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AN OVERVIEW OF ANEMIA IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

Anemia is a known side effect of chronic renal disease, yet it is still challenging to treat. The benefits of erythropoiesis-stimulating drugs (ESAs) seem to be limited to reducing the need for blood transfusions and possibly improving quality of life. Hemoglobin levels are increased by ESAs. Prolyl hydroxylase inhibitor of hypoxia-inducible factor (HIF-PHI), Prolyl hydroxylase inhibitors (PHIs) which increase endogenous erythropoietin production, have recently been developed and show promise for improving outcomes for those with anemia brought on by the chronic renal illness. These drugs are used internationally and have been found in randomized controlled trials to be at least as effective as ESAs.On the other hand, recent clinical trials have clarified significant iron supplementation features, which may alter future treatment aims. Oral iron supplementation is the preferred form of treatment because of its ease of use and cost-effectiveness. In severe cases, ESA therapy is preferred because it provides rapid relief of the symptoms of anemia and reduces the number of transfusions required.

KEYWORDS: Anemia, chronic kidney disease, Erythropoiesis stimulating agents, Prolyl hydroxylase inhibitor, iron, blood transfusion.

INTRODUCTION

Anemia is a condition when there are fewer red blood cells or their hemoglobin content is lower than usual. Anemia is a common chronic kidney disease consequence that is linked to a lower quality of life, as well as a higher risk of morbidity and mortality.[1] Anemia linked to CKD is caused by a variety of complex causes. Individuals with CKD typically experience chronic inflammation, which has a wide range of underlying causes, including increased infection rates, levels of pro-inflammatory cytokines, the uremic environment, the prevalence of arteriosclerosis, and others.[2] When the kidneys are damaged, they are unable to filter the blood as effectively as they should. This condition is known as chronic renal disease. Because kidney damage occurs gradually over a lengthy period of time, the condition is referred to as chronic. Wastes may accumulate in the body as a result of this harm.[3]

According to extensive population research, patients with CKD stages 1 and 2 have an anemia incidence of less than 10%, stage 3 patients have an incidence of 20–40%, stage 4 patients have an incidence of 50–60%, and stage 5 patients have an incidence of more than 70%.[3]

In stage 3 CKD patients, the prevalence of more severe anemia (hemoglobin 10g/dL) is 5.6%, and in stage 5 non-dialysis CKD patients, it is 27.2%.[3] Clinical manifestations include fatigue, shortness of breath, unusually pale skin, weakness, body aches, chest pain, dizziness, and fainting.[4]

Anemia is uncommon when the glomerular filtration rate (GFR) exceeds 80ml/min, but it becomes more severe as the GFR declines, marking the beginning of the illness.[5] Anemia is more common and affects almost all individuals with stage 5 CKD as the disease progresses. A type of normocytic normochromic hypo proliferation anemia is anemia caused by chronic kidney illness. It is usually linked, among other chronic kidney disease problems, to poor ckd outcomes and higher mortality.[6,7]

CAUSES

Relative lack of erythropoietin

Deficit in iron

Losing blood

Vitamin insufficiency causes shortened red blood cell life

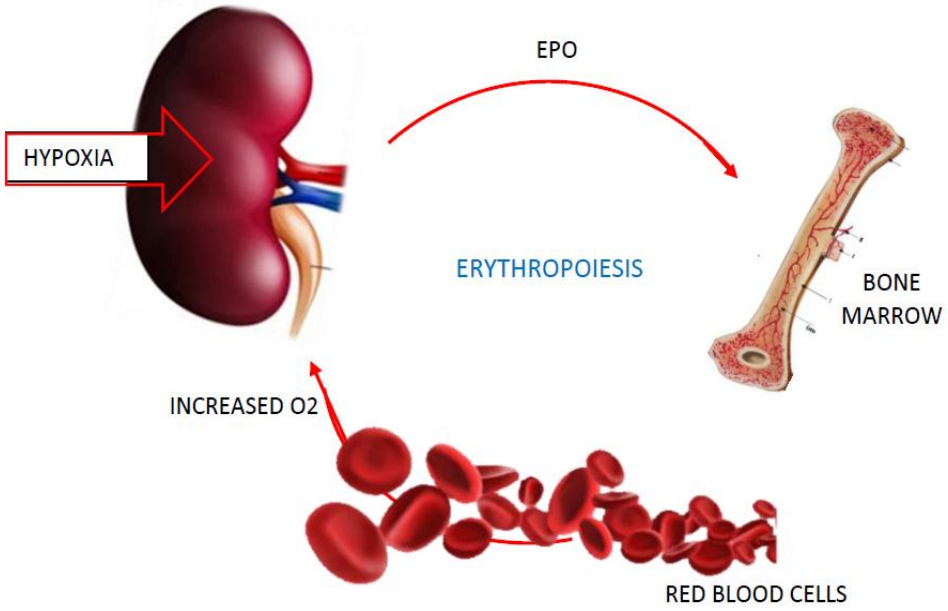
Bone marrow suppression or the uremic environment

Inflammation

Hyperparathyroidism[8]

PATHOPHYSIOLOGY

Anemia in CKD is caused by multiple factors. Endogenous erythropoietin (EPO) levels gradually decreasing have traditionally been thought to play a major impact. Other factors, such as an absolute iron deficiency caused by blood losses or impaired iron absorption, ineffective use of iron stores caused by elevated hepcidin levels, systemic inflammation brought on by CKD and associated comorbidities, a decreased bone marrow response to EPO because of uremic toxins, a shorter red cell life span, or vitamin B12 or folic acid deficiencies, have also been mentioned as contributing to anemia in CKD patients.[1]



HIF controls the erythropoietin gene, which is found on chromosome 7. A beta subunit, which is inherently present in the nucleus, and an alpha subunit, which is unstable under high Po2, make up HIF molecules.

The HIF dimer is transcriptionally active in hypoxic conditions and binds to particular DNA recognition sequences known as hypoxia response elements. Erythropoietin production is raised as a result of increased gene transcription. Therefore, erythropoietin production is upregulated in hypoxic conditions, whereas it is downregulated under conditions of normal oxygen tension.[5]

ERYTHROPOIETIN PRODUCTION

Erythropoietin is largely produced by a distinct population of peritubular interstitial cells in the deep cortex and outer medulla of the kidneys. Erythropoietin is also produced by parenchymal cells in the liver, though slightly less. Hypoxia induces erythropoietin synthesis through the HIF pathway. As the hemoglobin concentration and arterial oxygen tension fall, more renal erythropoietin is produced. This is because tissue oxygenation, not renal blood flow, determines the rate of erythropoietin synthesis.[2.5]

METABOLISM OF IRON

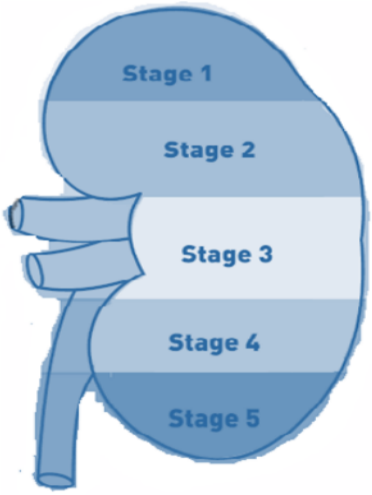
The ability of iron to accept or contribute electrons defines it. Because of this special quality, it is essential for numerous biochemical processes, including enzymatic activity, DNA synthesis, oxygen transport, and cell respiration.[5]

Many proteins that play various functions in iron absorption, recycling, and loss regulate iron metabolism.[5] The protein myoglobin, which carries oxygen inside muscle cells, depends on iron to function. The electron transport chain and oxidative phosphorylation are two additional oxidative processes involving iron that have a significant impact on intracellular metabolism. Several pathways of DNA synthesis, deterioration, and repair involve iron, and finally, iron is a crucial part of the cytochrome P450 family.[1]

Dietary iron largely exists in its insoluble trivalent ferric form (Fe+3), and in order to be absorbed, it must be converted by the enzyme ferric reductase to its soluble divalent ferrous form (Fe+2). Iron must be carried by a transporter known as ferroportin through the basolateral membrane in order to enter circulation.[5]

Hepcidin levels rise when there is an iron surplus, whereas they fall when there is an iron deficit. Moreover, appropriate intestinal iron absorption and the release of iron from the body's stores are inhibited by the uremic condition and other comorbidities that cause inflammation.[1]

Stages of CKD

Stages of CKD		Percentage of normal kidney function
NORMAL FUNCTION		90% or more
MILD LOSS OF FUNCTION		60-89%
MODERATE LOSS OF FUNCTION		30-59%
SEVERE LOSS OF FUNCTION		15-29%
KIDNEY FAILURE		<15%

TYPES OF ANEMIA

Common types of anemia and their causes are:

1. Iron deficiency anemia

- Iron deficiency anemia is caused by a lack of iron.
- Elemental iron in the body.
- Bone marrow needs iron to make hemoglobin. Without enough iron, the body cannot produce enough Hemoglobin for red blood cells.

2. Hemorrhagic anemia

- Hemorrhagic anemia is the specific type of anemia that causes it.
- Due to a sufficient decrease in red blood cells due to bleeding. Common causes include large wounds, stomach ulcers, and heavy menstrual bleeding.

3. Megaloblastic anemia

In addition to iron, the body needs folic acid and vitamin B12 to produce a sufficient number of healthy red blood cells. A diet deficient in these and other important nutrients reduces red blood cell production. (Megaloblastic anemia is characterized by the development of very large red blood cells, poorly developed cells)

4. Pernicious anemia

- In this condition, the body's inability to produce intrinsic factors results in insufficient red blood cell production. As a result, a person cannot absorb vitamins.

- B12 pernicious anemia is a vitamin B12 deficiency caused by an autoimmune attack on stomach cells and antibodies to intrinsic factors that occurs in megaloblastic anemia.

5. Anemia in chronic diseases

Certain chronic diseases such as cancer, HIV/AIDS, rheumatoid arthritis, Crohn's disease, and other chronic inflammatory diseases can impair red blood cell production and lead to chronic anemia. Kidney failure can also cause anemia.[9]

6. Aplastic anemia

This is a very rare, life-threatening anemia caused by the reduced ability of the bone marrow to produce red blood cells. Destruction or inhibition of red bone marrow causes aplastic anemia. Bone marrow is usually replaced by adipose tissue or tumor cells. Toxins, gamma rays, certain drugs, and autoimmune diseases cause aplastic anemia.

7. Anemia associated with bone marrow disease

Various diseases such as leukemia, myelodysplasia, and myelofibrosis can cause anemia by affecting blood production in the bone marrow. The effects of these cancers and cancer-like diseases range from subtle alterations in blood production to complete disruption of life-threatening blood formation processes. Other cancers of the blood and bone marrow can also cause anemia, such as multiple myeloma, myeloproliferative disorders, and lymphoma.

8. Hemolytic anemia

Anemia in this group occurs when red blood cells are destroyed faster than the bone marrow can replace them. Certain blood disorders can cause increased red blood cell destruction. When the red blood cell membrane ruptures prematurely, the red blood cell Hb is released into the plasma (hemolysis). Premature destruction of RBCs may result from intrinsic defects such as Hb defects, abnormal RBC enzymes, or defects in RBC cell membranes. Pathogens that can cause hemolytic anemia include parasites, toxins, and antibodies from incompatible blood. People can inherit or develop hemolytic anemia.

9. Sickle cell anemia

- The red blood cells of people with sickle cell anemia (SCA) produce an abnormal type of hemoglobin. When such RBCs oxygenate the interstitial fluid, abnormal hemoglobin tends to lose integrity rather than low levels.

- It reduces oxygen tension and forms long, rigid, rod-like structures that bind red blood cells into pathological shapes. Sickle cells are fragile. Prolonged oxygen depletion can ultimately lead to extensive tissue damage. In addition, because of their shape, sickle cells tend to get stuck in blood vessels and can completely block the blood supply to organs. SCA is characterized by several symptoms. Infants have hand-foot syndrome, which causes swelling and pain in the wrists and feet. Elderly patients have pain in the back and extremities, but no swelling or abdominal pain.
- Other complications include neuropathy (meningitis, seizures, stroke), pulmonary dysfunction, orthopedic abnormalities, genitourinary disorders (involuntary voiding, hematuria, renal failure), eye disorders (hemorrhage, retinal detachment, blindness), convulsions, coma, and infections.

10. Thalassemia

Thalassemia is a type of inherited autosomal recessive blood disorder in which the body makes an abnormal form of hemoglobin.[10,11]

TARGETS OF IRON LEVELS

Regarding iron stores, the guidelines recommend the following:

- Adult CKD patients who do not require dialysis should receive iron to maintain transferrin saturation >20% and ferritin saturation >100 ng/mL. Transferrin saturation should not exceed 30% and ferritin levels should not exceed 500 ng/ml.[12]
- Adult dialysis patients should receive iron supplementation to maintain transferrin saturation above 30% and ferritin saturation above 200 ng/ml.
- The upper saturation limits for ferritin and transferrin are somewhat controversial, as the safety of intentionally maintaining levels above 30% and 500 ng/ml has been evaluated in a very small number of patients. In general, transferrin saturation should not exceed 50%.[5]

MANAGEMENT

Treatment of anemia in chronic kidney disease aims to improve kidney function and increase red blood cell production. Therefore, erythropoiesis-stimulating agents (ESAs) and iron supplementation are the treatment of choice for anemia in CKD.[6]

Erythropoiesis Stimulating Agent (ESA)

The first available EPO analogue was epoetin α, followed shortly by epoetin β. It is produced in cell culture by recombinant DNA technology. Later, darbepoetin alfa (DA) and methoxy polyethylene glycol epoetin beta were developed and shown to have extended half-lives. More recently, biosimilars of the original epoetin have been marketed.[13]

Not all ESAs are the same, they have different pharmacokinetic and pharmacodynamic properties such as The different half-life and EPO receptor affinity make dosing less frequent and easier in NDD-CKD patients who use long-acting ESAs. Furthermore, it is important to note that the conversion factor between short-acting and long-acting ESAs is unlikely to be linear. In fact, long-acting ESAs are more dose effective at higher doses.[1]

Recombinant human erythropoietin and darbepoetin alfa are two commonly used ESAs to treat anemia in CKD. Except for the longer half-life of darbepoetin alfa, the efficacy and side effect profiles are very similar and require less frequent dosing.[6]

According to KIDGO guidelines, in patients with chronic kidney disease who are not on dialysis, ESAs are usually considered when hemoglobin levels are below 10 g/dl, the rate of reduction is individually adjusted for concentration and response to iron therapy. These patients are usually given erythropoietin (50 to 100 units/kg IV or subcutaneously) every 1 to 2 weeks and darbepoetin alfa every 2 to 4 weeks. ESAs are usually avoided in dialysis patients unless the hemoglobin level is 9-10 g/dl. In this subgroup, erythropoietin is administered per dialysis. Darbepoetin alfa is given once a week but is given three times a week.[6]

Iron supplement

Intravenous (IV) iron has been shown to be more effective in increasing ferritin and hb levels while reducing the need for ESAs and blood transfusions, thus providing benefits in both DD-CKD and more recently NDD-CKD is shown. Oral formulations, except for the phosphate-binding agent iron citrate, do not appear to help, especially in hemodialysis patients.[12] In addition, gastrointestinal intolerance and constipation reduce oral iron tolerance and compliance. However, some concerns have been raised about IV iron preparations, including Increased potential role in promoting oxidative stress, endothelial dysfunction, or infection.[14] In addition, intravenous iron administration is associated with an increased risk of hypotension, headache, or hypersensitivity reactions. Labile iron, the iron

that is released into the circulation after administration and does not bind to transferrin, is an important cause of such side effects.[15]

IV iron preparations are non-biologic combination drugs. They form an iron core surrounded by a complex structure of polysaccharides. Indeed, differences in molecular structure between different IV iron preparations could explain the difference in results for each IV iron preparation. Some studies have even shown differences in hb levels achieved between the 'original' brand and its generic form of iron sucrose.[3]

On the other hand, there is increasing evidence that oral compounds may have detrimental effects on the gut microbiota and exacerbate the uremic gut microbiota. Whether oral iron causes changes in the gut microbiota, and increases uremic toxin production and/or inflammation in CKD remains to be determined.[16]

A new recombinant of drug

Prolyl hydroxylase inhibitor

The hypoxia-inducible factor (HIF) pathway is a revolutionary discovery, and drugs aimed at it promise to improve outcomes in diseases such as anemia and chronic kidney disease. HIF is a heterodimer composed of alpha and beta subunits.[17] Heterodimerization of the two subunits activates the transcription of numerous genes and regulates various biological and metabolic processes such as angiogenesis, cell growth and differentiation, and erythropoiesis. HIF transcriptional activity is primarily controlled by its degradation rate.[18]

Blood transfusion

In some cases, healthcare providers use blood transfusions to treat severe anemia in CKD. A blood transfusion rapidly increases the number of red blood cells in the body and temporarily relieves the symptoms of anemia. Medical professionals may limit or avoid blood transfusions because they can cause other health problems.[19] The body produces antibodies over time that can damage or destroy the donor's blood cells, delaying or reducing the chances of a future kidney transplant. Iron NIH external links from transfused red blood cells can accumulate in the body and damage organs. This is a condition known as iron overload or hemochromatosis.[20]

CONCLUSION

Iron deficiency anemia is the most common form of anemia and a complication of CKD. CKD patients can develop either absolute iron deficiency or functional iron deficiency. Absolute iron deficiency is defined as a markedly reduced or absent iron store in CKD patients requiring hemodialysis with TSAT levels ≤20% and serum ferritin levels ≤200 ng/mL in predialysis CKD patients below 100 ng/mL. Adequate iron storage but insufficient iron availability for absorption into erythroid progenitor cells are the criteria for a functional iron shortage. Oral iron supplementation is the preferred form of treatment because of its ease of use and cost-effectiveness. In severe cases, ESA therapy is preferred because it provides rapid relief of the symptoms of anemia and reduces the number of transfusions required.

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CONFLICTS OF INTEREST

The authors confirm that this article's conflict has no conflict of interest.

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