CONTINUING MEDICAL EDUCATION

ANEMIA of CHRONIC KIDNEY DISEASE

Dr. Sandeep Mahajan
MBBS, MD, DM, FASN, FISN, FICP
Professor, Department of Nephrology, All India Institute of Medical Sciences, New Delhi, India

Dr. Manish Rathi
MBBS, MD, DM
Professor, Department of Nephrology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Dr. Pinaki Mukhopadhyay
MBBS, DCH, MD, DM
Associate Professor & Head, Dept. of Nephrology, NRS Medical College & Hospital, Kolkata, West Bengal, India

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Program Information

Need for this program

Anemia is a common complication of chronic kidney disease (CKD). It is associated with substantially high morbidity and mortality, additionally increasing hospitalizations, healthcare costs, and deteriorating quality of life of the affected patients. Its mechanism of development is complex and multifactorial. Administration of erythropoiesis stimulating agents (ESA) and iron supplementation is the cornerstone of its management. Anemia management was revolutionized in the 1980s with introduction of recombinant human erythropoietin (EPO). The ESA have been particularly beneficial in reducing need for repeat blood transfusions and its attendant complications. This certificate program has been designed to provide target participants with updated information on the pathophysiological concepts, current diagnostic and management approach that is recommended in anemia of CKD.

Learning objectives

- Understand patient evaluation and management approach for anemia in CKD
- To improve treatment practices and outcomes of patients of CKD with anemia

Reviewers

Dr. Sandeep Mahajan
MBBS, MD, DM, FASN, FISN, FICP
Professor, Department of Nephrology,
All India Institute of Medical Sciences,
New Delhi, India

Dr. Manish Rathi
MBBS, MD, DM
Professor, Department of Nephrology,
Post Graduate Institute of Medical Education and Research,
Chandigarh, India

Dr. Pinaki Mukhopadhyay
MBBS, DCH, MD, DM
Associate Professor & Head, Department of Nephrology,
NRS Medical College & Hospital,
Kolkata, West Bengal, India

Competing interest

None declared

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Self-assessment criteria and self-assessment threshold

Participants are requested to attempt the self-assessment questionnaire after completing their two modules and mail the questionnaire along with the feedback form to: info@cmecom.in. Those participants who successfully attempt the questionnaire with a score of 60% or better will be eligible to receive a CME certificate.

CONTENTS

SECTION 1

ANEMIA OF CKD – DEFINITION AND CURRENT BURDEN

ANEMIA OF CKD

The kidneys are vital organs of the body that perform several crucial functions, thereby maintaining homeostasis. Chronic kidney disease (CKD) is a commonly encountered disorder, associated with long-term loss of renal function.[1,2] It has emerged as an increasing healthcare problem worldwide. Due to paucity of data, its exact burden is difficult to assess; however, high prevalence of CKD has been reported in India.[3,4] Recently published results of the Screening and Early Evaluation of Kidney Disease (SEEK) study[4] confirmed high prevalence of CKD in the Indian population, i.e. 17.2%; with about 6% of evaluated population having advanced stages of CKD (stage 3 CKD or higher). High burden of CKD along with its attendant complications pose several challenges to the healthcare system in India, particularly high cost of treatment and limited access to centers offering renal replacement therapy (RRT). With increasing life expectancy and aging population, and relentlessly growing burden of both diabetes and hypertension – two prominent risk factors of CKD in India and the Western world – prevalence of CKD is expected to increase further in the coming years.[3] These are issues of grave concern, and should be addressed with appropriate interventional strategies to slow renal disease progression, improve outcomes and reduce CKD-related morbidity and mortality.

A vital, yet lesser known function of the kidneys is secretion of erythropoietin (EPO), a glycoprotein hormone that stimulates production and differentiation of erythroid precursor cells in the bone marrow, principally in response to hypoxia. Any form of disruption of this physiological process, as occurs in CKD, can significantly reduce circulating red cell mass, leading to anemia and its consequences. Anemia is a well-known complication of CKD. It accelerates renal disease progression, increases sleep disturbance and cognitive decline, elevates risk of cardiovascular (CV) diseases and overall mortality in CKD patients (Table 1). In particular, risk of CV morbidity and associated mortality is alarmingly high in patients with CKD. Patients with anemia of CKD have a higher risk of CV diseases compared to end-stage renal disease (ESRD).[1] Anemia can develop at an early stage in CKD, and its subsequent prevalence increases with advancing age and CKD progression.[1,5] The mechanism of development of CKD anemia is multifactorial, and include factors such as relative EPO deficiency due to reduced red cell mass, impairment of iron homeostasis in CKD leading to "true" and "functional" iron deficiency, and uremia-induced shortening of RBC lifespan. Management of anemia

Table 1. Consequences of anemia of CKD

- Progression towards ESRD
- Sleep disturbance
- Cognitive decline
- Risk of cardiovascular comorbidities
- Impairment of quality of life
- Increase in hospitalizations
- Increase in healthcare costs
- Increase in mortality

Source: Stauffer ME, Fan T. Prevalence of Anemia in Chronic Kidney Disease in the United States. *PLoS One*. 2014; 9(1): e84943

of CKD is challenging.[5] Erythropoiesis-stimulating agents (ESA) and iron supplements remain the cornerstone of its management.[6] Introduction of recombinant human EPO revolutionized anemia management in the late 1980s. Since then, ESA have replaced repeated blood transfusions as the front-line treatment option for chronic anemia in CKD.[5] Accumulating body of evidence confirms that ESA significantly benefit CKD patients by increasing their hemoglobin (Hb) concentration, reducing requirement for repeat blood transfusions and its complications, and substantially improving quality of life of the affected patients.[5,6] However, in the last few years several randomized controlled trials have critically assessed target Hb concentration that needs to be achieved in CKD patients to derive optimal treatment benefits. The current mandate is to increase Hb concentration in anemic patients with CKD to up to 10–11 g/dl using ESA; any further treatment intensification aiming for higher Hb targets may not translate into incremental benefits, and can even be counterproductive.[7]

DEFINITION OF ANEMIA AND ESTABLISHING CKD AS ITS CAUSE

Definition of anemia has traditionally been based on cut-off Hb concentration. It depends both on age and gender, and therefore differs in different population groups. The 2012 Kidney Disease Improving Global Outcome (KDIGO) guidelines[8] defined CKD anemia in adults and children (>15 years) as Hb concentration <13 g/dl in males and <12 g/dl in females. In contrast, in children <15 years of age with CKD, anemia was defined as Hb concentration <11 g/dl in children between 0.5–5 years, <11.5 g/dl in children between 5–12 years, and <12 g/dl in children between 12–15 years (Table 2). These thresholds of Hb concentration are however different from recommended Hb thresholds for initiation of anemia management in patients with CKD.

Table 2. Definition of anemia of CKD proposed by 2012 KDIGO Clinical Practice Guideline

Age group	Hb concentration
Adults and children > 15 years	<13 g/dl (males) and <12 g/dl (females)
Children 0.5-5 years	<11 g/dl
Children 5-12 years	<11.5 g/dl
Children 12-15 years	<12 g/dl

Source: Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney inter., Suppl.* 2012; 2: 279–335.

Levels of Hb should therefore be routinely evaluated in all patients with CKD to screen for anemia. Also, given the fact that anemia has multiple underlying causes, these patients should undergo systematic evaluation to identify cause of anemia with certainty. Of note, CKD should be considered the primary cause of anemia if glomerular filtration rate (GFR) is <60 ml/min/1.73m^2; and is certainly a cause when GFR is <45 ml/min/1.73m^2 in patients with diabetes and <30 ml/min/1.73m^2 in those without, and no underlying cause of anemia can be identified despite thorough investigations.[9]

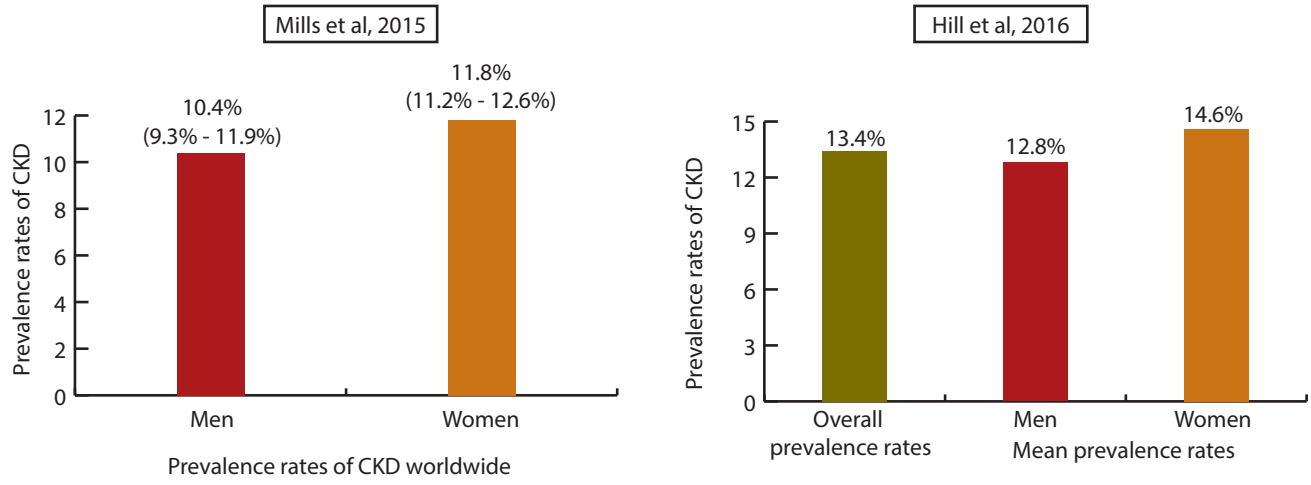
TAKE HOME POINTS

- Anemia is a well-known complication of CKD, accelerating CKD progression, increasing sleep disturbance and cognitive decline, elevating CV risk and overall mortality
- The 2012 KDIGO guidelines define anemia in adults and children (>15 years) with CKD as Hb concentration <13 g/dl in males and <12 g/dl in females
- CKD should be strongly suspected as the cause of anemia when GFR is <45 ml/min/1.73m^2 in patients with diabetes and <30 ml/min/1.73m^2 in those without, and no underlying cause of anemia can be identified despite thorough investigations
- Recombinant human EPO revolutionized anemia management in the late 1980s. Since then, ESA have replaced repeat blood transfusions as the front-line treatment for chronic anemia in CKD

BURDEN OF CKD AND ANEMIA AS ITS COMPLICATION

Chronic kidney disease (CKD) is widely prevalent across the world, and its global burden has dramatically increased in the last few years. It is a major risk factor for end-stage renal disease (ESRD) and premature deaths.[10] Burden of CKD is difficult to assess accurately. Two large meta-analyses[10,11] provided concordant data on high prevalence rates of CKD worldwide, underscoring its positioning as a major global public health challenge. The first meta-analysis,[10] which pooled data from 33 population-based studies conducted in different countries worldwide, showed age-standardized global prevalence rates of CKD to be

Figure 1 **Worldwide prevalence rates of CKD, as assessed in two large meta-analyses**

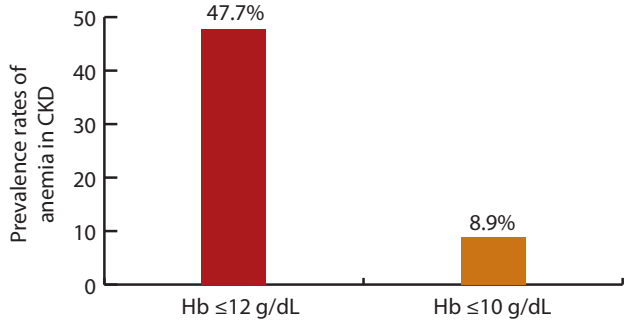


Sources: 1. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, Chen J, He J. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int*. 2015 Nov; 88(5):950-7. **2.** Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FD. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. *PLoS One*. 2016; 11(7):e0158765.

10.4% in men and 11.8% in women (Figure 1). In absolute numbers, a total of 225.7 million (205.7-257.4 million) men and 271.8 million (258.0-293.7 million) women were diagnosed with CKD. When region-wise prevalence of CKD was compared, this meta-analysis revealed higher burden of CKD in low- and middle-income countries than in high-income countries. The second meta-analysis[11] also evaluated pooled data of 100 observational studies and determined prevalence of CKD using random effects model. Result of this meta-analysis reiterated high global prevalence of CKD, showing mean prevalence of all CKD stages to be 13·4% (Figure 1) with majority of patients being in CKD stages 3-5 (prevalence 10·6%).

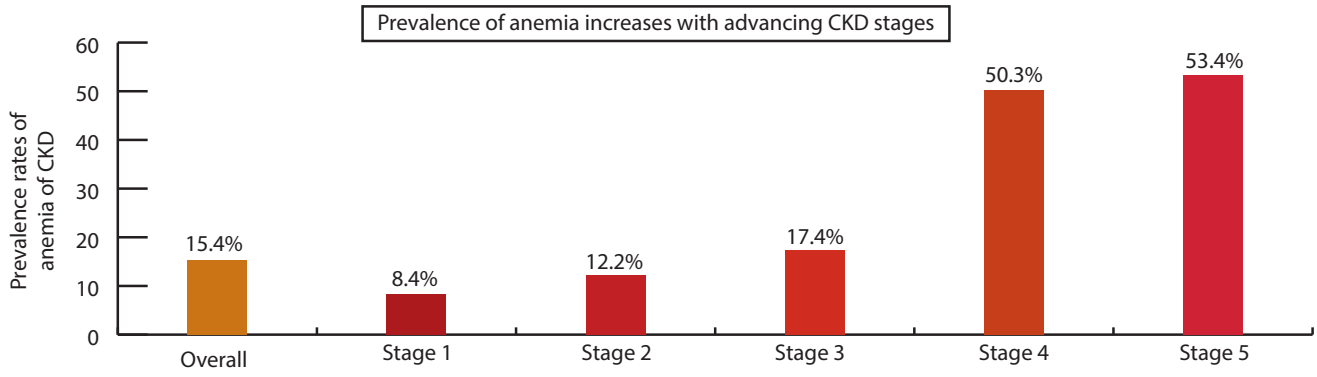
There is scarcity of data on the prevalence of CKD in India. An epidemiological evaluation[12] performed in Delhi involving 4172 urban subjects showed prevalence of CKD (defined as serum creatinine >1.8 mg% for greater than 3 months) to be 0.78%. However, since serum creatinine was the lone criteria used for detecting CKD in this study population, this prevalence rate was likely to have been underestimated.[3] Another cross-sectional study[13] involving evaluation of 3398 healthy Indian central government employees and their families showed semi-quantitative microalbuminuria (MAU) >30 mg/l in 9.96% and deranged albumin:creatinine ratio (ACR) in 11.47% of evaluated subjects. Using the Modification of Diet in Renal Diseases (MDRD) equation, 6.6% participants were shown to have CKD stage 1, 5.4% had CKD stage 2, and 3% had CKD stage 3. Alternatively, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, 6.7% had CKD stage 1, 4.3% had CKD stage 2, and 2.1% subjects had CKD stage 3. High prevalence of CKD in the Indian population was shown in the SEEK study,[4] in which overall prevalence rate of CKD was 17.2%, with about 6% patients being in CKD stage 3 or higher. Prominent risk factors of CKD in Indian population, similar to Western data, are diabetes and hypertension, both accounting for 40–60% of CKD cases.[14]

Figure 2 **Prevalence of anemia in CKD patients recruited in a large US multicenter survey (n=5222 patients, age ≥ 18 years)**



Source: McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, Tse TF, Wasserman B, Leiserowitz M. The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin*. 2004 Sep; 20(9):1501-10.

Figure 3 **Prevalence of anemia of CKD, as evaluated from pooled data of 2007-2008 and 2009-2010 NHANES surveys**



Source: Stauffer ME, Fan T. Prevalence of Anemia in Chronic Kidney Disease in the United States. *PLoS One*. 2014; 9(1): e84943.

A complex disorder such as CKD can presage development of several complications. Commonly encountered complications of CKD are dyslipidemia, bone and mineral disorders, and anemia.[15] Anemia frequently complicates the course of CKD. In a cross-sectional, US multicenter survey[16] which evaluated pre-dialysis patients with CKD, anemia (Hb ≤12 gm/dl) was diagnosed in 47.7% of patients (Figure 2). Its prevalence increased with declining renal functions; percentage of patients with anemia increased from 26.7% to 75.5% as GFR decreased from ≥60 ml/min/1.73 m^2 to <15 ml/min/1.73 m^2. Similarly, prevalence of severe anemia (Hb ≤10 g/dl) was 8.9% (Figure 2), and its prevalence also increased substantially from 5.2% to 27.2% as GFR decreased from ≥60 ml/min/1.73 m^2 to <15 ml/min/1.73 m^2. Another multi-ethnic study[17] performed in Singapore which also evaluated non-dialysis adult CKD patients, anemia (defined as Hb <10 g/dl) was diagnosed in 35.4% of patients. Recently, results of evaluation of pooled data of the National Health and Nutrition Examination Surveys (NHANES)[1] conducted in 2007–2008 and 2009–2010 were published, which confirmed higher prevalence of anemia in CKD population compared to the general population (15.4% vs 7.6%, respectively). Expectably, the results also showed increasing prevalence of anemia as kidney functions declined; prevalence of CKD anemia increasing from 8.4% in CKD stage 1 to 53.4% in CKD stage 5 (Figure 3).

Anemia has a much higher prevalence in patients on dialysis. Three different studies have reported prevalence rates of anemia being as high as 87.8%,[18] 96.2%,[19] and 79%[20] in CKD patients on chronic dialysis. Risk factors that increase risk of anemia in CKD have been identified. Being familiar with them can assist in screening high-risk patients for detecting anemia and initiating adequate preventive and treatment strategies. Prominent predictors of renal anemia are advanced CKD stage (OR 16.76), comorbid hematological disorders (OR 18.61), and respiratory disorders (OR 4.54); alternatively, risk of anemia is lower in patients taking iron supplements (OR 0.44) and those with higher pre-treatment Hb concentration (0.32).[17] Female gender and serum albumin concentration are also notable independent predictors of CKD anemia (Table 3). Diabetes is a strong risk factor for renal anemia. Anemia in diabetic CKD appears at an earlier stage and is of greater severity compared to anemia in non-diabetic patients.[21]

Table 3. Predictors of Hb status in CKD

- Stage of CKD
- Hematological disorders
- Respiratory disorders
- Diabetes
- Previous Hb status
- Female gender
- Serum albumin concentration
- Previous use of iron supplements

Sources: 1. Lau BC, Ong KY, Yap CW, Vathsala A, How P. Predictors of anemia in a multi-ethnic chronic kidney disease population: a case-control study. *Springerplus*. 2015 May 20;4:233. **2.** Al-Khoury S, Afzali B, Shah N, Covic A, Thomas S, Goldsmith DJ. Anaemia in diabetic patients with chronic kidney disease--prevalence and predictors. *Diabetologia*. 2006 Jun;49(6):1183-9.

TAKE HOME POINTS

- Meta-analyses and observational studies have provided concordant data on high prevalence of CKD worldwide, underscoring its positioning as a major global public health challenge
- CKD is a worldwide healthcare problem. Analysis of pooled data from NHANES surveys of 2007–2008 and 2009–2010 confirmed higher prevalence of anemia in CKD population compared to general population (15.4% vs 7.6%, respectively)
- Prevalence of anemia has been reported to be as high as 87.8%, 96.2%, and 79% in three different studies that evaluated patients on chronic dialysis
- Prominent predictors of renal anemia are advanced CKD stage, comorbid hematological disorders and respiratory disorders, female gender, and serum albumin concentration
- Anemia in patients with diabetic CKD appears at an earlier stage and is of greater severity compared to anemia in non-diabetic patients

CONCLUSION

Chronic kidney disease (CKD) is a widely prevalent healthcare disorder, including in India, and is associated with significantly high morbidity and mortality rates. Fuelled by relentless rise in the number of cases of hypertension and diabetes, two prominent risk factors of CKD, its burden is expected to increase further in the coming years. Anemia is a commonly encountered complication of CKD. It negatively impacts quality of life, overall compromising disease outcomes and increasing mortality rates. The mechanism of development of anemia in CKD is multifactorial. Common predictors of anemia are stage of CKD, previous Hb status, prior use of iron supplements, hematological disorders, and respiratory disorders, female gender, and serum albumin concentration. Anemia develops earlier in patients with diabetic CKD and is of greater severity in them compared to non-diabetic patients.

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SECTION 2

CONSEQUENCES OF ANEMIA OF CKD AND MECHANISMS OF ITS DEVELOPMENT

CONSEQUENCES OF ANEMIA OF CKD

Anemia has a profound impact on patients with CKD, and is associated with poor outcomes. Renal anemia accelerates progression towards ESRD, increases risk of CV comorbidities, negatively impacts quality of life, increases hospitalization rates and incurs significant healthcare costs.[1]

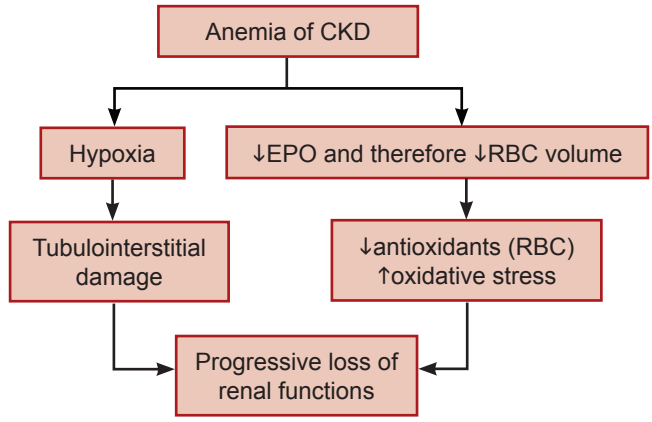
CKD progression

Several observational and small interventional studies[2-4] have provided credible evidence to support an association between anemia and renal disease progression. There is mounting evidence to show that anemia contributes to decline in renal functions, and therefore facilitates progression towards ESRD. Anemia is widely regarded as an independent risk factor as well as a complication of CKD. Experimental data has shown that anemia-associated hypoxia can lead to tubulointerstitial damage, which predisposes to failing renal functions. Also, red blood cells are deemed to have a major antioxidant role, and therefore incremental oxidative stress in anemic conditions can also contribute to progressive deterioration in renal functions (Figure 1).[4] This association between hematocrit and ESRD, although strong, however has not been unequivocally established.[5] Notwithstanding this, there are strong reasons to believe that appropriate correction of renal anemia can attenuate, at least to some extent, renal disease progression. Additionally, EPO has also been shown to have direct protective effects on renal tubular cells. A trial[6] confirmed benefits of EPO in preventing damage to the renal tubular cells. The study investigators also postulated that EPO can attenuate renal fibrosis by macrophage adjustment, and protect endothelial cells through uncertain mechanisms, therefore slowing renal damage. Hence, they proposed that EPO therapy should be introduced earlier in CKD patients for their renoprotective role than that for erythropoiesis. These findings, however, are still preliminary and require further attestation in clinical trials.

CV diseases

Anemia significantly increases risk of CV diseases and overall mortality in both diabetic and non-diabetic patients with CKD.[1,7] In fact, anemic patients with CKD are more likely to die from CV disease than develop ESRD. Mortality from CV diseases is 15-30 times higher in patients with CKD compared to general population. Anemia and resultant hypoxia triggers several hemodynamic

Figure 1 **Proposed mechanism of progression of CKD with anemia development**



Abbreviations: EPO - Erythropoietin

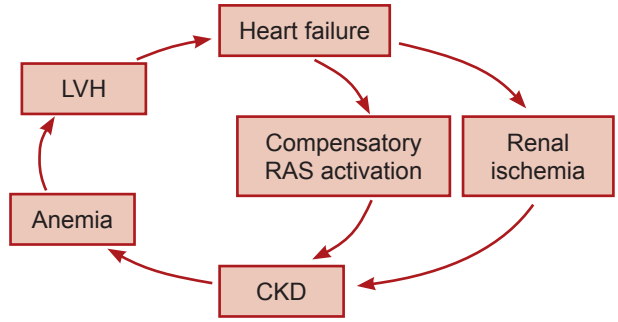
Source: Rossert J, Froissart M. Role of anemia in progression of chronic kidney disease. *Semin Nephrol*. 2006 Jul;26(4):283-9.

compensatory mechanisms, leading to increase in cardiac output and preload, and decrease in afterload; resulting in progressive cardiac enlargement and left ventricular hypertrophy (LVH). Heart failure can ensue. This worsening chronic hyperdynamic state in response to anemia along with remodeling of aorta or the carotids is the primary underlying cause of CV complications. Anemia of CKD is closely associated with LVH, and patients of renal dysfunction with both anemia and LVH are 4-times more likely to develop CV diseases compared to those with neither anemia nor LVH. Additionally, high serum creatinine also increases risk of coronary events and their attendant complications. Overall, anemia is of considerable prognostic significance in CKD patients, and is an independent predictor of CV deaths.[8]

The strength of this association between anemia, CKD and CV diseases has prompted clinicians to propose a novel clinical entity called "Cardio-Renal Anemia syndrome" (Figure 2). Anemia is a key player of this association, and if uncorrected, can worsen both CKD and cardiac performance.[9] One of the first studies that established anemia as an independent CV risk factor was the Atherosclerosis Risk in Communities (ARIC) study[10] which showed that anemia was associated with increased risk of CV diseases (adjusted hazard ratio of 1.41 for CV disease in the entire study cohort). Further analysis of a sample population drawn from the ARIC study cohort[11] showed that serum creatinine ≥1.2 mg/dl in females or ≥1.5 mg/dl in males was associated with 3-fold increased risk of coronary heart disease (CHD) in patients with anemia, although this association was not observed in non-anemic patients. More recently, evaluation of data from the multinational Adelphi CKD Disease-Specific Program[12] which was conducted in France, Germany, Italy, Spain, and the UK showed presence of anemia in 61.4% of patients with CKD. Patients who were anemic had higher mean number of CV diseases than those who were not (1.27 vs 0.95). Compared with non-anemic patients, those with anemia had significantly higher prevalence of CHD, myocardial infarction (MI)/heart attack/unstable angina, heart failure, arrhythmia, and peripheral arterial disease (PAD).

Given the strong association between anemia and CV diseases, it is prudent to examine whether hematocrit correction in CKD patients improves their adverse CV outcomes. Strangely, in the Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin Beta (CREATE) trial[13] which assigned 603 CKD patients having eGFR of 15-35 ml/min/1.73 m^2 and with mild-to-moderate anemia (Hb

Figure 2 **The cardio-renal-anemia syndrome**



Abbreviations: LVH - Left ventricular hypertrophy; CKD - Chronic kidney disease; RAS - Renin angiotensin system

Source: Schmidt RJ, Dalton CL. Treating anemia of chronic kidney disease in the primary care setting: cardiovascular outcomes and management recommendations. *Osteopath Med Prim Care*. 2007 Oct 2;1:14.

11-12.5 g/dl) to either target normal Hb (13-15g/dl; group 1) or subnormal Hb (10.5-11.5 g/dl; group 2); complete anemia correction (group 1) did not change likelihood of first CV event, although its partial correction to achieve subnormal Hb (group 2) significantly improved general health and physical functions of the patients. Left ventricular mass index (LVMI) was stable in both groups, and therefore correction of anemia did not appear to influence LVH progression. Similar findings were seen in the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study[14] which evaluated patients with diabetes, CKD, and moderate anemia and showed that achievement of normal post-treatment Hb of 13 g/dl did not reduce risk of death or a CV/renal event. Based on these study results, the Anemia Working Group of European Renal Best Practice (ERBP)[15] published a statement recommending Hb target of 11-12 g/dl in CKD patients, without deliberately aiming for targets above 13 g/dl.

Negative impact on quality of life

Quality of life is an acceptable measurement of patient-reported health outcomes. As in many other chronic illnesses, health-related quality of life (HRQOL) is frequently compromised in patients with CKD, particularly in those with ESRD, in turn increasing both morbidity and mortality rates. Anemia of CKD is an important contributor to impairment of quality of life.[16] Despite this, the profound effect that anemia has on quality of life and performance of CKD patients is often underappreciated. Studies[17,18] have shown that increase in Hb concentration following correction of anemia improves quality of life in patients with CKD, with HRQOL maximized by attaining

target Hb concentration between 11-12 gm/dl. Since a wide variety of instruments are employed in different studies for measurement of quality of life, comparison of their results and rendering generalizations is difficult. Overall, HRQOL domains that appear to significantly improve with ESA therapy are physical symptoms, energy, vitality, and performance. On the other hand, modest improvement is seen in social functioning and mental health domains.[19] Sleep disturbance, which is usually not measured by common HRQOL instruments, also improves with correction of anemia in CKD patients.[20]

Early data citing improvement in different domains of quality of life following correction of CKD anemia with ESA was reviewed by FDA, and they found the benefits to be small and inconsistent. Based on this assumption, FDA dismissed these claims and removed improvement of quality of life from the labeling of EPO. Nevertheless, considering the fact that correction of anemia in CKD improves some, if not all domains of quality of life; anemia treatment should be individualized in CKD patients noting patient-perceived quality of life most affected rather than setting post-treatment Hb goals, thereby maximizing treatment benefits and overall patient outcomes.[21]

Hospitalizations and healthcare costs

Anemia of CKD increases hospitalizations, both in non-dialysis patients and in those requiring dialysis. In a study[22] involving non-dialysis stage 3 CKD patients and evaluating association of anemia with progression of kidney disease and outcomes, significantly higher hospital admission rates were reported in anemic compared to non-anemic patients (31.4% vs. 16.1%, respectively); additionally, anemia also increased mean number of days of hospitalizations (10 vs. 5, respectively). Heart failure was the predominant cause for hospitalization in patients with anemia of CKD; other causes being infection, surgery, peripheral vascular disease, and other CV events. Similar results were seen in another study[23] in which records of hemodialysis patients obtained from more than 100 nephrology centers in France, Germany, Italy, Spain and UK were evaluated. Results showed that anemic patients with Hb <10 g/dl were 29% more likely to be hospitalized than those with Hb between 11-12 g/dl. In a more recent study[24] which evaluated patients with CKD stages 3-5 and examined impact of severe anemia (Hb <9 gm/dl) vs. less severe anemia (Hb >9 g/dl) on readmission rates and length of hospital stay, patients with severe anemia required longer length of hospital stays compared to those with less severe anemia (mean 6.4 days vs 4.5 days, respectively); however, there was no significant difference in readmission rates between the two groups (mean 11.5% vs. 10.2%, respectively).

Increased hospitalizations and/or length of hospital stays will expectably escalate inpatient treatment costs. Indeed treatment of CKD anemia imposes significant cost burden on both the patients and caregivers.[1,25] Cost depends on dialysis status and ESA treatment. Several factors contribute substantially to high costs which these patients are exposed to, including treatment-related costs, transportation expenses for hospital visits, and drug purchase costs.[26] Resource utilization, and therefore treatment costs are higher when anemia is poorly controlled or undertreated.[27] There is a strong need to routinely screen CKD patients for anemia and initiate early therapeutic intervention, particularly in those with severe anemia, to reduce hospitalizations, and thereby costs of treatment. Treatment of CKD in its early stages can improve patient outcomes, and result in cost savings.

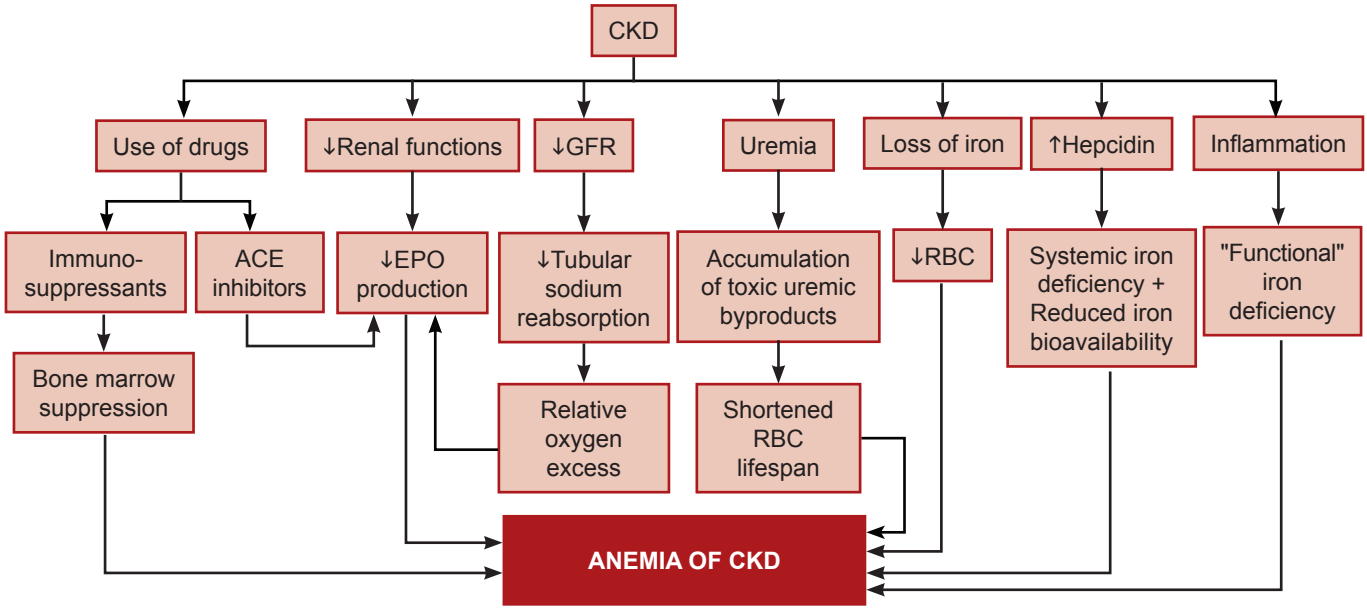
MECHANISMS OF ANEMIA IN CKD

Anemia of CKD is typically normocytic and normochromic in nature.[28] The mechanism of anemia in CKD is multifactorial, involving several pathogenic steps, all functioning in tandem and leading to anemia development (Figure 3). Although relative reduction in the production of EPO by the failing kidneys is the primary underlying cause, some other contributory mechanisms include disturbance of iron metabolism leading to "true" and "functional" iron deficiency, inhibition of erythropoiesis by toxic uremic byproducts, and shortening of the lifespan of erythrocytes in a uremic environment.[28,29]

Decreased EPO production

The main hormone involved in RBC production is EPO, a glycoprotein hormone chiefly produced and secreted by the kidneys. Liver accounts for about 10-15% of EPO production. EPO regulates RBC production by binding to specific receptors on the erythroid progenitor cells, specifically Burst Forming Unit Erythroid (BFU-E) and Colony Forming Unit Erythroid (CFU-E) in the bone marrow, signaling them to undergo proliferation and differentiation into mature RBCs. Hypoxia is a strong stimulant for EPO production.[30] In CKD, reduction in GFR is followed by decrease in tubular sodium reabsorption. Since sodium reabsorption is the main determinant of energy consumption in the nephron, its reduction is associated

Figure 3 **Proposed mechanism of development of anemia in CKD**



Abbreviations: CKD - Chronic kidney disease; ACE - Angiotensin converting enzyme; EPO - Erythropoietin; GFR - Glomerular filtration rate

Sources: 1. Babitt JL, Lin HY. Mechanisms of Anemia in CKD. *J Am Soc Nephrol.* 2012 Sep 28; 23(10): 1631–1634. **2.** Nangaku M, Eckardt KU. Pathogenesis of renal anemia. *Semin Nephrol.* 2006 Jul;26(4):261-8.

with relative oxygen excess, leading to decrease in EPO production.[31] Nonetheless, there is accumulating evidence to show that circulating EPO levels in CKD patients are either normal or mildly elevated in most if not all CKD patients, although their levels remain low relative to the extent of anemia; anemic patients without kidney disease having similar level of anemia have up to 100 times higher EPO levels compared to patients with CKD. In majority of CKD patients, EPO levels fail to show appropriate compensatory increase with reducing Hb levels.[28,29,32]

"True" and "functional" iron deficiency

Compelling evidence points to iron deficiency in significantly high percentage of patients with ESRD, particularly in those on dialysis. Both "true" and "functional" iron deficiency has been described in patients with CKD. Iron deficiency confers poor outcomes and is an important contributory cause of anemia in CKD. It requires aggressive management.[33] Iron losses are estimated to be between 1–3 gm/year in patients on hemodialysis.[28] Commonly implicated causes of iron deficiency in dialysis patients are occult gastrointestinal (GI) bleeding, blood loss from dialyzer and tubings, impairment of iron absorption from the GI tract, and frequent requirement for blood sampling. In non-dialyzed CKD patients, iron deficiency is usually due to reduced intake of dietary iron and impaired iron absorption secondary to high hepcidin levels.[33] Lot of current research has focused on the role of hepcidin in regulating iron metabolism, and its impact on development of anemia in CKD. Hepcidin is a hormone produced mainly by the liver, and is purported to mediate its effects by binding to ferroportin. This iron-regulated transporter facilitates absorption of iron from the duodenum, and release of stored iron both from hepatocytes and hepatic macrophages. Binding of hepcidin to ferroportin causes its proteolysis, hence reducing delivery of iron into the plasma.[34] Serum concentration of hepcidin is elevated by up to 100-fold in patients with CKD, secondary to a chronic inflammatory state and impairment of its renal clearance.[30,34] Its downstream consequences are reduced bioavailability of iron and systemic iron deficiency. Also, when ESA is administered, iron requirement increases to cater to augmented erythropoiesis, although in the presence of high hepcidin concentration iron cannot be made available despite sufficient iron stores (so called as "functional" iron deficiency). Therefore, in CKD patients, in addition to predisposing to iron deficiency, elevated

hepcidin levels also have a key role to play in increasing resistance to ESA therapy.[34,35]

"Functional" iron deficiency has also been reported in CKD. This form of iron deficiency involves insufficient availability of iron to sustain stimulated erythropoiesis following administration of ESA. The exact cause of "functional" iron deficiency in patients with CKD remains elusive, although a phenomenon known as "reticuloendothelial block" has been proposed as one of its possible causes. It involves block in the release of reticuloendothelial iron during erythropoiesis, despite sufficiently available stores of iron. It is plausible that an inflammatory state which accompanies CKD is associated with increase in serum concentration of different pro-inflammatory cytokines. Many of these cytokines, such as interleukin-1beta (IL-1β) and Tumor Necrosis Factor- alpha (TNF-α), not only reduce endogenous EPO production but also response of erythroid precursor cells to endogenous and exogenous EPO, thereby creating a state of "functional" iron deficiency. These findings, however, require further attestation in clinical trials.[36]

Shortened RBC lifespan

There is also strong evidence to show that lifespan of erythrocytes is shortened in CKD patients. It is now widely accepted as another contributory factor for renal anemia.[28,30,32,37] Median RBC survival is significantly reduced by almost 20% in CKD patients compared to their healthy counterparts.[37] There is incriminating evidence for the role of toxic uremic environment in this regard.[30,32] Several toxins accumulate in a uremic environment of CKD patients, and many of these uremic byproducts are supposedly lethal for the RBCs; important toxic products that accumulate in uremia and may contribute to premature death of the RBCs are spermine, spermidine, putrescine, and cadaverine.[30] It was recently proposed that accelerated clearance of RBCs in ESRD is, at least partly due to increased eryptosis, a phenomenon of suicidal RBC death. This process involves cell shrinkage and scrambling of the cell membrane of RBCs, leading to their early death. The uremic toxin indoxyl sulfate has been proposed as one of the prominent triggers for eryptosis, contributing to development and aggravation of anemia in CKD patients.[38]

Miscellaneous factors

Several other miscellaneous factors have been implicated in the development of anemia of CKD. Nutritional deficiencies, such as folic acid and/or vitamin B12 deficiency, although not frequent, can be present in CKD patients and contribute to anemia development. Although clinically relevant deficiencies of vitamin B12 and folate are rare in non-dialysis patients with CKD receiving adequate nutritional supplements; CKD patients on dialysis are at risk of folate deficiency since folic acid is dialyzable. Additionally, certain drugs, such as angiotensin-converting enzyme (ACE) inhibitors, often prescribed in CKD patients, can also lead to anemia development. ACE inhibitors can suppress EPO production in a dose-dependent manner, thereby leading to anemia. Immunosuppressive agents used in renal transplant patients have antiproliferative effects, and therefore by direct suppression of the bone marrow predispose to anemia.[30] Secondary hyperparathyroidism, a common and severe complication of CKD characterized by increase in the levels of parathyroid hormone, is one of the less recognized causes of anemia of CKD. Parathyroid hormones interfere with normal erythropoiesis, inhibiting proliferation of erythroid precursor cells. They additionally increase osmotic fragility of RBCs, reducing their survival in circulation. Severe secondary hyperparathyroidism in advanced CKD patients is associated with osteitis fibrosa; resultant bone marrow fibrosis also increases risk of anemia and resistance to EPO treatment.[30,39-41]

CONCLUSION

Anemia has a profound impact on CKD patients, accelerating their disease progression towards ESRD, increasing risk of CV complications, hospitalizations and healthcare costs, and negatively impacting their quality of life. Pathophysiological mechanisms of anemia in CKD have been extensively studied. Relative reduction in production of EPO appears to be its primary underlying cause, although several other causes appear to contribute, including disordered iron metabolism, in part because of elevated levels of hepcidin, "functional" iron deficiency secondary to chronic inflammatory state, and shortened erythrocyte survival due to accumulation of toxic uremic byproducts.

TAKE HOME POINTS

- EPO levels are either normal or mildly elevated in most if not all CKD patients, although their levels remain low relative to the extent of anemia

- Commonly implicated causes of iron deficiency in patients undergoing dialysis are occult GI bleeding, blood loss from dialyzer and tubing, impairment of iron absorption from the GI tract, and frequent requirement for blood sampling
- Inflammatory state which accompanies CKD is associated with increase in serum concentration of different pro-inflammatory cytokines. Many of these cytokines not only reduce endogenous EPO production but also response of erythroid precursor cells to endogenous and exogenous EPO, thereby creating a state of "functional" iron deficiency
- Median RBC survival is significantly reduced by almost 20% in CKD patients compared to their healthy counterparts.

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