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The Outcomes of Lactoferrin as New Treatment of Iron Deficiency Anaemia in Patients on Regular Haemodialysis: A Systematic Review

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ABSTRACT

Iron deficiency anaemia (IDA) is a common and significant complication among patients with chronic kidney disease (CKD), particularly those undergoing regular haemodialysis. Conventional iron supplementation, although widely used, is often limited by gastrointestinal side effects, inflammation, and suboptimal iron utilization. Therefore, alternative therapies such as lactoferrin, an iron-binding glycoprotein with anti-inflammatory and immunomodulatory properties, have gained increasing attention. This study aims to evaluate the effectiveness and safety of lactoferrin as a treatment for IDA in CKD patients on regular haemodialysis.
This research employed a systematic review design following PRISMA 2020 guidelines. A comprehensive literature search was conducted across major databases, including PubMed, Scopus, Google Scholar, ScienceDirect, and ProQuest. Eligible studies included randomized controlled trials, interventional, and observational studies involving adult CKD patients receiving lactoferrin therapy. Data were analyzed narratively to compare haematological and inflammatory outcomes. The findings indicate that lactoferrin significantly improves haemoglobin levels, serum iron, and transferrin saturation, while reducing inflammatory markers such as hepcidin, C-reactive protein, and interleukin-6. Compared to conventional iron therapy, lactoferrin demonstrates better tolerability and fewer adverse effects. In combination with erythropoiesis-stimulating agents, it provides comparable hematologic outcomes with additional anti-inflammatory benefits. In conclusion, lactoferrin is a promising and well-tolerated adjunct therapy for managing IDA in CKD patients undergoing haemodialysis. However, further large-scale studies are needed to confirm its long-term efficacy and optimal clinical application.

INTRODUCTION

Iron Deficiency Anaemia (IDA) is the most common form of anaemia worldwide, resulting from insufficient iron availability for haemoglobin (Hb) synthesis.(El Amrousy et al., 2022; Gafter-Gvili et al., 2019; Ocktariyana et al., 2024; Purandare et al., 2025) IDA remains a major public health problem affecting both developed and developing countries.(Ocktariyana et al., 2024; Purandare et al., 2025) According to the World Health Organization (WHO), approximately 30% of the global population suffers from IDA. The prevalence is particularly high among preschool children (40%), menstruating women (30%), and pregnant women (38%). Although more common in women and children, adult men are also at risk, depending on their socioeconomic and health status.(World Health Organization, 2025)

Iron deficiency frequently coexists with chronic diseases. It is reported in 37–61% of patients with chronic heart failure, 24–85% with chronic kidney disease (CKD), and 13–90% with inflammatory bowel disease (IBD).(Cappellini et al., 2017) Typical manifestations of iron deficiency include epithelial changes such as koilonychia (spoon-shaped nails), atrophy of tongue papillae, angular stomatitis, and dysphagia.(Gafter-Gvili et al., 2019; Ocktariyana et al., 2024)

Chronic Kidney Disease (CKD) is defined as kidney damage or a decline in glomerular filtration rate (GFR) < 60 mL/min/1.73 m² persisting for more than three months.(Gafter-Gvili et al., 2019) Renal anaemia, one of the most frequent complications of CKD, primarily results from reduced erythropoietin production by the damaged kidneys. Anaemia typically appears in stage 3 CKD and becomes almost universal in stage 5 CKD. Other contributing factors include iron deficiency, shortened red blood cell lifespan, secondary hyperparathyroidism, and chronic inflammation.(Cappellini et al., 2017; Gafter-Gvili et al., 2019; Ho et al., 2024)

The management of renal anaemia generally involves blood transfusions, erythropoiesis-stimulating agents (ESAs) such as recombinant erythropoietin, and iron supplementation (oral or intravenous).(Gafter-Gvili et al., 2019; Purandare et al., 2025) Emerging therapies include hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors. Among these, iron therapy, either intravenous (IV) or oral, remains essential for correcting haemoglobin levels in CKD patients, with or without ESA use.(Purandare et al., 2025)

Lactoferrin, an iron-binding glycoprotein found in milk, body fluids, and neutrophils, has attracted increasing attention due to its antimicrobial, anti-inflammatory, and immunomodulatory properties. Several studies in the general population have shown that lactoferrin supplementation increases haemoglobin, ferritin, and transferrin saturation (TSAT) levels while reducing hepcidin, a key regulator of iron metabolism.(Cappellini et al., 2017) Compared with traditional iron supplements such as ferrous sulfate, lactoferrin offers better gastrointestinal tolerance, fewer side effects, and enhanced iron absorption, even under inflammatory conditions.(Cappellini et al., 2017; El Amrousy et al., 2022)

Despite these promising findings, evidence regarding lactoferrin use in patients with CKD, particularly those undergoing haemodialysis, remains limited. To date, no systematic review have evaluated the efficacy of lactoferrin supplementation in stage V CKD patients with iron deficiency anaemia (IDA), especially in non-pregnant population.(Paesano et al., 2010) Therefore, this study aims to evaluate the effectiveness of oral lactoferrin supplementation in improving haemoglobin, ferritin, and transferrin saturation levels in stage V CKD patients undergoing regular haemodialysis with IDA.

Within this broader burden, patients undergoing regular haemodialysis represent a particularly high-risk subgroup because anaemia in CKD is not caused solely by reduced erythropoietin production, but also by chronic inflammation, impaired iron absorption, recurrent blood loss during dialysis procedures, and hepcidin-mediated functional iron deficiency. Contemporary CKD anaemia guidance and recent reviews emphasize that in CKD, inflammation increases hepcidin, which suppresses intestinal iron absorption and traps iron in storage sites, thereby limiting iron availability for erythropoiesis even when total body iron stores appear adequate. This pathophysiology explains why anaemia in dialysis patients is often difficult to correct with conventional approaches alone.

Current management of anaemia in haemodialysis commonly relies on oral or intravenous iron supplementation, erythropoiesis-stimulating agents, and, in selected cases, blood transfusion. However, conventional iron therapy is not always ideal. Oral iron often produces gastrointestinal intolerance and poor adherence, while intravenous iron may raise concerns regarding oxidative stress, infection risk, and long-term safety in chronically inflamed patients. For this reason, there is increasing academic and clinical interest in adjunctive therapies that can improve iron utilization while also addressing the inflammatory milieu that characterizes CKD-related anaemia.

Lactoferrin has emerged as one such candidate because it is an iron-binding glycoprotein with antimicrobial, anti-inflammatory, and immunomodulatory properties. In the uploaded manuscript, lactoferrin is positioned not merely as a nutritional supplement but as a potentially dual-action therapy capable of improving hematologic parameters and modulating inflammatory pathways in patients on regular haemodialysis. This rationale is clinically relevant because the challenge in dialysis-related anaemia is not only iron deficiency itself, but also reduced iron bioavailability caused by inflammation-driven metabolic disruption. Thus, lactoferrin is conceptually attractive for CKD populations in whom iron handling and inflammation are tightly intertwined.

Recent studies indexed in PubMed, Scopus, and related academic databases have begun to test this proposition in adult haemodialysis populations. Mahmoud and Mohammed's 2023 randomized controlled trial reported that oral bovine lactoferrin significantly improved haemoglobin, transferrin saturation, and hepcidin compared with ferrous glycine sulfate. Abdelwahab et al. in 2024 found that oral lactoferrin combined with erythropoiesis-stimulating agents improved haemoglobin and iron parameters, although the between-group advantage over ESA alone was limited. Aboalfarh et al. in 2025 further showed that lactoferrin plus ESA produced meaningful anti-inflammatory effects, particularly by reducing CRP and IL-6, while Kekan et al. reported improvement in haemoglobin with acceptable tolerability in advanced CKD patients receiving lactoferrin. Collectively, these studies suggest that lactoferrin may provide hematologic and anti-inflammatory benefits, but the magnitude and consistency of its effect remain under debate.

Despite these encouraging findings, an important research gap remains. First, the available studies are still few in number and mostly involve relatively small samples, short intervention durations, and heterogeneous treatment regimens. Second, some studies compare lactoferrin directly with oral iron, whereas others evaluate it only as an adjunct to ESA therapy, making cross-study interpretation difficult. Third, the reported outcomes vary across haemoglobin, ferritin, serum iron, transferrin saturation, hepcidin, CRP, and IL-6, so the overall clinical position of lactoferrin in anaemia management for dialysis patients has not yet been fully clarified. The uploaded manuscript itself highlights that evidence synthesis specifically focused on stage V CKD patients on regular haemodialysis with iron deficiency anaemia has remained limited.

This gap creates a clear research urgency. Haemodialysis patients require long-term and often repeated anaemia management, and any therapy that can improve haemoglobin response, enhance iron utilization, reduce inflammatory burden, and minimize adverse effects would have substantial clinical value. Given the rising global prevalence of CKD and kidney failure with replacement therapy, identifying safer and more effective adjunctive options is not only

scientifically important but also highly relevant for health systems and patient-centred care. In practical terms, a clearer understanding of lactoferrin's role may help clinicians refine supportive treatment strategies for patients who respond poorly to standard iron therapy or who cannot tolerate conventional supplementation.

The novelty of this research lies in its attempt to synthesize emerging evidence on lactoferrin specifically in adult CKD stage 5 patients undergoing regular haemodialysis, with a focus on both haematological and inflammatory outcomes. Rather than viewing anaemia correction only through haemoglobin improvement, this topic examines whether lactoferrin can address the more complex biology of CKD-related iron restriction by influencing markers such as transferrin saturation, ferritin, hepcidin, CRP, and IL-6. This broader analytical framing is important because it aligns the intervention with the modern understanding that anaemia in CKD is both a hematologic and inflammatory disorder.

Based on that background, the purpose of this research is to evaluate the effectiveness and safety of lactoferrin as a new or adjunctive treatment for iron deficiency anaemia in patients on regular haemodialysis. More specifically, the research aims to examine whether lactoferrin improves haemoglobin and iron status parameters, reduces inflammation-related biomarkers, and offers a tolerable alternative or complement to conventional therapy. The expected contribution of this study is the provision of a more integrated evidence base for clinicians, researchers, and policy-oriented readers concerning the therapeutic potential of lactoferrin in renal anaemia management, especially in settings where long-term tolerability and inflammation control are major concerns.

Ultimately, this research is expected to generate both scientific and practical benefits. Scientifically, it helps clarify the current state of evidence on lactoferrin in dialysis-related iron deficiency anaemia and identifies areas where future trials are still needed, such as larger multicentre randomized studies, standardized dosing, and longer follow-up. Practically, it may support more precise decision-making in nephrology practice by highlighting whether lactoferrin can serve as an effective adjunct for improving anaemia outcomes with fewer adverse effects. In this way, the study contributes not only to the literature on CKD anaemia treatment, but also to the broader goal of improving quality of life and treatment efficiency in patients who depend on regular haemodialysis.

METHOD

Data source and search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. A comprehensive literature search was conducted across five major biomedical databases: PubMed, Google Scholar, Science Direct, Scopus, and ProQuest. The search included all studies published up to April 2025 without restrictions on language or publication year. The main keywords and Medical Subject Headings (MeSH) terms used included: "lactoferrin," "iron deficiency anaemia," "haemodialysis," and "chronic kidney disease,". Boolean operators ("AND," "OR") were applied to ensure comprehensive retrieval. The full search strategy is provided in the **Supplementary Materials (Table S1).**

Two reviewers independently screened all titles and abstracts. Potentially eligible studies underwent full-text evaluation, and reasons for exclusion were documented. The reference lists

of all included articles were manually reviewed to identify additional relevant studies. Disagreements between reviewers were resolved by discussion and consensus.

Eligibility criteria and study selection

Studies were included if they met the following criteria: (1) adult patients diagnosed with chronic kidney disease (CKD) or end-stage renal disease (ESRD) undergoing regular haemodialysis, (2) the intervention of interest was the administration of oral or intravenous lactoferrin, either as a therapeutic agent or as an adjunctive treatment, (3) comparator groups included those receiving placebo, standard iron supplementation (oral or intravenous), erythropoiesis-stimulating agent (ESA) therapy, or none. Eligible studies were required to report outcomes related to haematological or biochemical parameters, such as haemoglobin (Hb), serum iron, ferritin, transferrin saturation (TSAT), hepcidin, C-reactive protein (CRP), or other inflammatory markers including interleukin-6 (IL-6) and growth differentiation factor-15 (GDF-15). Only randomized controlled trials (RCTs), interventional studies, and observational case–control studies were included. Exclusion criteria comprised review articles, animal studies, conference abstracts, and studies lacking primary data on the effects of lactoferrin in haemodialysis patients.

Data were extracted independently by two reviewers using a standardized extraction form. The following variables were collected: author, year of publication, country, study design, population characteristics, intervention details (dosage, route, duration), comparison group, and outcome measures. Extracted data were verified by a third reviewer to ensure accuracy and completeness. Any discrepancies were resolved through discussion and consensus.

Quality of evidence and risk of bias

Two independent reviewers evaluated the risk of bias for all included studies, and any discrepancies were resolved through discussion and consensus using the JBI checklist.(Peters et al., 2020) Each domain within the selected tool was rated as low risk, high risk, or some concerns/unclear risk. If any criterion within a domain was judged as high risk, that entire domain was classified as high risk. When one or more domains were rated as unclear, the overall risk of bias for the study was categorized as unclear.

Data Synthesis and Analysis

A narrative synthesis was performed to summarize findings due to expected heterogeneity in study design, patient population, and outcome measures. When possible, quantitative data were extracted to compare changes in haemoglobin, ferritin, and TSAT between lactoferrin and comparator groups.

RESULT AND DISCUSSION

Study selection

Initially, 2.777 articles were retrieved from five electronic databases. Following the removal of duplicates and a rigorous screening process, 14 full-text articles were assessed for eligibility. Citation tracking identified nine additional articles. Five studies were excluded due to incomplete outcome (n=1), incompatible population (n=2), and language other than English (n=2), resulting in a total of four studies in the final analysis. The overall screening process is illustrated in the PRISMA 2020 flow diagram (**Figure 1).**

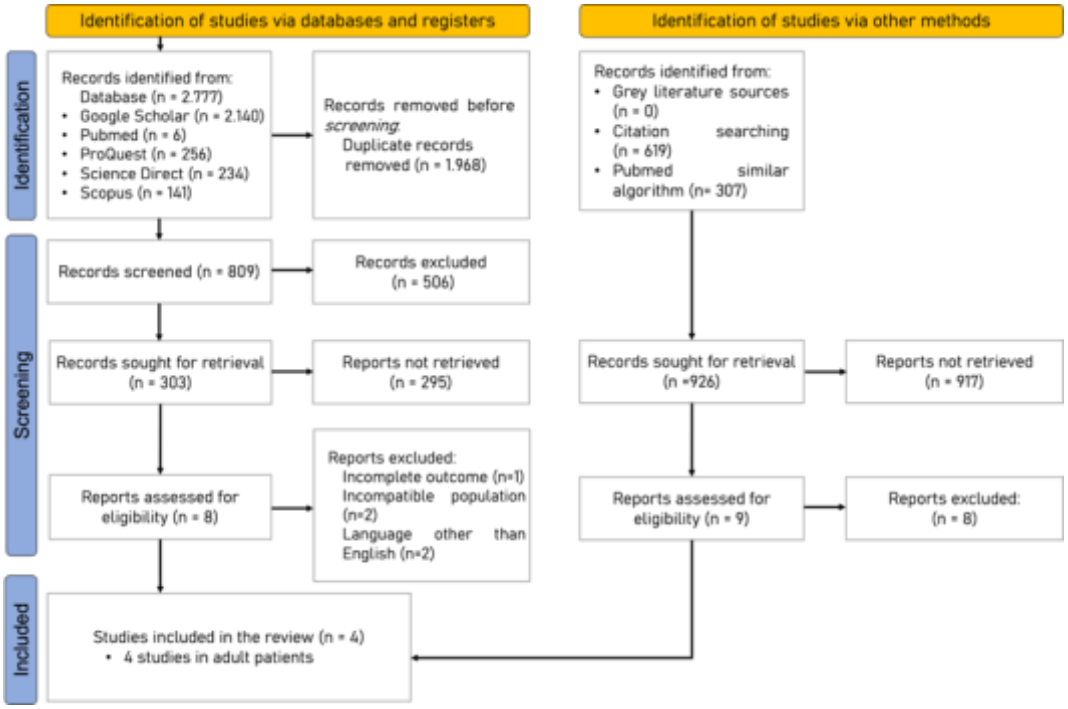

Figure 1. PRISMA flowchart

Risk of Bias

One study with RCT design was evaluated across thirteen domains. Mahmoud and Mohammed's study demonstrated an overall low risk of bias, with nearly all domains assessed as low risk and only a few remaining unclear.(Mahmoud et al., 2023) The case-control studies were evaluated across ten domains assessing factors such as comparability of groups, exposure measurement, confounding control, and statistical analysis, with all three studies demonstrated strong methodological quality, as most domains were marked low risk. A few unclear ratings in areas like exposure measurement or matching procedures, suggesting incomplete reporting rather than evident bias. None of the studies displayed any high-risk domains, which implies that the case-control designs were generally rigorous and well-controlled.(Abdelwahab et al., 2024; Aboalfarh et al., 2025) For the cohort studies, Kekan et al. (2023) was assessed across eleven domains. This study exhibited predominantly low-risk ratings, reflecting well-designed cohort methodologies with minimal potential for bias. Only a few domains were rated as unclear, typically involving follow-up completeness or handling of incomplete data, indicating some uncertainty in reporting rather than methodological flaws. No high-risk assessments were found in this group, underscoring the reliability and validity of the cohort evidence included.(Kekan et al., 2023) Overall, risk of bias across all studies is low, with only isolated instances of unclear or high risk. The RCTs showed slightly greater variability, primarily due to issues with blinding, whereas the case-control and cohort studies maintained consistently strong methodological standards. Thus, the body of evidence synthesized from these studies is generally reliable, with only limited potential risk of bias.

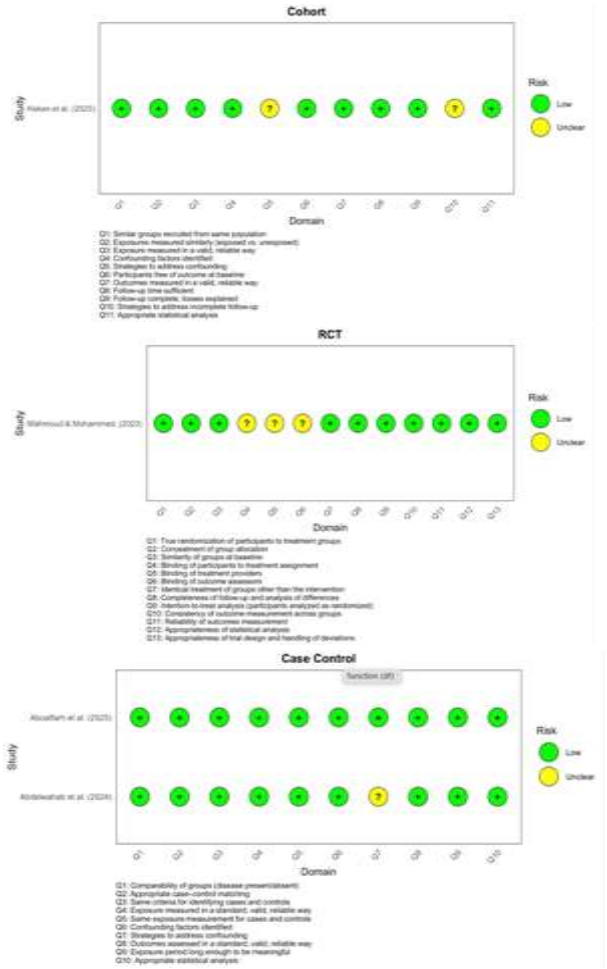

Figure 2. Risk of Bias

Study Outcomes

Four studies involving adult patients with chronic kidney disease (CKD) stage 5 on regular haemodialysis were included.(Abdelwahab et al., 2024; Aboalfarh et al., 2025; Kekan et al., 2023; Mahmoud et al., 2023) All investigated the effects of oral lactoferrin supplementation compared with standard treatments such as erythropoiesis-stimulating agents (ESAs) or oral iron therapy **(Table 1 and 2)**. Across studies, lactoferrin consistently improved haemoglobin and iron parameters, while also demonstrating anti-inflammatory effects and good tolerability. In randomized and interventional studies, lactoferrin led to significant increases in haemoglobin (Hb), transferrin saturation (TSAT), and serum iron, accompanied by a notable reduction in hepcidin levels. Compared to conventional oral iron, lactoferrin achieved greater improvements in iron utilization and anaemia correction.(Mahmoud et al., 2023)

Table 1. Summary of Outcomes in Adult Population

Author (Year)	Design; Duration	Problem	Intervention	Comparison	Outcomes
Mahmoud & Mohammed, (2023)(Mahmoud et al., 2023)	RCT; 6 months	140 adult patients with CKD stage 5 on regular haemodialysis	Oral bovine lactoferrin 100 mg twice daily (20–30% iron-saturated; ≈70–	Oral ferrous glycine sulfate 576 mg twice daily (100	Lactoferrin significantly improved haemoglobin levels, produced greater improvement in iron utilization markers

			84 µg elemental iron per dose) (n = 70)	mg elemental iron per dose) (n = 70)	(TSAT) and reduced hepcidin more than ferrous glycine sulfate, with clear superiority between comparison group.
Abdelwahab et al. (2024)(Abdelwahab et al., 2024)	Interventional case–control; 3 months	70 adult patients with CKD stage 5 on HD with functional iron deficiency anaemia	Oral lactoferrin 200 mg/day + ESA (4000 IU, 3× weekly) (n=35)	ESA alone (4000 IU, 3× weekly) (n=35)	Both lactoferrin + ESA and ESA alone improved, iron, ferritin, and TSAT similarly pre and post treatment with no significant difference between groups.
Aboalfarh et al. (2025)(Aboalfarh et al., 2025)	Interventional case–control; 3 months	70 adult patients with CKD stage 5 on haemodialysis with functional iron deficiency anaemia and inflammation	Oral lactoferrin 200 mg/day + ESA 4000 IU three times weekly (n = 35)	ESA alone (4000 IU, 3× weekly; n = 35)	• Haemoglobin and iron indices (iron, ferritin, TSAT) increased similarly in both lactoferrin + ESA and ESA-only groups, showing no significant between-group difference. • Lactoferrin significantly reduced inflammatory markers (CRP and IL-6), showing clear anti-inflammatory advantage over ESA alone.
Kekan et al. (2023)(Kekan et al., 2023)	Prospective observational single-arm pilot study; 4 weeks	46 adult CKD stage 5 patients with anaemia (Hb <10 g/dL, Tsat >20%)	Oral lactoferrin 100 mg twice daily ± iron supplementation (n = 46; 18 received iron)	No control group (within-group comparison)	• Haemoglobin increased slightly with lactoferrin, and patients receiving additional iron had somewhat greater improvement, though not significant. • Iron supplementation with lactoferrin showed minor non-significant changes in iron-related parameters. • ESR decreased slightly while CRP

increased, with no significant overall change in inflammation.
- Only one patient developed transient diarrhea; no major adverse events reported.

Abbreviation: Hb: Haemoglobin; RBC: Red Blood Cells; MCH: Mean Corpuscular Haemoglobin; MCHC: Mean Corpuscular Haemoglobin Concentration; RDW-SD: Red Cell Distribution Width (Standard Deviation); IL-6: Interleukin-6; GDF-15: Growth Differentiation Factor-15; GFR: Glomerular Filtration Rate; TSAT: Transferrin Saturation; TIBC: Total Iron Binding Capacity; CKD: Chronic Kidney Disease; ESRD: End-Stage Renal Disease; GIT: Gastrointestinal Tract

Table 2. Several Parameter Outcomes in Adult Population

Author (Year)	Design; Duration	Problem	Parameter	Intervention	Before	After	Comparison	Before	After	p-value
Mahmoud & Mohammed, (2023)(Mahmoud et al., 2023)	RCT; 6 months	140 adult patients with CKD stage 5 on regular haemodialysis	Hb	Oral bovine lactoferrin 100 mg twice daily	7.7 (7.5–8.1)	9.7 (9.3–10.0)*	Oral ferrous glycine sulfate 576 mg twice daily	7.7 (7.5–8.1)	8.1 (7.6–8.5)	**<0.0001**
			Hepcidin		345 (340–350)	105 (101–112)*		344 (335–350)	334 (330–341)*	**<0.0001**
			TSAT		7 (5–9)	28 (26–31)*		7 (5–9)	10 (7–12)*	**<0.0001**
Abdelwahab et al. (2024)(Abdelwahab et al., 2024)	RCT; 6 months	140 adult patients with CKD stage 5 on regular haemodialysis	Hb	Oral lactoferrin 200 mg/day + ESA (4000 IU, 3× weekly) (n=35)	8.70 ± 0.69	10.55 ± 1.47*	ESA alone (4000 IU, 3× weekly) (n=35)	8.80 ± 0.63	10.35 ± 1.36	0.541
			Ferritin		894 (856–950.5)	1032 (954–1141)*		882 (827.5–942.5)	1001 (956.5–1055)*	0.310
			SI		49.15 ± 24.09	65.89 ± 25.37*		52.65 ± 25.91	63.20 ± 26.40*	0.665
			TSAT		10.69 ± 5.41	13.14 ±		9.47 ± 5.82	11.07 ±	0.137

						5.58 *			5.93 *	
			WBC		4.72 ± 1.44	4.65 ± 1.43		4.63 ± 1.39	4.74 ± 1.52	0.802
Aboalfarh et al. (2025)(Aboalfarh et al., 2025)	Interventional case–control; 3 months	70 adult patients with CKD stage 5 on haemodialysis with functional iron deficiency anaemia	Hb	Oral lactoferrin 200 mg/day + ESA 4000 IU three times weekly (n = 35)	8.70 ± 0.69	10.55 ± 1.47 *	ESA alone (4000 IU, 3× weekly; n = 35)	8.80 ± 0.63	10.35 ± 1.36 *	0.541
			Ferritin		894 (856–951)	1032 (954–1141)*		882 (828–943)	1001 (957–1055)*	0.310
			SI		49.15 ± 24.09	65.89 ± 25.37*		52.65 ± 25.91	63.20 ± 26.40*	0.665
			TSAT		10.69 ± 5.41	13.14 ± 5.58 *		9.47 ± 5.82	11.07 ± 5.93 *	0.137
			CRP		14.5 (7.4–22.4)	6.1 (2.1–10.6)*		14.2 (7.8–20)	12.0 (5.3–17.9)	**0.01**
			IL-6		40.69 (27.1–52.1)	9.01 (5.7–21.0)*		42.15 (33.7–59.5)	31.34 (21.4–64.0)	
Kekan et al. (2023)(Kekan et al., 2023)	Interventional case–control; 3 months	70 adult patients with CKD stage 5 on HD with IDA and inflammation	Hb	Oral lactoferrin 100 mg twice daily ± iron supplementation (n = 46; 18 received iron)	8.18 ± 1.19	8.96 ± 1.93 *	No Control Group			
			ESR		74.22 ± 28.60	67.58 ± 34.31				
			CRP		8.23 ± 13.16	11.71 ± 24.63				

Abbreviations: Hb (haemoglobin), RBC (red blood cells), SI (serum iron), TSAT (transferrin saturation), GFR (glomerular filtration rate), IL-6 (interleukin-6), GDF-15 (growth differentiation factor-15), TIBC (total iron-binding capacity), CKD (chronic kidney disease), ESRD (end-stage renal disease), HD (haemodialysis), and GIT

(gastrointestinal tract). Data are expressed as mean ± standard deviation (SD) or median (interquartile range) as appropriate**.**

Asterisks (*) denote statistically significant within-group changes from baseline ($p < 0.05$), whereas bolded p-values indicate significant differences between treatment groups ($p < 0.05$). “Before” and “After” refer to measurements obtained at baseline and following the intervention period, respectively.

This systematic review evaluated the outcomes of lactoferrin supplementation as a therapeutic or adjunctive treatment for iron deficiency anaemia (IDA) in patients undergoing regular haemodialysis due to chronic kidney disease (CKD). Across the included studies, lactoferrin consistently demonstrated improvement in hematologic parameters and reduction in inflammatory markers, while being well tolerated and associated with fewer gastrointestinal adverse effects compared to conventional iron preparations.

Haematological Parameter

Lactoferrin is a natural, nonheme, iron-binding cationic glycoprotein that belongs to the transferrin family. It has an iron-binding affinity approximately 300 times greater than that of transferrin and is capable of retaining iron even at a pH below 4, such as in the gastrointestinal tract or sites of inflammation. Each lactoferrin molecule binds two iron ions, thereby facilitating iron absorption. It enters intestinal cells through specific lactoferrin receptors and releases the bound iron inside the cells, after which the iron is transported into the bloodstream via transferrin.(El Amrousy et al., 2022) Lactoferrin supplementation has been shown to significantly increase haemoglobin (Hb) levels and red blood cell (RBC) counts in most studies conducted among adult populations.(Abdelwahab et al., 2024; Aboalfarh et al., 2025; Mahmoud et al., 2023)

Iron Status

Iron status is another important consideration in treating anaemia in CKD patients. Adequate iron availability is crucial for effective erythropoiesis, as iron serves as the essential component for haemoglobin synthesis and oxygen transport.(Kawakami et al., 1988) Disturbances in iron metabolism, often mediated by inflammation-induced hepcidin elevation, can lead to functional iron deficiency despite normal or elevated ferritin levels.(Gaweda, 2017; Yoo et al., 2009) Maintaining optimal iron status not only supports red blood cell production but also enhances the responsiveness to erythropoiesis-stimulating agents (ESAs), thereby reducing the required ESA dose and associated treatment costs. Moreover, proper iron regulation minimizes oxidative stress and potential tissue damage from iron overload, which is particularly important in CKD patients who are vulnerable to inflammation and impaired renal clearance.(Clark, 2008; Gaweda, 2017)

Studies in adults showed that lactoferrin improved iron markers more effectively than ferrous sulfate.(Mahmoud et al., 2023) Similarly, in adult haemodialysis patients, lactoferrin increased Hb and transferrin saturation (TSAT) while significantly reducing hepcidin levels, a key regulator of iron metabolism whose overexpression in CKD impairs iron absorption and utilization.(Mahmoud et al., 2023) These findings suggest that lactoferrin may enchance both iron bioavailability and erythropoiesis through its dual iron-binding and anti-inflammatory mechanisms in adults.

Anti-Inflammatory Effects

Beyond hematologic benefits, lactoferrin also demonstrated notable anti-inflammatory effects, with several studies reporting reductions in C-reactive protein (CRP), interleukin-6 (IL-6), and hepcidin levels.(Legrand et al., 2005) This is clinically relevant because inflammation contributes significantly to functional iron deficiency and erythropoiesis-stimulating agent (ESA) resistance in CKD. Lactoferrin's ability to modulate inflammatory cytokines and oxidative stress may help restore iron mobilization and improve responsiveness to erythropoietin therapy.(Legrand et al., 2004) Conversely, traditional intravenous (IV) iron therapy, although effective for iron replacement, has been associated with oxidative stress and renal function deterioration. One study reported a significant reduction in inflammatory markers such as IL-6 and CRP,(Aboalfarh et al., 2025) whereas another observed a significant increase in CRP.(Kekan et al., 2023)

The anti-inflammatory effects of lactoferrin are thought to result from its ability to regulate immune pathways and inhibit pro-inflammatory cytokine synthesis. Lactoferrin can bind to lipopolysaccharides and prevent Toll-like receptor (TLR)-mediated activation of nuclear factor-kappa B (NF-κB), thereby reducing the release of IL-6, tumor necrosis factor-alpha (TNF-α), and CRP.(Legrand et al., 2005, 2004; Yoo et al., 2009) Additionally, by chelating free iron, lactoferrin limits the formation of reactive oxygen species (ROS), mitigating oxidative stress that further drives renal inflammation.(Conneely, 2001) These mechanisms not only contribute to improved iron metabolism but may also slow the progression of CKD-related inflammation and endothelial dysfunction. Consequently, lactoferrin represents a dual-action therapeutic approach, simultaneously targeting anaemia and the underlying inflammatory milieu that exacerbates CKD pathology.(Legrand et al., 2005)

Comparison with Other Regimens

When compared with standard iron supplements, lactoferrin demonstrated similar or superior efficacy in correcting anaemia and improving iron status, without the gastrointestinal discomfort commonly observed with ferrous salts.(Mahmoud et al., 2023) When combined with ESA therapy, lactoferrin did not further increase Hb beyond that achieved by ESA alone but did confer additional anti-inflammatory benefits, suggesting its potential as an adjunctive rather than replacement therapy.(Abdelwahab et al., 2024; Aboalfarh et al., 2025) Across all studies, adverse effects were minimal and primarily limited to mild gastrointestinal symptoms such as upset stomach or constipation, supporting lactoferrin's favorable safety profile.(Abdelwahab et al., 2024; Aboalfarh et al., 2025) The most commonly used dose is 100 mg once or twice daily, which has shown favorable effects on haemoglobin and inflammatory markers.(Hegazy et al., 2025; Turky et al., 2022)

The observed hematologic and anti-inflammatory benefits support lactoferrin as a safe and effective adjunct therapy for managing IDA in patients with chronic kidney disease CKD, particularly in those who are intolerant to conventional oral iron or at risk of complications from intravenous iron therapy. By enhancing iron utilization and reducing systemic inflammation, lactoferrin may also contribute to lowering ESA dose requirements and improving overall anaemia management outcomes in haemodialysis patients. However, variations in dosage, treatment duration, and iron saturation levels across studies highlight the need for standardized treatment protocols. Lactoferrin may serve as an adjunct to standard iron

regimens to maximize its combined benefits on inflammation, iron status, and haemoglobin levels. Nevertheless, its greatest therapeutic advantage may be achieved in earlier stages of CKD, although further research is warranted.

The findings should be interpreted with caution due to the limited number of high-quality randomized controlled trials, small sample sizes, and heterogeneity in study design and outcome measures. Most studies were short-term and did not assess long-term safety or cardiovascular outcomes. Future multicenter RCTs with standardized dosing regimens and extended follow-up are needed to confirm lactoferrin's efficacy, establish optimal dosing, and evaluate its cost-effectiveness compared to established therapies.

CONCLUSION

The findings of this systematic review indicate that lactoferrin demonstrates promising potential as an adjunctive therapy for managing iron deficiency anaemia in patients with chronic kidney disease undergoing regular haemodialysis. Across the included studies, lactoferrin consistently improved key haematological parameters such as haemoglobin, serum iron, and transferrin saturation, while also contributing to the reduction of inflammatory markers including hepcidin, C-reactive protein, and interleukin-6. These dual benefits highlight lactoferrin's unique role not only in enhancing iron bioavailability and erythropoiesis but also in addressing the inflammatory mechanisms underlying functional iron deficiency in CKD patients. Furthermore, compared with conventional iron supplementation, lactoferrin exhibited better tolerability with fewer gastrointestinal side effects, suggesting its suitability as a safer alternative or complementary therapy in long-term anaemia management. However, despite these encouraging outcomes, the current body of evidence remains limited by small sample sizes, short intervention durations, and heterogeneity in study design, dosage, and outcome measurements. Therefore, future research should focus on conducting large-scale, multicenter randomized controlled trials with standardized protocols to validate the efficacy and safety of lactoferrin over longer follow-up periods. In addition, further studies are needed to determine optimal dosing regimens, evaluate cost-effectiveness, and explore its impact on long-term clinical outcomes such as cardiovascular events and mortality in CKD patients. Investigating the role of lactoferrin in earlier stages of CKD and its interaction with other therapeutic modalities may also provide valuable insights for expanding its clinical application.

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