E-ISSN 2250-0944

ISSN 2250-1150
doi: 10.48047/ijprt/15.02.477

Research Article

Impact of Serum Ferritin Levels on Corneal Epithelial Healing in Recurrent Corneal Erosion Syndrome

Asad Ali Khan[1], Muhammad Amjad[2], Junaid Afsar Khan[3], Faiza Tariq[4], Abdul Rafe[5], Muhammad Imran Ali[6]

[1] Senior Registrar, Department of Ophthalmology, Wah Medical College.
[2] Consultant Ophthalmologist, Ophthalmology Department, Al-Shifa Eye Trust Hospital, Rawalpindi.
[3] Associate Professor, Department of Ophthalmology, CMH Lahore Medical College.
[4] Medical Officer, Tariq Eye Hospital, Khanpur.
[5] Assistant Professor of Eye, Avicenna Medical College, Lahore.
[6] Consultant Ophthalmology, King Khalid Hospital, Al-Majmaah, Kingdom of Saudi Arabia.
Corresponding author: Asad Ali Khan

Abstract: This observational study hypothesized that systemic iron status — as reflected by serum ferritin — influences the rate of corneal epithelial healing in eyes with Recurrent Corneal Erosion Syndrome (RCES). Thirty adult patients presenting with acute RCES episodes were recruited and grouped according to baseline serum ferritin: low (< 30 ng/mL), normal (30-150 ng/mL), and high (> 150 ng/mL). Corneal epithelial defects were induced by routine minor superficial debridement (standardized 3 mm epithelial abrasion) in the clinically affected eye; healing was monitored daily with fluorescein staining until re-epithelialization. The primary outcome was time to complete epithelial closure. Secondary outcomes included healing quality (smooth re-epithelialization without persistent defects) and recurrence rate over 3 months. Mean healing time in the low-ferritin group was significantly longer (7.6 ± 1.2 days) compared to the normal (5.1 ± 1.0 days) and high-ferritin (5.4 ± 1.1 days) groups ($p = 0.003$). The proportion of patients achieving smooth epithelium by day 10 was 40% in low, vs. 87% and 80% in normal and high groups, respectively ($p = 0.02$). Recurrence within 3 months occurred in 3/10 (30%) low-ferritin eyes versus 1/10 (10%) in normal and 1/10 (10%) in high group ($p = 0.15$). These findings suggest that low serum ferritin delays epithelial healing in RCES and may predispose to recurrent erosions. The data support a novel link between systemic iron deficiency and impaired corneal epithelial repair, indicating the potential value of assessing and correcting iron stores in RCES management.

Keywords: recurrent corneal erosion, serum ferritin, corneal epithelial healing

Introduction: The cornea, as the transparent anterior most component of the eye, forms a critical barrier against environmental insults and contributes the majority of the eye's refractive power. Its outermost layer — the corneal epithelium — is particularly vulnerable to mechanical or traumatic disruption yet normally undergoes rapid regeneration to restore barrier integrity and maintain optical clarity. Efficient re-epithelialization involves a coordinated sequence of epithelial cell migration, proliferation, differentiation, and eventual formation of stable adhesion complexes to the basement membrane and underlying stroma. However, in certain pathological or predisposed eyes, this process may be impaired, leading to repeated breakdown of the epithelium, a condition recognized as Recurrent Corneal Erosion Syndrome (RCES). RCES is characterized by recurrent painful episodes, often upon awakening, arising from defective adhesion between basal epithelial cells and the underlying basement membrane or Bowman's layer, leading to repeated detachment of the epithelium under eyelid shear stress. The clinical burden includes pain, photophobia, tearing, and blurred vision, with repeated episodes potentially compromising corneal integrity and visual performance.[1-4]

Current management strategies for RCES focus primarily on mechanical protection (lubricants, bandage contact lenses), inhibition of proteolytic degradation (e.g., matrix metalloproteinase inhibitors), and in more recalcitrant cases, surgical interventions (e.g., superficial keratectomy with diamond-burr polishing, phototherapeutic keratectomy) to remodel the basement membrane and strengthen epithelial adhesion. While many of these approaches offer symptomatic relief or reduce recurrence risk, a subset of patients continues to experience delayed epithelial healing or recurrent erosions, suggesting that additional factors — beyond local mechanical and structural abnormalities — may modulate corneal epithelial repair. Among these, little attention has been paid to systemic metabolic factors, including iron status, which might influence corneal cell biology.[5-9]

Iron is an essential trace element critical for numerous cellular processes, including mitochondrial respiration, DNA synthesis, and cell proliferation. However, dysregulation of iron homeostasis can be deleterious: excess labile iron can catalyze formation of reactive oxygen species (ROS) via Fenton chemistry, leading to oxidative damage, lipid peroxidation, and cell death; conversely, iron deficiency can impair energy-dependent processes, compromise cellular repair capacity, and diminish antioxidant defenses. In many tissues, optimal wound healing requires a delicate balance

in iron levels: low iron may impair cell proliferation and matrix synthesis, while iron overload may cause oxidative stress, chronic inflammation, or ferroptosis. In non-ocular tissues such as skin, disturbed iron balance has been associated with delayed wound closure, impaired fibroblast proliferation, and dysfunctional macrophage responses.[10-12]

Within the eye, iron metabolism is increasingly recognized as important in ocular surface and corneal physiology. Corneal epithelial cells express ferritin — the primary intracellular iron storage protein — which can localize to the nucleus and is thought to protect nuclear DNA from oxidative damage induced by UV exposure or environmental ROS. This nuclear ferritin is transported by a cornea-specific protein, ferritoid, highlighting a unique, tissue-specific iron-regulatory mechanism. Disruption of ferritin processing, or perturbations in iron regulation, have been shown in vitro to impair corneal epithelial barrier integrity and viability, especially under oxidative or toxic stress, with features including lipid peroxidation and cell death; moreover, inhibition of ferroptosis, an iron-dependent form of cell death, can enhance corneal epithelial wound healing in experimental models. Recent proteomic analyses in human ocular tissues also identify iron metabolic proteins — including ferritins and transferrin — as altered in disease states characterized by oxidative stress and structural corneal changes. These observations suggest that systemic iron status, reflected by serum iron-binding proteins such as ferritin, may influence corneal epithelial health and its capacity for repair following insult.

Despite this biologic plausibility, to date no clinical study has evaluated the relationship between systemic iron stores (serum ferritin) and corneal epithelial healing in RCES. Given the dependency of epithelial repair on cell proliferation, migration, and oxidative stress regulation, systemic iron deficiency could plausibly impair corneal healing and predispose to recurrent erosions. Conversely, normal or high iron stores may support robust epithelial repair by supplying necessary iron for metabolic needs, while intracellular ferritin limits iron-mediated oxidative injury. This gap in knowledge represents an important unmet need, as identification of systemic modifiable risk factors would open novel avenues for adjunctive therapy in RCES beyond local mechanical or surgical measures.

Therefore, the present study aimed to investigate whether baseline serum ferritin levels are associated with the rate and quality of corneal epithelial healing following standardized minor

epithelial abrasion in patients with RCES. It was hypothesized that eyes of patients with low serum ferritin would demonstrate delayed healing compared to those with normal or high ferritin levels, and may show a higher risk of subsequent recurrent erosions. Establishing such a link would provide novel insight into the role of systemic iron homeostasis in corneal epithelial biology and potentially justify iron status assessment and correction as part of comprehensive RCES management.

Methodology: This prospective observational study enrolled adult patients (aged 18-65 years) presenting with symptomatic RCES at Wah medical college. Prior to enrollment, verbal informed consent was obtained, and the protocol adhered to the principles of the Declaration of Helsinki. Serum ferritin was measured at baseline using standard immunoassay; subjects were stratified into three groups based on ferritin level: low (< 30 ng/mL), normal (30–150 ng/mL), and high (> 150 ng/mL), thresholds chosen according to widely accepted clinical reference ranges. Sample size calculation was performed using Epi Info software: assuming a difference of 2.5 days in mean healing time between low and normal ferritin groups, a standard deviation of 1.2 days, power 80%, alpha 0.05, and equal group sizes, a minimum of 9 subjects per group was required; to account for drop-outs, 10 per group (total n=30) were enrolled. Inclusion criteria comprised: confirmed diagnosis of RCES (history of recurrent erosions, slit-lamp evidence, previous documentation), ability to consent, and absence of systemic anemia treatment. Exclusion criteria included: active ocular infection, previous ocular surgery within 6 months, systemic iron supplementation in last 3 months, known systemic inflammatory disease, diabetes mellitus, or ocular surface disease (e.g., severe dry eye, ocular rosacea) that could independently impair healing.

Each participant underwent a standardized superficial corneal epithelial abrasion in the clinically affected eye under topical anesthesia — a 3-mm central epithelial debridement was created using a sterile blade, following strict aseptic protocol. After abrasion, patients received a uniform postoperative regimen: preservative-free artificial tears q.i.d. and topical antibiotic prophylaxis for 5 days. No serum drops, bandage lenses, or adjunctive agents were used so as to isolate the effect of systemic iron status on intrinsic epithelial healing. Daily fluorescein staining with slit-lamp examination was performed until complete closure of the epithelial defect, defined as absence of fluorescein uptake. Patients were followed for 3 months to document any recurrence.

Primary endpoint was time (in days) to complete epithelial closure. Secondary endpoints included quality of healing (smooth epithelium without persistent defects) at day 10, and recurrence rate over 3 months. Data were analyzed using ANOVA to compare mean healing times between groups, and chi-square tests for categorical outcomes (healing quality, recurrence). A p-value < 0.05 was considered statistically significant.

Results

Table 1. Demographic and Baseline Characteristics of Study Groups

Parameter	**Low-Ferritin (n=10)**	**Normal-Ferritin (n=10)**	**High-Ferritin (n=10)**
Age (years), mean ± SD	42.3 ± 11.5	45.1 ± 9.8	43.7 ± 10.2
Gender (M/F)	6/4	5/5	6/4
Baseline serum ferritin (ng/mL), mean ± SD	22.4 ± 5.1	78.6 ± 25.4	183.2 ± 35.7

Table 2. Corneal Epithelial Healing Outcomes

Outcome	**Low-Ferritin**	**Normal-Ferritin**	**High-Ferritin**	**p-value**
Time to complete healing (days), mean ± SD	7.6 ± 1.2	5.1 ± 1.0	5.4 ± 1.1	0.003
Smooth epithelium at day 10, n (%)	4 (40%)	9 (90%)	8 (80%)	0.02
Recurrence within 3 months, n (%)	3 (30%)	1 (10%)	1 (10%)	0.15

Table 3. Healing Quality and Recurrence — Combined Outcome

Combined outcome (smooth healing by day 10 and no recurrence)	**Low-Ferritin**	**Normal-Ferritin**	**High-Ferritin**	**p-value**
Yes, n (%)	4 (40%)	9 (90%)	8 (80%)	0.04

Short explanation: Table 2 shows that the low-ferritin group had significantly delayed re-epithelialization compared to the normal and high ferritin groups. The proportion of eyes achieving smooth healing by day 10 was significantly lower in the low-ferritin group. Table 3 demonstrates that combined favorable outcome (smooth healing + no recurrence) was significantly less likely in low-ferritin eyes versus normal or high.

Discussion: The present findings reveal a significant association between low systemic ferritin levels and delayed corneal epithelial healing in patients with RCES. Eyes from subjects with low baseline ferritin exhibited a mean healing time markedly longer than those with normal or elevated ferritin, and were less likely to achieve smooth epithelial recovery by day 10. Moreover, overall favorable outcomes (healing without recurrence) were substantially less frequent in low-ferritin eyes. These observations suggest that systemic iron deficiency may impair the intrinsic capacity of corneal epithelium to regenerate efficiently after insult — a novel insight into the pathophysiology of RCES beyond local adhesion defects.[13-15]

The mechanistic plausibility of such a link is supported by emerging evidence on the role of iron metabolism in corneal biology. Corneal epithelial cells uniquely express nuclear ferritin, transported by a cornea-specific protein (ferritoid), which protects nuclear DNA from oxidative damage induced by ultraviolet light or environmental ROS; this nuclear ferritin is believed to guard against DNA damage during normal turnover or after injury. In systemic iron deficiency, reduced availability of iron may limit ferritin production, impair antioxidant defense, and compromise DNA repair, thereby hindering cell proliferation and migration necessary for wound closure. In addition, insufficient iron may impair energy production in corneal epithelial cells, slowing down the rapid metabolic demands of migration and proliferation required during healing.[16-18]

Conversely, although excess iron has been implicated in oxidative stress and tissue damage in other ocular pathologies (through iron-dependent reactive oxygen species generation), in the context of an acute, controlled epithelial abrasion as in this study, adequate iron stores appear beneficial — but not excessive to the point of overt toxicity. This suggests that a balanced iron status — enough to supply metabolic and proliferative demands, yet managed by adequate ferritin-mediated sequestration — may be optimal for corneal epithelial repair.[19-20]

Moreover, these findings may help explain previously unaccounted variability in healing outcomes and recurrence rates among RCES patients undergoing similar local treatments or surgical interventions: systemic factors such as iron deficiency may render some eyes less capable of prompt, stable re-epithelialization, predisposing them to persistent defects or recurrent erosions despite optimal local management. Recognizing systemic iron status as a modifiable risk factor expands the therapeutic paradigm of RCES beyond mechanical and surgical approaches to include metabolic evaluation and correction.

The study also fills a critical gap in the literature, as no prior clinical investigations have examined the influence of systemic iron stores on corneal epithelial healing. Given the well-documented role of iron metabolism and ferritin in other tissues' wound healing — and growing ocular research implicating iron dysregulation in corneal and refractive disease — this first clinical evidence opens a new research avenue linking systemic iron homeostasis to corneal health and wound repair.

However, several limitations deserve acknowledgment. The modest sample size and single-center design may limit generalizability; the artificial standardized epithelial abrasion may not fully replicate the complex microtrauma or spontaneous erosions experienced in typical RCES. Also, the use of systemic ferritin as surrogate for tissue iron availability may not fully reflect local corneal iron dynamics or ferritin expression. Further studies including tear film iron-related proteins, local ocular iron assays, and larger, multicenter cohorts are warranted to validate and extend these findings.

Conclusion: Low systemic ferritin levels are associated with significantly delayed corneal epithelial healing in RCES and lower rates of stable re-epithelialization without recurrence. These results highlight serum ferritin — and by extension systemic iron stores — as a potential modifiable risk factor in RCES management. Future studies should explore whether correcting iron deficiency improves healing outcomes and reduces recurrence, and investigate local corneal iron dynamics and ferritin expression in RCES.

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