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Anemia in chronic kidney disease

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ABSTRACT

Anemia associated with chronic kidney disease is a common complication and a cause of increased morbidity and mortality. Hemoglobin levels should be closely monitored in all stages of chronic kidney disease. In this review, current clinical practice for anemia associated with chronic kidney disease, including pathophysiology, diagnosis, and treatment management, is reviewed.

Keywords: Chronic kidney disease, anemia, erythropoietin, darbepoetin

INTRODUCTION

Chronic kidney disease (CKD) is defined as the presence of kidney damage or a glomerular filtration rate (GFR) below 60 ml/min/1.73 m2, persisting for 3 months or longer due to any cause.[1] The disease is characterized by a progressive loss of renal function, which may necessitate renal replacement therapies such as dialysis or transplantation.

Kidney damage refers to pathologic conditions demonstrated by radiologic imaging or renal biopsy, urinary sediment pathologies, or an increased urinary albumin excretion rate. Kidney Disease: Improving Global Outcomes (KDIGO) divided CKD into 5 stages with the guidelines published in 2012.[2] Accordingly, there are 5 stages (Stage 3 is also divided into two subgroups: 3a and 3b) based on GFR, and 3 stages based on albuminuria. The CKD stages are compiled in Tables 1 and 2.[2]

Table 1. CKD classification

Category	GFR
Stage 1	>90
Stage 2	60-89
Stage 3a	45-59
Stage 3b	30-44
Stage 4	15-29
Stage 5	<15 or Hemodialysis

CKD: Chronic kidney disease, GFR: Glomerular filtration rate

Table 2. CKD classification based on albuminuria amount

Category	Albumin/creatine ratio
A1	<30 mg/g
A2	30-300 mg/g
A3	>300 mg/g

CKD: Chronic kidney disease

EPIDEMIOLOGY

Anemia is one of the most common complications of CKD. It has been found to be associated with various conditions in studies. These include decreased quality of life,[3] increased morbidity and mortality[4,5] and increased costs.[6]

Although the prevalence of CKD has increased in recent years, it is estimated that its prevalence is above 10% and affects more than 800 million people worldwide.[7] It is predicted that the prevalence of CKD will gradually increase in the coming years, especially with the increasing prevalence of underlying hypertension and diabetes mellitus.

Studies have shown that the prevalence of anemia in non-dialysis-dependent chronic kidney disease patients exceeds 60%.[8] In the same study, it was found that the prevalence of anemia increased as the CKD stage progressed, and the prevalence of chronic disease anemia was found to be over 90% in dialysis-dependent patients.[9] In addition, it has been demonstrated that the development of anemia leads to an increase in the rate of progression of CKD, and accordingly, the frequency of hospitalization, major cardiovascular events, and mortality increases.[10]

In Turkiye, the rate of chronic kidney disease in the general adult population was found to be 15.7%.[11] In the Chronic Kidney Disease Prevalence Survey of Turkiye (CREDIT) study, it was reported that CKD was more common in women (18.4%) compared to men (12.8%), the risk increased significantly with age, and the risk was higher in those living in rural areas.[11]

The frequency of kidney transplantation, which is the cheapest and best treatment option for CKD, was found to be quite low in Turkiye compared to diaysis modalities. Studies have shown that the renal transplantation rate in Turkiye is 24.68%.[12] This situation directs patients to high-cost dialysis treatments for many years.

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PATHOPHYSIOLOGY

Many mechanisms cause or predispose to anemia in chronic kidney disease. The leading cause is the progressive decrease in erythropoietin levels. In addition, inadequate iron absorption as a result of increased hepcidin levels associated with inflammation, shortened erythrocyte lifespan due to uremic toxins, weakened bone marrow response to erythropoietin, folate, and B12 deficiencies, and residual blood in the dialysis circuit during hemodialysis sessions also cause anemia. The pathophysiological mechanisms of chronic kidney disease are summarized in Figure 1.[13]

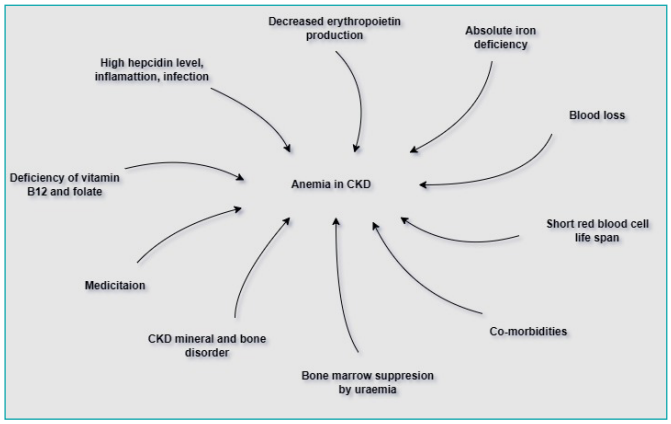

Figure 1. Pathophysiological mechanisms causing chronic kidney disease

Erythropoietin is a glycoprotein hormone, and most of it is synthesized by the peritubular cells of the kidney. In addition, it is also known to be synthesized in small amounts in the spleen, liver, bone marrow, brain, and lung.[14]

Erythropoietin has many functions in the body. Basically, it triggers differentiation into mature red blood cells and proliferation by binding to receptors on the surface of erythroid progenitor cells. In addition to this function, it is known to be effective in heart and brain protective mechanisms by reducing ischemia, regulating vascular tone by affecting nitric oxide levels, and on adipose tissue to regulate metabolic regulation.[15]

The main determinant of erythropoietin production is the decrease in oxygen levels in blood and tissue. As a result of the decrease in oxygen levels in blood and tissue, the amount of hypoxia-inducible factor (HIF) increases. This results in an increase in erythropoietin gene expression and production. Naturally, in cases of low hemoglobin, erythropoietin production increases as the oxygen level in the blood decreases. In chronic kidney disease, there is a decrease in EPO level due to inadequate function of the renal cortex, which is the main production site of EPO. This leads to a decrease in the production of erythroid serum and anemia. Anemia due to the EPO decrease in chronic kidney disease is summarized in Figure 2.

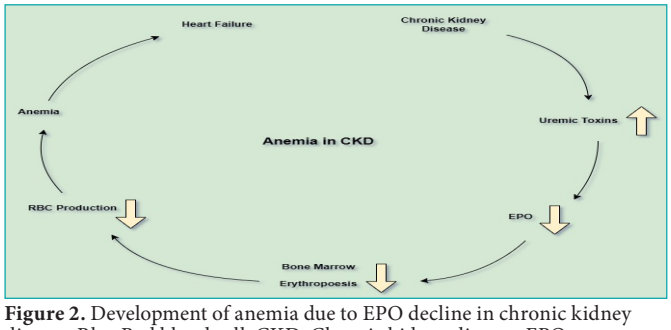

Figure 2. Development of anemia due to EPO decline in chronic kidney disease. Rbc: Red blood cell, CKD: Chronic kidney disease, EPO: Erythyropoietin

Hepcidin is a peptide hormone synthesized mostly by the liver, excreted renally, and is the main regulator of iron balance in the body. Hepcidin inhibits iron absorption through several pathways. Reduction of iron absorption from the small intestine, inhibition of iron delivery from aged erythrocytes to plasma, and inhibition of iron mobilization from liver stores are some of the mechanisms that have been identified so far. Due to its excretion from the kidney, blood levels are high in chronic kidney disease. In addition, recent studies have shown that hepcidin is an acute-phase reactant, and its levels increase in acute and chronic inflammations. Especially in chronic kidney disease, which is considered to be a chronic inflammatory process, it has been found that increased levels of hepcidin disrupt the proliferation and differentiation of erythroid series cells, and anemia develops accordingly. The increase in hepcidin and related effects are summarized in Figure 3.[16]

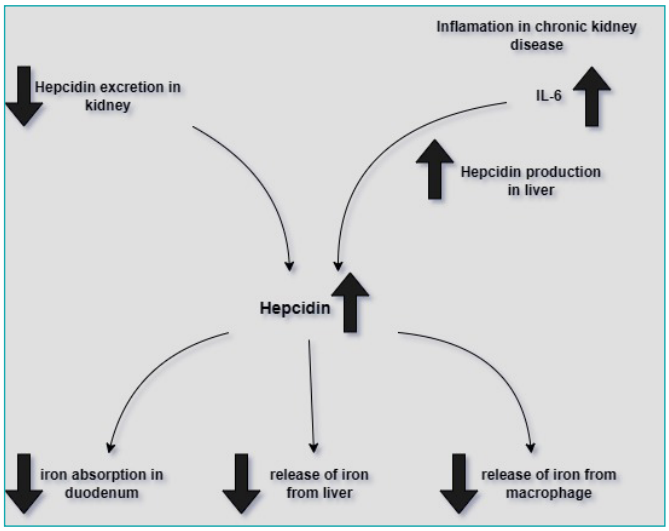

Figure 3. Increased hepcidin and related effects in chronic kidney disease

A large number of uremic toxins are present in the circulation and are continuously cleared and excreted from the blood by the renal route. In chronic kidney disease, increased levels of uremic toxins that cannot be excreted due to insufficient renal function play a key role in shortening erythrocyte life span. The reasons for this can be listed as increased erythrocyte osmotic fragility,[17] disruption of the asymmetry of erythrocyte membrane phospholipids[18] and impaired erythrocyte deformability.[19]

Another cause of anemia in chronic renal failure is blood loss. Especially in patients receiving routine hemodialysis, blood loss may occur due to both dialyzer membranes and anticoagulant use. Also, people with chronic kidney disease produce more gastric and duodenal acid because they have high uremia, which can lead to the formation of ulcers in these areas. Therefore, the incidence of gastrointestinal bleeding increases.[20]

TREATMENT AND MANAGEMENT

In addition to routine renal function monitoring, hemoglobin, transferrin saturation, and ferritin values should be measured every three months in patients with chronic kidney disease. Treatment of anemia in chronic kidney disease consists of several components. First of all, it should be aimed to improve the underlying renal dysfunction if possible. After this, it should be aimed at increasing the erythrocytic series. For this purpose,

the preferred treatment modalities for chronic kidney disease are erythropoiesis-stimulating agents and iron supplementation when necessary. Erythropoiesis-stimulating agents and recombinant erythropoietins are avoided unless the hemoglobin level falls below 10 mg/dl.[21]

In the past few years, the main treatment for chronic kidney disease has been blood transfusions. As a result of this situation, iron overload occurred in patients. In the 1980s, recombinant erythropoietin and then erythropoiesis-stimulating agents were discovered in studies conducted primarily to avoid transfusions.[22] In studies conducted over a short period of time, it was demonstrated that it increased survival and quality of life, improved cardiac functions, and decreased mortality and hospitalization.[23,24]

There are two main erythropoiesis-stimulating agents that are generally preferred in the treatment of anemia in chronic kidney disease. These are recombinant human erythropoietin and darbepoetin alfa. The initial dosing of recombinant human erythropoietin is 50-100 units/kg intravenously or subcutaneously three times a week. The standard starting dose of darbepoetin alfa is 0.45 mcg/kg intravenously or subcutaneously once a week.[25]

Knowledge of the side effects of these two agents is of great importance in patient follow-up. Predisposition to thrombotic events secondary to increased blood viscosity is considered to be the most important side effect. In addition, studies have shown an increased risk of ischemic stroke and myocardial infarction. Therefore, prophylactic antithrombotic use is recommended in some patient groups.[26,27] Benefits and risks of erythropoiesis-stimulating agents for anemia in chronic kidney disease are summarized in **Table 3**.

Table 3. Benefits and risks of erythropoiesis stimulating agents for anemia in CKD

Benefits
Increase Hb level and corrects anemia
Lessen the need for RBC transfusion
Risks
Higher rates of vascular access thrombosis, cerebrovascular events and cardiovascular events
Earlier requirement for kidney replacement theraphy
Higher rates of mortality

The peak erythrocyte level in response to both treatment regimens usually occurs between 8 and 12 weeks. In rare groups, anemia resistant to these agents may be observed, and the cause of this is thought to be the inflammatory process. Some publications have shown that high CRP levels are associated with erythropoiesis-stimulating agent resistance.[28]

Roxadustat is another preferred agent in the treatment of chronic kidney disease related anemia. Roxadustat has been in use in recent years and is also available in Turkiye. The effect is demonstrated by HIF stabilization through inhibition of prolyl hydroxylase, which activates HIF.[29] It is an oral agent, primarily metabolized in the liver.[30] There are side effects such as vomiting, peripheral edema, headache, fatigue and hypercalemia.[31] Some studies have even shown that it increases the incidence of pulmonary hypertension.[32] However, it has been found that, unlike erythropoiesis-stimulating agents, it does not significantly increase the risk of cardiovascular events.[33] Compared to erythropoiesis stimulant agents, Roxadustat has been found to normalize intestinal iron absorption, which is due to its greater suppression of hepcidin.[34] Positive effects of Roxadustat on lipid profile have also been observed. Total cholesterol, LDL cholesterol and triglyceride levels have been significantly reduced. This effect is believed to be due to HIF stabilization.[35]

Iron treatment should also be considered as an option for patients with anemia due to chronic renal failure. Especially the increase in hepcidin due to the inflammatory process and impaired iron absorption leads to the need for iron. In patients receiving hemodialysis, intravenous iron supplementation is recommended due to decreased oral iron absorption.[36]

Chronic kidney disease, anemia, is a process that requires treatment and follow-up. Clinical studies have shown that each 1 mg/dL decrease in hemoglobin level leads to a 42% increase in left ventricular dilatation.[37] Accordingly, an increase in cardiovascular mortality rates has been found.[38]

CONCLUSION

The management of anemia in CKD poses a complex challenge, as it goes beyond simply administering blood transfusions or erythropoietin to patients. Both of these products can have significant negative effects when used over a long period of time. It is important to avoid making assumptions about the cause of anemia in renal disease. There are various factors to consider, such as nutrition and chronic illness. Therefore, conducting a comprehensive evaluation is crucial in order to identify the underlying cause.

Managing patients on dialysis with anemia necessitates a comprehensive approach involving a team of healthcare professionals. This team typically includes the nephrologist, primary care provider (including nurse practitioners, physician assistants, and physicians), nursing staff, pharmacy personnel, and, in some cases, a hematologist. By working together, they can optimize patient outcomes. A healthcare professional should closely monitor vital signs and obtain complete blood counts to assess the severity of anemia. Furthermore, it is crucial for pharmacists to provide patients with thorough education regarding the significance of iron supplements. This is due to the fact that the absence of iron can lead to the development of resistance to erythropoietin in many patients.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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