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Anemia and the Heart in Chronic Kidney Disease

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Cardiovascular disease is highly prevalent at all stages of chronic kidney disease (CKD) and is the leading cause of morbidity and mortality. Individuals with CKD commonly have multiple risk factors for the development of cardiovascular disease, including both traditional and nontraditional risk factors. Anemia is a nontraditional cardiovascular risk factor found in CKD that contributes to the development and progression of structural abnormalities of the heart, namely left ventricular hypertrophy and dilation. In addition, a deficiency of erythropoietin per se also may have important pathophysiologic consequences. In this review we summarize the evidence from observational studies showing an association between anemia and adverse cardiac outcomes at all stages of CKD. In addition, we provide an overview of the evidence accumulating from randomized controlled trials conducted in both nondialysis and dialysis CKD populations evaluating the effect of anemia correction on cardiac outcomes such as changes in left ventricular hypertrophy.
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Cardiovascular disease is highly prevalent at all stages of chronic kidney disease (CKD) and is the leading cause of morbidity and mortality. The risk of CVD increases early in the course of CKD and its manifestations include those related to atherosclerosis, vascular calcification, and cardiac structural abnormalities such as left ventricular hypertrophy (LVH) and congestive heart failure (CHF). Individuals with CKD commonly have multiple risk factors for the development of cardiovascular disease. These include both traditional risk factors such as diabetes, hypertension, and dyslipidemia, and nontraditional risk factors. Anemia is a nontraditional cardiovascular risk factor that predisposes to the development and progression of structural abnormalities of the heart, namely LVH and dilation, which in turn are associated with adverse outcomes such as increased mortality in CKD. The goals of this review are to describe the pathophysiologic consequences of anemia and erythropoietin deficiency on the heart in CKD, to provide an overview of the observational studies showing an association between anemia and adverse cardiac outcomes in CKD, and to review the evidence from recent randomized trials of anemia correction in CKD with a particular emphasis on the cardiac effects of erythropoietin replacement.

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Physiologic Consequences of Anemia in CKD

The physiologic response to anemia has been well described and involves both hemodynamic and nonhemodynamic adaptations. Nonhemodynamic adaptations aimed at increasing tissue oxygen delivery include increases in red blood cell 2,3-diphosphoglycerate levels and increased erythropoietin synthesis to stimulate red blood cell production.[1] Hemodynamic changes include increased preload, decreased peripheral vascular resistance, and increased cardiac output.[2] The net result is an increased workload imposed on the left ventricle, contributing to the development of eccentric LVH. This response initially is adaptive; however, when sustained, it has adverse consequences on the myocardium. At the cellular level, myocytes experience an energy deficit, partly caused by ischemia, and cell death results. Cardiac fibroblasts proliferate, expanding the extracellular matrix of the myocardium, and causing myocardial fibrosis.[3] Cardiomyopathy and heart failure may result. In addition, anemia may exacerbate symptoms of ischemia and provoke acute coronary syndromes in individuals with underlying coronary artery disease.

Although most discussions of anemia in the CKD setting

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focus on the effects of reduced levels of hemoglobin, a deficiency of erythropoietin per se also may have important consequences. Erythropoietin has been shown in both animal and human studies to have activity beyond the stimulation of erythropoiesis, including effects on platelets, vascular endothelium, vascular smooth muscle cells, and cardiac myocytes.[4] Some of these effects may be cardioprotective, thus a deficiency of erythropoietin itself may contribute to the rampant cardiac disease in the CKD population. For example, experiments in patients with CKD have shown that erythropoietin increases the number of circulating stem cells and promotes the differentiation and proliferation of endothelial progenitor cells.[5] This implies a role for erythropoietin in repair from injury. In animal and in vitro models, erythropoietin stimulates angiogenesis and has antiapoptotic effects when administered to hypoxic cardiac myocytes in experiments designed to mimic the stress of myocardial infarction. One obvious extension of this is that erythropoietin may have a role in limiting myocardial infarct size. This hypothesis has been supported by several in vivo animal experiments in which high doses of erythropoietin were administered preceding or after coronary artery ligation. In a study by Tramontano et al,[6] adult rats were injected with erythropoietin at a dose of 5,000 U/kg intraperitoneally immediately after the ligation of the left anterior descending coronary artery. After 1 hour of ligation, the number of apoptotic myocytes was lower in the erythropoietin-treated animals than controls. In a similar experiment by Parsa et al[7] with adult rabbits, animals receiving erythropoietin showed improvements in peak left ventricular pressure and left ventricular relaxation at 3 days compared with control animals. Reductions in postinfarct cardiac myocyte apoptosis and improvements in left ventricular hemodynamic function also have been shown in other studies.[8,9] In short, erythropoietin replacement in CKD may have cardiac effects beyond those related strictly to increasing hemoglobin levels.

Although erythropoietin may have a role in cardioprotection, there is evidence that this hormone also may exert less favorable effects on the cardiovascular system. For example, an increase in the number of circulating young platelet forms early in the course of erythropoietin therapy in hemodialysis patients improves the bleeding diathesis of kidney disease, but in theory also may contribute to an increased risk of thrombosis.[10] Some studies have shown that erythropoietin affects other hemostatic parameters, for example by increasing the level of von Willebrand Factor (vWF) and decreasing the levels of proteins C and S.[11,12] However, these findings have not been universal, and at least 2 studies in hemodialysis patients have found almost no sustained effect of erythropoietin on the levels of factors such as protein C, protein S, factor VII, factor XII, and fibrinogen.[13,14] Some evidence also suggests that erythropoietin may activate vascular endothelium, potentially contributing to an increase in thrombogenicity. In practice, the prothrombotic risk associated with erythropoietin appears to be a concern mainly when hemoglobin approaches more normal hemoglobin levels; at which point it then has been associated with an increased risk of vascular access thrombosis in some studies.[15]

Observational Studies of Anemia in CKD

The association between anemia and adverse cardiac outcomes in the dialysis population is well established. In a prospective cohort study by Harnett et al,[16] 433 dialysis patients with a mean hemoglobin level of 8.4 g/dL at the time of study initiation were followed-up for a mean of 41 months. LVH was present in an alarming 75% of subjects at initiation of renal replacement therapy. The investigators found that anemia was associated independently with the development of CHF and mortality. The relative risk for mortality was 1.18 per 1.0 g/dL decrease in hemoglobin level. In addition, LVH, similar to anemia, was an independent predictor of mortality. Subsequent studies in the hemodialysis population have confirmed that anemic patients are at increased risk of death, much of which is cardiac death. In a retrospective Medicare database study of more than 95,000 prevalent US hemodialysis patients, the relative risk of cardiac death was 1.40 and 1.18 for those with hematocrit levels of less than 27% and 27% to less than 30%, respectively, compared with the reference group with a hematocrit level of 30% to less than 33% after adjustment for baseline characteristics and comorbidities.[17]

Several observational studies in hemodialysis patients have evaluated the association between hematocrit levels greater than the currently recommended K/DOQI guideline target of 33% to 36% and outcomes such as cardiac hospitalization and mortality. In contrast to the evidence accumulating from randomized controlled trials, most of these have shown no excess in adverse outcomes in the high-level hematocrit groups. In a retrospective study by Li and Collins,[18] Medicare data from approximately 50,000 incident hemodialysis patients in the United States was analyzed to determine the association between hematocrit levels greater than the target set by K/DOQI and morbidity and mortality caused by cardiovascular disease including CHF and ischemic heart disease. With respect to hospitalization rate for any cardiac cause, patients with hematocrit values of more than 36% to 39% and more than 39% had risk ratios of 0.92 and 0.79, respectively, compared with those with values of more than 33% to 36%. The risk of death from cardiac causes also was lower in the higher-level hematocrit groups, with risk ratios of 0.92 and 0.83, respectively. In a recent study of the 5,517 hemodialysis patients involved in the US arm of the Dialysis Outcomes and Practice Patterns Phase I Study, patients with hemoglobin levels of more than 12 g/dL were not at increased risk of death compared with those with hemoglobin levels of 11 to less than 12 g/dL.[19] A similar result was obtained by Ofsthun et al[20] in an analysis of hemodialysis patients in the Fresenius Medical Care North America database.

In contrast to the hemodialysis population, the association between anemia and cardiac outcomes and mortality in the peritoneal dialysis population has been investigated less extensively; however, the 2 appear to be very similar, with an increased risk of mortality associated with decreasing levels of hemoglobin. A recent retrospective study of almost 14,000

US Medicare patients with end-stage renal disease treated by peritoneal dialysis evaluated the association between the averaged hemoglobin level within the first 6 months of treatment and mortality over the subsequent 2-year period. All subjects were receiving erythropoietin therapy. Compared with the reference group with hemoglobin levels of 11 to 11.9 g/dL, the risk of all-cause mortality for those with hemoglobin levels of 10 to 10.9 g/dL and less than 10 g/dL were 1.13 and 1.43 for nondiabetics, and 1.18 and 1.34 for diabetics, respectively.[21]

The associations between anemia, LVH, and mortality also extend to the predialysis population. In a cross-sectional study by Levin et al[22] of 175 patients with a mean creatinine clearance of 25 mL/min, the prevalence of LVH was 40%, and anemia was associated independently with LVH, with an increase in risk by 6% for each 10-g/L decrease in hemoglobin level. The association between anemia and LVH was confirmed in a subsequent multicenter prospective cohort study of 246 predialysis patients with varying degrees of renal dysfunction, in which 10% developed de novo LVH over the 12-month follow-up period. Decreasing hemoglobin level, in addition to systolic blood pressure and baseline left ventricular mass index (LVMI), were associated with left ventricular growth.[23]

Recent observational studies have shown that even early in the course of CKD, anemia is associated with an increased risk of coronary events and mortality. The Atherosclerosis Risk in Communities Study was a population-based cohort study of more than 13,000 middle-aged individuals without documented coronary heart disease followed-up for a median of 7.2 years. Anemia was defined as a hemoglobin level of less than 12 g/dL in women and less than 13 g/dL in men. The risk of cardiovascular events, including myocardial infarction and coronary heart disease–associated death, was 2.7-fold greater among the subjects with a high serum creatinine level ($\geqslant$1.2 mg/dL for women and $\geqslant$1.5 mg/dL for men) in conjunction with anemia compared with anemic individuals without an increased serum creatinine level. Interestingly, individuals with increased serum creatinine levels in the absence of anemia were not at increased risk for these events. Although an alternate explanation for these findings is that the presence of anemia may be reflective of a longer duration of kidney disease, which in itself would be expected to increase the risk of CHD events, the results nonetheless suggest that hemoglobin level may have an important interaction with renal dysfunction in potentiating the risk of cardiovascular events. In addition, although a greater proportion of individuals in the anemic group had more severe degrees of renal dysfunction, the observed associations persisted when the sample was limited to subjects with a serum creatinine of level of 2.8 mg/dL or less.[24]

A secondary analysis of pooled data from four community-based longitudinal studies (Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, and Framingham Offspring Study) recently was published, examining the association between anemia and cardiovascular outcomes in CKD. A total of 2,333 subjects with predominantly stage 3 CKD (mean glomerular filtration rate [GFR], 51.0 mL/min) followed-up for a median of 102 months were analyzed to determine whether anemia and LVH are associated with an increased risk of a composite end point of myocardial infarction, stroke, and all-cause mortality. In the adjusted Cox proportional hazards model, the hazard for the composite end point was 1.51 in anemic subjects (anemia was defined as a hematocrit level $<$ 39% in men and $<$ 36% in women) compared with those without anemia, and 1.67 in those with LVH compared with those without LVH. In addition, the presence of anemia in conjunction with LVH was found to exert a synergistic effect on the risk of development of the composite end point with a hazard ratio of 4.15, adding further support to the idea that anemia and renal dysfunction interact to increase the risk of adverse cardiovascular outcomes.[25]

The relationship between anemia and increased cardiac risk in early CKD was confirmed recently in an analysis of 3,074 subjects enrolled in the Blue Mountains Eye Study database, a population-based cohort study in Australia initially designed to report on the incidence of eye-related health outcomes and later expanded to report on other systemic health outcomes. The objective of the study was to evaluate whether low hemoglobin levels modified the effect of CKD on CHD-related mortality. The mean GFR in the CKD group was 48.3 mL/min compared with 70.2 mL/min in the non-CKD group and the mean follow-up period was 8.2 years for the study population. In this study, subjects with CKD and hemoglobin levels within the lowest quintile had almost 1.5 times the risk of CHD-related deaths compared with those with higher hemoglobin levels. The association persisted when the Cockcroft-Gault and Bjornsson equations were used to estimate GFR, but not when the abbreviated modified diet in renal disease (MDRD) formula was used. It is of note that the hemoglobin levels of the lowest quintile were still within the normal range (mean, 13.2 g/dL) and yet the associations between hemoglobin level and CHD events still were observed in CKD.[26]

Observational evidence not only suggests that anemia is associated with adverse cardiac outcomes, but that treatment of anemia by replacement of erythropoietin can lead to regression of LVH. In a prospective cohort study by Frank et al,[27] the effect of normalization of hemoglobin level in hemodialysis patients, all of whom had LVH at baseline, was evaluated. Twenty-three subjects were treated with erythropoietin to achieve a target hemoglobin level of more than 12.5 g/dL for a mean of 8 months. The predialytic hemoglobin level increased from 10.5 g/dL at the time of study initiation to 13.4 g/dL. The normalization of hemoglobin level statistically significantly improved indices of left ventricular wall thickness and LVMI. The predialysis population was evaluated in a prospective open-label study conducted by the Spanish Group for the Study of Left Ventricular Hypertrophy in Predialysis Patients. Erythropoietin-naive patients with a creatinine clearance of 10 to 30 mL/min (20-40 mL/min in diabetics) were recruited. Forty individuals found to be anemic (hemoglobin level, $<$10 g/dL) were treated with erythropoietin replacement to achieve a target hemoglobin level of 12 g/dL, whereas those with a hemoglobin level of greater

than 10 g/dL formed the control group (N = 61). Echocardiographic assessments were performed at baseline and at 6 months. At 6 months, the hemoglobin level increased from a mean of 9.1 to 11.3 g/dL. Among patients treated with erythropoietin, the LVMI statistically significantly decreased from 157 g/m^2 to 142 g/m^2 and the difference remained statistically significant after adjustment for multiple potential confounders including age, sex, baseline hemoglobin level, baseline LVMI, and medication use. Although the prevalence of LVH decreased in the erythropoietin-treated group, the difference was not statistically significant. In comparison, the control group experienced a significant increase in the prevalence of LVH over the 6-month follow-up period.[28]

Randomized Controlled Studies of Anemia in CKD

Although observational studies have shown improvements in left ventricular geometry and other cardiovascular end points when hemoglobin levels approach the normal range, these findings largely have gone unsupported in randomized trials of either partial correction or normalization of hemoglobin levels in the CKD population, regardless of the stage of CKD studied. This disparity highlights the importance of exercising caution in drawing causal conclusions from observational data. In particular, analyses based on observational data are susceptible to bias and residual confounding, which are both less likely in well-conducted, randomized, controlled studies.

Initial studies of anemia correction in CKD focused on patients with end-stage renal disease on hemodialysis with pre-existing cardiac disease. Among the most well known of these studies was that conducted by Besarab et al,[15] in which 1,233 hemodialysis patients with pre-existing CHF or ischemic heart disease were randomized to treatment with epoetin α to achieve a target hematocrit level of 30% versus 42%. The study was terminated at the third interim analysis because of safety concerns regarding a trend of increased risk of death or nonfatal myocardial infarction in the high-level hematocrit group (although the prespecified stopping boundary was not reached) and because of futility because it was unlikely that continuation of the trial would show a benefit in favor of the normal-level hematocrit group. In addition, the higher-level hematocrit group had higher rates of vascular access thrombosis. Although various explanations have been proposed for these results, including a potential detrimental effect of higher doses of intravenous iron dextran and lower hemodialytic clearances in the high-level hematocrit group, the results of this study nonetheless were sobering in the face of observational data supporting a higher hematocrit level.

Subsequent randomized studies of anemia correction in end-stage renal disease largely have used changes in cardiac dimensions as the surrogate primary outcome given the association of LVH with increased mortality in CKD. Thus, the assumption is that improvements in left ventricular morphology will translate into improved cardiac outcomes and reductions in mortality. In the Canadian Normalization of Hemoglobin Study, 146 hemodialysis patients with concentric LVH or LV dilation were randomized to treatment with epoetin α to achieve a target hemoglobin level of 10 g/dL versus 13.5 g/dL. In patients with concentric LVH at baseline, there was no difference between treatment groups in the change in LVMI on echocardiography repeated at 40 weeks. Similarly, in subjects with LV dilation at baseline, there was no difference between treatment groups in the change in LV volume index at the end of the study. In short, normalization of hemoglobin level did not lead to regression of established LVH or dilation. The investigators suggested that the data were supportive of a potential role for a higher hemoglobin target level in the prevention of LV dilation in those with established LVH, providing a rationale for further studies evaluating earlier intervention to prevent the development of structural cardiac disease.[29]

The Canadian-European Normalization of Hemoglobin Study was a randomized, double-blind study of 596 incident hemodialysis without LV dilation or symptoms of cardiac disease. Subjects were allocated randomly to a target predialysis hemoglobin level of 13.5 to 14.5 g/dL (mean hemoglobin level achieved, 13.3 g/dL at 24 weeks) or to partial correction of anemia with a target hemoglobin level of 9.5 to 11.5 g/dL (mean hemoglobin level achieved, 10.9 g/dL at 24 weeks) and serial echocardiograms were performed at 24, 48, and 96 weeks after study start. At the study conclusion, there was no difference in the primary outcome or change in LV volume index between treatment and control groups. In the lower target level hemoglobin group, the LV volume index increased by 8.3%, and it increased by 7.6% in the higher target group.[30] Thus, in this study, normalization of hemoglobin level was not effective in preventing cardiac structural changes in incident hemodialysis patients. In addition, there was an excess of adverse events in the higher-level hemoglobin group, specifically, the cerebrovascular event rate was increased.

Based on the biologic plausibility that intervention earlier in the course of CKD may prevent the adverse alterations in cardiac dimensions observed with kidney disease progression, the predialysis population has been evaluated in several recent randomized controlled trials. The Australian study by Roger, McMahon and colleagues study enrolled 155 patients with stage 3 or 4 CKD, 30% of whom had LVH at baseline, to a maintenance hemoglobin level of 9 to 10 g/dL (mean hemoglobin level achieved, 10.8 g/dL) or 11 to 13 g/dL (mean hemoglobin level achieved, 12 g/dL). At the end of the 2-year follow-up period, there was no difference between the 2 groups with respect to the primary outcome or change in LVMI.[31] It has been hypothesized that perhaps the development and progression of LVH was not clearly affected because the actual observed difference in hemoglobin level between the 2 groups was relatively small.

In an open-label, blinded end point, randomized, controlled trial designed to test early versus late anemia correction in predialysis patients, Levin et al[32] randomized 152 subjects with a mean GFR of approximately 30 mL/min and either a progressive decrease in hemoglobin level of at least

1.0 g/dL or greater within the previous year to a current hemoglobin level between 11.0 and 13.5 g/dL for men and 10.0 and 13.5 g/dL for women or, alternatively, a current hemoglobin level between 11.5 and 12.5 g/dL for men and 11.0 and 12.0 g/dL for women. The treatment arm received erythropoietin alfa to maintain hemoglobin levels in the target range of 12 to 14 g/dL. Subjects randomly assigned to the control arm did not receive additional treatment unless their hemoglobin level decreased to 9.0 g/dL or less, at which point erythropoietin alfa could be administered to maintain their hemoglobin levels between 9.0 and 10.5 g/dL. The mean hemoglobin level in the treatment group was between 12.6 and 13.0 g/dL, and in the control group it was between 11.5 and 11.7 g/dL for most of the study. The primary end point, the change in LVMI as assessed by serial echocardiography over a follow-up period of 2 years, was no different between treatment and control arms in this trial.

The hypothesis that a more preventive strategy with earlier treatment of anemia may be more successful not only in reducing LVH but cardiovascular events and mortality was tested most recently in the Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin β study. This randomized, open-label trial investigated the effect of early anemia correction on cardiovascular risk in approximately 600 CKD patients not yet on dialysis with mild to moderate anemia at baseline (hemoglobin level, 11-12.5 g/dL). The early treatment group began epoetin β therapy immediately, aiming for a target hemoglobin level of 13 to 15 g/dL. The late treatment group began therapy once the hemoglobin level decreased to less than 10.5 g/dL, aiming for a target hemoglobin level of 10.5 to 11.5 g/dL.[33] Primary outcomes of interest were the change in LVMI and time to first cardiovascular event. Similar to other recently published studies, preliminary reports have revealed that there was no difference in LVMI between treatment and control groups. An analysis of the cardiovascular event data is pending at this time.

At least 2 other randomized studies in the predialysis population are aimed at evaluating the effect of anemia treatment on cardiovascular morbidity and mortality. The Trial to Reduce Cardiovascular Events in Aranesp Therapy is a randomized, double-blind, placebo-controlled trial of approximately 3,800 type 2 diabetics with CKD in the predialysis stages with baseline hemoglobin levels of 11 g/dL or less. The primary outcome is time to development of the composite end point of cardiovascular mortality or nonfatal cardiovascular events including myocardial infarction, stroke, CHF requiring hospitalization, and coronary artery disease requiring revascularization.[34] This study is still in progress. The goal of the Correction of Hemoglobin and Outcomes In Renal Insufficiency trial was to determine whether normalization of the hematocrit level (13.5 g/dL in the treatment group versus 11.3 g/dL in the control group) in approximately 2,000 predialysis patients with a baseline hemoglobin level of 10.5 to 11 g/dL would have a beneficial effect on the composite end point of death, myocardial infarction, stroke, or CHF requiring hospitalization. This study recently was terminated early. Further details were unavailable at the time of this writing.

Conclusions and Future Directions

The relationship between hemoglobin level, cardiac disease, and CKD has been well described. The biological plausibility of the hypothesis that anemia contributes to cardiovascular disease in CKD is substantiated by both human and animal studies. The fact that no randomized controlled trials have been able to confirm a benefit of higher hemoglobin levels should lead nephrologists to examine new hypotheses. For example, the presence of anemia may be a powerful marker of inflammation, which in turn contributes to adverse cardiovascular and CKD outcomes. This may explain the associative data seen in observational studies, and the lack of effect in randomized controlled trials that focused on targeting a hemoglobin value and that tended to enroll relatively healthy patients. It may be that the focus should be on designing trials to differentiate the effect of erythropoietin replacement itself versus the effect of a higher hemoglobin level in patients at all stages of CKD, and understanding more clearly the relationship between anemia, inflammation, CKD, and CVD.

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