Diagnosis of Iron-Deficiency Anemia in Chronic Kidney Disease

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Summary: Anemia is a common and clinically important consequence of chronic kidney disease (CKD). It is most commonly a result of decreased erythropoietin production by the kidneys and/or iron deficiency. Deciding on the appropriate treatment for anemia associated with CKD with iron replacement and erythropoietic-stimulating agents requires an ability to accurately diagnose iron-deficiency anemia. However, the diagnosis of iron-deficiency anemia in CKD patients is complicated by the relatively poor predictive ability of easily obtained routine serum iron indices (eg, ferritin and transferrin saturation) and more invasive gold standard measures of iron deficiency (eg, bone marrow iron stores) or erythropoietic response to supplemental iron. In this review, we discuss the diagnostic utility of currently used serum iron indices and emerging alternative markers of iron stores.

Keywords: Anemia, chronic kidney disease, diagnosis, iron deficiency, ferritin, transferrin, serum marker

Anemia is a common and significant consequence of chronic kidney disease (CKD). It can occur early in CKD and it increases in severity as kidney function decreases. The major symptoms of anemia include fatigue and dyspnea, which negatively impact patients' quality of life.[1]

The common reasons for anemia are decreased erythropoietin production by the kidney and iron-deficiency anemia (IDA). There are several causes for iron-deficiency anemia in chronic hemodialysis patients, some of which do not apply to the peritoneal dialysis population and the predialysis CKD population. These include frequent laboratory testing, occult gastrointestinal bleeding, access bleeding, retention of blood in the dialysis tubing and dialyzers, decreased duodenal iron absorption (resulting from inflammation), interference with iron absorption (resulting from medications such as gastric acid inhibitors and phosphate binders), decreased iron binding capacity resulting from a decreased concentration of transferrin[2,3] and supraphysiologic levels of erythropoiesis in the setting of erythropoietin-stimulating agents (ESA) therapy. Annual blood losses in this population can approximate 1.5 to 3 g.[2]

Treatment for anemia during CKD is largely dependent on iron replacement and use of ESAs, with the goal being maintenance of stable hemoglobin levels individualized for each patient, a reduction in the frequency of blood transfusions, and improvement in the patient's quality of life. Iron therapies may help prevent initiation of ESAs or allow a reduction in ESA doses in both the nondialysis CKD population and patients on chronic dialysis. To successfully achieve these goals, physicians must be able to assess iron stores accurately to determine when to intensify treatment regimens versus when to stop iron therapies that may be harmful and costly.[4] The lack of a universal definition of IDA in patients with kidney disease using current biomarkers makes it particularly challenging to accurately measure iron stores. In this article, we review the forms of IDA in the CKD population and the various markers used for the diagnosis of IDA.

DIAGNOSIS OF IRON-DEFICIENCY ANEMIA

The gold standard for diagnosing IDA is assessment of iron stores in the bone marrow, an invasive and impractical method for routine testing.[5] The conventional indices used in current practice include serum concentrations of iron and ferritin and the transferrin percentage saturation (TSAT). Ferritin is a marker of tissue iron stores, whereas TSAT is a marker of iron available for erythropoiesis in the circulation. TSAT is calculated as follows: (serum ferritin/total iron binding capacity) × 100.[2,6] Absolute or true IDA is present when the body iron stores are low and usually is represented by ferritin levels less than 100 ng/mL in predialysis and peritoneal dialysis patients and by ferritin levels less than 200 ng/mL in hemodialysis patients and a TSAT less than 20%.[7] However, these indices do not correlate well with bone marrow iron stores or hemoglobin response to iron. Nonetheless, they are still the most widely used surrogate markers for body iron stores because they are inexpensive, readily available, and physicians have the most familiarity with them.[6]

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FORMS OF IRON-DEFICIENCY ANEMIA

The diagnosis of IDA in CKD and end-stage renal disease patients is complicated by the relatively poor association between serum iron indices and either bone marrow iron stores or erythropoietic response to iron supplementation. This is caused in part by the underlying inflammatory state commonly present in CKD patients resulting from uremia, infections, the presence of indwelling dialysis catheters, and other comorbidities, and the fact that ferritin, as discussed further later, is an acute phase reactant. In the presence of inflammation, hepcidin synthesis by the liver is stimulated and hepcidin levels in the blood increase.[6] Hepcidin decreases both gastrointestinal absorption of dietary iron and mobilization of stored iron from the reticuloendothelial system. The TSAT value is usually low ($<20\%$) because iron is not released for binding to transferrin. The ferritin value is increased (>100 ng/mL), which can indicate adequate body stores, the presence of inflammation, or both.[6] During such inflammatory states, patients may not respond to iron and can have refractory anemia.

Patients with CKD also may have functional IDA, which occurs in the setting of induced erythropoiesis during ESA use. ESA therapies lead to marked increases in the utilization of iron as they stimulate the production of millions of new red blood cells.[8] Functional IDA cannot be diagnosed using a bone marrow biopsy because there is a discrepancy between the demands of the bone marrow for iron and the supply of circulating iron via transferrin.[9] Because the marrow uses the available iron faster than transferrin can replace it with the release of stored iron, the TSAT level may be less than 20%. The ferritin level may be normal or increased.[2,6,10] Patients with functional IDA respond to iron supplementation, which helps to distinguish it from anemia caused by inflammation.

Thus, discordant values of TSAT and ferritin can be present in many CKD patients, potentially leading to incorrect concern for iron overload and the withholding or withdrawing of iron therapies, increasing a patient's risk for IDA.[11] The entire clinical scenario (symptoms, comorbidities, history of iron therapies, and the presence of inflammation) must be taken into consideration to help the physician decide on the appropriate use of iron supplementation.

LIMITATIONS OF CONVENTIONAL MARKERS

Serum ferritin is a positive acute phase reactant and is increased in inflammatory states and other conditions including hyperthyroidism, liver disease, malignancy, infection, and autoimmune diseases.[5,12] Lower levels of ferritin are seen in hypothyroidism and vitamin C deficiency. There are also gender differences, with lower ferritin levels seen in women. Serum iron concentrations are affected by assay methodology and hemolysis, which tends to increase the iron level. Serum iron and TSAT also are affected by diurnal variations, with serum iron being higher later in the day, and increased with iron supplements and dietary intake.[13] Transferrin is also an acute phase reactant, with higher levels seen in inflammatory states; this will lead to a lower TSAT value if circulating iron levels are constant. In poor nutritional states, transferrin production decreases. This would increase TSAT if iron levels in the circulation are stable.[6] Serum transferrin levels also can be increased with the use of oral contraceptives.[13]

A recent study by Stancu et al[14] showed the limited diagnostic utility of conventional indices in identifying IDA. The investigators measured iron indices (TSAT and ferritin), hemoglobin response to intravenous iron in non–dialysis-dependent CKD patients, and also obtained bone marrow iron aspirates. Although iron deficiency was diagnosed in 48% of patients based on bone marrow aspirates, conventional peripheral iron markers (TSAT $<$ 20% and ferritin $<$ 100 ng/mL) only identified iron deficiency in 17% of patients. To fully investigate the diagnostic utility of peripheral iron indices in identifying IDA, the investigators evaluated sensitivities and specificities for the iron indices at various cut-off values in identifying IDA (as measured by bone marrow aspirates). They found that the most informative value was a ferritin level less than 175 ng/mL that had both a sensitivity and specificity of approximately 70%. Although these values are both greater than those that would be achieved by chance, they provide limited diagnostic value in identifying IDA.[14] Other studies have shown that a ferritin level less than 100 ng/mL has a sensitivity of 35% to 48% and a specificity of 75% to 78% when validated using a functional IDA definition, whereas a ferritin level less than 200 ng/mL has a sensitivity of 41% and a specificity of 100% when validated against a bone marrow biopsy. Studies have shown that a TSAT less than 20% has moderate sensitivity (59%-88%) and a low specificity (63%-78%) for diagnosing IDA.[6,9,15,16]

Discordant values of ferritin and TSAT make the diagnosis of IDA and the decision to use iron therapies challenging. Recent Kidney Disease: Improving Global Outcomes (KDIGO) anemia guidelines recommend a course of intravenous iron in adults with CKD and anemia (or in CKD patients not on dialysis or, alternatively, a 1- to 3-month trial of oral iron therapy) if an increase in hemoglobin concentration is desired if the TSAT is less than 30% and the serum ferritin level is less than 500 ng/mL. The 2006 Kidney Disease Outcomes Quality Initiative guidelines and more recent KDIGO guidelines caution about the use of iron therapies when the ferritin level is greater than 500