Feature Editor: Stacey Phillips, MS, RD

Evolution of Treatment for Anemia in Chronic Kidney Disease

Katelyn Vaught, BS, and Sara Kerber, BS

Intended Audience: Individuals With Chronic Kidney Disease

IN 2019, THE Centers for Disease Control and Prevention estimated that more than 1 in 7 (15%) adults in the United States have chronic kidney disease (CKD).[1] A common comorbidity of CKD is anemia. The type of anemia seen in patients with CKD is normocytic, normochromic, and hypoproliferative.[2] Early studies showed that the main cause for CKD anemia was from erythropoietin (EPO) deficiency. Damaged kidneys, as seen in CKD, do not produce enough EPO, resulting in decreased production of red blood cells by the bone marrow.

The use of erythropoiesis-stimulating agents (ESAs) was endorsed by the National Kidney Disease Outcomes Quality Initiative in their first anemia in CKD treatment guidelines. ESAs were used to reach normal hemoglobin (Hgb) levels by imitating EPO to stimulate red blood cell production. Patients with CKD benefited from ESA use as it reduced their dependence on blood transfusions.[3] However, treating anemia in CKD patients with ESAs increased their risk for hypertension, seizures, and dialysis access clotting. No improvement has been seen with ESA use in the progression of kidney disease, cardiovascular events, hospitalizations, and mortality. It was also discovered that approximately 10-20% of patients with anemia of CKD are resistant to ESAs.[2]

Treatment with ESA can be limited by iron deficiency. Therefore, supplementation has been used to treat the deficiency, either orally or intravenously (IV). The Kidney Disease: Improving Global Outcomes, National Kidney Disease Outcomes Quality Initiative guidelines, and the European Renal Best Practice recommend iron supplementation in those with CKD anemia and iron deficiency. In patients receiving dialysis, these groups support the use of IV iron. In patients not dependent on dialysis, both IV and oral supplementation are appropriate. Oral iron is cheaper and more accessible but has been linked to increased GI side effects. Both are able to increase Hgb levels; however, IV iron can be tolerated in larger doses and sustain a better Hgb level decreasing the need for transfusions. The potential risks associated with IV iron include anaphylaxis and bacterial line infections. While there are risks, IV iron was thought to decrease the use of ESAs to increase Hgb.[4]

Initially, it was believed that aiming for normal healthy adult Hgb levels by utilizing higher doses of ESAs would treat anemia. However, it has been documented that using higher doses of ESAs may be the main contributing factor to the adverse effects seen in a multitude of studies. With this new research, the US Food and Drug Administration updated its ESA dosage recommendation in June 2011. The new labeling of ESA no longer supports aiming for Hgb levels between 10 and 12 g/dL. Instead, it is recommended that patients now have Hgb concentrations below 10 g/dL and are symptomatic to start ESA therapy.[3] Scientific advances in the study of CKD-associated anemia have created new interest in understanding the pathophysiology of anemia with the hopes of discovering more targeted therapies.[2]

Recent studies suggest the impaired dietary absorption of iron present in patients with CKD is caused by an excess of hepcidin, the main hormone regulating iron homeostasis throughout the body. Hepcidin is increased with inflammatory diseases such as CKD, as cytokines are present and stimulate the transcription of hepcidin. Excess hepcidin has been found to interfere with the absorption of iron in patients with CKD by deteriorating ferroportin and preventing the movement of iron into the plasma. Therefore, it has been suggested, to treat CKD anemia, preventing excess hepcidin is a crucial step. Blocking hepcidin could improve the absorption of iron from dietary sources and one's body stores.[2]

Hepcidin expression is limited by EPO. The production of EPO can be stimulated by hypoxia-inducible factor (HIF) accumulation. HIF plays a role in the homeostasis of oxygen. This transcription factor activates gene expressions to protect against cell damage and restore balance as blood oxygen levels drop because of CKD-associated

Dietetic Interns, Grand Rapids, Michigan.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Address correspondence to: Katelyn Vaught, BS and Sara Kerber, BS, Dietetic Interns, Grand Rapids, MI. E-mails: khvaught@gmail.com, sara.kerbs@yahoo.com

1051-2276/$36.00

https://doi.org/10.1053/j.jrn.2020.03.004

anemia. For HIF to accumulate, it must be stabilized by suppressing hypoxia-inducible factor prolyl hydroxylase (HIF-PH). HIF promotes iron uptake and transport which stimulates EPO production, increased iron availability, and the maturation of erythrocytes.[5]

HIF-PH inhibitors are now undergoing clinical trials as a treatment for anemia in CKD. Studies of HIF-PH inhibitors have found to increase endogenous EPO to a level similar to the normal physiological range, without increasing hypertension or thrombosis of patients with CKD not on dialysis. This leads researchers to consider that HIF-PH inhibitors may be able to avoid the risks associated with ESA use.[5] The possible risks associated with HIF-PH inhibitors revolve around concern for the other genes, unrelated to anemia, that are regulated by HIF and the effect HIF-PH inhibitors may have on tumor growth.[5] Further long-term studies are needed to provide enough evidence on the success and safety of HIF-PH inhibitors.

In summary, anemia is a common feature of CKD and is often associated with poor outcomes. Successful treatment of CKD anemia has the potential to improve quality of life and decrease the risk of morbidity and mortality. Supplementation is used to treat the iron deficiency seen in these patients, either orally or intravenously. In patients with CKD receiving dialysis, IV iron is most supported. In patients not dependent on dialysis, both IV and oral supplementation are appropriate.[4] The current treatment of anemia in patients with CKD is controversial and varies in effectiveness. Historically, ESAs were the most widely used course of action, but recent clinical trials have shown increased risk factors with ESA use.[2] Studies have begun to further examine the pathophysiology of anemia of CKD to develop better treatments. The most current research is examining the effect of HIF-PH inhibitors as a potential treatment for anemia in CKD. They are thought to minimize the morbidity and mortality risks commonly associated with ESA use.[5] However, further studies into the long-term effects of all potential treatments of CKD-associated anemia are warranted to further develop evidence-based treatment plans.

References

1. Chronic Kidney Disease in the United States, 2019. https://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html.
2. Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am Soc Nephrol*. 2012;23:1631-1634.
3. Park H, Liu X, Henry L, Harman J, Ross EA. Trends in anemia care in non-dialysis-dependent chronic kidney disease (CKD) patients in the United States (2006–2015). *BMC Nephrol*. 2018;19:1-10.
4. Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. *Am J Kidney Dis*. 2016;68:677-690.
5. Kaplan JM, Sharma N, Dikdan S. Hypoxia-inducible factor and its role in the management of anemia in chronic kidney disease. *Int J Mol Sci*. 2018;19:E389.

Additional Websites

National Institute of Diabetes and Digestive and Kidney Disease: https://www.niddk.nih.gov/health-information/kidney-disease/anemia. Accessed January 10, 2020.

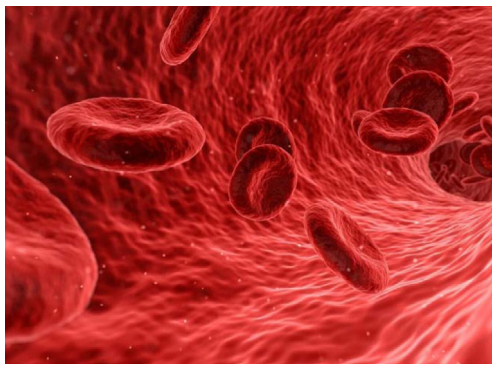
American Kidney Fund: https://www.kidneyfund.org/assets/pdf/anemia/anemia-backgrounder.pdf. https://www.kidneyfund.org/assets/pdf/anemia/anemia-brochure-for-esrd.pdf. Accessed January 10, 2020.

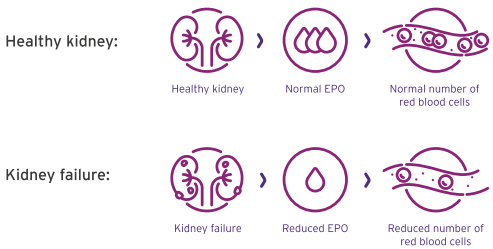
Kidney Disease: Improving Global Outcomes: http://www.treatalgo.com/kdigo-anemia/ http://www.treatalgo.com/kdigo-anemia/dia-iron.html. Accessed January 10, 2020.

Anemia and Chronic Kidney Disease (CKD)

WHAT IS ANEMIA?

Anemia is a condition in which the body has fewer red blood cells (RBC) than normal. RBCs carry oxygen throughout the blood to your organs. With anemia, your body has less RBCs to carry oxygen around the body.





ANEMIA FROM CKD

Healthy kidneys make a hormone called EPO. EPO signals your bone marrow to produce more RBCs. With CKD, kidneys don't make enough EPO and fewer RBCs are made resulting in anemia.

SIGNS AND SYMPTOMS

Anemia can occur with or without symptoms.

Common signs and symptoms: weakness, fatigue, headaches, problems concentrating, dizziness, shortness of breath, chest pain

Anemia and CKD

WHY IS IRON IMPORTANT?

Iron is a mineral found in many different foods. Your body needs iron to make hemoglobin, the oxygen-carrying component of RBCs.

WHAT CAN YOU DO?

Work with a registered dietitian to try increasing your dietary iron intake.

Dietary sources of iron: cooked meats; shellfish; tofu; cooked beans; potatoes with skin; spinach; enriched cereals

Combine plant-based sources of iron with Vitamin C (orange, bell peppers) to increase absorption of iron.

TREATMENTS

Currently researchers are looking into using newer medications to increase EPO production and better treat CKD-associated anemia.