Anemia: A Modifiable Risk Factor for Heart Disease

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There is increasing recognition of the associations between blood hemoglobin (Hb) level, renal function, and cardiovascular disease. Anemia is associated with accelerated loss of renal function, left ventricular hypertrophy, cardiovascular morbidity, poor quality of life, and all-cause mortality. Anemia of chronic kidney disease (CKD) appears to act as a mortality multiplier. With every decrease in Hb below 12 g/dL, mortality increases in patients with CKD. Treatment of anemic patients with CKD using exogenous erythrocyte stimulating proteins has shown promise in reducing morbidity, particularly that of cardiovascular origin, and in improving survival and quality of life. Increasing

the Hb level from below 10 g/dL to 12 g/dL has resulted in favorable changes in left ventricular remodeling, improved ejection fraction, improved functional classification, and higher levels of peak oxygen consumption with exercise testing. Clinical trials are underway, testing the role of erythrocyte stimulating proteins on cardiovascular outcomes. This supplemental issue of *Reviews in Cardiovascular Medicine* will review the evidence base for anemia as a potential diagnostic and therapeutic target in patients with chronic kidney and heart disease.

Complex Pathophysiology of Anemia in Heart and Kidney Disease

The most commonly used definition of anemia is put forth by the World Health Organization and calls for an Hb level less than 13 g/dL in men and less than 12 g/dL in women. Approximately 9% of the general adult population meets the definition of anemia at these levels. In general, anemia is present in 30% and 60% of patients with heart failure and significant CKD, respectively. Hence, anemia is a common and easily identifiable potential diagnostic and therapeutic target.[1,2]

Anemia is one of the most characteristic and visible manifestations of CKD. It contributes to multiple adverse outcomes, in part due to decreased tissue oxygen delivery and utilization.[3] The cause of anemia in patients with CKD is multifactorial. Essentially, a relative deficiency of erythropoietin-α (EPO), an erythrocyte stimulating protein (ESP) normally produced by renal parenchymal cells in response to blood partial pressure of oxygen, is thought responsible. In patients with CKD and heart failure (HF), there appears to be a relative EPO deficiency with an inappropriately low EPO level for the measured blood Hb level. This relative deficiency of EPO may not only be related to anemia, but may play a role in impaired vascular repair, thus contributing indirectly to the progression of atherosclerosis. In addition, in the setting of CKD and HF, there are increased levels of tumor necrosis factor-α, interleukins 1 and 6, endothelin, matrix metalloproteinases, and other inflammation-related proteins, which are produced by the heart itself. These factors can work to directly reduce red cell production at the level of the bone marrow and further worsen the anemia.

Anemia as a Mortality Multiplier in Cardiorenal Disease

In patients with CKD, anemia is a straightforward multiplier of mortality. In a recent review, 28 of 29 large prospective studies of HF found anemia to be an independent predictor of mortality.[4] On average, among those patients with HF, for each 1 g/dL decrement in Hb, there is a 13% increase in risk for all-cause mortality.[3] In addition, those patients with anemia and CKD are more likely to progress to end-stage renal disease irrespective of their baseline level of renal function. That is, anemia is an independent contributor to the progression of CKD.[3]

The Impact of Worsening Anemia

Not only have baseline Hb levels been consistently found to be an important diagnostic and prognostic indicator, as discussed above; the relative change in blood Hb levels in cardiovascular disease (CVD) patients has also proved important. As Hb drops over time, there is a graded increase in HF hospitalizations and death. Conversely, those patients who have experienced a relative rise in Hb, whether due to improved nutrition, reduced neurohormonal factors, or other unknown factors, have enjoyed a significant reduction in the likelihood of adverse endpoints over the ensuing several years. In the RENAISSANCE Trial of patients with New York Heart Association class II to IV HF, those who experienced a spontaneous increase in Hb over time (not administered exogenous ESP) had a significant reduction in left ventricular mass index, suggesting a favorable change in left ventricular remodeling.[5] Observational data suggest that changes in Hb, either up or down, are associated with clinical consequences. Hence, there is a rationale for direct intervention targeting Hb level, in order to change the natural history of cardiorenal disease.

Anemia Correction With Erythrocyte Stimulating Proteins

Beyond their effect on Hb levels, the pleiotropic effects of ESPs include enhanced performance of the coronary endothelium, resulting in an increase in coronary flow reserve. This effect may be mediated through the activation of endothelial nitric oxide synthase via protein kinase B phosphorylation and prevention of endothelial cell apoptosis. These proteins may also have the potential for enhancing myocardial repair in patients with myocardial injury. By recruiting vascular progenitor cells which can become functional myocardial cells, thereby increasing the contractile function of the injured ventricle, ESPs could minimize the progression of left ventricular dysfunction. The molecular targets for ESPs include receptors expressed on cardiac myocytes, endothelial cells, and endothelial progenitor cells in addition to hematopoietic stem cells.

Treatment of anemia in patients with CKD with exogenous ESPs

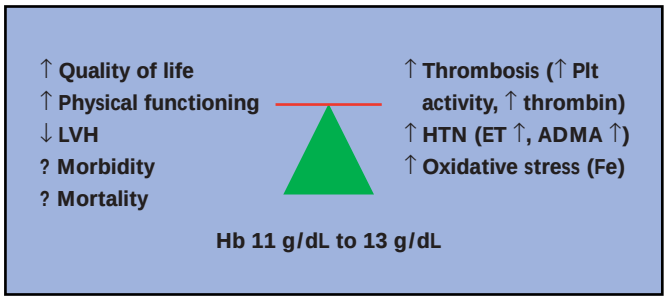

Figure 1. *Balance of potential risks and benefits of partial correction of anemia with erythrocyte-stimulating protein therapy in patients with combined heart and kidney disease. LVH, left ventricular hypertrophy; Hb, hemoglobin; Plt, platelet; HTN, hypertension; ET, endothelin; ADMA, asymmetric dimethylarginine; Fe, iron.*

(erythropoietin-α and darbepoetin alfa), has shown promise in reducing morbidity, particularly that of cardiovascular origin, and in improving survival and quality of life. Darbepoetin alfa is a genetically engineered form of EPO designed with an extended half-life, making once monthly injections an attractive and viable treatment option.[3] Increasing the Hb level from below 10 g/dL to 12 g/dL has been linked to favorable changes in left ventricular remodeling, improved ejection fraction, improved functional classification, and higher levels of peak oxygen consumption as measured by exercise testing. However there is a state of equipoise on this issue because treatment with EPO and supplemental iron, which is needed in approximately 70% of cases, has been associated with three problems: 1) increased platelet activity, thrombin generation, and resultant increased risk of thrombosis; 2) increased endothelin levels, increased asymmetric dimethylarginine, which theoretically reduces nitric oxide availability, and results in hypertension; and 3) worsened measures of oxidative stress. The largest and most definitive trial to date of ESPs in CVD is the Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT). TREAT is a multicenter, double-blind, placebo-controlled randomized trial specifically designed to determine whether patients with CKD (estimated glomerular filtration rate of 20-60 mL/min/1.73 m^2), type 2 diabetes, and anemia (Hb $<$ 11 g/dL) will experience a reduction in the risk of the composite endpoint of death or cardiovascular morbidity (nonfatal myocardial infarction, hospitalization for myocardial ischemia, HF, or stroke) when treated with darbepoetin alfa to raise Hb to 13 g/dL.[6]

Conclusion

The role of ESPs and endothelial progenitor cells in the repair of injury to endothelial cells, other components of blood vessels, and ventricular myocytes, represents the forefront of translational research. The more we study the impact of anemia on patients with CVD, the more we appreciate the potential role of ESPs as a CVD treatment. At the present time, we are in a state of equipoise regarding the partial correction of lowered Hb levels in patients with CKD and CVD and await large, prospective, randomized trials with definitive endpoints in this area. ■

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