Anemia of Chronic Kidney Disease: A Review

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Anaemia is an extremely prevalent condition in patients with renal failure. It occurs early in the disease and its severity tends to worsen in parallel with decline of renal function. [1,2,3] Equally important are the facts that anaemia is one of the very important complications of chronic kidney disease (CKD) that cause progression of renal function impairment [4,5] and contribute significantly to morbidity and mortality in these patients.[6]

Although essentially a hypoproliferative anaemia resulting primarily from erythropoietin (EPO) deficiency, [7,8] other factors such as iron deficiency, [9] Bone marrow suppression,[10] chronic inflammation and malnutrition[11] blood losses during haemodialysis[12,13] and haemolysis due to contaminants in dialysis water treatment units[14] have been shown to contribute in a variety of ways to its development.

This article reviews our knowledge of the pathogenesis, clinical significance and management of anaemia of renal failure.

Epidemiology

Anaemia is one of the common consequences of chronic kidney disease. It begins early in the course of CKD and its prevalence and severity increases with progression of renal function impairment. Once End-Stage Renal Disease (ESRD) occurs, without treatment, almost all patients become affected. For instance, Astor et al.[15] in an analysis of a population-based sample of 15419 participants 20 years and older, in the Third National Health and Nutrition Examination Survey (NANHES), conducted from 1988 to 1994, found that the prevalence of anaemia increased from 1% at an estimated GFR of 60 mL/min to 9% at an estimated GFR of 30 mL/min and to 33% at an estimated GFR of 15 mL/min among men and to 67% at an estimated GFR of 15 mL/min among women. A similar finding of 68% prevalence rate of anaemia was documented by Valderra´bano et al.[3] in a pre-dialysis survey of anaemia in CKD patients.

Diabetic patients tend to have higher prevalence of anaemia compared with non-diabetic subjects, and in all CKD stages, anaemia prevalence appears to be significantly greater and mean haemoglobin levels lower in patients with diabetes compared with non-diabetic patients. Al-Khoury et al. [16] found an overall mean difference of approximately 1g/dl at each CKD stage when diabetics are compared with non-diabetic patients. A similar observation of lower haemoglobin levels has also been noticed in CKD patients with HIV infection.[17,18]
In contrast to the observations in diabetic and HIV positive patients, Autosomal Dominant Polycystic Kidney Disease (ADPKD) patients have been noted to have significantly higher pre-dialysis haemoglobin and EPO levels compared with patients having other aetiologies of CKD.[19]

Pathogenesis

The major mechanisms that have been recognized to contribute to the anaemia of ESRD are decreased erythropoietin production for the degree of anaemia, [7,8] a shortened red cell survival as a result of haemolysis,[14,20] iron deficiency,[9] chronic inflammation and malnutrition,[11] blood losses during haemodialysis,[12,13] contaminants in dialysis water treatment units[14] aluminium toxicity,[21] osteitis fibrosa associated with

hyperparathyroidism[22] and pure red cell aplasia complicating erythropoietin administration.[23]

Role of relative erythropoietin deficiency

Erythropoietin (a glycoprotein with a molecular weight of 34,000 daltons) is a circulating hormone that governs the rate of red blood cell production. In response to anaemia or hypoxemia circulating levels of erythropoietin can increase a thousand-fold. The site of production was first demonstrated by Jacobson and colleagues[24] who showed that removal of the kidneys prevented the erythropoietic response to haemorrhage or cobalt, whereas ablation of a number of other organs did not. Other investigators have confirmed that the kidneys are the principal site of erythropoietin production in the adult, and the cells responsible have now been identified as the cortical and outer medullary fibroblasts in the intestitium of the kidneys.[25] In addition to the kidneys, it has also been established that the adult liver is an important source of extra-renal erythropoietin, and the cell populations involved have been identified as the hepatocytes and the Ito cells.[26]

Although serum levels of EPO in patients with CRF are about five times as high in patients with CRF than in normal human subjects,[27] this response appears to be blunted given the potential of more than a thousand fold increase in EPO production by normal kidneys in response to anaemia. Secondly, the significant efficacy of therapeutic doses of erythropoietin in correcting anaemia in CKD patients underscores the importance of relative deficiency of erythropoietin in patients with chronic kidney disease. Thus, it appears that the primary cause of the anaemia in CKD is due to the lack of sufficient amounts of EPO to maintain steady-state erythropoiesis in the instance of multiple factors such as reduced red cell life span, deficiency of iron and folic acid, hyperparathyroidism with myelofibrosis, aluminium toxicity, blood losses, and inhibition of erythropoiesis caused by "uremic toxins."[28]

Iron deficiency

Although a normocytic normochromic red blood cell morphology is seen in most patients with chronic kidney disease, studies of iron metabolism have shown impaired iron utility similar to that seen in patients with anaemia of chronic diseases.[29] Secondly, iron deficiency may occur as a result of blood losses during haemodialysis, occult gastrointestinal losses and increased demand for iron imposed by heightened erythropoiesis with erythropoietin stimulating agent therapy.[30] The observation that iron deficiency is the most common cause of hyporesponsiveness of these patients to erythropoietin therapy buttresses the importance of iron in the pathogenesis of anaemia in renal failure.[31]

Recently, a key regulator of iron metabolism - hepcidin antimicrobial peptide - has been described.[32] It is a hormone produced in the liver, and acts at distal sites such as the absorptive cells of the intestine and the iron recycling macrophages of the spleen. The receptor of hepcidin is the cell surface ferroportin (FPN), which is expressed in macrophages, hepatocytes, and enterocytes. Ferroportin is the only known iron exporter in mammalian cells.[33] Hepcidin binding to FPN causes its internalization and subsequent lysosomal degradation. Without FPN at the surface of macrophages, iron transport to serum slows, causing accumulation of iron within the cells. Similarly, when FPN is removed from the basolateral surface of enterocytes, transfer of dietary iron to the serum is diminished, and retained intracellular iron is lost through exfoliation of the intestinal epithelium.[34] These

effects of hepcidin on iron balance readily explain hypoferremia and macrophage iron sequestration in the anaemia of chronic inflammation. It may also explain the poor oral absorption of iron in chronic kidney disease and the dysregulation of iron homeostasis seen in these patients.

Other Causes

Other aetiological causes known to impact on anaemia in CKD include Inflammation-malnutrition status of the CKD patients[11], Blood losses during dialysis, [12] Bone marrow suppression[35], Water contaminants[14], use of drugs such as the angiotensin converting enzyme inhibitors (ACE-I)[36], anti-retroviral drugs[18] and interestingly pure red cell aplasia (PRCA) from erythropoietin therapy.[37,38] Pure red cell aplasia is caused by antibody production against EPO

PRCA is diagnosed in the presence of a progressively developing, severe, isolated anaemia, with sudden onset and almost complete absence of red cell precursors from an otherwise normal bone marrow. The blood reticulocyte count is very low (<10 000/mm3). Hemoglobin concentration declines at a rate of approximately 0.1 g/dl/day, corresponding to the red cell life span. Lastly, the presence of anti-erythropoietin antibodies and evidence for their neutralizing capacity should be demonstrated [37]

Clinical significance

Anemia is associated with lower exercise tolerance, poorer quality of life, and left ventricular hypertrophy among patients with chronic renal insufficiency and with left ventricular hypertrophy and heart failure among patients undergoing dialysis.[15] The prevalence of LVH progressively increases with declining hematocrit values during the progression of renal disease.[39,40]

Anemia is recognised as one of the non-traditional risk factors of cardiovascular diseases in CKD patients.[41] Its role in the pathogenesis of the cardio-renal-anemia syndrome has been well described by various authors.[42,43] Anemia also causes progression of renal function impairment,[44] and has been associated with a higher mortality in the CKD population[45,46]

Management

Evaluation of anemia in chronic renal disease

Evaluation of chronic renal failure patients for anemia should be undertaken at presentation. This is important for several reasons. First, it may signify the presence of other systemic illnesses that warrant treatment. Secondly, anemia is a factor for a number of significant adverse patient outcomes, including cardiovascular diseases, cognitive impairment, hospitalizations and mortality. Regardless of whether concurrent disorders are treatable, awareness of their presence is likely to be helpful in the management of the patient.

Two prominent clinical guidelines on management of anemia of chronic kidney disease; European Best Practice guidelines (EBPG)[47] and K/DOQI[48] provide evidence based recommendations for the management of CKD anemia. Both recommend that assessment of anemia should involve laboratory measurement of hemoglobin concentration to assess the

degree of anemia and red blood cell indices [mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), to assess the type of anemia. Also, absolute reticulocyte count should be done to assess erythropoietic activity.

The plasma or serum ferritin concentration is performed to assess iron stores. Functional iron available for erythropoiesis is measured by Total Iron Binding Capacity (TIBC) and calculation of serum transferrin saturation (TSAT). The percentage of hypochromic red blood cells or reticulocyte hemoglobin content is other parameters useful in the assessment of functional available iron for erythropoiesis.

Plasma/serum C-reactive protein (CRP) to assess inflammation should also be measured.
In patients on dialysis, the frequency and the received dose of dialysis should also be evaluated.[47] Also, investigation of other etiologies suspected from the patients history and physical examination should be undertaken accordingly.

The mainstay of treatment of anemia of chronic renal failure is the administration of an erythropoietin stimulating agent (ESA) with intravenous iron therapy.

EPO therapy including newer drugs

Administration of erythropoietin to stimulate erythropoiesis is the primary step in treating anemia of chronic kidney disease. Available erythropoietin stimulating agents include: α-erythropoietin, β-erythropoietin, darbopoietin and continuous erythropoietin stimulating agents (CERA). Darbopoietin and CERA agents have longer duration of action than the other EPOs thereby resulting in less frequent drug administrations.

The EBPG on anemia in CKD recommends that erythropoiesis-stimulating agents (ESAs) should be given to all patients with chronic kidney disease (CKD) with hemoglobin levels consistently (i.e. measured twice at least 2 weeks apart) below 11 g/dl [hematocrit <33%], where all other causes of anemia have been excluded.[47]

The EBPG further recommends subcutaneous route of administration of the ESAs. This is based on strong evidence from randomized trials in CKD patients receiving dialysis that subcutaneous erythropoietin is as effective as intravenous erythropoietin and may allow lower doses to be used, thereby reducing costs. Dose requirements for subcutaneous erythropoietin (alfa or beta) are reported to be 22% lower than those of intravenous erythropoietin. The intravenous route may however be considered in hemodialysis patients for convenience.[47]

Complications of erythropoietin treatment include Hypertension by inducing vascular constriction through enhanced endothelin-1 production and by reducing the vasodilatory response of resistance vessels mediated by a decrease in endothelial nitric oxide production[49]. Erythropoietin-mediated platelet-derived growth factor release by vascular smooth muscle cells[50] may promote atherogenesis and myointimal hyperplasia causing vascular access thrombosis particularly in vascular access grafts. Pure red cell aplasia is another complication of erythropoietin therapy. It is due to neutralizing antibody production to erythropoietin thereby reducing its efficacy at stimulating erythropoiesis.[37,38]

Iron therapy

Iron is very crucial in hemoglobin synthesis and many studies indicate that adequate iron stores are critically necessary to achieve optimal responses to erythropoietin. Initiation of erythropoietin therapy increases iron requirement thus creating a functional deficiency of iron in the treated CKD patients. Thus iron deficiency becomes the major factor responsible in erythropoietin resistance.[51]

The KDOQI guideline recommends that sufficient iron should be administered to maintain a TSAT of ≥20%, and a serum ferritin level of ≥100 ng/mL.[48] Available intravenously administered iron include iron dextran, iron gluconate, iron-hydroxide sucrose complex and ferric saccharate. Newer iron preparations include ferumoxytol, heme iron peptide and dialysate iron pyrophosphate.

Some concerns have been raised concerning safety of intravenously administered iron. These include induction of anaphylactic reactions[52], oxidative stress[53] and increased predisposition to bacterial infection.[54] It however appears that the clinical benefits of intravenous iron overweighs the potential side effects.[55, 56]

Target Haemoglobin and guidelines and recommendations

Though the EBPG guidelines recommends that haemoglobin be maintained at between 11 – 12g/dl, the most recent recommendation of the KDOQI guideline recommends 13g/dl as the upper hemoglobin target. These recommendations are based on available evidence that lower hemoglobin values are associated with increased complications from anemia and higher values with increased mortality. The CREATE [57] and CHOIR [58] are two large randomized clinical trials that have demonstrated that significant benefits do not occur with higher hemoglobin targets.

Role of blood transfusions

Although one primary aim of management of anemia of CKD is to prevent transfusion, instances do arise in which blood transfusion may be beneficial to the patient. The KDOQI guideline recommends blood transfusion in the severely anemic patient with recognized symptoms or signs due to the anemia, for example the patient with acute blood loss associated with hemodynamic instability and also in the epoetin-resistant patient who has chronic blood loss.[48]

Summary

Anemia is a very common complication of chronic kidney disease with severe consequences if left untreated. Early evaluation of all CKD patients for anemia is recommended as institution of erythropoietin therapy with iron supplementation early in the course of the disease have been shown to prevent severe consequences of anaemia in the patients.

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