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.

- The incidence and prevalence of diabetes mellitus are increasing worldwide, including the disease burden caused by its consequences.

- A considerable proportion of this burden is attributable to the impact of diabetes on the kidneys, accounting for increased incidence of DKD.

- 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. 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.

- Patients with DKD and anemia have poorer outcomes and an impaired quality of life; anemia being a

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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 presence of diabetes and progression of CKD are associated with increased incidence of anemia, especially in females. The presence of 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.

- 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 common to both DKD and diabetes; therefore, an important therapeutic strategy to improve outcomes in patients with DKD.

- 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. Increase of Hb to more than 13 g/dL should be avoided.

- 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.

- ESA therapy in 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.

- 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.

- 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. 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. Iron can be replenished by oral or intravenous route.

- 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.

- 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.

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**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).[11-12] 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 endpoints” such as 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 patients with diabetes in India was 56.7 million, whereas the number of diabetics with CKD was significantly lower, and in 2015, the total number of patients with CKD was 5.7 million. Diabetes is the leading cause of CKD and ESKD in the country. ESKD is the most common form of end-stage renal disease (ESRD), and its incidence has increased dramatically in recent years. The number of patients requiring dialysis due to diabetes has increased from 1.5% in 1992 to 12% in 2010, and it is expected to rise to 15% by 2020. In the year 2014, the number of patients on dialysis due to diabetes was 280,000, and it is predicted to increase to 500,000 by 2020. The number of patients with diabetes on dialysis has increased from 241 in 1998 to 265 in 2008, and it is expected to reach 275 by 2020. The number of patients with diabetes on dialysis has increased from 241 in 1998 to 265 in 2008, and it is expected to reach 275 by 2020. The number of patients with diabetes on dialysis has increased from 241 in 1998 to 265 in 2008, and it is expected to reach 275 by 2020. The number of patients with diabetes on dialysis has increased from 241 in 1998 to 265 in 2008, and it is expected to reach 275 by 2020.

**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 |

**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                                           |

**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. Chronic 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-S246, 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, Perrense RD, Lau J, Eknoyan G; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am Intern Med. 2003 Jul 15;139 (2):137-47.
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. 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. Besides, it allows for adequate exposure to educational programs, psychosocial preparation, and participation in the decision for renal replacement therapy. Nevertheless, early identification of kidney damage in DKD is usually hampered by the fact that

Table 4: Stages of diabetic kidney disease (DKD)*

| 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* |
| 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* | <30 |
| 5     | Dialysis therapy | Any status on continued dialysis therapy | |

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

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, Tsujiha 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

| CKD stage | DKD stage 1 | DKD stage 2 | DKD stage 3 |
|-----------|-------------|-------------|-------------|
| stage 1   | DKD stage 1 | DKD stage 2 | DKD stage 3 |
| stage 2   | DKD stage 2 | DKD stage 3 | DKD stage 3 |
| stage 3   | DKD stage 4 | DKD stage 4 | DKD stage 5 |
| stage 4   | DKD stage 5 | DKD stage 5 | DKD stage 5 |

*Diagnostic 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, Tsujiha 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.
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. 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 m² within 1 year or >10 ml/min/1.73 m² 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. In addition, identification of anemia, which occurs more frequently in subjects with diabetes than in those with non-DKD, may be a pointer for screening for CKD in patients with diabetes 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. 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. 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. 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, and the severity tends to be more marked in them compared to nondiabetic subjects, notwithstanding the stage of CKD. 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. Likewise, female sex is also associated with high prevalence of anemia.

Thus, in general, (i) anemia is common to CKD and diabetes, (ii) occurs early in DKD, and (iii) is more severe in DKD than other causes of CKD. 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). 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.

**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<sub>12</sub>, chronic inflammation and inflammatory cytokines, and blood loss during dialysis or comorbidities. 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. 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. In addition, thyroid function disorders that are highly prevalent in diabetic CKD patients also can contribute to anemia in CKD. All these factors may contribute to decline Hb values and exacerbate anemia in CKD patients.

**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. 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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[60]} 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.\textsuperscript{[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.\textsuperscript{[75]} DKD patients with anemia also exhibit marked elevation of serum levels of high-molecular weight adiponectin; this elevation is independent of kidney function.\textsuperscript{[58]} Sufficient iron should therefore be administered to maintain a TSAT of >20% and serum ferritin well-above 100 µg/L.\textsuperscript{[74]}

**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.\textsuperscript{[73,76]} 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.\textsuperscript{[43]} 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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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
The presence of diabetes compounds

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. 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.

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.

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. 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. 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.

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. 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, or glycated albumin, 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. The recommended HbA1c goal for these patients is <7.0%. However, vigilance is recommended in order to avoid severe hypoglycemia when trying to tighten glycemic control and lower HbA1C when values are >8.5%.

Complications associated with anemia in diabetic kidney disease

Anemia in CKD acts as a risk multiplier and is associated with poor outcomes. The presence of diabetes compounds the risk even further, and the triad – diabetes, CKD, and anemia – puts patients at a high CV risk. 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. 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.

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.

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). DKD patients thus have poor outcome and an impaired QOL, with anemia contributing significantly to both poor outcome and QOL. 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.

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.

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.\textsuperscript{46} Especially, targeting anemia, which is common to both CKD and diabetes,\textsuperscript{88} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{42,48} 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.\textsuperscript{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.\textsuperscript{111} Apart from vitamin B\textsubscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{83,113} The target Hb can be tailored for each patient taking into consideration the age, physical activity, comorbidity, and response to treatment.\textsuperscript{109} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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].\textsuperscript{117} For instance, anemia is associated with a rapid decline in kidney function in patients with coexisting CKD and heart failure.\textsuperscript{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 electrocardiogram |
| Elevated serum N-terminal pro B-type natriuretic peptide |
| Elevated troponin T |

Source: McMurray JJ, Uro H, Jardim P, Desa AS, de Zeeuw D, Eckardt KU, Ivanovich P, Levy AS, Lewis EF, McGill JB, Parfrey P, Parving HU, 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. 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. 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.

The supplementation of iron should essentially begin prior to initiate the ESA therapy in order to maintain adequate ESA response. 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%. This applies differently to IV forms of iron dextran preparations, which are preferred for the hemodialysis-dependent patients, whereas oral iron is preferred for the hemodialysis-dependent patients, 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.

Oral versus intravenous iron preparations

Iron can be replenished through oral or intravenous (IV) route, 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. 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, 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.

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. 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. 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.

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. 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 iron, ferric gluconate, and iron sucrose, 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. 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. 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.

Erythropoiesis stimulating agent therapy in diabetic kidney disease

ESAs are widely used to treat anemias associated with a range of conditions, including CKD. 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 severe compared to the nondiabetic counterparts. 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. Some patients may however show an incomplete response to ESA therapy, and fail to maintain the recommended level of Hb. 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 B₁₂, and folate.¹⁹

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 g/dL is associated with reduced risk of blood transfusion and initial hospitalization.¹³⁸ 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.¹⁰⁵ 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.²¹,¹⁴⁰ For maintenance, it can be administered every other week at beginning, followed by once monthly administration to maintain Hb target.⁸⁶

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.¹⁷¹,¹⁴⁴ 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.[7,8]

**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.[10] 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.[7] Even so, the route of administration may have limited influence on Hb levels for IV. For instance, there is evidence that darbepoetin-alfa is associated with stable Hb concentrations regardless of the route of administration.[11]

**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.

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