Oral riboflavin, sunlight exposure, and keratoconus care: prudence, not passivity

Riboflavina oral, exposição à luz solar e cuidados com o ceratocone: prudência, não passividade

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The data that support the findings of this study are not openly available but are available from the corresponding author upon reasonable request.

Conflict of interest:
Dr. Ambrósio and Dr. Salomão are associated with B2n3™, an oral nutritional supplement containing riboflavin, omega-3 essential fatty acids, and vitamin D. B2n3™ (www.b2n3.com.br) is an adjunctive nutritional supplement; it is not corneal cross-linking, is not a substitute for cross-linking, and no claim is made here regarding any specific commercial formulation. This disclosure is directly relevant and requires rigor in distinguishing biological plausibility, hypothesis generation, and clinical recommendation.

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"If we begin with certainties, we shall end in doubts; but if we begin with doubts, and are patient in them, we shall end in certainties."
Francis Bacon (1561-1626)

Dear Editor,

We commend the observational report by Almodin et al.,[1] the critical letter by Torres-Netto et al.,[2] and the response by Almodin et al.[3] This discussion is valuable because both perspectives aim to protect patients: one, by exploring a potentially accessible adjunctive strategy, and the other, by preserving the evidentiary standards required before any approach is presented as disease-modifying treatment.

The fundamental clarification is conceptual. The expression "oral corneal cross-linking" or "oral corneal cross-linking" is inadequate because it implies mechanistic and clinical equivalence to corneal cross-linking (CXL). Oral riboflavin with ambient sunlight has not been shown to halt the objective progression of keratoconus. At the same time, this should not close the comprehensive discussion of nutritional supplementation in keratoconus. These are different questions: oral riboflavin as a substitute for CXL is unsupported. Nutritional supplementation as part of individualized clinical care, allergy control, ocular-surface optimization, and antioxidant support is biologically plausible and deserves responsible investigation.

This distinction aligns with the broader paradigm shift in ectasia care. Modern management is no longer a binary choice between observation and surgery, but an individualized treatment based on diagnosis, staging, prognosis, patient behavior, ocular surface status, and documented progression.[4] It also reflects the persistent paradoxes and controversies of keratoconus care.

Benjamin Franklin's aphorism that "an ounce of prevention is worth a pound of cure" is appropriate. In keratoconus, prevention means acting early enough to halt ectatic progression before meaningful visual deterioration, irregular astigmatism, scarring, or contact lens intolerance develop. Yet, prevention must not be confused with indiscriminate intervention. The Hippocratic aphorism *Primum non nocere* cuts in two directions at once: we must avoid the harm of doing too much in a stable eye, and the harm of withholding or delaying what has been proven to work in a progressing ectasia case. Therefore, when treatment is needed, it should not be delayed. When it is not needed, it should be reconsidered, because every intervention has a purpose, cost, risk, harm, and a defined objective.[5,6]

DOSE, PURPOSE, AND PATIENT SELECTION

Paracelsus' dictum that the dose separates poison from remedy is useful here, applied beyond a slogan. Modern toxicology reminds us that the decisive variables are not merely the substance, but dose, timing, susceptibility, exposure assessment, and individual biological response.[7] Applied to CXL, the same photochemical principle may be therapeutic when delivered with adequate dose and indication, insufficient when delivered weakly or variably, and harmful when delivered without proper indication.

The practical sequence is, therefore, what is being delivered, how much reaches the corneal stroma, who is being treated, when is it delivered in the course of disease, and how is it performed? Conventional epithelium-off CXL using the Dresden protocol is a controlled intervention: topical stromal riboflavin saturation followed by calibrated ultraviolet-A irradiation.[8] Professor Theo Seiler's 2021 guest editorial appropriately returned the discussion to corneal biomechanics, eye rubbing, and the need to understand how much stiffening is achieved, in whom, and with what protocol.[9]

CXL-related complications are uncommon but real, and this matters ethically. The 2021 JCRS consultation on stromal scar after CXL described a 32-year-old patient with decreased vision due to scarring and irregular astigmatism after CXL in one eye, while the fellow untreated eye had no definitive ectasia warning signs.[10] In the March consultation response, it was emphasized that, without pre-CXL clinical data, judgment about indication was not adequate; nevertheless, the case illustrates why patient education, allergy control, and eye-rubbing avoidance may be the best option in some mild or suspect cases, whereas timely CXL remains indispensable when progression is objectively documented.[11] The goal is to match the treatment to the individualized characteristics of the patient, considering the risk of CXL.[12]

SIGNAL, NOT PROOF

The ex vivo work by Torres-Netto et al. showed that direct sunlight can induce measurable stiffening in de-epithelialized, riboflavin-soaked porcine corneas under controlled conditions.[13] This is an important proof of concept, but it should not be extrapolated to mean that oral riboflavin plus ambient sunlight produces clinically meaningful in vivo CXL. The observational series by Almodin et al.[1] and the prospective cohort by Campêlo et al.[14] suggest a possible clinical signal and should be respected as hypothesis-generating reports.[1,14] Their limitations remain decisive, including the lack of randomized controls, incomplete confirmation of progression at baseline, unquantified sunlight exposure, and co-interventions such as rubbing avoidance and allergy treatment.

The Swiss Air Force anecdote attributed to Professor Seiler, in which pilots allegedly used high-dose dietary riboflavin and direct sunlight exposure during vacation periods, does not prove efficacy and should not be treated as a clinical protocol.[15] However, it deserves more scientific attention than casual dismissal. It is a reason to study the hypothesis rigorously, not a reason to replace proven treatment.

STABLE ECTASIA AND ACTIVE CONSERVATIVE CARE

The absence of progression is not proof of therapeutic arrest. Stable ectasia without CXL has been described, including in asymmetric keratoconus.[16] More recently, most non-operated fellow eyes in an asymmetric keratoconus cohort remained tomographically and biomechanically stable under conservative management and multimodal surveillance, while a minority progressed and were referred for CXL.[17] Such data support active observation. They do not prove that supplementation halted the disease, especially when eye-rubbing avoidance, ocular surface control, and structured follow-up are applied simultaneously.

This is the central clinical paradox: CXL should be promptly performed once progression is confirmed or when risk warrants treatment, particularly in children or in rapidly progressing eyes.[18,19] But CXL should not become mandatory for every keratoconic eye at first diagnosis. Conservative management does not mean "no treatment". In fact, it includes education, control of allergies and ocular surface disease, behavioral modification, optimized glasses or contact lenses for visual rehabilitation, and objective multimodal monitoring.

Preventive care must also address the behavioral and public health dimensions of keratoconus. Eye rubbing remains an important potentially modifiable factor in the development and progression of corneal ectasia, reinforcing the need for patient education and behavioral intervention.[20] Awareness initiatives, such as the Violet June campaign, emphasize the importance of early recognition, appropriate referral, and prevention of avoidable visual impairment.[21] Nevertheless, gaps in public knowledge about keratoconus persist, underscoring the need for sustained educational strategies.[22]

Population-based screening research incorporating corneal tomography and biomechanics further highlights the importance of identifying keratoconus and associated risk factors before advanced clinical manifestations develop.[23] Together, these considerations support a proactive and individualized approach in which education, behavioral modification, early diagnosis, and multimodal surveillance are essential components of comprehensive keratoconus care.[4]

NUTRITIONAL SUPPLEMENTATION: DISTINCT FROM ORAL CORNEAL CROSS-LINKING

Nutrition is not just riboflavin. The second Global Consensus reached full agreement that keratoconus may be associated with low serum levels of vitamin D, zinc, copper, and selenium, an oxidant-antioxidant imbalance, and inflammation, all contributing to its pathogenesis. It was also agreed that oral riboflavin supplementation is not a substitute for conventional CXL.[19] In the CXL panel, oral riboflavin with sunlight was unanimously rejected as a replacement for CXL in progressive keratoconus. Moreover, oral riboflavin, vitamin D, lysyl oxidase/copper supplementation, and biomarker modulation were rejected as standalone treatments. If these are used, they should be adjuncts.[19]

Within these limits, nutritional supplementation should be considered as part of the clinical assessment and management conversation for every keratoconus patient. This does not mean prescribing the same supplement to all patients. It means actively looking for allergies, rubbing, ocular surface inflammation, nutritional deficiencies, systemic inflammatory context, and oxidative imbalance. Vitamin D deficiency should be identified and corrected when present; copper, zinc, selenium, and related antioxidant status may deserve assessment. Also, omega-3 essential fatty acids (n3-EFAs) may be useful as part of ocular surface and anti-inflammatory management, especially when dry eye or meibomian gland dysfunction coexists.[24]

In addition, Leça et al. proposed tear vitamin D, Nrf2, and ferritin as a potential biomarker for keratoconus, supporting the concept that molecular information may eventually complement tomography, biomechanics, epithelial mapping, and clinical history in individualized risk stratification.[25] Additional studies linking keratoconus to serum vitamin D deficiency, oxidative stress pathways, and vitamin D supplementation in deficient adolescents reinforce biological plausibility, but still do not establish nutritional therapy as a substitute for CXL in progressive ectasia.[26-28]

Thus, nutritional supplementation in keratoconus is, at present, not yet standardized science. It may play a legitimate adjunctive role in controlling inflammation, supporting ocular-surface health, correcting deficiencies, and possibly reducing oxidative imbalance. But it should be framed as supportive clinical care, not as "oral corneal cross-linking", not as a proven disease-stabilizing treatment, and not as a reason to delay CXL when progression is objectively documented.

A RESPONSIBLE PATH FORWARD

The defensible position is neither therapeutic enthusiasm nor categorical dismissal. Oral riboflavin with sunlight should not be promoted as a proven alternative to CXL. Its biological plausibility, preliminary signals, and historical anecdotes justify rigorous prospective study with objective progression criteria, standardized allergy and eye-rubbing management, quantified sunlight or ultraviolet exposure, adherence documentation, and predefined rescue criteria for conventional CXL.

Until stronger evidence becomes available, the clinical message should be straightforward: educate all patients; treat allergies and ocular surface inflammation. Prevent eye rubbing and ocular trauma; assess nutritional and inflammatory factors when appropriate; monitor with validated multimodal criteria; perform CXL when progression is objectively documented; and avoid CXL when unnecessary. Oral riboflavin should not be framed as "oral corneal cross-linking", but nutritional supplementation may eventually have a defined adjunctive role in comprehensive keratoconus care.

AUTHORS' CONTRIBUTION

Renato Ambrósio Jr.: Conceptualization, methodology, literature review, writing – original draft, writing – review and editing, supervision, and final approval. Nelson Batista Sena Junior: Literature review, critical analysis, writing – review and editing, and final approval. Nycholas Tavares: Literature review, critical analysis, writing – review and editing, and final approval. Louise Pellegrino-Esporcatte: Literature review, critical analysis, writing – review and editing, and final approval. Marcella Q. Salomão: Conceptualization, literature review, critical analysis, writing – review and editing, supervision, and final approval. All authors critically reviewed the manuscript, approved the final version, and agreed to be accountable for its content.

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