Review Article

Management of anemia in patients with diabetic kidney disease: A consensus statement

Sarita Bajaj[1], Brij Mohan Makkar[2], Vinod K. Abichandani[3], Pradeep G. Talwalkar[4], Banshi Saboo[5], S. S. Srikanta[6], Ashok Das[7], Sruti Chandrasekaran[8], P. Venkata Krishnan[9], Arun Shah[10], Georgi Abraham[11], Pankaj Tikku[12], Sushil Kumar[13]

[1]Director-Professor and Head, Department of Medicine, MLN Medical College, Allahabad, [2]Sr. Consultant Physician and Diabetologist, Diabetes and Obesity Centre, Paschim Vihar, New Delhi, [3]Hon. Diabetologist, Bodyline Hospitals, Paldi, Ahmedabad, [4]Hon. Diabetologist, S.L. Raheja Hospital, Mumbai, [5]Consultant Diabetologist, Dia Care - Diabetes Care and Hormone Clinic, Ambawadi, Ahmedabad, [6]Medical Director and Senior Consultant Endocrinology Diabetes, Samatvam Endocrinology Diabetes Center, Samatvam: Science and Research for Human Welfare Trust, Jnana Sanjeevini Diabetes Hospital and Medical Center, [7]Professor of Medicine and Head of Endocrinology, Pondicherry Institute of Medical Sciences, Puducherry, [8]Consultant Endocrinology, Diabetology and Metabolism, Global Hospitals, Adyar Cancer Institute, Vikas Center for Hormones and Mental Health, Chennai, [9]Consultant, Division of Internal Medicine, Medanta - The Medicity Hospital, Gurgaon, Haryana, [10]Consultant Nephrologist, Lilavati Hospital and Bharatiya Arogyanidhi Hospital, Mumbai, [11]Professor of Medicine, Pondicherry Institute of Medical Sciences, Puducherry and Consultant – Nephrologist, Madras Medical Mission, Chennai, [12]Executive Chief Editor and Editorial Head, Passi HealthCom Pvt. Ltd., Delhi, [13]Sr. Executive Editor, Passi HealthCom Pvt. Ltd, Delhi, India

ABSTRACT

This consensus statement focuses on the window of opportunity, which exists while treating patients with diabetic kidney disease and anemia.

Key words: Anemia, consensus, diabetic kidney disease, erythropoietin

The statement is an outcome of a roundtable meeting attended by Indian Diabetologists and Nephrologists on 29/03/2015 at Chennai (India). The term diabetic kidney disease, unless specified, has been used in this document in place of chronic kidney disease due to diabetes.

Executive Summary

- This consensus statement focuses on the window of opportunity, which exists while treating patients with diabetic kidney disease (DKD) and anemia

Corresponding Author: Dr. Sushil Kumar,
Passi HealthCom Pvt. Ltd., Postal Address: 303-4, 17–18, Virat Bhawan, Commercial Complex, Dr. Mukherjee Nagar, New Delhi - 110 009, India.
E-mail: drsushil@passi.org

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.176348

- The incidence and prevalence of diabetes mellitus are increasing worldwide, including the disease burden caused by its consequences[1]
- A considerable proportion of this burden is attributable to the impact of diabetes on the kidneys, accounting for increased incidence of DKD[2]
- Indian data in this context matches global trends. The first report of the Indian chronic kidney disease (CKD) registry – published in 2012 – confirmed diabetic nephropathy as an important problem in the Indian population.[3] A similar trend is shown by the interim analysis of the START–India trial, an observational, cross-sectional study assessing the prevalence of CKD in Indian type 2 diabetics[4]
- Patients with DKD and anemia have poorer outcomes and an impaired quality of life; anemia being a

Cite this article as: Bajaj S, Makkar BM, Abichandani VK, Talwalkar PG, Saboo B, Srikanta SS, *et al*. Management of anemia in patients with diabetic kidney disease: A consensus statement. Indian J Endocr Metab 2016;20:268-81.

significant contributor to both.[5-7] The presence of diabetes and progression of CKD are associated with increased incidence of anemia, especially in females[8]

- Early identification and treatment of anemia, which are common to both DKD and diabetes,[6] are, therefore, an important therapeutic strategy to improve outcomes in patients with DKD
- Treatment should be timely, and needs to be individualized according to patient's clinical status. Apart from vitamin B_{12} and folate deficiency, lower erythropoietin (EPO) and iron levels are considered prime factors responsible for anemia of CKD. Follow-up and maintenance of adequate levels of EPO and iron in the body are important
- It is recommended to maintain hemoglobin (Hb) levels between 10 and 12 g/dL in all adults with DKD. Higher Hb levels may be associated with increased mortality. The Hb target should be individualized for each patient considering variables such as age, physical activity, and comorbidity.[9] Increase of Hb to more than 13 g/dl should be avoided[6,10]
- Due to reduced EPO secretion in the body, CKD patients with iron deficiency often need therapy with erythropoiesis-stimulating agents (ESA) coupled with parenteral iron therapy since constant iron availability is required for effective erythropoiesis in conjunction with ESA[11]
- ESA therapy in dialysis patients should be started when Hb levels are <10 g/dl, even in the absence of symptoms directly attributable to anemia. This would help in reducing the need for transfusion[12]
- In nondialysis CKD patients, ESA initiation at Hb 10–11 g/dl as compared with Hb 8–9.9 g/dl is associated with reduced risk of blood transfusion and initial hospitalization[13]
- The choice of ESA is based on patient's clinical status, preferences, and characteristics of the formulations. Epoetin-α, epoetin-β, or darbepoetin alfa can be used. Darbepoetin has significant advantages with reduced dose and dosing frequency; Hb concentration is maintained as effectively and safely as epoetin.[14,15] The subcutaneous route usually results in less frequent injections, and may be preferred especially in diabetics, not on dialysis
- Iron deficiency − either absolute or functional– is a common cause of incomplete response to ESAs. It is recommended to treat iron deficiency before starting ESAs.[16] Iron can be replenished by oral or intravenous route[17]
- CKD patients on ESA therapy also require monitoring of the ferritin levels. Ferritin levels >200 mcg/l, transferrin saturation >20% and hypochromic red blood cells (RBCs) <6% are recommended[11]
- Regular monitoring of the patient's cardiovascular status is important to identify the risk of future adverse cardiovascular events
- There is a need for further Indian studies to help maximize clinical benefits and minimize adverse outcomes in patients with DKD receiving treatment for anemia associated with diabetes.

References

1. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, *et al.* Diabetic kidney disease: A report from an ADA Consensus Conference. Am J Kidney Dis 2014;64:510-33.
2. Ioannidis I. Diabetes treatment in patients with renal disease: Is the landscape clear enough? World J Diabetes 2014;5:651-8.
3. Rajapurkar MM, John GT, Kirpalani AL, Abraham G, Agarwal SK, Almeida AF, *et al.* What do we know about chronic kidney disease in India: First report of the Indian CKD registry. BMC Nephrol 2012;13:10.
4. Prasannakumar M, Rajput R, Seshadri K, Talwalkar P, Agarwal P, Gokulnath G, *et al.* An observational, cross-sectional study to assess the prevalence of chronic kidney disease in type 2 diabetes patients in India (START -India). Indian J Endocrinol Metab 2015;19:520-3.
5. Tajima R, Kondo M, Kai H, Saito C, Okada M, Takahashi H, *et al.* Measurement of health-related quality of life in patients with chronic kidney disease in Japan with EuroQol (EQ-5D). Clin Exp Nephrol 2010;14:340-8.
6. Mehdi U, Toto RD. Anemia, diabetes, and chronic kidney disease. Diabetes Care 2009;32:1320-6.
7. Singh AK. Diabetes, anemia and CKD: Why TREAT? Curr Diab Rep 2010;10:291-6.
8. McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, *et al.* The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin 2004;20:1501-10.
9. Choukroun G, Renou M, Lecaque C, Jauréguy M. TREAT or not to treat: Anemia in type 2 diabetes and chronic kidney disease at stages 3 and 4. Nephrol Ther 2011;7:2-9.
10. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012;2:279-335.
11. Perhar R, Shukla R, Mishra N. Management of iron deficiency anemia-recent challenges. Indian J Res 2015;4:100-2.
12. Berns JS, Schwab SJ, Curhan GC, Sheridan AM. Anemia of Chronic Kidney Disease: Target Hemoglobin/Hematocrit for Patients Treated with Erythropoietic Agents. Available from: http://www.cursoenarm.net/UPTODATE/contents/mobipreview.htm?11/51/12081. [Last cited on 2015 Apr 21].
13. Seliger S, Fox KM, Gandra SR, Bradbury B, Hsu VD, Walker L, *et al.* Timing of erythropoiesis-stimulating agent initiation and adverse outcomes in nondialysis CKD: A propensity-matched observational study. Clin J Am Soc Nephrol 2010;5:882-8.
14. Nissenson AR, Swan SK, Lindberg JS, Soroka SD, Beatey R, Wang C, *et al.* Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. Am J Kidney Dis 2002;40:110-8.
15. Hayat A, Haria D, Salifu MO. Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. Patient Prefer Adherence 2008;2:195-200.
16. Section IV. Failure to respond to treatment. Nephrol Dial Transplant 2004;19 Suppl 2:ii32-6. Available from: http://www.ndt.oxfordjournals.org/content/19/suppl_2/ii32.full.pdf. [Last cited on 2015 Apr 06].
17. Liles AM. Intravenous versus oral iron for treatment of iron deficiency in non-hemodialysis-dependent patients with chronic kidney disease. Am J Health Syst Pharm 2012;69:1206-11.

Section 1

Diabetes and chronic kidney disease

Diabetic kidney disease

There has been a significant increase in the global prevalence of diabetes mellitus, which can be mostly ascribed to the persistently rising incidence rates of type 2 diabetes. These growing trends of epidemiological transitions have a high clinical impact as they gradually transform into similarly augmented incidence of the disease complications. Diabetic kidney disease (DKD) – traditionally referred as diabetic nephropathy – is one such major complication of diabetes, which is also the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD).[1-12] This prototype of genetic and environmental interactions has in fact been identified as the single strongest predictor of mortality in diabetes patients, possibly due to the exceptionally high rates of cardiovascular (CV) risk seen in patients with DKD.[13-16]

Progression and staging of diabetic kidney disease

A number of risk factors – both modifiable and nonmodifiable [Table 1] – affect the development and progression of CKD in patients with diabetes, which *per se* is mediated by multiple pathways.[17,18] Particularly, hypertension is prevalent in this cohort and is perhaps the most important risk factor accelerating the progression of CKD.[19,20] In succession, patients who develop DKD are at a significant risk of transition from CKD to ESKD. In this event, hyperglycemia-induced metabolic and hemodynamic pathways act as concurrent disease mediators, facilitated by the subject common pathway of oxidative stress and inflammation.[17,21] These derangements, coupled with hemodynamic changes, activate various cytokines and growth factors that contribute to the progression of kidney disease.[22]

Various parameters, including albuminuria, changes in creatinine level or glomerular filtration rate (GFR), and the development of "hard end points" such ESKD, have been examined in the staging of the DKD patients. Yet, there is a lack of an accepted gold standard for the diagnosis and progression of DKD. Even so, microalbuminuria has been recognized as a definable early stage in this event of natural history of increasing albuminuria in DKD, and a decline in GFR often predates persistent macroalbuminuria, a trait of DKD [Table 2].[17,23] It is however important to note that albuminuria progression may not be consistent across different stages, and not all diabetics developing kidney dysfunction have preceding albuminuria.[24] Clinically, gender may be a marker in this pathway of kidney disease progression. It has been observed that males are more likely to follow an albuminuric pathway to decreased kidney function, whereas females have an independent high risk of kidney impairment, not necessarily preceded by albuminuric pathway.[17,24] Overall, CKD of all forms can be staged based on the degree of impairment of estimated GFR (eGFR), which is a common method for estimating the kidney function [Tables 3-5].[25]

Chronic kidney disease in India

The discussion on CKD in diabetes shall not be complete without a mention on its impact in India, which *per se* is among the countries worst affected by diabetes. With more than 62 million diabetic individuals, estimates suggest every fifth diabetic in the world being an Indian. This trend in prevalence is likely to continue in future as well as projections estimate great Indian contribution to the absolute number of diabetics in 2030. The total number of

Table 1: Risk factors for diabetic kidney disease in patients with diabetes

Modifiable	Non-modifiable
Hyperglycemia	Age
Hypertension	Sex
Albuminuria	Ethnicity
Dyslipidemia	Family history
Smoking	Duration of diabetes

Source: Macisaac RJ, Ekinci EI, Jerums G. Markers of and risk factors for the development and progression of diabetic kidney disease. Am J Kidney Dis. 2014 Feb; 63 (2 Suppl 2):S39-62

Table 2: Nephropathy according to urinary albumin level

Stages	24-hour urine collection for albumin (mg/day)	Urine albumin-to-creatinine ratio (ACR; mg/mmol)
Normal	<30	<2
Microalbuminuria	30-300	2-20
Macroalbuminuria (overt nephropathy)	>300	>20

Source: Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Clinical Practice Guidelines. Chronic Kidney Disease in Diabetes. Can J Diabetes 2013;37:S129-S136

Table 3: Stages of chronic kidney disease

Stages	Description	Renal function (GFR; mL/min/1.73m²)
CKD stage 1	Kidney damage + normal or reduced GFR	≥90
CKD stage 2	Kidney damage + mild reduction in GFR	60-89
CKD stage 3	Moderate reduction in GFR	30-59
CKD stage 4	Severe reduction in GFR	15-29
CKD stage 5	Kidney failure	<15/dialysis

Sources: 1. National Kidney Foundation Kidney Disease Outcome Quality Initiative. Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Available at: https://www.kidney.org/sites/default/files/docs/ckd_evaluation_classification_stratification.pdf [Accessed on 24/6/2015]. 2. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1). 3. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Clinical Practice Guidelines. Chronic Kidney Disease in Diabetes. Can J Diabetes 2013;37:S129-S136. 4. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003 Jul 15;139 (2):137-47

diabetics is projected to rise from 171 million in 2000–366 million in 2030, of which up to 79.4 million may be from India.[26-28] Indeed, these high rates of diabetes prevalence will clinically translate into similarly high rates of consequent kidney failure in India. Save for the future, this has associated epidemiological and clinical implications currently as well. It is seen that compared to the Western population, Indian patients with CKD are about two decades younger, and many of them present with small kidneys and a rather unclear etiology. A possible reason for this epidemiological variation may be the difference in phenotype among Indian and Western individuals. Indian subjects, those are less muscular and predominantly vegetarian, have lower normal ranges of GFR and different creatinine generation rates compared to their Western counterparts.[29]

In India, community-based studies have reported CKD prevalence between 0.16% and 0.79%; though seeing the huge population of India, the absolute numbers of patients can be enormous. The ESKD incidences have been reported to be 151–232/million population.[29,30] The Indian CKD Registry, a voluntary reporting body of CKD patients' data, was initiated in June 2005. The registry has a database of more than 50,000 patients, 73.6% of whom have CKD stage 4 and 5.[30] First report of the Indian CKD registry − published in 2012 – confirms that diabetes is the preeminent cause of CKD in India as well [Figure 1].[31] This pattern of continuously increasing the prevalence of DKD has been recently validated by interim analysis of an ongoing observational, cross-sectional Indian study (START–India), aimed to assess the prevalence of CKD in type 2 diabetes patients in India. Interim analysis of START–India suggests that over 40% of patients with type 2 diabetes have CKD at present.[3]

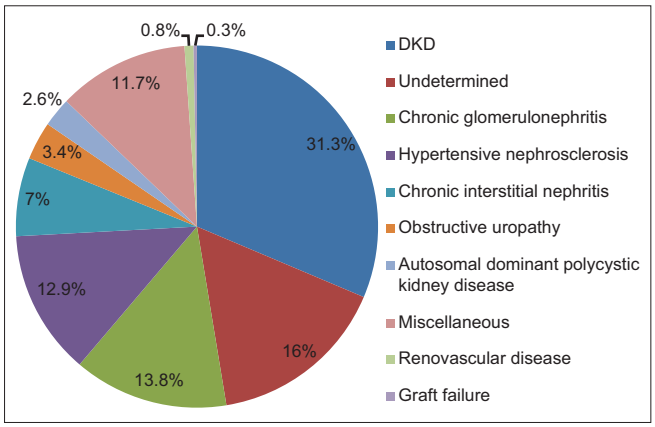

Figure 1: Chronic kidney disease in India: Diabetes as the pre-eminent cause

Source: Rajapurkar MM, John GT, Kirpalani AL, Abraham G, Agarwal SK, Almeida AF, Gang S, Gupta A, Modi G, Pahari D, Pisharody R, Prakash J, Raman A, Rana DS, Sharma RK, Sahoo RN, Sakhuja V, Tatapudi RR, Jha V. What do we know about chronic kidney disease in India: first report of the Indian CKD registry. BMC Nephrol. 2012 Mar 6;13:10

Early detection of diabetic kidney disease

The significant clinical impact of DKD on CV morbidity and prognosis makes it important that efforts be taken for early detection of the condition; staging and prevention of DKD should, therefore, begin right from the beginning to delay the progression of DKD.[32,33] In addition, early identification could allow patients to benefit from an early nephrology referral, which provides an opportunity for significant delay of disease progression and timely institution of strategies to reduce the overall disease burden and initial morbidity and mortality.[34-36] Besides, it allows for adequate exposure to educational programs, psychosocial preparation, and participation in the decision for renal replacement therapy.[33] Nevertheless, early identification of kidney damage in DKD is usually hampered by the fact that

Table 4: Stages of diabetic kidney disease (DKD)[a]

Stage	Description	Urinary albumin (mg/g Cr) or urinary protein (g/g Cr)	GFR (eGFR) (mL/min/ 1.73 m²)
1	Pre-nephropathy	Normoalbuminuria (<30)	≥30[b]
2	Incipient nephropathy	Microalbuminuria (30-299)	≥30
3	Overt nephropathy	Macroalbuminuria (≥300) or persistent proteinuria (≥0.5)	≥30
4	Kidney failure	Any albuminuria/proteinuria status[c]	<30
5	Dialysis therapy	Any status on continued dialysis therapy	

[a]DKD does not always progress from one stage to the next. [b]Although GFR of <60 mL/min/1.73m² denotes CKD, a differential diagnosis of DKD should be considered due to possibility of other causes for this reduced GFR. [c]Differential diagnosis is required between diabetic and any other potential non-diabetic kidney diseases in those with normoalbuminuria or micro-albuminuria

Source: Haneda M, Utsunomiya K, Koya D, Babazono T, Moriya T, Makino H, Kimura K, Suzuki Y, Wada T, Ogawa S, Inaba M, Kanno Y, Shigematsu T, Masakane I, Tsuchiya K, Honda K, Ichikawa K, Shide K, Joint Committee on Diabetic Nephropathy. A new Classification of Diabetic Nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy. J Diabetes Invest 2015;6(2):242–246

Table 5: Potential relationship between chronic kidney disease severity categories and categories for diabetic kidney disease stages

	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
CKD stage 1	DKD stage 1	DKD stage 2	DKD stage 3
CKD stage 2			
CKD stage 3	Unlikely DKD*		
CKD stage 4	DKD stage 4*	DKD stage 4	
CKD stage 5	DKD stage 5		

*Differential diagnosis is required between diabetic and any other potential non-diabetic kidney diseases

Sources: 1. Haneda M, Utsunomiya K, Koya D, Babazono T, Moriya T, Makino H, Kimura K, Suzuki Y, Wada T, Ogawa S, Inaba M, Kanno Y, Shigematsu T, Masakane I, Tsuchiya K, Honda K, Ichikawa K, Shide K, Joint Committee on Diabetic Nephropathy. A new Classification of Diabetic Nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy. J Diabetes Invest 2015;6 (2):242–246. 2. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Available at: http://www2.kidney.org/professionals/KDOQI/guideline_diabetes/guide1.htm#tab6 [Accessed on 23/6/2015]

diabetes-induced nephron hypertrophy maintains GFR, and an increased elevated plasma creatinine concentration is relatively seen late in DKD.

In clinical settings, other than diabetic glomerulopathy-related albuminuria is another key event and major manifestation of DKD that is important.[37,38] However, since evaluation of albuminuria and eGFR might have inherent limitations, a combination of them is expected to provide better clinical picture for identifying the progression of DKD in a particular individual. This clinical impression differentiating those with progressive CKD (defined as a decline in GFR of >5 ml/min/1.73 m^2 within 1 year or >10 ml/min/1.73 m^2 within 5 years) from stable ones has potential implications on management that may be tailored according to the patients age and stage of the DKD.[32] In addition, identification of anemia, which occurs more frequently in subjects with diabetes than in those with non-DKD,[39,40] may be a pointer for screening for CKD in patients with diabetes,[41] and is the subject of this discussion.

Section 2

Anemia in diabetic kidney disease

Anemia: A common problem in patients with chronic kidney disease

Anemia − defined as hemoglobin (Hb) level <13.0 g/dL in men and <12.0 g/dL in women − is a common and frequently encountered consequence seen in CKD patients. The disorder begins early in the course of kidney disease, progresses with deterioration of kidney function, and associated with poor disease outcomes.[42-47] Objectively considering it in terms of GFR, it is seen that the risk of anemia progressively increases with decreasing GFR (from about 27% in stage 1 CKD to 76% in stage 5 [GFR <15 ml/min]), and its severity roughly approximates the severity of CKD.[48-50] Usually, the form of anemia in CKD is normocytic normochromic, associated with shortened survival of red blood cell (RBCs) and iron deficiency.

Anemia in diabetic kidney disease

Although noteworthy in CKD regardless of the underlying cause, the significance of anemia is *per se* higher in those with DKD because diabetes itself affects the hematological system in several ways; anemia can be seen in two out of every three diabetics admitted to a hospital.[51,52] Various factors, including CKD, dietary iron, vitamin deficiency, and glycemic control, might assimilate to increase the prevalence of anemia in patients with DKD. The result is that anemia develops earlier in the course of DKD, even before the GFR is severely reduced,[53] and the severity tends to be more marked in them compared to nondiabetic subjects, notwithstanding the stage of CKD.[54] Ethnicity and sex may also have an impact on prevalence of anemia and CKD. It has been observed that prevalence of diabetes and anemia, and rate of CKD progression may be higher in blacks compared to other populations.[55,56] Likewise, female sex is also associated with high prevalence of anemia.[57]

Thus, in general, (i) anemia is common to CKD and diabetes, (ii) occurs early in DKD, and (ii) is more sever in DKD than other causes of CKD.[58-60] Acting as a risk multiplier, it significantly increases the risk of death in anemic versus nonanemic patients with DKD; those are at very high risk of CV disease (CVD).[42,60,61] Despite this high prognostic significance, however, a persistent clinical inertia in anemia management, both for initiation of erythropoiesis stimulating agents (ESAs) and iron supplementation, raises concerns.[62]

Causes and pathophysiology of anemia in diabetic kidney disease

Anemia of CKD is a multifactorial process and can be influenced by numerous mechanisms, such as insufficient production and loss of erythropoietin (EPO) by diseased kidneys, urinary losses of transferrin, diminished survival of RBCs, hemolysis secondary to uremic toxin accumulation, nutritional deficiencies of iron, folate, Vitamin B_{12}, chronic inflammation and inflammatory cytokines, and blood loss during dialysis or comorbidities.[63-65] Nonetheless, an early decrease in the endogenous EPO response to anemia and then EPO deficiency with inhibition of erythroid progenitor cells formation are likely the main determinants of anemia in patients with CKD.[66,67] This occurs under deranged homeostatic milieu possibly affected by several other possible factors, including the local kidney effects, such as glomerular hyper filtration, proteinuria, renal tubular dysfunction and interstitial fibrosis, and systemic effects, such as chronic inflammation, autonomic neuropathy, and the renin-angiotensin system.[54] In addition, thyroid function disorders that are highly prevalent in diabetic CKD patients also can contribute to anemia in CKD.[68,69] All these factors may contribute to decline Hb values and exacerbate anemia in CKD patients.[70]

Erythropoietin deficiency

EPO is a hematopoietic cytokine, mainly generated in the renal cortex, the secretion and action of which is impaired in patients with CKD, resulting in its deficiency.[41] EPO deficiency delays the maturation of RBCs from progenitor cells into normoblasts and reticulocytes, and additionally decreases survival of these immature RBCs, thereby resulting in anemia. Usually, in absence of other causes, anemia due to EPO deficiency is normocytic and

normochromic, implying a reduction in number but not quality of RBCs.[71]

The EPO production from kidneys follows a negative feedback. Under normal conditions, the production of EPO from kidneys, which is approximately 90% of the total hormone in the body, increases in response to tissue (kidney) hypoxia, then stimulating erythropoiesis.[72] In sequence, kidneys sense increased oxygenation with formation of new erythrocytes and in response decreases EPO production. This normal process is disrupted in CKD, and even earlier in CKD due to diabetes because tubulointerstitial damage occurs early in the course of DKD, even before a reduction in GFR or albuminuria.[53] This decline of functional tissue renders body of DKD patients unable to produce adequate amounts of EPO in response to tissue (kidney) hypoxia. In addition, the systemic inflammation associated with diabetes or the medications used in diabetes may also contribute to anemia.[72] Finally, several medications are also considered to aggravate anemia associated with DKD.

Iron deficiency

Further to reduced EPO, iron deficiency is another major cause of anemia in CKD that continues to be underdiagnosed and undertreated. This deficiency can occur due to a number of factors, such as reduced intake and impaired intestinal absorption of dietary iron, chronic inflammation, and increased iron requirements during ESAs therapy.[50] The phenomenon of reduced absorption, decreased stores, or inflammatory iron block are particularly relevant to the CKD population; ESAs cause an increased demand for iron (increased iron utilization), resulting in iron deficiency in hemodialysis patients, those are already prone to iron deficiency due to blood loss from dialysis.

Absolute versus relative iron deficiency

Iron deficiency can be absolute or functional in nature. In absolute iron deficiency, there is insufficient iron to produce Hb because of depleted iron stores. In contrast, iron stores are adequate in functional iron deficiency, but there is an inability to mobilize it adequately from the reticuloendothelial system to maintain RBCs production during erythropoiesis. Functional iron deficiency is particularly important in anemic CKD patients receiving ESAs, and results in failure to reach target Hb levels despite large doses of ESAs.[50]

The two forms of iron deficiency can be clinically distinguished based on laboratory values for transferrin saturation (TSAT) and ferritin [Table 6]. However, a combined index of serum ferritin (<40 ng/ml), (TSAT <20%) and total iron binding capacity (TIBC <50 μmol/L) will possibly have better utility in the management of iron therapy in CKD.[73] DKD patients with anemia also exhibit marked elevation of serum levels of high-molecular weight adiponectin; this elevation is independent of kidney function.[42] Sufficient iron should therefore be administered to maintain a TSAT of >20% and serum ferritin well-above 100 μg/L.[74]

Table 6: Tests to distinguish absolute vs. functional iron deficiency

	Absolute iron deficiency anemia	Functional iron deficiency anemia	Target range
Transferrin saturation (TSAT)	<20%	<20%	≥ 20%
Ferritin	<100 ng/mL (non-dialysis dependent patients) <200 ng/mL (hemodialysis-dependent patients)	Elevated >100 ng/mL (non-dialysis dependent patients) >200 ng/mL (hemodialysis-dependent patients)	100-500 ng/mL (non-dialysis dependent patients) 200-500 ng/mL (hemodialysis-dependent patients)

Sources: 1. Krikorian S, Shafai G, Shamim K. Managing Iron Deficiency Anemia of CKD with IV Iron. US Pharm. 2013;8 (38):22-26. 2. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 47:S1-S146, 2006 (suppl 3). 3. Hayat A, Haria D, Salifu MO. Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. Patient Prefer Adherence. 2008;2:195-200

Role of hepcidin in iron homeostasis

Hepcidin is a small peptide hormone synthesized primarily in liver that plays key role in regulation of iron metabolism.[75,76] Its excess is being increasingly identified as a main contributor to the disordered iron homeostasis and anemia of CKD since it impairs dietary iron absorption and iron mobilization from body stores.[47] Hepcidin increases the production of ferritin, thus increasing ability to sequester iron intracellularly; but decreases levels of transferrin, this decreasing the intravascular transport of iron. The hormone negatively regulates the process of ferroportin mediated outflow of Fe2+ from intestinal cells and macrophages into the plasma that is essential for iron homeostasis.[77] Overall, it thus decreases the body's ability to absorb iron from the gut, or access existing stores of iron, thus causing and an effective iron deficiency.[78]

Clinical significance of hepcidin

The presence of CKD has an impact on generation and metabolism of hepcidin, dependent on iron status, anemia, inflammation, and hypoxia and the EPO levels.[79] Except in absolute iron deficiency, however, levels of hepcidin are not down regulated in CKD anemia − absolute iron deficiency is associated with lower hepcidin values, while CKD-inflammation together with a normal or functional

iron profile is associated with higher values of hepcidin, which impairs oral iron absorption.[80] Nevertheless, despite a positive association, the marker may have a limited specificity for the diagnosis of absolute iron deficiency in patients with CKD, wherein its concentration increases otherwise due to CKD-related inflammation and reduced clearance. Thus, due to hepcidin, there is often an accessible iron deficiency in inflammatory states in presence of a normal or elevated, often markedly elevated ferritin.[78] Hepcidin may therefore not be a reliable marker for clinical decisions regarding management of iron status in CKD, nor is it a valid marker in predicting ESA responsiveness in hemodialysis patients.[80-83]

Prohepcidin, an inactive precursor, having no impact on iron metabolism in either healthy individuals or those with CKD, increase with worsening of anemia, and also show positive correlation with inflammatory markers, suggesting potential benefit in measuring prohepcidin level with ferritin among these patients.[79]

Drug-induced anemia in diabetic kidney disease

Drug-related anemia is an important entity among iatrogenic causes of anemia. There is a growing list of commonly used medications implicated as factors underlying anemia, including important oral antidiabetic medications, like metformin.[65] Particularly, anemia may be seen in diabetic patients treated with thiazolidinediones (pioglitazone, rosiglitazone). These drugs increase the plasma volume, and consequently anemia due to hemodilution, thus complicating the existing problem of anemia in patients with DKD.[11,84] In addition, inactivation of the renin-angiotensin system may confer susceptibility to Hb/hematocrit lowering effects of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. These important classes of drugs may hence induce or worsen symptomatic anemia in patients with kidney disease.[85-87]

HbA1c variation due to medications

Drug-induced anemia complicates the overall management of hyperglycemia in DKD patients. Often these patients may present with marked decline in HbA1c. Certain drugs such as ribavirin can induce mild hemolysis, decreasing erythrocyte life span, and thus decreasing the ability of Hb to become glycated. In addition, EPO could also lower the percentage of glycated Hb as it leads to greater proportion of new RBCs. Similar is the problem with exogenous iron, which causes a significant fall in A1C values without a change to glycemic control in patients with DKD.[88,89] It is therefore important to consider that HbA1c value may be a broad, but should not be a sole criterion for adjusting the patient's diabetes medications; the choice of which is *per se* limited because a reduced GFR results in accumulation of certain drugs and/or their metabolites. Regular capillary glucose measurements together with continuous glucose monitoring,[88] or glycated albumin,[90] can be used as alternative measurements of glycemic control in this patient group with DKD. Insulin therapy is usually the mainstay of hyperglycemia treatment in patients with moderate to advanced DKD, mainly in that receiving dialysis therapy.[91] The recommended HbA1c goal for these patients is <7.0%.[92] However, vigilance is recommended in order to avoid severe hypoglycemia when trying to tighten glycemic control and lower HbA1C when values are >8.5%.[93]

Complications associated with anemia in diabetic kidney disease

Anemia in CKD acts as a risk multiplier and is associated with poor outcomes.[94] The presence of diabetes compounds the risk even further,[95] and the triad − diabetes, CKD, and anemia − puts patients at a high CV risk.[96] Anemia in DKD is therefore increasingly recognized as risk factor for CVD, which *per se* is the major cause of morbidity and mortality in this cohort.[60] All these combinations clearly suggest that anemia may be central in the vicious relationship of DKD, anemia and CVD, and play a key role in modulating the morbidity and mortality profile of DKD patients.[44,46,97,98] It is generally more severe and occurs at an earlier stage of kidney impairment in DKD and is associated with an increased risk of CV, cerebrovascular (stroke), and kidney complications that in turn results in increased hospitalization, increased hospital length of stay, and increased all-cause mortality.[71,95,99,100]

Impact of anemia on overall quality-of-life in diabetic kidney disease

Although CKD itself is associated with impaired living quality, development of anemia in patients with DKD further influences the overall living quality, making it an important predictor of quality-of-life (QOL).[54,101,102] DKD patients thus have poor outcome and an impaired QOL, with anemia contributing significantly to both poor outcome and QOL.[47,103] The impact extends from general well-known symptoms of fatigue, dizziness, decreased physical capacity, and dyspnea, to progressive loss of kidney function and more severe complications cited above.[72,104-106] It is so rational that correction of anemia in DKD would improve the QOL by improving the symptoms, reduce morbidity, and improve survival by possibly alleviating the impact of anemia or even delaying the progression of kidney and cardiac disease.[46,51,59,107,108]

Section 3

Management of Anemia in diabetic kidney disease

The rising prevalence and impact of diabetes and its complications, including anemia, which put patients at

high risk of mortality, clearly mandates the need for early identification and institution of therapy in DKD patients.[46] Especially, targeting anemia, which is common to both CKD and diabetes,[85] can be an important therapeutic strategy to optimize outcomes in these patients. This could follow an initial clinical assessment of anemia by distinct laboratory investigations, including a complete blood count, absolute reticulocyte count, serum ferritin to assess iron stores, serum TSAT or content of Hb in reticulocytes to assess adequacy of iron for erythropoiesis.[109] Yet, the decision to initiate treatment is generally based on the potential benefits (improvements in QOL and symptoms and avoidance of the need for blood transfusions) and risks in individual cases.[72] In general, while treatment of anemia using ESAs is well-accepted in patients on dialysis, emerging evidence suggests that earlier initiation of anemia treatment in CKD may delay the onset of ESKD and decrease mortality.[42,46] Even so, anemia is frequently under-recognized and undertreated during the predialysis stage of kidney disease, a period when anemia correction may have the greatest impact on disease outcome. It is often seen that few patients receive ESAs in the predialysis period and Hb concentrations are often <9 g/dl at the start of hemodialysis.[110] This lagging strategy becomes more important when considering the fact that the size of anemic patient population is much larger in the nondialysis dependent population than the hemodialysis population.[111]

Apart from vitamin B_{12} and folate deficiency, lowered EPO and iron are prime factors underlying anemia of CKD. Therefore, the treatment ought to be focused on timely initiation, response and maintenance of levels of EPO and serum iron in the body. Accordingly, ESAs and iron remain the two mainstays of treatment for patients with anemia associated with CKD.[72] Finally, regularly monitoring of CV status of the patient should be done to identify the risk of future adverse CV events.

Need for individualization of therapy

Timely start of ESA therapy, iron supplementation and 'active' monitoring of patients may allow achievement of Hb target levels and permit a greater steadiness of these levels during the maintenance phase of ESA therapy.[111] However, the treatment needs to be individualized dependent on the patient's clinical status, together considering numerous variables affecting the complex management, and mostly due to the possible narrow therapeutic window, i.e. unclear optimal level of Hb for greatest clinical benefit.[46,96] Furthermore, although, all ESAs effectively increase Hb levels, differences concerning route of administration, pharmacokinetics, and dosing frequency and efficiency should be considered to maximize the treatment benefits for the individual patient.

Hemoglobin target

The optimal Hb target in patients with CKD anemia is a matter of debate. However, based on overall available evidences, Hb level of 10–12 g/dl seems adequate for most patients of CKD anemia.[100,106,112] The rationale is further supported by observation that maintaining this close range of Hb levels in CKD patients is associated with maximum improvements in QOL, reduced morbidity, and improved cardiac health and survival.[51,113] The target Hb can be tailored for each patient taking into consideration the age, physical activity, comorbidity, and response to treatment.[100] However, rapid increases in Hb level should always be avoided, and lowest appropriate ESA doses should be used while trying to achieve treatment target of 10–12 g/dl in most patients.[114] It is critical to maintain Hb levels between 10 g/dL and 12 g/dL in all adults with DKD because higher Hb levels may be associated with increased mortality. Particularly, targeting Hb >13 g/dl is harmful and may increase risk of hypertension and vascular thrombosis.[74,85,115] The strategy may require changes to the ESA dose, dosing frequency, and iron supplementation over the course of treatment and considering proactive management of conditions affecting ESA responsiveness.[116]

Variables affecting the risk and management

In DKD, anemia acts as independent risk factor associated with the loss of kidney function, and defines a group of patients at high risk for death and CV complications, thus making early identification and intervention important.[58,72,96] Nonetheless, screening and subsequent management may be influenced by certain variables, such as age and comorbidity, that differ among patients. Furthermore, numerous factors have been identified as predictors of CV risk in these patients, which may be useful in risk stratification in clinical practice, and tailor treatment accordingly [Table 7].[117] For instance, anemia is associated with a rapid decline in kidney function in patients with coexisting CKD and heart failure.[97] These variables have implications that encompass management as well.

Table 7: Factors strongly predicting the cardiovascular risk in diabetic kidney disease patients with anemia

Age
History of heart failure
C-reactive protein
Urinary protein/creatinine ratio
Abnormal electrocardiogram
Elevated serum N-terminal pro B-type natriuretic peptide
Elevated troponin T

Source: McMurray JJ, Uno H, Jarolim P, Desai AS, de Zeeuw D, Eckardt KU, Ivanovich P, Levey AS, Lewis EF, McGill JB, Parfrey P, Parving HH, Toto RM, Solomon SD, Pfeffer MA. Predictors of fatal and nonfatal cardiovascular events in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia: an analysis of the Trial to Reduce cardiovascular Events with Aranesp (darbepoetin-alfa) Therapy (TREAT). Am Heart J. 2011 Oct; 162 (4):748-755.e3

Iron therapy in diabetic kidney disease

Due to reduced EPO secretion in the body, CKD patients with iron deficiency most often need ESA therapy coupled with parenteral iron therapy since constant iron availability is required for effective erythropoiesis when the process is stimulated using ESAs.[118] This is because once ESAs are commenced, a rapid depletion of iron stores occurs because of erythropoiesis, and failure to correct iron deficiency will lead to EPO resistance.[74] As an adjunct to ESA therapy, iron can therefore effectively relieve iron-restricted erythropoiesis, improve ESA response, help to maintain the target Hb levels, reduce ESA dosing requirements, and consequently balance the risks of therapy.[50]

The supplementation of iron should essentially begin prior to initiate the ESA therapy in order to maintain adequate ESA response.[119] Broadly, an increase in Hb >1 g/dL over 1 month would indicate a therapeutic response to iron therapy, but monitoring is important to avoid iron overload or toxicity. Care should be taken to prevent the serum ferritin rising >800–1000 m/l and the TSAT >50%.[120]

Oral versus intravenous iron preparations

Iron can be replenished through oral or intravenous (IV) route,[121] with their limitations and benefits to affect use in patients' subgroups. For instance, oral agents do not ensure complete bioavailability of iron, nor are they able to replenish body iron stores adequately. Moreover, drug interactions and occurrence of common gastrointestinal side effects could further hamper patient compliance with oral iron therapy.[85,118] This applies differently to IV forms where multiple doses and visits may be a limitation for compliance.

In addition, the choice among oral versus IV iron preparations would depend on clinical profile of the patient, besides convenience and compliance. While nondialysis dependent patients can receive iron orally or IV, based on their clinical status and convenience, IV iron is preferred for the hemodialysis-dependent patients,[109] who often exhibit limited absorption of oral iron. IV iron therapy may result in more rapid increase in both Hb and ferritin in CKD patients; in contrast, oral iron may increase Hb without increases in iron stores.[122]

Safety concerns with different intravenous iron preparations

There are concerns regarding the safety of IV iron supplementation due to increased risk of serious adverse events especially among nondialyzed patients.[123,124] These products, generally administered as bolus injections, result in an increased plasma level of catalytically active nontransferrin bound iron and increased CKD-associated oxidative stress and inflammation. Indiscriminate use of IV preparations may hence increase risk of CV disease, promote microbial infections, and worsen diabetes and diabetic complications.[125] The alternative proposition is that if used judiciously, parenteral iron supplementation would usually be without major side effects, and possibly provide better outcomes than oral preparation.[126] This is perhaps the reason that IV iron is considered an integral part in the everyday management of anemia in patients with CKD.[127]

Various forms of IV iron are available for managing anemia of CKD that are not identical and differ in safety and tolerability based on differences in molecular size, degradation kinetics, and bioavailability.[50] All these forms are composed of a carbohydrate shell that stabilize and maintain iron in the core in a colloid form, controlling its release. The size of the iron core and type and density of the surrounding carbohydrate shell differs among the formulations. The carbohydrate shell can be either dextran or nondextran, which is an important parameter determining the tolerability. The low molecular weight iron dextran preparations are considered safer to high molecular weight preparations, but the newer IV irons, ferric gluconate, and iron sucrose,[128] which do not contain dextran overall have better safety profile compared to the dextran formulations while being superior to oral iron therapy as well. In July 2013, the FDA approved a new single-dose nondextran IV iron preparation − ferric carboxymaltose, which requires fewer clinic visits and venipunctures.[50,129] Ferric carboxymaltose is a robust and stable iron (III) hydroxide-carbohydrate complex, which lacks hypersensitivity associated with iron dextran, and can be infused in high doses in a single-IV infusion over 15 min.[77,130] The preparation has been observed to be more effective and better tolerated than oral iron for treatment of iron deficiency in nondialysis dependent-CKD patients.[129]

Erythropoiesis stimulating agent therapy in diabetic kidney disease

ESAs are widely used to treat anemias associated with a range of conditions, including CKD.[131] They have been an effective therapeutic agent in CKD anemia and seem to be more effective in patients with DKD, in whom anemia occurs early and is more sever compared to the nondiabetic counterparts.[41] They are not only useful in treating the anemia but could possibly slow the progression of CKD as well by reducing the oxidative stress and rendering tubular protection through antiapoptotic properties.[132] Some patients may however show an incomplete response to ESA therapy, and fail to maintain the recommended level of Hb.[133] Inadequate response in such patients with

anemia and CKD could be attributable to short survival of RBCs, presence of unknown inhibitors of erythropoiesis in uremia, hyperparathyroidism, an accumulation of aluminum, and nutritional deficiency, such as that of iron, Vitamin B_{12}, and folate.[98]

The timing of initiation of ESA therapy in dialysis patients may vary among patients. For some dialysis patients, ESAs may be started at lower Hb levels; whereas, ESAs can be started even at comparatively higher Hb levels for other dialysis patients, such as those with definite symptoms of anemia, or functional or other of QOL limitations related to anemia. Regardless, it is rational that ESA therapy in dialysis patients be started when Hb levels are <10 g/dL, even in the absence of symptoms directly attributable to anemia. This would help in reducing the need for transfusion.[134] Especially, when used to maintain the close specified range of 10−12 g/dL, ESAs can improve QOL and exercise tolerance, reduce the need for transfusions, and can alleviate the complications.[112] Early correction of anemia is beneficial in nondialysis CKD also. In nondialysis CKD, ESA initiation at Hb 10–11 g/dl compared with 8–9.9 g/dl is associated with reduced risk of blood transfusion and initial hospitalization.[135] This clearly signifies the need to start treatment early in all patients with CKD anemia.

Patients on ESA therapy should be evaluated for improvement in symptoms such as fatigue and physical functioning, and monitored for the ferritin and Hb levels. Hb concentrations should be monitored regularly after starting the ESA therapy − weekly until Hb is stable, followed by every other week, and then at least monthly so that doses of ESAs can be adjusted accordingly.[85] Ferritin levels >200 mcg/l, TSAT >20% and percentage of hypochromic RBCs <6% are required to be maintained.[118]

Types of erythropoiesis stimulating agents

Varieties of ESAs are available for use in patients with anemia of CKD, including epoetins and darbepoetin-alfa [Table 8]. All these preparations effectively increase the Hb but have distinguishable properties to influence the selection amongst them. The choice amongst them may be based on patient's clinical status and preferences, and characteristics of individual formulations.

Table 8: Types of erythropoiesis-stimulating agents

First-generation	Epoetin-alfa
	Epoetin-beta
Second-generation	Darbepoetin-alfa
Third-generation	Continuous erythropoietin receptor activator (CERA)

Source: Hayat A, Haria D, Salifu MO. Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. Patient Prefer Adherence. 2008;2:195-200

First-generation erythropoiesis stimulating agents

Recombinant human EPO or epoetin, is the first ESA to be used clinically. It is a sialo glycoprotein hormone immunologically and biologically indistinguishable from the endogenous form. There are two forms of epoetins (epoetin-alfa and epoetin-beta), which differ in their glycosylation. These first-generation ESAs have a relatively shorter half-life and have traditionally been administered up to 3 times weekly to maintain adequate Hb levels in CKD patients on hemodialysis; later extended dosing interval of at least once per week were also tested. In CKD patients not yet on dialysis, epoetin-alfa is usually administered once weekly or once every other week.[72] Extended dosing intervals with maintenance doses of once-weekly, once every 2 weeks, and once every 3 or 4 weeks epoetin, have also been shown effective and well-tolerated in subgroups of nondialysis CKD/DKD patients with stable Hb level;[108,136] however, the inherent shorter half-life of epoetins still seems to limit trial of these extended intervals in larger population.

Second-generation erythropoiesis stimulating agents

The limitation with the first-generation ESAs led to the introduction of darbepoetin-alfa, the hyperglycosylated form, which confer greater metabolic stability *in vivo* owing to two additional N-linked carbohydrate chains attached to the protein backbone.[74] Darbepoetin-alfa has a half-life 3 times longer than that of epoetin, suggesting that it can be effectively administered less frequently than epoetin while maintaining similar EPO response.[71,137] Based on this, once-weekly darbepoetin-alfa is considered equipotent to thrice-weekly epoetin, with further proposition that stable patients on once a week epoetin can be converted to once every 2 weeks darbepoetin-alfa.[74] In addition, monthly administration of darb epoetin has also shown effectiveness in the treatment of anemia in dialysis and nondialysis patients with CKD.[138,139] This therapeutically translates into an advantage of better patient compliance. Typically, darbepoetin-alfa can hence be given once weekly in patients on dialysis, while the dosing may be reduced to up to once every 4 weeks in patients not yet on dialysis.[72,140] For maintenance, it can be administered every other week at beginning, followed by once monthly administration to maintain Hb target.[85]

Third-generation erythropoiesis stimulating agents

The latest in this category of ESAs is the continuous erythropoiesis receptor activator (CERA), which is the third-generation ESA, modified from EPO by insertion of a large pegylation chain to make it longer acting.[71,74] CERA has a significantly longer elimination half-life *in vivo*, allowing for extension of dosing intervals to once every 2 weeks or once

every month. However, the limited clinical experiences with CERA suggest the predecessor – darbepoetin-alfa– could be chosen in subsets of patients with CKD anemia.[74,85]

Route of administration: Subcutaneous versus intravenous

ESAs can be administered through either subcutaneous (SC) or IV route. A number of factors may influence the choice of route, including staging of the CKD, properties of individual preparations, tolerability, and mainly the clinical profile of the patient. In dialysis patients, IV administration of ESAs is preferred, while those not yet on dialysis may preferably receive SC preparations since it results in less frequent injections.[109] Another factor for preference of IV route over SC route in hemodialysis population may be the small increased risk for pure red cell aplasia associated with SC versus IV route.[72] Even so, the route of administration may have limited influence on Hb levels. For instance, there is evidence that darbepoetin-alfa is associated with stable Hb concentrations regardless of the route of administration.[141]

Conclusion

Anemia is a common problem seen in CKD patients, and the risk is accentuated in the presence of diabetes, which *per* se is the most common cause of CKD. In DKD, anemia occurs early and is more severe for similar CKD stages as compared to the nondiabetics. The pathophysiology of anemia in DKD is multifactorial, but EPO and iron deficiency are the main underlying factors. Anemia multiplies several folds the risk of adverse events in DKD patients. Therefore, early identification and prompt institution of therapy, mostly directed at maintaining EPO and iron homeostasis, is important to improve the morbidity and mortality outcomes and the QOL of the patients. Varieties of ESAs and iron preparations are available for administration through different routes, the choice of which should consider risks of adverse events, tolerability, and compliance, dependent on individual preparations and clinical profile of patients. Further Indian studies are required to help maximize clinical benefits and minimize adverse outcomes in patients of DKD receiving treatment for diabetes as well as anemia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, *et al.* Diabetic kidney disease: A report from an ADA Consensus Conference. Am J Kidney Dis 2014;64:510-33.
2. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, *et al.* Diabetic kidney disease: A report from an ADA Consensus Conference. Diabetes Care 2014;37:2864-83.
3. Prasannakumar M, Rajput R, Seshadri K, Talwalkar P, Agarwal P, Gokulnath G, *et al.* An observational, cross-sectional study to assess the prevalence of chronic kidney disease in type 2 diabetes patients in India (START -India). Indian J Endocrinol Metab 2015;19:520-3.
4. Fu J, Lee K, Chuang PY, Liu Z, He JC. Glomerular endothelial cell injury and cross talk in diabetic kidney disease. Am J Physiol Renal Physiol 2015;308:F287-97.
5. McKnight AJ, McKay GJ, Maxwell AP. Genetic and epigenetic risk factors for diabetic kidney disease. Adv Chronic Kidney Dis 2014;21:287-96.
6. Harjutsalo V, Groop PH. Epidemiology and risk factors for diabetic kidney disease. Adv Chronic Kidney Dis 2014;21:260-6.
7. Badal SS, Danesh FR. New insights into molecular mechanisms of diabetic kidney disease. Am J Kidney Dis 2014;63 2 Suppl 2:S63-83.
8. Komorowsky CV, Brosius FC 3rd, Pennathur S, Kretzler M. Perspectives on systems biology applications in diabetic kidney disease. J Cardiovasc Transl Res 2012;5:491-508.
9. Li J, Wu HM, Zhang L, Zhu B, Dong BR. Heparin and related substances for preventing diabetic kidney disease. Cochrane Database Syst Rev 2010;9:CD005631.
10. Oates PJ. Aldose reductase inhibitors and diabetic kidney disease. Curr Opin Investig Drugs 2010;11:402-17.
11. Ioannidis I. Diabetes treatment in patients with renal disease: Is the landscape clear enough? World J Diabetes 2014;5:651-8.
12. Atkins RC, Zimmet P. Diabetic kidney disease: Act now or pay later. Saudi J Kidney Dis Transpl 2010;21:217-21.
13. Reidy K, Kang HM, Hostetter T, Susztak K. Molecular mechanisms of diabetic kidney disease. J Clin Invest 2014;124:2333-40.
14. Pálsson R, Patel UD. Cardiovascular complications of diabetic kidney disease. Adv Chronic Kidney Dis 2014;21:273-80.
15. Alicic RZ, Tuttle KR. Novel therapies for diabetic kidney disease. Adv Chronic Kidney Dis 2014;21:121-33.
16. Gosmanov AR, Wall BM, Gosmanova EO. Diagnosis and treatment of diabetic kidney disease. Am J Med Sci 2014;347:406-13.
17. Macisaac RJ, Ekinci EI, Jerums G. Markers of and risk factors for the development and progression of diabetic kidney disease. Am J Kidney Dis 2014;63 2 Suppl 2:S39-62.
18. Prasad P, Tiwari AK, Kumar KM, Ammini AC, Gupta A, Gupta R, *et al.* Chronic renal insufficiency among Asian Indians with type 2 diabetes: I. Role of RAAS gene polymorphisms. BMC Med Genet 2006;7:42.
19. Yamout H, Lazich I, Bakris GL. Blood pressure, hypertension, RAAS blockade, and drug therapy in diabetic kidney disease. Adv Chronic Kidney Dis 2014;21:281-6.
20. Van Buren PN, Toto RD. The pathogenesis and management of hypertension in diabetic kidney disease. Med Clin North Am 2013;97:31-51.
21. Vasanthakumar R, Mohan V, Anand G, Deepa M, Babu S, Aravindhan V. Serum IL-9, IL-17, and TGF-ß levels in subjects with diabetic kidney disease (CURES-134). Cytokine 2015;72:109-12.
22. Satirapoj B. Review on pathophysiology and treatment of diabetic kidney disease. J Med Assoc Thai 2010;93 Suppl 6:S228-41.
23. Jefferson JA, Shankland SJ, Pichler RH. Proteinuria in diabetic kidney disease: A mechanistic viewpoint. Kidney Int 2008;74:22-36.
24. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR; UKPDS Study Group. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes 2006;55:1832-9.
25. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Clinical practice guidelines. Chronic kidney disease in diabetes. Can J Diabetes 2013;37:S129-36.

26. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australas Med J 2014;7:45-8.
27. Kumar A, Goel MK, Jain RB, Khanna P, Chaudhary V. India towards diabetes control: Key issues. Australas Med J 2013;6:524-31.
28. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
29. Rao M, Pereira BJ. Chronic kidney disease in India – A hidden epidemic. Indian J Med Res 2007;126:6-9.
30. Veerappan I, Abraham G. Chronic kidney disease: Current status, challenges and management in India. Ch. 130. The Association of Physicians of India, Medicine Update 2013. p. 593-7. Available from: http://www.apiindia.org/medicine_update_2013/chap130.pdf. [Last accessed on 2015 Jun 24].
31. Rajapurkar MM, John GT, Kirpalani AL, Abraham G, Agarwal SK, Almeida AF, *et al.* What do we know about chronic kidney disease in India: First report of the Indian CKD registry. BMC Nephrol 2012;13:10.
32. Agarwal P. Management of diabetic kidney disease: Recent advances. Indian J Endocrinol Metab 2013;17 Suppl 1:S55-8.
33. Karkar A. The value of pre-dialysis care. Saudi J Kidney Dis Transpl 2011;22:419-27.
34. Parameswaran S, Geda SB, Rathi M, Kohli HS, Gupta KL, Sakhuja V, *et al.* Referral pattern of patients with end-stage renal disease at a public sector hospital and its impact on outcome. Natl Med J India 2011;24:208-13.
35. Levin A. Consequences of late referral on patient outcomes. Nephrol Dial Transplant 2000;15 Suppl 3:8-13.
36. Bastos MG, Kirsztajn GM. Chronic kidney disease: Importance of early diagnosis, immediate referral and structured interdisciplinary approach to improve outcomes in patients not yet on dialysis. J Bras Nefrol 2011;33:74-87.
37. Hung CC, Tsai JC, Kuo HT, Chang JM, Hwang SJ, Chen HC. Dyslipoproteinemia and impairment of renal function in diabetic kidney disease: An analysis of animal studies, observational studies, and clinical trials. Rev Diabet Stud 2013;10:110-20.
38. Fernández Fernández B, Elewa U, Sánchez-Niño MD, Rojas-Rivera JE, Martin-Cleary C, Egido J, *et al.* 2012 update on diabetic kidney disease: The expanding spectrum, novel pathogenic insights and recent clinical trials. Minerva Med 2012;103:219-34.
39. Thomas S, Rampersad M. Anaemia in diabetes. Acta Diabetol 2004;41 Suppl 1:S13-7.
40. Hosseini MS, Rostami Z, Saadat A, Saadatmand SM, Naeimi E. Anemia and microvascular complications in patients with type 2 diabetes mellitus. Nephrourol Mon 2014;6:e19976.
41. Khoshdel A, Carney S, Gillies A, Mourad A, Jones B, Nanra R, *et al.* Potential roles of erythropoietin in the management of anaemia and other complications diabetes. Diabetes Obes Metab 2008;10:1-9.
42. Aso Y, Suganuma R, Wakabayashi S, Hara K, Nakano T, Suetsugu M, *et al*. Anemia is associated with an elevated serum level of high-molecular-weight adiponectin in patients with type 2 diabetes independently of renal dysfunction. Transl Res 2009;154:175-82.
43. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. World Health Organization (WHO). VMNIS | Vitamin and Mineral Nutrition Information System. WHO/NMH/NHD/MNM/11.1. Available from: http://www.who.int/vmnis/indicators/haemoglobin.pdf. [Last accessed on 2015 Jun 24].
44. Kazmi WH, Kausz AT, Khan S, Abichandani R, Ruthazer R, Obrador GT, *et al.* Anemia: An early complication of chronic renal insufficiency. Am J Kidney Dis 2001;38:803-12.
45. Basile JN. Clinical considerations and practical recommendations for the primary care practitioner in the management of anemia of chronic kidney disease. South Med J 2007;100:1200-7.
46. Tarng DC. Cardiorenal anemia syndrome in chronic kidney disease. J Chin Med Assoc 2007;70:424-9.
47. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol 2012;23:1631-4.
48. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: The Third National Health and Nutrition Examination Survey (1988-1994). Arch Intern Med 2002;162:1401-8.
49. Rossert J, Froissart M. Role of anemia in progression of chronic kidney disease. Semin Nephrol 2006;26:283-9.
50. Krikorian S, Shafai G, Shamim K. Managing Iron deficiency Anemia of CKD with IV Iron. US Pharm 2013;8:22-6.
51. McCullough PA, Lepor NE. The deadly triangle of anemia, renal insufficiency, and cardiovascular disease: Implications for prognosis and treatment. Rev Cardiovasc Med 2005;6:1-10.
52. Shams N, Osmani MH. Newly diagnosed anemia in admitted diabetics, frequency, etiology and associated factors. J Coll Physicians Surg Pak 2015;25:242-6.
53. Gjata M, Nelaj E, Sadiku E, Collaku E, Tase M. Prevalence of anemia in early stage of diabetic nephropathy (chronic kidney disease stage II) and its impact on the progression of renal function: PP. 17.123. J Hypertens 2010;28:e288.
54. Pappa M, Dounousi E, Duni A, Katopodis K. Less known pathophysiological mechanisms of anemia in patients with diabetic nephropathy. Int Urol Nephrol 2015;47:1365-72.
55. McFarlane SI, Chen SC, Whaley-Connell AT, Sowers JR, Vassalotti JA, Salifu MO, *et al.* Prevalence and associations of anemia of CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis 2008;51 4 Suppl 2:S46-55.
56. Lea JP, Norris K, Agodoa L. The role of anemia management in improving outcomes for African-Americans with chronic kidney disease. Am J Nephrol 2008;28:732-43.
57. McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, *et al.* The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin 2004;20:1501-10.
58. Abaterusso C, Pertica N, Lupo A, Ortalda V, Gambaro G. Anaemia in diabetic renal failure: Is there a role for early erythropoietin treatment in preventing cardiovascular mortality? Diabetes Obes Metab 2008;10:843-9.
59. Thomas DR. Anemia in diabetic patients. Clin Geriatr Med 2008;24:529-40, vii.
60. McFarlane SI, Salifu MO, Makaryus J, Sowers JR. Anemia and cardiovascular disease in diabetic nephropathy. Curr Diab Rep 2006;6:213-8.
61. Van der Meer IM, Ruggenenti P, Remuzzi G. The diabetic CKD patient – A major cardiovascular challenge. J Ren Care 2010;36 Suppl 1:34-46.
62. Minutolo R, Locatelli F, Gallieni M, Bonofiglio R, Fuiano G, Oldrizzi L, *et al.* Anaemia management in non-dialysis chronic kidney disease (CKD) patients: A multicentre prospective study in renal clinics. Nephrol Dial Transplant 2013;28:3035-45.
63. Sandhu A, Soman S, Hudson M, Besarab A. Managing anemia in patients with chronic heart failure: What do we know? Vasc Health Risk Manag 2010;6:237-52.
64. McEvoy MT, Shander A. Anemia, bleeding, and blood transfusion in the intensive care unit: Causes, risks, costs, and new strategies. Am J Crit Care 2013;22 6 Suppl: eS1-13.
65. Shander A, Goodnough LT, Javidroozi M, Auerbach M, Carson J, Ershler WB, *et al.* Iron deficiency anemia – Bridging the knowledge and practice gap. Transfus Med Rev 2014;28:156-66.
66. Mercadal L, Metzger M, Casadevall N, Haymann JP, Karras A, Boffa JJ, *et al.* Timing and determinants of erythropoietin deficiency in chronic kidney disease. Clin J Am Soc Nephrol 2012;7:35-42.
67. McGonigle RJ, Wallin JD, Shadduck RK, Fisher JW. Erythropoietin deficiency and inhibition of erythropoiesis in renal insufficiency. Kidney Int 1984;25:437-44.

68. Miulescu RD, Neamţu MC, Margină D, Poiană C, Păun DL. Associations between thyroid dysfunction and chronic kidney disease. Rom J Diabetes Nutr Metab Dis 2014;21:37-42.
69. Basu G, Mohapatra A. Interactions between thyroid disorders and kidney disease. Indian J Endocrinol Metab 2012;16:204-13.
70. Chung M, Chan JA, Moorthy D, Hadar N, Ratichek SJ, Concannon TW, *et al*. Biomarkers for Assessing and Managing Iron Deficiency Anemia in Late-Stage Chronic Kidney Disease: Future Research Needs: Identification of Future Research Needs From Comparative Effectiveness Review No. 83. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Jan. Report No.: 13-EHC038-EF. AHRQ Future Research Needs Papers, No. 33; 2013.
71. Hayat A, Haria D, Salifu MO. Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. Patient Prefer Adherence 2008;2:195-200.
72. O'Mara NB. Anemia in patients with chronic kidney disease. Diabetes Spectr 2008;21:12-9.
73. Mercadal L, Metzger M, Haymann JP, Thervet E, Boffa JJ, Flamant M, *et al.* A 3-marker index improves the identification of iron disorders in CKD anaemia. PLoS One 2014;9:e84144.
74. Panchapakesan U, Sumual S, Pollock C. Nanomedicines in the treatment of anemia in renal disease: Focus on CERA (Continuous Erythropoietin Receptor Activator). Int J Nanomedicine 2007;2:33-8.
75. Strnad P, Schwarz P, Rasenack MC, Kucukoglu O, Habib RI, Heuberger D, *et al.* Hepcidin is an antibacterial, stress-inducible peptide of the biliary system. PLoS One 2011;6:e16454.
76. Young B, Zaritsky J. Hepcidin for clinicians. Clin J Am Soc Nephrol 2009;4:1384-7.
77. Toblli JE, Angerosa M. Optimizing iron delivery in the management of anemia: Patient considerations and the role of ferric carboxymaltose. Drug Des Devel Ther 2014;8:2475-91.
78. Abbasi A, Verma S, Kaplan JM. Anemia of chronic kidney disease. Austin J Clin Med 2014;1:1006.
79. Aydin Z, Gursu M, Karadag S, Uzun S, Sumnu A, Doventas Y, *et al.* The relationship of prohepcidin levels with anemia and inflammatory markers in non-diabetic uremic patients: A controlled study. Ren Fail 2014;36:1253-7.
80. Mercadal L, Metzger M, Haymann JP, Thervet E, Boffa JJ, Flamant M, *et al.* The relation of hepcidin to iron disorders, inflammation and hemoglobin in chronic kidney disease. PLoS One 2014;9:e99781.
81. Ford BA, Eby CS, Scott MG, Coyne DW. Intra-individual variability in serum hepcidin precludes its use as a marker of iron status in hemodialysis patients. Kidney Int 2010;78:769-73.
82. Kato A, Tsuji T, Luo J, Sakao Y, Yasuda H, Hishida A. Association of prohepcidin and hepcidin-25 with erythropoietin response and ferritin in hemodialysis patients. Am J Nephrol 2008;28:115-21.
83. Malyszko J, Malyszko JS, Mysliwiec M. Hyporesponsiveness to erythropoietin therapy in hemodialyzed patients: Potential role of prohepcidin, hepcidin, and inflammation. Ren Fail 2009;31:544-8.
84. Sampanis C. Management of hyperglycemia in patients with diabetes mellitus and chronic renal failure. Hippokratia 2008;12:22-7.
85. Mehdi U, Toto RD. Anemia, diabetes, and chronic kidney disease. Diabetes Care 2009;32:1320-6.
86. Marathias KP, Agroyannis B, Mavromoustakos T, Matsoukas J, Vlahakos DV. Hematocrit-lowering effect following inactivation of renin-angiotensin system with angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Curr Top Med Chem 2004;4:483-6.
87. Mohanram A, Zhang Z, Shahinfar S, Lyle PA, Toto RD. The effect of losartan on hemoglobin concentration and renal outcome in diabetic nephropathy of type 2 diabetes. Kidney Int 2008;73:630-6.
88. Ng JM, Cooke M, Bhandari S, Atkin SL, Kilpatrick ES. The effect of iron and erythropoietin treatment on the A1C of patients with diabetes and chronic kidney disease. Diabetes Care 2010;33:2310-3.
89. Trask LE, Abbott D, Lee HK. Low hemoglobin A (1c) – Good diabetic control? Clin Chem 2012;58:648-9.
90. Inaba M, Okuno S, Kumeda Y, Yamada S, Imanishi Y, Tabata T, *et al.* Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: Effect of anemia and erythropoietin injection. J Am Soc Nephrol 2007;18:896-903.
91. Abe M, Okada K, Soma M. Antidiabetic agents in patients with chronic kidney disease and end-stage renal disease on dialysis: Metabolism and clinical practice. Curr Drug Metab 2011;12:57-69.
92. Cavanaugh KL. Diabetes management issues for patients with chronic kidney disease. Clin Diabetes 2007;25:90-7.
93. Bilo H, Coentrão L, Couchoud C, Covic A, De Sutter J, Drechsler C, *et al.* Guideline development group. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). Nephrol Dial Transplant 2015;30 Suppl 2:ii1-142.
94. Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Association of anemia with outcomes in men with moderate and severe chronic kidney disease. Kidney Int 2006;69:560-4.
95. Alicic RZ, Tuttle KR. Management of the diabetic patient with advanced chronic kidney disease. Semin Dial 2010;23:140-7.
96. Singh AK. Diabetes, anemia and CKD: Why TREAT? Curr Diab Rep 2010;10:291-6.
97. Bansal N, Tighiouart H, Weiner D, Griffith J, Vlagopoulos P, Salem D, *et al.* Anemia as a risk factor for kidney function decline in individuals with heart failure. Am J Cardiol 2007;99:1137-42.
98. Kim DH, Kim TY, Kim SM, Yoo SJ, Oh DJ, Yu SH. IGF-1 is an independent risk factor for anemia in diabetic pre-dialysis patients. Korean J Intern Med 2007;22:186-91.
99. Shaheen FA, Souqiyyeh MZ, Al-Attar BA, Karkar A, Al Jazairi AM, Badawi LS, *et al.* Prevalence of anemia in predialysis chronic kidney disease patients. Saudi J Kidney Dis Transpl 2011;22:456-63.
100. Choukroun G, Renou M, Lecaque C, Jauréguy M. TREAT or not to treat: Anemia in type 2 diabetes and chronic kidney disease at stages 3 and 4. Nephrol Ther 2011;7:2-9.
101. Kalender B. Malnutrition in chronic kidney disease and relationship to quality of life. Handbook of Disease Burdens and Quality of Life Measures. New York: Springer; 2010. p. 3159-70.
102. Perlman RL, Finkelstein FO, Liu L, Roys E, Kiser M, Eisele G, *et al.* Quality of life in chronic kidney disease (CKD): A cross-sectional analysis in the Renal Research Institute-CKD study. Am J Kidney Dis 2005;45:658-66.
103. Tajima R, Kondo M, Kai H, Saito C, Okada M, Takahashi H, *et al.* Measurement of health-related quality of life in patients with chronic kidney disease in Japan with EuroQol (EQ-5D). Clin Exp Nephrol 2010;14:340-8.
104. Parfrey PS, Wish T. Quality of life in CKD patients treated with erythropoiesis-stimulating agents. Am J Kidney Dis 2010;55:423-5.
105. Thomas DR. Anemia and quality of life: Unrecognized and undertreated. J Gerontol A Biol Sci Med Sci 2004;59:238-41.
106. Dmitrieva O, de Lusignan S, Macdougall IC, Gallagher H, Tomson C, Harris K, *et al.* Association of anaemia in primary care patients with chronic kidney disease: Cross sectional study of quality improvement in chronic kidney disease (QICKD) trial data. BMC Nephrol 2013;14:24.
107. Johansen KL, Finkelstein FO, Revicki DA, Evans C, Wan S, Gitlin M, *et al.* Systematic review of the impact of erythropoiesis-stimulating agents on fatigue in dialysis patients. Nephrol Dial Transplant 2012;27:2418-25.
108. Provenzano R, Bhaduri S, Singh AK; PROMPT Study Group. Extended epoetin alfa dosing as maintenance treatment for the anemia of chronic kidney disease: The PROMPT study. Clin Nephrol 2005;64:113-23.
109. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney

disease. Am J Kidney Dis 2006;47 Suppl 3:S1-146. Available from: https://www.kidney.org/sites/default/files/docs/anemiainckd.pdf. [Last accessed on 2015 Jun 24].
110. Hörl WH. Non-erythropoietin-based anaemia management in chronic kidney disease. Nephrol Dial Transplant 2002;17 Suppl 11:35-8.
111. De Nicola L, Minutolo R, Conte G. Anaemia management in non-dialysis chronic kidney disease: Flexibility of target to target stability? Nephron Clin Pract 2010;114:c236-41.
112. Teehan G, Benz RL. An update on the controversies in anemia management in chronic kidney disease: Lessons learned and lost. Anemia 2011;2011:623673.
113. Parfrey PS. Critical appraisal of randomized controlled trials of anemia correction in patients with renal failure. Curr Opin Nephrol Hypertens 2011;20:177-81.
114. Berns JS. Are there implications from the Trial to Reduce Cardiovascular Events with Aranesp Therapy study for anemia management in dialysis patients? Curr Opin Nephrol Hypertens 2010;19:567-72.
115. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012;2:279-335.
116. De Francisco AL, Piñera C. Anemia trials in CKD and clinical practice: Refining the approach to erythropoiesis-stimulating agents. Contrib Nephrol 2011;171:248-54.
117. McMurray JJ, Uno H, Jarolim P, Desai AS, de Zeeuw D, Eckardt KU, *et al*. Predictors of fatal and nonfatal cardiovascular events in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia: An analysis of the Trial to Reduce cardiovascular Events with Aranesp (darbepoetin-alfa) Therapy (TREAT). Am Heart J 2011;162:748-55.e3.
118. Perhar R, Shukla R, Mishra N. Management of iron deficiency anemia-recent challenges. Indian J Res 2015;4:100-2.
119. Section IV. Failure to Respond to Treatment. Nephrol Dial Transplant 2004;19 Suppl 2:ii32-6. Available from: http://www.ndt.oxfordjournals.org/content/19/suppl_2/ii32.full.pdf. [Last accessed on 2015 Jun 24].
120. Macdougall IC. Strategies for iron supplementation: Oral versus intravenous. Kidney Int Suppl 1999;69:S61-6.
121. Liles AM. Intravenous versus oral iron for treatment of iron deficiency in non-hemodialysis-dependent patients with chronic kidney disease. Am J Health Syst Pharm 2012;69:1206-11.
122. Charytan C, Qunibi W, Bailie GR; Venofer Clinical Studies Group. Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. Nephron Clin Pract 2005;100:c55-62.
123. Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int 2015;88:905-14.
124. Agarwal R, Rizkala AR, Bastani B, Kaskas MO, Leehey DJ, Besarab A. A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. Am J Nephrol 2006;26:445-54.
125. Vaziri ND. Toxic effects of IV iron preparations in CKD patients. Nephrol News Issues 2014;28:4-5.
126. Potthoff SA, Münch HG. Safety aspects of parenteral iron supplementation therapies in patients with chronic kidney disease. Dtsch Med Wochenschr 2013;138:1312-7.
127. Jenkins K. Creative iron management – A practical guide. J Ren Care 2009;35 Suppl 2:32-5.
128. Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurray S; United States Iron Sucrose (Venofer) Clinical Trials Group. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. Kidney Int 2005;68:2846-56.
129. Qunibi WY, Martinez C, Smith M, Benjamin J, Mangione A, Roger SD. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis-dependent chronic kidney disease patients. Nephrol Dial Transplant 2011;26:1599-607.
130. Bailie GR, Mason NA, Valaoras TG. Safety and tolerability of intravenous ferric carboxymaltose in patients with iron deficiency anemia. Hemodial Int 2010;14:47-54.
131. Hodges VM, Rainey S, Lappin TR, Maxwell AP. Pathophysiology of anemia and erythrocytosis. Crit Rev Oncol Hematol 2007;64:139-58.
132. Rossert J, Froissart M, Jacquot C. Anemia management and chronic renal failure progression. Kidney Int Suppl 2005;99:S76-81.
133. Akizawa T, Makino H, Matsuo S, Watanabe T, Imai E, Nitta K, *et al*. Management of anemia in chronic kidney disease patients: Baseline findings from Chronic Kidney Disease Japan Cohort Study. Clin Exp Nephrol 2011;15:248-57.
134. Berns JS, Schwab SJ, Curhan GC, Sheridan AM. Anemia of Chronic Kidney Disease: Target Hemoglobin/Hematocrit for Patients Treated with Erythropoietic Agents. Available from: http://www.cursoenarm.net/UPTODATE/contents/mobipreview.htm?11/51/12081. [Last cited on 2015 Jun 29].
135. Seliger S, Fox KM, Gandra SR, Bradbury B, Hsu VD, Walker L, *et al*. Timing of erythropoiesis-stimulating agent initiation and adverse outcomes in nondialysis CKD: A propensity-matched observational study. Clin J Am Soc Nephrol 2010;5:882-8.
136. Lorber DL, Provenzano R, McClellan W. Prevalence and treatment of anemia with once-weekly epoetin alfa in patients with diabetes and chronic kidney disease. Endocr Pract 2006;12:506-13.
137. Nissenson AR, Swan SK, Lindberg JS, Soroka SD, Beatey R, Wang C, *et al*. Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. Am J Kidney Dis 2002;40:110-8.
138. Jadoul M, Vanrenterghem Y, Foret M, Walker R, Gray SJ. Darbepoetin alfa administered once monthly maintains haemoglobin levels in stable dialysis patients. Nephrol Dial Transplant 2004;19:898-903.
139. Ling B, Walczyk M, Agarwal A, Carroll W, Liu W, Brenner R. Darbepoetin alfa administered once monthly maintains hemoglobin concentrations in patients with chronic kidney disease. Clin Nephrol 2005;63:327-34.
140. Locatelli F, Canaud B, Giacardy F, Martin-Malo A, Baker N, Wilson J. Treatment of anaemia in dialysis patients with unit dosing of darbepoetin alfa at a reduced dose frequency relative to recombinant human erythropoietin (rHuEpo). Nephrol Dial Transplant 2003;18:362-9.
141. Brunkhorst R, Bommer J, Braun J, Haag-Weber M, Gill C, Wagner J, *et al*. Darbepoetin alfa effectively maintains haemoglobin concentrations at extended dose intervals relative to intravenous or subcutaneous recombinant human erythropoietin in dialysis patients. Nephrol Dial Transplant 2004;19:1224-30.