Chapter 11

Anemia of Chronic Kidney Disease — A Modifiable Risk Factor in a Growing High Cardiovascular Risk Population

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1. Introduction

Diabetes Mellitus (DM) has become a modern day epidemic, affecting millions of people around the globe. It has grown parallel to the rising epidemic of obesity, leading to increased cardiovascular disease (CVD) morbidity and mortality. Currently, DM is the most common cause of chronic kidney disease (CKD) and subsequent end stage renal disease (ESRD) requiring renal replacement therapy. Although statistics indicate a leveling off in the incidence of ESRD among diabetics, these statistics do not hold true for some of the most vulnerable populations such as minority populations.

CVD is the primary cause of death in people with DM who also possess traditional risk factors such as hypertension (HTN), obesity (particularly central obesity), dyslipidemia (decreased HDL, and elevated triglycerides), increased age, sedentary lifestyle and smoking. Nontraditional risk factors for CVD include increased inflammation, stimulation of the renin-angiotensin-aldosterone system (RAAS), increased fibrinogen, increased platelet activator inhibitor factor -1 (PAI-1) among others. Diabetic kidney disease (DKD) is a well established cause of CVD and currently, it is considered a cardiovascular equivalent. In fact, people with CKD generally die of CVD prior to the initiation of dialysis.

The exact cause of increased CVD risk in CKD is likely multifactorial but is largely unknown. Anemia has been shown to increase cardiovascular risk in this vulnerable population and prior studies have demonstrated that treatment of anemia reduces this risk and improves quality of life [5]. On the other hand, recent trials have shown an increased risk of CVD in those with higher hemoglobin values being treated with ESA [56]. It is unclear whether the ESA in large doses confers this harm or whether the correction of anemia to high hemoglobin levels is

responsible. These uncertainties explain why many clinicians prefer transfusion therapy over the use of ESA. Several questions remain unanswered including the mechanisms by which anemia confers increased cardiovascular risk in CKD and dialysis patients. Another important issue surrounded by controversy is the degree to which anemia should be corrected with erythropoietic stimulating agents (ESA).

In this chapter, we discuss the relationship between DM and CKD and the associated CVD risk factors, highlighting the pathophysiologic mechanisms that link anemia and CVD. We also explore the therapeutic rationale behind the current guidelines provided by the National Kidney Foundation for the management of anemia. These guidelines are constantly updated as new randomized controlled trials continuue to emerge.

1.1. Definition and risk factors for anemia in CKD

According to the WHO criteria published in 1997, the Hemoglobin and Hematorcrit cutoffs for defining anemia are <13 g/dL and 39%, respectively, in men and <12 and 36%, respectively, in non pregnant women [1]. Newer research differentiates anemia cutoffs based on both race and age in addition to sex. Table 1 lists proposed lower limits of normal for hemoglobin concentration based on Scripps-Kaiser data for the 5th percentiles and the NHANES data published in 2006 [2].

White Men 20-59 yrs	13.7	White Men 60+ yrs	13.2
White Women 20-49 yrs	12.2	White Women 50+ yrs	12.2
Black Men 20-59 yrs	12.9	Black Men 60+ yrs	12.7
Black Women 20-49 yrs	11.5	Black Women 50+ yrs	11.5

Based on reference 3 Beutler et al.

Table 1. Lower Limits of normal Hemoglobin concentration (g/dL)

Multiple risk factors increase the risk of developing anemia. Among multiple factors, individuals with CVD, DM and CKD, HTN(HTN) and of African American race are at significantly high risk than the general population [4,5,6].

1.2. Postulated mechanisms of anemia in CKD, CVD and DM

CKD, CVD and DM are intricately interconnected with one another. CKD is extremely prevalent among the United States adult population. According to the Center for Disease Control (CDC), more than 35% of people aged 20 years or older with DM have CKD and more than 20% of people aged 20 years or older with HTN have CKD [9].

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Regardless of the level of estimated glomerular filtration rate (e-GFR), anemia is both more frequent and more severe in diabetics compared to non-diabetic patients [10]. Diabetes types 1 and 2, are the leading cause of CKD in the western world, accounting for approximately 30-40% of cases. DM is therefore the most common cause of renal anemia [7,8]. A number of mechanisms contribute to the development of anemia in diabetics with CKD such as decreased red blood cell (RBC) life span, iron deficiency, nutritional folate deficiency, occult blood loss, systemic inflammation and what appears to be the most dominant causal factor, erythropoietin deficiency [11].

Renal anemia is associated with a reduction in the number of RBCs and with an increase in oxidative stress to RBCs [23]. RBC lifespan is reduced by approximately 50% in uremia. While this phenomenon has been recognized for over 50 years, the mechanism is not completely understood [12]. Some studies show that the decrease in RBC half life is partially caused by the uremic environment present in CKD patients. [13,14,15,16]. Studies have also shown that the RBCs in diabetics have multiple metabolic and functional abnormalities [17,18]. RBC properties are significantly modified by hyperglycemia. Prior reports suggest that increased levels of glucose decrease the activity of the RBC Na/K ATPase and generate multiple oxidative changes [19,20,21]. According to Manodori et al, as a result of these changes, RBC life span in diabetic patients is decreased compared to nondiabetic patients with similar degrees of renal impairment [22].

Iron homeostasis is altered in those with CKD. Transferrin is a protein that captures iron that has been absorbed from the GI tract and that has been released from macrophages and delivers it to maturing RBCs. In CKD, transferrin levels are decreased, impairing iron mobilization. As uremia leads to platelet dysfunction, CKD patients are at increased risk for bleeding and iron loss [24]. Hemodialysis patients are at particular risk because of the chance for blood loss during dialysis [25]. Diabetics with nephropathy are at an added risk for iron loss by urinary excretion as their proteinuria progresses [26].

Systemic Inflammation is one of the leading features of diabetics with CKD that appears to contribute to anemia. This inflammatory response is secondary to a variety of factors including elevated levels of inflammatory cytokines, volume overload and oxidative stress. Increased level of cytokines impair bone marrow function and significantly alter iron metabolism.

Erythropoietin (EPO) is a glycoprotein growth factor that is produced by the peritubular interstitial fibroblasts of the renal cortex and outer medulla [27]. The release of EPO is regulated by a complex feedback mechanism at the level of the kidney. in which. One major role of the kidney is to “sense” an imbalance between oxygen supply and demand. In response, it stimulates hematopoietic precursors through the production of EPO. EPO deficiency is currently considered a leading cause of anemia in patients with CKD. In this group, EPO deficiency is regarded as functional as it stems from a failure to increase EPO levels in response to a falling hemoglobin level, even though the absolute value of EPO may be within normal limits. EPO deficiency appears to contribute largely to the development of anemia in patients with diabetic nephropathy and CKD [28, 29]. Multiple explanations have been postulated to account for the EPO deficiency in this patient population including microvascular damage, chronic hypoxia, oxidative stress, and autonomic neuropathy. Damage to the tubulointerstitial

cells has been observed in the early stages of diabetic nephropathy resulting in impairment of the signaling cascade that triggers transcription and release of EPO [29]. Unregulated activation of the Renin-Angiotensin-Aldosterone System (RAAS) in diabetics may also contribute to impaired erythropoietin release. Similarly, experimental models have illustrated that autonomic dysfunction, as seen in diabetics who tend to develop splanchnic nerve dysfunction, have impaired production of EPO [30].

CVD is a common co-morbidity among anemic patients with both DM and CKD. CVD, DM and CKD are strongly intertwined. Many of the same risk factors that contribute to DM, CKD and CVD, both independently and synergistically. These risk factors can be divided into two categories: traditional and non traditional. Some of the traditional risk factors include obesity, hypertension, dyslipidemia and smoking. Among the non traditional risk factors are anemia, chronic systemic inflammation, oxidative stress, hyperparathyroidism, hyperhomocysteinemia, endothelial dysfunction and prothrombin states [34].

Diabetic kidney disease, also known as diabetic nephropathy, is one of the major complications of type 2 diabetes. Elevated blood glucose levels activate various biochemical pathways within renal cells. The increased intracellular glucose leads to increased production of glucose intermediaries cycling through multiple metabolic pathways. This leads to the production of advanced glycation products (AGEs), activation of protein kinase C (PKC), increased expression of transforming growth factor-beta (TGF-beta), GTP-binding proteins, and the formation of reactive oxygen species (ROS) [64]. The ROS may also be responsible for the activation of the RAAS [65, 66]. In addition to these metabolic events, there is also a hemodynamic component to diabetic kidney disease. Hyperglycemia impairs glomerular circulation, mainly dilation of the afferent arteriole, which subsequently leads to increased glomerular capillary pressure [67, 68]. The culmination of these hyperglycemia induced metabolic and hemodynamic derangements sets off a cascade of aberrant cell growth, angiogenesis, extracellular matrix abnormalities, hyalinization of arterioles, proteinuria, and hyperfiltration, ultimately resulting in diabetic kidney injury [64].

Type 2 diabetes is the most common cause of CKD among the US adult population and both DM and CKD can cause anemia. The decreased oxygen carrying capacity associated with anemia may aggravate myocardial hypoxia, increase cardiac output, cause volume overload, increase heart rate, stimulate the RAAS, and can lead to left ventricular hypertrophy (LVH). The damage caused as a result produces myocyte loss, progressive fibrosis, coronary heart disease (CHD) and heart failure [32,33]. DM is both a CHD equivalent and the leading cause of CKD. Type 2 diabetes increases the risk of CHD events by at least by two- to three fold compared with non-diabetics [31]. Ultimately, patients with CKD are most likely to die from a cardiovascular event.

2. Epidemiology

Given the constant influx of immigrants to the western world, addressing the medical issues facing minorities holds critical relevance. Approximately one third of American population

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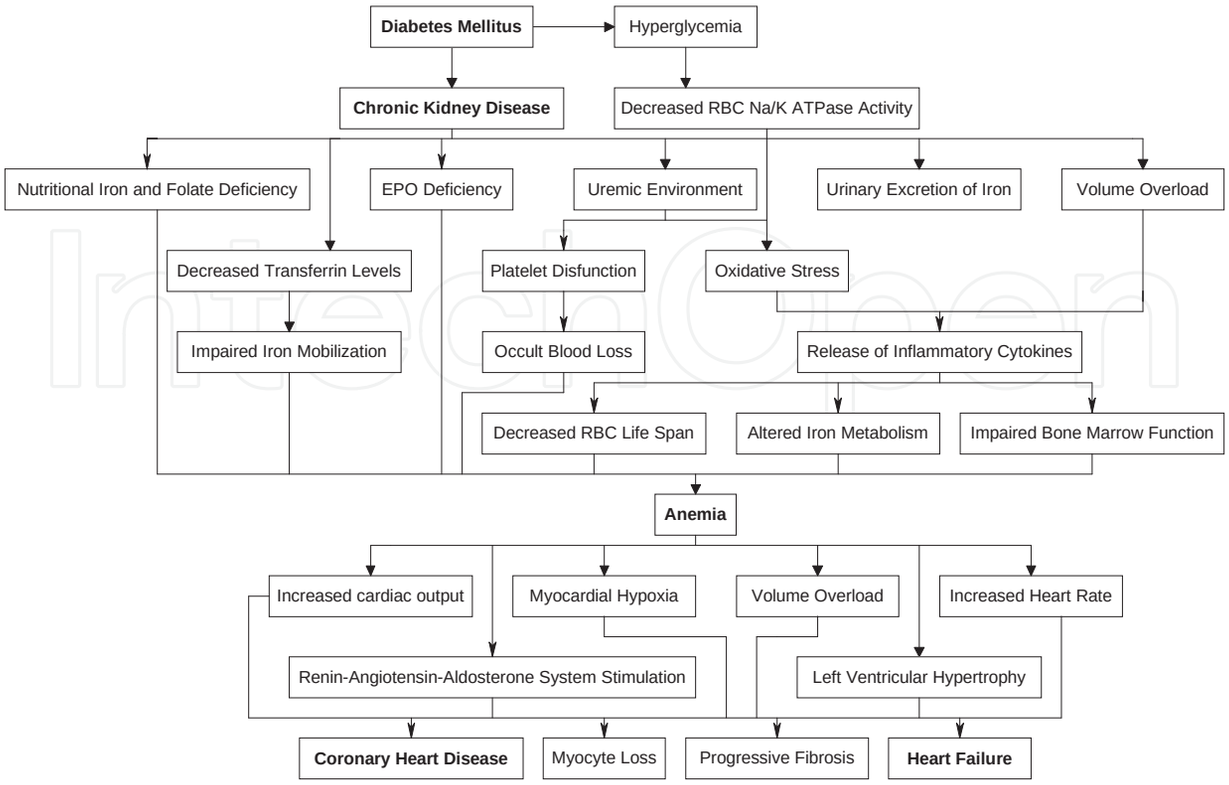

Figure 1. Highlights the postulated mechanisms of anemia in CKD, CVD and DM

currently identifies as minority, including Hispanics, African Americans, Asians, and Native Americans [35]. Between 2010 and 2050, this population is expected to grow geometrically, most markedly in the Asian and Hispanic American populations, which are both anticipated to double during this period [36].

2.1. Ethnic differences in CKD

ESRD is much more common among ethnic minorities with rates per million as high as 925 among blacks, 501 among Hispanics, and 465 among Native Americans compared with 276 among NHWs. ESRD as caused by HTN, the second leading cause, is also much more common in minorities with a nearly 11 times greater prevalence among blacks than whites [48]. On top of that, in patients with ESRD, the prevalence of HTN is greater in both Hispanic and NHBs compared with NHWs. Several biomarkers have been associated with this increased risk. Levels of C-reactive protein (CRP) and white blood cells are highest among blacks in this population, suggesting a role for inflammation in disease progression [49]. Elevated levels of CRP are associated with the development of Type 2 diabetes [50], an increased risk for coronary events [51] and symptomatic PAD [52] and may help to explain the increased prevalence of CKD in the black population.

CKD puts patients at greater risk for MI, stroke and death, with approximately 6 million Americans suffering from both CVD and CKD. According to NHANES, the prevalence of CVD

is 63 percent in those with CKD stages 3–5, compared with 5.8 percent in those without kidney disease [48]. The risk for these cardiovascular endpoints is even higher among African Americans with CKD. One pooled analysis of several community based studies found that among subjects with CKD the hazard ratio for myocardial infarction, fatal CHD, stroke, and death was 1.76 in blacks compared with 1.13 in whites [53].

2.2. Ethnic differences in diabetic CKD

DM is significantly more prevalent among Non Hispanic Blacks (NHB) than among non-Hispanic whites (NHW). Whereas between 1980 and 2010, DM rose to a rate of 6.8 percent among white males and 5.4 percent among white females, it increased to 9.7 percent among black males and 9.5 percent among black females [37]. Because of the increased risk of Type 2 diabetes among blacks and among other ethnic minorities [38], the number of Americans with DM is expected to triple from 20 million [37] to more than 60 million over the next forty years [39].

In addition, the rate of DM induced ESRD is growing faster among blacks than among whites. Among those aged 30–39, the rate of ESRD in diabetics has risen by 69 percent between 2000 and 2010 whereas it has dropped by one percent in age matched whites. Similarly, Native Americans in this age group have seen an increase of ESRD by 30.1 percent during this period. This contrasts with rates of ESRD in diabetics older than sixty where ESRD has dropped more dramatically among ethnic minorities than among whites.

2.3. Ethnic differences in CKD as one of diabetic CVD complications

DM is also linked with a greatly increased risk of CVD. The rise in prevalence of both coronary heart disease (CHD) and peripheral arterial disease (PAD) ranges between double and quadruple the risk of the general population [40]. The risk of PAD increases by 28 percent with each one percent increase in glycosylated hemoglobin, a marker for blood glucose levels [41].

Furthermore, NHBs are at significantly greater risk of both PAD and CVD than NHWs [39]. Based on the third National Health and Nutrition Examination Survey (NHANES III), 5 million US adults above age 40 have PAD. Among NHBs older than 40, the prevalence of PAD is 7.9 percent compared with a prevalence of 4.3 percent among age matched NHWs [42]. Furthermore, NHBs have a 1.5 times greater rate of heart disease related deaths and a 1.8 times greater rate of fatal stroke relative to NHWs [43]. According to the NAACP, NHB males have a 30 percent greater chance of dying from heart disease than NHW males [44].

The development and the worsening of CKD as a complication of diabetic CVD is the result of a number of interacting pathways. These include enhanced levels of oxidative stress, inflammation, endothelial dysfunction, and RAAS activation [48]. In addition, hypertriglyceridemia, associated with CVD, promotes lipid accumulation in renal cells and consequent dysfunction [49]. Furthermore, vascular calcification in CVD is commonplace among the renal vessels, fostering CKD progression [63]. The intersection of CVD CKD, and DM is complex with each player exacerbating one another. Thus, ethnic minorities are more likely to develop these conditions both independently and as part of cardiorenal syndrome.

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Part of the racial discrepancy in CKD, diabetic CKD and the associated complications may be explained by an increase in metabolic risk factors among minorities. Based on a three-year, cross-sectional sample of 15,826 patients with Type 2 diabetes, both Hispanics and NHBs were found to have higher body mass index, HbA1c, and LDL values in comparison with NHWs. NHBs also had significantly higher blood pressures compared to NHWs [45]. Moreover, ethnic minorities are both less physically active and have worse dietary behaviors compared to NHWs [46]. Minorities are also less likely to have health insurance coverage or to have a regular doctor [44]. As a result of the lower levels of glycemic control and the higher prevalence of both vascular disease and metabolic risk factors, rates of mortality from DM are persistently higher among NHBs than among NHWs [47].

The difference in the prevalence of cardiovascular disease in those with DM and CKD among different ethnicities is striking. It is likely a result of genetic susceptibility exacerbated by lifestyle differences. As health disparities continue to grow, a closer investigation into the root of these ethnic differences will help clinicians to create a more targeted approach.

3. Therapeutic rationale

Anemia is a risk factor for cardiovascular morbidity and mortality that is reversible [54]. According to the national Kidney Foundation Guidelines published in 2007, erythropoeisis stimulating agents (ESAs) should be used when the hemoglobin falls below the target range of 11-12 g/dL in both dialysis and non-dialysis patients. The goal for those receiving ESAs should be no greater than 13 g/dL. There are currently two Food and Drug Administration (FDA) approved ESAs in the United States, Epoetin alfa (Epogen, Procrit) and Darbepoetin alfa (Aranesp).

According to the Kidney Foundation Guidelines, all patients with CKD should be screened at least annually for anemia with a set of labs that include a complete blood count (CBC), a hemoglobin concentration (MCHC), iron studies, folate and Vitamin B12. Their stool should also be analyzed for occult blood loss [7]. Patients found to be iron deficient need to be started on iron supplementation, especially hemodialysis patients who may lose up to 3-5g of iron per year. Patients who qualify for ESAs should also receive iron therapy.

The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE), both landmark studies, provide an analysis of all-cause mortality and adverse cardiovascular events in patients with CKD with a therapeutic target of a hemoglobin greater than 13.0 g/dL compared with lower targets. None of the trials showed a benefit in those subjects with hemoglobin levels of greater than 13.0 g/dL. Investigators in the CHOIR study found that the 13.5g/dL target resulted in increased cardiovascular risk and no improvement in quality of life [58]. The CREATE study divided subjects with mild to moderate anemia (11-12.5 g/dl) into two groups. In one population, the goal was to raise the hemoglobin into the normal range (13-15g/dl) and while among the other subjects, the aim was to increase their hemoglobin to subnormal values (10.5-11.5g/dl). During this three 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 [59].

According the Anemia Correction in DM (ACORD) study, in diabetics with mild to moderate anemia and moderate LVH, correction of hemoglobin target level of 13 to 15 g/dL (130 to 150 g/L) does not decrease left ventricular mass index. However, normalization of the hemoglobin value prevented any further increase in LVH [55]. The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trial in 2009 is randomized, double blind placebo controlled trial that 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 CKD. 2,012 patients were randomly assigned to receive darbepoetin in order to achieve a hemoglobin level of approximately 13g/dL, while 2,026 patients received a placebo, with administration of rescue darbepoetin when the hemoglobin level dropped below 9g/dL. Darbepoetin did not reduce the primary endpoints of death, cardiovascular events or ESRD in patients with DM and CKD. There was also an increased incidence of stroke to 2.1 percent in the darbepoetin arm compared with a 1.1 percent incidence in the placebo group [56].

In 2011, McMurray et al. published an analysis of TREAT, which aimed to examine predictors of cardiovascular morbidity and mortality in those patients with DM, CKD and anemia. They concluded that in this particularly high risk population, CVD risk is most strongly predicted by age, history of heart failure, CRP, urinary protein/creatinine ratio, abnormal electrocardiogram, and 2 specific cardiac biomarkers, serum N-terminal pro B-type natriuretic peptide and troponin T. Their findings brought to light several important ways to improve CVD risk stratification [57].

A 2012 update to the National Kidney Foundation clinical practice guidelines for DM and CKD was recently published to address new evidence that has emerged since the release of the 2007 guidelines. Recommendations include [58]:

1. Target hemoglobin A1c (HbA1c) of approximately 7.0 percent to prevent or delay the progression of the microvascular complications of DM including kidney disease

2. Use of Low density Lipoprotein cholesterol (LDL-C) lowering medicines, such as statins or statin/ezetimibe combination to reduce risk of major atherosclerotic events in patients with DM and CKD given that LDL-C with statin based therapies reduce the risk of major atherosclerotic events but not all-cause mortality in patients with CKD including those with DM

3. Use of an angiotensin converting enzyme inhibitor (ACE-I) or an angiotensive receptor Blocking agent (ARB) in normotensive patients with DM and albuminuria levels >30 mg who are at high risk for both the development of and the worsening of DKD

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4. Conclusion

Anemia in CKD is a modifiable risk factor for CVD. If the anemia is addressed in its early stages, the risk of complications can be significantly reduced, especially those related to cardiovascular morbidity and mortality among the diabetic population. In addition, appropriate and timely treatment can improve the quality of life for these patients. It is important that physicians screen patients who are at risk for developing anemia as per accepted guidelines. This is especially important given that based on data collected from 1998-2008, NHANES found that the prevalence of DKD has steadily been increasing. The latest United States Renal Data System (USRDS) reported a 30 percent increase in the incidence of ESRD in diabetics in the United States between 1992 and 2008 [59, 60]. These figures indicate that anemia as caused by CKD in diabetics is an ongoing and ever-increasing problem in which all of the risk factors involved need to be addressed as part of regular preventative health measures.

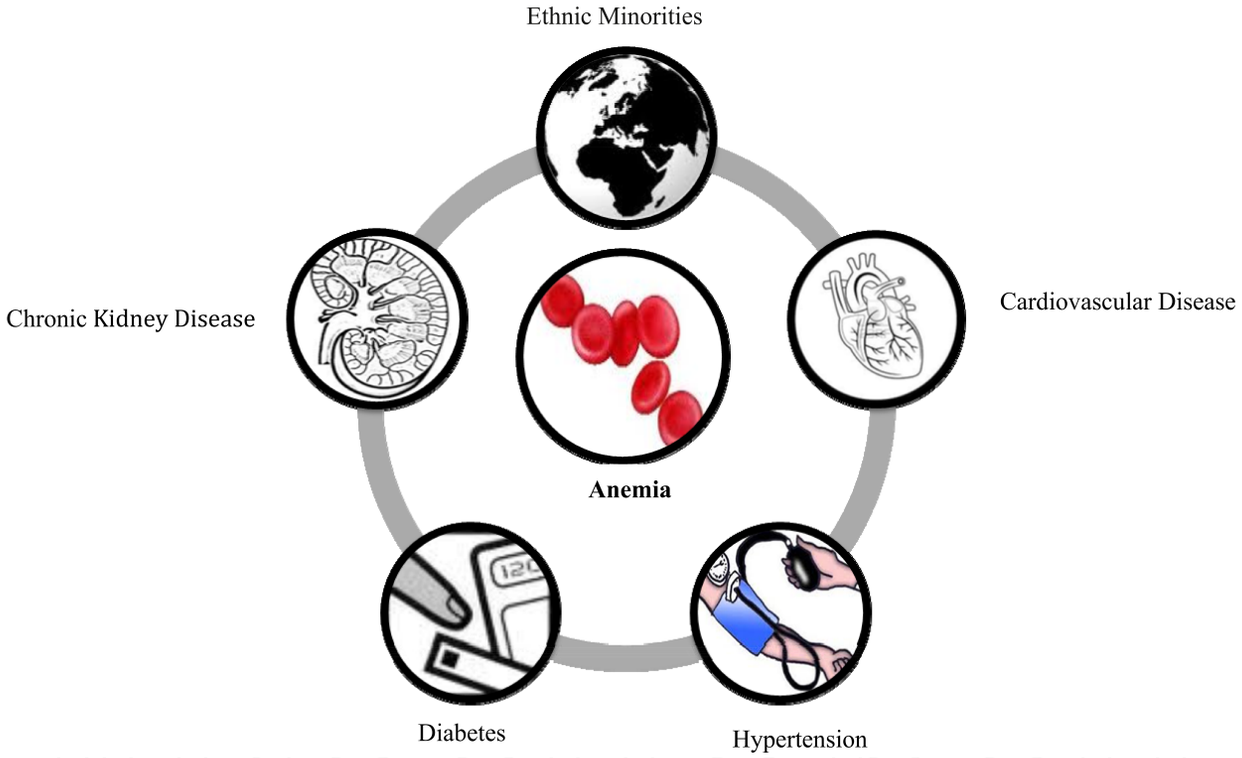

Figure 2. Highlights risk factors for anemia in this patient population.

Summary

1. With the rising epidemic of obesity in the western world, CVD, DM and CKD are becoming significant public health problems and each serves as risk factors for developing anemia.

2. Anemia is a modifiable risk factor for cardiovascular morbidity and mortality.

3. There are multiple postulated mechanisms for the development of anemia in diabetics with CKD such as decreased RBC life span, iron deficiency, nutritional folate deficiency, occult blood loss, systemic inflammation and erythropoietin deficiency, which appears to be the most dominant factor.

4. CVD is very common in patients with DM and CKD. The risk of developing CVD is significantly increased in diabetics with CKD compared with non-diabetics with CKD.

5. Regardless of the level of e-GFR, anemia is more frequent and severe in a diabetic compared to a non-diabetic patient.

6. Patients with CKD should be screened annually for anemia.

7. Patients who are found to be iron deficient need to be started on iron supplementation, especially hemodialysis patients.

8. ESAs are the mainstay of therapy for anemia in patients with CKD. Patients receiving ESA therapy should also be started on iron supplementation.

9. Correcting the hemoglobin level in this patient population to values greater than 13g/dL showed no benefit. It did, however, infer greater cardiac risk with no improvement in quality of life.

10. Guidelines currently recommend maintaining a hemoglobin level of 11-12 g/dL.

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