

# Letter to: Corneal collagen cross-linking by sun exposure and high dose oral riboflavin: a multicentric longitudinal observational study

Carta para: Crosslinking de colágeno corneano por exposição solar e riboflavina oral em altas doses: um estudo observacional longitudinal multicêntrico

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Dear Editor,

We read with interest the article by Almodin et al. entitled “Corneal collagen cross-linking by sun exposure and high dose oral riboflavin: a multicentric longitudinal observational study”.<sup>(1)</sup> The authors conclude that “Oral riboflavin treatment combined with sun exposure appears to be effective in stabilizing the progression of keratoconus”.

While we commend their effort to address accessibility in keratoconus care, we believe the conclusions drawn from this study are not supported by either its design or by known pharmacokinetic and photochemical constraints.

## STUDY DESIGN LIMITATIONS

The authors report a retrospective, uncontrolled, multicenter series of 53 patients, with attrition to 42 patients after only 6 months. The absence of a control group or blinding means that natural variability, regression to the mean, or periods of spontaneous stability cannot be excluded as explanations for their findings. The authors acknowledge that “the absence of a control group and blinding, as well as the relatively small number of individuals followed, can be mentioned”.

Furthermore, the inclusion criteria did not specify progressive keratoconus. Stabilization in eyes that may not have been progressing at baseline cannot be interpreted as a therapeutic effect. This omission further limits the validity of the conclusions.

These are not minor limitations, but fundamental barriers to establishing causal efficacy.

## OUTCOME MEASURES AND CONFOUNDERS

The study relies exclusively on keratometric measurements without reference to repeatability thresholds or established progression criteria. Reported changes were small, sporadic, and in several cases not statistically significant. Importantly, patients were instructed to avoid eye rubbing and received anti-allergic therapy. Both interventions can independently reduce disease progression, yet these confounders are not disentangled from the purported effects of oral riboflavin and sunlight.

## MECHANISTIC IMPLAUSIBILITY

The premise that oral riboflavin combined with ambient sunlight could induce corneal cross-linking is contradicted by controlled translational evidence. In a prospective randomized rabbit study (Torres-Netto, submitted), we quantified mean stromal riboflavin concentrations after 14 days of oral riboflavin. The concentration was more than 400-fold lower than the concentration typically achieved with topical instillation in clinical CXL.

At these concentrations, the absorbed UVA fluence from sunlight was three orders of magnitude below that delivered in the Dresden protocol. Biomechanical testing confirmed the following: uniaxial extensometry showed no increase in stiffness, and optical coherence tomography elastography revealed significantly higher posterior strain in treated eyes (5.51‰ vs. 3.98‰,  $p = 0.039$ ), consistent with softening rather than stiffening.

## ENVIRONMENTAL VARIABILITY

The article does not address the massive variations in sunlight exposure that occur depending on the angle of incidence, the time of year, and the presence of cloudy or sunny days. Patients were instructed to take daily walks in the sun without a cap, sunglasses, or sunscreen, yet the actual ocular exposure would have varied considerably between individuals. Such variability has long been recognized in photobiological research, where even in the 1980s and 1990s attempts to standardize natural light exposure proved almost impossible. Without precise dosimetry, attributing any keratometric stability to sunlight-mediated cross-linking is speculative at best.

We are concerned about the reliance on anecdotal reports in the manuscript. The authors' observational article cites case reports and meeting abstracts as supportive evidence. For example, it notes that "Jarstad et al. conducted a report of three cases... where all individuals treated with high doses of oral riboflavin and sunlight exposure showed flattening of the corneal curvature". However, such anecdotal observations cannot substitute for biomechanical validation or controlled clinical trials, particularly when the underlying pharmacokinetics render the proposed mechanism implausible.

We share the authors' concern for equitable access to keratoconus treatment. However, suggesting that oral riboflavin and daily sunlight may stabilize disease risks delaying or displacing corneal cross-linking, the only intervention with proven efficacy to halt progression. The potential for harm is considerable if patients forego timely CXL based on unsupported claims.

While the intention to expand access to keratoconus therapy is laudable, the claim that oral riboflavin and sunlight stabilize keratoconus is not supported by controlled experimental data. Rigorous translational evidence demonstrates that oral riboflavin yields stromal concentrations far too low for cross-linking, and biomechanical testing shows no stiffening effect. The additional, uncontrolled variability of natural sunlight further undermines the plausibility of this approach. Until randomized controlled trials demonstrate otherwise, this regimen should not be promoted as a therapeutic alternative.

## AUTHORS' CONTRIBUTION

All authors actively contributed to the production of the manuscript

## REFERENCE

1. Almodin EM, Almodin F, Almodin J. Corneal collagen cross-linking by sun exposure and high dose oral riboflavin: a multicentric longitudinal observational study. *Rev Bras Oftalmol.* 2025;84:e0036.