Anaemia and Chronic Kidney Disease: A Brief Review on the Direction of Their Relationship

ABSTRACT

Chronic kidney disease (CKD) is a significant global health concern, affecting approximately 10% of the adult population worldwide. Anaemia is the common complication in CKD, which severely impacts patient quality of life and increases the risk of cardiovascular complications. The primary cause of anaemia in CKD patients is insufficient production of erythropoietin (EPO), a hormone essential for red blood cell production, due to impaired kidney function. Other contributing factors include disruptions in iron metabolism, chronic inflammation, and elevated hepcidin levels, which hinder iron absorption and availability. Anaemia exacerbates symptoms such as fatigue, weakness, and cognitive impairment in CKD patients, significantly diminishing their daily functioning and overall well-being. Effective management of anaemia in CKD patients necessitates a comprehensive approach involving regular monitoring of haemoglobin and iron levels, timely administration of treatments such as EPO and intravenous iron, and addressing underlying causes. This review provides an overall overview of the pathophysiological connections, clinical implications, diagnosis, and management strategies for anaemia in CKD patients, highlighting the need for ongoing research and integrated care approaches

Keywords: *Chronic Kidney Disease (CKD), Anaemia, End-Stage Renal Disease (ESRD), Renal Function, Quality of Life*

1. INTRODUCTION

"Chronic kidney disease (CKD) is a pervasive global health issue, that affects approximately 10% of the adult population worldwide and with a high prevalence in women than in men. Characterized by a progressive decline in renal function over months or years, CKD often culminates in end-stage renal disease (ESRD), necessitating dialysis or kidney transplantation" [1][2][3]. According to studies, an estimated 850 million people worldwide have kidney disease, with the majority living in low-income and lower-middle-income countries. Nine out of ten individuals with chronic kidney disease (CKD) are in resource-poor settings and are unaware of their condition, so they refrain from seeking specific treatment [2][4][5].

"Anaemia is a common complication in patients with chronic kidney disease, where haemoglobin levels decrease as renal function deteriorates" [6][7]. "Chronic kidney disease has five stages of disease progression, with the third stage subdivided into stages 3A and 3B. Anaemia occurs in 1% of individuals with stage 3 CKD, 9% with stage 4 CKD, and 33% with stage 5 CKD. Anaemia impacts more than two-thirds (68%) of individuals beginning dialysis" [51-53]. "Additionally, 49.6% of men and 51.2% of women with stage 4 or 5 CKD who do not receive referrals from renal specialists experience anaemia" [8][9][10].

The most prominent cause of anaemia in CKD patients is insufficient production of erythropoietin (EPO), a hormone primarily synthesized by the kidneys [11]. EPO plays a critical role in erythropoiesis, the process of red blood cell production in the bone marrow. In CKD, the inability of damaged kidneys to produce adequate EPO leads to reduced red blood cell production, culminating in anaemia. This form of anaemia is distinct from other types, such as iron- deficiency anaemia, as it is directly related to renal impairment [12][13][14]. In addition to EPO deficiency, several other mechanisms contribute to anaemia in CKD patients. Iron metabolism disruption from decreased dietary iron absorption, chronic blood loss, and inflammation-induced iron sequestration in the reticuloendothelial system all contribute to iron

deficiency. Although iron stores are adequate, its bioavailability for erythropoiesis is limited, leading to anaemia [15][16].

The clinical complications of anaemia in CKD patients are profound and multifaceted. A range of symptoms, including fatigue, weakness, dyspnoea, and cognitive impairment, severely impact patients' quality of life. These symptoms can lead to decreased physical activity, depression, and overall diminished functional capacity [17][18].

Furthermore, anaemia is a well-recognized risk factor for cardiovascular complications in CKD patients [19]. It increases cardiac workload by necessitating a higher cardiac output to compensate for reduced oxygen-carrying capacity, potentially leading to left ventricular hypertrophy, heart failure, and ischaemic heart disease. These cardiovascular risks significantly contribute to the heightened mortality observed in CKD patients with anaemia [20][21][22].

Given its profound impact on patient outcomes, the management of anaemia in CKD patients is a critical aspect of nephrology care. It is evident that anaemia in chronic kidney disease (CKD) patients is a complicated condition characterized by multiple interrelated mechanisms, resulting in significant clinical complications. Understanding the connection between anaemia and CKD is essential for developing therapies, improving patient care and management, and ultimately enhancing patient outcomes. This review attempts to clarify the gray areas of pathophysiological connections, clinical implications, and management strategies for anaemia in CKD patients, providing a comprehensive overview of this critical issue.

2. Pathophysiology of Anaemia in Chronic Kidney Disease

Erythropoietin Deficiency (EPO)

EPO is a hormone produced by the kidneys that stimulates RBC production. In CKD, damaged kidneys produce less EPO, leading to decreased red blood cell production and anaemia. EPO deficiency is a primary driver of anaemia in CKD patients [23][24]. Erythropoietin administration is crucial for managing anaemia in CKD patients. Currently, there are limited data available regarding the effective management of anaemia in CKD patients. Some studies suggest that the use of erythropoietin along with iron for the treatment of renal failure-associated anaemia is more beneficial for CKD patients with low Hb. EPO alone can stimulate the bone marrow to produce RBCs, but without sufficient iron, these new RBCs will be immature and non-functional [25].

Disruption of Iron Metabolism

Iron deficiency is common in CKD patients due to impaired iron absorption, increased blood loss, and iron sequestration in the reticuloendothelial system. Increased levels of hepcidin;- a peptide hormone produced primarily by the liver regulates iron homeostasis by controlling the absorption, distribution, and storage of iron in the body. In CKD, it inhibits iron absorption and release, exacerbating IDA [24][26]. Mitochondrial dysfunction is also observed in CKD, as iron is essential for mitochondrial function as a component of cytochromes. Timely administration of intravenous iron may help to mitigate mitochondrial dysfunction. Adequate iron is crucial for efficient ATP production. IV iron administration helps quickly replenish iron stores, ensuring an adequate supply for mitochondrial function. This is especially important in CKD patients who may have impaired gastrointestinal absorption or significant iron losses. [27].

Inflammation and cytokine

Chronic inflammation in CKD contributes to anaemia through the production of pro-inflammatory cytokines such as interleukin-6 (IL-6). These cytokines can increase hepcidin levels. IL-6 stimulates the liver to produce hepcidin. Increased hepcidin levels lead to the internalization and degradation of ferroportin, the only known iron exporter on cell surfaces of enterocytes, macrophages, and hepatocytes. With reduced ferroportin activity, iron is sequestered within cells and less is available for erythropoiesis, despite adequate or increased total body iron stores. [24][28]

3. Clinical Implications of Anaemia in Chronic Kidney Disease Patients

3.1. Impact on Quality of Life

CKD patients with anaemia suffer from symptoms such as fatigue, weakness, and shortness of breath, which significantly affect quality of life. These symptoms often result in reduced physical and cognitive function, affecting daily activities and overall well-being [29]. “Hence, patient-centered management of CKD plays a critical role in these conditions. Patients with kidney disease, including those who depend on dialysis or transplantation, should feel actively supported in their symptom management through the identification and targeting of unpleasant symptoms via a tailored palliative care approach. Such an approach may help minimize the burden and consequences of kidney disease, and lead to improved patient outcomes, including health-related quality of life and better life participation” [30][31].

3.2. Cardiovascular Complications

Anaemia exacerbates cardiovascular issues in CKD patients, increasing the risk of left ventricular hypertrophy, heart failure, and ischaemic heart disease. The heart compensates for reduced oxygen delivery by increasing cardiac output, leading to hypertrophy and subsequent heart failure [32][33]. According to a secondary analysis of four community-based, longitudinal data sets, anaemia was found to be a risk factor for CVD outcomes and all-cause mortality in a community-based cohort of patients with diabetes and whether this risk is modified by the presence of CKD. The concurrent presence of anaemia and chronic kidney disease (CKD) may pose a particularly high risk for individuals with diabetes, who are already dealing with decreased oxygen supply and heightened oxygen demand [34].

4. Diagnosis of Anaemia in Chronic Kidney Disease Patients

4.1. Laboratory assessments

The diagnosis of anaemia in CKD involves measuring haemoglobin levels, serum ferritin, transferrin saturation, and EPO levels. A complete blood count (CBC) helps determine the severity of anaemia, while iron studies assess iron status [35].

In CKD patients with stable kidney function, the onset or worsening of anaemia may signal new problems causing blood loss or interfering with red cell production [35]. The clinical practice guidelines and recommendations of the 2006 National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) advise conducting annual screenings for various types of anaemia to exclude CKD-related outcomes [37].

“For CKD patients without anaemia, the Hb concentration should be measured when clinically indicated and: at least annually in patients with CKD stage 3. At least twice per year in patients with CKD stages 4–5 not on dialysis. At least every 3 months in patients with CKD stage 5 on haemodialysis (HD) or peritoneal dialysis (PD). For CKD patients with anaemia not treated with erythropoiesis-stimulating agents (ESAs), the Hb concentration should be measured when clinically indicated and: at least every 3 months in patients with CKD stages 3–5 not on dialysis and CKD stage 5 on peritoneal dialysis. At least monthly in patients with CKD stage 5 on haemodialysis” [38]. “The optimal frequency for monitoring Hb levels cannot be precisely determined. The recommendation for periodic evaluation is based on observations that, in the absence of ESA use, Hb levels often decline gradually over time in CKD patients as their glomerular filtration rate (GFR) decreases. This necessitates regular Hb surveillance. The frequency of Hb monitoring should be influenced by the severity of anaemia and the rate of Hb decline. As kidney function declines, the incidence and prevalence of anaemia increase, particularly in advanced CKD stages” [37].

“For adult CKD stage 5 patients on haemodialysis (CKD 5HD) or peritoneal dialysis (CKD 5PD) with anaemia not receiving ESA, monthly monitoring is recommended for CKD 5HD patients, and monthly monitoring is recommended every 3 months for CKD 5PD patients. In CKD 5HD patients, Hb monitoring is traditionally performed before a midweek hemodialysis session to minimize variability due to the interdialytic interval. Hb testing should also be performed whenever clinically indicated, such as after major surgery, hospitalization, or bleeding episodes” [37]. The Hb concentration thresholds for diagnosing anaemia depend on sex and age, following the World Health Organization (WHO) definitions. These benchmarks are widely applied across populations and are used to evaluate anaemia causes [39][40].

In CKD patients with anaemia, the initial evaluation should include, complete blood count (CBC), including Hb concentration, red cell indices, white blood cell count and differential, and platelet count, absolute reticulocyte count, serum ferritin level, serum transferrin saturation (TSAT), serum vitamin B12 and folate levels [38][41].

The CBC provides information about the severity of anaemia and bone marrow function. The anaemia of CKD is typically hypoproliferative, normochromic, and normocytic, similar to the anaemia of chronic disease [41]. Macrocytosis suggests folate or vitamin B12 deficiency, while microcytosis can indicate iron deficiency or haemoglobinopathies. The reticulocyte count helps assess erythropoietic activity. Iron status assessment included serum ferritin for iron storage and TSAT for iron availability. Ferritin levels are affected by inflammation, so interpretation requires caution. Additional tests, such as high - sensitivity C-reactive protein (CRP), may be appropriate in specific clinical settings to rule out inflammation due to other causes [42][43].

5. Prevalence of anaemia in CKD patients

The Indian population has a high incidence of anaemia associated with CKD and other conditions.

Zaawari et al. (2022) conducted a six-month single-center, cross-sectional, prospective observational study at a tertiary care hospital to assess the prevalence of anaemia among CKD patients. A total of 715 patients were enrolled in the study, with 432 (59.2%) being male and 292 (40.8%) being female. The mean age was 56.4±15 years. Of the 715 patients, 531 (74.3%) were found to be anaemic, and 58 (8.1%) were severely anaemic, resulting in an overall prevalence of 82.4% among the study participants. The study revealed that hypertension, diabetes, and CKD stage were associated with a high incidence of anaemia [44].

In 2016, Sathyan et al. (2017) conducted a study for a period of six months at a government tertiary referral institution in southern India. Among the 333 newly diagnosed CKD patients, a large majority (264, 79.28%) presented with stage 5 CKD. The mean Hb in the study was 8.42±2.20 g/dl. Anaemia was present in 90.39% of the patients, while 25.53% had an Hb of <7 g/dl. The prevalence of anaemia increased from stage 3 (66.6%) to stage 5 (94.7%). A total of 167 (50.15%) patients were found to have some form of CVD, of which 120 (71.86%) were males and 47 (28.14%) were females. Cardiovascular disease was more common when the cause of CKD was diabetic nephropathy (65.8%) and hypertensive nephrosclerosis (84.6%) [45].

In a cross-sectional analysis of survey data evaluating the physical health of the noninstitutionalized civilian population in the United States, it was found that approximately 15% of chronic kidney disease (CKD) patients had anaemia, which was more common in advanced stages of CKD. Additionally, only a small number of CKD patients with anaemia receive treatment for it [46].

Similarly, another institution-based cross-sectional study conducted in southwest Ethiopia revealed that the incidence of anaemia was proportional to CKD stage. Specifically, 52.67%, 19.33%, and 13.33% had stage 5, stage 4, and stage 3 CKD, respectively. The severity of anaemia also varied across CKD stages, with a greater percentage of severe anaemia found in stage 5 CKD patients (11.33%), followed by stage 3 (5.33%), stage 5 (3.33%), and stage 4 (2.33%) CKD patients. Furthermore, moderate and severe stages of anaemia are more common in patients with hypertension as a cause of CKD [47].

CONCLUSION

It is clear that anaemia in chronic kidney disease (CKD) patients is a significant health issue that requires focused attention due to its complex clinical challenges that negatively impact patient outcomes and quality of life. Patients with CKD and anaemia often experience debilitating symptoms such as fatigue, weakness, and cognitive impairment, which severely affect their daily functioning and overall well-being. Furthermore, anaemia appears to be a critical risk factor for cardiovascular complications. The effective management of anaemia in CKD patients requires a comprehensive approach that includes regular monitoring of haemoglobin levels and iron status. By addressing the underlying causes

and implementing comprehensive management strategies, it is possible to mitigate the adverse effects of anaemia on CKD patients, thereby enhancing their quality of life and survival. Continued efforts in research, clinical practice, and public health initiatives are crucial for combating the burden of anaemia in CKD patients and improving outcomes for CKD patients worldwide.

Future Directions

Research on New Therapies

Ongoing research into novel therapies such as HIF-PHIs (hypoxia-inducible factor (HIF) prolyl hydroxylase (PH)) and other agents offers hope for more effective and safer anaemia management in CKD patients. Future studies should focus on the long-term outcomes, safety profiles, and cost-effectiveness of these treatments [48].

Integrated Care Models

Integrated care models that address both CKD and its complications, including anaemia, are crucial for comprehensive patient management. Multidisciplinary teams involving nephrologists, haematologists, dietitians, and primary care physicians can provide holistic care [49].

Patient Education and Engagement

Educating patients about the importance of anaemia management and engaging them in their treatment plans can improve adherence and outcomes. Patient-centered approaches that consider individual preferences and concerns are vital [50].

ACKNOWLEDGEMENTS

This study did not receive any type of funding assistance from the government or private organizations.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

'Prajeesha. k' designed the study, performed the literature searches, and wrote the first draft of the manuscript. 'Dr. Swathi. D' managed the literature analyses and final correction of the study. 'Harsha. V 'managed the literature searches and analysis. All authors read and approved the final manuscript.

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