

What is the cause of renal anemia?

The pathogenesis of renal anemia is multifactorial, with a number of contributory processes involved, to a greater or lesser extent.

Erythropoietin deficiency

As discussed in Chapter 1, the major cause of renal anemia is a relative deficiency of erythropoietin from the kidneys [1]. Erythropoietin is a single-chain, polypeptide hormone with a molecular weight of 30.4 kDa. Approximately 40% of the molecule is carbohydrate in the form of three N-linked glycosylation chains and one O-linked glycosylation chain (Figure 2.1) [2]. The erythropoietin gene is located on chromosome 7, and there is minimal post-translational modification [3,4].

Erythropoietin is synthesized in the peritubular interstitial cells of the kidneys, and a small amount is also produced in the liver. There are no preformed stores of erythropoietin, and the production of this hormone is stimulated by hypoxia (Figure 2.2). It was previously believed that the reason for inappropriately low circulating erythropoietin levels in patients with CKD was that the main cells in the body producing erythropoietin were damaged by the same process that was causing the renal failure. Recently, however, it became clear that with an appropriate stimulus (eg, hypoxia, or a mimic of hypoxia caused by pharmacological stabilization of hypoxia-inducible factor [HIF], the main transcription factor for the erythropoietin gene; see Chapter 9), patients with end-stage renal failure are still able to increase their plasma concentrations of

Structure of erythropoietin

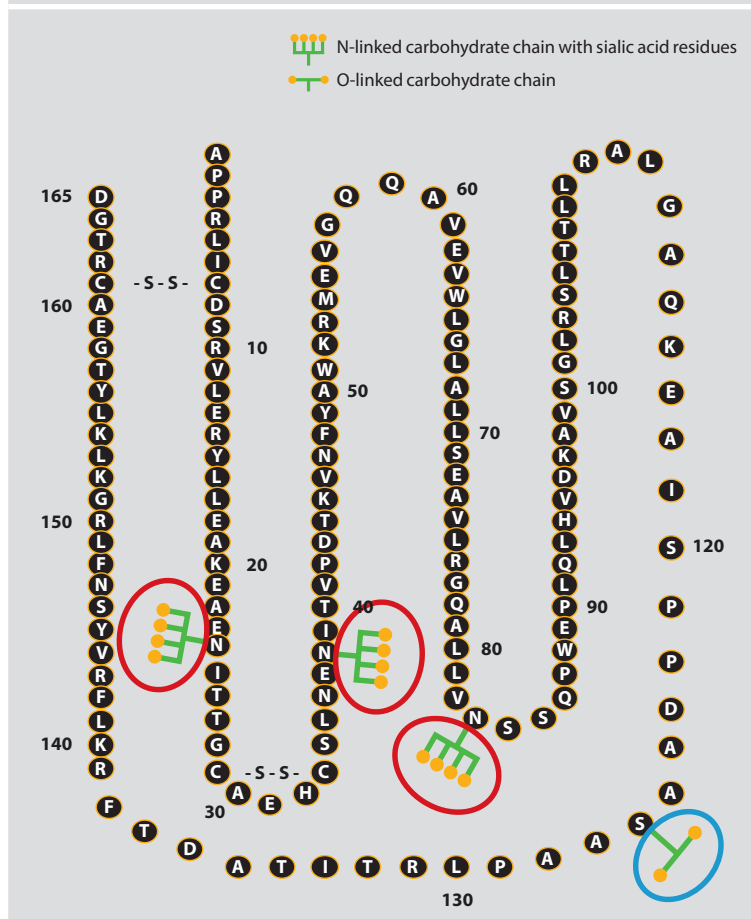


Figure 2.1 Structure of erythropoietin.

erythropoietin [5]. Indeed, even anephric individuals are able to show some response, and in this context it is believed that erythropoietin is probably being produced by liver cells, which are known to possess mRNA for the protein [5]. Thus, the inappropriately low erythropoietin production in patients with end-stage renal failure may be partly related to loss of the kidney cells synthesizing the hormone, but also partly due to a malfunction of the oxygen-sensing stimulus.

Hypoxia-stimulated erythropoietin and red blood cell production

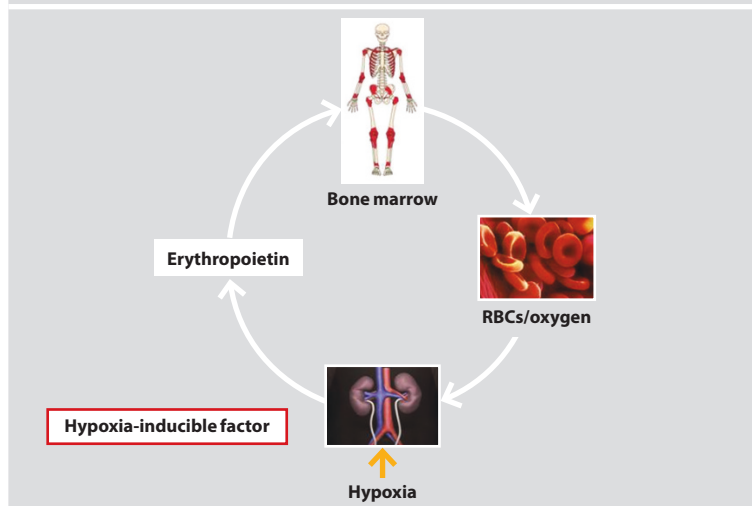


Figure 2.2 Hypoxia-stimulated erythropoietin and red blood cell production.

RBC, red blood cells.

In the absence of anemia or hypoxia, the plasma erythropoietin level is normally very constant in any given individual. Erythropoietin acts on erythroid progenitor cells in the bone marrow, preventing their apoptosis and allowing them to proliferate (Figure 2.3). The normal range of plasma erythropoietin is around 4–30 mU/mL, but levels 100–1000 times higher may be found in several nonrenal causes of anemia [1].

Uremic inhibitors

In the 1970s, it was recognized that uremic serum inhibited erythroid colony growth (Figure 2.4). Prior to the advent of recombinant human erythropoietin, it was believed that several substances in uremic serum could inhibit erythropoiesis [7], including spermine, spermidine, putrescine, cadaverine, and parathyroid hormone.

Inflammation

Uremia is now recognized to be a chronic inflammatory state, and at least part of the pathogenesis of renal anemia is similar to the pathogenesis of the anemia of chronic inflammation. Proinflammatory cytokines,

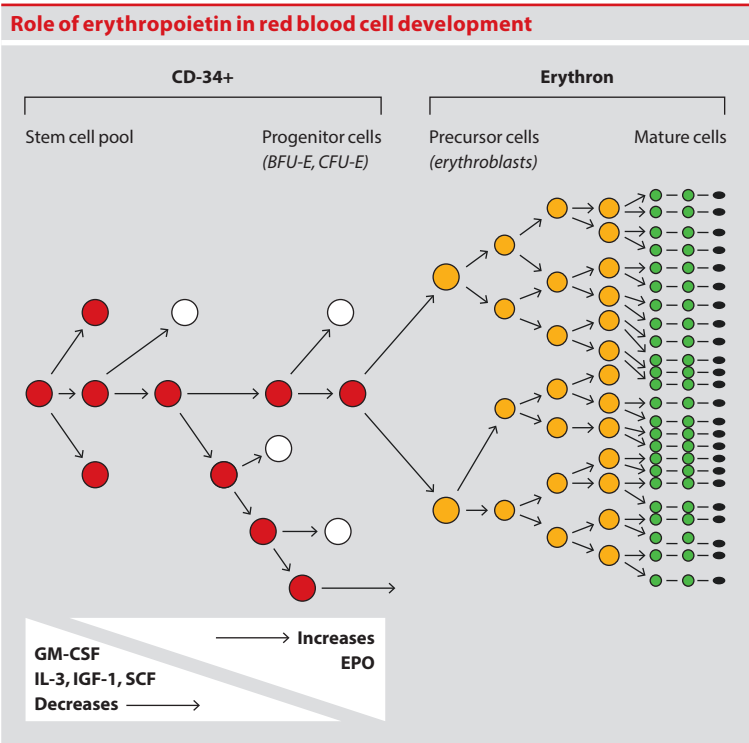


Figure 2.3 Role of erythropoietin in red blood cell development. BFU-E, burst-forming units – erythroid; CFU-E, colony-forming units – erythroid; EPO, erythropoietin; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL-3, interleukin-3; IGF-1, insulin-like growth factor-1; SCF, stem cell factor.

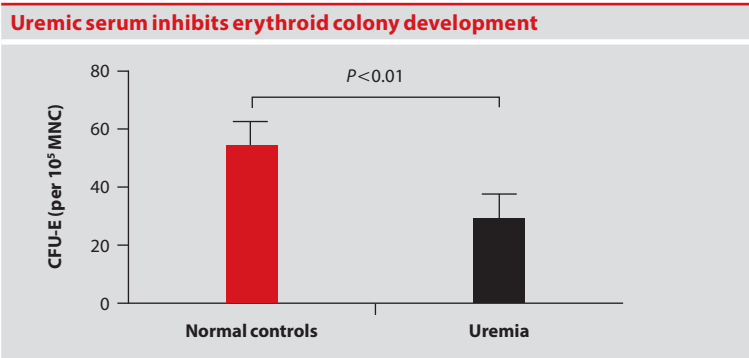


Figure 2.4 Uremic serum inhibits erythroid colony development. CFU-E, colony-forming units – erythroid; MNC, mononuclear cells. Adapted with permission from Allen et al [6].

such as tumor necrosis factor alfa and interferon gamma may also play a part in causing suppression of erythropoiesis in renal failure. Removal of such substances by increasing the dialysis prescription may improve erythropoiesis in renal patients [8]. In addition, it is now recognized that hepcidin, the master regulator of iron homeostasis in the body, also plays a major role in inflammatory anemia, by limiting iron availability to the bone marrow. Hepcidin is upregulated by proinflammatory cytokines, particularly interleukin-6 (IL-6) [9].

Hepcidin

Hepcidin is a 25-amino-acid peptide, which is produced in the liver in response to a number of stimuli, including inflammation and iron overload. The regulation of hepcidin is beginning to be understood, and certain factors such as hemojuvelin and bone morphogenetic protein-6 are implicated in its production in hepatocytes and macrophages. Its principal physiological role is to regulate the amount of iron available to the bone marrow for erythropoiesis by acting on enterocytes in the duodenum to limit iron absorption from the gut, as well as iron release from hepatocytes, macrophages, and splenic cells (Figure 2.5) [10]. Its main action is to bind to ferroportin, the sole cellular exporter of iron

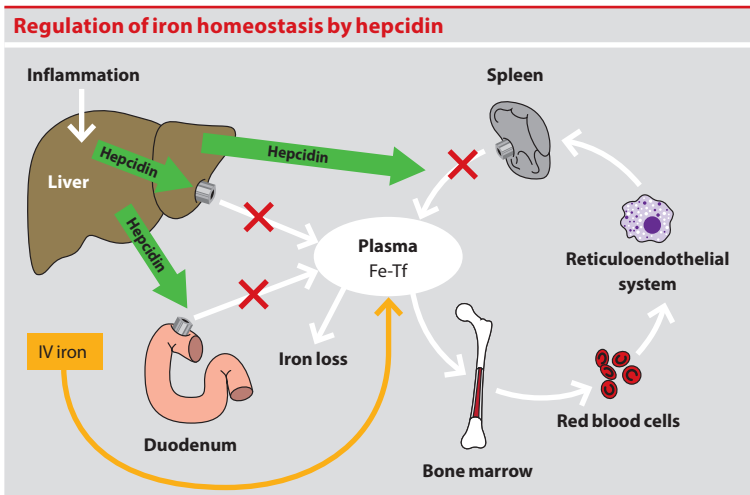


Figure 2.5 Regulation of iron homeostasis by hepcidin. Fe-Tf, iron-transferrin complex.

in mammals. Patients with CKD, particularly those on hemodialysis, are known to have high circulating levels of hepcidin, and this is partly due to their chronic inflammatory state, and partly due to reduced clearance of hepcidin via the kidneys [11].

Iron deficiency

Patients with CKD are often in negative iron balance due to a combination of low dietary intake of iron as well as increased iron losses. The low dietary intake of iron is caused by poor appetite in patients with uremia, and by poor absorption from the gut due to hepcidin upregulation. Certain drugs may also inhibit iron absorption such as proton pump inhibitors and phosphate binders. Also, certain foods, such as tea can have the same effect.

Increased iron losses are due to a number of factors, including platelet dysfunction secondary to uremia and increased mucosal inflammation and ulceration in the gastrointestinal tract, the use of anticoagulants such as heparin on dialysis, and the use of aspirin and antiplatelet drugs in cardiovascular prophylaxis (Table 2.1) [12]. Iron losses in hemodialysis patients are known to be up to 5 or 6 times higher than those of normal healthy individuals [13]. There are two types of iron deficiency: absolute, when the total body stores of iron are exhausted, and functional, when there are adequate or increased stores of iron, but an inability to release the iron rapidly enough to satisfy the demands of the bone marrow for erythropoiesis (Table 2.2).

Hyperparathyroidism

Patients with hyperparathyroidism may become anemic, and indeed it was previously believed that severe hyperparathyroidism may exacerbate

Causes of iron deficiency in patients with chronic kidney disease	
Reduced intake	Increased loss
Poor appetite	Occult gastrointestinal losses
Poor gastrointestinal absorption	Peptic ulceration
Concurrent medication (eg, omeprazole)	Blood sampling
Food interactions	Dialysis losses
	Concurrent medications (eg, aspirin)
	Heparin on dialysis

Table 2.1 Causes of iron deficiency in patients with chronic kidney disease.

Definition of absolute and functional iron deficiency

Absolute	Reduced body iron stores Low serum ferritin levels
Functional	Normal body iron stores, but a failure to release iron rapidly enough to satisfy demands of bone marrow Normal/high serum ferritin ↓ Transferrin saturation (<20%) ↑ Hypochromic red blood cells (>10%)

Table 2.2 Definition of absolute and functional iron deficiency.

renal anemia. Several mechanisms were proposed to account for this effect, including the development of fibrosis in the bone marrow (a condition known as osteitis fibrosa cystica), along with direct suppression of erythroid colony growth by parathyroid hormone. In the absence of bone marrow fibrosis, hyperparathyroidism per se contributes little to the development of renal anemia, as this can easily be overcome by recombinant human erythropoietin therapy. Nevertheless, some patients with resistance to this treatment have shown enhanced erythropoietic activity after parathyroidectomy (Figure 2.6) [14].

Aluminum toxicity

In previous times, this was an important contributory factor in the pathogenesis of renal anemia. The anemia was characteristically microcytic

Effect of parathyroidectomy on hemoglobin response to erythropoietin

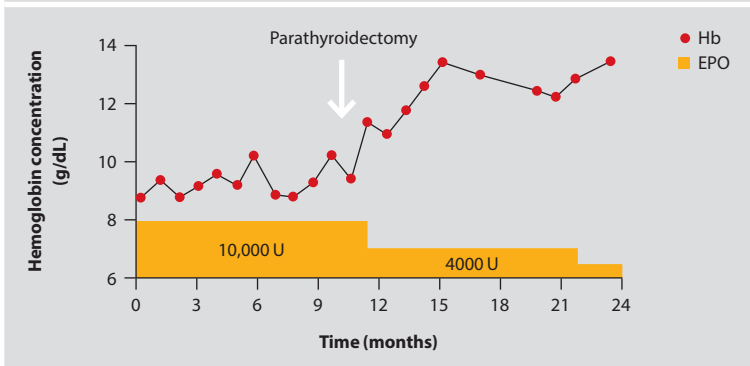


Figure 2.6 Effect of parathyroidectomy on hemoglobin response to erythropoietin.
Hb, hemoglobin; EPO, erythropoietin.

in origin, even in the absence of iron deficiency. With the introduction of improved water purification and deionization, and the decreased use of aluminum-containing phosphate-binders, aluminum toxicity no longer occurs. It was previously treated with intravenous desferrioxamine on dialysis [15].

Shortened red blood cell life span

The life span of an RBC in normal healthy individuals is approximately 120 days. RBC survival studies in uremic patients have indicated that the average life span of an RBC is generally shorter than this, as low as 60–90 days; this is due to increased RBC fragility, causing low-grade hemolysis [16,17].

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