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Review

CKD-Induced Anemia Revisited: Interplay of inflammation, Iron, and Novel Therapies

Chiluka Purvi*[1], Chelle Laxmiprasanna[1], Dara Harika[1], Cheganti Rahul[1], Chethireddy Rajasimha[1], Dr.Pratap devi shankar sai prakash[2], Dr. Meesala Gowthami[3]

[1]Student, Malla Reddy College of Pharmacy, Maisammaguda, Hyderabad, Telangana. 500014.
[2]Associate Professor, Malla Reddy College of Pharmacy, Maisammaguda, Hyderabad, Telangana. 500014.
[3]Assistant professor, Malla Reddy College of Pharmacy, Maisammaguda, Hyderabad, Telangana. 500014.

*Author for Correspondence: Chiluka Purvi,student
Email: purviic03@gmail.com

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Abstract

CKD anaemia, commonly referred to as anaemia of chronic renal disease, is a subtype of hypoproliferative anaemia and normocytic normochromic anaemia. This condition is prevalent among people with renal illness and is linked to poor outcomes and a higher risk of death in CKD patients. While there are many similarities between it and the chronic inflammatory elements of CKD anaemia, a significant difference is that CKD anaemia is characterised by a severe erythropoietin shortage. Therefore, the goal of treatment is to increase the generation of red blood cells, decrease functional iron shortage, and improve renal function wherever possible. A full blood count with differential, peripheral smear, and tests to rule out other causes of anaemia, such as B12, folate, haptoglobin, thyroid studies, and iron indices (iron, ferritin, total iron-binding capacity, saturation of transferrin and folate), are necessary for the diagnosis. Iron supplements and erythropoiesis-stimulating agents (ESAs) are presently the mainstays of treatment for anaemia associated with chronic renal illness. Since the first ESA and intravenous iron formulations were used, guidelines have changed considerably, and numerous novel therapeutic approaches are now on the market or being investigated in advanced-phase clinical trials. The assessment and treatment of anaemia in chronic renal illness are reviewed in this activity. In order to provide the best possible care for those impacted by this illness, this activity also emphasises the need of the interprofessional healthcare team.

Keywords: Anemia, Chronic kidney disease, Erythropoiesis stimulating agents.

INTRODUCTION

In general, anaemia is defined as having a haemoglobin level below 12 g/dL in women and less than 13 g/dL in men[1]. Individuals with renal disease frequently suffer from normocytic, normochromic, and hypoproliferative anaemia, which is referred to as anaemia of chronic renal disease (CKD). Along with other CKD problems, it is commonly linked to poor outcomes, a lower quality of life, and a higher death rate [2].In 1836, Renal illness and anaemia were initially connected by Richard Bright, dubbed the "Father of Nephrology"[3,4]. Anaemia is more common as kidney disease worsens and affects nearly all individuals with stage 5 CKD. Reduced erythropoietin production, decreased gastrointestinal iron absorption from chronic inflammation, and a shorter lifespan of red blood cells (RBCs) are the main causes of anaemia in chronic kidney disease (CKD), including end-stage renal disease (ESRD). Over the past 20 years, significant progress has been made in treating CKD-related anaemia. The majority of treatment prior to the present therapeutic choices was blood transfusion, which had a number of drawbacks, such as infections, hemosiderosis, fluid overload, and transfusion responses. Furthermore, if a renal transplant is an option, repeated blood transfusions raise the risk of allosensitization, which can impair the results. Androgens were used to help patients with chronic kidney disease (CKD) avoid transfusions in the 1970s, but this practice is now strongly discouraged[5,6]. The treatment of CKD anaemia was completely transformed in the late 1980s with the introduction of recombinant erythropoietin and erythropoiesis-stimulating agents (ESAs)[7]. These treatments, which were first developed to prevent transfusions, were quickly shown to have a number of beneficial outcomes, such as increased heart function, less hospitalisations, better survival and quality of life, and lower total expenses[8]. Dialysis patients' mean haemoglobin levels rose from 9.6 g/dL in 1991 to 12.5 g/dL in 2005, and they required fewer transfusions overall[9]. The Normal Hematocrocrit Trial, conducted in 1998, however, raised questions over side effects linked to greater haemoglobin or haematocrit targets[10]. Several studies have since evaluated the advantages of focussing on higher versus lower haemoglobin ranges. The revelation of ESA side effects sparked concerns about the drugs' overall advantages and heightened interest in developing alternate approaches to treating CKD anaemia. Cardiovascular events and higher mortality are strongly linked to anaemia in chronic kidney disease. Furthermore, a higher rate of hospitalisations and a lower quality of life are associated with more severe anaemia. To properly manage this condition, it is essential to comprehend the many mechanisms at play, suggested treatment protocols, and emerging therapeutic advancements.

Etiology

Chronic renal illness anaemia has a complex aetiology, but its main causes include aberrant iron metabolism brought on by chronic inflammation and diminished renal synthesis of erythropoietin, the hormone that stimulates the creation of red blood cells. The downregulation of hypoxia-inducible factor (HIF), a transcription factor that controls erythropoietin gene expression, has recently been connected to decreased erythropoietin[11][12]. Additional mechanisms include folate and vitamin B12 deficiency, bleeding from defective platelets, uremia (which causes haemolysis and RBC deformation), and blood loss from haemodialysis[13]. A characteristic of renal disease is erythropoietin deficiency. In the renal cortex and outer medulla, peritubular type 1 interstitial cells generate erythropoietin, which promotes erythroid cell development. When it is absent, erythroid precursors undergo programmed apoptosis. Furthermore, erythropoietin synthesis is inhibited and erythroid progenitor cell proliferation is reduced by proinflammatory cytokines. Anaemia associated with chronic kidney disease (CKD) is also significantly influenced by iron shortage. This is due to both absolute and relative iron deficiency, which are induced by chronic inflammation that prevents iron from being released from cellular reserves. Transferrin binds iron after it has been absorbed from the gastrointestinal tract. The liver and spleen thereafter receive bound iron, which is either transferred to the bone marrow for erythropoiesis or retained in ferritin. Additionally, erythropoietin-dependent macrophages recycle iron by phagocytosing senescent red blood cells[14]. Hypochromia and microcytosis can also result from severe iron deficit, even though CKD anaemia is typically characterised as normochromic. An important hormone in iron metabolism is hepcidin. The liver produces hepcidin, which controls the release of stored iron and controls the absorption of iron from the gastrointestinal tract. Adipocytes and macrophages also secrete trace levels of hepcidin. The production of ferroportin, the cell-surface iron exporter, is elevated by chronic inflammation, infection, and renal failure, while hepcidin inhibits its expression. It also inhibits the growth of erythroid progenitor cells, lessens iron absorption, and promotes iron storage. Because hepcidin is also eliminated by the kidneys, elevated levels occur when the glomerular filtration rate (GFR) decreases[15]. One important transcription factor that controls how cells react to hypoxia is HIF. HIF controls erythropoietin (EPO) and other iron-metabolism genes. It is made up of a stable β-unit and an oxygen-binding α-unit. The von Hippel Lindau protein complex ubiquitinates HIF-α, causing its destruction, when oxygen levels are normal because prolyl-4-hydroxylase domain-containing proteins 1-3 (PHD 1-3) hydroxylate HIF-α. Erythropoietin transcription is elevated in hypoxemic circumstances due to the stabilisation of HIF-α. Additionally, HIF indirectly lowers hepcidin levels by causing erythroblasts to secrete more erythroferrone[16].

Epidemiology

Anaemia of CKD usually appears when the GFR drops below 60 mL/min/1.73 m2, and it can occur in as many as 20% of individuals with stage 3 CKD. After becoming dialysis dependent, anaemia will eventually strike at least 90% of patients. A decreasing GFR increases the prevalence and severity of anaemia. Between 2007 and 2008 and 2009 and 2010, the National Health and Nutrition Examination Survey (NHANES) found that anaemia was twice as common in CKD patients as it was in the general population [17]. Comparable findings were noted in the CKD Prognosis Consortium[18].

Pathophysiology

In CKD anaemia, there are both functional and absolute iron deficits. Intra-dialytic blood losses (an estimated 161 mg of intra-dialytic iron loss occurs annually), frequent phlebotomy losses, poor nutrition, and impaired iron absorption can all lead to absolute iron shortage[19]. An inability to efficiently use iron stores results in functional iron deficiency. Any inflammatory condition, including CKD, can result in anaemia of CKD, sometimes referred to as reticuloendothelial cell iron blockage. A mismatch between supply and demand can also occur when exogenous erythropoietin therapy depletes easily available iron more quickly than it can be released from storage cells. As was previously mentioned, erythropoietin insufficiency and poor iron metabolism are the main causes of anaemia in CKD. However, patients with chronic renal disease may also acquire anaemia due to other processes, as discussed below.

- More than half of CKD patients have hypocellular bone marrow, while no particular inhibitors have been found[20].
- According to research on radioisotope labelling, anaemia is also a result of RBCs' shorter lifespan. Among the contributing mechanisms include unidentified factors and uremia[21].
- Anaemia may result from nutritional deficiencies, such as those in vitamin B12 and folate, brought on by anorexia or dialysate losses. Haemodialysis patients typically receive routine water-soluble vitamin supplements, although micronutrients may still be lost during the procedure.
- Copper, an essential part of ferroxidase enzymes (such as ceruloplasmin and hephaestin) involved in iron processing, is thought to be eliminated by haemodialysis.
- The hormone known as fibroblast growth factor 23 (FGF23), which is generated by osteoblasts and osteocytes, is noticeably increased in CKD because of metabolic bone disease. In animal studies, FGF23 antagonists alleviate renal anaemia, and research has demonstrated that it inhibits the formation of erythropoiesis and erythropoietin[22].
- Anaemia can also be caused by medications that are frequently prescribed to CKD patients. Anti-rejection drugs can result in bone marrow hypocellularity, which is especially true for kidney transplant recipients.

All things considered, anaemia of chronic renal disease is a complex condition that can be caused by a number of reasons, including a relative erythropoietin shortage, uremia-induced erythropoiesis inhibitors, a reduced erythrocyte lifespan, and abnormal iron homeostasis.

Symptoms

Severe weakness Weary The dyspnoea Diminished focus Feeling lightheaded Usually associated with severe anaemia, chest pain Headaches The dyspnoea decreased capacity to tolerate exercise Typical indications include: Conjunctival and skin pallor Distressed breathing tachycardia Heart failure, typically associated with severe and persistent anaemia).

Treatment

Agents that Induce Erythropoiesis

The two erythropoietin analogues that are typically used to treat CKD anaemia are epoetin alfa and darbepoetin alfa. Their efficacy and side effect profiles are comparable, with the exception of darbepoetin alfa's extended half-life, which permits less frequent dosage. They are produced using recombinant DNA technology in cell cultures[23].

According to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, when haemoglobin levels in CKD patients fall below 10 g/dL, ESAs are usually taken into consideration. Treatment for ESA is customised, though, depending on variables such the rate of haemoglobin drop, the symptoms of anaemia, the need for transfusions, and the patient's reaction to iron therapy. It is customary to provide erythropoietin (50–100 units/kg IV or subcutaneously [SC]) every one to two weeks, and darbepoetin alfa every two to four weeks. Darbepoetin alfa is given once a week to dialysis patients, while erythropoietin is given with each dialysis session three times a week. The US Food and Drug Administration (FDA) approved epoetin alfa-epbx, a genetically modified recombinant human erythropoietin, in 2018 as a treatment for anaemia in patients with chronic kidney disease (CKD). This medication is an alternative to the ESAs mentioned above. Research has indicated comparable efficacy and adverse event rates to those of epoetin alfa. This biosimilar product, which has been on

the market in Europe since 2007, could save money if it is used extensively[24]. The longer-acting, more recent ESA known as continuous erythropoiesis receptor activator (CERA) may be better than other ESAs because it requires less frequent administration. A methoxy polyethylene glycol chain is attached to epoetin beta in this molecule. In addition to having a lesser affinity for the soluble erythropoietin receptor, CERA may also have a decreased activity of cellular proliferation. CERA has a much longer half-life of roughly 130 hours, can be given SC every two to four weeks, and has been available in the US since 2007. There is currently no concrete evidence to support or refute its use in comparison to other ESAs[25]. RBCs often peak in response to ESAs between 8 and 12 weeks. However, anaemia may be resistant to ESAs in 10% to 20% of instances. In this case, relative iron insufficiency should always be taken into account. For additional information, please refer to "Epoetin Alfa," a companion resource to StatPearls. Using ESAs, the target haemoglobin level in all CKD patients is less than 11.5 g/dL, regardless of whether dialysis is required. The superiority of aiming haemoglobin to "normal" versus lower ranges has been evaluated in a number of trials, including CHOIR, NHCT, and TREAT. Higher levels of ESAs were linked to increased mortality, thrombosis, and adverse cerebrovascular and cardiovascular events, according to these trials. Additionally, when ESAs are used to target Hb levels above 11 g/dL, the FDA has warned about the increased risk of death, serious adverse cardiovascular events, and stroke[26]. The negative effects seem to be caused by the greater ESA dosage rather than the ensuing elevated haemoglobin levels; this could be connected to the way ESAs affect vasoconstriction and vascular remodelling [27]. The possible impact on cancer is another issue with ESA use. Erythropoietin receptors are expressed by certain cancerous cells, which makes them vulnerable to accelerated proliferation when ESA is administered. ESA administration was linked to higher mortality, according to a meta-analysis. [28], KDIGO guidelines advise that individuals with chronic kidney disease (CKD) who have an active malignancy (grade 1B), a history of stroke (grade 1B), or a history of malignancy (grade 2C) should use ESAs with caution.

An allergic reaction or the formation of anti-erythropoietin antibodies are uncommon but serious side effects of using ESA. Early cases that were recorded between 1998 and 2006 are believed to have been caused by an earlier version of epoetin. The drug's other ingredients or the recombinant erythropoietin itself may be the cause of the allergy. ESA treatment may exacerbate pure red cell aplasia caused by erythropoietin-neutralizing antibodies that target both natural and recombinant erythropoietin. Anti-erythropoietin antibodies are linked to this disorder, which is more likely to occur with SC than with IV injection. Their titers are correlated with the severity of anaemia. These anti-erythropoietin antibodies include neutralising anti-erythropoietin antibodies. Erythroid precursors may be missing or their development may be stopped in bone marrow biopsies in cases with pure red cell aplasia. Usually immunosuppressive drugs are used to address this disease, although stopping the ESA can be enough[29].

Treatment with Iron

Iron deficiency is more likely to occur in patients with renal disease because of things like poor dietary iron absorption, repeated phlebotomy, blood trapped in the dialysis machine, and persistent bleeding from platelet dysfunction brought on by uremia. Iron supplements are crucial for treating CKD anaemia because of this deficit as well as the reduction in circulating iron caused by erythropoiesis triggered by ESAs. IV iron is recommended for haemodialysis patients and those with advanced chronic kidney disease (CKD) because oral iron supplementation is mainly ineffective due to high hepcidin levels[30]. For individuals with CKD and anaemia, KDIGO suggests a goal TSAT of 20% to 30% and ferritin levels of 100 to 500 ng/mL. According to the 2013 European Renal Best Practice Guidelines, ferritin should not exceed 500 ng/mL and TSAT should not exceed 30%. Furthermore, dialysis facilities may have unique objectives and procedures. A ferritin maximum of 800 ng/mL is recommended by the Renal Association (2017) and the National Institute for Healthcare and Excellence (2015) [31]. According to data from recent trials, such as the Randomised Trial Comparing Proactive, High-Dose vs Reactive, Low-Dose IV Iron Supplementation in Haemodialysis (PIVOTAL) trial, guidelines for iron administration may need to be even more lenient. In the PIVOTAL study, the administration of IV iron sucrose was held at a cutoff of 400 ng/mL for ferritin and 40% for TSAT. Significantly decreased ESAs and transfusion needs were observed in the high-cutoff therapy arm, together with a lower incidence of death, hospitalisation, and nonfatal cardiovascular events. Interestingly, the two study arms' infection rates were identical. With high cutoff values, the outcomes of DRIVE I and DRIVE II shown comparable gains. Interestingly, the mean ferritin level for dialysis patients in the US was 800 ng/mL on average in 2013, with 18% of patients having ferritin levels more than 1200 ng/mL. Further research is therefore necessary to fully comprehend the ramifications of extremely high ferritin levels. High ferritin or TSAT levels raise concerns regarding IV iron administration because they may result in iron overload, which raises the risk of infection, oxidative stress damage, and tissue iron deposition. Observational studies have not supported the theoretical risk of infection or neutrophil impairment, despite the fact that investigations and meta-analyses on the effect of IV iron on mortality and morbidity in ESRD patients have produced conflicting findings. Although it can happen with iron gluconate, iron sucrose, or ferumoxytol, anaphylaxis is still a risk, especially with iron dextran (which is used less frequently these days). The overall risk for all IV iron formulations is estimated to be between 24 and 68 per 100,000. The

majority of dialysis facilities reduce this risk by cautiously starting IV treatments or giving a test dosage. The possibility that some IV iron formulations may raise FGF23 levels as a result of interactions with the iron's carbohydrate shell is another serious worry[32]. In clinical practice, new-generation IV iron compounds including ferric derisomaltose, ferric carboxymaltose, and ferumoxytol are now often utilised. Their main benefit is their extremely stable carbohydrate coating, which inhibits the unchecked release of toxic-free iron and enables full replacement dosages to be administered in just one or two infusions. These agents' stable polynuclear iron cores with low redox potentials reduce the possibility of damaging oxidative stress events, which is another crucial characteristic.

Novel Iron Therapies

Ferric citrate serves as a phosphate binder and is FDA-approved for the treatment of iron-deficiency anaemia in individuals with CKD or ESRD. This substance releases ferric ions in the alkaline duodenum and forms insoluble complexes with phosphates in the stomach's acidic environment. Its dual function as a phosphate binder may lessen the overall pill burden for patients, and the oral formulation enables a more physiological replacement of iron[33]. Ferric citrate has been found to be just as effective as phosphate binders that are based on calcium as well as those that are not. Furthermore, regardless of its effects on phosphorus reduction, ferric citrate decreases FGF23 levels in individuals who are dialysis dependent as well as those who are not. This could have important ramifications because elevated FGF23 levels are independently linked to anaemia and cardiovascular death. A new oral iron treatment called ferric maltol is made up of a stable combination of ferric iron and maltol, a naturally occurring sugar derivative. With its hydrophilic and lipophilic qualities, this formulation enables the release of accessible iron in the digestive tract's neutral pH. When taken orally, ferric iron is transported to the intestinal mucosa as a combination with maltol, which may improve the absorption of ferric iron into enterocytes in comparison to ferrous iron salts.It has been investigated for treatment of irritable bowel syndrome and has less gastrointestinal side effects since it avoids stomach metabolism. In both the US and the EU, ferric maltol is authorised for the treatment of iron-deficient anaemia. Sucrosomial iron is an oral iron supplement that contains ferric pyrophosphate and a phospholipid bilayer membrane that forms a "sucrosome." Bypassing the stomach, this structure enables intestinal enterocytes to absorb the iron. Sucrosome improves bioavailability by being absorbed without hepcidin control. In the short term, sucrosomial iron was found to be just as effective as intravenous ferrous gluconate in an open-label research, with fewer side effects. In 2015, the FDA approved ferric pyrophosphate, a new water-soluble, complex iron salt that is free of carbohydrates and given through the dialysate during haemodialysis. This substance is intended to be added to each dialysis treatment's bicarbonate concentration, providing roughly 7 mg of iron per treatment. It may be possible to prevent iron sequestration in reticuloendothelial macrophages by directly donating iron to transferrin. Ferric pyrophosphate considerably raises iron indices as compared to a placebo, according to the CRUISE 1 and 2 trials, with few side effects [34].

Ziltivekimab

Ziltivekimab is a human immunoglobulin G (IgG) monoclonal antibody that targets the inflammatory cytokine interleukin (IL)-6. When compared to a placebo, ziltivekimab has been shown to elevate albumin and haemoglobin levels, decrease inflammation, and enhance iron indices in patients with CKD stages 3 to 5. IL-6 is linked to elevated hepcidin expression, which could account for Ziltivekimab's therapeutic advantages[35].

Gobal Impact

A common health problem that affects 13% of people worldwide, chronic kidney disease (CKD) is having an increasing negative influence on the economy and environment. Its complex burden, driven by ageing populations and comorbidities, is predicted to make chronic kidney disease (CKD) the fifth most common cause of death by 2040. Globally, it is estimated that one in four women and one in five men between the ages of 65 and 74 suffer from CKD. There are several possible outcomes from anaemia. It can have an impact on adult productivity, general quality of life, and developmental delays and behavioural abnormalities such reduced motor activity, social engagement, and attention to tasks. Anaemia during pregnancy has been linked to adverse birth and mother outcomes, such as low birth weight, early birth, and maternal death. Apart from the physical ramifications, anaemia can have significant economic effects on people, families, communities, and nations. Anaemia brought on by chronic kidney disease (CKD) is a severe side effect that affects millions of people worldwide, raising healthcare expenses and lowering quality of life. Growing rates of obesity and diabetes, as well as ageing populations, are contributing contributors to the condition's growing public health concern. YLDs (years lived with disability) and prevalence have usually decreased, although the number of cases of CKD-related anaemia has increased globally.

Key aspects of the global impact:

- High prevalence: It is estimated that 11–13% of people worldwide suffer from chronic kidney disease (CKD).

- Anaemia is a common CKD consequence, and as the disease worsens, so does its incidence. The number of cases of CKD-related anaemia has increased, reaching 63.7 million in 2021, despite a drop in global incidence and YLD rates.
- The burden of anaemia associated to chronic kidney disease (CKD) is disproportionately concentrated in less developed nations and territories.
- The frequency and YLDs of CKF-related anaemia are higher in women than in men, indicating a gender difference. Impact on Health and Quality of Life: Anaemia brought on by chronic kidney disease (CKD) can cause exhaustion, dyspnoea, and other incapacitating symptoms, which can have a major negative influence on quality of life.
- Costs associated with treating CKD-related anaemia, such as erythropoiesis-stimulating agents (ESAs) and iron supplements, raise the total cost of managing CKD.
- Anaemia is linked to a higher risk of cardiovascular events, death, and other consequences in people with chronic kidney disease (CKD).
- Need for complete Management: Treating the underlying causes of anaemia, maximising iron levels, and maybe utilising cutting-edge treatments like HIF-PHIs are all essential components of a complete strategy for managing anaemia in CKD.

CONCLUSION

CKD-induced anemia would synthesize the key aspects of its pathophysiology, clinical implications, and management strategies. It is also known as “the silent killer” because there are usually no symptoms until the late stages of the disease when dialysis or a kidney transplant may be needed.

Chronic Kidney Disease (CKD) – induced anemia is a pervasive and significant complication that profoundly impacts the quality of life, morbidity, and mortality of patients with impaired renal function. Far from being a mere consequence of erythropoietin deficiency, its pathophysiology is multifaceted, encompassing iron dysregulation (absolute and functional iron deficiency), chronic inflammation, reduced red blood cell lifespan, and the accumulation of uremic toxins that inhibit erythropoiesis. This complex interplay renders CKD-anemia a formidable clinical challenge. Clinically, CKD-anemia manifests as fatigue, reduced exercise tolerance, cognitive impairment, and exacerbation of cardiovascular complications, further burdening an already vulnerable patient population. Its presence is independently associated with increased hospitalization rates and progression of CKD. Effective management hinges on a holistic approach that prioritizes early detection and systemic intervention. The cornerstone of treatment involves the judicious use of Erythropoiesis-Stimulating Agents (ESAs) in conjunction with aggressive iron repletion, often requiring intravenous iron supplementation due to impaired gastrointestinal absorption and functional iron deficiency. However, the pursuit of higher hemoglobin targets with ESAs has been tempered by concerns regarding cardiovascular risks, necessitating a personalized approach to therapy aims at achieving a balance between symptom relief and minimizing adverse events.

Ongoing research continues to explore novel therapeutic targets, including HIF-1 alpha stabilizers and alternative iron delivery systems, promising a more refined and effective armamentarium against this debilitating complication. Ultimately, addressing CKD-induced anemia is not merely about normalizing hemoglobin levels; it is about improving patient well-being, preserving cardiovascular health, and enhancing overall survival in individuals living with chronic kidney disease. Its management remains an integral component of comprehensive nephrology care, underscoring the critical need for continued vigilance, personalized treatment strategies, and further advancements in the field.

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