INPLASY

Natural History and Progression of Untreated Keratoconus: An Updated Systematic Review and Meta-Analysis

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Tsai, TH; Hsu, JH; Tsai, CL.

Corresponding author:
Tsung-Hsien Tsai

drtsaith@gmail.com

Author Affiliation:
Chang Gung Memorial Hospital, Keelung, Taiwan.

ADMINISTRATIVE INFORMATION

Support - N/A.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202520005

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 February 2025 and was last updated on 2 February 2025.

INTRODUCTION

Review question / Objective To provide an updated and comprehensive systematic review and meta-analysis that characterizes the natural progression of untreated keratoconus by quantifying longitudinal changes in clinical and imaging parameters—including corneal curvature, pachymetry, refractive error, visual acuity, higher-order aberrations, tomographic indices, and biomechanical properties—and to identify key predictors (such as age, ethnicity, and baseline corneal metrics) that influence disease progression over various follow-up intervals.

Rationale Patients diagnosed with keratoconus who have not undergone any therapeutic intervention (e.g., corneal crosslinking, intracorneal ring segments, keratoplasty).

Condition being studied Patients diagnosed with keratoconus who have not undergone any therapeutic intervention (e.g., corneal crosslinking, intracorneal ring segments, keratoplasty).

METHODS

Participant or population Patients diagnosed with keratoconus who have not undergone any therapeutic intervention (e.g., corneal crosslinking, intracorneal ring segments, keratoplasty).

Intervention The “exposure” in this context is the natural, untreated course of keratoconus. This includes the observation of disease progression over time without any active surgical or therapeutic intervention.

Comparator 1. Within-Subject Comparisons: Baseline measurements versus follow-up measurements at specified intervals (e.g., 12 months).
2. Subgroup Comparisons: Differences in progression based on baseline factors such as age, ethnicity, or baseline corneal parameters (e.g., Kmax, Kmean).

Study designs to be included A systematic review and meta-analysis that includes:

Randomized controlled trials (RCTs), Prospective observational studies, Retrospective observational studies, Case series (with >10 eyes), Studies must report longitudinal data on the progression of untreated keratoconus, with a minimum follow-up duration of 6 months.

Eligibility criteria
Inclusion Criteria:
1. Population:
- Studies enrolling patients diagnosed with keratoconus
- Participants must be untreated with any active surgical or therapeutic interventions for keratoconus (e.g., corneal crosslinking, intracorneal ring segments, keratoplasty).
2. Study Designs:
- Randomized controlled trials (RCTs)
- Prospective observational studies
- Retrospective observational studies
- Case series that include more than 10 eyes
3. Follow-up Duration:
- Studies must provide longitudinal data with a minimum follow-up period of 6 months to adequately capture the natural progression of the disease.

Information sources Pubmed/Medline, Embase, Web of Science, Scopus, Google Scholar.

Main outcome(s)
1. Corneal Curvature Parameters:
- Kmax
- Kmean
- K1 and K2
2. Pachymetry Measurements:
- Thinnest Corneal Thickness (TCT)
- Central Corneal Thickness (CCT)
3. Visual Acuity Outcomes:
Best-Corrected Distance Visual Acuity (BCVA)
Uncorrected Distance Visual Acuity (UDVA)
4. Refractive Outcomes:
Sphere, Spherical Equivalent, and Cylinder
5. Higher-Order Aberrations (HOAs):
Total HOAs and Coma Aberration
6. Scheimpflug Imaging–Derived Tomographic Indices:
7. Corneal Biomechanics
8. Others: Corneal Volume (CV), Endothelial Cell Density (ECD), Epithelial Thickness (ET).

Quality assessment / Risk of bias analysis 1. The Cochrane Risk of Bias tool was employed to assess RCTs.
2. A modified version of Joanna Briggs Institute critical appraisal checklist was used to assess non-RCTs.

Strategy of data synthesis The primary outcomes were synthesized as paired mean differences (with standard deviations) between baseline and follow-up measurements. A random-effects model was used to pool effect sizes. The inverse-variance method was applied for weighting individual studies.

Subgroup analysis Data were stratified by follow-up intervals and key baseline characteristics (e.g., age groups, ethnicity, baseline Kmax or Kmean) to assess differences in progression rates. These analyses helped to identify specific patient subgroups that may exhibit more rapid progression.

Sensitivity analysis Sensitivity analyses were performed to determine the robustness of the pooled estimates. Studies with high risk of bias or extreme effect sizes were excluded in sensitivity analyses to assess their influence on overall findings.

Country(ies) involved Taiwan.

Keywords Keratoconus, natural history, progression, untreated.

Contributions of each author
Author 1 - Tsung-Hsien Tsai.
Author 2 - Jui-Hung Hsu.
Author 3 - Chin-Ling Tsai.