Anaemia and chronic renal failure

Iain C Macdougall

Abstract

Anaemia is a common complication of chronic kidney disease. Of the various contributory factors, the most important is an inappropriately low circulating concentration of erythropoietin, a hormone largely produced by the peritubular cells of the kidney. Chronic anaemia, particularly if severe, causes debilitating symptoms including tiredness and lethargy, muscle fatigue, reduced exercise capacity and breathlessness on exertion. There are adverse consequences for a number of physiological systems, particularly those of the heart and brain. The anaemia of kidney disease tends to develop once the glomerular filtration rate falls below 60 ml/min, and anaemic patients with a lesser degree of renal impairment should be screened carefully for another cause of anaemia. Synthetic erythropoietin therapy has transformed the management of renal anaemia; it induces an increase in haemoglobin concentration and prevents the need for repeated blood transfusions, particularly in dialysis patients. Many patients given erythropoietin therapy will require supplemental iron, and this is often given intravenously. Several new strategies for stimulating erythropoiesis are currently in development, including prolyl hydroxylase inhibition (HIF stabilizers), erythropoietin gene therapy, and modulation of hepcidin activity.

Keywords Anaemia; CERA; chronic kidney disease; darbepoetin alfa; erythropoiesis-stimulating agents; erythropoietin; hepcidin; HIF stabilizers; iron

Chronic anaemia is an almost invariable consequence of renal failure. As renal function deteriorates, there is a slow, progressive decrease in haemoglobin concentration that becomes particularly evident once the glomerular filtration rate (GFR) falls below 60 ml/min[1] leading to many debilitating symptoms (e.g. tiredness and lethargy, muscle fatigue, intolerance to cold, breathlessness on exertion, and poor exercise capacity). It is also associated with the high prevalence of cardiovascular disease in renal patients, and their consequent increased morbidity and mortality; cardiovascular disease accounts for more than 50% of deaths in these patients.

The anaemia of chronic kidney disease (CKD) is normochromic and normocytic (unless superimposed iron deficiency is present), and hypoproliferative (because of reduced erythropoietic activity in the marrow). The reticulocyte count is, therefore, inappropriately low for the degree of anaemia, but the peripheral blood film often looks normal except perhaps for occasional fragmented red blood cells (RBCs). Blood volume studies show a reduced RBC mass, but normal total blood volume.

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Epidemiology

Before the advent of erythropoietin (EPO) therapy (see section on 'ESA therapy' below), haemoglobin concentration was normal in only about 3% of patients requiring dialysis; most patients had values of 60–80 g/L. In the late 1980s, about 10% of dialysis patients required regular blood transfusions, and many more required an occasional top-up transfusion.

Haemodialysis patients tend to have more severe anaemia than those undergoing peritoneal dialysis, partly because of greater blood loss and haemolysis in haemodialysis patients, and partly because of better removal of uncharacterized 'middle molecules' that inhibit erythropoiesis in peritoneal dialysis patients. The severity of the anaemia is independent of the cause of renal failure, except in patients with polycystic kidneys, whose serum EPO (and haemoglobin) concentrations tend to be higher because of increased production of EPO by the cells lining the cysts.

Pathogenesis

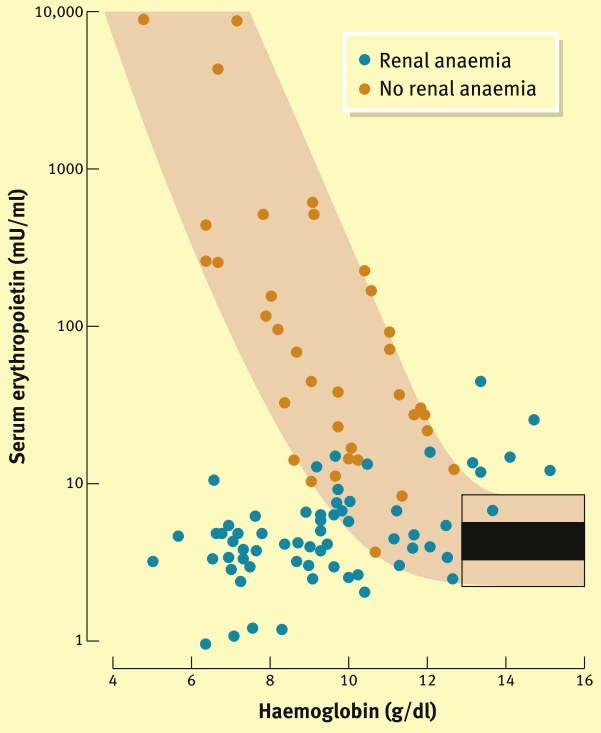
The main cause of renal anaemia was previously thought to be a loss of peritubular cells in the kidney, which are responsible for the synthesis and secretion of EPO, resulting in an inappropriately low concentration of EPO circulating in the blood for the degree of anaemia (Figure 1).[2] More recently, it has become clear that there is no loss of capacity for the cellular production of EPO, but the oxygen-sensing mechanism that upregulates this process is deficient. EPO is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow, and renal anaemia can be regarded as a hormone deficiency state. Other factors contribute to or exacerbate this anaemia (Table 1).

- Iron deficiency is common in renal failure because of poor dietary intake and increased iron losses; the latter result from increased blood loss, mainly in the gastrointestinal tract (patients on dialysis often lose up to 3–4 mg of iron per day compared with the normal daily loss of 1–2 mg).
- Inflammation may also play a major role in the pathogenesis of renal anaemia, since uraemia is a chronic inflammatory state.
- Hepcidin upregulation occurs in all inflammatory states, including that associated with chronic kidney disease, and this restricts the availability of iron supply to the bone marrow for erythropoiesis (Figure 2). Hepcidin is a 25-amino acid peptide produced by the liver in response to a variety of stimuli.
- Hyperparathyroidism is a complication of renal failure, and may exacerbate anaemia by causing fibrosis in the bone marrow.
- In many patients with uraemia, red cell life span is reduced because of low-grade haemolysis.
- Folate deficiency is less common than iron deficiency, but poor dietary intake and excessive loss of folate during dialysis can exacerbate the anaemia.

Clinical features

Patients with long-standing renal anaemia complain of tiredness, lethargy, muscle fatigue, reduced exercise capacity, poor

Serum immunoreactive erythropoietin and haemoglobin



The graph shows the relationship between serum immunoreactive erythropoietin levels and haemoglobin concentration in non-renal anaemia and in patients with chronic renal failure (excluding those with polycystic kidneys). The rectangle indicates the interquartile range and 95% confidence range of erythropoietin levels in non-anaemic healthy adults.

Figure 1

concentration, impaired memory and intellectual ability, breathlessness at rest and on exercise, angina, palpitations, loss of appetite, reduced libido and a sensation of feeling cold. Cognitive function may be adversely affected. Tests of exercise physiology are abnormal; maximum oxygen consumption and anaerobic threshold are reduced. In more severe anaemia, the cardiac output increases to compensate for the reduced oxygen-carrying capacity of the blood, and this is achieved by an increase in both stroke volume and heart rate. Platelet function may also be compromised, causing an enhanced bleeding tendency.

Factors contributing to renal anaemia

- Relative deficiency of erythropoietin
- Chronic inflammation
- Hepcidin upregulation
- Iron deficiency
- Reduced red cell survival
- Blood loss
- Hyperparathyroidism with marrow fibrosis
- Folate deficiency

Table 1

Diagnosis

In patients with a GFR of less than 60 ml/min, it is reasonable to assume that the anaemia is secondary to renal failure. However, it is important to exclude other contributory causes, particularly iron deficiency because this is easily corrected. In patients whose anaemia seems disproportionate to the degree of renal impairment (e.g. haemoglobin 90 g/L with a serum creatinine of 200 micromol/L), another cause for the anaemia, such as myeloma, should be sought.

Iron status is usually assessed by measurement of serum ferritin (a concentration less than 100 micrograms/L suggests a need for iron supplementation), as well as transferrin saturation (serum iron divided by total iron-binding capacity). A transferrin saturation of less than 20% is suggestive of iron deficiency. Other laboratory tests that may be useful in the investigation of anaemia include full blood count, reticulocyte count, serum vitamin B_{12} and folate, and serum C-reactive protein. In certain instances, a haemoglobinopathy screen may be indicated, along with investigations for haemolysis (serum bilirubin, lactate dehydrogenase and haptoglobins). In rare instances, a bone marrow may be indicated if a haematological cause is suspected.

Management

Prior to the 1990s, the management of renal anaemia comprised androgen therapy, iron supplementation, vitamin supplements and repeated blood transfusions. None of these measures was adequate in achieving a sustained correction of anaemia. The modern-day management of renal anaemia consists of a combination of erythropoiesis-stimulating agent (ESA) therapy and iron supplementation.

ESA therapy

The management of renal anaemia was transformed following the purification of human EPO in 1977, and the subsequent isolation and cloning of its gene in 1983, allowing for the first time the large-scale synthesis of recombinant human EPO in sufficient quantities for use in clinical practice. The first clinical trials of recombinant human EPO began in 1985.

EPO is a large glycoprotein (molecular weight 34 kDa) containing 165 amino acids. It is inactive when given by mouth, and must therefore be administered intravenously (IV) or subcutaneously (SC). IV administration is practical for haemodialysis patients, but for other patients (peritoneal dialysis, non-dialysis, and transplant patients), the drug is administered SC. The usual starting dose is around 2000 units two or three times per week. A reticulocyte response is usually obtained within 3–4 days of starting treatment and the haemoglobin concentration usually begins to increase after 2 weeks.

Darbepoetin alfa is a second-generation erythropoietic agent that became available for the treatment of renal anaemia in 1991. It is a hyperglycosylated analogue of EPO that differs from native and recombinant human EPO by the substitution of five amino acids and the addition of two extra carbohydrate side-chains. These molecular modifications to EPO make the molecule more