ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

CAROTID ATHEROSCLEROSIS AND HEPCIDIN IN CHRONIC KIDNEY DISEASE PATIENTS

Osama Nady Mohamed Abd El-Azeem*; Ahmed Mohamed saad El-Deen Salama*; Fatma El-Zahraa Sayed Bukhary*; Asmaa Kasem Ahmed*; Emad Allam abd El-Naem**

*Internal Medicine Department, Faculty of Medicine, Minia University, Egypt

**Clinical Pathology Department, Faculty of Medicine, Minia University, Egypt

Corresponding Author

Osama Nady Mohamed Abd El-Azeem

osama.nady@mu.edu.eg

+20 109 292 9597

1 Hepcidin

1.1 Structure

In 2001, the hepcidin was identified and termed a peptide with anti-microbial effects [(1)]. It consists of 84 amino acids and is known as preprohepcidin. The peptide is subsequently split together to generate a 60-amino-acid protein called prohepcidin and then processed to make a 25-amino-acid protein called hepcidin. Prohepcidine's last conversion to hepcidin is catalyzed by furin [(2)]. The 25 amino acid peptides are the main form of human urine, despite the shorter peptides of 20 and 22 amino acids [(3)].

1.2 Synthesis

Systemic hepcidin can largely be found in the liver and can also be found in the renal tubules, the heart, the retina, fat, lungs and brains, stomach and pancreas. In unique biological liquors such as the bile, the ascetic, the pleural fluid and the cerebral fluid, hepcidin was also found [(3)]. The bioactive type is hepcidin-25, a 25 amino acid peptide with a molecular weight of 2.8 kD. Hepcidin-20, -22, and -24 are hepcidin isoforms with no biological relevance [(4)]. The production of hepatic hepcidin is boosted by high availability of iron and inflammation of the body. It is blocked by low flowing iron, erythropoiesis and hypoxia [(5)].

1.3 Kinetics

Hepcidin-25 either circulates freely or is bound to a minimum of α 2-macroglobulin, and albumin. The amount of hepcidin bound to protein is uncertain and the free circulating fracture varies between 11 to 98% [(6)]. Protein-connected hepcidin may be biologically more active than hepcidin unbound [(7)]. However, the fact that hepcidin clearance bound by protein is reduced, hence leading to an improved half-life and activity can be elucidated. Hepcidin is removed from its action and urine excretion sites by cellular breakdown. In healthy persons, hepcidin fractional excretion is low (not beyond 3 to 5 percent) [(8)], implied that hepcidin under normal conditions is either reabsorbed nearly fully in the renal tubule and depleted in the renal tubule (due to its protein-bound character) [(9)].

1.4 Function

In the duodenum and upper jejunum, dietary iron is absorbed. Ferroportin (FPN) transporter of iron mediates the systemic circulation of cellular iron efflux at the enterocytes basolateral location. FPN is an efflux transmembrane channel that carries cellular iron to the plasma. In cells regulating plasma iron levels, such as duodenal enterocytes, hepatocytes, is found in abundance. A crucial FPN regulator is Hepcidin, the peptide hormone. It binds to FPN on cells exporting iron, including hepatocytes, macrophages and enterocytes. Binding hepcidin to ferroportin results in ferroportin endocytosis and lysosomal breakdown, reduced plasma iron supply and reduced iron availability for erythropoiesis [(10)].

2 Chronic kidney disease (CKD)

CKD, which has been established for at least three months and has health repercussions, is described as defecting the structure or function of the kidney [(11)]. Recurrent inflammation and high inflammatory markers are characteristic of CKD. A positive phase reactant, highly sensitive C-reactive protein (hs-CRP), predicts inflammation and is associated with cardiovascular mortality in individuals with renal insufficiency. Highly sensitive C-reactive protein (hs-CRP) and high serum hepcidin levels in individuals with CKD reflect an inflammatory condition associated with progressive renal failure, loss of renal function, and development of chronic disease anemia. The inflammatory mediator hs-CRP is higher in people with CKD. CKD is chronically inflamed by chronic disequilibrium between the variables prooxidant and antioxidant. Oxidative stress, which causes reduced insulin internalization and an increased ferritin production, results in resistance to insulin [(12)].

2.1 Anemia in CKD

Anemia has been considered one of the most frequent concomitants for CKD, and is produced by many reasons such decreasing the production of endogenous erythropoietin in the kidney, decreasing the

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

survival of erythrocytes and dietary shortcomings (folate and vitamin B12). In patients with CKD with a main therapy that involved regular blood transfusions, recombinant human erythropoietin (rHuEpo) developed treatment for anemia that resulted in secondary iron overload. While rHuEpo protects patients from blood transfusions and minimises the risk of iron excess, it does also play an important role in the anemia of CKD patients. Although it carries oxygen, it is also able to harm cells via free radicals, and systemic iron must thus be maintained under control. Iron is recycled and transferred by the reticuloendothelial system (RES) to bone marrow (BM) in healthy humans from senescent erythrocytes where it is mixed with erythroblasts. Normal iron homeostasis is maintained by offsetting daily loss by duodenal dietary iron absorption. Due to increased blood loss and possible deficiencies in gastrointestinal absorption and notably in dialysis-dependent CKD patients, total body iron levels in CKD patients are likely to become depleted, causing a deficit of iron. Furthermore, many CKD patients exhibit iron functional deficiencies due to reticuloendothelial iron blockages, which are described as being unable to produce adequate iron for erythroblast formation in spite of suitable storage. The complex character of the disease makes it challenging to quantify the iron status in CKD patients. Ferritin is the major iron storage protein whose intracellular iron concentration controls production [(13)].

Hepcidin anemias may be classed as low and high hepcidin anemias. High hepcidin concentrations only cause anemia of the iron deficit, limiting iron uptake and lowering the supply of iron to erythropoiesis. Ineffective erythropoiesis characterizes the so-called anemias marked by low hepcidin levels and iron excess [(14)]. Two rare, inherited illnesses (iron-refractory iron deficiency and hepcidin-generating adenomas in an inborn error of glucose metabolism) and a common condition have been shown to have high hepcidin anemias (anemia of inflammation) [(15)]. The "iron-loading anemia" is characterized by ineffective erythropoiesis and low or unsuitable normal hepcidin concentrations which causes iron overload. The prototype is β-thalassemia, a recessive genetic disease that results in anemia and excessive α-globin chain formation caused by mutations in the β-globin gene. Last formed hemichroms in the bone marrow, resulting in ineffective erythropoiesis and damage maturating erythroid precursors [(14)].

2.2 Hepcidin in CKD

In non-dialysis patients and dialysis patients, Serum levels of hepcidin-25 are increased, potentially due to increased synthesis or decreased clearance (caused by increasing body iron and inflammatory levels). Both hemodialysis and peritoneal dialysis removes hepcidin from the blood. Hepcidin was found in the ultrafiltrate and linked to a dialyser membrane following a hemodialysis session [(16)].

3 Atherosclerosis in CKD

CKD patients have an increased risk, mainly due to cardiovascular reason, for premature mortality. More than 40 years ago, CKD's relationship with hemodialysis was discovered with speeded atherosclerosis. However, it has been postulated recently that the increased risk of atherosclerosis in the early stages of CKD arises [(17)]. The main contributors to CV death in elderly CKD patients seem to be traditional risk factors for atherosclerosis. Traditional and new risk factors are equally essential at CKD stage 4 according to the Community Data for the Risk of Atherosclerosis (ARIC) and new risk factors in dialysis patients are significantly more prevalent than those in the general population. Age, smoking, DM and hypertension (HTN), dyslipidemia and resistance to insulin are traditional risk factors. Oxidative stress, inflammation, intestinal dysbiosis, endothelial dysfunction, subsequent hyperparathyroidism, advanced glycation products, and vascular calcification are non-traditional new risk factors [(18)]. Dyslipidemia is frequent in CKD patients and has a significantly atherogenic profile with low levels of HDL cholesterol and high levels of triglyceride, oxidized LDL [(19)].

Iron release from macrophages can be blocked predominantly in the liver by systemic hepcidin. Hepcidin causes FPN to breakdown and increases macrophage intracellular iron. An increased oxidized LDL cholesterol input, enhanced inflammatory signaling, decreased cholesterol efflux and intracellular reactive oxygen species (ROS) formation might lead to intracellular iron buildup. These cells usually exhibit a characteristic of pro-inflammatory foamy macrophage. In these settings, macrophages play a part in the development of atherosclerosis [(10)].

1. Park CH, Valore EV, Waring AJ, Ganz T. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. Journal of biological chemistry. 2001;276(11):7806-10.
2. Litwack G. Human biochemistry: Academic Press; 2017.
3. Daher R, Lefebvre T, Puy H, Karim Z. Extrahepatic hepcidin production: The intriguing outcomes of recent years. World journal of clinical cases. 2019;7(15):1926.

4. Laarakkers CM, Wiegerinck ET, Klaver S, Kolodziejczyk M, Gille H, Hohlbaum AM, et al. Improved mass spectrometry assay for plasma hepcidin: detection and characterization of a novel hepcidin isoform. PloS one. 2013;8(10):e75518.
5. El Gendy FM, EL-Hawy MA, El Shennawy NK. Role of hepcidin in iron metabolism and pathophysiology of different types of anemia. Menoufia Medical Journal. 2019;32(3):818.
6. Antunes SA, Canziani MEF. Hepcidin: an important iron metabolism regulator in chronic kidney disease. Brazilian Journal of Nephrology. 2016;38(3):351-5.
7. Huang ML-H, Austin CJ, Sari M-A, Rahmanto YS, Ponka P, Vyoral D, et al. Hepcidin bound to α2-macroglobulin reduces ferroportin-1 expression and enhances its activity at reducing serum iron levels. Journal of Biological Chemistry. 2013;288(35):25450-65.
8. Ganz T, Olbina G, Girelli D, Nemeth E, Westerman M. Immunoassay for human serum hepcidin. Blood. 2008;112(10):4292-7.
9. Peters HP, Laarakkers CM, Pickkers P, Masereeuw R, Boerman OC, Eek A, et al. Tubular reabsorption and local production of urine hepcidin-25. BMC nephrology. 2013;14(1):70.
10. Cornelissen A, Guo L, Sakamoto A, Virmani R, Finn AV. New insights into the role of iron in inflammation and atherosclerosis. EBioMedicine. 2019;47:598-606.
11. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, et al. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney international supplements. 2013;3(1):1-150.
12. Roy JE, Shanthi B, Selvi VK. Serum Hepcidin as an Inflammatory Marker in Chronic Kidney Disease. Journal of Pharmaceutical Research International. 2020:40-5.
13. Gaweda AE. Markers of iron status in chronic kidney disease. Hemodialysis International. 2017;21:S21-S7.
14. Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. British journal of haematology. 2016;172(4):512-23.
15. Finberg KE, Heeney MM, Campagna DR, Aydınok Y, Pearson HA, Hartman KR, et al. Mutations in TMPRSS6 cause iron-refractory iron deficiency anemia (IRIDA). Nature genetics. 2008;40(5):569.
16. Peters HP, Laarakkers CM, Swinkels DW, Wetzels JF. Serum hepcidin-25 levels in patients with chronic kidney disease are independent of glomerular filtration rate. Nephrology Dialysis Transplantation. 2010;25(3):848-53.
17. Valdivielso JM, Rodríguez-Puyol D, Pascual J, Barrios C, Bermúdez-López M, Sánchez-Niño MD, et al. Atherosclerosis in chronic kidney disease: more, less, or just different? Arteriosclerosis, thrombosis, and vascular biology. 2019;39(10):1938-66.
18. Johnson JFJFMTRJ. comprehensive clinical nephrology. 2019;3:903-58.
19. Rampanelli E, Ochodnicky P, Vissers JP, Butter LM, Claessen N, Calcagni A, et al. Excessive dietary lipid intake provokes an acquired form of lysosomal lipid storage disease in the kidney. The Journal of pathology. 2018;246(4):470-84.