Commentary: Predictors of outcomes after corneal collagen cross linking: Present, and future directions

Corneal collagen -cross-linking (CXL) as we know is a procedure to enhance the biomechanical strength of the cornea, thereby, halting the progression of corneal weakening in Keratoconus (KC). CXL has been in vogue for around two decades now, and along with newer contact lens developments, it has helped considerably in reducing the rates of keratoplasty. CXL is known to have complications such as post-CXL haze or scar, sterile infiltrates, failure, excessive flattening, and endothelial damage, among a few others. A lot of cornea practices across the world are confidently performing CXL as these complications are relatively low. However, in this upcoming era of personalized medicine, there are still a lot of unanswered questions about CXL. Predicting which kind of patients are likely to develop a haze or scarring or excessive or no flattening or failure post-CXL is not possible yet. We do not have the ability to predict the outcomes or complications after CXL to personalize care for different patients.

Variables affecting the assessment of outcomes

Before we delve into the known aspects that could determine the outcomes of CXL, it is very important to understand the variables that can affect the assessment of the outcomes. Assessment of topographic flattening or tomographic stability is highly dependent on the device used to measure and its repeatability of the topo/tomographic measurements.[1] Alterations in the tear film[2] and changes in corneal densitometry (haze)[3] are also important factors that alter the measurement of keratometry and pachymetry. Another well-understood variable that can alter the topography is epithelial morphology.[4] A combination of the above factors or even one of the above in isolation can falsely depict progression or mask progression post-CXL. During follow-ups, factors like the use of scleral lenses before imaging the cornea should also be taken into consideration as it can alter the topography and pachymetry.[5] In pediatric cases or patients with developmental delay, it may not be possible to obtain repeatable scans, and the overall clinical impression may be important in determining outcomes. Hence, it is important for both clinicians and researchers to at least perform three scans using their tomo/topographers, utilize ASOCT (anterior segment Ocular Coherence Tomography [OCT]), and also include clinical parameters whenever they need to ascertain a good or bad outcome following CXL.

Predicting Outcomes Post-CXL

At present, there are only a few factors that are known to predict visual and topographic outcomes following CXL. In general, it is known that CXL failure is higher among pediatric patients and those with active ocular allergy/eye rubbing.[6] Higher pre-operative keratometry (Kmax) and lower pre-op Best Corrected Visual Acuity (BCVA) have been shown to result in greater flattening and visual gain.[7] Central cones (Kmax within 3 mm from the center) usually have better flattening compared to peripheral cones (beyond 3 mm).[8] There have only been a few studies on the above, and the overall predictive ability is quite low.

Apart from patient factors, the type of CXL is also known to help in predicting outcomes. Though all forms of epi-off CXL have been shown to halt progression, there are differences in visual and topographic outcomes. This is explained by the oxygen availability during CXL. A longer duration of UV time ensures better O2 availability/replenishment compared to a shorter duration. Even if the total energy is the same, the standard Dresden protocol (3 mW/cm^2) for 30 min produces better flattening than the accelerated protocols. Among the accelerated protocols, studies have shown that reducing the fluence time to less than 5 min may not lead to good CXL outcomes.[9]

Future Directions

Research in the last decade has brought about so many newer perspectives to understanding CXL outcomes from a molecular and ultrastructural imaging point of view. Pre-operatively higher levels of tear inflammatory mediators like MMP9 (Matrix metalloproteinases) and certain interleukins correlate with poorer keratometric flattening and visual outcomes post-CXL.[10] Specific systemic inflammatory markers have also been shown to have a good predictive ability for KC.[11] Ocular levels of endogenous cross-linking enzyme Lysyl oxidase (LOX) have a positive correlation with keratometric flattening.[12] LOX

enhancer eye drops are now under investigation,[13] and they could be utilized in a customized way in patients with lower ocular LOX levels to obtain better keratometric and visual outcomes post-CXL. Other newer biomarkers of oxidative phosphorylation and metabolomic markers are being studied concerning KC and progression.[14] Newer point-of-care diagnostic biomarkers kits are being studied that can help assess tear levels of several of the above molecular markers at the bedside without the need for costly molecular laboratories. Ultrastructural collagen density and orientation analysis using newer polarization-sensitive OCT will also be an important predictor of topographic outcomes soon.[10,15]

Overall, in this era of artificial intelligence and big data, a combination of the above biomarkers will pave the way for personalized medicine in the field of KC and CXL. This will help in customizing the approach to managing KC in different patient sub-groups.

Vaitheeswaran Ganesan Lalgudi[1,2], Shakeel Qazi[1], Kashif Baig[1], Rohit Shetty[3]

[1]Department of Cornea, Precision Cornea Centre, Ottawa, Ontario, Canada, [2]Department of Cornea, External Disease and Refractive Surgery, The Ottawa Hospital (TOH), University of Ottawa Eye Institute, The Ottawa Hospital, Ontario, Canada, [3]Department of Cornea and Refractive Surgery, Narayana Nethralaya Eye Hospital, Bangalore, Karnataka, India

Correspondence to: Dr. Vaitheeswaran Ganesan Lalgudi, Department of Cornea, External Disease and Refractive Surgery, University of Ottawa Eye Institute, The Ottawa Hospital, Ottawa - K1H 8M2, Ontario, Canada.
E-mail: kanthjipmer@gmail.com

References

1. Kundu G, Shetty R, Ranade R, Trivedi D, Lalgudi VG, Nuijts R, *et al*. Repeatability and agreement of a new scheimpflug device and a Hartmann-Shack aberrometer with a ray-tracing aberrometer in normal, keratoconus, and CXL groups. J Refract Surg 2022;38:201-8.
2. Kundu G, Shetty R, Khamar P, Gupta S, Mullick R, Ganesan VL, *et al*. Impact of tear optics on the repeatability of Pentacam AXL wave and iTrace in measuring anterior segment parameters and aberrations. Indian J Ophthalmol 2022;70:1150-7.
3. Shetty R, Agrawal A, Deshmukh R, Kaweri L, Rao HL, Nagaraja H, *et al*. Effect of post crosslinking haze on the repeatability of Scheimpflug-based and slit-scanning imaging devices. Indian J Ophthalmol 2017;65:305-10.
4. Gupta K, Lalgudi VG, Arora V, Gupta S, Khamar P. Epithelial remodelling masquerading as keratoconus progression: An interesting case report. Indian J Ophthalmol 2020;68:3053-7.
5. Kumar M, Shetty R, Lalgudi VG, Khamar P, Vincent SJ, Atchison DA. The effect of scleral lenses on vision, refraction and aberrations in post-LASIK ectasia, keratoconus and pellucid marginal degeneration. Ophthalmic Physiol Opt 2021;41:664-72.
6. Lalgudi VG, Nischal KK. Pediatric corneal collagen cross-linking for keratoconus: Not an experimental procedure. J AAPOS 2019;23:63-5.
7. Chan TC, Tsui RW, Chow VW, Lam JK, Wong VW, Wan KH. Accelerated corneal collagen cross-linking in progressive keratoconus: Five-year results and predictors of visual and topographic outcomes. Indian J Ophthalmol 2022;70:2930-5.
8. Mimouni M, Sorkin N, Trinh T, Group KCS, Hatch W, Singal N. Central versus paracentral cone location and outcomes of accelerated cross-linking in keratoconus patients. Eye (Lond) 2021;35:3311-7.
9. Shetty R, Pahuja NK, Nuijts RM, Ajani A, Jayadev C, Sharma C, *et al*. Current protocols of corneal collagen cross-linking: Visual, refractive, and tomographic outcomes. Am J Ophthalmol 2015;160:243-9.
10. Lalgudi VG, Shetty R, Nischal KK, Ziai S, Koaik M, Sethu S. Biochemical and molecular alterations and potential clinical applications of biomarkers in keratoconus. Saudi J Ophthalmol 2022;00.
11. Elbeyli A, Kurtul BE. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio levels are associated with keratoconus. Indian J Ophthalmol 2021;69:1725-9.
12. Shetty R, Rajiv Kumar N, Pahuja N, Deshmukh R, Vunnava K, Abilash VG, *et al*. Outcomes of corneal cross-linking correlate with cone-specific lysyl oxidase expression in patients with keratoconus. Cornea 2018;37:369-74.
13. Molokhia S, Muddana SK, Hauritz H, Qiu Y, Burr M, Chayet A, *et al*. IVMED 80 eye drops for treatment of keratoconus in patients-Phase 1/2a. Invest Ophthalmol Vis Sci 2020;61:2587.
14. Nazifova-Tasinova N, Radeva M, Galunska B, Grupcheva C. Metabolomic analysis in ophthalmology. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2020;164:236-46.
15. Beer F, Patil RP, Sinha-Roy A, Baumann B, Pircher M, Hitzenberger CK. Ultrahigh resolution polarization sensitive optical coherence tomography of the human cornea with conical scanning pattern and variable dispersion compensation. Appl Sci (Basel) 2019;9:4245.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Access this article online

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_882_22

Cite this article as: Lalgudi VG, Qazi S, Baig K, Shetty R. Commentary: Predictors of outcomes after corneal collagen cross linking: Present, and future directions. Indian J Ophthalmol 2022;70:2937-8.