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COMMENTARY

Novel insights into renovascular hypertension and cardio-renal protection by iron restriction

Atsushi Tanaka and Koichi Node

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Iron is one of the essential elements and has pivotal roles in biological systems. In particular, iron is needed for the growth and synthesis of hemoglobin; a shortage of iron is associated with the development of iron deficiency anemia. Because this pathological condition is associated closely with increased morbidity and mortality in patients with heart failure,[1] oral iron supplements are often administered to treat iron deficiency. A shortage of iron is therefore a more common focus in the clinical setting than excess of iron, which tends to be less recognized. Excess accumulation of iron can lead to increased production of reactive oxygen species (ROS) via Fenton/Haber–Weiss catalytic reactions, and it is therefore important to recognize the clinical importance of appropriate systemic iron balance. Because excess production of ROS may lead to cellular and organ damage,[2] it is likely that the pathogenesis of cardiovascular disease can be attenuated by iron restriction. This possibility is supported by the finding in apoE-knockout mice that an increased burden of iron deposition is associated with the progression of atherosclerosis.[3] Furthermore, the signal intensity of iron-based magnetic resonance imaging of the arterial wall has been shown to reflect the degree of systemic inflammation in younger women.[4]

Naito *et al.*[5] have actively investigated the pathological roles of iron in cardiovascular and renal diseases in several rodent models. In 2011, they first reported that dietary iron restriction (IR) in Dahl salt-sensitive rats fed with a high-salt diet attenuated the development of hypertension, heart failure and aortic remodeling by inhibiting oxidative stress. The authors subsequently demonstrated in a rat model of chronic kidney disease (CKD) that dietary IR prevented or rescued the development of hypertension and renal histopathological damage by inhibiting renal mineralocorticoid receptor (MR) signaling.[6,7] They also found that dietary IR attenuated renal injury in aldosterone/salt-induced hypertensive mice.[8] Because iron accumulation is related to dysfunction in various organs, including the kidney, liver and heart, the therapeutic effects of iron chelation by deferoxamine have been investigated.[9,10] More recently, Naito and coworkers[11] reported that iron chelation in a CKD rat model inhibited the development of renal interstitial fibrosis and reduced inflammatory biomarkers. These data indicate a potent therapeutic role for iron-targeted dietary and/or pharmacological interventions in cardiovascular and renal diseases.

As reported in the current issue, Oboshi and Naito *et al.*[12] further investigated the therapeutic effect of iron restriction on hypertension and renal damage in an established rat model of renovascular hypertension (RVHT) using the Goldblatt two-kidney one-clip (2K1C) method. The 2K1C rat develops hypertension and renal hypertrophy in association with tissue remodeling. In contrast, the 2K1C rat with dietary IR exhibits attenuation of hypertension at an early phase after the operation and vascular remodeling during the late phase. Although no structural differences were observed in the clipped kidney, the IR regimen suppressed compensatory hypertrophy and decreased superoxide production and urinary 8-OHdG levels in the unclipped kidney. Consistent with Naito and colleagues' previous reports, dietary IR attenuated renal MR signaling and fibrosis in the 2K1C rat. As expected, dietary IR caused severe anemia and a compensatory increase in serum erythropoietin (Epo) levels. Importantly, mild IR (a 30% iron-restricted diet) also attenuated hypertension, proteinuria and renal remodeling. These results are the first evidence that dietary IR can ameliorate RVHT in 2K1C rats.

RVHT is a common type of secondary hypertension that is associated closely with increased oxidative stress. Tanemoto *et al.*[13] reported that the prevalence of atherosclerotic renal artery stenosis (ARAS) was 21% in Japanese patients with risk factors for atherosclerosis, and patients with ARAS and CKD had a higher morbidity from coronary artery disease. Elevated systolic blood pressure and diabetes also contribute to the progression of ARAS.[14] Therefore, ARAS and atherosclerotic RVHT are linked closely to atherosclerotic risk factors and subsequent diseases in the kidney and other systemic organs, followed by increased morbidity and mortality. Because there is no incremental benefit of adding renal-artery stenting to high-quality medications in patients with ARAS,[15] novel medical approaches against local and systemic pathophysiology are required to improve the prognosis of these patients. As Naito and colleagues show in the current issue, dietary IR has effectively attenuated the development of hypertension and renal damage in several rodent models. The next step will therefore be application of this treatment in humans. However, we wonder if the progression of iron deficiency anemia caused by IR may have unfavorable effects on patients' quality of life and/or pathological conditions. However, the authors demonstrated successfully that mild IR may also attenuate phenotypes with slightly decreased levels of hemoglobin.

A Tanaka and K Node are at Department of Cardiovascular Medicine, Saga University, Saga, Japan
E-mail: node@cc.saga-u.ac.jp

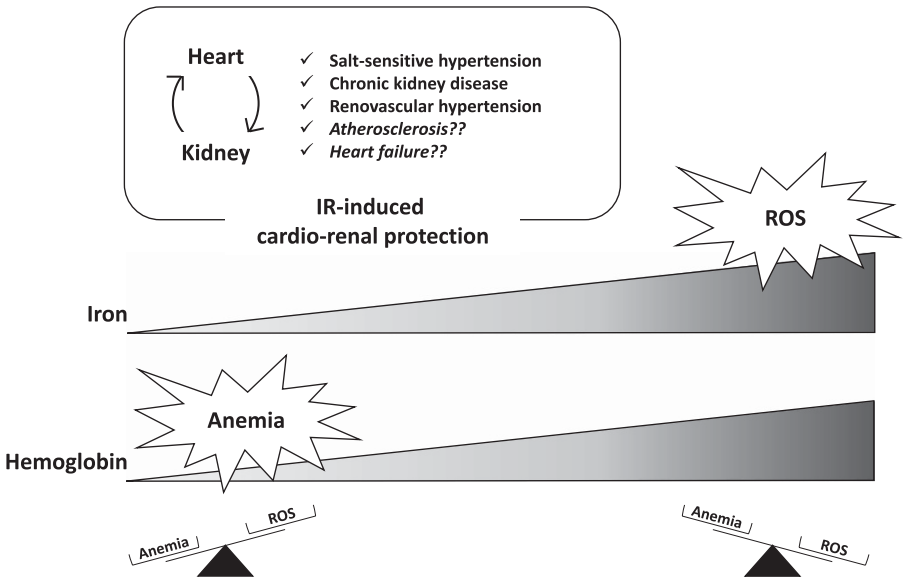

Figure 1 Possible cardio-renal protective effects are induced by dietary iron restriction (IR) through a reduction in oxidative stress in some rodent models, including those with renovascular hypertension. Importantly, an appropriate iron balance in the body is an important issue in cardio-renal association.

Heart failure is often complicated by anemia, which is generally recognized as an exacerbating factor for the condition. Although anemia in patients with heart failure is not necessarily caused by iron deficiency, a lack of iron may adversely affect clinical outcomes in these patients.[1] Several randomized placebo-controlled clinical trials have demonstrated clearly that intravenous iron therapy improves clinical symptoms in patients with heart failure and iron deficiency.[16,17] Naito *et al.*[18] reported previously that the Epo-cardiac Epo receptor signaling axis is involved in the mechanism of cardiac remodeling, with an anti-apoptotic effect observed following chronic iron deficiency. In addition to iron levels, Epo treatment also improves cardiac function, cardiac remodeling, and clinical symptoms in patients with chronic heart failure and anemia.[19,20] However, the higher levels of hemoglobin caused by Epo treatment do not reduce the risk of cardiovascular events in patients with CKD.[21,22] Of note, a trial group with high hemoglobin levels showed an unexpected increase in the risk of death, hospitalization for congestive heart failure and renal replacement therapy.[22]

Given the possible increase in ROS production caused by excessive iron accumulation, the current evidence indicates that the correction of anemia via excessive iron or Epo treatment may not always lead to a reduction in morbidity and mortality, but instead result in worse outcomes for patients with a high risk of cardiovascular events such as those with CKD. Although the precise mechanisms of this adverse effect have yet to be elucidated in humans, excessive iron accumulation and exaggerated Epo signaling are important issues to avoid in certain clinical settings. Importantly, the establishment of appropriate iron and/or Epo signaling levels is clinically required to prevent the development of severe anemia. In addition, the emerging role of dietary IR in cardio-renal association in humans, as proposed by Naito *et al.*,[12] suggests its potential as an effective treatment with cardio-renal protective action (Figure 1).

CONFLICT OF INTEREST

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