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Advanced epithelial mapping for refractive surgery

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One of the leading challenges in refractive surgery today is the presence of underlying subclinical early-stage keratoconus (KC), which can lead to iatrogenic post laser *in situ* keratomileusis ectasia. Timely detection of this condition could aid the refractive surgeons in better decision-making. This includes being able to defer refractive surgery in subclinical cases as well as providing treatment for the same in the form of appropriate corneal collagen crosslinking treatments. Corneal topography is considered the gold standard for the diagnosis of corneal ectatic disorders. However, there is a likelihood that topographers are overlooking certain subclinical cases. The corneal epithelium is known to remodel, which may mask underlying stromal irregularities. Imaging and analyzing corneal epithelium and stroma independently will undoubtedly open newer avenues to supplement our understanding of postrefractive surgery outcomes and KC. This review encapsulates the various Optical coherence tomography-based epithelial mapping devices particularly RTVue (Optovue, Fremont, USA) and MS-39 (Costruzione Strumenti Oftalmici, Florence, Italy) in terms of their utility in these conditions. It will help guide the clinician on how including an epithelial mapping in clinical practice can aid in diagnosis, management, and interpretation of outcomes both for refractive surgery as well as KC.

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One of the leading causes of iatrogenic post laser *in situ* keratomileusis (LASIK) ectasia (PLE) is the presence of underlying subclinical early-stage keratoconus (KC) in patients. This continues to remain a major challenge in preoperative refractive surgery workup and is rather unforgiving.[1] Timely detection of this condition could aid refractive surgeons in better decision-making. This includes being able to defer refractive surgery in subclinical cases as well as providing treatment for the same in the form of appropriate corneal collagen crosslinking (CXL) treatments.[2] Studies have cited KC to be the most common reason for deferring refractive surgery, found in 17.5–24.0% of cases.[3]

Corneal topography is considered the gold standard for diagnosis of corneal ectatic disorders.[4] However, there have been reports of eyes with seemingly normal topography and no other known risk factors going on to develop PLE.[5,6] There is a likelihood that topographers are overlooking certain subclinical cases. The corneal epithelium is known to remodel as a result of underlying stromal irregularities and helps to mask them,[7,8] enhancing the need for imaging and analysis of the corneal epithelium and stroma independently, which would open newer avenues to supplement our understanding of KC and its diagnosis.[9]

Optical coherence tomography (OCT) is a noncontact procedure which is based on the principle of interferometry.[10] The precise delineation of corneal surfaces is a result of high axial resolution of OCT-based devices. Accurate pachymetry (corneal thickness CT) and corneal epithelial thickness (ET) mapping are provided by these devices.[11]

Ideally, any therapeutic profile applied to the eye should be based on the shape of the stromal surface, resulting in a true stromal surface topography-guided ablation.[12] However, due to epithelial masking, topography and wavefront measurements may not deliver an accurate picture of the underlying pathology that needs correction – the irregular stromal surface.[12] Consequently, topography-guided treatment may lead to suboptimal outcomes as they only correct for the proportion of the stromal irregularity that is not masked by the epithelium.

Matalia *et al.* have recently described a novel noncontact method to quantify the topography and corneal surface aberrations using anterior segment OCT (AS-OCT).[13] OCT generates higher curvature and aberrations measurements than Scheimpflug-based topographers in both normal and keratoconic eyes. In general, the yield of aberrations from OCT epithelium–Bowman's layer interface was significantly greater than those from the Pentacam's anterior corneal surface imaging. These techniques could have potentially far reaching implications for refractive surgery.

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This review encapsulates the various OCT-based epithelial mapping devices in depth. It aims to shed light on their diagnostic accuracy and repeatability. It will help guide the clinician on how including an epithelial mapping in clinical practice can aid in diagnosis, management, and interpretation of outcomes for both refractive surgery and KC.

OCT-Based Devices for Measuring Epithelial Thickness

AS-OCT produces a high-resolution two-dimensional image of a three-dimensional structure by comparing the delay and difference intensity from the scattering of two distinct light beams.[14]

There are multiple AS-OCT imaging devices available commercially: Time-domain OCT, first introduced as the Visante OCT (Carl Zeiss, Jena, Germany), and Fourier-domain OCT introduced as the RTVue and Avanti devices (Optovue, Fremont, USA), CASIA-2 (Tomey, Aichi, Japan) and Cirrus HD-OCT (Carl Zeiss, Jana, Germany). The MS-39 (Costruzione Strumenti Oftalmici, Florence, Italy) is a topographer that combines Placido disk corneal topography, with high-resolution AS-OCT-based tomography.

The newer generation of the RTVue system, RTVue-XR, has incorporated an epithelial thickness mapping software customization that furnishes measurements of ET and CT for a 9-mm diameter region of the cornea. The pachymetric scan of the RTVue spectral-domain OCT (SD-OCT) device gives a color-coded pachymetry map of the central 6 mm of the corneal epithelium along with zonal (regional) thickness parameters and summary statistics derived from various regions of the pachymetry map.[15] A corneal ET profile over a 9-mm-diameter zone available on the latest devices provides important information on remodeling of the corneal epithelium over the transition zone after refractive surgery and on the apex and base of the cone in cases of KC.[16]

Parameters measured on the epithelial map of RTVue®

RTVue® (Optovue Inc, Fremont, CA) uses a wavelength of 830 nm. It takes a scan of width 4–6 mm with transverse resolution of 10–15 μ. It measures the anterior and posterior corneal curvatures and power. It consists of eight high-definition meridional scans acquired in 0.31 seconds (s).[17] Commercial software of epithelial mapping measures the following corneal thickness and ET parameters: [Fig. 1]

1. Minimum corneal thickness,
2. Superonasal–inferotemporal (SN–IT) corneal thickness
3. Inferior–superior corneal thickness
4. Minimum–median (min–med) corneal thickness
5. I–S ET, thinnest ET
6. Minimum–maximum (min–max) ET
7. Standard deviation (SD) of the ET.

The cornea is divided into quadrants [Fig. 1]: IT, Infero-nasal, Supero-temporal, and SN. The localization of the thinnest corneal point, the thinnest epithelial point, and the ET in the thinnest corneal zone can also be recorded. The ET in the thinnest corneal zone can be obtained automatically by pointing the mouse tracker to the corresponding zone on the pachymetry map and recording the ET.

Repeatability of current OCT devices

In normal controls, Vidal *et al.* reported the Fourier-domain SOCT Copernicus HR system to have poor repeatability and reproducibility of corneal ET measurements.[14] However, Prakash *et al.* found reliable and reproducible measurements of corneal ET at the vertex using the Fourier domain-based Cirrus HD-OCT.[18] Ma *et al.* used the RTVue to collect corneal ET and reported that in LASIK-treated eyes, the SD values were 0.7 mm at the central zone, and </= 1.7 mm in the paracentral zones. The CoV values were low, and the ICC values were high in both groups, indicating excellent repeatability.[19]

Role of ET in Refractive Surgery

The role of the corneal epithelium in the corneal net power and thus total ocular refraction is gaining more importance. It is reported that epithelial refractive power alone is an average of 1.03 D (range 0.55–1.85 D) over the central 2 mm diameter zone and 0.85 D (range 0.29–1.60 D) at the 3.6 mm diameter zone.[20]

Knowledge of ET distribution patterns may be crucial in deciding whether or not to operate in cases with suspicious topographies. This is because the epithelium is not evenly distributed over the Bowman's layer and is often nonhomogeneously thinned, masking underlying stromal abnormalities. The epithelium attempts to smoothen abrupt changes of the stromal surface by thinning focally over "hills" and thickening locally over the "valleys" of an irregular stroma.[21] Accurate and repeatable measurements of the corneal epithelium can thus provide sensitive information to help measure remodeling post corneal refractive surgery and detecting the development of iatrogenic ectasia.[9,22]

ET evaluations for refractive surgery planning

Trans-epithelial photorefractive keratectomy (Trans-PRK) and LASIK flap planning

The role of epithelium in the Trans-PRK planning cannot be overlooked as illustrated in case 1.

Case 1: A patient with a normal topography [Fig. 2a-c] and ET of 121 μm [Fig. 2d]. In such cases, one needs customized planning of the flap thickness for LASIK and ablation depth for trans-PRK based on the ET. If one plans a routine LASIK with a standard 110 μm flap or Trans-PRK maintaining the ET as 50 μm; an undercorrection is inevitable as lesser stromal ablation will still render the patient myopic. This particular case emphasizes the role of epithelial mapping as a part of routine preoperative workup in refractive surgery patients to avoid under-correction.

Phototherapeutic keratectomy (PTK) planning

PTK utilizes an excimer laser to treat opacities and irregularities of the corneal surface. Accurate ET measurements have improved the ability to accurately treat underlying stromal irregularities. With accurate epithelial mapping, transepithelial PTK reaching the depth of epithelium using a stepwise protocol improves the regularity of the stromal surface, along with the visual acuity.[22] Additionally, epithelial mapping can assist in a more accurate assessment of the depth and extent of corneal scarring and help guide treatment.

Role of ET in evaluating outcomes postrefractive surgery

Irregular epithelial remodeling postrefractive surgery can result in regression. Apical syndrome following high hyperopic refractive correction can result in irregular astigmatism.[23] Previously, topography and total corneal thickness have been used to plan recorrection as indirect tools. AS-OCT enables direct measurement of ET, thus the clinicians can customize treatments accurately improving both recorrection safety and efficacy.[23]

Regression after Myopic LASIK

Epithelial thickening at the ablated optical zone is a causative factor for regression.[24] A curvature gradient topography can

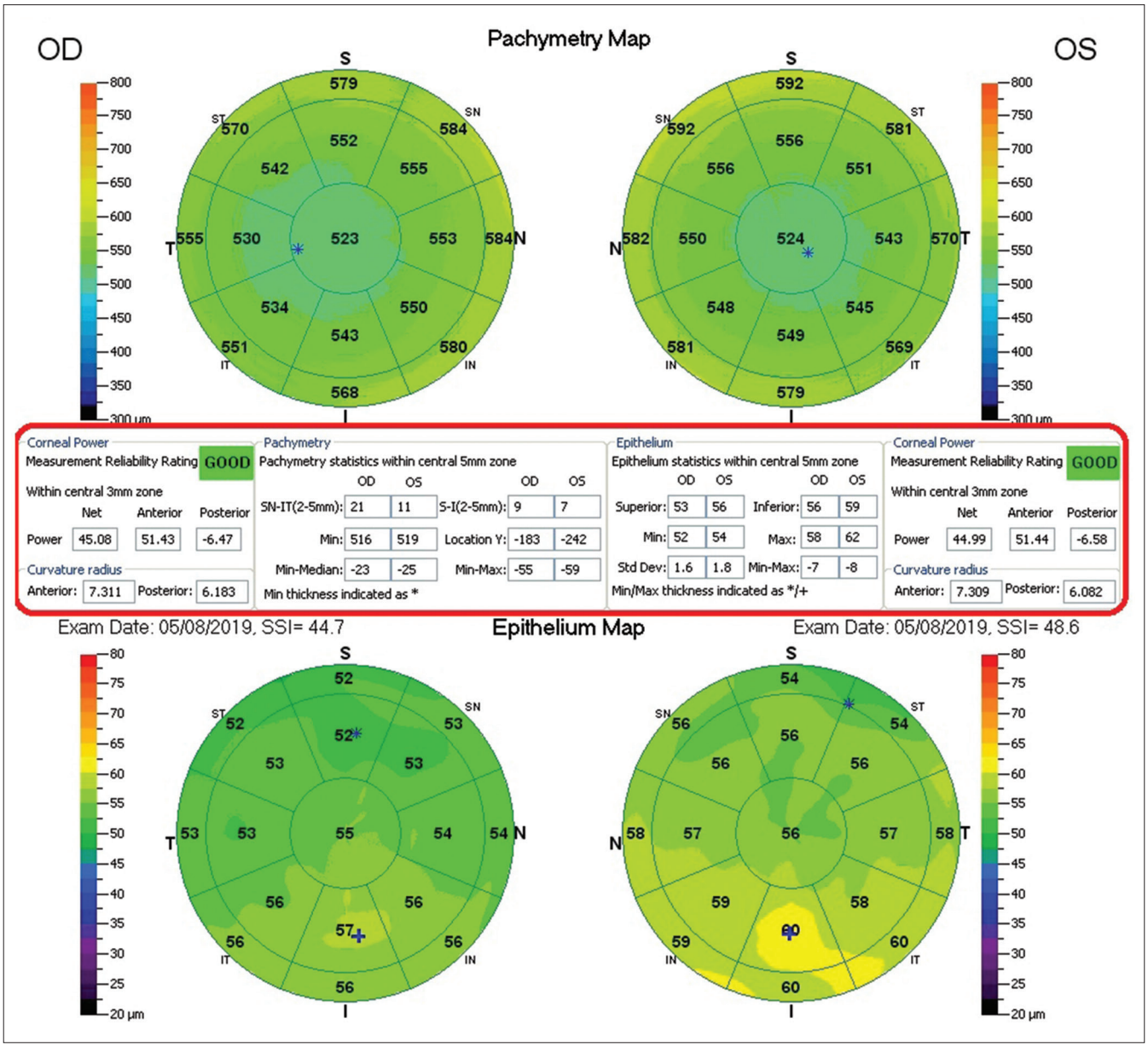

Figure 1: Pachymetric map of RTVue® (Optovue Inc, Fremont, CA) showing (red box).1. Minimum: The thinnest corneal thickness. 2. Minimum–Maximum: The thinnest corneal thickness minus the thickest corneal thickness. 3. SN-IT: Average thickness of Supero-Nasal (SN) octant minus average thickness of Infero-Temporal (IT) octant. 4.S-I: Average thickness of the superior (S) octant minus average thickness of the inferior (I) octant

help in predicting the postoperative epithelial remodeling, thus improving the refractive planning. The corneal regions with higher postoperative curvature gradients contribute to changes in the tangential curvature over 1 year.[25] To minimize the occurrence of epithelial remodeling in these high-gradient regions, clinicians should plan ablation profiles in a manner that minimizes high-curvature gradients postoperatively.

Case 2: A case of epithelial hyperplasia masquerading as regression postrefractive surgery [Fig. 3a]. In this case, the suboptimal outcome postrefractive surgery can be attributed to the epithelial hyperplasia. This can be easily demonstrated with an epithelial map.

Contact lens warpage

Epithelial irregularities are also commonly seen in contact lens wearers – who often show signs of warping or arcuate lesions [Fig. 3b and c]. This may lead to anterior surface topography changes presenting as corneal warpage and inconsistent refraction.[26,27] Schallhorn *et al.* reported a strong agreement between the location of maximum corneal power and minimum ET in KC patients. However, the eyes with contact lens warpage showed a strong agreement between the maximum corneal power and maximum ET.[28]

Case 3 [Fig. 3d]: This is an example of a post LASIK patient complaining of poor vision. Such an outcome may not always be attributed to regression, undercorrection or ectasia. The epithelial map is suggestive of multiple epithelial irregularities due to remodeling postsurgery that be the culprit in this case.

Role of Epithelial Mapping in KC

Changes in the posterior corneal surface are one of the earliest signs observed in KC.[29,30] Factors like changes in corneal

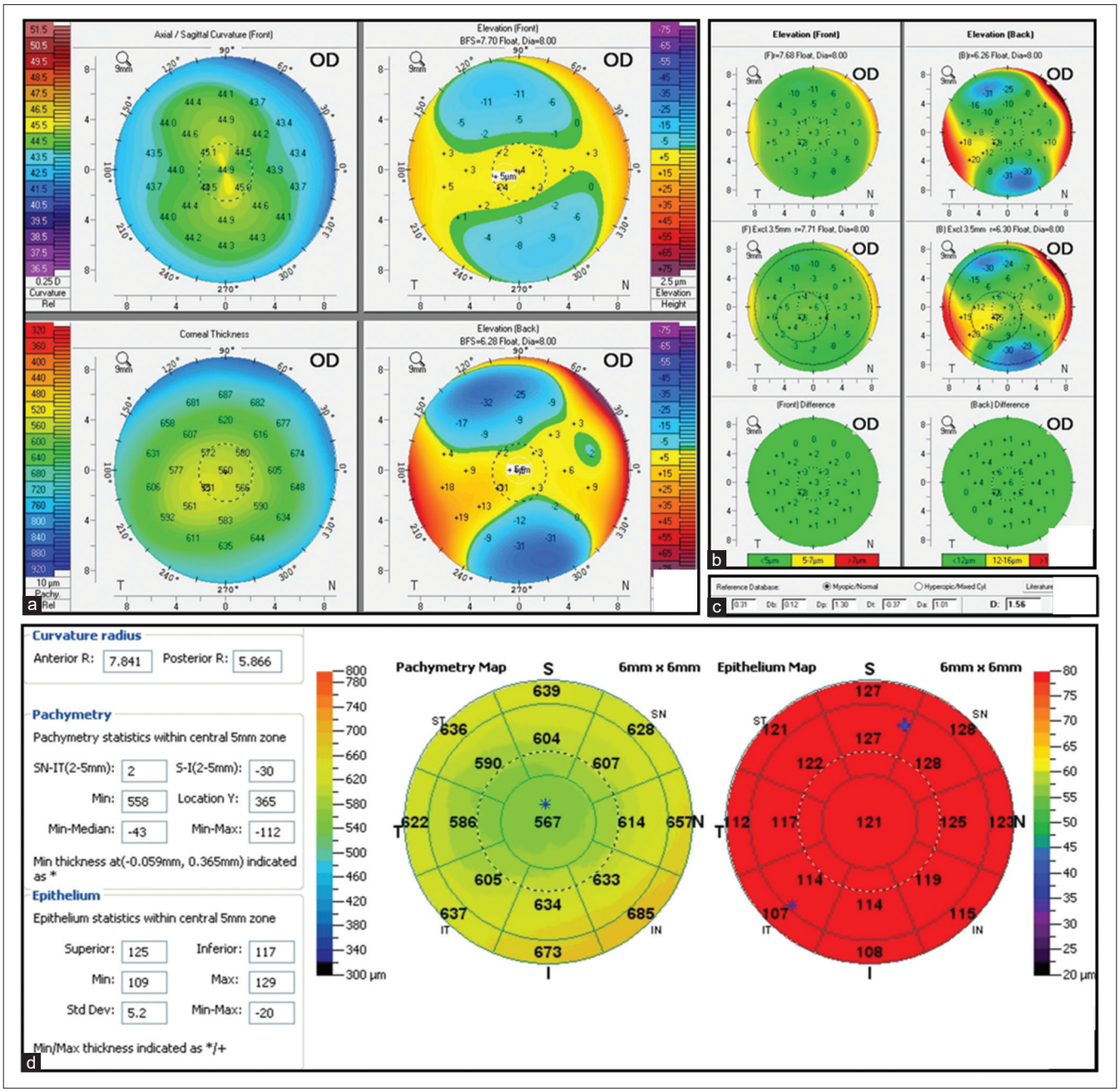

Figure 2: Case 1: A patient with normal cornea topography on Pentacam HR refrative 4 maps (a), normal BAD-D (b); D 1.56 (c) and ET of 121μm (d)

elevation, curvature, and thinning of the stroma serve as important landmarks in gauging the alterations of the posterior corneal surface.[31] In order to make the diagnosis more reliable and accurate, indicators like corneal ET profile have come into play. Reinstein *et al*. observed that epithelial remodeling masks the area of cone in the early stages of KC. This hides subsequent modifications of corneal stroma, which may go undetected on topography making diagnosis the difficult.[32,33] It is clear that the study of these compensatory changes in the corneal epithelium will supplement the detection of the subclinical stages of KC.[34]

Reinstein *et al*. studied the ET profile in KC. It is donut shaped [Fig. 3e], typically displaying an area of stromal thinning at the cone surrounded by a rim of thickened epithelium.[35] In KC, thinning of the epithelium is present in areas of relative increase in corneal curvature and thickening in areas of relative flattening, which is commonly seen in the inferior paracentral region.[36,37] Preliminary changes occur first in the basal layer of epithelium.[38] Taking into account the published literature and the utility of AS-OCT, it can be inferred with a degree of certainty that the use of corneal ET profile is crucial and that it can be effectively used as an adjunct to the existing criteria for detecting progression in KC.[39,40]

Case 4: A patient with grade 2 KC (Amsler-Krumeich[41] classification) in both eyes. [Fig. 4a]. Note that both the eyes of the patient have thinning of the epithelium overlying the cone area as seen in the pachymetry maps [Fig. 4b]. KC is characterized by inferotemporal thinning of the cornea, along with the classic sign of thinning of the overlying epithelium.

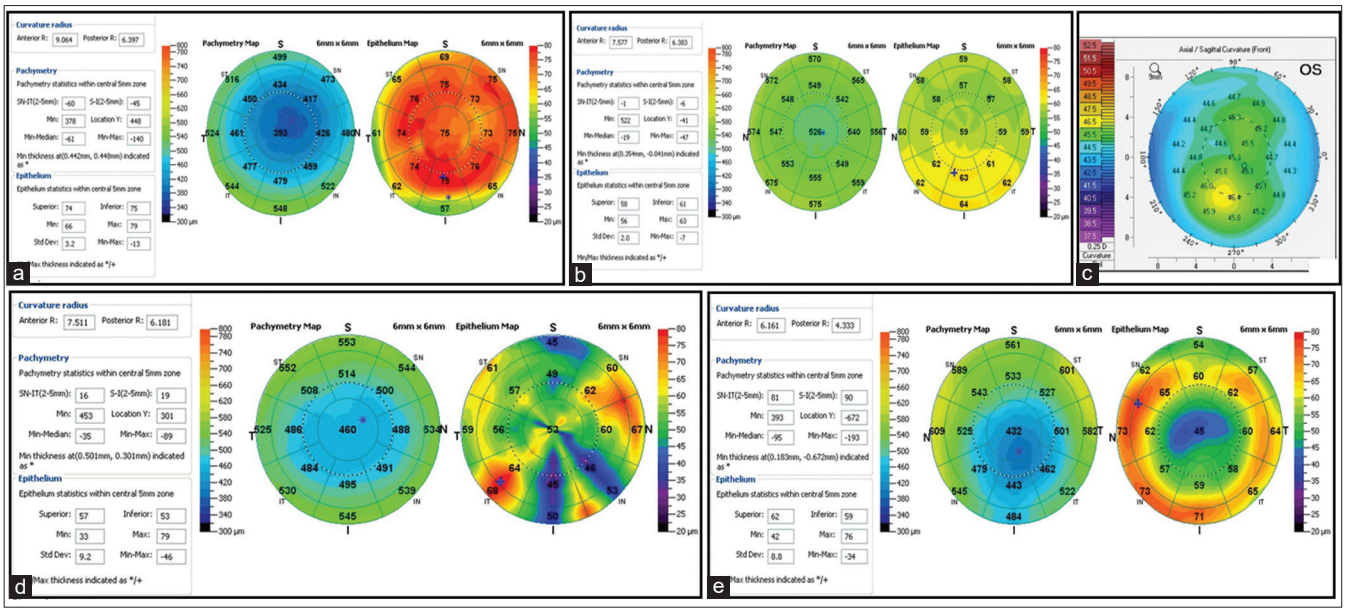

Figure 3: (a) Case 2: A case of epithelial hyperplasia masquerading as Regression post refractive surgery. (b) epithelial map of a patient with both eye contact lens warpage and the corresponding axial/saggital map on the Pentacam (c). (d) Case 3: A patient who underwent LASIK, presenting with blurring of vision and glares postoperatively, found to have irregularity of epithelium as the underlying cause. (e) Epithelial map showing donut-shaped rim of thickened peripheral epithelium in a case of keratoconus

Role of epithelial mapping in planning topography-guided custom ablation for the treatment of KC.

While planning a topography-guided custom ablation treatment (TCAT) or topography-guided removal of epithelium in KC (TREK), we need to keep the maximal stromal ablation at 50 µm for TCAT and 25 µm for TREK.[42,43] Thus, the ET at the thinnest location of the cone is of utmost importance while customizing the treatment.

Epithelial remodeling after CXL

CXL in keratoconic eyes results in epithelial remodeling. Thinning of peripheral epithelium and decreased corneal epithelium SD is noted after 1 and 3 months of CXL.[23] The improvements in visual acuity post CXL can to an extent be attributed to the epithelial remodeling resulting in a smoother anterior corneal surface.[23]

Role of hybrid devices for epithelial and stromal mapping

MS-39 combines the Placido-based corneal topography with data obtained by SD-OCT transverse sections: The reason why the designers deemed it necessary to equip an advanced OCT, characterized by a 3.5-µm resolution (in tissue) with placido disc, is very simple: if we compute the resolution needed to discriminate surfaces differing for 0.25D of curvature from their elevation profile, we discover that the two surfaces differs less than 3.5 µm for the three central millimeters where Placido based does. The reason of this unexpected result is that Arc-Step algorithm (algorithm on which modern keratoscopes base) provides curvature as a direct and primary output and elevation-based devices need fitting procedures to derive curvatures.

For the above reason, in MS-39 software, for all cases where keratoscopy is available and reliable, the measurement of the anterior surface obtained with Placido disc is preferred to the measurement done with the OCT subsystem.

Corneal epithelium and stromal maps

As an evolution of the Scheimpflug-based Sirius topographer, MS-39 is able to measure all classical maps of the anterior segment such as sagittal and tangential curvature maps of both the anterior and posterior corneal surfaces, elevation maps, refractive power maps, and corneal thickness maps [Fig. 5d].

By exploiting its superior imaging capability in resolving corneal layers, the MS-39 is also able to calculate the epithelial and stromal thickness maps over an 8-mm diameter [Fig. 5d]. As mentioned above, the corneal epithelium compensates for possible stromal irregularities. Therefore, corneal analysis based on topography and pachymetry with no knowledge of ET may be misleading and result in an incorrect assessment of preoperative KC and postrefractive surgery ectasia progression.

Role in refractive surgery preoperative workup, in cases of suspicious topography

Case 5: A 29-year-old male wanted to undergo refractive surgery. His corneal topography on Pentacam HR revealed an asymmetric bowtie pattern with inferior steepening in the right eye (OD) [Fig. 5a]. The BAD-D was 1.14 with suspicious df-1.76 [Fig. 5b and c]. The MS-39 epithelial map OD revealed an increased ET in the area of inferior steepening as compared the normal ET. However, there was no obvious stromal elevation or posterior elevation in that area on the MS39 maps [Fig. 5d]. Hence, possibility of a subclinical KCs was ruled out and refractive surgery was planned.

Case 6: A 21-year male came for a refractive surgery opinion. His preoperative workup revealed a suspicious looking topography with inferior steepening on the Pentacam HR [Fig. 6a] with a normal BAD-D display in the left eye (OS) [Fig. 6b and c]. On AS-OCT examination using the MS39, 6 map scan revealed an area of increased ET inferiorly with absence of corresponding stromal elevation [Fig. 6d]. With

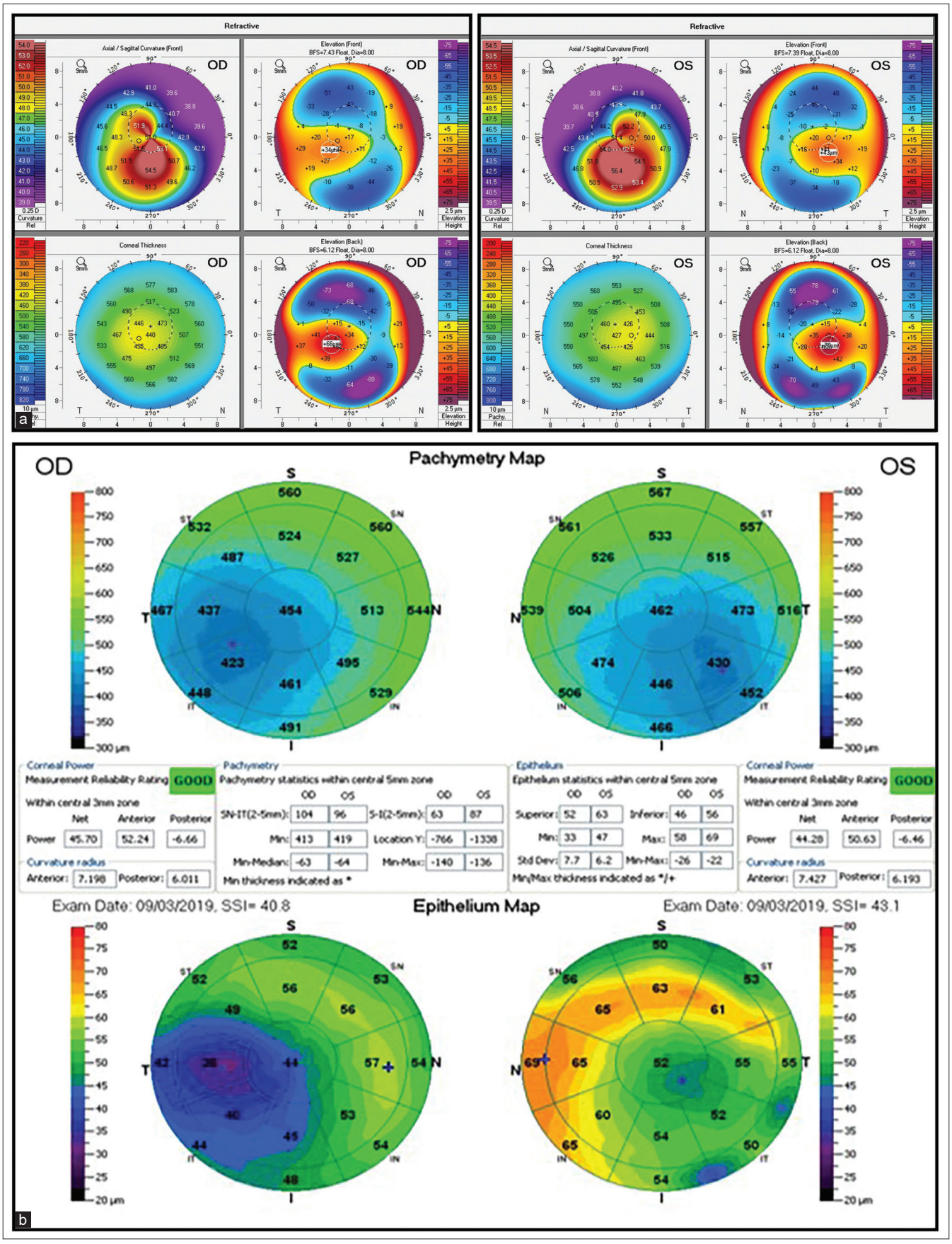

Figure 4: (a) Case 4: Pentacam refractive four maps showing grade 2 KC in both the eyes. (b) Corneal pachymetry map of Keratoconic patient characterized by the inferotemporal thinning of the cornea, along with the corresponding thinning of the overlying epithelium in cone area

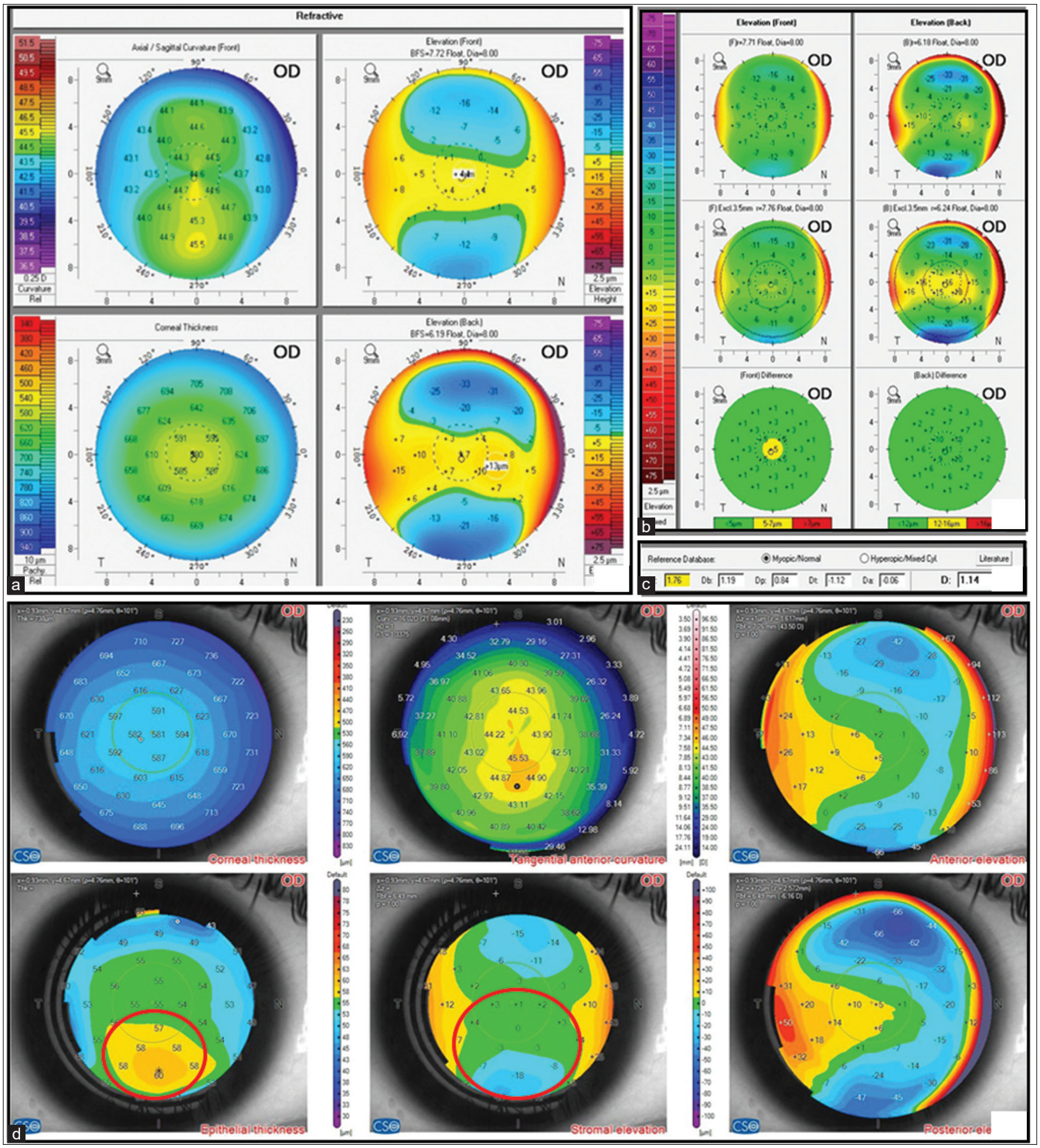

Figure 5: OD Refractive 4 map showing an asymmetric bowtie pattern with inferior steepening (a), Normal BAD-D, (b) Suspicious Df 1.76 (c), and (d) OD MS-39 6 map – Epithelial map showing a an increased epithelial thickness with no obvious stromal elevation and posterior elevation in the area corresponding to the inferior steepening (red circles)

no evidence of stromal or posterior elevation, this patient was planned for a refractive procedure: PRK being the treatment of choice.

Case 7: The refractive 4 map on Pentacam HR of a 27-year-old-female revealed an asymmetric bowtie pattern with inferior steepening, no posterior elevation [Fig. 7a] and a normal BAD-D OD [Fig. 7b]. As she wished to undergo refractive surgery an AS-OCT for epithelial mapping was performed. The 6 map of MS-39 did reveal an area of epithelial irregularity corresponding to the area of steepening. However, the area of posterior and stromal elevation on MS39 did not coincide with the area of steepening [Fig. 7c]. Hence, this suggests that a suspicious topography on axial/tangential

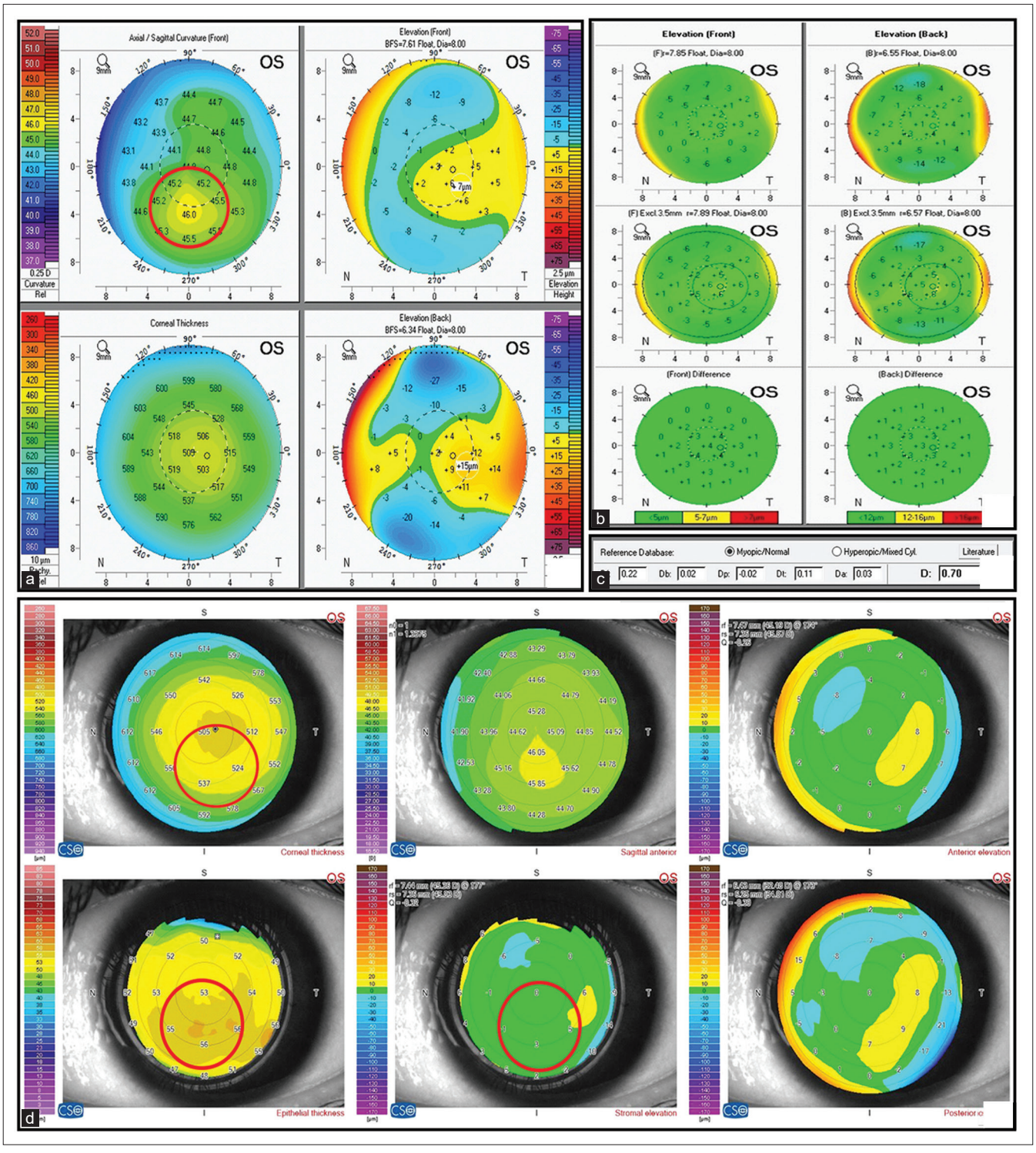

Figure 6: OS Refractive 4 map on Pentacam HR showing inferior steepening on the axial/sagittal map (a) with an normal BAD-D display ((b and c). (d) OS MS-39 6 map scan showing an area of increased epithelial thickness inferiorly with no stromal elevation (red circles)

curvature map could be because of epithelial issues and not an underlying disease. Such a patient can be posted for PRK Xtra.

Role of MS 39-based epithelial and stromal maps in assessing true progression of KC

Case 8: A 22-year-old female, who was a known case of KC OD, underwent corneal topography on Pentacam HR. Her comparative examination 4 months apart showed progression (three points of steepening in the cone area -1.8, -1.9, -2.7) [Fig. 8a]. MS-39 comparative maps revealed areas of epithelial hypertrophy [Fig. 8b] around the area of thinning (donut sign) on the epithelial maps, and an increase in the stomal and posterior elevation was documented between the two visits [Fig. 8b]. Hence, OD CXL was planned.

Case 9: A 30-year-old male, who was a known case of KC OD, underwent corneal topography 3 months and 9 days apart as he was under observation. The comparative map on the Pentacam showed progression (three points of steepening in the -0.7, -0.7, -0.7) [Fig. 9a]. However, contrary to the previous case (Case 8), the MS 39 comparative map shows no evidence of progression on stromal and posterior elevation comparative map and shows presence of the epithelial remodeling in the area corresponding with cone on the Pentacam [Fig. 9b]. This is a case of apparent progression as per the Pentacam comparative map; however, the MS39 comparative map shows that epithelium has become thicker in the cone area between the two visits, which is contrary to the donut sign where the epithelium over the cone is thinner. Also, since the stromal and posterior elevation comparative map is stable, the apparent progression on the Pentacam comparative map is due to the epithelial remodeling. Thus, this is a case of pseudoprogression because of epithelial changes, and the patient can be kept under observation.

Role of epithelial mapping in identifying the masquerades of KC

Case 10: A case of epithelial hyperplasia masquerading as OS suspicious topography. If we just go by the topography [Fig. 10a] in this case, a diagnosis of subclinical KC OS can be made since the patient complains of ghosting of images with BCVA of 20/20. However, epithelial map on RTVue and MS-39 map does reveal epithelial hyperplasia in the central and superior quadrant [Fig. 10b and c]**.** The MS-39 stromal map shows no elevation and no posterior elevation [Fig. 10 c], thus confirming that it is purely epithelial hypertrophy and the patient does not have a suspicious topography.

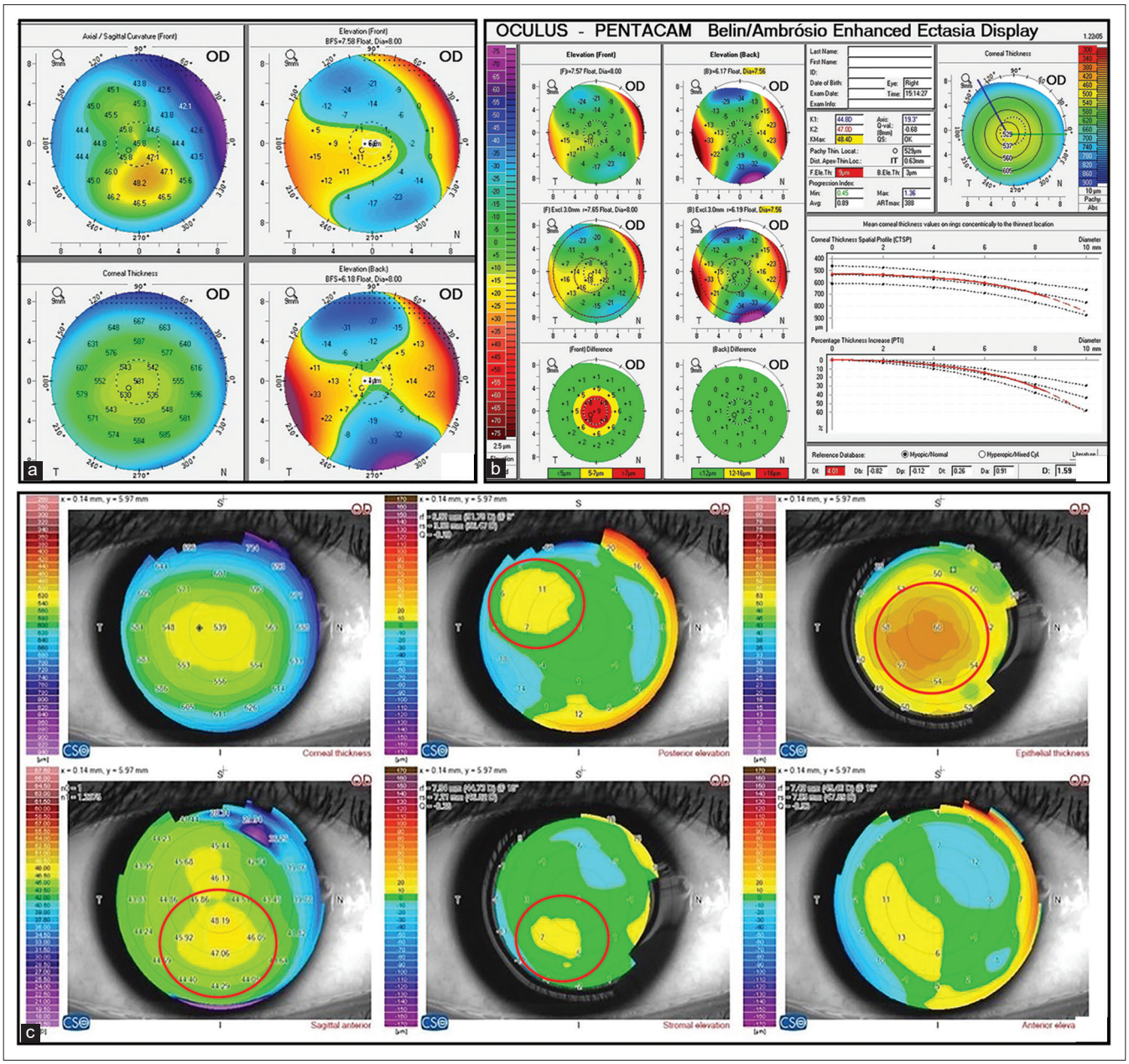

Figure 7 : OD axial/sagittal map showing asymmetric bowtie pattern with inferior steepening (a). Normal BAD-D examination (b)**.** (c) OD MS-39 6 map scan showing epithelial irregularity corresponding to the area of steepening on sagittal map. However, the area of posterior and stromal elevation on MS-39 does not coincide with the area of steepening (red circles)

This case highlights the advantages of the MS-39, which apart from tangential and sagittal anterior curvature maps provides separate ET and stromal elevation map over a 9-mm zone. Stromal elevation map is a novel tool to a refractive surgeon, as in ectatic disorders, the true pathology lies in the stroma and thus helps in early detection of pre/subclinical cases.

Key Points

- ET aids in differentiating the suspicious from normal cases and helps rule out subclinical corneal ectasia with certainty.
- It helps in customizing the type of refractive surgery on the basis of epithelial regularity and thickness to provide the most optimal outcomes.
- It allows the refractive surgeon to differentiate true regression from pseudoregression in patients who have undergone refractive surgery and aids in planning subsequent management.
- It helps to unmask any epithelial irregularities, which may be the cause for blurred vision postrefractive surgery.
- Comparative epithelial, stromal, and posterior elevation maps on MS 39 can aid in differentiating true-progression from pseudoprogression in KC especially in cases where the Pentacam comparative map shows an obvious progression.
- Measuring ET plays an important role in planning TCAT, TREK treatment for CXL, and evaluation of post CXL outcomes.

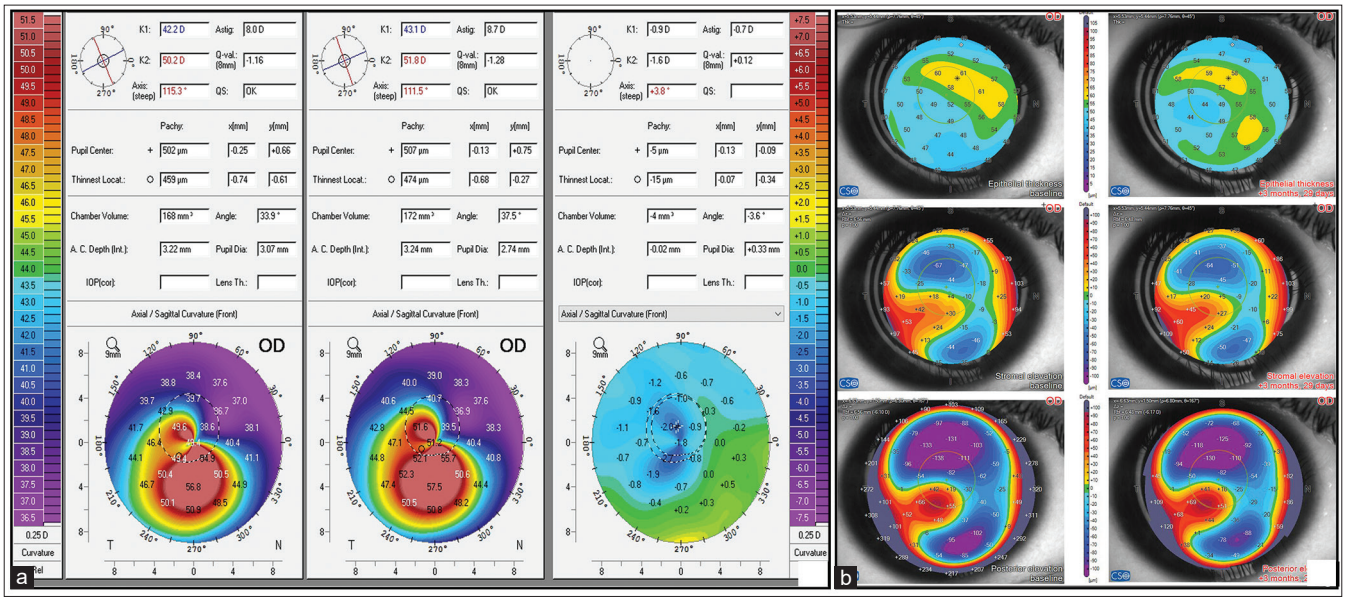

Figure 8: (a) OD comparative map on the Pentacam showing progression in right eye (three points of steepening in the cone area > 1D). (b) OD MS 39 comparative map shows an area of compensatory hypertrophy around the area of thinning (donut sign) on the epithelial maps and an increase in the stomal elevation map, documented two visits apart

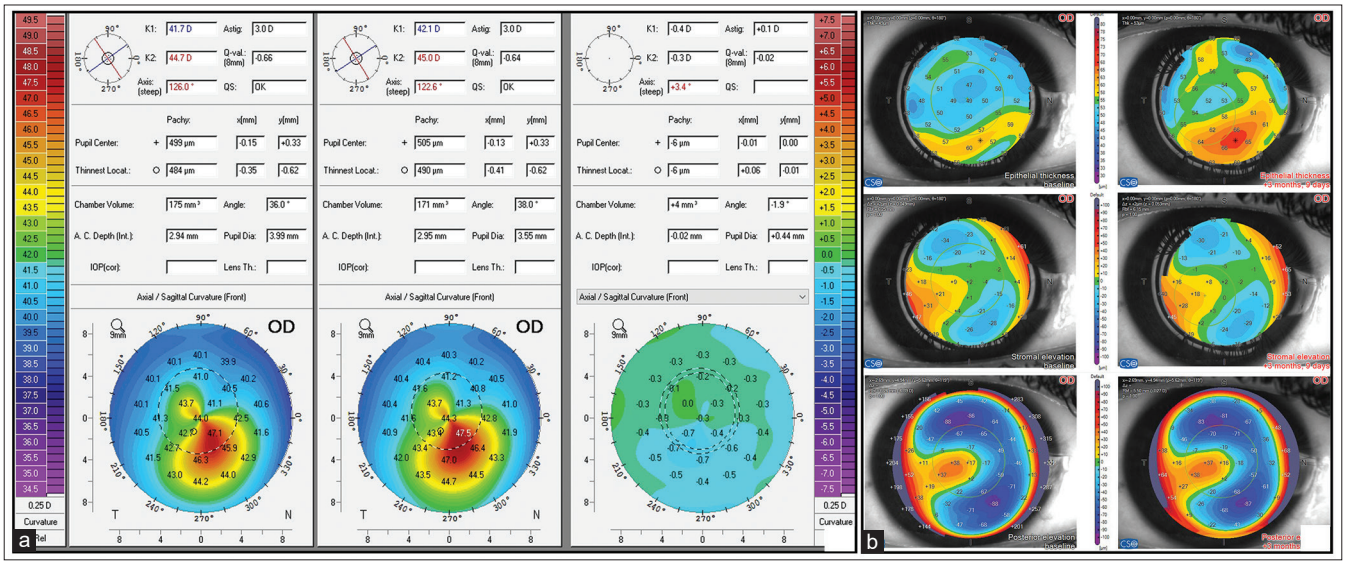

Figure 9: (a) OD comparative map on the Pentacam showing progression in the left eye (three points of steepening in the cone area >1D). (b) OD MS 39 Comparative epithelial map shows an obvious epithelial remodeling (b) with no evidence of progression on the stromal or posterior elevation comparative map (b)

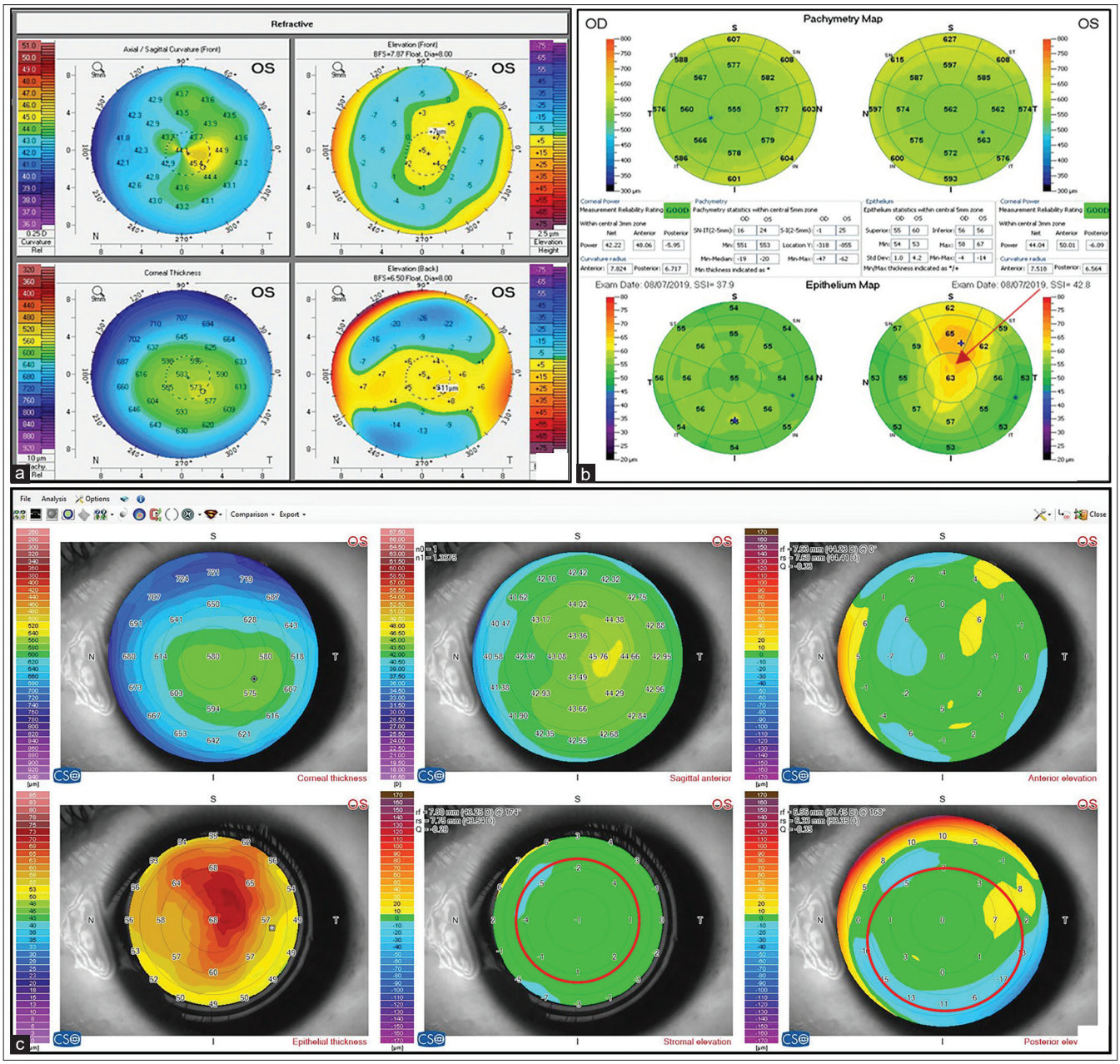

Figure 10: (a) OS Refractive 4 map on Pentacam HR showing subclinical keratoconus. (b) OS Pachymetric and epithelial map showing epithelial hyperplasia. (c) OS MS-39 epithelial map showing hyperplasia with no evidence of elevation on the stromal elevation map

Conclusion

In conclusion, epithelial mapping seems to be an important tool in a refractive surgeon's armamentarium for differentiating suspicious from normal corneas and identifying those with true progression of corneal ectasia. The authors believe that the addition of the epithelial map to the preoperative refractive surgery workup and in postoperative evaluation in case of suboptimal results will go a long way in making more accurate management decision, with improved outcomes.

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Conflicts of interest

There are no conflicts of interest.

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