REVIEW

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Anemia in chronic kidney disease: Causes, diagnosis, treatment

ABSTRACT

Most patients with chronic kidney disease eventually become anemic. We should view the management of anemia in these patients as part of the overall management of the many clinically relevant manifestations of chronic kidney disease. Erythropoiesis-stimulating agents (ESAs) are safe and should be used, as treating anemia may forestall some of the target-organ damage of chronic kidney disease.

KEY POINTS

Anemia increases in prevalence and severity as renal function decreases, becoming much more common when the glomerular filtration rate reaches 60 mL/minute or less. It is a risk factor associated with worse prognosis.

Deficiency of erythropoietin is the primary cause of anemia in chronic renal failure, but it is not the only cause. A minimal workup is necessary to rule out iron deficiency and other cell-line abnormalities.

Patients with chronic kidney disease should be periodically checked for anemia by measuring the serum hemoglobin level. If the level is 12.0 g/dL or less in a man or postmenopausal woman or 11.0 g/dL or less in a premenopausal woman, he or she should undergo further workup for anemia.

Patients receiving ESAs should also receive supplemental iron, probably parenterally. The target hemoglobin range is lower than the normal range: 11.0 to 12.0 g/dL.

TREATMENT WITH RECOMBINANT erythropoiesis-stimulating agents (ESAs) has greatly improved the management of anemia in patients with chronic kidney disease, permitting better outcomes and a higher quality of life for most.

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In chronic kidney disease, as nephrons are progressively lost, the body attempts to maintain homeostasis via multiple adaptive and maladaptive processes, including a complex range of biochemical and physiologic abnormalities. Almost every organ and system seems to be affected, but the main complications are cardiovascular, neurologic, hematologic, musculoskeletal, and immunologic—and all worsen as kidney function declines.

Therefore, patients with chronic kidney disease, even those with moderate disease not yet requiring dialysis, need to be periodically monitored for anemia. Although most patients are anemic when they start dialysis, only about a third are receiving treatment for it.

This article offers an update on the pathogenesis of anemia in this disease, diagnostic testing, and treatments, including the data published to date regarding the benefits of treating anemia in chronic kidney disease.

DEFINING ANEMIA

The World Health Organization defines anemia as a hemoglobin concentration lower than 13.0 g/dL in men and postmenopausal women and lower than 12.0 g/dL in other women.

TABLE 1

Stages of chronic kidney disease

STAGE	DESCRIPTION	GLOMERULAR FILTRATION RATE (GFR) (ML/MIN/1.73 M²)
1	Kidney damage with normal or increased GFR	> 90
2	Mild decrease in GFR	60 – 89*
3	Moderate decrease in GFR	30 – 59
4	Severe decrease in GFR	15 – 29
5	Kidney failure	< 15 or dialysis

*May be normal

BASED ON GUIDELINES OF THE NATIONAL KIDNEY FOUNDATION. K/DOQI CLINICAL PRACTICE GUIDELINES FOR CHRONIC KIDNEY DISEASE: EVALUATION, CLASSIFICATION, AND STRATIFICATION. AM J KIDNEY DIS 2002; 39(2 SUPPL 1):1–266.

The European Best Practice Guidelines for the management of anemia in patients with chronic kidney disease propose that the lower limit of normal for hemoglobin be 11.5 g/dL in women, 13.5 g/dL in men age 70 and under, and 12.0 g/dL in men older than age 70.[1]

In the United States, the working definition of anemia in chronic kidney disease has been influenced by government policy, as the Medicare program is the primary payer for its therapy. The National Kidney Foundation's Kidney Dialysis Outcomes Quality Initiative (K/DOQI)[2] recommends a workup for anemia in patients with chronic kidney disease if the hemoglobin level is less than 11.0 g/dL (hematocrit < 33%) in premenopausal women and prepubertal patients, and when the hemoglobin is less than 12.0 g/dL (hematocrit < 37%) in adult men and postmenopausal women.[2] These levels correspond to a decline to approximately 80% of the mean level for defined healthy subgroups.

Anemia is almost universal in stage 5 chronic kidney disease

ANEMIA IS COMMON IN KIDNEY DISEASE

Anemia is very common in patients with chronic kidney disease and probably causes many of its symptoms.

Physicians should start thinking about anemia when their patient's glomerular filtration rate (GFR) declines to 60 mL/minute/1.73 m² or less. In the third National Health and Nutrition Examination Survey (NHANES),[3] the prevalence of anemia in stage 3 chronic kidney disease (ie, a GFR of 30 to 59 mL/minute/1.73 m², TABLE 1) was 5.2%, rising to 44.1% in stage 4, and becoming almost universal in stage 5. (NHANES defined anemia as hemoglobin < 12.0 g/dL in men and < 11.0 g/dL in women.)

African Americans[3,4] and patients with diabetes[5] have even higher rates of anemia at each stage of kidney disease.[5]

Moreover, chronic kidney disease itself is very common: nearly 6 million Americans are estimated to have stage 3 chronic kidney disease.[4]

WHAT CAUSES ANEMIA IN CHRONIC KIDNEY DISEASE?

Factors likely contributing to anemia in chronic kidney disease include blood loss, shortened red cell life span, vitamin deficiencies, the "uremic milieu," erythropoietin (EPO) deficiency, iron deficiency, and inflammation. Unfortunately, we know little about the relative contributions of the different factors and conditions in the early stages of chronic kidney disease.

Blood loss

Patients with chronic kidney disease are at risk of blood loss due to platelet dysfunction. The main cause of blood loss is dialysis, especially hemodialysis, and the loss results in absolute

Iron homeostasis is perturbed in chronic kidney disease

Iron homeostasis is perturbed in patients with chronic kidney disease. The ability to provide enough iron for erythropoiesis is disrupted at several points in the iron cycle for reasons not yet clear. Thus, patients receiving erythropoiesis-stimulating agents will require iron supplementation, often intravenously, in order to produce additional red blood cells.

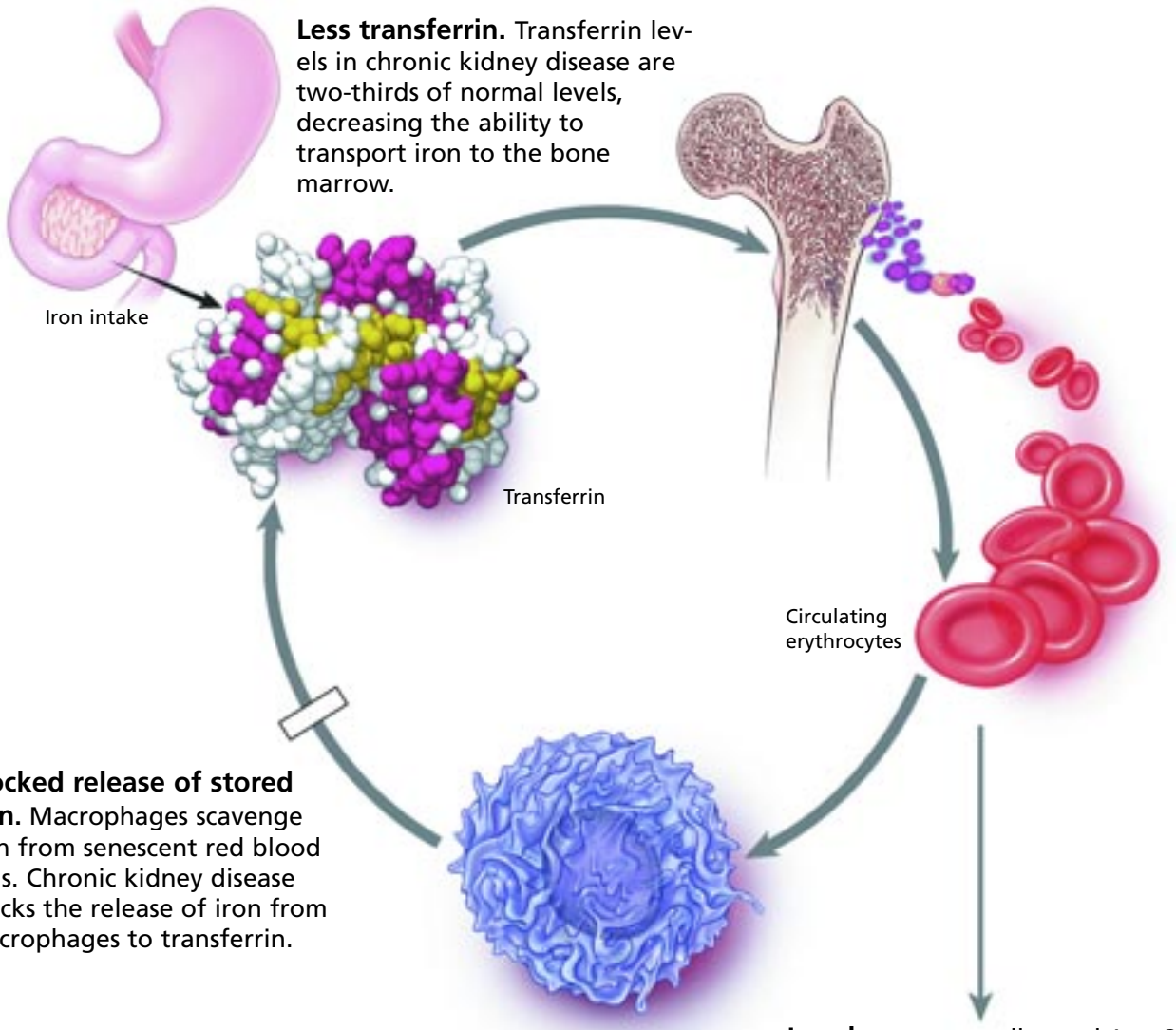

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FIGURE 1

iron deficiency. Hemodialysis patients may lose 3 to 5 g of iron per year.[6] Normally, we lose 1 to 2 mg per day (FIGURE 1), so the iron loss in dialysis patients is 10 to 20 times higher. Therefore, iron supplementation is a mainstay of anemia management.

Shortened red blood cell life span

The life span of red cells is reduced by approximately one third in hemodialysis patients.[7]

Vitamin deficiencies

It is difficult to determine whether vitamin deficiencies play a significant role in causing anemia in chronic kidney disease. Most patients with chronic kidney disease take a multivitamin daily, although there is no strong evidence that this is beneficial.[8] Therefore, even the prevalence of vitamin deficiencies in chronic kidney disease has been hard to establish.

'Uremic milieu'

The "uremic milieu" is a term that is overused in attempts to explain the multiple organ dysfunction of chronic kidney disease.

Hemodialysis patients may lose 3–5 g of iron per year, so iron supplements are essential

In studies in vitro, the term has been invoked when cultured cells were exposed to serum from patients with chronic kidney disease, with results that mimicked some of the clinical observations. For example, "uremic" serum has been shown to inhibit primary bone marrow cultures of early erythroid cell lines.[9] However, the lack of specificity in these studies has been criticized because this serum also affects other cell lines.

In studies in vivo, the concept of a uremic milieu may explain why the level and prevalence of anemia correlate with the severity of the kidney disease.[4] A GFR lower than 60 mL/minute/1.73 m^2 has been associated with a higher prevalence of anemia, which reached 75% in some studies.[10]

In addition, in a study in patients who had been receiving hemodialysis,[11] the hematocrit rose when the intensity of dialysis was increased, implying that reducing uremia restores or improves bone marrow function. However, this study could not distinguish the independent effects of the increased dialysis dose and the effect of changing to a more permeable dialysis membrane during the study.

EPO deficiency

EPO deficiency is considered the most important cause of anemia in chronic kidney disease. Researchers postulate that the specialized peritubular cells that produce EPO are partially or completely depleted or injured as renal disease progresses, so that EPO production is inappropriately low relative to the degree of anemia. Thus, measuring EPO levels in this population is of no use and should not be ordered: in fact, it can even be misleading if the value is normal when it ought to be high. However, the reason for this inappropriately low EPO production is not well understood.

EPO is produced when its gene is transcribed, in a process that depends on the binding of a molecule called hypoxia-inducible factor 1 alpha to the hypoxia-responsive element on the erythropoietin gene. Production of this factor increases in states of relative oxygen deficiency. Therefore, the balance between oxygen supply and consumption determines the production of hypoxia-inducible factor 1 alpha and, in turn, production of EPO.

Donnelly[12] proposed that the relative EPO deficiency in chronic kidney disease could be a functional response to a decreased glomerular filtration rate. The theory is that the EPO-producing kidney cells themselves may not be hypoxic: if the glomerular filtration rate is low, there is less sodium reabsorption—and sodium reabsorption is the main determinant of oxygen consumption in the kidney. In this situation there may be a local relative excess of oxygen that could down-regulate EPO production.[12]

Moreover, dialysis patients in one study maintained the ability to increase EPO production when exposed to high altitude.[13]

However, the best example that native kidneys have the potential for restoring EPO production is seen in some patients who developed erythrocytosis after receiving kidney transplants,[14] a situation in which the uremic milieu is eliminated.

Iron deficiency

Human iron metabolism is unique because no excretory route exists: it is mostly regulated via uptake. Iron homeostasis depends on iron

being absorbed in the duodenum and also recycled from senescent red blood cells. Most of the iron is bound to hemoglobin and is stored in hepatocytes and macrophages of the reticuloendothelial system (**FIGURE 1**).[15]

Iron is delivered to the maturing erythrocytes by a protein called transferrin, which transports both the iron absorbed and the iron released from macrophages (mainly from recycled senescent red blood cells).

Iron homeostasis appears to be altered in chronic kidney disease. For reasons not yet known (perhaps malnutrition), transferrin levels in chronic kidney disease are one half to one third of normal levels, diminishing the capacity of the iron-transporting system.[16] This situation is then aggravated by the well-known inability to release stored iron from macrophages and hepatocytes in chronic kidney disease.

Clinically, diminished iron transport and accumulated iron stores are manifested as low transferrin saturation and elevated serum ferritin levels. These characteristics suggest that the interorgan iron transport pathways may be rate-limiting factors in erythropoiesis in these patients. Interplay between increased iron losses (as discussed previously) and abnormal interorgan iron transport results in an absolute or functional iron deficiency that can be corrected only by aggressive iron replacement therapy.[17]

Inflammation

Interestingly, the anemia of inflammation is also characterized by low serum iron, low transferrin saturation, and impaired release of stored iron, manifested as high serum ferritin. Chronic kidney disease shares several features of the inflammatory state. Elevated circulating levels of inflammatory cytokines such as interleukin 6 have been associated with poor response to EPO treatment in end-stage renal disease.[18] These cytokines can impair bone marrow function and can significantly alter iron metabolism. The molecular mechanisms involved in the altered interorgan iron communication in both inflammation and chronic kidney disease are yet to be elucidated.

Newly discovered molecules have increased our understanding of iron metabolism. For example, hepcidin, a 25-amino-acid peptide secreted by the liver, profoundly influences iron metabolism. Recent studies indicate that hepcidin inhibits iron absorption, placental iron transfer, and iron release from the reticuloendothelial macrophages, and it mediates the anemia of inflammation.[19,20] However, hepcidin's role in the anemia of chronic kidney disease still needs to be elucidated.

BENEFITS OF TREATING ANEMIA

Although no randomized trial has fully assessed the consequences of not treating anemia in chronic kidney disease, the consensus is that untreated anemia contributes to the large cardiovascular disease burden in this population.

Most information comes from studies in patients who already had stage 5 chronic kidney disease and were on dialysis. Most of the data are epidemiologic, showing association but not causality. Nevertheless, these studies suggest that treating anemia with a goal of raising the hematocrit to at least 36% improves quality of life,[20] decreases the need for transfusions,[21,22] improves muscle strength[23] and cognitive function,[24] and decreases rates of hospitalization and death.[25,26]

Treating anemia appears safe in patients with stage 3 or 4 kidney disease

In patients with nephropathy due to type 2 diabetes who were not on dialysis, anemia was identified as an independent risk factor for progression of chronic kidney disease after blood pressure control.[27] Other independent risk factors include the degree of renal dysfunction, the serum albumin level, and proteinuria.

Studies of patients with chronic kidney disease not on dialysis have been designed to answer two fundamental questions:

- Does treating anemia influence the rate of progression of chronic kidney disease?
- Does treating anemia affect the presence or regression of left ventricular abnormalities, especially left ventricular hypertrophy?

Three recent papers address the effects of treating anemia with epoietin alfa on the progression of kidney disease.[28–30] However, only one[30] used progression of renal disease as the primary end point. The total number of patients treated in this triad of studies was 246, of which 167 were women and 58 had

diabetes. All patients were white. The approximate average GFR was 27 mL/minute/1.73 m^2 (this was measured by creatinine clearance using the Cockroft-Gault formula in one study[30] and by nuclear estimates in the other two[28,29]). Follow-up time after anemia treatment was 1 to 2 years. None of the studies showed progression of renal disease (measured as a change in creatinine clearance) associated with the anemia treatment, and one study[30] was able to detect even a slight decrease in progression of disease.

Moreover, an epidemiological study[31] showed that the use of and response to epoietin alfa in predialysis patients offers a modest early survival benefit after starting dialysis.

Based on these studies, treating anemia appears safe in patients with stage 3 or 4 chronic kidney disease. However, we have no specific data yet for African Americans.

If treating anemia slows the progression of chronic kidney disease, the mechanism is still a matter of speculation. Some of the currently proposed mechanisms are that treatment reduces oxidative stress, ameliorates the effects of hypoxia at the tubular level (thus protecting against nephron loss), lowers the accumulation of extracellular matrix, promotes angiogenesis, and prevents apoptosis.[32]

No proof yet that normalizing the hemoglobin level offers significant clinical advantage

Does treating anemia reduce left ventricular hypertrophy?

Left ventricular hypertrophy is closely linked to chronic kidney disease. The estimated prevalence in stage 3 and 4 is 39%, and it is even higher in patients with lower renal function.[33,34] At the start of dialysis nearly 74% of patients have left ventricular hypertrophy.[35]

A multivariate prospective study of 246 patients showed that a declining hemoglobin level was an independent contributor to the development of left ventricular hypertrophy (odds ratio 1.32 for each 0.5-g/dL decrease; P = 004).[33]

In a recent 2-year randomized controlled trial,[29] Roger et al randomized 155 patients with stage 3 or 4 chronic kidney disease and hemoglobin levels of 11.0 to 12.0 g/dL (in women) or 11.0 to 13.0 g/dL (in men) to receive epoietin alfa as necessary to maintain their hemoglobin levels between either 12.0 and 13.0 g/dL or 9.0 and 10.0 g/dL. Using intention-to-treat analysis, the authors found no statistical differences in the left ventricular mass index between the two study groups at 2 years, suggesting that normalizing hemoglobin had no advantages. However, the difference in hemoglobin concentration between the groups was narrow and may have had a confounding effect on the results. In spite of the negative results, anemia was identified as an independent predictor of left ventricular hypertrophy in patients achieving the protocol targets.

In a subsequent nested analysis of the same study,[36] McMahon et al described the effects of change in hemoglobin level on left ventricular mass in patients with or without left ventricular hypertrophy at baseline.[36] Among patients without hypertrophy at baseline, 68% showed no change at 2 years, and 32% developed hypertrophy. Among those with hypertrophy at baseline, 50% showed no change, and 22% had some evidence of regression. The factors associated with left ventricular hypertrophy were age, elevated systolic blood pressure, elevated pulse pressure, anemia, and a lower GFR.

From these two studies one can conclude that there is some association between anemia and left ventricular hypertrophy, but keeping the hemoglobin level in the normal range offers no significant advantage over a lower stable hemoglobin level. The authors advocated aggressive treatment of the clinically relevant manifestations of the chronic kidney disease (ie, high blood pressure, anemia) in the prevention and reversal of left ventricular hypertrophy, as hypertrophy either did not progress or regressed in close to 70% of the patients with hypertrophy.

Moreover, a decrease in left ventricular mass index at 6 months was recently reported in an open-label interventional trial.[37] In this study, patients who had stage 4 chronic kidney disease and a hemoglobin level less than 10 g/dL were treated with epoietin alfa with a target hemoglobin of 12 g/dL.

However, whether treatment lowers the death rate is not yet known. This question may be answered when several ongoing multicenter trials are completed.

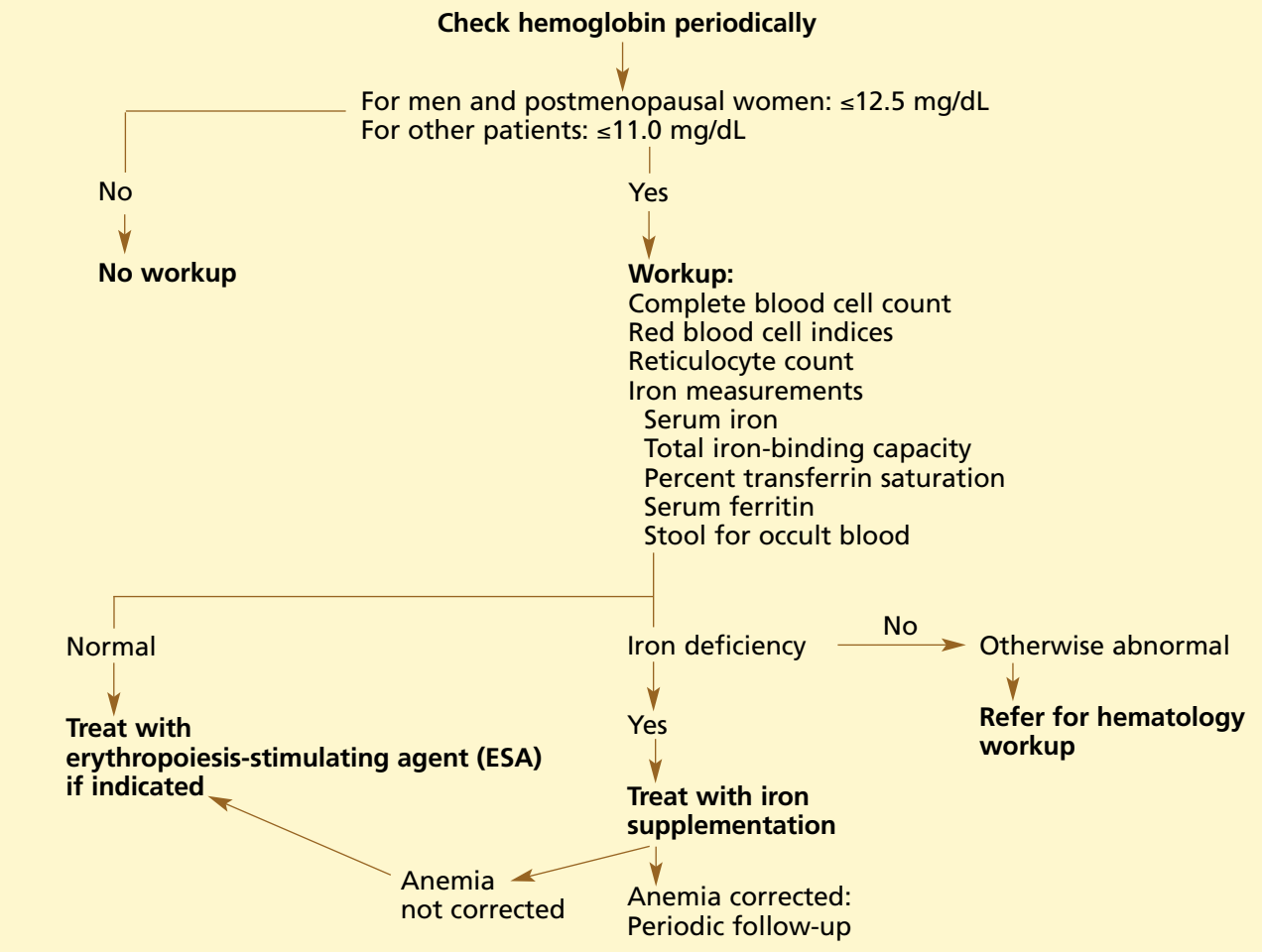

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FIGURE 2

DIAGNOSIS: DON'T ASSUME RENAL DISEASE IS THE ONLY CAUSE

In chronic kidney disease, anemia may not be entirely attributable to the kidney disease. Anemia of chronic kidney disease should be almost a diagnosis of exclusion after ruling out iron deficiency and nonerythroid cell-line abnormalities.

A minimal workup is recommended before starting therapy with an ESA (FIGURE 2). It should include:

- A complete blood cell count
- Red blood cell indices
- A reticulocyte count
- Iron measurements (serum iron, total iron-binding capacity, percent transferrin saturation, serum ferritin)
- Testing for occult blood in the stool.

Depending on clinical and laboratory circumstances, a more extensive workup may be indicated, ie:

- Serum vitamin B_{12} level
- Parathyroid hormone level
- Serum or urine protein electrophoresis
- A hemolysis panel.[1,2]

As already mentioned, measuring EPO levels is not useful.[1]

TREATMENT

ESAs should be given to achieve and maintain a target hemoglobin concentration of 11.0 to 12.0 g/dL.[38] There is currently no evidence that raising the hemoglobin to normal levels offers any significant clinical advantage over this target goal.

Two ESAs: Epoietin alfa and darbepoetin alfa

In the United States, the two agents available for treating anemia in chronic kidney disease are recombinant epoietin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp). In my opinion, both are effective and safe. Patients on dialysis can receive them intravenously; those not on dialysis can receive them subcutaneously.

According to the manufacturers, these products differ in pharmacodynamic and pharmacokinetic properties, affinity for the EPO receptor,[39] and half-life.[38,40] These different characteristics could be used to apply different dosing regimens.

Side effects of ESAs include hypertension and injection site problems

Iron supplementation

Patients should receive iron supplementation while on ESA therapy, because pharmacologically induced erythropoiesis is limited by the iron supply,[17] as shown by lower ESA requirements after iron supplementation.

In addition, as patients make more red blood cells they use up more iron, which can lead to iron deficiency. Serum ferritin and percent transferrin saturation have been shown to drop after 1 week of ESA therapy in both healthy people and iron-replete patients with chronic kidney disease on dialysis.[41]

Because patients with kidney disease have altered iron metabolism, their serum ferritin levels and percent transferrin saturation should be maintained at levels higher than in the normal population.[16] Recommended maintenance levels for serum ferritin are at least 200 ng/mL; for percent transferrin saturation at least 20%.[2]

Most patients with chronic kidney disease need parenteral iron supplementation to achieve the recommended iron levels.[2] Possible explanations for the failure of oral iron supplementation include a diminished ability of the oral mucosa to absorb iron and poor patient compliance (due to difficult dosing, side effects, and cost).

Monitoring and controlling side effects

Side effects of treatment with ESAs (mainly with recombinant epoietin alfa because it has been studied more thoroughly) include worsening of hypertension and problems at the site of injection. The K/DOQI panel reviewed 47 reports that included a total 3,428 patients. About 23% of patients had a new onset of hypertension or an increase in blood pressure, or both. If hypertension worsens, one should adjust the antihypertensive regimen rather than withhold the ESA treatment.

At The Cleveland Clinic Foundation, nearly all patients with chronic kidney disease who receive ESAs are seen in a special EPO clinic in the Department of Nephrology and Hypertension. More than 80% of the patients enrolled reach their hemoglobin target. Because this therapy requires frequent monitoring, such centralized care with algorithm-based management works well.

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