J Korean Med Sci. 2020 Jan 6;35(1):e20
https://doi.org/10.3346/jkms.2020.35.e20
eISSN 1598-6357·pISSN 1011-8934

JKMS

Editorial

Hepcidin as a Biomarker of Cardiorenal Syndrome

Gheun-Ho Kim

Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea

▸ See the article "Relationship between cardiac geometry and serum hepcidin in chronic kidney disease: analysis from the KNOW-CKD Study" in volume 35, number 1, e2.

Received: Dec 7, 2019
Accepted: Dec 23, 2019

Address for Correspondence:
Gheun-Ho Kim, MD, PhD
Department of Internal Medicine, Hanyang University College of Medicine, 222-1 Wansimni-ro, Seongdong-gu, Seoul 04763, Korea.
E-mail: kimgh@hanyang.ac.kr

ORCID iD
Gheun-Ho Kim
https://orcid.org/0000-0002-8445-9892

Disclosure
The author has no potential conflicts of interest to disclose.

Anemia is frequently accompanied with advanced chronic kidney disease (CKD), and its prevalence was reported to be 45% among 2,198 non-dialysis CKD patients from stage 1 to 5 in Korea.[1] Treatment of anemia is very important in CKD because anemia itself can cause high-output heart failure and lead to cardiovascular mortality. Thus, anemia may be the common denominator in progression of cardiorenal syndrome. The importance of managing cardiorenal syndrome is recently reemerging because CKD and heart failure are frequently associated and influence each other in a vicious cycle of comorbidity that increases the risk of mortality.

In current practices, correction of anemia became feasible in CKD patients because of introducing erythropoiesis-stimulating agents (ESAs). Although erythropoietin deficiency is the major cause of renal anemia, a certain proportion of CKD patients are hyporesponsive to ESA treatment. This is called ESA resistance, and CKD patients with ESA resistance have a poorer prognosis than those without ESA-resistant renal anemia.[2]

Different causes of ESA resistance were proposed, among which iron deficiency is the first one to be considered. However, other causes may be difficult to be eliminated because chronic or systemic inflammation mainly underlies the mechanism of ESA resistance. Anemia of chronic disease including renal anemia is currently known as anemia of inflammation. Furthermore, congestive heart failure as well as CKD may be the condition of systemic inflammation and immune activation, in which overproduction of cytokines such as interleukin-1β, tumor necrosis factor-α (TNF-α), and interleukin-6 by macrophages and interferon-γ by lymphocytes may blunt erythropoietin production, impair the erythropoiesis response, and increase hepcidin levels.[3]

Hepcidin, a 25-amino-acid peptide hormone, is predominantly synthesized in the liver. It binds to the cellular iron exporter ferroportin, which mediates all the major flows of iron into plasma and extracellular fluid.[4] Thus, plasma iron falls when the hepcidin level is increased because of iron trapping within duodenal enterocytes, splenic and hepatic macrophages, and hepatocytes. This typically occurs in systemic inflammation and leads to anemia due to iron underutilization. Hepcidin production is transcriptionally regulated by plasma iron concentration, iron stores in the liver, erythropoietic activity, and inflammation. In CKD,

inflammation and impaired renal clearance increase plasma hepcidin, inhibiting duodenal iron absorption and sequestering iron in macrophages. Hepcidin inhibition should be the reasonable option to treat renal anemia because abnormal upregulation of hepcidin is an important cause of ESA resistance in CKD.

In this issue of Journal, Min et al,[5] reported that the serum hepcidin level was independently associated with cardiac geometry in CKD patients. In particular, the increased relative wall thickness (RWT) measured in echocardiography could represent hepcidin upregulation. This result may offer an explanation why we more frequently encounter ESA resistance in CKD patients with heart failure than in those without. RWT may be an important prognostic factor in patients with diastolic heart failure.

Left ventricular mass (LVM) is the other important parameter of left ventricular geometry. Four types of left ventricular geometry are grouped based on RWT and LVM: normal geometry, concentric remodeling, eccentric left ventricular hypertrophy, and concentric left ventricular hypertrophy. The present study showed that both RWT and LVM were associated with the serum hepcidin level.[5] According to multivariate analysis results, however, RWT only was independently associated with hepcidin upregulation. Interestingly, this association was independent of inflammatory markers such as C-reactive protein concentration and white blood cell count.

The authors interpreted their results from the liver-heart link. They postulated that the congested liver induced by diastolic heart failure might enhance hepatic production of hepcidin. However, they showed no association between hepcidin and E/e′, a reliable echocardiographic parameter of diastolic dysfunction.

Circulating (systemic) hepcidin is mainly derived from liver, and its serum level is correlated with hepcidin expression in liver. Besides, local hepcidin was known to be synthesized in organs including heart. The role of local hepcidin may be independent of iron metabolism because cardiac hepcidin expression but not ferritin staining was increased in rats with coronary artery ligation. Interestingly, similar results were obtained from rats with subtotal nephrectomy.[6] The latter finding suggests a role of cardiac hepcidin in renocardiac failure. Whether cardiac expression of hepcidin is connected to the serum level needs to be verified in clinical studies. Hepcidin inhibitors can be promising therapeutic agents to correct anemia in cardiorenal syndrome.

REFERENCES

1. Ryu SR, Park SK, Jung JY, Kim YH, Oh YK, Yoo TH, et al. The prevalence and management of anemia in chronic kidney disease patients: result from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). *J Korean Med Sci* 2017;32(2):249-56.
PUBMED | CROSSREF
2. Biggar P, Kim GH. Treatment of renal anemia: erythropoiesis stimulating agents and beyond. *Kidney Res Clin Pract* 2017;36(3):209-23.
PUBMED | CROSSREF
3. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. *Blood* 2019;133(1):40-50.
PUBMED | CROSSREF
4. Ganz T, Nemeth E. Iron balance and the role of hepcidin in chronic kidney disease. *Semin Nephrol* 2016;36(2):87-93.
PUBMED | CROSSREF

5. Min HK, Oh YK, Choi KH, Lee KB, Park SK, Ahn C, et al. Relationship between cardiac geometry and serum hepcidin in chronic kidney disease: analysis from the KNOW-CKD Study. *J Korean Med Sci* 2020;35(1):e2.
CROSSREF
6. van Breda GF, Bongartz LG, Zhuang W, van Swelm RP, Pertijs J, Braam B, et al. Cardiac hepcidin expression associates with injury independent of iron. *Am J Nephrol* 2016;44(5):368-78.
PUBMED | CROSSREF