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ASSESSMENT OF ERYTHROPOIETIN FOR TREATMENT OF ANEMIC PATIENTS WITH CHRONIC KIDNEY DISEASE UNDERGOING MAINTENANCE HEAMODIALYSIS: A REVIEW

Saman Ka Phawa[1]*, Shyamal Koley[2]

[1]Post Graduate Student, Department of Dialysis Therapy Technology, University School of Allied Health Sciences, Lamrin Tech Skills University Punjab, India.
[2]Professor and Dean, University School of Allied Health Sciences, Lamrin Tech Skills University, Punjab, India.

***Corresponding Author: Saman Ka Phawa**
Post Graduate Student, Department of Dialysis Therapy Technology, University School of Allied Health Sciences, Lamrin Tech Skills University Punjab, India. **DOI:** https://doi.org/10.5281/zenodo.17221594

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ABSTRACT

Background: Anaemia is a common complication in chronic kidney disease (CKD), and is associated with a reduced quality of life, and an increased morbidity and mortality. The mechanisms involved in anaemia associated to CKD are diverse and complex. They include a decrease in endogenous erythropoietin (EPO) production, absolute and/or functional iron deficiency, and inflammation with increased hepcidin levels**. Objectives:** The objectives of the study were to review the current knowledge of the efficacy of erythropoietin in the treatment of anaemic patients with CKD undergoing maintenance haemodialysis. **Results:** In this study, the pathophysiology of CKD-related anaemia, role of EPO and oxygen sensing, molecular functioning of HIF, regulation of HIF activity, EPO production in CKD, iron metabolism and treatment of patients with anaemic CKD were discussed extensively. Patients are most commonly managed with oral or intravenous iron supplements and with erythropoiesis stimulating agents (ESA). However, these treatments have associated risks, and sometimes are insufficiently effective. Nonetheless, in the last few years, there have been some remarkable advances in the treatment of CKD-related anaemia, which have raised great expectations. **Conclusion:** The findings of the study would be highly beneficial in the field of renal treatment, transplantation and research applying the efficacy of endogenous erythropoietin in the treatment of anaemic patients with chronic kidney disease undergoing maintenance haemodialysis.

KEYWORDS: Erythropoietin. Anaemia. Chronic Kidney Disease. Haemodialysis.

INTRODUCTION

Anaemia is a frequent and clinically significant complication observed in patients with chronic kidney disease (CKD). It contributes not only to poorer quality of life (QoL)[1,2] and worse renal survival[3], but also to heightened risks of morbidity and mortality[4;5] increasing the cost of hospitalization.[6] The underlying causes of anaemia in CKD are multifactorial and intricate, involving several interrelated mechanisms. A primary factor is the inadequate production of endogenous erythropoietin (EPO) by the diseased kidneys, coupled with absolute or functional iron deficiency. Additionally, persistent inflammation and increased levels of hepcidin further disrupt erythropoiesis and iron metabolism, worsening the condition. The high incident of CKD (approximately 13.4%) makes it more vulnerable. reporting that anaemia was twice as prevalent in patients with CKD as in the general population.[7] The prevalence of anaemia raised with the progression of CKD: (8.4% at stage 1 to 53.4% at stage 5.[8] One study revealed that those that had developed anaemia significantly progressed more rapidly to CKD stages 4–5.[9] An Italian observational study evaluated the prevalence of severe and mild anaemia was 18 and 44%.[10]

In clinical practice, anaemia in CKD is generally treated with oral or intravenous iron supplementation and the administration of erythropoiesis-stimulating agents (ESAs). While these therapies are widely used, they are not without limitations. Some patients exhibit suboptimal responses, and concerns regarding adverse effects, such as cardiovascular risks and iron overload, remain relevant. Despite these challenges, recent years have witnessed substantial progress in the management of CKD-associated anaemia, generating considerable optimism in both research and patient care.[11]

One of the most promising advancements is the development of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs). This emerging class of drugs triggers adaptive responses resembling those seen under hypoxic conditions, thereby enhancing endogenous EPO synthesis, lowering hepcidin concentrations, and optimizing iron utilization. A number of these agents have proceeded through clinical evaluation, with several already being approved for therapeutic use. Parallel to this, newer clinical trials focusing on iron supplementation strategies have provided novel insights, suggesting the potential for updated treatment goals and more individualized patient management.

Overall, the evolving understanding of CKD-related anaemia has driven the refinement of existing therapies while also encouraging the introduction of innovative treatment modalities. Current research emphasizes not only the pathophysiological mechanisms underlying this condition but also a forward-looking perspective on therapies and personalized management strategies aimed at improving patient outcomes.

MATERIALS AND METHODS

A total of 66 references were reviewed which were closely related to the assessment of erythropoietin for treatment of anaemic patients with chronic kidney disease undergoing maintenance haemodialysis. These articles were consulted from databases such as PubMed, Google Scholar, and Web of Science. The inclusion criteria were as followed: (1) articles containing the anaemic patients with CKD undergoing haemodialysis and (2) reports regarding QoL of the CKD patients.

RESULTS AND DISCUSSION

Pathophysiology of Anaemia in CKD

The pathophysiology of anaemia in CKD is highly complex and involves multiple overlapping mechanisms rather than a single cause. Historically, the central explanation has been the progressive decline in endogenous EPO production, which is critical for stimulating red blood cell production in the bone marrow. However, a broader range of mechanisms has since been identified as equally important contributors. These include absolute iron deficiency caused by chronic blood losses or impaired gastrointestinal absorption, as well as functional iron deficiency, where iron stores exist but remain biologically unavailable due to elevated hepcidin. Hepcidin, whose levels increase with inflammation and reduced renal clearance, blocks the release of iron from storage sites and reduces intestinal absorption.

Additional factors that worsen anaemia in CKD are the persistent systemic inflammation associated with CKD and its comorbidities, which further suppresses erythropoiesis; the toxic effects of uremic solutes that blunt the responsiveness of bone marrow precursor cells to EPO; the shortened survival of circulating red blood cells compared to healthy individuals; and nutritional deficiencies of essential vitamins such as folic acid and vitamin B12 needed for erythropoiesis.[12] Taken together, these processes explain why anaemia in CKD is not solely the result of low EPO levels but rather a systemic disorder involving impaired iron metabolism, marrow dysfunction, and inflammatory inhibition.

Hypoxia Inducible Factor (HIF) System

Role of EPO and oxygen sensing

Erythropoietin is a 30.4 kDa glycoprotein hormone that is indispensable for red cell survival, proliferation, and differentiation. It acts by binding to its receptor located on the surface of erythroid progenitor cells in the bone marrow. The main source of EPO in the human body is the kidney, specifically fibroblast-like peritubular interstitial cells, while the liver's perisinusoidal cells provide a minor contribution. EPO release from these sites is tightly regulated by tissue oxygen levels, allowing the body to maintain homeostasis in the number of circulating red blood cells.[13]

The regulation of EPO expression at the gene level is largely controlled by the hypoxia-inducible factor (HIF) transcription system. HIF acts as a cellular oxygen sensor and is central to coordinating adaptive responses to hypoxia.

Molecular functioning of HIF

Under hypoxia or anaemic stress, HIF-1 binds to the promoter region of the EPO gene, switching on its expression. Structurally, HIF-1 is a heterodimer comprising two subunits: HIF-1β, which is stably expressed, and HIF-1α, which is oxygen-sensitive. In normoxic conditions, HIF-1α undergoes rapid degradation, leaving little to exert transcriptional activity. However, when oxygen tension drops, HIF-1α levels rise, enter the nucleus, and pair with HIF-1β. This α-β heterodimer binds to DNA sequences called hypoxia response elements (HREs), thereby activating genes essential for adaptation to hypoxia.

This cascade of events is biologically advantageous: it enhances oxygen delivery (by stimulating red blood cell production and angiogenesis) while simultaneously reducing tissue oxygen consumption through metabolic adjustments. Beyond activating the EPO gene, the HIF complex also stimulates transcription of genes encoding the EPO receptor, transferrin, transferrin receptor, vascular endothelial growth factor (VEGF), and endothelin-1.[14] In this way, HIF serves as a master regulator of erythropoiesis, iron homeostasis, vascular remodelling, and cellular metabolism.

Recent studies have extended the functional significance of the HIF system. It is now recognized as an important regulator of cell metabolism, influencing not only oxygen handling but also lipid pathways.[15-17] HIF activity has been shown to affect LDL- and total cholesterol levels, in part by modulating degradation of the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase, the rate-limiting step in cholesterol biosynthesis.[18-20] These effects resemble metabolic changes observed in individuals living at high altitudes, where chronic hypoxia induces similar adaptive pathways.[21]

Regulation of HIF activity

Under normal oxygen levels, HIF-1α is quickly degraded through hydroxylation at two specific proline residues. This modification is carried out by prolyl hydroxylase domain (PHD) enzymes, which require oxygen, iron, and 2-oxoglutarate as cofactors. Of the three isoforms identified - PHD1, PHD2, and PHD3, PHD2 is considered the principal regulator of HIF stability.[22] Once hydroxylated, HIF-1α becomes a target for the von Hippel–Lindau (pVHL) E3 ubiquitin ligase, which attaches ubiquitin to the protein, marking it for rapid proteasomal degradation.

In hypoxia, however, the activity of PHDs is diminished due to lack of oxygen, preventing hydroxylation of HIF-1α. As a result, HIF-1α becomes stabilized, translocate to the nucleus, and activates hypoxia-responsive gene expression.[23,24] This oxygen-sensing pathway has become the pharmacological target for hypoxia-inducible factor prolyl-hydroxylase inhibitors (HIF-PHIs), a novel therapeutic class for managing anaemia in CKD. These drugs artificially stabilize HIF-1α, mimicking hypoxic conditions and thereby boosting EPO production and iron availability.

Additional regulation by FIH and angiotensin II

HIF activity undergoes further fine-tuning through regulation by factor-inhibiting HIF (FIH), which hydroxylates an asparagine residue on HIF-1α in normoxic conditions. Unlike PHD-mediated hydroxylation that leads to degradation, asparagine hydroxylation by FIH directly reduces HIF's transcriptional capacity. It achieves this by preventing recruitment of transcriptional co-activators such as CBP and p300, both of which are necessary for full gene transactivation.[24-27]

Additionally, angiotensin II, which is commonly elevated in CKD patients, plays a modulatory role in this process. It triggers increased formation of reactive oxygen species (ROS), which inhibit PHD enzyme activity, thereby promoting higher EPO synthesis through stabilization of HIF-1α.[28–30] This highlights the interconnectedness of the renin–angiotensin system, oxidative stress, and erythropoietic control in CKD.

EPO Production in CKD

In patients with CKD, circulating EPO concentrations are typically inappropriately low for the severity of anaemia. The decline in EPO production begins relatively early in the disease, but the defect becomes much more clinically evident once the estimated glomerular filtration rate (eGFR) falls below 30 mL/min/1.73 m².[31] This state of absolute EPO deficiency results from two main mechanisms: reduced EPO synthesis within the kidney and impaired oxygen sensing by the EPO-producing cells.

A defining feature of CKD is altered renal hemodynamic, as blood flow to the kidneys decreases progressively with worsening disease. This alteration leads to an adaptive metabolic response, where renal tissues lower their oxygen consumption to preserve a normal oxygen gradient. While protective, this adaptation keeps prolyl hydroxylase domain (PHD) enzymes active, thereby preventing HIF stabilization. In turn, the formation of the HIF heterodimer is impaired and the EPO gene remains transcriptionally inactive, even in the presence of marked anaemia.[32]

Experimental studies have further demonstrated that inflammatory cytokines, including interleukin-1α (IL-1α), interleukin-1β (IL-1β), transforming growth factor-β (TGF-β), and tumor necrosis factor-α (TNF-α), interfere with hypoxia-driven EPO production.[33,34] Considering that CKD is inherently associated with chronic inflammation and heightened immune activation, the combined effect significantly blunts EPO gene expression under hypoxic stress.[35,36] However, this suppression is not absolute. Clinical observations suggest that in some CKD patients, EPO-producing capacity can be partially restored under specific conditions, such as acute bleeding episodes or exposure to high altitude. These circumstances enhance HIF signalling, reactivating previously quiescent renal erythropoietin-producing (REPOS) cells and occasionally liver cells, thus augmenting endogenous EPO synthesis.[37] Supporting this, observational data show that haemodialysis patients living at higher altitudes need lower doses of recombinant human EPO (rhuEPO), reflecting enhanced native hormone production under chronic hypoxia.[38]

Beyond absolute deficiency, a subset of CKD patients experiences what is termed functional EPO deficiency or EPO resistance, characterized by normal or near-normal circulating EPO concentrations but persistently low haemoglobin (Hb) levels.[39] This indicates inadequate responsiveness of the bone marrow to both endogenous and exogenous EPO. Several interconnected mechanisms explain this resistance. First, pro-inflammatory cytokines can promote apoptosis of erythroid progenitors or exert direct cytotoxicity through nitric oxide and oxidative stress pathways.[40,41] Second, cytokines may downregulate surface expression of EPO receptors on erythroid precursors, diminishing their ability to respond.[42–45] Additionally, evidence suggests cytokines can stimulate the generation of antagonistic peptides that competitively bind EPO receptors and block downstream signalling.

Another major player is hepcidin, a liver-derived hormone whose production is strongly upregulated by inflammation and inadequate renal clearance. Elevated hepcidin not only reduces iron absorption and release from stores but also directly inhibits proliferation and survival of erythroid progenitors, thereby amplifying EPO resistance.[46] Finally, the process of neocytolysis, a physiological mechanism by which newly formed red cells are selectively destroyed, has also been implicated. In CKD patients receiving exogenous rhuEPO therapy, neocytolysis may worsen anaemia control and contribute significantly to treatment resistance.[47]

Taken together, these multiple converging factors - absolute deficiency, cytokine-mediated suppression, iron-restricted erythropoiesis, and neocytolysi, explain why EPO dysfunction in CKD is not merely a matter of reduced hormone levels but also of diminished erythroid responsiveness.

Iron Metabolism

Iron plays a critical role in erythropoiesis, as it is an essential component for haemoglobin synthesis and for an appropriate response to EPO. In anaemic patients, correcting iron deficiency not only improves red blood cell production but also allows for the use of lower doses of exogenous EPO, reducing treatment burden and potential risks.[48] Importantly, iron is not only vital for red blood cell formation but also participates in several non-erythropoietic functions. Iron deficiency, even in the absence of anaemia, has been linked to impaired exercise capacity, neurocognitive dysfunction, reduced QoL, and higher risks of hospitalization or death in heart failure patients with reduced ejection fraction. These findings highlight the importance of addressing iron deficiency independently of haemoglobin status.[49]

On a molecular level, iron is indispensable beyond haemoglobin. It serves as a core component of myoglobin, which mediates oxygen transport in muscle cells. Iron also participates in intracellular metabolic activity by being integrated into enzymes involved in the electron transport chain and oxidative phosphorylation, which are fundamental processes for cellular energy production. Furthermore, iron contributes to DNA synthesis, degradation, and repair mechanisms, and is a structural element in the cytochrome P450 enzyme family, which governs drug metabolism and detoxification.[50] Given these broad physiological roles, it is not surprising that accumulating evidence from observational studies shows that iron deficiency correlates with adverse outcomes in CKD patients.[51–53]

Most of the body's iron supply is derived not from dietary intake but from recycling of iron within macrophages. Senescent red blood cells are engulfed by macrophages, which then reclaim iron for reuse. Additional iron is mobilized from hepatocytes and enterocytes. Only a smaller proportion is contributed by dietary absorption. Notably, iron losses from the body are limited to non-regulated processes such as the shedding of skin and intestinal cells, or through blood loss. Since there is no active excretory pathway for iron, regulation relies entirely on control of intestinal iron absorption, which is mediated by the hormone hepcidin.

The release of stored or recycled iron into circulation is accomplished via ferroprotin, the only known cellular iron exporter. Once in the bloodstream, iron is bound to transferrin, which delivers it to tissues via interaction with transferrin receptors on target cells.[54] The activity of transferrin receptors adjusts dynamically in response to intracellular iron concentration and the cell's proliferative needs. Hepcidin, a peptide hormone primarily synthesized in the liver and acting as an acute-phase protein, is the master regulator of systemic iron metabolism. Its primary function is to maintain iron homeostasis.

Hepcidin accomplishes this by downregulating the absorption of dietary iron and regulating iron release from storage sites. It inhibits the function of divalent metal transporter 1 (DMT1) in the intestinal mucosa, thereby lowering duodenal uptake of dietary iron. Simultaneously, hepcidin promotes the internalization and degradation of ferroportin, effectively trapping iron within enterocytes, macrophages, and hepatocytes, and preventing its entry into the circulation. In states of iron overload, hepcidin levels rise, further limiting iron release. Conversely, iron deficiency suppresses hepcidin production, allowing for greater intestinal absorption and mobilization from stores.[55]

In CKD, absolute and functional iron deficiency are very common. Blood loss (such as that occurring in haemodialysis circuits), reduced intestinal absorption, and an inflammatory milieu all contribute. The uremic state and comorbid conditions create a chronic inflammatory burden, which disrupts iron metabolism. Proinflammatory cytokines increase hepatic hepcidin synthesis, upregulate DMT1 and ferritin in macrophages, and suppress ferroportin expression. They also enhance iron sequestration within macrophages by stimulating transferrin receptor activity, thereby increasing uptake of transferrin-bound iron. In CKD, hepcidin clearance is reduced because of declining eGFR, leading to even higher systemic levels. Collectively, these mechanisms trap iron within cells, reduce plasma iron availability, and worsen anaemia.[56]

During stress erythropoiesis, EPO stimulates the production of erythroferrone (ERFE), a hormone secreted by erythroblasts. ERFE suppresses hepatic hepcidin production, thereby facilitating the release of iron needed for red blood cell synthesis.[57] Additionally, HIF-1α, and possibly HIF-2α, play direct roles in modulating hepcidin expression, with HIF binding to its promoter to repress transcription.[58] HIF-2α further promotes iron availability by inducing expression of transport proteins such as DMT1 and duodenal cytochrome b (DCYTB), which support both dietary iron absorption from the intestinal lumen and mobilization of iron from lysosomes within cells.[59]

Treatment of Patients with Anaemic CKD: Erythropoiesis-Stimulating Agents (ESAs)

The introduction of erythropoiesis-stimulating agents (ESAs) represented a major milestone in the treatment of anaemia associated with CKD. The first available ESA was epoetin-α, produced through recombinant DNA technology in mammalian cell cultures. Shortly after, epoetin-β was developed with a similar mechanism of action. Efforts to improve dosing convenience and drug half-life led to the development of second-generation agents such as darbepoetin alfa (DA) and methoxy polyethylene glycol-epoetin beta, both of which have prolonged half-lives, thereby reducing the frequency of administration. More recently, biosimilar formulations of epoetin have entered clinical practice, expanding therapeutic options and potentially lowering overall treatment costs.[60]

It is important to note, however, that ESAs are not identical. They differ in their pharmacokinetic and pharmacodynamic characteristics, including half-life, receptor-binding affinity, and dose-response relationships. These differences make long-acting ESAs particularly attractive for non-dialysis dependent CKD (ND-CKD) patients by enabling less frequent dosing schedules and greater convenience in therapy. An additional consideration is that the dose conversion factor between short-acting and long-acting ESAs is not linear. Indeed, at higher administered doses, long-acting ESAs appear to demonstrate greater dose efficiency compared to their short-acting counterparts.[60]

Despite these pharmacological distinctions, clinical evidence has not yet demonstrated a clear superiority of one ESA formulation or dosing regimen over another. Systematic reviews and Cochrane meta-analyses have consistently found insufficient evidence to conclude that any individual agent, or any particular pattern of administration, leads to better efficacy or safety outcomes compared with alternatives.[61,62]

Observational studies further highlight that results remain inconsistent. For example, an analysis from the Japanese Dialysis Registry reported that patients receiving long-acting ESAs had a 20% higher all-cause mortality risk compared to those treated with short-acting preparations.[63] In contrast, an Italian cohort study in ND-CKD patients demonstrated a higher risk of CKD progression to end-stage kidney disease (ESKD) and mortality among those who were treated with high doses of short-acting ESAs.[64] Interpretations of these findings must be cautious due to inherent biases and study design limitations in observational research.

To address these uncertainties, randomized controlled trials (RCTs) provide more robust evidence. A recent trial compared once-monthly continuous erythropoietin receptor activator (CERA) to standard shorter-acting agents such as epoetin-α/β and darbepoetin alfa across both dialysis-dependent (DD) and non-dialysis CKD populations. Results demonstrated non-inferiority in terms of haemoglobin maintenance, incidence of major adverse cardiovascular events (MACE), and all-cause mortality.[65,66] However, subgroup analyses revealed that patients who failed to maintain haemoglobin above 10 g/dL, as well as those requiring the highest quartile of ESA dosing, were at significantly increased risk of cardiovascular complications and death, irrespective of which agent they were assigned.

These findings underscore the need for further RCTs designed to directly evaluate differences between ESA formulations, particularly in patients requiring higher doses, where the balance between therapeutic efficacy and cardiovascular risk remains most uncertain.

CONCLUSION

The optimal haemoglobin (Hb) target in patients with CKD undergoing treatment with erythropoiesis-stimulating agents (ESAs) remains a subject of ongoing debate. Current clinical evidence supports a clear benefit from correcting anaemia when Hb falls below 10 g/dL, since such correction is associated with improved patient outcomes and QoL. However, elevating Hb concentrations beyond 13 g/dL has been consistently linked to increased risks, particularly cardiovascular events. Based on available data, the recommended Hb range during therapy generally lies between 10 and 12 g/dL, striking a balance between therapeutic benefit and safety concerns. Importantly, tailoring the Hb target to each patient - considering their comorbidities, underlying cardiovascular risk profile, clinical status, and individual preferences, remains the most prudent approach.

Another controversial aspect concerns the interpretation of circulating EPO levels in CKD. Unlike in primary bone marrow disorders where low EPO has clear diagnostic value, patients with kidney disease may present with “normal” EPO levels that are nonetheless inadequate relative to the severity of their anaemia. This concept, termed relative erythropoietin deficiency, reflects the inability of the kidneys to increase EPO secretion proportionally to the falling haemoglobin levels. The absence of a definitive biomarker that directly quantifies insufficient renal EPO synthesis further complicates the assessment. Consequently, both clinical judgment and individualized patient evaluation are necessary when addressing anaemia management in the context of renal insufficiency.

Declaration by Authors

The authors hereby declared that it was their original peace of research and had not been sent to any other journal for publication.

Ethical Approval

Approved.

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Conflict of Interest
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