REVIEW ARTICLE

Iron-deficiency Anemia and Chronic Kidney Disease: An Overview

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Abstract

Anemia is known to be a common and clinically important cause of chronic kidney disease (CKD). With progression of CKD, various factors can be attributed to reduction in hemoglobin (Hb) levels. However, reduced production of erythropoietin (EPO) due to impaired functioning of kidneys remains the central cause. The most effective treatment of anemia associated with CKD involves iron replacement and erythropoietic-stimulating agents (ESAs). Diagnosis of iron-deficiency anemia (IDA) in CKD patients is complicated due to the relatively poor predictive ability of routine serum iron indices such as ferritin and transferrin saturation. Invasive methods such as bone marrow iron stores or erythropoietic response to supplemental iron for detection of iron deficiency serve as the gold standard and are required for confirmation of diagnosis.

Keywords: Anemia, Chronic kidney disease, Hemoglobin, Hepcidin, Iron deficiency, Iron loss.

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Introduction

Iron-deficiency anemia is a common complication of chronic kidney disease (CKD).[1] Per records in 2010, the worldwide prevalence rate of anemia was estimated at 33%, with iron deficiency being the leading cause in half of these cases. In patients with CKD, anemia is a clinically significant burden and it becomes more prevalent with declining glomerular filtration rate (GFR). Anemia is associated with reduced quality of life (QoL) and increased cardiovascular (CV) morbidity and mortality.[2]

Chronic kidney disease can lead to either absolute or functional iron deficiency. In functional iron deficiency, while the total body stores are adequate, slow release of iron from store into circulation is insufficient to compensate the loss due to increased rate of erythropoiesis driven by erythropoietic-stimulating agents (ESAs).[3–5]

The World Health Organization (WHO) defines anemia as hemoglobin (Hb) level <12 g/dL in women and <13 g/dL in men (13.2 g/dL in men >70 years).[6] The potential CKD patients with estimated GFR (eGFR) <60 mL/minute/1.73 m^2 should also be screened for anemia during initial evaluation.[2]

Life expectancy from kidney failure is shorter than most common cancers;[7,8] and most hospital admissions and deaths in CKD patients are due to CV causes.[9,10]

Causes of Iron-deficiency Anemia

When kidneys fail to function, the amount of erythropoietin (EPO) produced is significantly reduced. This, in turn, reduces the number of red blood cells produced by the bone marrow that leads to the development of anemia. Therefore, blood which has a few red blood cells deprives oxygen required by the body (Fig. 1).

Apart from the reduced production of RBCs, some of the major causes of iron-deficiency anemia (IDA) in CKD include blood loss due to blood retention in tubes and apparatus during hemodialysis, malnutrition or low levels of nutrients in food, inflammatory problems such as lupus, arthritis, or inflammatory bowel disease, diabetic ulcers, or problems associated with bone marrow (Figs 2 and 3).[12]

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Signs and Symptoms

Fatigue, paleness, weakness, dizziness, headaches, chest pain, and shortness of breath are the various symptoms of iron deficiency in CKD patients.[13]

Metabolism of Iron in Chronic Kidney Disease

Iron is a requisite for the synthesis of Hb which further aids in transporting oxygen to various tissues across the body. Additionally, heme- and nonheme iron are elementary components of enzymes in the mitochondrial chain which utilizes oxygen in energy production. Therefore, iron is indispensable for transporting and storing oxygen and for energy metabolism.[14]

Iron has the ability to recycle within the body as the red blood cells are phagocytosed by reticuloendothelial macrophage and the content of iron is either taken up for hematopoiesis in case it is required or stored up for later use.

Hepcidin is a main factor responsible for regulation of iron metabolism. It is a small peptide hormone which is further synthesized and secreted by liver[15] and prevents the transport of iron by binding to ferroportin located on the basal membrane of enterocytes, reticuloendothelial cells, and hepatocytes. The binding of hepcidin leads to internalization of ferroportin from

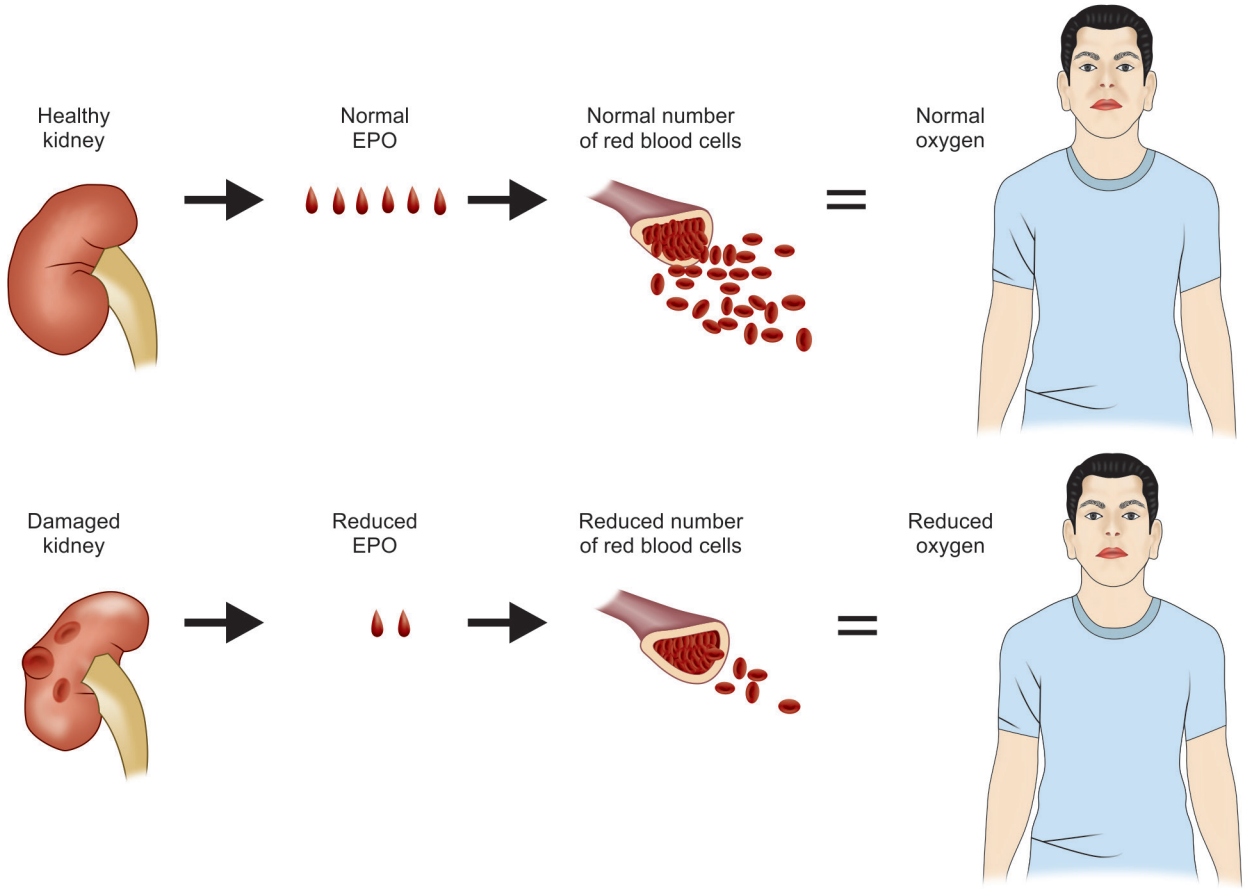

Fig. 1: Effects of damaged kidney on anemia. *Source*: NIH: Department of Health and Human Services. (2014). Anemia in Chronic Kidney Disease [online]. Available from http://www.pkdiet.com/pdf/anemia_508.pdf [Last accessed December, 2019][11]

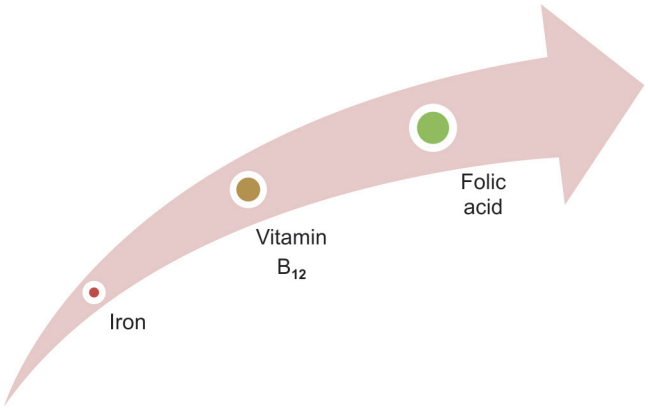

Fig. 2: Types of nutrients present in food

plasma membrane into the cell and further causes degradation.[16] Various physiology stimuli such as iron stores, hypoxia, inflammation, and erythropoiesis alone or in combination regulate the hepcidin levels in the body.[17–21]

However, hepcidin levels are raised in CKD patients and negatively correlated with GFR.[4,22] The factors responsible for CKD include increased inflammatory cytokines, reduced renal clearance, and reduced EPO levels.[5–23]

In CKD patients, absolute iron deficiency arise from an increased rate of blood loss during dialysis.[24] Iron loss is contributed by frequent phlebotomies and blood remaining in the dialysis tubing.[25]

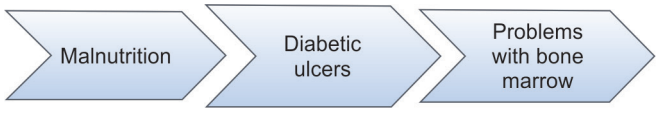

Fig. 3: Some of the major causes of iron-deficiency anemia in chronic kidney disease (CKD)

The rate of iron loss is getting high per year, i.e., 1 to 3 g/year due to gastrointestinal bleeding from the combination of gastritis and platelet dysfunction. This phenomenon is common in dialysis- and nondialysis-dependent CKD patients.[26]

Various Outcomes of Iron Deficiency in Chronic Kidney Disease

Anemia is associated with reduced QoL and increased CV morbidity and mortality.[2] A study was conducted in which 27,998 patients with CKD were enrolled. The follow-up was done for almost 5.5 years. The prevalence rate of anemia, congestive heart failure, coronary artery disease, and type 2 diabetes mellitus was higher in patients who died compared to those who survived, despite shorter observation period.[27–30] It was stated that patients who died because of increased rates of heart disease and anemia suggested that anemia increases the progression of heart disease and risk of death.[27]

A cohort study was conducted among 5,885 patients with CKD in whom the Hb levels were measured.[31] Anemia is known to be a predictor of excess CV hospitalizations, excess mortality, and excess end-stage renal disease (ESRD). Patients with the most

severe anemia levels <10.5 g/dL, with an increased rate of mortality with hazard ratio (HR): 5.27, 95% confidence interval (CI): 4.37–6.35; CV hospitalizations with HR: 2.18, 95% CI: 1.76–2.70; and ESRD with HR: 5.46, 95% CI: 3.38–8.82 when compared to those who were not anemic.

In a prospective study on 853 CKD stage 3–5, predialysis patients reported an association between mortality rates and severity of anemia.[28] Over the period of 2 years, the Hb values were longitudinally collected over a median follow-up of about 2 years. A time-averaged Hb with <11 g/dL was associated with increased mortality, compared to the group with a time-averaged Hb of >13 g/dL.[21] Even those with a time-averaged Hb of 11–12 g/dL had a significantly higher HR for mortality (HR: 1.8; 95% CI: 1.23–2.63) compared to the group with a time-averaged Hb of >13 g/dL. Lower time-averaged Hb levels also correlated with a statistically significant increased risk in the composite end point of predialysis mortality and ESRD as follows: HR: 2.57 (95% CI: 1.85–3.58) for Hb < 11 g/dL, HR: 1.97 (95% CI: 1.45–2.66) for Hb < 12 g/dL, again, compared with Hb > 13 g/dL.[32] Anemia in CKD may be frequently associated with a reduced QoL. In a study that examined the relationship between kidney disease quality of life (KDQofL) questionnaire domains and Hb levels in 1,200 patients with stages 3, 4, and 5 of CKD, higher Hb levels were associated with improved QoL domains of the KDQofL questionnaire. The most dramatic improvements in the various QoL domains occurred between the groups with Hb < 11 g/dL and Hb of 11–12 g/dL.[32]

Diagnosis of Iron Deficiency in CKD Patients

For diagnosis of IDA, various parameters such as serum iron, ferritin, total iron-binding capacity, and transferrin saturation (TSAT = plasma iron divided by the total iron-binding capacity × 100). Absolute IDA in CKD leads to depletion of iron reserves and TSAT values drop to ≤20%, and serum ferritin is <100 ng/m in predialysis and peritoneal dialysis (PD) patients or ≤200 ng/mL among patients undergoing hemodialysis. In functional IDA, despite sufficient iron reserves, deficiency occurs due to inadequate mobilization and inability to keep up with RBC production during erythropoiesis driven by ESA therapy which leads to TSAT < 20% with significantly elevated ferritin (i.e., as high as 800 ng/mL).[33–36] In such conditions, the body fails to reach the target HB levels despite high doses of ESA.

Reference range of various parameters essential for diagnosis of IDA is given in Table 1.

National Institute for Health and Care Excellence guidelines (2015) suggest the measurement of hypochromic red blood cells' (HRCs) percentage and reticulocyte Hb content (CHr) to determine whether the Hb content of RBCs is a better predictor of functional iron deficiency, iron availability for Hb synthesis, and responsiveness to iron supplementation as compared to TSAT and ferritin. Although the cutoff CHr < 29 pg and HRC > 6% are used to diagnose iron deficiency, neither the percentage of HRC nor the CHr can be used to differentiate between absolute and functional iron deficiency.[37]

Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend anemia screening only when clinical symptoms are present. In CKD stage 3, annual testing is recommended, CKD stage 4–5 twice per year, and every 3 months in dialysis patients in CKD-5 stage. In iron-deficient CKD patients not undergoing any ESA, the Hb concentration should be screened once in every 3 months in CKD stage 3–5 (nondialytic patients) and CKD stage 5 (PD) and monthly in CKD stage 5 hemodialysis.[38]

Table 1: Normal reference range

Parameter	*Normal reference range*
Hb	11.0–12.0 g/dL
Fe	>30 µg/dL
TIBC	<400 µg/dL
TSAT	≥20%
Ferritin	100–799 ng/mL (NDD); 200–799 ng/mL (HDD)

Fe, ferritin; Hb, hemoglobin; HDD, hemodialysis dependent; NDD, nondialysis dependent; TIBC, total iron-binding capacity; TSAT, transferrin saturation

Treatment and Management of IDA

According to KDIGO guidelines,[38] the course of treatment for IDA in CKD patients with TSAT is ≤30% and ferritin is ≤500 ng/mL is summarized in Table 2.

Nonhemodialysis in CKD Patients

The primary step in the management of iron deficiency is improving iron and Hb levels. Iron can be administered either orally or intravenously (IV). While oral iron supplementation is a preferred mode of treatment due to its cost-effectiveness and ease of use, IV administration is preferred in severe anemia case when administration of larger doses of iron is required to rapidly obtain optimal Hb levels.[35,39–41]

Literature suggests that IV iron supplementation has greater efficacy over iron supplementation. In a 2008 meta-analysis of randomized controlled trial (RCT) by Rozen-Zvi et al., the effect of IV and oral iron supplementation were evaluated in anemic CKD patients and it was concluded that CKD patients on hemodialysis therapy have better Hb level response when treated with IV iron.[42] Avni et al. evaluated the efficacy and safe of oral, intramuscular, and IV iron and reported that IV iron therapy has comparable safety profile to oral iron, had fewer gastrointestinal side effects, and was not associated with increased risk of severe adverse events or infections.[43] A systemic review and meta-analysis by Shepshelovich

Table 2: Course of treatment

Patients	*Therapy type*	*Dialysis status*	*Treatment*
CKD + IDA	Neither iron supplementation nor ESA therapy	Dialysis	IV iron supplementation
		Nondialysis	1–3 months oral iron supplementation
	ESA therapy but not iron supplementation	Dialysis	IV iron supplementation
		Nondialysis	1–3 months oral iron supplementation

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; IDA, iron-deficiency anemia; IV, intravenous

et al. also recommends IV iron replacement for patients with CKD stage 5D and support the use of IV iron over oral supplementation for patients with CKD stages 3–5.[44] Similar findings were reported by Sargent et al. who assessed the safety and effectiveness of IV iron supplementation in CKD stage 5 patients who have not yet received dialysis (CKD 5 ND). According to this prospective cohort study, iron supplementation is associated with 15% lower risk of death among CKD 5 ND patients who received ESA treatment.[45]

Based on these studies, it can be concluded that the benefits of IV iron supplementation is the preferred route of administration in ND-CKD.

Over the years, ESA therapy has become the choice of treatment for the management of anemia in CKD. The ESAs not only reduce the symptoms of anemia but also improve QoL, increase survival rates, reduce the number of transfusions required, and decrease the progression of renal failure.[46,47] However, various factors such as etiology of anemia, target Hb, route of administration, and presence of hypertension should be considered before prescribing ESAs.[48] In contrast to the available data, some studies report the association between administration of high doses of ESA and increased mortality rates and high incidence of development of thrombotic and cerebrovascular complications.[49] Thus, the potential risk of ESA treatment in anemia management remains debatable.

Chronic Kidney Disease Patients on Dialysis

Chronic kidney disease patients with a history of dialysis or who are currently on dialysis are at high risk of developing IDA due to iron loss from blood retention in the dialysis machine and tubes.[45–50] The first-line treatment of choice is repeated loading dose of 1,000 mg of iron administered via IV until the Hb level rises, followed by maintenance phase with regular small doses of iron.

Numerous studies on CKD patients undergoing hemodialysis report the effectiveness of IV iron supplementation in correcting Hb levels as compared to oral iron supplementation, regardless of ESA treatment.[38,42] Similar findings were reported by Locatelli et al., where IV iron treatment had better response time as opposed to oral supplementation recommended by KDIGO and European Renal Best Practice (ERBP) guidelines.[35,44] Another study by Coyne et al. reported the association of elevated ferritin levels and increased mortality.[51] However, dialysis patients' response to IV iron with elevated ferritin (DRIVE) trial did not show any such results.[51] A prospective RCT by Macdougall et al. showed that a high-dose proactively administered IV iron regimen on patients undergoing hemodialysis was much more effective than a low-dose regimen administered reactively, and it significantly reduced the risk of death and nonfatal CV events. The high-dose strategy also lowered the dose of ESA, number of blood transfusions and hospitalizations.[52]

Conclusion

Iron-deficiency anemia is the most common form of anemia and an associated complication of CKD. The CKD patients can develop either absolute or functional iron deficiency. Absolute iron deficiency is defined by severely reduced or absent iron stores, leading to ≤20% TSAT levels and ≤200 ng/mL serum ferritin levels in hemodialysis-dependent CKD patients and ≤100 ng/mL in predialysis CKD patients. Functional iron deficiency is defined by adequate iron stores but insufficient iron availability for incorporation into erythroid precursors. Oral iron supplementation is the preferred form of treatment due to the ease of use and cost-effectiveness. In severe cases, ESA therapy is preferred to readily relief symptoms of anemia and reduce the number of transfusions required.

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