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Anemia of Chronic Kidney Disease in Diabetic Patients: Pathophysiologic Insights and Implications of Recent Clinical Trials

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1. Introduction

The goals for this chapter are to succinctly describe the definition of anemia, and to describe the pathophysiology and the epidemiology of anemia in diabetic patients with chronic kidney disease. In addition, the cardiovascular risk factors of anemic patients will be explained and a table will be included. A comprehensive visualization will be included which will incorporate the pathophysiology of anemia in chronic kidney disease and the negative impact of anemia on the cardiovascular system. Reasons to treat anemia in this population will be presented. Furthermore, the recent clinical trials on anemia treatment in the diabetic patient with chronic kidney disease will be discussed, including but not limited to the CHOIR, CREATE, ACORD and TREAT trials. Lastly, there will be a summary of the most important points of the chapter. CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency), CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta), ACORD (Anemia Correction in Diabetes) and TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) trials.

With the ongoing pandemic of obesity, diabetes and hypertension, chronic kidney disease is becoming a leading global health problem. Diabetes is currently the most common cause of chronic kidney disease [1]. Patients with diabetes and chronic kidney disease have an increased risk for anemia. Anemia is a risk factor for cardiac dysfunction and is potentially modifiable. Therefore it should be screened for readily in the diabetic population, a particularly vulnerable population, and it should be identified and rectified promptly. However all too often this is not the case.

2. Definition of anemia

According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI), anemia is defined as hemoglobin levels of less than 13.5g/dL (135 g/L) for men and less than 12.0g/dL (120 g/L) for women [2]. The WHO criteria defines anemia to be less than 13.0g/dL (130 g/L) for men and less than 12.0g/dL for premenopausal women [3].

3. Risk factors for anemia

Patients with diabetes and CKD had the highest risk of anemia (odds ratio 1.73, 95% CI 1.63-1.83) [6,7]. Other risk factors that significantly increase the odds of anemia included lower educational level, diabetes mellitus, hypertension, cardiovascular disease (CVD), and chronic kidney disease (CKD), with risk greatest for patients with diabetes and CKD [6].

Risk Factors For Anemia in CKD patients:
1. Diabetes
2. Chronic Kidney Disease
3. Cardiovascular Disease
4. Hypertension
5. Low Education Levels
6. African American race

4. Ethnicity

African Americans have significantly greater incidences of anemia, with mean hemoglobin being 13.5g/dL for African American vs. 15.3g/dL for white men and 12.5g/dL vs. 14.7g/dL for African American and White Women respectively [4]. This difference can be due in part to the fact that approximately 30 percent of African Americans carry a 3.7kb deletion in the alpha thalassemia gene. Homozygotes for alpha thalassemia exhibit a mild, microcytic anemia, while even heterozygotes may have a low-normal or mildly decreased hemoglobin. However even when people with alpha thalassemia gene, iron deficiency, renal insufficiency and sickle cell trait are excluded, the difference between the hemoglobin of African Americans and whites still persists, albeit to a lower degree [5]. The cause of this phenomenon still remains to be discovered. In the meantime, it has been debated whether the definition of anemia should be modified for different racial and ethnic groups, although this has not yet been implemented in clinical practice guidelines.

5. Pathophysiology of anemia in diabetics with chronic kidney disease

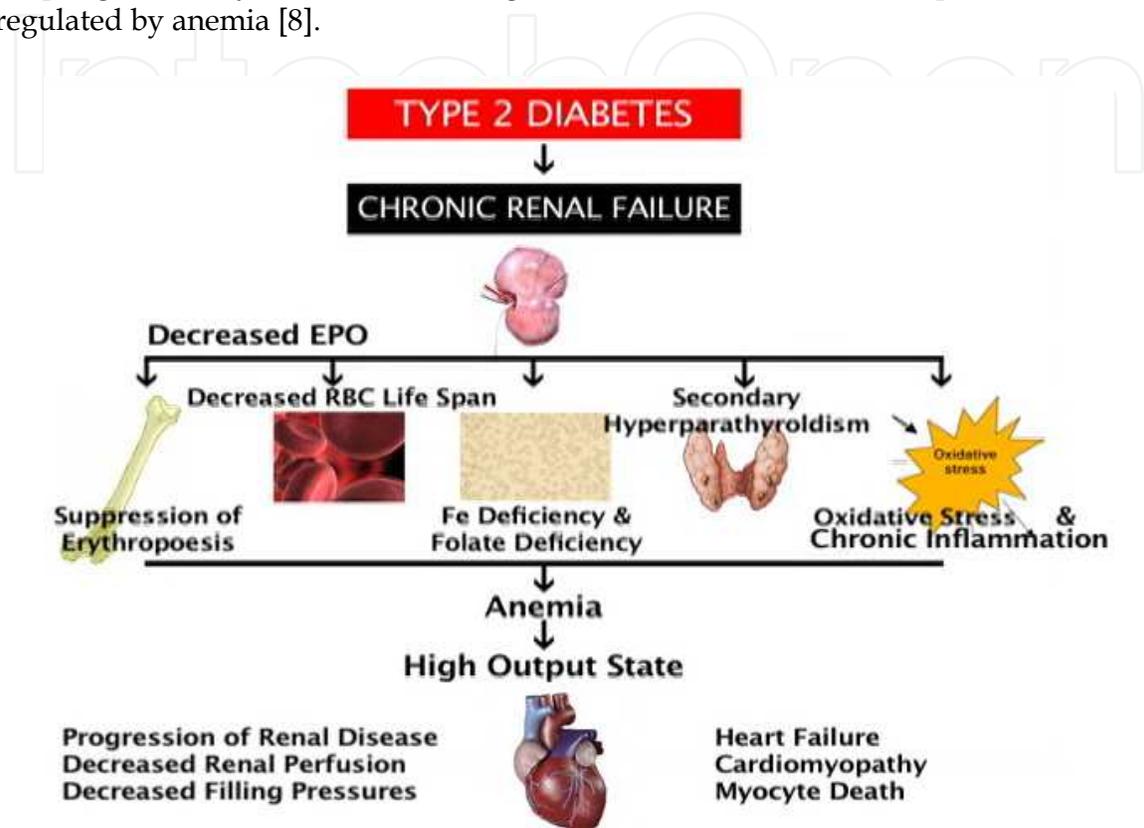
There are several factors which have been implicated in the development of anemia in CKD which include erythropoietin deficiency, iron deficiency, decreased lifespan of red blood cells, chronic blood loss, secondary hyperparathyroidism, chronic inflammation, oxidative stress, nutritional folate deficiency, uremia and chronic suppression of erythropoiesis [6,7].

Diabetes exacerbates many of these factors, leading to a higher degree of anemia in patients with diabetic nephropathy than in patients with kidney disease from other causes.

6. Erythropoietin deficiency

Erythropoietin (EPO) is a glycoprotein hormone that regulates proliferation, differentiation and maturation of red blood cells. EPO is produced by the peritubular capillary cells within the kidney, and this process is mediated by oxygen availability. In normal kidneys, EPO production increases in proportion to the degree of anemia.

Relative deficiency of EPO is the most important cause of anemia in patients with chronic kidney disease. The ability of the kidneys to produce erythropoietin is not impaired in renal disease - the absolute value of EPO can be in the normal or even high, so measuring EPO levels does not aid clinical management. However EPO levels will be inappropriately low relative to the degree of anemia, resulting in a functional EPO deficiency. This is due to the uncoupling of EPO synthesis from hemoglobin concentration so that the protein is no longer upregulated by anemia [8].



In the diabetic kidney tubulointerstitial dysfunction is observed early in the course of disease [9]. This could cause disruption of the intricate signaling mechanism between the capillaries, interstitial fibroblasts and tubular cells regulating EPO production, thus contributing to the uncoupling of EPO synthesis from hemoglobin levels.

Diabetes also negatively affects hypoxia-inducible factor (HIF), a transcription factor that plays a crucial role in regulating the renal response to hypoxia. HIF regulates the transcriptional activation of many oxygen-sensitive genes, including EPO. Hyperglycemia has been shown to inhibit stabilization of the HIF protein [10].

Autonomic dysfunction has also been suggested as another factor that may contribute to EPO deficiency in diabetic patients. In experimental models, EPO production is impaired when the kidney is denervated [11]. Also, patients with primary disorders of the autonomic nervous system have blunted production of EPO and a high risk of developing anemia [12].

7. Decreased red blood cell lifespan

Patients with renal disease have a 30 to 70 percent reduction in RBC lifespan. The mechanism of this phenomenon has yet to be elucidated satisfactorily. Blood from uremic donors transfused into normal recipients result in normal RBC survival, implying that the

uremic environment of patients with chronic kidney disease is the underlying cause of this phenomenon. However advancements in chronic renal replacement therapy does not lead to improvement in RBC survival [13].

The red blood cells of patients with diabetes are metabolically and functionally abnormal. These changes contribute to reduced erythrocyte survival in diabetic patients to a greater degree than in nondiabetic patients with a similar degree of renal impairment [14].

8. Iron deficiency

Uremia causes platelet dysfunction, putting patients with chronic kidney disease at increased risk of bleeding and iron loss. Patients on hemodialysis in particular are prone to losing iron through blood trapping in dialysis machine and repeated phlebotomy.

It has also been shown that patients with chronic kidney disease have impaired absorption of dietary iron. Transferrin is a protein that delivers iron from the gastrointestinal tract and the reticuloendothelial system into the bone marrow to be utilized by maturing erythrocytes. Patients with chronic kidney disease have decreased levels of transferrin, impairing iron mobilization [15].

The overall prevalence of iron deficiency in patients with diabetes is not significantly different from that in the general adult population. However, normal iron indices do not preclude these patients from achieving benefit with iron supplementation. In particular, patients on dialysis are often found to have a functional iron deficiency, in which their iron studies are normal but their anemia improves with parenteral iron supplementation.

9. Chronic inflammation and oxidative stress

Anemia of chronic inflammation is characterized by an impairment of the ability to release iron from the hepatocytes and macrophages of the reticuloendothelial system. Patients with chronic kidney disease exhibit a generalized increase in the inflammatory response due to a variety of factors, including decreased clearance of inflammatory cytokines, volume overload, oxidative stress and their underlying comorbid conditions.

Although decreased GFR and decreased iron stores are major contributing factors to anemia in diabetic patients, EPO deficiency and inflammation are becoming a leading factors in explaining the high prevalence of anemia in diabetics with CKD. These factors lead to anemia and lead to heart failure, cardiomyopathy and myocyte death [16].

10. Epidemiology of anemia in diabetic populations with chronic kidney disease

Anemia occurs earlier, and is more severe in chronic kidney disease related to diabetes than in non-diabetic kidney disease. It often develops when creatinine is within the normal range, and therefore is undiagnosed by primary care physicians. Anemia has a negative impact on patient's quality of life contributing to morbidity, for instance worsening exercise tolerance, lethargy and erectile dysfunction [17]. Furthermore anemia causes hypoxia induced diseases, including angina, cardiac failure and claudication, which are also independently associated with diabetes. Studies have shown that approximately 20 to 30 percent of people with diabetes will be anemic [18]. Unfortunately anemia within the diabetic population anemia is often unrecognized, undetected and untreated in patients with chronic kidney disease [19].

Anemia in diabetic patients although prevalent is often overlooked and undertreated. A cross sectional study comprised of a questionnaire-based interview with 1054 respondents from 6 European countries (Belgium, France, Germany, Greece Italy and the UK) showed that only 32 percent of respondents had been given information about anemia, although 83 percent had heard of anemia. One fifth of those with anemia received no treatment. Although anemia is highly prevalent in those with diabetes, patients are often unaware and undertreated for their anemia [20].

11. Cardiovascular risks of anemic patients with chronic kidney disease

Cardiovascular disease is very common in patients with diabetes and with CKD. There are numerous important interactions between heart disease and renal disease, a term defined as cardiorenal syndrome (CRS). A 2004 report from the National Heart, Lung, and Blood Institute defined CRS as a condition in which therapy to relieve congestive symptoms of heart failure is limited by a decline in renal function as manifested by a reduction in glomerular filtration rate. For instance acute heart failure results in acute kidney injury and chronic heart failure causes progressive chronic kidney disease [21]. This association leads to the vicious circle contributing to premature death [22].

As randomized, placebo-controlled trials have so far been disappointing and unable to show a survival benefit of various treatment strategies, such as lipid-lowering, the risk factor profile seems to be different in CKD compared with the general population. Indeed, seemingly paradoxical associations between traditional risk factors and cardiovascular outcome in patients with advanced CKD have complicated our efforts to identify the real cardiovascular culprits. There are several non-traditional cardiovascular risk factors that are directly linked with CKD such as hyperparathyroidism, hyperphosphatemia, hyperhomocysteinemia and anemia, which are increasingly, recognized as cardiovascular risks [23]. Patients with CKD are more likely to die from cardiovascular events than of end stage renal disease.

12. Cardiovascular risk factors

In a study done involving 69,244 participants in a voluntary screening program and 17,061 participants randomly selected national survey population, CKD was independently associated with MI or stroke [6]. In diabetic patients with CKD the risk of CVD is increased by 20 to 40 percent compared with that in CKD in patients without diabetes [24].

Traditional Risk Factors	Non traditional risk Factors
Diabetes	Chronic inflammation
Dyslipidemia	Anemia
HTN	Oxidative stress
Central obesity	Hyperparathyroidism
Smoking	Hyperhomocysteinemia
Male or postmenopausal female	Endothelial Dysfunction
Family history of MI event	Prothrombotic states

13. Reasons to treat anemia

Type 2 diabetes mellitus and chronic kidney disease frequently coexist, and each disease independently increases the risk of cardiovascular events and end stage renal disease. Intensive treatment of risk factors such as hypertension and elevated LDL reduces cardiovascular morbidity and mortality and slows the progression of the kidney disease [25-27]. Anemia is a risk factor for cardiovascular morbidity and mortality, and is evolving as an attractive target and potentially correctable risk factor [24].

14. Treatment recommendations

All patients with CKD should be screened at least annually for anemia, regardless of stage. Further evaluation of anemia should be initiated in patients with CKD if hemoglobin levels found to be below normal, including iron studies. Erythropoiesis-stimulating agents (ESAs) can be initiated when hemoglobin falls below the target range of 11-12g/dL [16].

ESAs are the mainstay of therapy for anemia of chronic kidney disease. There are currently two agents commercially available, recombinant epoetin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp). The selection of ESA can be individualized according to clinical circumstances and patient/provider preference.

Patients with serum ferritin, transferrin saturation and/or content of hemoglobin in reticulocytes below target levels should be started on iron supplementation. Patients on hemodialysis should be given parenteral iron therapy as their iron deficiency often fails to correct with oral supplementation.

15. Recent clinical trials

Recommendations regarding the use of erythropoietin and the target hemoglobin are forever changing. In 1994 The FDA first approved a target hemoglobin of 10-11g/dl which was subsequently increased to 10-12g/dl in 1998. The National Kidney Foundation recommended a level of hemoglobin of 11-12g/dl in 2007 [2,6].

In 1998 a study was performed to assess the risks and benefits of normalizing the hematocrit in patients with cardiac disease who were undergoing hemodialysis. There were 1233 patients evaluated in the study, of which 618 were assigned to achieve a hematocrit of 42 percent, and 615 received erythropoietin sufficient to achieve and maintain a hematocrit of 30 percent. After 29 months there were 183 deaths and 19 first nonfatal myocardial infarcts among the patients in the normal hematocrit group and 150 deaths and 14 non-fatal myocardial infarcts among those in the low hematocrit group. The study was prematurely halted due to the higher mortality rate in the normal hematocrit group. The investigators recommended against normalization of hematocrit in patients with clinically evident congestive heart failure or ischemic heart disease who are receiving hemodialysis [28].

In 2006 two other landmark trials were published. The studies were conducted to determine optimal hemoglobin levels in predialysis patients looking at cardiovascular disease outcomes.

The CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) study was an open-label trial of 1432 patients with CKD. 715 were randomly assigned to receive epoetin alpha to achieve a hemoglobin of 13.5g/dl and 717 were assigned to achieve a level of 11.3g/dl. The endpoint was a composite of death, myocardial infarction, hospitalization for

congestive heart failure, and stroke. There were 222 composite events: 125 in the high hemoglobin group and 97 in the low hemoglobin group. Investigators concluded that the 13.5g/dl target resulted in increased risk, and no improvement in quality of life [29].

The second landmark trial at this time was the CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta) study, which randomly assigned 603 patients with an estimated GFR of 15-35 ml/min and mild to moderate anemia (11-12.5 g/dl) to a target hemoglobin in the normal range (13-15g/dl) or to subnormal values (10.5-11.5g/dl). During the 3 year study complete correction of anemia did not affect the likelihood of a first cardiac death. There was no significant incidence of adverse events between the two groups. Investigators concluded that in patients with CKD, early complete correction of anemia does not reduce the risk of cardiovascular events [30].

The ACORD (Anemia Correction in Diabetes) study, published in 2007, investigated the effect of correcting anemia on heart function in diabetic patients with anemia and early diabetic nephropathy. 172 patients with type 1 or 2 diabetes mellitus, mild to moderate anemia, and stage 1 to 3 chronic kidney disease were randomly assigned to attain a target hemoglobin level of either 13 to 15 g/dL (group 1) or 10.5 to 11.5 g/dL (group 2). The primary end point was change in left ventricular mass index (LVMI), measured by echocardiogram. At study end, hemoglobin levels were 13.5 g/dL in group 1 and 12.1 g/dL in group 2, but no significant differences between study groups were observed in median LVMI after 15 months [31].

In 2009 the TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) trial was conducted to evaluate whether increasing the hemoglobin level with the use of darbepoetin would lower the rate of death, cardiovascular events or end stage renal disease in patients with type 2 diabetes and chronic kidney disease. This was a randomized, double blind placebo controlled trial conducted at 623 sites in 24 countries consisting of 4038 patients. 2012 patients were randomly assigned to receive darbepoetin to achieve a hemoglobin level of approximately 13g/dL, while 2026 patients received placebo, with rescue darbepoetin when the hemoglobin level was less than 9g/dL. Darbepoetin did not reduce the primary end points of death, cardiovascular events or end stage renal disease in patients with diabetes and chronic kidney disease. There was also an increased incident of stroke of 2.1 percent in the darbepoetin arm vs. 1.1 percent in the placebo arm [32].

A subset analysis of TREAT that was published in September 2010 assessed the relationship between responsiveness to darbepoetin, hemoglobin levels achieved, and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. Patients with less than 2 percent change in hemoglobin level after the first two doses of darbepoetin were defined as poor responders. These patients had a lower hemoglobin level at 12 weeks despite receiving higher doses of darbepoetin. They also had higher rates of composite cardiovascular end points or death. The study was unable to determine whether poor response to darbepoetin is a risk factor for adverse outcomes, or whether the risk was augmented by the higher doses of darbepoetin they received [33].

16. Conclusion

Although anemia in chronic kidney disease is often unrecognized and under diagnosed, it is an important predictor of quality of life and contributes to cardiovascular morbidity and mortality in patients with diabetes. Anemia causes hypoxia induced diseases, including angina, cardiac failure and claudication, which are also independently associated with

diabetes. Anemia also causes worsening exercise tolerance, lethargy and erectile dysfunction. Anemia, like hypertension and hyperlipidemia is an important modifiable risk factor in patients with chronic kidney disease and diabetes, therefore should be treated as such.

Currently it is recommended to maintain a hemoglobin of 11-12g/dl in patients with chronic kidney disease with correction of nutritional deficiencies and the use of erythropoietin-stimulating agents. Evidence from randomized controlled trials including the CHOIR, CREATE and ACORD studies show that normalization of hemoglobin beyond 12g/dl does not improve outcomes. The TREAT trial showed that using ESAs to increase hemoglobin to a target of 13g/dL increases the risk of stroke. It was also found that patients who had a poor response to ESAs had a higher rate of cardiovascular events.

17. Summary

1. Anemia is pervasive in the diabetic patient with CKD.
2. Anemia occurs earlier, and is more severe in chronic kidney disease related to diabetes than in non-diabetic kidney disease.
3. Reasons for anemia in CKD include EPO deficiency, iron deficiency, decreased lifespan of red blood cells, chronic blood loss, secondary hyperparathyroidism, chronic inflammation, oxidative stress, nutritional folate deficiency, uremia and chronic suppression of erythropoiesis.
4. Anemia in diabetic patients although prevalent is often overlooked and undertreated.
5. Cardiovascular disease is very common in patients with diabetes and with CKD.
6. In diabetic patients with CKD the risk of CVD is increased by 20 to 40 percent compared with that in CKD in patients without diabetes.
7. Anemia is a risk factor for cardiovascular morbidity and mortality, and is evolving as an attractive target and potentially correctable risk factor.
8. All patients with CKD should be screened at least annually for anemia, regardless of stage.
9. ESAs are the mainstay of therapy for anemia of chronic kidney disease.
10. Maintaining a hemoglobin of 11-12g/dl is currently recommended.

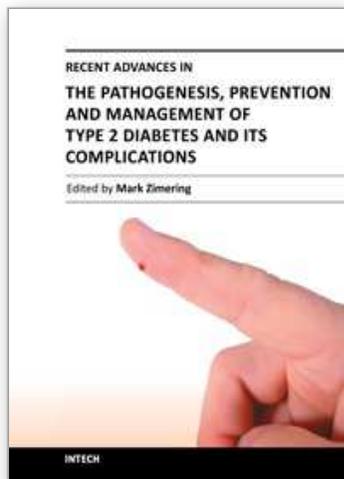
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Type 2 diabetes (diabetes mellitus) affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

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