CKD anemia

StatPearls 2023

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Background

- Anaemia is a common complication of CKD.
- The disorder starts to develop when the glomerular filtration rate drops below 60 mg/ml. The anemia is rare when the GFR exceeds 80 mL/min/1.73 m2. However, as the GFR worsens, the anemia gets more severe.
- a form of normocytic, normochromic, hypoproliferative anemia
- associated with left ventricular dysfunction and heart failure
- a reduction in exercise capacity and quality of life
- associated with poor outcomes in chronic kidney disease and confers an increased mortality risk

Objectives

- Explain the pathophysiology of anemia of chronic renal disease.
- Describe how to diagnose anemia of chronic renal disease.
- Review the management of the anemia of chronic renal disease.
- Summarize the interprofessional team strategies for improving coordination and communication to enhance the management of patients with anemia of chronic renal disease.

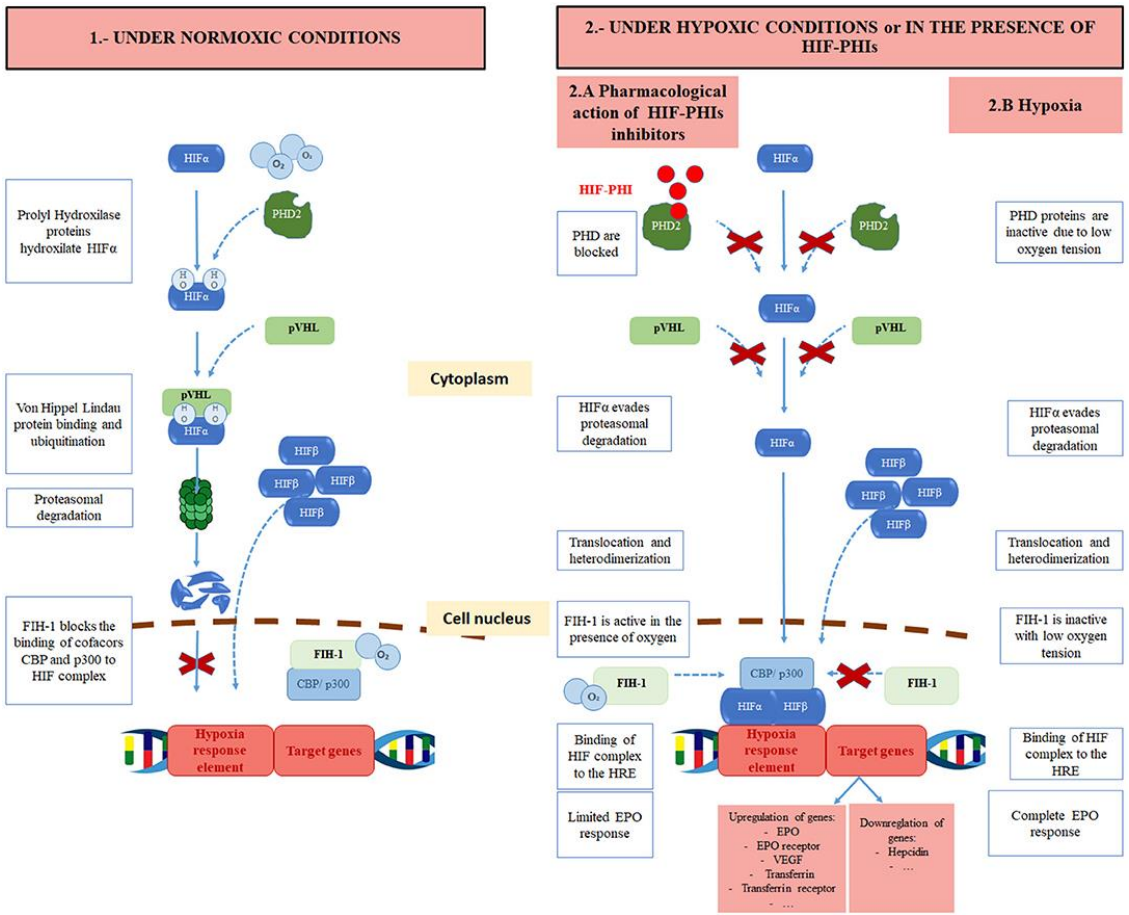
Etiology

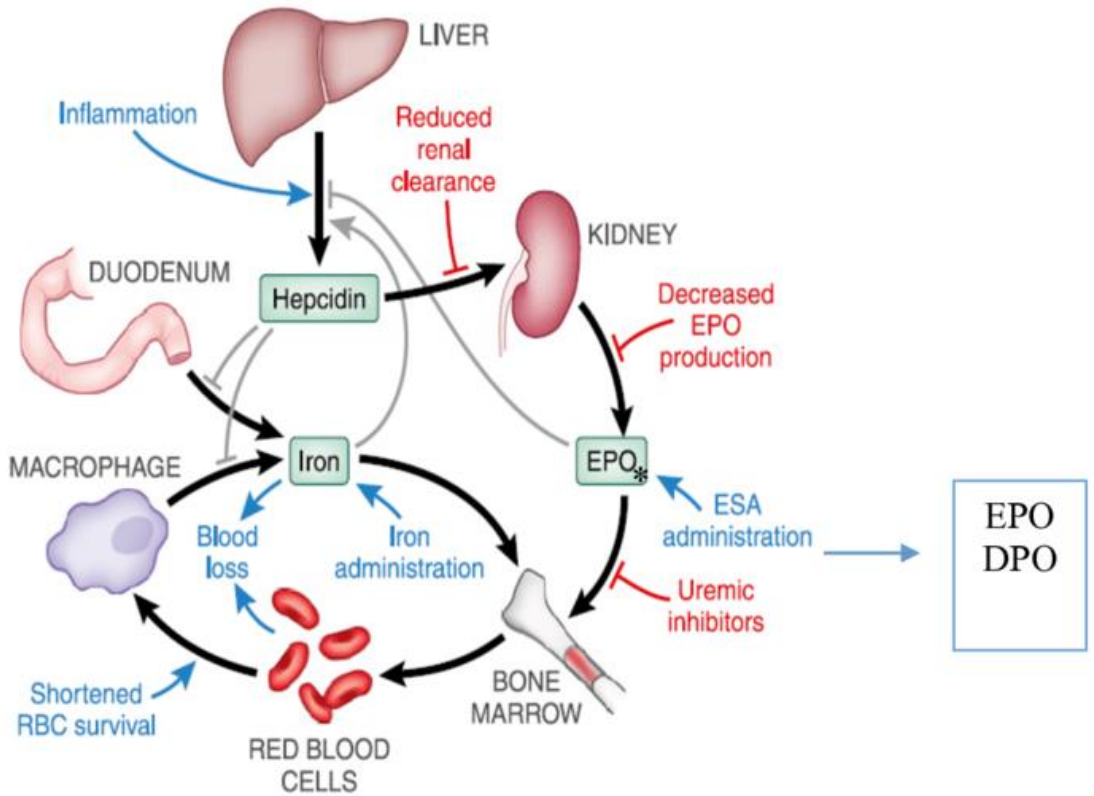
- multifactorial origin
- decreased renal production of erythropoietin (EPO)
- uremia (leading to RBC deformity responsible for hemolysis)
- folate and vitamin B12 deficiency,
- iron deficiency,
- bleeding due to dysfunctional platelets, and rarely blood loss from hemodialysis

Epidemiology

- Several studies report the prevalence of anemia in non-dialysis dependent (NDD) CKD up to 60%.
- At least 90% of patients who end up on dialysis will eventually develop anemia of chronic disease.
- anemia was twice as prevalent in CKD patients as in the general population.

Pathophysiology





History and Physical

- **Common symptoms include:**
- Dyspnea (shortness of breath)
- Fatigue[20]
- Generalized weakness
- Headaches
- Decreased concentration
- Dizziness
- Reduced exercise tolerance.
- **Commonly observable signs include:**
- Skin and conjunctival pallor
- Respiratory distress
- Tachycardia
- Chest pain (mostly with severe anemia)
- Heart failure (usually with chronic severe anemia)

Evaluation

- Complete blood count (CBC) with differential
- Peripheral smear
- Iron indices (iron, ferritin, total iron binding capacity, transferrin saturation)
- Iron, vitamin B, and folate levels (included in initial workup to rule out other reversible causes of anemia)
- Thyroid function tests (rule out alternate etiology of hypoproliferative normocytic anemia)

- Normocytic normochromic anemia and peripheral reticulocytopenia are observable on CBC with a peripheral smear.
- Bone marrow may show erythroid hypoplasia, which correlates to the reports of resistance of bone marrow to erythropoietin.

Iron/serum ferritin

- Due to high serum ferritin levels secondary to chronic inflammation in CKD, serum iron indices are not accurately indicative of the degree of iron deficiency in dialysis patients, thus raising the standard cutoffs of iron responsiveness.
- The Dialysis Patients' Response to IV Iron With Elevated Ferritin (DRIVE) study demonstrated that intravenous iron is beneficial in dialysis patients even in the setting of ferritin as high as 1200 ng/mL if the transferrin saturation is less than 30%.

EPO

- Measuring serum erythropoietin levels are discouraged in CKD.
- There is 'relative erythropoietin deficiency,' that is, an inappropriate rise in erythropoietin levels for the severity of anemia.

Treatment / Management

	Diagnosis of iron deficiency	Treatment initiation	Hb target under treatment with ESAs	SF and TSAT objectives in patients under treatment	FE oral vs. IV
NICE (2015)	**Test every 3 months (1–3 m in HD)** - Use %HRC > 6%, only if blood processing within 6 h. - if not possible, use CHr < 29 pg - If not, use a combi-nation SF < 100 ng/mL and TSAT < 20%	**Correct iron deficiency before ESA therapy.** - Patient-centered: discuss risks benefits of treatment options. Take into account the person's choice. Avoid Hb < 10 g/dL.	**Hb 10–12 g/dl**	**Avoid SF > 800 ng/mL** To prevent this, review iron dose if SF > 500 ng/mL	**ND-CKD with anemia and iron deficiency:** - offer a 3 months trial of oral iron therapy. - If it fails, offer IV iron therapy. **- DD-CKD:** Preference for IV iron - **If IV iron, consider high dose, low frequency** formulations for ND and DD-CKD patients.
KDIGO (2012)	**SF ≤ 100 ng/mL and TSAT ≤ 20%.**	**A trial with IV iron** if Hb increase or ESA dose reduction is desired and SF≤ 500 ng/mL and TSAT ≤ 30% **ND-CKD: When Hb < 10 g/dL:** Individualize decision based on the rate of fall of Hb, risks and symptoms. **DD-CKD:** When Hb 9-10 g/dL. Avoid Hb < 9 g/dl.	**Hb ≤ 11.5 g/dl** - **Target to Hb > 11.5 g/dl if QoL improve** is foreseen and patient accepts risks. Avoid Hb >13 g/dL	**Stop iron supplements** if SF > 500 ng/mL	**ND-CKD: Select route based on severity of ID, prior response, side effects, costs**, A trial of iv iron, or a 1–3 month trial of oral iron therapy. **- DD- CKD**: Preference for IV iron
ERBP (2009)	**SF < 100 ng/mL and TSAT <20% if ESA naïve. SF ≤ 300 ng/mL and TSAT ≤ 30% if ESA treated**	**Avoid Hb < 10 g/dL.** - If low risk patients or a benefit in QoL foreseen ESA could start at ↑ Hb (avoid Hb >12 g/dL) - In high risk patients with worsening heart disease, treatment initiation at Hb9-10 g/dL.	**Hb 10–12 g/dl** - High risk patients with asymptomatic disease: target Hb around 10 g/dL	**Avoid SF > 500 ng/ml and TSAT > 30%.**	**ND-CKD and mild-moderate anemia:** Oral iron as first line therapy for > 3 months. **ND-CKD and severe anemia or when oral iron ineffective:** IV iron as first choice.

SF, serum ferritin; TSAT, Transferrin saturation; %HRC, percentage of hypochromic red blood cells; CHr, hemoglobin content in reticulocytes; Hob, Hemoglobin; ND-CKD, Non dialysis dependent Chronic kidney disease; DD-CKD, dialysis dependent CKD; QoL, quality of life; IV, intravenous ESA erythropoiesis stimulating agent; Fe, iron.

EPO

- In patients with CKD who are not on dialysis, ESAs are typically considered when hemoglobin level drops below 10 g/dl but are individualized depending on various factors, including symptoms related to anemia, dependence on transfusions, the rate of drop in hemoglobin concentration, and response to iron therapy.
- In CKD patients, erythropoietin (50 to 100 units/kg IV or SC) is usually given every 1 to 2 weeks, and darbepoetin alfa dosing is every 2 to 4 weeks.
- n patients on dialysis, ESAs are usually avoided unless the hemoglobin level is between 9 and 10 g/dL. In this subset, erythropoietin is given with every dialysis, i.e., three times a week, whereas darbepoetin alfa is dosed once weekly.

- Generally, the peak rise in RBCs in response to ESAs occurs at 8 to 12 weeks. However, in around 10% to 20% of cases, anemia can be resistant to ESAs. Common adverse effects of ESAs include seizures, the progression of hypertension, clotting of dialysis access, the progression of malignancy, and higher mortality in cancer patients.
- In all patients with CKD, regardless of the need for dialysis, the goal hemoglobin using ESAs is less than 11.5 g/dL.

Iron

- KIDGO recommends target transferrin saturation between 20 to 30% and ferritin level 100 to 500 ng/mL in patients with CKD who are not on dialysis.
- In patients with ESRD on dialysis receiving intravenous iron, goal transferrin saturation of 30 to 50% and ferritin higher than 200 ng/mL.
- Iron correlates with acute toxicity and infection risk, which should be weighed against the benefits in individual patients.

Complications

- an independent risk factor for death.
- left ventricular hypertrophy, peripheral oxygen demand, and worsening cardiac outcomes
- depression, fatigue, stroke, reduced exercise tolerance, and an increased rate of re-admissions.
- Long-term treatment with erythropoietin can cause hypertension, vasoconstriction, and seizures.

Differential Diagnosis

- Alcohol misuse disorder
- Aplastic anemia
- Dialysis complications
- Hypothyroidism
- Hyperthyroidism
- Methemoglobinemia
- Sickle cell anemia
- Systemic lupus erythematosus
- Hypoadrenalism
- Panhypopituitarism
- Primary and secondary hyperparathyroidism
- Myelophthisic anemia

Prognosis

- Anemia of chronic renal disease is associated with cardiorenal anemia syndrome. Foley et al. observed that for every 1-g decrease in hemoglobin concentration, a 42% increase in left ventricular dilatation is seen in patients with stage 5 CKD.
- The Dialysis Outcomes Practice Pattern Study (DOPPS), involving countries, reported that with the decrease in hemoglobin to less than 11 g/dL, there was an increase in hospitalization and mortality in CKD patients.
- Many patients with renal failure will not respond to erythropoietin, which is crucial as it is an important predictor of adverse cardiac events.
- Two factors that lead to unresponsiveness include iron deficiency and inflammation.

Deterrence and Patient Education

- Patients should be given information that when they have chronic kidney disease.
- Patients should store ESA or iron as advised by the manufacturer, as some products need to be kept in the fridge.

Enhancing Healthcare Team Outcomes

- The management of the anemia of CKD is complex.
- One should never assume that anemia of renal disease is solely due to a lack of erythropoietin; it may be due to poor nutrition or chronic illness- so a thorough workup is essential to determine the cause.
- Managing patients on dialysis with anemia requires an integrated approach by an interprofessional team.
- The dialysis nurse should monitor vital signs and obtain total blood counts to determine the level of anemia.

HIF-1 stabilizer

	Roxadustat (FBG-4592)	Vadadustat (AKB-6548)	Daprodustat (GSK 1278863)	Molidustat (BAY-3934)
Affinity IC50 (uM)	0.027	0.029	0.067	0.007
PHD Isoform Selectivity	PHD 1-3	PHD 3>2	PHD 2-3	PHD 2< 1 and 3
HIFα selectivity	HIF1α and 2α	HIF2α > 1α	HIF1α and 2α	HIF1α and 2α
Inhibitory concen-tration IC 50 (μM)	>100	29	21	65
Half life humans (h)	12	4.5	4	Not available
Current status of development	2019 approval in Japan and China Phase III reported at ASN 2019	Ongoing phase III Preliminary report at ASN 2020	Ongoing phase III	Completed phase II
Phase III clinical trials	DD (HD/DP) and NDD Correction and maintenance	DD (HD/DP) and NDD Correction and maintenance	DD (HD/DP) and NDD Correction and maintenance	Not available

IC50, half maximal receptor inhibitory concentration; PHD, prolyl hydroxylase domain protein; HIF, hypoxia-inducible factor; ASN, American Society of Nephrology; DD, Dialysis Dependent; HD, Hemodialysis; DP, Peritoneal dialysis; NDD, Non-dialysis dependent.

Pearls and Other Issues

- Anemia of renal disease is common and is chiefly due to decreased erythropoietin production.
- Investigating other treatable causes of anemia in renal failure patients is necessary.
- Anemia of renal disease is associated with adverse cardiac events, heart failure, MI, and death.
- Erythropoietin levels are not indicative of anemia in renal failure patients. Therefore, one should target a hemoglobin level of no more than 11.5 g/dl.

Quiz: Anemia of Chronic Renal Disease

A 42-year-old woman presents with chronic fatigue and dyspnea. Her medical history includes chronic renal failure and hypertension. She takes ramipril and calcium supplements and is on dialysis twice weekly. Vital signs are blood pressure 155/75 mm Hg, heart rate 88 bpm, and oxygen saturation 94% on room air. On physical examination, she has pallor with pale conjunctivae and moderate peripheral edema. Auscultation of the chest reveals a normal S1 and S2 and fine crackles at both lung bases. Laboratory test results show creatinine 4.9 mg/dL, blood urea nitrogen 176 mg/dL, glucose 112 mg/dL, hemoglobin 8.2 g/dL, sodium 131 mEq/L, potassium 5.6 mEq/L, and erythropoietin level 0.8 U/L (3.7 to 36 U/L). Which of the following laboratory values is used to evaluate the proper response to the underlying cause of this patient's condition?

- A. Erythropoietin level
- B. Reticulocyte count
- C. Serum iron level
- D. Hemoglobin

D

Teaching Points

- This patient has anemia of chronic disease, which is a diagnosis of exclusion in a patient with chronic renal failure. The patient's eGFR being <30 mL/kg/min and no other explanation for the anemia are the 2 major clues toward the diagnosis.

- The hemoglobin target should be in the range of 10 to 12 g/dL.

- The hemoglobin levels should be checked periodically, first before the initiation of therapy and then a month after the treatment. Most of the patients, as presented in the above vignette, require periodic monitoring.

- Reticulocyte count has no specific role in the monitoring of the disease.

A 65-year-old patient presents with a chief complaint of fatigue and dyspnea on exertion. Her medical history is significant for stage 2 chronic kidney disease and type 2 diabetes mellitus. Her physical examination is unremarkable except for tachycardia and a grade 2 systolic murmur heard best at the upper left sternal border. Her laboratory evaluation shows hemoglobin 8.5 g/dL, mean corpuscular volume 70 fL, ferritin 1000 ng/mL, and transferrin saturation 10%. Her estimated glomerular filtration rate is 60 mL/min. What is the next step in the management of this patient?

- A. Iron supplementation
- B. Blood transfusion
- C. Bone marrow biopsy
- D. Emergent upper and lower gastrointestinal endoscopies

A

Teaching Points

- The anemia of chronic kidney disease is a type of hypoproliferative normocytic anemia. Normocytic normochromic anemia and peripheral reticulocytopenia are observed on a peripheral smear in anemia of chronic kidney disease. In most patients with chronic renal dysfunction, serum ferritin levels are an unreliable indicator of iron stores.

- The chronic inflammation of chronic renal disease can increase serum ferritin levels. A low transferrin saturation with microcytic anemia is consistent with iron deficiency anemia. This patient would, therefore, benefit from iron supplementation.

- Her symptoms suggest a somewhat rapid development of anemia rather than a slow, indolent course. Therefore, she should be evaluated for blood loss anemia with gastrointestinal endoscopies after iron supplementation.