric distribution (dp), and vertical displacement of the thinnest in relation to the apex (dy). The "d" values are calculated so that a value of zero represents the average of the normal population and 1 represents the value of one standard deviation towards the disease (ectasia) value. A final "D" is calculated based on a regression analysis that weights differently each parameter. Each parameter is indicated in yellow (suspicious) when it is $\geq$1.6 SD from the mean and turns red (abnormal) at $\geq$2.6 SD from the mean (Fig. 1.7). Values below 1.6 SD are reported in white and are viewed as within the normal range [4, 7, 29, 30].

Regarding KC diagnosis, previous studies have demonstrated higher accuracy of tomographic indices in comparison to front-surface derived parameters [31]. Corneal tomography has also proven to be more effective for enhancing specificity among patients with mild ectasia. For example, there are cases with subtle ectatic disease in which corneal topography appears normal since the ectatic change is not yet present on the front surface [20, 28, 30]. We refer to these patients as with high susceptibility or predisposition to developing ectasia, but they may be also referred as forme fruste keratoconus (FFKC), a concept introduced by Amsler in 1961 [32]. Clinical examples of such patients include the contralateral eyes with normal topographies from patients with very asymmetric KC and cases with natural progression of KC, which have been documented to earlier have normal anterior curvature exams, in the other eye. It is also essential to recognize that keratoconus suspect (KCS) is a topographic diagnosis and does not always imply an ectatic disease (i.e., lower specificity), while FFKC (ectasia susceptibility) is a pre-topographical condition, which may be present despite normal topography and central corneal thickness (CCT) [4, 24, 29].

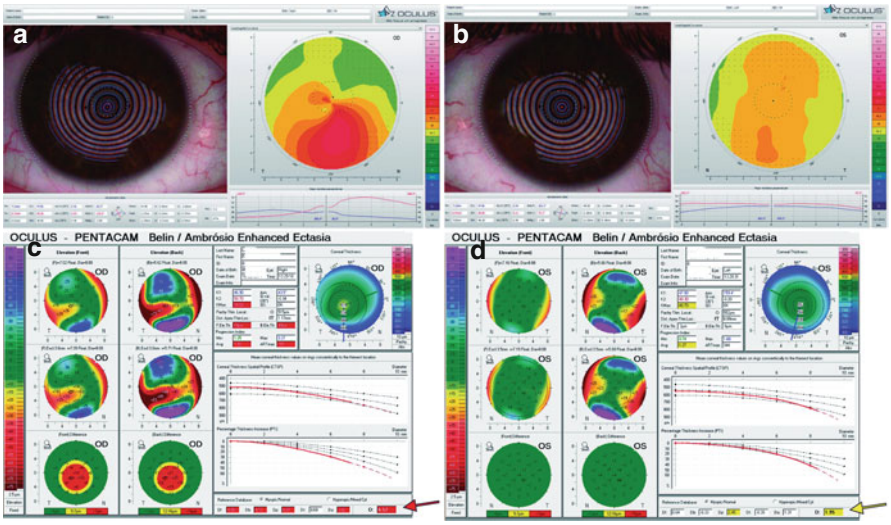

Fig. 1.7 The D index in *red* showing ectasia (**a**–**c**) and suspicious in *yellow* (**b**–**d**)

Wavefront Analysis

KC creates significant visual problems derived from the corneal irregular astigmatism. Corneal aberration evaluation helps to describe the optical quality of the cornea and the measurement of the total ocular wavefront aberration provides a reliable tool to detect early KC and to follow its progression [33, 34]. It is important to note that each instrument will reconstruct Zernike terms differently, using smoothing functions from the acquired data. Thereby, the clinical guidelines for interpretation of the data should be used accordingly to studies from each instrument.

The anterior surface of the cornea is the most important refracting element of the eye. Corneal high-order aberrations are significantly increased in KC compared to normal corneas (Fig. 1.8). However, there are some discrepancies on the performance of such parameters to discriminate KC compared to normals. Gobbe and coworkers showed that the best detector to differentiate between suspected KC and normal corneas was vertical coma with a specificity of 71.9 % and sensitivity of 89.3 % [35]. Alio and Shabayek also proposed a modified Amsler-Krumeich classification for KC, which integrates corneal aberrometry, mainly from the magnitude of coma-like aberrations [36].

Total ocular wavefront was also analyzed in KC eyes. In a prospective observational case control study, Maeda and coworkers reported the corneal and ocular wavefront aberrations of normal and keratoconic eyes, using a Hartmann-Shack sensor combined to a Placido's disc-based topography (KR-9000 PWc – Topcon, Corporation, Tokyo, Japan). There were significantly more total ocular higher-order (HOA) aberrations, such as coma, which was found to be 2.32 times higher than spherical-like aberrations in keratoconic eyes [37].

As mentioned before, this technology can assist refraction in KC patients. This approach also can improve CDVA in cases with advanced KC [19].

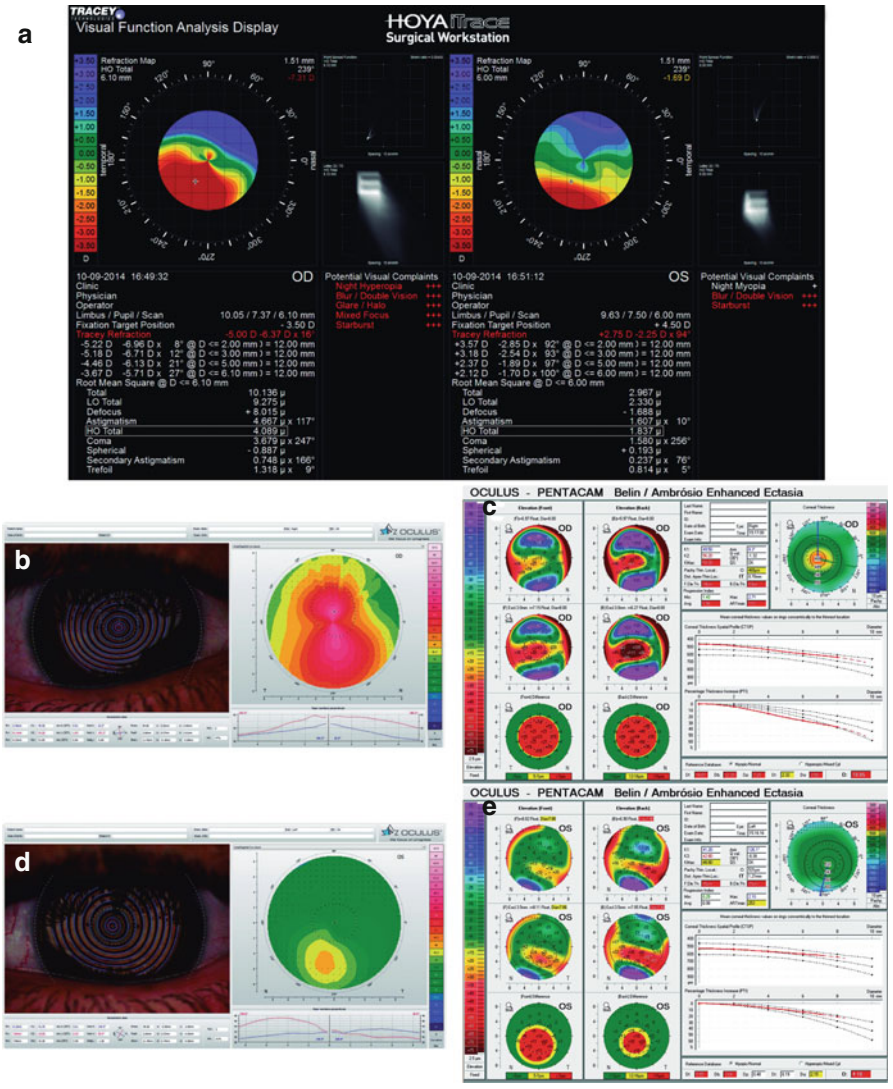

Fig. 1.8 Clinical example of a moderate keratoconus. Ocular aberrometry (**a**), Placido-disk based topography (**b**, **d**) and corneal tomography (**c**, **e**)

Segmental Tomography with Corneal Epithelial Mapping

The study of the epithelium thickness, which was only possible with very-high frequency ultrasound [38, 39], is now available with spectral-domain or Fourier-domain OCT [38, 40]. The epithelium reacts to underlying stromal protrusion in such a way that the knowledge of its thickness and pattern is very important for the evaluation of KC suspects or FFKC patients [38]. Analyzing the corneal epithelial thickness profile over a central 10-mm diameter area in a population of normal

eyes, Reinstein demonstrated in normal eyes that epithelium is significantly thicker inferiorly than superiorly and also significantly thicker nasally than temporally [39]. The corneal epithelium has the ability to mask the presence of a stromal irregularity by changing its thickness profile. The epithelial pattern found in keratoconic eyes is distinct from the pattern found in normal corneas (Fig. 1.9). Known as the "doughnut pattern" of corneal epithelial compensatory changes, the epithelium appears to remodel to reduce the anterior stromal surface protrusion and to smooth the anterior corneal surface by thinning over the cone and thickening around the cone [38]. In mild KC, it is also possible to see a similar pattern with the thinnest epithelium point coincident with the point of maximum protrusion on the elevation maps. Therefore, in the presence of a normal front surface topography, an epithelial doughnut pattern often times can indicate the presence of very mild KC. As the disease becomes more severe, the difference between the thinnest and thickest epithelium increases. Thus, epithelial thickness profile changes with the progression of the disorder [38, 41].

Corneal Biomechanics

As an attempt to increase the accuracy for diagnosing corneal ectasia and its susceptibility, it is important to characterize the cornea beyond its geometry [42]. The biomechanical analysis can be performed with dynamic systems of noncontact tonometry, which monitor the deformation of the cornea by means of infrared reflection (Ocular Response Analyzer; Reichert Inc, Depew, NY) or by Scheimpflug imaging (Corvis ST; Oculus Optikgerate GmbH, Wetzlar, Germany) [43, 44].

The ocular response analyzer measures corneal hysteresis (CH) and corneal resistance factor (CRF) from the applanation pressures. Both CH and CRF have a statistically different distribution among normals and KC. However, there is a significant overlap among the groups for CH and CRF, which limits the value of such parameters for KC diagnosis [45, 46]. Interestingly, new parameters derived from the waveform signal of the corneal reflex during the noncontact tonometry (NCT) provide further biomechanical characterization resulting in a higher diagnostic performance.

The CorVis ST (Oculus Gmb, Wetzlar, Germany) uses an ultrahigh speed (UHS) Scheimpflug camera to monitor corneal response to the air pulse in an NCT system. Besides the intraocular pressure, this device provides the deformation amplitude, the radius of curvature at highest concavity, the applanation lengths, and the corneal velocities during the ingoing and outgoing phases [44, 47]. Studies comparing keratoconic and normal corneas found statistically significant differences for most parameters derived from this device, but again with a relatively high overlap among the groups, which limits diagnostic applications [5]. The combination of parameters using linear discriminant analysis and other artificial intelligence techniques has been the subject of intense studies by the Brazilian Study Group of Artificial Intelligence. For example, the "Corvis Factor 1" was efficient for enhancing the ability of distinguishing normals

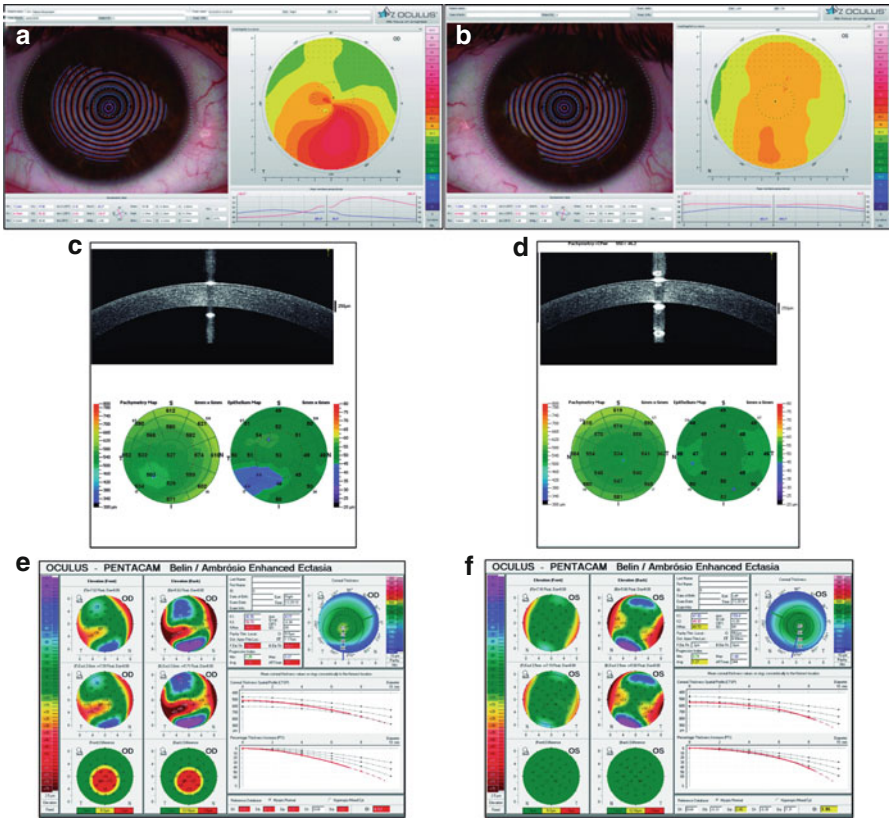

Fig. 1.9 Example of a very asymmetric ectasia case with Placido-disk based topography (**a**, **b**), OCT segmental tomography (**c**, **d**) and corneal tomography (**e**, **f**)

from ectatic corneas, including cases of FFKC ($P<0.001$; Kruskall–Wallis test with Dunn's post hoc test; Ambrósio et al. unpublished data 2011). There are already peer-reviewed published studies showing that corneal tomographic evaluation along with corneal biomechanical analysis lead to a more sensitive and specific methodology to detect KC.

Other tests such as the Brillouin microscopy revealed notable differences between healthy and keratoconic corneas in vivo and in vitro [48]. Interestingly, Brillouin imaging demonstrated that the mechanical weakening is focused within the area of the protrusion, while Brillouin shift was comparable with that of healthy corneas in the opposite area from the cone [48]. These findings go in agreement with the concept from Roberts and Dupps which proposes that there is focal biomechanical modification rather than an uniform generalized weakening, so that the focal reduction in elastic modulus precipitates a cycle of biomechanical decompensation [5].

Corneal biomechanics will be discussed in detail in Chap. 3.

Confocal Microscopy

Corneal confocal microscopy is a relatively new corneal imaging technique, which allows the study of corneal cellular structure. As a noninvasive procedure, it provides images of every corneal layer, providing to clinicians the possibility to investigate and to detect numerous corneal diseases at the cellular level [49].

In KC corneas, this technology can be useful to determine the cellular and/or microstructural changes early, even before mild topographic signs. When compared with normal corneas, the anterior and posterior stromal keratocyte densities were statistically lower and the stromal nerve diameter was statistically higher in this ectatic disorder [50–52].

The use of rigid contact lens, which helps keratoconic patients to neutralize corneal irregular astigmatism in order to achieve a satisfactory vision, may induce inflammatory mediators release, such as interleukin-1, due to physical trauma on corneal epithelium. As the keratocytes in this disease have four times more interleukin-1 receptors compared to a normal cornea, an increased number of anterior keratocytes exhibiting signs of apoptosis might be spotted with this ancillary exam [50, 53].

Specular Microscopy

This imaging technique allows the study of the corneal endothelium, which is essential for the corneal transparency. When enough of these cells are damaged or lost, loss of endothelial pump function occurs resulting in corneal edema and, consequently, visual impairment [54, 55].

In KC disorder, the corneal endothelium has been reported to be normal, even after prolonged use of rigid hard contact lenses. The endothelium has a normal appearance in early stages of KC. As the disorder becomes more severe, specular microscopy has revealed an increase in the pleomorphism rate and a higher proportion of small endothelial cells [56].

Specular microscopy can also be used to document or to identify other diseases that can appear simultaneously with KC [57] (Fig. 1.10).

Evaluating Patients for Refractive Surgery

The challenge faced by refractive surgeons in daily practice is to identify individuals who have increased susceptibility for developing biomechanical failure (progressive ectasia), without excluding candidates who may safely benefit from LVC procedures.

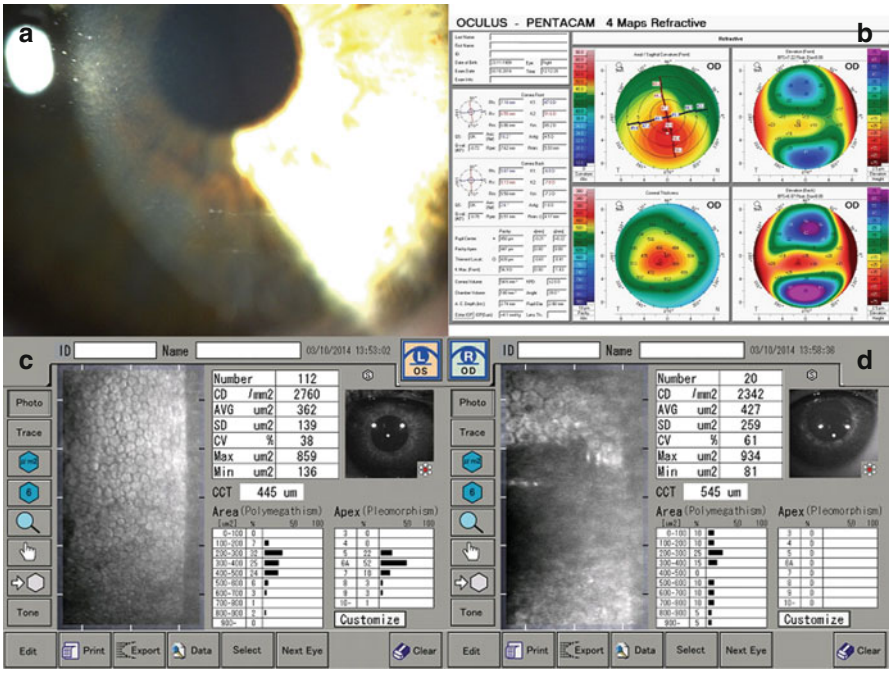

Fig. 1.10 KC and Posterior Polymorphous Corneal Dystrophy (PPCD). This patient has a bilateral keratoconus with assymetric PPCD disease as we can see in the following part figures: a- slit lamp cornea of the right eye shows a inferior horizontal railroad track image with irregular borders in combination with Fleischer´s ring.; b- same patient´s right eye corneal topography with inferior steepening of the cornea; c- specular microscope with well-delimited vesicular areas with endothelial absence combined with areas with polymorphism and polymegathism in the left eye; d- clear alteration of the specular microscope showing classic PPCD with small black spots at the endothelium representing miniature vesicles in combination with a large band as a strip at the Descemet´s membrane delineated by dark, frequently scalloped, approximately parallel borders.

In fact, ectasia occurs due to chronic biomechanical failure process of the corneal stroma and is much more common after LASIK, but has been also reported after surface ablations procedures. Preoperative innate abnormally weak biomechanical properties of corneal stroma and the degree of biomechanical weakening caused by LVC are both considered as physiopathological mechanism for biomechanical failure and ectasia progression after LVC.

Basic aspects as sensitivity (the ability to detect disease) and specificity (the ability to confirm absence of disease) are helpful to evaluate the efficacy of diagnostic tests and help to identify individuals who have developed a specific complication (ectasia after LASIK) or those who are at known risk to develop the complications. Patients “at risk” are a population with subclinical or very mild disease, because these are closest to the individuals that need to be identified. Among eyes known to be susceptible for ectasia progression are those with relatively normal corneal topography from patients with clinical KC detected in their fellow eyes. Such cases