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Professor Special Lecture: 157th Regular Meeting of the Medical Society of Toho University

Review Article

Cardio-Renal Anemia Iron Deficiency Syndrome

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ABSTRACT: It is theoretically reasonable to hypothesize that correcting of anemia could lead to better condition of the heart and prognosis in patients with chronic kidney disease (CKD) with/without cardiac disease. Unexpectedly, complete correction of anemia by erythropoietin stimulating agents (ESA) has not improved cardiovascular outcomes in patients with CKD. Iron is known to play a crucial role in oxygen transport as a component of hemoglobin and in cardiac and skeletal muscle metabolism as a component of oxidative enzymes. These physiological roles of iron led us to hypothesize that iron deficiency in itself may directly contribute to cardiac morphological and functional abnormalities independent of anemia. Recently, it is reported that a high prevalence of iron deficiency was seen at the initiation of dialysis and a marker of circulatory iron was inversely correlated with cardiothoracic ratio, as one of the surrogate markers of cardiac enlargement. These findings suggest that not only Hb but also circulatory iron may play an important role in promoting cardiac remodeling. The role of iron deficiency in patients with CKD, with or without anemia, therefore merits clinical awareness, and more insight into the pathophysiology and interplay between iron deficiency, anemia, and CKD is warranted, especially in patients with heart failure. Iron supplementation in the predialysis phase and dialysis phase of CKD may help prevent cardiac remodeling and would be a better outcome.

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KEYWORDS: iron deficiency, cardiac myocyte, TSAT, ferritin, heart failure

Introduction

Among patients with end-stage kidney disease (ESKD), cardiovascular disease (CVD) is a major concern. The Dialysis Outcomes and Practice Patterns Study has reported that patients with hemodialysis have a high prevalence of CVD in Europe, Japan, and the United States.[1] In spite of renal replacement therapy advances, CVD remains the leading cause of morbidity and mortality among patients with hemodialysis, with cardiac disease alone accounting for 30%-40% of deaths[2] and cardiovascular mortality 10-30 times greater than in the general population.[3] The mechanism of the cardio-renal syndrome (CRS) suggesting an interaction between chronic kidney disease (CKD) and CVD has been elucidated in considerable detail over the past decade. CRS type 4 is defined as primary CKD contributing to decrease cardiac function, cardiac hypertrophy, fibrosis, or increased risk of adverse cardiovascular events.[4] An understanding of the factors that cause CRS 4 in patients

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with both CKD and CVD is important for determining optimal therapeutic strategies for these patients. Anemia has been recognized as an important comorbidity in both CKD and CVD including congestive heart failure (CHF). A previous study has suggested that anemia, CHF, and CKD are interrelated, each causing the other to worsen.[5] This vicious cycle of disease progression is called the cardio-renal anemia syndrome (CRAS).[6]

Anemia in CKD

Renal anemia associated with declining kidney function is mainly due to inadequate renal production of erythropoietin in response to low hemoglobin levels, regardless of the etiology. Erythropoietin is predominantly produced by peritubular fibroblast cells in the kidney[7] and is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow. Loss of peritubular fibroblast cells leads to an inappropriately low level of circulating erythropoietin in the face of anemia. Other factors in the genesis of renal anemia include functional or absolute iron deficiency, blood loss, the presence of uremic inhibitors (for example, parathyroid hormone, inflammatory cytokines), reduced half-life of circulating blood cells, and deficiencies of folate or vitamin B_{12}.[8]

The Third National Health and Nutrition Examination Survey (NHANES III) evaluated the association between kidney function and hemoglobin levels across the range of kidney function among noninstitutionalized adults in the United States and reported that the prevalence of anemia (hemoglobin level below 12 g/dL in men and below 11 g/dL in women) increased from 1% at an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 to 9% at an eGFR of 30 mL/min/1.73 m^2 and to 33% at an eGFR of 15 mL/min/1.73 m^2 among men and to 67% at an eGFR of 15 mL/min/1.73 m^2 among women.[9] Anemia advances exponentially along with declining kidney function in patients with CKD, especially those with diabetes, and anemia develops more severely and requires a greater amount of erythropoietin stimulating agents (ESA) therapy before dialysis initiation in patients with ESKD.

Influence of Anemia on Cardiovascular Function

Anemia is a nontraditional cardiovascular risk factor that predisposes patients to the development and progression of heart structural and functional abnormalities as represented by cardiac hypertrophy, including left ventricular (LV) dilatation (i.e., eccentric LV hypertrophy) and hypertrophy (LVH) (i.e., concentric LV hypertrophy). The physiologic response to anemia and its influence on heart structure and function has been well described. The most important compensatory mechanisms caused by the reduced oxygen tension are the nonhemodynamic and hemodynamic responses. Nonhemodynamic responses aimed at increasing tissue oxygen delivery include increases in red blood cell 2,3-diphosphoglycerate levels and erythropoietin synthesis to stimulate red blood cell production.[10] Hemodynamic changes include increased preload, decreased peripheral vascular resistance, and increased output.[11] The initial hemodynamic response to anemia is a decrease in the vascular resistance, which causes a reduction of the systemic blood pressure. To maintain blood pressure, peripheral vasoconstriction, heart rate, and stroke volume are all increased through elevated sympathetic activity.[12,13] However, increased sympathetic activity also causes renal vasoconstriction and a resulting reduction in renal blood flow and GFR, leading to renal ischemia. The reduced renal blood flow is further aggravated by activation of the renin-angiotensin-aldosterone system, coupled with the release of antidiuretic hormone. All of this leads to salt and water retention, with a subsequent expansion in the extracellular plasma volume. Extracellular plasma expansion associated with vasodilation causes LV dilatation and increased cardiac output.

The Effect of Correcting Anemia in Patients with CKD

It is theoretically reasonable to hypothesize that correcting of anemia could lead to better condition of the heart and prognosis in patients with CKD with/without cardiac disease. To date, three four randomized trials were performed to test the complete correction of anemia by using ESAs to improve cardiovascular outcomes as compared with partial correction of anemia in patients with stage 3 or 4 CKD. Unexpectedly, all trials have shown the same finding that complete correction of anemia by ESAs has not improved cardiovascular outcomes in patients with CKD.[14)-17)] These results suggest that other than Hb level in itself, some other factors associated with anemia management may play a role in cardiac function and the onset of cardiovascular events.

Iron Deficiency and Heart Failure

Iron is known to play a crucial role in oxygen transport as a component of Hb, in oxygen storage as a component of myoglobin, and in cardiac and skeletal muscle metabolism as a component of oxidative enzymes.[18,19] These physiological roles of iron led us to hypothesize that iron deficiency in itself may directly contribute to cardiac morphological and functional abnormalities independent of anemia. Actually, a recent study revealed that among 546 patients with systolic dysfunction, iron deficiency was observed in 32% of patients with anemia and 57% of patients without anemia.[20] Moreover, the FERRIC-HF study[21] demonstrated that intravenous iron therapy for patients with heart failure improved exercise tolerance and symptoms. Interestingly, these benefits have been confirmed in nonanemic iron deficiency (ID) patients. Optimum management of iron status may thus be extremely beneficial for maintaining normal function and morphology of the heart in humans.

ID in Patients with CKD

Data from the National Health and Nutritional Examination Survey have demonstrated that with declining renal function, percentages of individuals with transferrin saturation (TSAT) $<$20% or ferritin $<$100 ng/dL increase in men and decrease in women.[22] Approximately 60% of men and 70% of women were showing TSAT $<$20% or ferritin $<$100 ng/dL at creatinine clearance rates below 15 mL/min.[22] Hamano et al. demonstrated that approximately 30% of Japanese patients on maintenance dialysis met the criteria of both TSAT $<$20% and ferritin $<$100 ng/dL in the Japanese renal data registry.[23] Although the prevalence of ID among patients with ESKD is speculated to be higher than that of the general population, whether a high prevalence of ID is linked to the high incidence and prevalence of cardiac disease in ESKD patients remains unclear. It is well known that higher prevalence of ID,[22] anemia,[24] and cardiac remodeling[25] are observed simultaneously in patients with CKD incident dialysis. ID might result in cardiac enlargement independent of anemia, which indicates cardiac remodeling in patients with CKD.

Cardio-Renal Anemia ID Syndrome

Recently, our group conducted a multicenter cross-sectional study by using 1974 patients with incident dialysis and reported four findings that 1) a high prevalence of ID that is defined as TSAT $<$20% and ferritin level $<$100 ng/dL was seen at the initiation of dialysis, 2) a marker of circulatory iron TSAT was inversely correlated with cardiothoracic ratio from chest X-ray, as one of the surrogate markers of cardiac enlargement, 3) ferritin showed no significant relationship with CTR, and 4) a significantly higher odds ratio for cardiac enlargement was observed in patients with TSAT $<$20% independent of Hb level.[26] These findings suggest that not only Hb but also circulatory iron may play an important role in promoting cardiac remodeling. This is in line with the results of previous study that ID, either alone or in combination with anemia, CKD, or both, is associated with increased mortality in patients with heart failure.[27] The authors in that study also emphasized that the term CRAS may underestimate the clinical and prognostic importance of ID in chronic heart failure patients. This concept is thought to be applicable to patients with CKD with or without cardiac disease because iron plays an important role in oxygen storage in myoglobin and oxygen metabolism in skeletal and cardiomyocyte. Even in patients without anemia, ID has been associated with decreased aerobic performance and exercise intolerance.[28] Moreover, structural abnormalities in cardiomyocytes have been reported.[29] Therefore, maintaining normal iron metabolism is crucial, especially for cells of high mitogenic potential such as hematopoietic cells or high energy demand such as cardiomyocytes. The role of ID in patients with CKD, with or without anemia, therefore merits clinical awareness, and more insight into the pathophysiology and interplay between ID, anemia, and CKD is warranted, especially in patients with heart failure.

Conclusion

Independent of the presence of anemia, deficiency of circulatory iron is closely correlated with cardiac remodeling in patients with CKD. Iron supplementation in the predialysis phase of CKD may help prevent cardiac remodeling regardless of the presence or absence of optimal Hb level in patients with CKD with ID and would be a better outcome.

Conflicts of interest: None declared.

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