Keratoconus and Ectatic Disease: Evolving Criteria for Diagnosis

Keratokonus und Hornhautektasie: Weiterentwicklung der diagnostischen Kriterien

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ABSTRACT

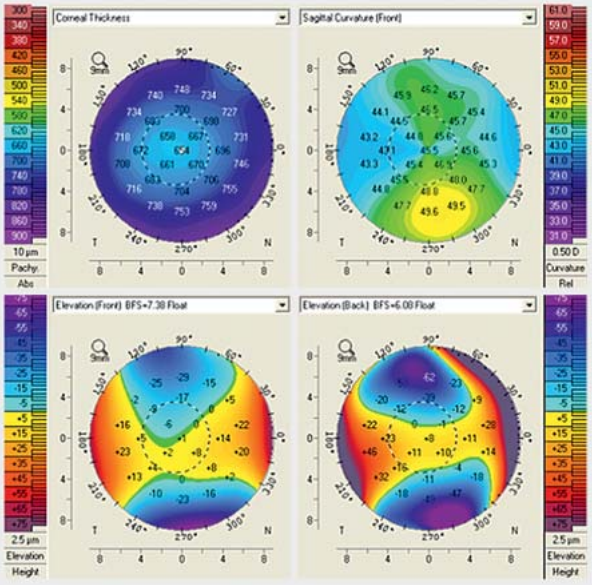
The approach to corneal ectatic disease has changed dramatically over the last decade with advances in both diagnosis and treatment. Newer treatments, such as corneal cross-linking, have the potential to slow or stop the progression of the disease, but benefit from earlier identification of the disease than had previously been possible or required. The continued use of older diagnostic criteria and ambiguous terminology can lead to erroneous study conclusions that may not be applicable to patients with true pathology.

ZUSAMMENFASSUNG

Nachdem in den letzten 10 Jahren wesentliche Fortschritte sowohl bei der Diagnose als auch bei der Behandlung der Hornhautektasie zu verzeichnen waren, kam es zu einer dramatischen Veränderung der Vorgehensweise bei der Diagnostik und Therapie dieser Erkrankung. Neuere Behandlungsansätze, wie z. B. das Crosslinking der Hornhaut, können ein Fortschreiten der Erkrankung verlangsamen oder gar aufhalten. Dazu bedarf es aber einer früheren Bestimmung der Erkrankung als zuvor möglich oder nötig. Die weitere Nutzung veralteter diagnostischer Kriterien in Verbindung mit der oft mehrdeutigen Terminologie kann zu irrtümlichen Studienergebnissen führen, die für Patienten mit tatsächlicher Hornhautektasie nicht zutreffen.

The importance of diagnosing ectatic corneal disease has dramatically increased, coinciding with the emergence of refractive surgery and newer treatment modalities such as corneal cross-linking (CXL). Prior to both entities, the only treatments commonly afforded keratoconus patients were rigid contact lenses, and if they failed, a full thickness penetrating keratoplasty. Both of these treatment modalities were for late or advanced disease, associated with significant changes on the anterior corneal surface. Since there were no available treatments to alter the natural disease progression, and the past treatments were for late-stage disease, diagnosing the disease early was neither important nor its need appreciated.

The first dramatic change came with the emergence of refractive surgery. Iatrogenic ectasia (i.e., Post-LASIK ectasia) was first reported by Seiler et al. in 1998, years after the introduction of the excimer laser for refractive surgery [1]. Subsequent to that report, and with the identification of "abnormal" topography as a significant risk factor for post-LASIK ectasia, anterior surface topography quickly became the standard of care for the preoperative evaluation of any refractive surgical patient [2]. Suddenly, a large number of presumed "normal" patients seeking refractive surgery were being imaged with devices that were, in the past, reserved for patients with known disease (e.g., keratoconus). It has been estimated that more than 10 % of patients seeking refractive surgery were initially considered to be contraindicated due to abnormalities noted on their preoperative anterior curvature topography [3]. Commonly used exclusion criteria included asymmetry on curvature (i.e., asymmetric bowtie patterns), inferior steepening, corneal thinning, or keratometry in excess of 47.0 diopters (▶ **Fig. 1**).

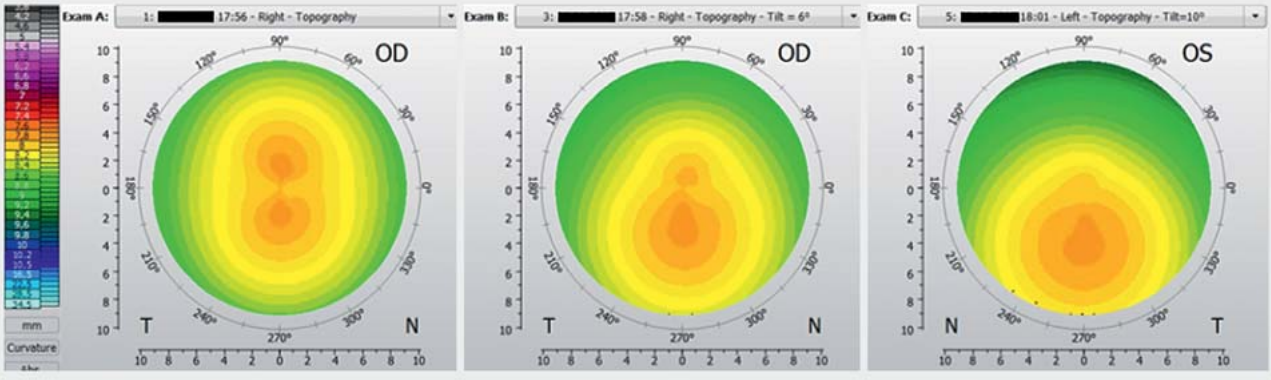


▶ **Fig. 1** A 4-map composite display. The upper right anterior curvature maps show asymmetric curvature with inferior steepening in an eye with normal anterior and posterior elevation and a thick cornea. This is a curvature false positive due to a displaced corneal apex.

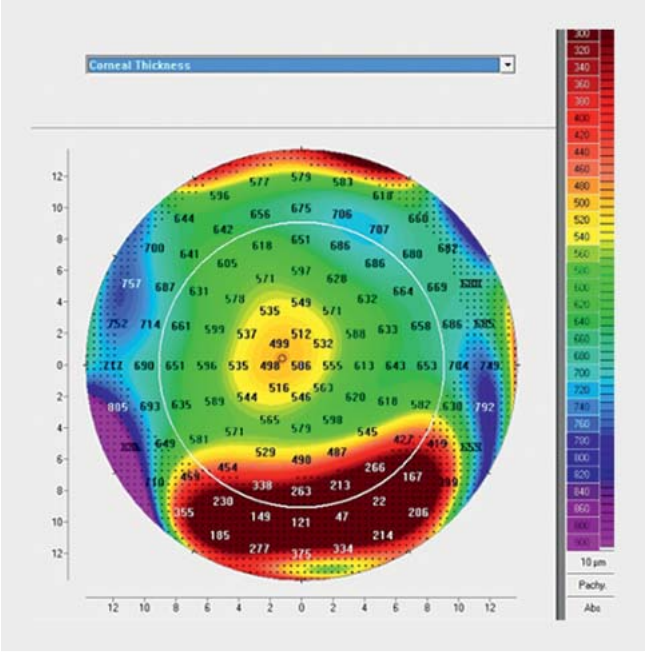
While eye care providers were familiar with clinically advanced keratoconus, this new, larger number of individuals with so-called "abnormal" topography did not comfortably fit into any pre-existing taxonomy. New terms were created, such as "keratoconus suspect", or older terms, such as "Forme Fruste" keratoconus, were modified in an attempt to classify newly diagnosed topographic abnormalities.

"Forme Fruste" keratoconus was first described by Amsler in 1937. It was originally used to describe the contralateral eye of a patient with known clinical keratoconus, whose other eye was biomicroscopically normal [4]. Amsler's description predated any modern imaging technologies. Another term, Keratoconus "suspect", is even more vaguely defined and is commonly applied to any eye with curvature asymmetry, inferior steepening, or thinning or steep keratometry readings. The problem arises when such terms and criteria used to screen patients for an elective surgical procedure (i.e., refractive surgery) are then applied as diagnostic criteria for the disease process itself. Inferior steepening and/or asymmetric bowtie patterns are more commonly seen in normal eyes where the measurement axis of the Placido-based topography instrument does not align with the corneal apex (▶ **Fig. 2**). While these criteria may be useful as an exclusionary screening tool (albeit with a high false positive rate), they are not specific enough to use as sole diagnostic criterion to confirm the diagnosis of keratoconus. While newer and more precise diagnostic imaging techniques have emerged [Scheimpflug and optical coherence tomography (OCT)], a large number of papers continue to utilize diagnostic criteria that dates back more than 25 years [5–7].

A 2% false positive rate may seem like an excellent performing screening parameter, but when used to confirm a diagnosis of keratoconus, it is lacking. More indicative is the positive predictive value (PPV), not just sensitivity or specificity. PPV is the probability that subjects with a positive screening test truly have the disease. Conversely, negative predictive value (NPV) is the probability that subjects with a negative screening test do not have the disease. PPV and NPV are not inherent measurements of the test but depend additionally on the prevalence of the disease. When screening for refractive surgery one would desire a test/parameter with a high NVP, since one would be willing to accept some false positives to ensure that surgery is not being performed on patients with undiagnosed ectatic disease. The opposite is true, however, when designing treatment protocols where a very high PPV is required to ensure that the recommended treatments are actually being evaluated in patients who truly have the disease. For example, if one assumes keratoconus occurs in 1 : 1000 (variable in different populations) and your test has a 2% false positive rate, then you would have 20 positive tests for each true keratoconus patient. The PPV is 0.05, which is a poorly performing parameter to use as a sole inclusion criterion. The clinical significance is that there are multitudes of papers, presentations, and studies that



▶ **Fig. 2** Anterior curvature maps generated from the same aspheric astigmatic test object with different degrees of angular decentration, demonstrating that significant inferior steepening and curvature asymmetry can be generated with moderate tilt.



▶ **Fig. 3** Corneal thickness map (full corneal coverage) depicting the inferior band of corneal thinning seen in true pellucid marginal degeneration.

utilize patients who have failed refractive screening and purport safe and effective treatments in so-called pathologic eyes [5 – 7], while, in truth, the vast majority of the patients studied are actually normal. The problem arises, however, when conclusions drawn from these studies based on a majority of normal individuals are then applied to patients with true pathology.

The recognition of the need to modernize our diagnostic criteria leads to the formation of the Global Consensus on Keratoconus and Ectatic Diseases. This was an international coalition of the four major multinational corneal societies (The Cornea Society, PanCornea, Asia Corneal Society, and EuCornea) whose finding were published in the journal Cornea in 2015 [8]. While the consensus covered a multitude of topics, their conclusions/agreements reached on the definition/diagnosis of keratoconus was as follows:

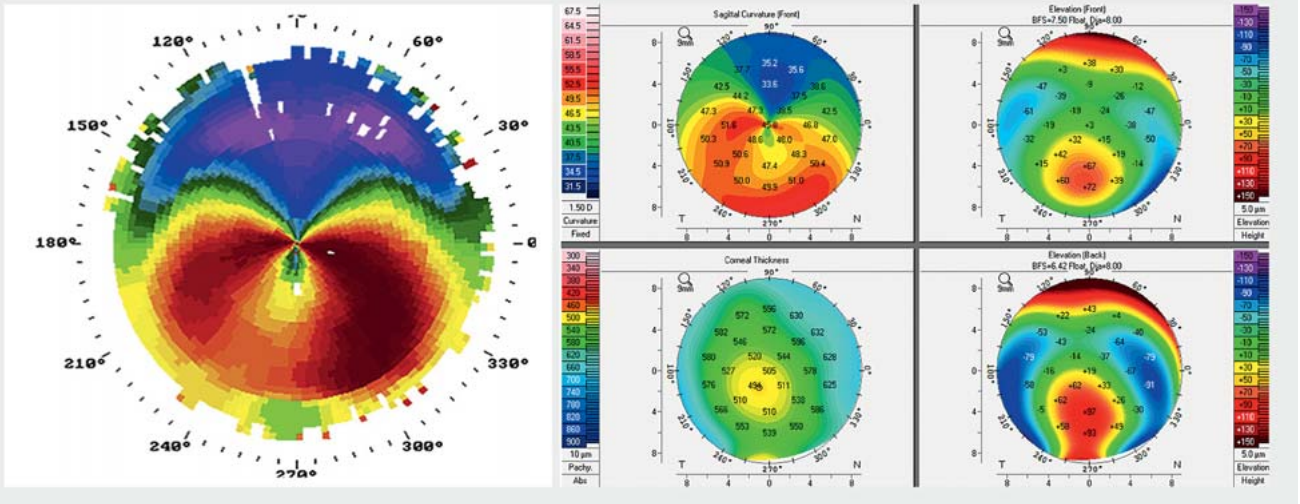
The following findings are mandatory to diagnose keratoconus

- Abnormal posterior elevation
- Abnormal corneal thickness distribution
- Clinical noninflammatory corneal thinning
- The best current and widely available diagnostic test to diagnose early keratoconus is tomography (Scheimpflug or OCT)

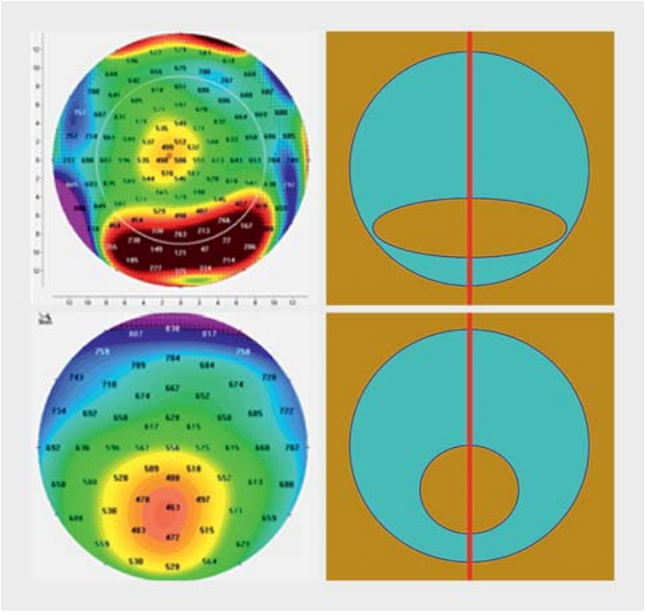
Additionally, the consensus document also concluded that currently (2015), no clinically acceptable classification system exists. The ABCD classification (which will not be discussed here) was created partly in response to this documented need [9].

In order to properly evaluate and apply any clinical study, one needs to have strict inclusion/exclusion criteria. This simple appearing task is often the most difficult part of developing a study protocol. One needs to ensure that the vast majority of study patients truly have a disease, but the criteria cannot be so strict that the study population represents only a small percentage of patients with that disease. In prior consultations, we have suggested the following entrance criteria for a keratoconus treatment trail:

- Posterior elevation at the thinnest point ≥ 13 microns (best-fit sphere from 8.0 mm optical zone)
- Final "D" from the Belin/Ambrosio Enhanced Ectasia Display (BAD) ≥ 3.0
- Minimal corneal thickness < 550
- Spherical equivalent < zero (myopic)



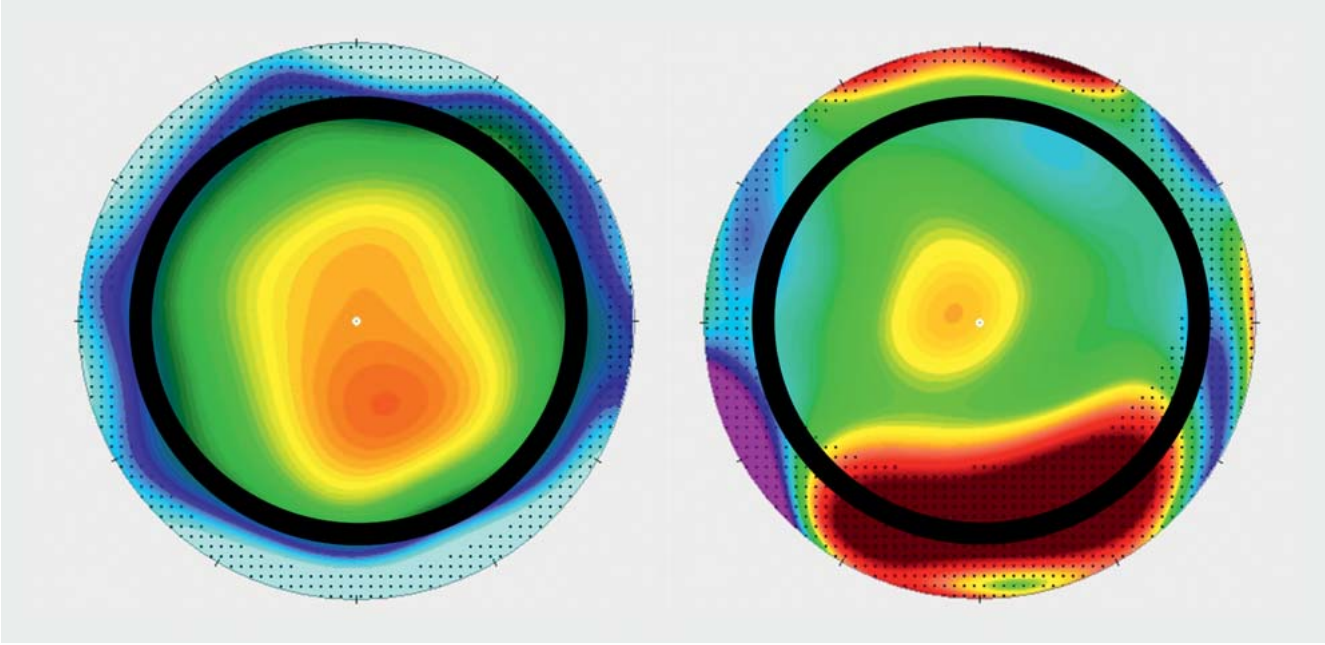
▶ **Fig. 4** "Crab claw" type curvature pattern seen with both a Placido-derived image (left) and a Scheimpflug-derived image (upper left composite). The corneal thickness map (lower left composite) and the anterior and posterior elevation maps (upper and lower right composite) are compatible with inferior keratoconus.



▶ **Fig. 5** A vertical optical cross-section taken from true PMD and inferior keratoconus will look remarkably similar. The full corneal thickness map, however, differentiates true PMD (upper left) from inferior keratoconus (lower left).

This is a sample of possible entrance criteria in an attempt to better define the study population and to make future studies more applicable to the appropriate population [10]. While these criteria are, in part, machine specific (Pentacam, Oculus GmbH, Wetzler, Germany), similar criteria can be developed for most tomographic devices, while following the guidelines in the consensus document.

Another case where lax diagnostic criterion can lead to inappropriate treatment decisions is what many call pellucid marginal degeneration (PMD). PMD has been classically described as an inferior band of thinning, 1–2 mm from the inferior limbus (▶ **Fig. 3**) with excessive corneal flattening and a sharp transition above the band of thinning [11]. Anterior curvature patterns described as "crab claw" or "lobster claw" have been considered the topographic hallmark of this condition, however, these patterns are curvature anomalies and do not accurately represent the corneal shape. This is true regardless of whether the curvature patterns are produced from Placido-based, Scheimpflug, or OCT systems (▶ **Fig. 4**) [12]. Recently, some have advocated for the use of the vertical Scheimpflug image as a diagnostic tool for PMD, yet the vertical Scheimpflug in inferior keratoconus and PMD can be identical (▶ **Fig. 5**) [12]. This is not just semantics, as treatments recommended for pseudo-PMD, such as intracorneal ring segments (ICRS), CXL, or DALK, may be either less effective, ineffective, or, in the case of ICRS, potentially dangerous (▶ **Fig. 6**) [13–15].



▶ **Fig. 6** Corneal thickness map. Inferior keratoconus (left) and true PMD (right). While the ICRS would encompass the cone for inferior keratoconus, the ICRS in true PMD would both miss a majority of the pathology and the proposed intra-stromal channel would traverse the area of maximal corneal thinning.

While diagnostic and treatment modalities were relatively stagnant for much of the 20th century, the Global Consensus of Keratoconus and Ectatic Corneal Disease (2015) [8] attempted to update our terminology, criteria, and available treatments. The last decade has seen a rapid change in technology and treatments, and discussions are currently ongoing for a second international consensus.

Conflict of Interest

Consultant OCULUS GmbH CMO CXLOphthalmics but received no financial support for any of this work.

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