

Anaemia and chronic kidney disease

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Abstract

Anaemia is a common complication of chronic kidney disease. The most important contributory factor is an abnormally low circulating concentration of erythropoietin, which is produced by the kidney peritubular cells. Anaemia of kidney disease is likely to develop once the glomerular filtration rate (GFR) is <60 ml/minute/1.73 m², and is most evident at lower levels of renal function (estimated GFR <30 ml/minute/1.73 m²). Anaemic patients with a lesser degree of renal function should be screened for other causes. The combination of intravenous iron and recombinant erythropoietin therapy has transformed the management of renal anaemia and drastically reduced the need for repeated blood transfusions, particularly in patients requiring haemodialysis. The monthly use of 400 mg iron in haemodialysis patients (safety cut-off for ferritin 700 micrograms/litre, safety cut-off for transferrin saturation 40%) is associated with fewer cardiovascular events compared with patients given half this dose.

Keywords Anaemia; chronic kidney disease; erythropoietin; hepcidin; hypoxia-inducible factor stabilizers; iron

Introduction

The development of chronic anaemia is one of the sequelae that is invariably associated with chronic kidney disease (CKD); it usually appears once the estimated glomerular filtration rate (eGFR) has fallen to <60 ml/minute (stage 3a CKD).¹ Very often, however, the anaemia tends to become overtly apparent when the eGFR is <30 ml/minute (stage 4 CKD). A possible exception to this is seen in patients with diabetes mellitus, who tend to develop anaemia at an earlier stage (CKD stage 3b, eGFR <45 ml/minute) compared with non-diabetic patients.

Many of the symptoms experienced by patients with declining kidney function can be directly attributed to the anaemia of CKD, including tiredness, lethargy, muscle fatigue, intolerance to cold, exertional dyspnoea and poor exercise capacity. There is a significant association with cardiovascular mortality, which accounts for $>50\%$ of deaths in these patients.

Pathogenesis

Owing to the reduction in bone marrow erythropoiesis, the anaemia of CKD is typically normochromic, normocytic and hypoproliferative, leading to an inappropriately low reticulocyte count (out of keeping with the degree of anaemia). In normal

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Key points

- The anaemia of chronic kidney disease is typically normochromic and normocytic
- Renal anaemia can develop when the estimated glomerular filtration rate falls to <60 ml/minute/1.73 m², but is typically evident at <30 ml/minute/1.73 m²
- Anaemia of chronic kidney disease can be corrected by erythropoietin in 90–95% of patients
- Many patients require intravenous iron to target a ferritin concentration >100 micrograms/litre or a transferrin saturation $>20\%$
- The results of several studies suggest that completely correcting the anaemia may be harmful, and that partial correction (haemoglobin 100–120 g/litre) should be the goal instead
- Intravenous iron should not be administered in patients with overt sepsis

circumstances, the anaemic state should produce a compensatory increase in circulating blood levels of erythropoietin (EPO), therefore increasing red cell production in the bone marrow. However, it is now clear that there is a defect in the oxygen-sensing ability of the kidney (as opposed to a loss of peritubular cells) and a consequent reduction in appropriate EPO production (Figure 1). Although individuals with CKD retain the capacity to increase serum EPO levels, the mechanism is attenuated.

In addition to the relative reduction in EPO production, a number of other contributory factors affect haemoglobin concentration, albeit to a lesser extent:

- Iron deficiency is caused by increased iron losses via the gastrointestinal tract, and poor dietary intake and absorption of iron. Folate deficiency is less common but can worsen the anaemia.
- Hepcidin is the main hormone responsible for iron metabolism and is produced by the liver. Excess hepcidin locks iron into the reticuloendothelial system, preventing its use in erythropoiesis, while also blocking the absorption of dietary iron. Hepcidin is excreted by the kidneys, so levels are higher in renal failure. It is also significantly upregulated in inflammatory states such as uraemia, inflammatory bowel disease and rheumatoid arthritis.
- The lifespan of red cells (usually 120 days) is significantly reduced in advanced kidney disease (to 60–90 days) because of low-grade haemolysis.
- Disordered bone metabolism is a complication of advanced CKD, and hyperparathyroidism is associated with a worsening of anaemia, possibly as a result of bone marrow fibrosis.
- Some patients with renal disease are treated with immunosuppressive drugs such as azathioprine or mycophenolate mofetil, and these can cause direct bone marrow suppression.

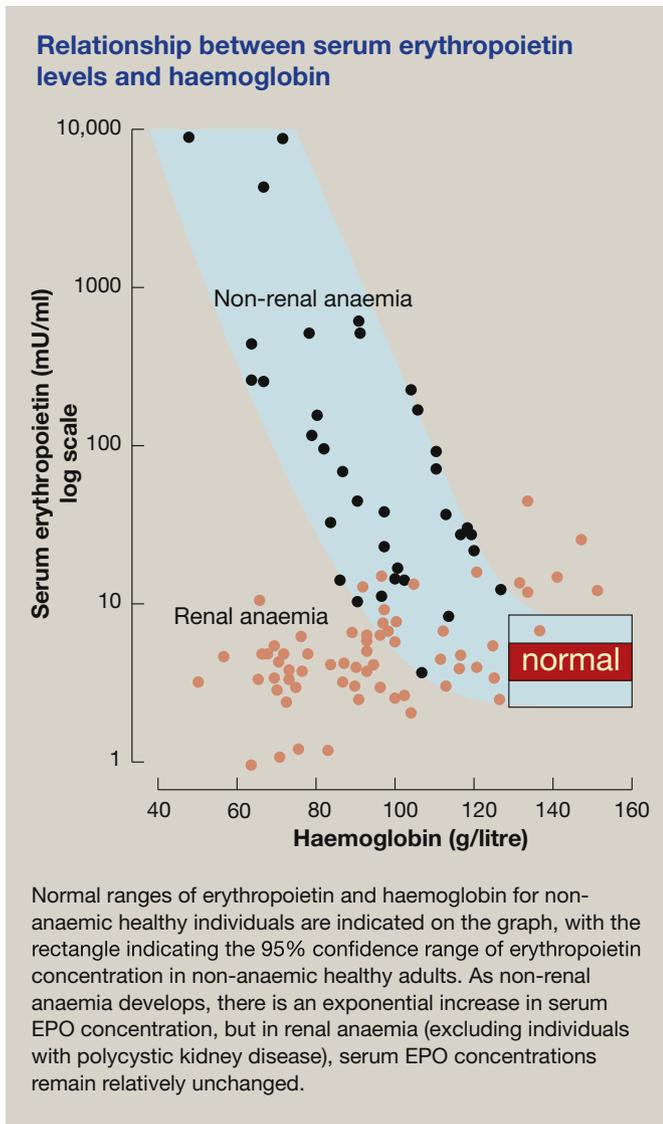


Figure 1

- Most haemodialysis patients are given anticoagulation to prevent clotting of the extracorporeal circuit. Blood can be lost directly via the circuit or the arteriovenous dialysis access, or indirectly via the gastrointestinal tract (usually occult). For several reasons, patients who undergo haemodialysis have a more severe anaemia than those on peritoneal dialysis (Table 1).

The severity of the anaemia is not related to the cause of the renal failure, except in patients with polycystic kidney disease; this group tend to show higher EPO and haemoglobin concentrations as the cells lining the cysts produce increased amounts of EPO. An underlying EPO-producing tumour (rarely renal cell carcinoma) should be considered in patients with advanced CKD and erythrocytosis.

Diagnosis

The diagnosis of CKD-associated anaemia relies on the degree of anaemia being proportionate to the degree of renal impairment, and on the exclusion of other causes of anaemia. For instance, if

a patient has an eGFR of 45 ml/minute with a blood haemoglobin concentration of 95 g/litre, it is unlikely that CKD is the main contributor to the low haemoglobin concentration. As a general rule, renal anaemia should not be assumed to be a factor in patients with an eGFR ≥ 60 ml/minute; in this situation, other causes, such as iron deficiency, gastrointestinal bleeding or multiple myeloma, should be sought.

Laboratory tests that can help to elucidate an underlying cause include a full blood count, reticulocyte count and ferritin, B₁₂, folate and C-reactive protein concentrations. A haemoglobinopathy screen is useful in certain instances, as are investigations for haemolysis (serum bilirubin, lactate dehydrogenase and haptoglobin concentrations). If a haematological cause is suspected, protein electrophoresis, circulating serum free light chains or a bone marrow examination can be indicated.

Once other causes of anaemia have been excluded, a dedicated evaluation of the patient's iron status should be made. A number of biomarkers can be measured, including serum ferritin, transferrin saturation (TSAT; calculated by dividing the serum iron concentration by the total iron-binding capacity) or the percentage of hypochromic red cells. In the context of CKD, a serum ferritin concentration < 100 micrograms/litre or TSAT $< 20\%$ is highly suggestive of iron deficiency.²

Management

Recombinant human erythropoietin became available in the early 1990s. Before this, anaemia in CKD was treated by regular blood transfusions, androgen therapy and vitamin and iron supplements, but this approach was insufficient to correct the anaemia. Current therapy combines erythropoiesis-stimulating agents (ESAs) and iron supplementation. Newer therapies such as hypoxia-inducible factor stabilizers are also available.

Erythropoiesis-stimulating agent therapy

The management of renal anaemia was revolutionized after the purification of EPO in 1977, with its first trials in human subjects in 1985. Recombinant human EPO causes a reticulocyte response within 3–4 days, and a rise in haemoglobin concentration after 2 weeks. ESAs have been routinely used since the 1990s, leading to a striking reduction in requirements for blood transfusion.

During the early years after the introduction of ESAs, full correction of anaemia was the desired goal, but the results of several large randomized clinical trials (US Normal Hematocrit Trial, CREATE Study, CHOIR Study, TREAT Study³) soon indicated that this strategy was in fact harmful. Because of the increased risk of cardiovascular events such as stroke or exacerbation of venous thromboembolism with higher doses of ESA,⁴ current UK NICE guidance suggests partial correction of anaemia, with a target haemoglobin concentration of 100–120 g/litre.

Once ESA therapy has been initiated, it is important to monitor iron status, because many patients given ESA become iron-deficient as the available stores are used up by the increased erythropoietic demand. Most patients given ESA therapy are concurrently given interval intravenous iron (according to their iron status) in order to maintain a serum ferritin > 100 micrograms/litre. There are several scenarios in which ESAs become ineffective, including iron deficiency and high-inflammation states such as sepsis.

The most common factors that cause or exacerbate the anaemia associated with chronic kidney disease

Factors contributing to renal anaemia

- Relative deficiency of erythropoietin
- Iron deficiency
- Chronic inflammation
- Heparin upregulation
- Blood loss
- Reduced red cell survival
- Folate deficiency
- Hyperparathyroidism with marrow fibrosis
- Bone marrow suppression as a result of immunosuppression

Table 1

Iron supplementation

The negative iron balance commonly seen in CKD means that iron supplementation is often required to correct the resultant anaemia. However, gastrointestinal absorption of iron in patients with CKD is often impaired because of the action of hepcidin (Figure 2). Thus, intravenous iron is often necessary to maintain serum ferritin levels in the desired range. Potential adverse effects of intravenous iron include anaphylaxis (rare),

hypotension, arthralgia and abdominal pain, and pre-clinical data suggest that oxidative stress and bacterial infections are exacerbated by excess iron. It is therefore current practice to withhold iron in patients with overt sepsis.

The recently published PIVOTAL trial concluded that patients on haemodialysis benefited from higher monthly doses of intravenous iron (400 mg iron sucrose per month, with a safety cut-off for ferritin of 700 micrograms/litre and a safety cut-off for TSAT of 40%); in this trial, fewer cardiovascular events and similar rates of infection were seen despite being given double the dose of iron compared with participants in the low-dose group.⁵

The future

Although ESAs and iron remain the standard of care, newer agents that target the enzyme prolyl hydroxylase are in late-stage clinical development. These agents stabilize hypoxia-inducible factor (the main transcription factor acting on the *EPO* gene), causing a rise in haemoglobin concentration. The main attraction of these products is that they are orally available, providing some advantage over current treatments. Roxadustat is the most advanced in development, and the results of Phase 3 trials should be available within the next couple of years. ◆

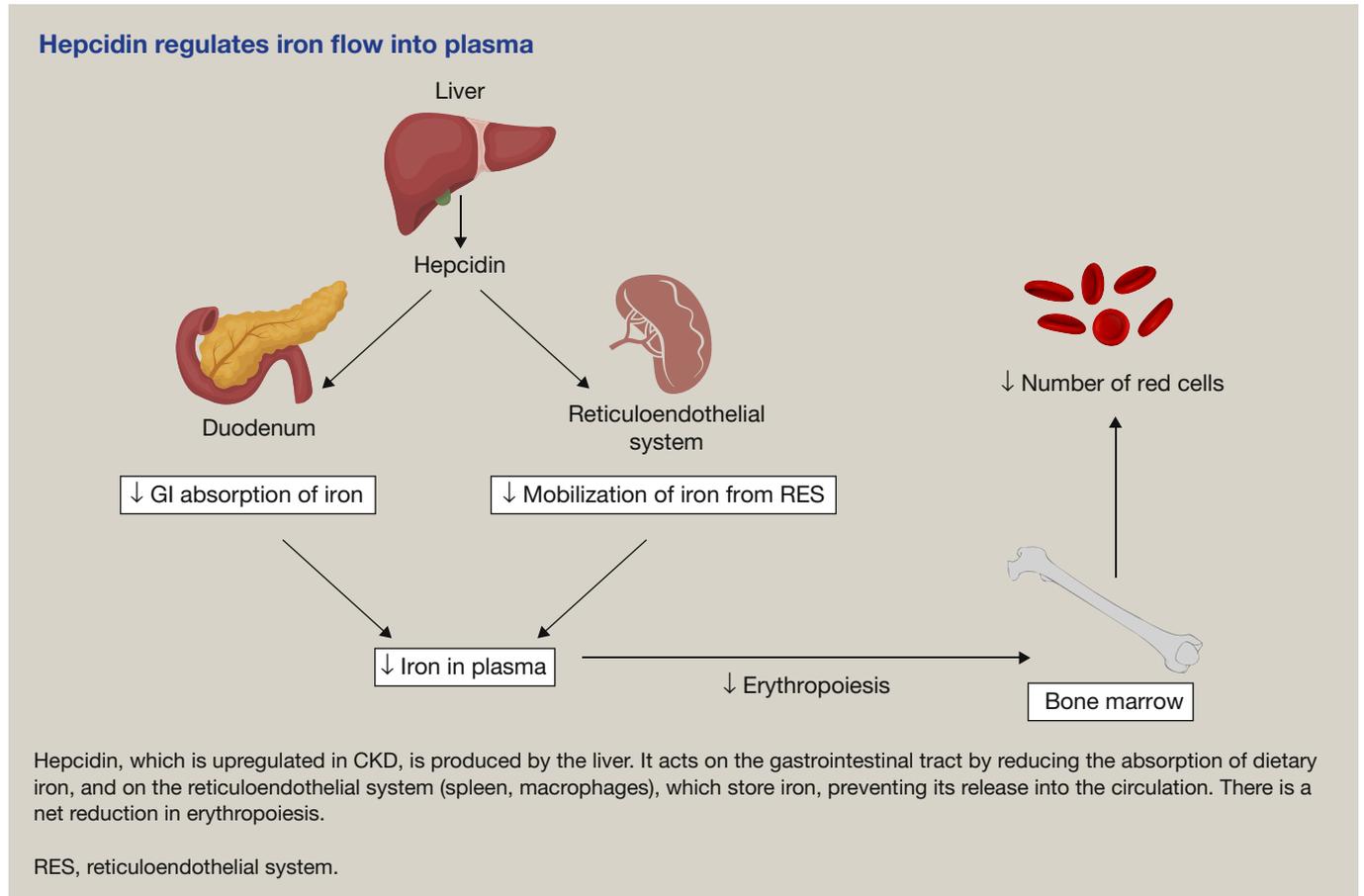


Figure 2

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online [here](#).

Question 1

A 65-year-old man presented with a 2-week history of increasing lethargy, breathlessness on exertion and occasional postural dizziness. He had no gastrointestinal symptoms. He had a history of chronic kidney disease, hypertension and peripheral vascular disease, and a 100 pack-year smoking history. He was taking amlodipine, aspirin, bisoprolol, doxazosin, furosemide, losartan and simvastatin. He had been given 1000 mg of intravenous iron (ferric carboxymaltose) 5 weeks previously.

On clinical examination, the man was pale. His temperature was 36.2°C, heart rate 96 beats/minute, and blood pressure 112/54 mmHg, with no postural drop.

Investigations

- Haemoglobin 74 g/litre (130–180)
- Mean cell volume 82 fl (80–96)
- White cell count 4.1×10^9 /litre (4.0–11.0)
- Platelets 611×10^9 /litre (150–400)
- Reticulocyte count 98×10^9 /litre (25–85)
- Serum ferritin 22 micrograms/litre (15–300)
- Estimated glomerular filtration rate (eGFR) (using the MDRD equation) 28 ml/minute/1.73 m² (>60)

What is the most appropriate next investigation?

- A. Blood film
- B. Chest X-ray
- C. Echocardiogram
- D. Endoscopy
- E. Myeloma screen

Question 2

A 44-year-old woman presented with sudden-onset left-sided weakness and ipsilateral facial droop. She had a history of polycystic kidney disease, stage 4 chronic kidney disease and hypertension. She had been taking her antihypertensive medications sporadically. On admission, the Glasgow Coma Scale score was 15/15, and blood pressure 220/120 mmHg. She underwent an emergency CT scan of the brain and was given antihypertensive agents to lower her blood pressure.

Investigations

- Haemoglobin 178 g/litre (130–180)
- Mean cell volume 94 fl (80–96)
- White cell count 13.1×10^9 /litre (4.0–11.0)
- Platelets 411×10^9 /litre (150–400)
- Reticulocyte count 55×10^9 /litre (25–85)
- Serum ferritin 102 micrograms/litre (15–300)
- Potassium 6.1 mmol/litre (3.5–4.9)
- Bicarbonate 16 mmol/litre (20–28)
- eGFR (using the MDRD equation) 16 ml/minute/1.73 m² (>60)
- CT scan of head showed a right-sided intracerebral bleed with no mass effect

What is the most appropriate next investigation?

- A. Blood cultures
- B. Bone marrow aspirate
- C. CT of the abdomen
- D. Echocardiogram
- E. Renal angiogram

Question 3

A 57-year-old man presented with a 1-week history of cough productive of green sputum, with fevers, lethargy and breathlessness on exertion. He had a history of stage 5 chronic kidney disease as a result of immunoglobulin A nephropathy. He had been treated with antibiotics for a lower respiratory tract infection. After 2 weeks, he had improved though he remained weak and had had difficulty mobilizing on the ward.

On clinical examination, his heart rate was 90 beats/minute, and blood pressure was 122/82 mmHg sitting, 116/84 mmHg standing. Auscultation of the lungs revealed a few sparse crackles at the right base. Abdominal (including rectal) examination was unremarkable.

Investigations

- Haemoglobin 72 g/litre (130–180)
- Mean cell volume 84 fl (80–96)
- White cell count 6.3×10^9 /litre (4.0–11.0)
- Platelets 301×10^9 /litre (150–400)
- Reticulocyte count 48×10^9 /litre (25–85)
- Serum ferritin 34 micrograms/litre (15–300)
- eGFR (using the MDRD equation) 14 ml/minute/1.73 m² (>60)
- Serum C-reactive protein 12 mg/litre (<10)

What is the most appropriate next step in management?

- A. Blood transfusion
- B. Endoscopy
- C. Intravenous iron
- D. Oral iron
- E. Corticosteroid