REVIEW ARTICLE

NOVEL IRON BIOMARKERS IN CHRONIC KIDNEY DISEASE

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ABSTRACT

CKD is one of the fastest growing causes of death in the world and in 2040, it is estimated that it will be in the top five causes of death. In order to slow down this process, it is necessary to improve prevention, inhibit development and treat complications including anemia. Anemia is one of the common complication of chronic kidney disease (CKD), which is a significant clinical problem. It is most often the result of decreased renal production of erythropoietin and / or iron deficiency. Iron deficiency anemia is one of the most common problems in CKD that increases mortality. In order to successfully treat anemia in CKD with erythropoiesis-stimulating agentsand (ESA) and iron substitution, it is necessary to determine iron iron level. The diagnosis of iron deficiency anemia in patients with CKD is complicated due to the relatively low predictive ability of routine serum iron markers (e.g., ferritin and transferrin saturation) and more invasive measurements such as bone marrow iron stores. In the review novel biomarkers of iron metabolism are discussed such as hypoxia-inducible factor, erythroferon, growth differentiation factor 15 etc. with their possible clinical relevance.

KEY WORDS: biomarkers, chronic kidney disease, iron, anemia

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INTRODUCTION

CKD is one of the fastest growing causes of death in the world and in 2040, it is estimated that it will be in the top five causes of death [1]. In order to slow down this process, it is necessary to improve prevention, inhibit development and treat complications including anemia. Iron deficiency anemia is one of the most common problems in CKD that increases mortality. Iron deficiency (ID) is common in CKD and affects 30-45% of patients, and plays a significant role in the development of anemia [2, 3]. In CKD iron deficiency may be multifactorial and result from increased blood loss, impaired iron absorption from the gastrointestinal tract, and iron retention in the reticulo-endothelial system. Iron deficiency in CKD can take the form of absolute or functional deficiency. Absolute iron deficiency occurs in the absence of iron stores in the body, while functional iron deficiency is characterized by insufficient iron availability to ensure normal erythropoiesis with normal or increased iron in the body [4]. Determining the optimal iron level for normal erythropoiesis is important in avoiding the adverse consequences of anemia and, on the other hand, it prevents iron overload. Iron homeostasis in the body is regulated mainly at the level of iron absorption by enterocytes and recycling from erythrocytes. The most accessible indicators used in the diagnosis of iron deficiency anemia (IDA) are the concentration of ferritin and transferrin saturation (TSAT). The laboratory criteria used to diagnose deficiency are different in CKD compared to normal renal function. In CKD, absolute iron deficiency is found at TSAT concentration ≤20% and ferritin concentration ≤100 ng / mL in non-dialysed and peritoneally dialysed patients, while in hemodialysed patients ≤200 ng / mL. With normal renal function, iron deficiency anemia is diagnosed at serum ferritin <30 ng / mL. Functional iron deficiency is usually characterized by TSAT ≤20% and an increased concentration of ferritin (even up to 800 ng / mL). However, both of these parameters depend on the presence of inflammation, which makes diagnosis difficult and causes the ID not to be detected. Bone marrow aspiration biopsy is still the best method to diagnose IDA in CKD, but due to its invasiveness, it is not used as a standard in everyday practice. For this reason, non-invasive and effective methods in the diagnosis of iron status are needed. Standard parameters used to assess iron resources in CKD are not sensitive enough, therefore many studies have assessed new diagnostic parameters of iron status in CKD (5-9). In CKD patients, iron deficiency was identified by only 17% of patients using TSAT and ferritin, while 50% of patients with bone marrow biopsy were iron deficient [3].

THE AIM

In order to successfully treat anemia in CKD with erythropoiesis-stimulating agents and (ESA) and iron substitution, it is necessary to determine iron level. The diagnosis of iron deficiency anemia in patients with CKD is complicated due to the relatively low predictive ability of routine serum iron markers (e.g., ferritin and transferrin saturation) and more invasive measurements such as bone marrow iron stores. The aim of the paper is to review novel biomarkers of iron

metabolism such as hypoxia-inducible factor, erythroferon, growth differentiation factor 15 etc. with their possible clinical relevance.

REVIEW AND DISCUSSION

HEPCIDIN

Hepcidin is considered the main regulator of iron metabolism. It is a 25-amino acid peptide mainly produced in the liver [10]. Hepcidin, after combining with ferroportin, causes its ubiquitization and degradation [11]. Reducing the presence of ferroportin on cell membranes reduces the absorption of iron by enterocytes and the outflow of iron from macrophages and hepatocytes, which are iron stores. Hepcidin synthesis is regulated by iron stores, hypoxia, inflammation and erythropoiesis. Hepcidin is a small peptide that is filtered and destroyed by the kidneys. In patients with CKD, elevated hepcidin levels are frequently observed and negatively correlated with the glomerular filtration rate (GFR) [12, 13]. The higher concentration of hepcidin in CKD is attributed to the presence of inflammation, decreased hepcidin filtration by the kidneys and decreased concentration of erythropoietin [14-16]. The effect is to reduce the absorption of iron in the gut and its release from iron stores, which contributes to the development of functional iron deficiency and anemia. Inflammation in CKD interferes with the interpretation of most iron hemostasis biomarkers, including ferritin and hepcidin.

ERYTHROFERON

Erythroferon (ERFE) was discovered in 2014 as an erythroid regulator of iron metabolism, inhibiting hepcidin suppression in conditions of increased erythropoiesis [17]. ERFE is released from erythroblast precursors in the marrow and spleen under the influence of erythropoietin. It reduces the production of hepcidin, resulting in increased availability of iron for hemoglobin synthesis [17]. The pathological effect of ERFE contributes to iron overload in anemia with ineffective erythropoiesis such as b-thalassemia [18]. Patients with CKD who have a relative increase in EPO levels or who are treated with EPO have increased levels of ERFE. ERFE levels and activity are not well characterized in patients with CKD. Information on ERFE in the CKD is limited. Several studies have confirmed a positive correlation between serum ERFE concentration and EPO concentration and ESA dose, but no clear correlation between ERFE and biomarkers of iron metabolism has been demonstrated [19-21]. Honda et al. In a study of hemodialysis (HD) patients treated with long-acting ESA found a statistically significant negative correlation between ERFE and the level of hepcidin and ferritin, while the correlation was positive with the soluble transferrin receptor. This study may suggest that ERFE may be an important regulator of iron release from body stores during ESA-stimulated erythropoiesis and may be helpful in monitoring iron metabolism in patients with CKD [20]. However, no correlation of ERFE with hepcidin in CKD in the Hanudel et al. the study may indicate masking or weakening the influence of ERFE on hepcidin by inflammation, uremic environment and decreased hepcidin clearance [19].

HYPOXIA-INDUCED FACTOR

Hypoxia-induced factor (HIF) is a transcription factor involved in the regulation of erythropoiesis and iron metabolism [22-25]. HIF activity is oxygen-dependent and plays a key role in adapting cells to hypoxia. HIF consists of an oxygen-sensitive α subunit (HIF-1α, HIF-2α or HIF-3α) and a stable β subunit. Under normoxemia, the HIF1 -1α protein is hydroxylated by propylhydroxylase (PDH) and then degraded. In hypoxia, the degradation of HIF1 is inhibited, which leads to its accumulation and translocation to the cell nucleus, where it activates genes involved in iron metabolism, including EPO. HIF also lowers hepcidin levels by stimulating erythropoiesis [26]. PDH inhibitors lead to increased EPO production, increased iron availability and its uptake from the gastrointestinal tract. It was found that PDH inhibitors increase hemoglobin concentration and lower hepcidin concentration in patients with CKD [27].

SOLUBLE TRANSFERRIN RECEPTOR

The transferrin receptor (TfR) is a membrane protein by which transferrin transports iron into the cell. Iron bound to transferrin is internalized by endosomes upon binding to TfR present on the plasma membrane. TfR synthesis is regulated mainly by the body's iron requirements and the interaction of erythropoietin (EPO) with its surface receptors on erythroid cells. Transferrin receptors are released into the blood in the form of a truncated soluble transferrin receptor (sTfR). Blood concentration (sTfR) is decreased in erythroid hypoplasia and aplastic anemia and increases in severe erythropoiesis and iron deficiency anemia. In the case of erythropoiesis limited by iron deficiency, the release of sTfR from the surface of the erythroblasts increases, causing an increase in sTfR in the blood. The concentration of sTfR in the blood is a useful marker in the diagnosis of anemia and in monitoring the erythropoietic response during the treatment of anemia (28). In dialysis patients undergoing treatment with ESAs, sTfR has been found to be a promising marker for bone marrow erythropoietic activity and iron status [29, 30]. Also, several studies in patients with anemia and CKD have suggested better efficacy of sTfR in assessing iron status [30, 32]. Clinical studies have confirmed the value of sTfR in the diagnosis of ID and in the differentiation of IDA from anemia of chronic diseases (ACD) [32-35]. The concentration of sTfR in the blood is not dependent on inflammation and is therefore a clinically better indicator of the status of iron in inflammation [36]. In the study of dialysis patients, it was found that sTfR does not detect functional iron deficiency, and positively correlates with hematological parameters under

the conditions of EPO administration [29, 37]. Since there is an increase in erythroblast weight and sTfR during ESA therapy, it is not entirely known whether the increased sTfR suggests iron deficiency anemia or a response to ESA.

GROWTH AND DIFFERENTIATION FACTOR 15

Growth and Differentiation Factor 15 (GDF-15) also called macrophage inhibitory cytokine (MIC) -1 Belongs to the superfamily growth factor-β (TGF-β) and has anti-inflammatory effects. The concentration of GDF-15 increases in response to ineffective erythropoiesis, inflammation, acute trauma, and cancer [38]. It is one of the regulators of hepcidin synthesis and thus participates in iron homeostasis [39]. It has been shown that high concentration of GDF-15 is responsible for the reduced synthesis of hepcidin [40]. Significantly increased levels of GDF-15 have been found in CKD patients with iron deficiency anemia. Nalado et al. found that found GDF-15 levels to be significantly higher in CKD patients with IDA as compared to CKD patients without IDA [43] as shown in other studies [41, 42]. Li et al. showed an increase in the concentration of gdf-15 in dialysis patients, but they did not find a correlation between gdf-15 and iron indices [44]. Elevated levels of GDF -15 in IDA patients may be due to negative feedback loop inhibition of hepcidin synthesis. Also, iron deficiency itself can induce GDF-15 in the erythroid precursor cells as a result of iron sequestration in macrophages [45]. Another study reported that GDF-15hy levels were significantly higher in elderly patients with CKD and in patients with anemia, and only in the population over 65 years of age, GDF-15 was negatively correlated with iron levels, and GDF-15 was associated with renal function and hemoglobin [46].

CONCLUSIONS

Iron is the fourth most common element in the Earth's crust and the most abundant transition redox-active metal in our body [47]. systemic iron balance needs to be tightly regulated by the pathways that supply, utilize, recycle, and store iron thus specialized transport system and membrane carriers have evolved in humans to maintain iron in a soluble state that is suitable for circulation into the blood and transfer across cell membranes [48]. The diagnosis of iron deficiency anemia in patients with CKD is complicated due to the relatively low predictive ability of routine serum iron markers (e.g., ferritin and transferrin saturation) and more invasive measurements such as bone marrow iron stores. There are new biomarkers on the horizon, however, studies on their prognostic values, validity and clinical relevance are limited. Thus we have to rely in the old markers such as ferritin and transferrin saturation with hope for new biomarkers to come into clinical practice in the future.

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The Authors declare no conflict of interest.

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