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Targeting Inflammation in CKD-Related Anemia: The Emerging Role of Lactoferrin as an Adjunctive Therapy

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Abstract

Objective: Chronic kidney disease (CKD)-associated anemia is substantially driven by chronic inflammation, which promotes hepcidin upregulation, restricts iron availability, and impairs erythropoiesis. Conventional therapies, including erythropoiesis-stimulating agents and iron supplementation, primarily address erythropoietin deficiency and iron depletion but do not directly target the underlying inflammatory pathways. This narrative review evaluates the role of inflammation in CKD-associated anemia and examines the emerging potential of lactoferrin as an adjunctive therapeutic approach.

Methods: This narrative review was based on a literature search of PubMed, Scopus, and Google Scholar for articles published between January 2000 and March 2026, using combinations of the terms "chronic kidney disease," "anemia," "inflammation," "hepcidin," and "lactoferrin."

Results: Chronic inflammation contributes to CKD-associated anemia through interleukin-6-mediated hepcidin upregulation, ferroportin degradation, impaired iron absorption and mobilization, and cytokinemediated suppression of erythropoiesis. Lactoferrin, an iron-binding glycoprotein with anti-inflammatory, immunomodulatory, and iron-regulatory properties, may counter these mechanisms by reducing inflammatory signaling, modulating hepcidin expression, and improving functional iron availability. Clinical studies have generally reported improvements in hemoglobin, with several studies also reporting favorable changes in hepcidin levels and inflammatory markers, supporting the potential anti-inflammatory and iron-regulatory effects of lactoferrin.

Conclusion: Lactoferrin represents a promising adjunctive approach for inflammation-driven CKD-associated anemia, particularly functional iron deficiency. Its potential effects on the IL-6–hepcidin–ferroportin axis may complement established ESA and iron therapy.

Keywords: Chronic kidney disease, CKD-associated anemia, Hepcidin dysregulation, Inflammation, Lactoferrin

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INTRODUCTION

Chronic kidney disease (CKD) is characterized by structural or functional abnormalities of the kidneys, or a persistent decline in renal function defined by a glomerular filtration rate (GFR) below 60 mL/min/1.73 m² for a duration of at least three months, regardless of the underlying cause, in accordance with the Kidney Disease Outcomes Quality Initiative (KDOQI) classification [1]. CKD has emerged as a major global health challenge, currently affecting more than 800 million individuals — over 10% of the world's population. It has risen to become the 9th leading cause of death globally and ranks 12th in disability-adjusted life years (DALYs), and is projected to become the fifth leading cause of mortality by 2040 [2,3].

Over the past two decades, growing evidence has identified chronic inflammation as a central pathophysiological feature of CKD progression [4]. Persistent low-grade inflammation, arising from oxidative stress, hypoxia, cellular senescence, mitochondrial dysfunction, and accumulation of uremic toxins, contributes not only to renal injury but also to the high burden of CKD-related complications [5]. In patients requiring dialysis, persistent systemic inflammation contributes to the accelerated development of atherosclerosis, heightened cardiovascular risk, protein–energy wasting, and features of early biological aging. Despite advances in the understanding of inflammatory biology, strategies to effectively prevent or treat chronic inflammation in CKD remain limited [6].

Anemia represents one of the most common and clinically relevant complications of CKD and is associated with impaired quality of life, increased rates of hospitalization, heightened cardiovascular risk, and excess mortality. The development of anemia in CKD is multifactorial, arising from inadequate endogenous erythropoietin (EPO) synthesis, absolute and functional iron deficiency, reduced lifespan of circulating erythrocytes, and inflammation-mediated dysregulation of iron metabolism [7,8]. Inflammatory cytokines play a pivotal role in this process, particularly interleukin-6 (IL-6), which stimulates hepatic hepcidin expression through activation of the JAK–STAT3 signaling pathway. Elevated hepcidin levels promote ferroportin degradation, thereby limiting iron efflux from enterocytes and macrophages and resulting in functional iron deficiency despite preserved iron stores.

Although erythropoiesis-stimulating agents (ESAs) and iron supplementation remain the cornerstone of CKD anemia management, these therapies primarily address EPO deficiency and iron depletion. Importantly, they do not target the chronic inflammatory milieu responsible for hepcidin overproduction, iron sequestration, and impaired erythropoiesis. Consequently, inflammation-driven mechanisms often persist despite treatment, contributing to functional iron deficiency, variable hemoglobin responses, and ESA hyporesponsiveness. This therapeutic gap highlights the need for adjunctive strategies capable of modulating inflammation in addition to correcting iron and erythropoietic deficits [7].

In this context, lactoferrin has recently gained interest as a potential adjunctive therapeutic agent. Although clinical evidence of lactoferrin in anemia of CKD populations remains limited, early studies suggest that lactoferrin may reduce IL-6 levels, modulate hepcidin expression, and improve functional iron availability, mechanisms that directly address inflammation-mediated disturbances in iron metabolism. Considering these emerging data, the purpose of this review is to examine the role of inflammation as a central driver of anemia in CKD and to summarize the current evidence supporting lactoferrin as a potential adjunct therapy targeting both iron dysregulation and inflammation. This review focuses on adult and pediatric CKD populations across both dialysis-dependent and non-dialysis-dependent disease stages, with emphasis on inflammation-driven functional iron-deficiency anemia; post-transplant anemia and anemia unrelated to CKD are outside its scope.

LITERATURE SEARCH STRATEGY

A narrative literature search was conducted in PubMed, Scopus, and Google Scholar for articles published between January 2000 and March 2026, using combinations of the terms "chronic kidney

disease," "anemia," "inflammation," "hepcidin," and "lactoferrin." Reference lists of relevant articles were hand-searched for additional sources. Studies were included if they addressed the pathophysiology of inflammation-related anemia in CKD or reported clinical or mechanistic data on lactoferrin in CKD populations; non-English-language articles and studies without available full text were excluded.

EPIDEMIOLOGY AND BURDEN OF CKD

Prevalence of CKD

According to the Global Burden of Disease (GBD) 2023 estimates, approximately 788 million adults aged 20 years and older are affected by chronic kidney disease worldwide, compared to 378 million in 1990, reflecting a substantial escalation in global disease burden [3]. China and India account for the largest absolute disease burden, with 152 million and 138 million individuals affected, respectively [9]. In high-income regions, diabetes mellitus and hypertension account for more than two-thirds of CKD cases. A similar pattern is reported in India, where these conditions contribute to 40–60% of CKD prevalence [10]. The GBD 2023 analysis also identifies high body mass index and dietary risks, especially excess sodium intake, as major contributors to the rising global burden of CKD [2,3].

Chronic kidney disease is currently responsible for an estimated 1.48 million deaths [3]. Hypertension and type 2 diabetes mellitus remain the principal etiologies associated with CKD mortality. CKD itself acts as an independent cardiovascular risk factor, promoting conditions like myocardial infarction and heart failure through a bidirectional cardiorenal relationship [2,3]. Deaths attributable to hypertensive CKD increased from 169,100 to 447,700, and those related to diabetes rose from 146,000 to 406,300 between 1990 and 2019 [11].

INFLAMMATION AS A HALLMARK OF CKD PATHOPHYSIOLOGY

Sources of Systemic Inflammation in CKD

Uremic Toxins

Uremic toxins (UTs) such as indoxyl sulfate and p-cresyl sulfate, derived from gut microbial metabolism and subsequently modified hepatically, are particularly pathogenic. Their retention disrupts intestinal barrier integrity, promotes vascular dysfunction, and accelerates renal fibrosis, thereby reinforcing CKD progression [12]. Beyond their direct cytotoxicity, UTs exert potent immunomodulatory effects by activating monocytes and macrophages, which induce tumor necrosis factor-α (TNF-α), IL-6, and Monocyte Chemoattractant Protein-1 (MCP-1) release, and stimulating Toll-like receptor–dependent Nuclear factor-κB (NF-κB) signaling [13]. As CKD advances, especially beyond stage 3, the rising burden of these toxins amplifies oxidative stress, endothelial injury, and macrophage activation, contributing substantially to the chronic inflammatory state characteristic of advanced CKD and related complications such as anemia [14].

Impaired Renal Clearance of Cytokines

Impaired renal clearance is a central driver of systemic inflammation in CKD. The physiological balance between pro-inflammatory M1 and anti-inflammatory M2 macrophage phenotypes is disrupted, with a shift toward M1 predominance that sustains chronic cytokine release. Impaired clearance of inflammatory mediators, including IL-1, IL-6, IL-18, interferon-γ, and tumor necrosis factor-α, leads to prolonged systemic exposure. Concurrently, renal parenchymal cells—such as mesangial cells, endothelial cells, tubular epithelial cells, and podocytes—are activated in response to uremic stress and hypoxic conditions. These cells secrete chemokines and cytokines that recruit leukocytes and propagate chronic inflammatory signaling. This combination of impaired cytokine clearance and intrarenal immune activation creates a self-reinforcing inflammatory milieu that accelerates CKD progression and contributes to systemic sequelae, including anemia [14,15].

Oxidative Stress and Chronic Renal Hypoxia

Oxidative stress contributes to the progression of renal damage through excessive production of reactive oxygen species (ROS). These ROS activate multiple inflammatory and profibrotic signaling pathways, including transforming growth factor-β, monocyte chemoattractant protein-1, connective tissue growth factor, and pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-18, as well as adhesion molecules, thereby accelerating structural and functional deterioration of renal tissue [16]. Beyond direct ROS-mediated injury, chronic tubulointerstitial hypoxia in CKD with impaired Hypoxia-Inducible Factor (HIF) pathway signaling disrupts adaptive oxygen responses, contributing to inflammation and disease progression [17,18]. The clinical relevance of impaired hypoxia-inducible factor (HIF) signaling is highlighted by the development of HIF prolyl hydroxylase inhibitors—including roxadustat, daprodustat, vadadustat, and molidustat as an established and increasingly utilized therapeutic class for the management of CKD-associated anemia. Notably, desidustat received regulatory approval in India in March 2022 for the treatment of anemia in adult CKD patients, both dialysis-dependent and non-dialysis-dependent, representing a significant milestone for the region [19,20]. These agents exert their effects through stabilization of HIF-α, thereby enhancing endogenous erythropoietin synthesis, promoting iron utilization, and suppressing hepcidin levels, with additional potential anti-inflammatory benefits. Their efficacy and safety have been substantiated in over 30 phase III clinical trials involving both dialysis-dependent and non–dialysis-dependent CKD populations [21-23]. Additionally, excess iron can itself drive ROS formation via Fenton chemistry, so that iron overload (for example, in transfused or dialyzed patients) intensifies hydroxyl-radical generation and worsens renal injury and fibrosis [24]. By contrast, inflammation induces hepcidin, which sequesters iron in macrophages and limits free Fe, an adaptive host defense thought to reduce oxidative damage. For example, hepcidin pretreatment in mice blunted Lipopolysaccharide (LPS)-induced cytokine release [25], consistent with the idea that iron trapping protects tissues from Fe-driven oxidative toxicity [26].

Dysregulated Gut Microbiota

Dysbiosis promotes excessive generation of gut-derived uremic toxins, reduces short-chain fatty acid (SCFA) production, and impairs intestinal barrier integrity, resulting in increased intestinal permeability [27]. This "leaky gut" facilitates the translocation of bacterial components into the bloodstream, thereby amplifying systemic inflammation. Circulating bacterial DNA and elevated concentrations of microbial toxins such as indoxyl sulfate and p-cresyl sulfate correlate strongly with inflammatory markers, vascular dysfunction, and cardiovascular risk in CKD and dialysis populations [28].

Dialysis Related Inflammation

Serum inflammatory biomarkers, including C-reactive protein (CRP) and IL-6, are elevated in approximately 30–50% of patients with CKD, reflecting a multifactorial inflammatory state driven by both patient-related and hemodialysis-related factors. IL-6 contributes to malnutrition-inflammation-atherosclerosis (MIA) syndrome by promoting muscle protein catabolism, suppressing IGF-1 production, altering appetite regulation, and reducing serum albumin and transferrin levels [29]. Beyond patient-related factors, the dialysis procedure itself contributes significantly to this inflammatory burden. Bioincompatible dialysis membranes can provoke sustained immune activation, while exposure to LPS-containing dialysate introduces exogenous inflammatory stimuli into the circulation. Furthermore, repeated blood–membrane interactions trigger complement activation, generating anaphylatoxins C3a and C5a that drive downstream release of pro-inflammatory cytokines, collectively intensifying the systemic inflammatory state in dialysis-dependent patients [30,31].

KEY INFLAMMATORY MEDIATORS

IL-6/STAT3 Pathway

Chronic kidney disease is characterized by persistent immune activation, with IL-6 emerging as one of the most consistently elevated and clinically meaningful cytokines. Sustained IL-6 elevation is strongly associated with faster CKD progression, higher hospitalization rates, and increased cardiovascular and all-cause mortality, and provides more robust prognostic value than biomarkers such as C-reactive protein, albumin, or tumor necrosis factor. IL-6 signals through the IL-6Rα–gp130 receptor complex, leading to Janus kinase (JAK) activation and phosphorylation of signal transducer and activator of transcription 3 (STAT3). Nuclear STAT3 drives transcription of inflammatory and stress-response genes, establishing the IL-6–JAK/STAT3 pathway as a principal mediator of the chronic low-grade inflammation characteristic of CKD [32]. Within the kidney, IL-6/STAT3 activation promotes mesangial and tubular epithelial cell dysfunction, enhances leukocyte recruitment, and contributes to a profibrotic microenvironment. STAT3 also interacts with oxidative stress pathways, amplifying tissue injury and perpetuating the inflammatory cascade [33].

TNF-α and IL-1β–Mediated Suppression

Chronic kidney disease is characterized by persistent low-grade inflammation in which TNF-α and interleukin-1β (IL-1β) act as key upstream mediators. Their circulating levels increase with declining kidney function due to reduced renal clearance, accumulation of uremic toxins, and heightened production by activated monocytes/macrophages and injured tubular, mesangial, and endothelial cells [34,35]. IL-1β acts synergistically with TNF-α to induce chemokine and adhesion molecule expression, promoting leukocyte recruitment, endothelial dysfunction, and tubulointerstitial injury. Together, TNF-α and IL-1β constitute a core inflammatory axis that accelerates CKD progression, contributes to cardiovascular complications, and sustains chronic immune activation within the renal microenvironment [6]. The broader challenge of targeting upstream inflammatory mediators in CKD is further illustrated by the failure of anti-IL-6 strategies; the Phase 3 IMAGINE trial (NCT03744910), which evaluated clazakizumab in kidney transplant recipients with chronic antibody-mediated rejection, was terminated early due to futility, underscoring the complexity of cytokine-targeted therapy in the renal inflammatory milieu [36].

NF-κB Activation and Broad Inflammatory Upregulation

Nuclear factor-κB (NF-κB) serves as a central regulator of inflammatory responses, and its sustained activation is a characteristic feature of CKD [4]. Upon activation, NF-κB drives the transcription of key pro-inflammatory mediators, including tumor necrosis factor-α, interleukin-1, interleukin-6, and monocyte chemoattractant protein-1, thereby perpetuating systemic inflammation and facilitating macrophage infiltration, tubular damage, and the development of glomerulosclerosis [37,38].

NLRP3 Inflammasome Activation

Growing evidence identifies activation of the NLRP3 inflammasome as a critical mediator of renal inflammation and fibrotic progression. This multiprotein complex is activated in infiltrating immune cells (primarily macrophages and dendritic cells) as well as tubular epithelial cells and contributes to disease mechanisms across AKI, CKD, and diabetic nephropathy. NLRP3 activation results in caspase-1–dependent maturation of IL-1β and IL-18, promoting inflammatory amplification, pyroptotic cell death, and maladaptive immune responses. These cytokines also influence Th1/Th17 polarization, linking innate and adaptive immune activation [39].

NLRP3 activation follows a two-step process involving NF-κB–mediated priming and subsequent activation by diverse danger-associated signals such as urate crystals, cholesterol crystals, mitochondrial ROS, and lysosomal injury. Upon assembly, NLRP3 recruits ASC and pro–caspase-1, leading to

cytokine maturation and pyroptosis. Beyond canonical effects, NLRP3 may also enhance renal fibrosis via TGF-β activation independent of IL-1β/IL-18, contributing to epithelial–mesenchymal transition and tubulointerstitial scarring [40,41].

Inflammation-Driven Anemia in CKD

Anemia is a common and clinically significant complication of CKD, contributing to reduced quality of life, accelerated disease progression, and increased cardiovascular morbidity and mortality [8,18,42-46]. Chronic low-grade inflammation, a hallmark of CKD, is a major determinant of hemoglobin variability and hyporesponsiveness to ESAs [42]. Elevated systemic inflammatory markers, including C-reactive protein, along with increased circulating pro-inflammatory cytokines such as IL-6, IL-1β, TNF-α, and interferon-γ, inhibit erythropoiesis through multiple interrelated pathways [8,47]. IL-6–driven induction of hepatic hepcidin synthesis leads to marked disturbances in iron homeostasis by suppressing intestinal iron absorption and macrophage iron efflux via ferroportin degradation. This process results in a characteristic pattern of hypoferremia with normal or increased iron stores, commonly reflected by elevated ferritin levels [45,47,48]. This inflammation-driven iron sequestration restricts iron availability to erythroid precursors and underlies the development of functional iron deficiency despite adequate total body iron [45,47]. Concurrently, IL-1β and TNF-α directly inhibit erythroid progenitor proliferation (BFU-E and CFU-E) and attenuate endogenous erythropoietin signaling, further impairing effective erythropoiesis and contributing to ESA resistance [8,45]. In parallel, relative erythropoietin deficiency due to loss of renal peritubular EPO-producing cells remains a central pathogenic factor [45]. Oxidative stress and accumulation of uremic toxins further destabilize erythrocyte membranes, accelerate eryptosis, and progressively shorten red blood cell survival with advancing CKD stage, particularly in stage G5 disease [18,46,49-51]. Collectively, the convergence of inflammation-induced iron dysregulation, impaired erythropoiesis, reduced erythropoietin responsiveness, and shortened RBC lifespan culminates in functional iron-deficiency anemia and poor therapeutic response to recombinant human erythropoietin and ESAs in patients with CKD (Figure 1) [42,45,47].

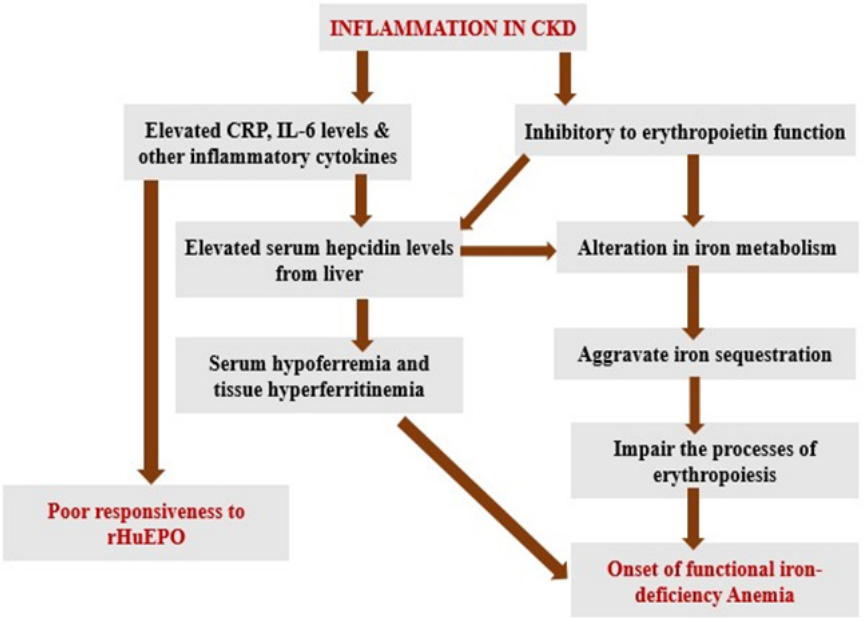


Figure 1. Mechanism of inflammation-driven anemia in CKD. Elevated IL-6 drives hepatic hepcidin synthesis via JAK–STAT3 signaling, leading to ferroportin degradation and iron sequestration in enterocytes and macrophages despite adequate iron stores. Concurrently, IL-1β and TNF-α suppress erythropoietin synthesis and inhibit erythroid progenitor proliferation, together producing functional iron-deficiency anemia and ESA hyporesponsiveness.

CURRENT THERAPEUTIC LANDSCAPE AND ITS LIMITATIONS TREATING ANEMIA OF CKD

Current evaluation of anemia and iron deficiency in CKD is primarily guided by hemoglobin concentration and conventional iron indices, including transferrin saturation (TSAT) and serum ferritin. However, diagnostic thresholds and recommended laboratory parameters vary substantially across international guidelines, particularly between KDOQI, Renal Association, and ERBP recommendations (Table 1).

These inconsistencies highlight the lack of standardized criteria for identifying inflammation-mediated iron restriction, underscoring the need for therapies that target hepcidin dysregulation rather than relying solely on hemoglobin, ferritin, or TSAT thresholds.

Table 1. Differences in measurements to evaluate anemia according to different guidelines [8]

Guideline source	Population criteria	Hb threshold (g/dL)	TSAT cutoff (%)	Ferritin cutoff (ng/mL)	Additional indices
KDOQI (2006)	Females	<12.0	≤20	≤100 (ND/PD)	—
	Males	<13.5	≤20	≤200 (HD)	—
Renal Association (2017)	Men & postmenopausal women	<13.0	≤20	<100 (ND/PD)	CHr ≤29 pg
	Premenopausal women	<12.0	≤20	<200 (HD)	%HRC ≥6%
ERBP (2017)	Females	<12.0	<20 (ND)	<100 (ND)	—
	Males	<13.5 (<13.2 if >70 yrs)	<25 (HD/PD)	<300 (HD/PD)	—
	ESA-treated patients	—	<30	<300	—

CURRENT TREATMENTS FOR CKD ASSOCIATED ANEMIA AND THEIR KEY LIMITATIONS

Moreover, despite advances in anemia management, current therapeutic approaches primarily target hemoglobin correction rather than the underlying inflammatory milieu driving functional iron deficiency. The major treatment modalities, such as ESAs, oral iron, and intravenous iron, remain central to current practice; however, their effectiveness is substantially attenuated in the presence of inflammation, as summarized in Table 2.

Table 2. Current treatments for CKD anemia and their key limitations

Therapy	Mechanism / Rationale	Targets Inflammation?	Key Limitation
ESAs [52]	Compensate for inadequate endogenous EPO; stimulate erythroid progenitor proliferation.	No	IL-6–hepcidin axis induces functional iron deficiency; leads to ESA hyporesponsiveness
Oral Iron [53,54]	Replenishes iron stores; supports erythropoiesis	No	Hepcidin-mediated ferroportin inhibition blocks intestinal absorption, especially during inflammation.
IV Iron [55,56]	Bypasses intestinal absorption; reliably replenishes stores	No	Iron mobilization from macrophage stores remains impaired in high-inflammation states.
HIF-Prolyl Hydroxylase Inhibitors [21-23]	Stabilize HIF-α; raise endogenous EPO; suppress hepcidin	Partial	Newer class; long-term cardiovascular safety still being established

Note: Existing therapies often perpetuate a cycle of dose intensification without addressing the inflammatory root cause of anemia in CKD.

KDIGO 2026 Guidelines: Updated Recommendations for Anemia Evaluation and Management in CKD

The Kidney Disease: Improving Global Outcomes (KDIGO) 2026 guidelines emphasize that persistent inflammation and increased hepcidin levels are key determinants of functional iron deficiency and reduced responsiveness to erythropoiesis-stimulating agents. KDIGO advises restricting ESA therapy initiation to symptomatic patients or those with persistently low hemoglobin and highlights that inflammation should be evaluated and corrected before escalating ESA doses, due to increased cardiovascular risk associated with high ESA requirements.

In iron management, KDIGO 2026 supports a trial of iron therapy in hemodialysis patients when ferritin ≤500 ng/mL and TSAT ≤30%, even when ferritin is moderately elevated due to inflammation. In non-dialysis and peritoneal dialysis patients, therapy is suggested when ferritin <100 ng/mL and TSAT <40%, or when ferritin is 100–300 ng/mL with TSAT <25%. The guidelines acknowledge the impact of hepcidin-driven iron sequestration and recommend considering non–iron-overload causes of hyperferritinemia, including systemic inflammation. Importantly, KDIGO recognizes that IV iron may be less effective in highly inflamed states due to impaired iron mobilization [43], supporting the need for adjunctive therapies that modulate inflammation and improve iron handling.

LACTOFERRIN: A PROMISING ADJUNCT TARGETING INFLAMMATION AND IRON DYSREGULATION

What is Lactoferrin?

Lactoferrin (Lf) is a multifunctional iron-binding glycoprotein found in neutrophil secondary granules and mucosal secretions. It possesses well-established antibacterial, antiviral, antioxidant, and anti-inflammatory properties [57]. Lf mitigates tissue injury by suppressing excessive cytokine release, particularly IL-6 and TNF-α, and by modulating oxidative stress–driven inflammatory cascades. Beyond its immunomodulatory properties, Lf has been explored as a therapeutic option for anemia. Clinical studies from diverse populations, including individuals with chronic diseases, pregnant women, children, and oncology patients, reported that Lf, alone or in combination with iron, improves hemoglobin and iron indices [58]. However, evidence in CKD-associated anemia populations is still limited.

MECHANISTIC RATIONALE FOR TARGETING CKD-RELATED ANEMIA

Hepcidin Modulation

Bovine Lactoferrin (bLf) exerts anti-inflammatory effects primarily through IL-6 suppression, leading to downstream reductions in hepcidin synthesis and restoration of ferroportin expression on macrophages and enterocytes [59]. Experimental models show that bLf reverses IL-6–induced ferroportin degradation, thereby enhancing cellular iron export and contributing to normalization of iron homeostasis (Figure 2) [60]. Clinical studies in hemodialysis patients report significant reductions in IL-6 and hepcidin following oral Lf administration, accompanied by improved iron mobilization and erythropoietic response [59].

Serum hepcidin quantification is limited by significant assay heterogeneity, as methodologies such as ELISA, LC-MS/MS, and TRIFMA generate non-comparable absolute values [61]. In addition, hepcidin demonstrates substantial biological variability, including diurnal variation and dynamic regulation by inflammatory status, iron availability, and erythropoietic activity. In the context of CKD, circulating hepcidin levels progressively increase with declining glomerular filtration rate, reflecting both reduced renal clearance and persistent inflammation [59]. However, the absence of standardized calibration methods and universally accepted reporting units continues to hinder inter-study comparability and clinical interpretation [62].

Improving Functional Iron Deficiency

As described above, lactoferrin's suppression of IL-6 reduces hepcidin and restores ferroportin function; this cascade increases circulating iron availability for erythropoiesis and reverses inflammation-driven iron restriction (Figure 2) [63].

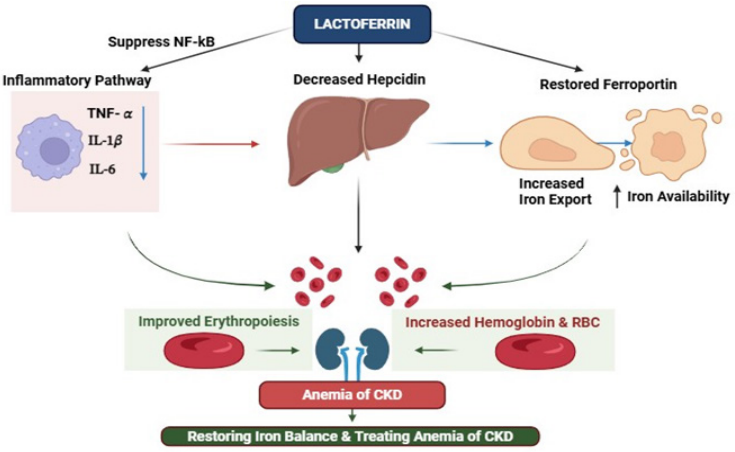


Figure 2. Proposed mechanism of lactoferrin's effect on inflammation-driven anemia in CKD. By suppressing IL-6, lactoferrin reduces hepcidin synthesis, restores ferroportin-mediated iron export, and increases iron availability for erythropoiesis.

Anti-Inflammatory Effects

Beyond its effects on the IL-6–hepcidin axis described above, lactoferrin also suppresses upstream inflammatory signaling via the NF-κB pathway. A recent meta-analysis shows that Lf reduces expression of TNF-α, IL-1β, IL-6, IKK-β, IκB-α, and multiple NF-κB components, although the magnitude of suppression requires further clarification [64]. NF-κB dysregulation contributes to vascular inflammation, insulin resistance, impaired tissue repair, and CKD progression, suggesting that LF-mediated modulation may have broad therapeutic implications (Figure 2).

Beyond hematological benefits, Lf exhibits reno-protective and systemic metabolic effects. In murine CKD models, Lf reduced renal atrophy, preserved kidney function, and mitigated tubulointerstitial injury [65]. It improved CKD-induced skeletal muscle wasting by correcting aberrant mTOR1 signaling, restoring autophagy, and normalizing branched-chain amino acid metabolism. Lf also attenuated accumulation of gut-derived uremic toxins such as indoxyl sulfate, highlighting its role in modulating the gut–kidney–muscle axis.

CLINICAL EVIDENCE SUPPORTING LACTOFERRIN IN ANEMIA OF CKD

Clinical Studies (Table 3)

Table 3. Clinical evidence on the impact of lactoferrin in CKD-associated anemia and inflammation

Author (Year)	Study Design	Sample Size	Key Findings	Limitation
Kashyap M et al. (2023) (WCN23-0108) [66]	Observational, single-center pilot study evaluating lactoferrin with or without iron supplementation	n = 46	Lactoferrin therapy produced a significant increase in hemoglobin at 4 weeks ($p<0.001$). ESR showed a non-significant decline, while CRP demonstrated a non-significant rise.	Single-center, no control arm, short follow-up (4 weeks)
Kekan K et al. (2024) (WCN24-1274) [67]	Single-arm, 1-month intervention study	n = 40	Lactoferrin administration improved hemoglobin and reduced erythroferrone levels; hepcidin concentrations remained unchanged.	Single-arm, no comparator, 1-month duration only

Khaled A et al. (2024) [68]	Interventional case–control study comparing lactoferrin + ESA vs ESA alone	n = 70	Lactoferrin did not demonstrate efficacy as monotherapy in functional iron-deficiency. Anemia among end-stage kidney disease (ESKD) patients but showed benefit as an adjunct to ESA therapy.	Case–control (not randomized), ESKD-only population
Divyaveer S et al. (2024) (WCN24-1323) [69]	Randomized study in CKD-5D and CKD-ND patients comparing lactoferrin + iron with iron alone	n = 78	The lactoferrin + iron arm exhibited a greater rise in hemoglobin (p=0.038). Hepcidin, CRP, and ESR changes were not statistically significant between groups.	Randomized but likely underpowered for inflammatory endpoints
Kekan K et al. (2024) [60]	Prospective pilot study evaluating oral lactoferrin with or without iron	n = 46	Hemoglobin increased progressively (p<0.001). ESR decreased, and CRP increased, although neither change reached statistical significance.	Single-center, no control arm, short follow-up (4 weeks)
Yadav R et al. (2024) [59]	Randomized, open-label trial assessing lactoferrin + Guanosine Monophosphate (GMP) vs standard CKD care	n = 40	Combination therapy produced significant reductions in pro-inflammatory markers (TNF-α, IL-6, IL-10), indicating a robust immunomodulatory effect.	Open-label (no blinding); combination arm limits attribution to lactoferrin alone
Mahamoud RMA et al. (2023) [61]	Randomized controlled trial comparing bovine lactoferrin with ferrous glycine sulfate	n = 140	Bovine lactoferrin resulted in marked reductions in hepcidin and significant improvements in hemoglobin and TSAT, outperforming ferrous glycine sulfate (all p<0.0001).	Single-center RCT, active comparator only (no placebo arm)
Hegazy SK et al. (2025) [63]	Randomized, parallel-group pediatric trial comparing lactoferrin with IV iron dextran	n = 60	Lactoferrin significantly enhanced hemoglobin, RBC indices, serum iron, IL-6, and growth differentiation factor-15 (GDF-15). IV iron demonstrated significant improvements in iron parameters, GFR, IL-6, and GDF-15.	Only pediatric trial available; not generalizable to adults

Across the studies summarized in Table 3, hemoglobin improvement is a relatively consistent finding, reported in six of eight studies [59-61,63,66,69]. In contrast, effects on hepcidin, CRP, and ESR are inconsistent: some studies report significant hepcidin reduction [61], others no significant change [67], and CRP changes are non-significant or even directionally opposite across studies [66,69]. This divergence likely reflects differences in lactoferrin formulation, dosing, co-administration with iron or GMP, and small sample sizes rather than a true absence of anti-inflammatory effect, but it means inflammatory marker response cannot yet be relied upon as a consistent treatment endpoint.

Lactoferrin is generally well tolerated; reported side effects are mild, primarily transient gastrointestinal upset such as nausea or diarrhea, with no serious adverse events reported even at high oral doses in controlled trials [70]. No harmful drug–drug interactions are known, and lactoferrin has been administered alongside stable ESA therapy without issue [58]. However, it cannot replace standard CKD anemia treatments: a trial in dialysis patients found that oral lactoferrin alone, without IV iron, could not maintain hemoglobin levels, and some patients experienced GI intolerance.

Formulations, Dosing, and Special Populations

Most clinical studies to date have used bovine lactoferrin (bLf), given its structural similarity to human lactoferrin and commercial availability; direct comparative data between bovine and human lactoferrin in CKD populations are lacking. Because bovine Lf is a cow-milk protein, allergic reactions can occur in individuals with milk-protein sensitivity [71]. Typical dosing in anemia studies is on the order of a few hundred milligrams daily, often ~100 mg once or twice a day [58,63], though no

dose-ranging trial has established an optimal regimen specific to CKD-associated anemia. Treatment duration in existing trials has been short (typically ≤3 months) [63], and long-term safety data beyond this window are not available. Evidence in kidney transplant recipients is currently absent; given that post-transplant anemia has a distinct pathophysiology — calcineurin inhibitor effects, graft function, immunosuppression-related marrow suppression — rather than the CKD-native inflammatory drivers addressed here, extrapolation to this population should be made cautiously pending dedicated study.

Positioning Lactoferrin in the CKD Anemia Care Pathway

Unlike the therapies summarized in Table 2, which either stimulate erythropoiesis directly (ESAs) or replenish iron stores without addressing its inflammatory sequestration (oral and IV iron) or partially suppress hepcidin as a secondary effect of HIF prolyl hydroxylase inhibitors (HIF-PHIs), lactoferrin acts directly on the IL-6–hepcidin axis itself. This distinguishes it mechanistically from all four established approaches: rather than compensating for inflammation's downstream consequences, it targets the inflammatory driver directly. However, its evidence base remains considerably less mature than any of the therapies in Table 2, with current data limited to small, short-duration, largely single-center trials rather than the larger controlled trial programs underlying ESA, iron, and HIF-PHI use in CKD anemia management.

The proposed positioning reflects the authors' interpretation of the potential role of lactoferrin within the KDIGO treatment pathway, based on its proposed mechanisms of action. KDIGO 2026 guidance advises evaluating and correcting inflammation before escalating ESA dose, and supports iron trialing within defined ferritin/TSAT thresholds even when ferritin is inflammation-elevated. Lactoferrin's mechanism — IL-6 suppression, hepcidin downregulation, and restored ferroportin-mediated iron mobilization — maps directly onto this inflammation-correction step, positioning it as a candidate adjunct at the point in the KDIGO pathway where inflammation is identified as the barrier to ESA response or iron mobilization, rather than as a substitute for ESA or iron therapy itself. In practice, this would place lactoferrin alongside — not instead of — standard ESA and iron management, specifically for patients in whom the KDIGO-recommended inflammation work-up identifies elevated IL-6/hepcidin as the dominant driver of anemia.

To translate this positioning into a practical clinical pathway, Figure 3 outlines a proposed stepwise approach: following initial evaluation of hemoglobin, ferritin, and TSAT, patients are categorized into absolute, functional, or inflammatory iron deficiency. In patients with functional or inflammatory iron deficiency — where iron reserves are present but not mobilized — correcting iron homeostasis by acting on hepcidin represents the therapeutic target, and lactoferrin is proposed as a candidate adjunct at this step [58,63].

Target Populations by CKD Stage and Dialysis Modality

Based on current evidence, CKD stage 3–5 patients with inflammation-driven (functional) iron-deficiency anemia — low TSAT with normal or elevated ferritin and elevated IL-6/hepcidin — particularly those showing ESA hyporesponsiveness, represent a potential target population for future studies [58,63]. Evidence across CKD stages and dialysis modalities remains uneven: most trial data derive from hemodialysis populations [59,61,66,67,69], where inflammation from bioincompatible membranes and dialysate exposure independently elevates IL-6 and hepcidin, potentially amplifying lactoferrin's relative benefit. Peritoneal dialysis populations are comparatively underrepresented, and non-dialysis CKD stage 3–4 patients — who may have lower baseline inflammatory burden — have limited dedicated data [69]. Pediatric evidence is similarly limited to a single trial [63]. Stratifying future trials by CKD stage and dialysis modality, rather than pooling CKD-5D and CKD-ND populations as in current studies, would clarify whether the benefit is uniform or concentrated in the highest-inflammation subgroup.

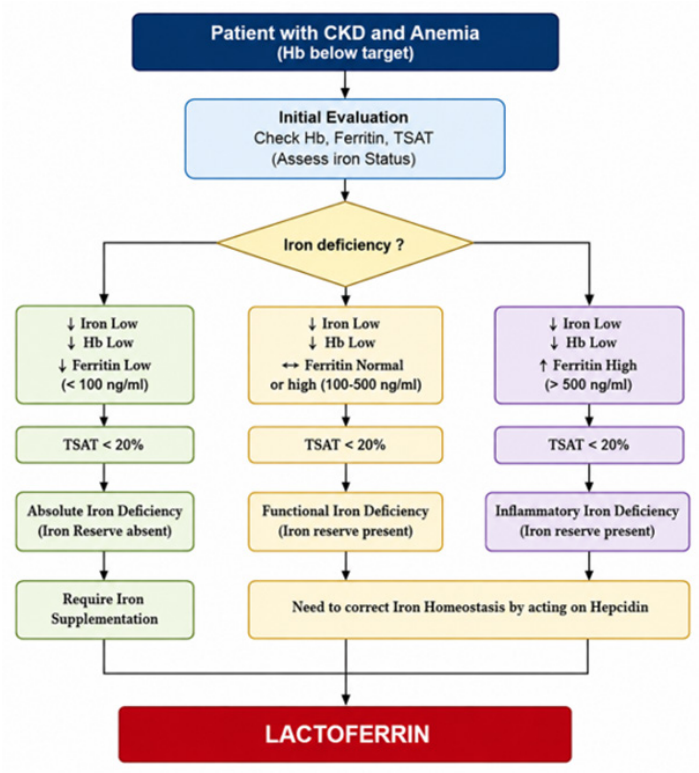


Figure 3. Proposed clinical pathway for considering lactoferrin in CKD-associated anemia. Following assessment of hemoglobin, ferritin, and TSAT, patients with absolute iron deficiency (low ferritin, depleted iron reserves) are managed with standard iron supplementation. Patients with functional iron deficiency (normal-to-moderately elevated ferritin) or inflammatory iron deficiency (markedly elevated ferritin), in whom iron reserves are present but not mobilized due to hepcidin-mediated sequestration, represent the population in whom correcting iron homeostasis via hepcidin modulation is the therapeutic target, the proposed context for lactoferrin as an adjunct to, rather than a replacement for, standard ESA and iron therapy

Monitoring and Treatment Approach

In such patients, hematologic response can be monitored via serial hemoglobin and iron indices (ferritin, TSAT) alongside inflammation markers (CRP, IL-6, hepcidin) [56]. In trials, modest hemoglobin increases were observed by ~4 weeks of therapy, with IL-6 (and presumably hepcidin) declines typically emerging over 2–3 months [63]. Trials combining lactoferrin with ESA or iron therapy [68] report better outcomes than lactoferrin monotherapy, supporting its use as a combination adjunct rather than a standalone agent.

LIMITATIONS OF CURRENT EVIDENCE

Despite growing interest, existing clinical evidence for lactoferrin in CKD remains limited by methodological constraints. Sample sizes are small, follow-up durations are short, and most investigations are single-center studies, reducing external validity. Considerable heterogeneity exists across patient populations, lactoferrin formulations, dosing strategies, co-interventions [e.g., iron or GMP], and endpoints, limiting comparability. Effects on inflammatory markers are inconsistent across studies, and pediatric evidence is derived from a single small-scale trial. Importantly, no studies have evaluated long-term clinical outcomes such as cardiovascular events, quality of life, hospitalization rates, or CKD progression. Robust, multicentre randomized trials are required to define lactoferrin's therapeutic role.

FUTURE DIRECTIONS

Future Randomized Controlled Trials (RCTs) should evaluate lactoferrin across diverse CKD stages, assess hepcidin reduction as a mechanistic endpoint, examine ESA dose-sparing effects, and explore broader anti-inflammatory benefits, including effects on IL-6, TNF-α, and CKD progression. Precision-based strategies using hepcidin or CRP may help identify responders.

CONCLUSION

Current evidence positions lactoferrin as a biologically plausible adjunct for CKD-associated anemia driven by inflammation and hepcidin dysregulation, with the most consistent benefit observed in hemoglobin response among ESA-hyporesponsive patients with functional iron-deficiency anemia. Early evidence shows improvement in hemoglobin across adult, pediatric, and dialysis populations, though corresponding changes in inflammatory markers remain variable across studies. Larger, multicenter randomized trials with standardized dosing and long-term clinical endpoints are needed to support the use of lactoferrin as an adjunctive therapy in routine CKD anemia management.

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