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Clinical management of anaemia pre-endstage renal failure

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Anaemia is an early complication of chronic renal failure (CRF) and part of the growing public health problem presented by chronic kidney disease (CKD). Solutions to public health problems require strategies for early identification and prevention of the associated adverse outcomes; these in turn require an understanding of those adverse outcomes and their prevalence. The National Kidney Foundation-Kidney Dialysis Outcomes Quality Initiative (NKF-KDOQI) recommends a target haemoglobin (Hb) range for renal anaemia treatment of 11–12 g/dl.[1] The European Best Practice Guidelines (EBPG) recommend that 85% of patients with CRF should attain an Hb level of above 11 g/dl.[2] Despite these recommendations, surveys demonstrate that less than a quarter of pre-endstage renal failure (pre-ESRF) patients in the USA and less than a third in Europe receive active anaemia management. Management of renal anaemia is further complicated by the role played by iron, and the concept of functional iron deficiency. This article will review the following:

- the definition of pre-ESRF, renal anaemia and iron deficiency
- the pathogenesis, prevalence and adverse outcomes of anaemia in this patient group
- the investigation and treatment of anaemia
- target levels of Hb, and
- the adverse effects of treatment.

Definition of pre-endstage renal failure, renal anaemia and iron deficiency

Pre-endstage renal failure

A recent KDOQI workshop clearly defined five stages of CKD related to glomerular filtration rate (GFR) corrected for body surface area (Table 1).[3] For the purposes of this article, patients with pre-ESRF are considered to be those with stage 3–4 CKD or stage 5 CKD not requiring renal replacement therapy. In evaluating patients with kidney disease it is essential to think in terms of renal function rather than to rely on measurements of serum creatinine (SCr) alone. An estimate of renal function may be obtained by either the Cockcroft-Gault calculation of creatinine clearance (CrCl) or the modified Modification of Diet in Renal Disease (MDRD) equation for GFR (Box 1).

Renal anaemia

Anaemia in CKD is currently defined as Hb less than 11 g/dl in premenopausal women and prepubertal patients, and

Table 1. Stages of chronic kidney disease.

Stage	GFR (ml/min)	Descriptor
1	>90	Kidney disease with normal or increased GFR
2	60–89	Kidney disease with mildly reduced GFR
3	30–59	Moderately severe renal failure
4	15–29	Severe renal failure
5	<15	End-stage renal failure

GFR = glomerular filtration rate.

BOX 1

Cockcroft-Gault (estimated CrCl)

Men: CrCl = (140-age) × (weight/SCr × 72)

Women: CrCl = 0.85 × (140-age) × (weight/SCr × 72)

Age in years, SCr in μmol/l

Modified MDRD equation (estimated GFR)

GFR = 186 × $(SCr/88)^{-1.154}$ × $age^{-0.203}$ × (0.742 for women) × (1.212 for afro-carribeans)

SCr level (μmol/l)

less than 12 g/dl in adult males and postmenopausal women. Causes of anaemia other than CKD should be actively looked for and excluded before a diagnosis of renal anaemia can be made (Table 2).

Iron deficiency

The most commonly used methods to detect iron deficiency are serum ferritin and transferrin saturation (TSAT). Serum ferritin measures iron stores, but does not reflect the availability of functional iron. Iron deficiency may be absolute when iron stores are depleted such that ferritin levels are less than 20 μg/l.

Functional iron deficiency describes the situation where ferritin levels are normal but insufficient iron is available for erythropoiesis. Commonly used measures of functional iron deficiency include TSAT and percentage of hypochromic red cells (Box 2).

A serum ferritin level of 100 μg/l or less in patients with CKD is considered to be iron deficiency. A serum ferritin of 100–200 μg/l in association with a TSAT of less than 20% or more than 10% hypochromic red cells represents functional iron deficiency.

Pathogenesis of renal anaemia and prevalence of anaemia and iron deficiency in pre-endstage renal failure

Renal anaemia in CKD may develop in response to a wide variety of causes, but erythropoietin (EPO) deficiency is the primary cause. Predominantly produced by peritubular cells in the kidney, EPO is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow. Loss of peritubular cells leads to an inappropriately low level of circulating EPO in the face of anaemia. Other factors in the genesis of renal anaemia include:

- functional or absolute iron deficiency
- blood loss (either occult or overt)
- the presence of uraemic inhibitors (eg parathyroid hormone)
- reduced half-life of circulating blood cells, and
- folate or vitamin B12 deficiency.

It is generally accepted that anaemia as a complication of CRF develops at a GFR below 45 ml/min and below 30 ml/min in patients with diabetic renal disease and nondiabetic renal disease, respectively. However, the relationship between Hb level and reduced renal function begins much earlier. Data from NHANES III (see end of text for explanation of studies) suggest that the decline in Hb level starts at a GFR of 70 ml/min in men and 50 ml/min in women.[4] The prevalence of renal anaemia increased from 1% at an estimated GFR of 60 ml/min, to 9% and 33% at estimated GFRs of 30 ml/min and 15 ml/min, respectively. In terms of absolute numbers, the authors estimated that 800,000 adults in the USA have Hb levels below 11 g/dl in association with CKD. There are no similar published data in the UK, but our study of unreferred CRF (defined as a median GFR of 28.5 ml/min) has identified a prevalence of 1,295 adults per million with significant anaemia (Hb <11 g/dl).

Iron availability is crucial for optimal erythropoiesis but there are few studies of iron status in pre-ESRF. Analysis of the NHANES III data revealed that in the

Table 2. Other causes of anaemia in chronic kidney disease.

- Chronic blood loss
- Vitamin B12 or folate deficiency
- Hypothyroidism
- Chronic infection or inflammation
- Hyperparathyroidism
- Aluminium toxicity
- Malignancy
- Haemolysis
- Bone marrow infiltration
- Pure red cell aplasia

BOX 2

TSAT

TSAT = serum iron × 100/TIBC *or*

= serum iron (μg/dl) × 70.9 divided by serum transferrin (mg/dl)

TSAT <20% – serum ferritin 100–200 μg/l suggests functional iron deficiency

(TIBC = total iron binding capacity)

Percentage of hypochromic red cells

Reflects the number of red blood cells with suboptimal Hb:

- normal <2.5%
- indeterminate 2.5-10%
- functional iron deficiency >10%

NB: serum ferritin levels are increased by inflammation and liver disease, without any change in iron stores. Transferrin levels are also influenced by inflammation and nutrition (correlating with serum albumin levels).

GFR range 30–50 ml/min fewer than one-third of men and women with Hb levels below 12 g/dl and 11 g/dl, respectively, had ferritin levels above 100 µg/l and TSAT greater than 20%.[5] In addition, TSAT levels above 20% were independently associated with higher Hb levels.

Adverse outcomes associated with renal anaemia

Anaemia has a number of adverse consequences ranging from effects on quality of life, cognitive function and libido through to increased mortality and morbidity (Table 3). Of paramount importance is the strong association between anaemia, CKD and cardiovascular disease (CVD). The link between CKD and increased mortality and morbidity from CVD has been demonstrated in a variety of studies, some of which are summarised in Table 4.[6–12] Anaemia has both direct and indirect effects on left ventricular (LV) function and growth leading to eccentric LV hypertrophy (LVH). In the Canadian multicentre cohort study,[8] Levin *et al* found an inverse correlation between Hb level and the degree of LVH. A number of studies have shown that anaemia predicts increased LV mass, LV dilatation, heart failure and death.

Table 3. Adverse effects of anaemia.

- Reduced oxygen utilisation and increased cardiac output
- LV hypertrophy – LV dilatation
- Reduced capillary skin perfusion
- Muscle weakness and leg cramps
- Reduced physical functioning
- Reduced cognition and sleep disturbance
- Reduced libido and altered menstrual cycle in women
- Reduced immune responsiveness
- Reduced appetite and poor nutrition

LV = left ventricular.

Anaemia is also associated with increased hospitalisation rates and increased mortality, while correction of anaemia reduces mortality (cardiovascular and all-cause) and hospitalisation in dialysis patients treated for anaemia predialysis.[13] The key question to be answered is whether anaemia treatment earlier in the course of CKD would affect cardiovascular outcomes.

Relationship between anaemia, heart failure and renal failure

Recent reports suggest that mild to moderate anaemia is prevalent in patients with heart failure. Analysis of patients in SOLVD found that anaemia and CKD were independent risk factors for mortality amongst patients with heart failure due to LV dysfunction.[9] A recent retrospective study of 665 patients admitted with a principal diagnosis of heart failure demonstrated that Hb level and SCr at time of admission were independently associated with increased subsequent risk of death.[14] In a cohort of 1,061 patients with New York Heart Association (NYHA) class III or IV heart failure each 1 g/dl decrease in Hb level was associated with a 16% increased risk of death.[15]

In the UK, 6,000 deaths per year are due to heart failure associated with coro-

Table 4. The association of chronic kidney diseases with cardiovascular risk.

Study	Level of renal function	Cardiovascular outcomes
HDFP[6]	SCr (µmol/l) >150 vs <150	At 8 years, subjects with SCr >150 µmol/l had 2.2 increased OR of death
Framingham[7]	Renal insufficiency SCr (µmol/l) 136–265 in men, 120–265 in women	Those with renal insufficiency had 19.2% incidence of CVD vs 11.7% in those without and 15.3% incidence of CHD vs 7.9%
Canadian multicentre cohort of renal insufficiency (predialysis)[8]	Mean GFR 36.3 ml/min	Incidence of CVD rose from 35.2% in those with GFR >50 ml/min to 45.3% in those with GFR <25 ml/min
SOLVD[9]	GFR (ml/min) <60 vs >60	Increased RR all-cause mortality of 1.41 and RR of mortality from pump failure of 1.68
HOPE[10]	Renal insufficiency defined by SCr 124–200 µmol/l	Incidence of cardiovascular mortality, MI or stroke 22.2% vs 15.1% in those with SCr <124 µmol/l
Birmingham predialysis[11]	Mean creatinine clearance 26 ml/min	21% of the cohort had LVH at presentation with a prevalence of LV dysfunction 3 times that of the normal population
Cardiovascular health[12]	SCr (µmol/l) >132 in men, >114 in women	Renal insufficiency conveyed an OR of 2.34 for CVD

CHD = coronary heart disease; CVD = cardiovascular disease; GFR = glomerular filtration rate; LVH = left ventricular hypertrophy; MI = myocardial infarction; OR = odds ratio; RR = relative risk; SCr = serum creatinine.

Table 5. Anaemia treatment in congestive heart failure.

Study	Patients	Intervention & outcome
Retrospective, observational[17]	26 patients with severe CCF, Hb <12 g/dl	sc EPO and iv Fe to increase Hb to >12 g/dl, follow-up 7.2 – 5.5 months LVEF increased and hospitalisations fell by 91.9% cf pretreatment
Randomised controlled trial[18]	32 patients with NYHA III-IV heart failure, LVEF #40%, Hb 10–11.5 g/dl randomised to anaemia treatment (Group A, n=16) or no anaemia treatment (Group B, n=16)	Group A treated with sc EPO – iv Fe to achieve Hb $12.5 g/dl, follow-up 8.2 – 2.6 months NYHA class improved by 42.1% in Group A, deteriorated by 11.4% in Group B LVEF improved by 5.5% in Group A, worsened by 5.4% in Group B Hospitalisation fell by 79% in Group A, increased by 57.6% in Group B
Open uncontrolled, observational[19]	179 patients with NYHA III-IV heart failure, 84 with type 2 diabetes mellitus (mean Hb 10.41 – 1.0 g/dl, mean SCr 188 – 70 μmol/l), 95 nondiabetic (mean Hb 10.5 – 1.0 g/dl, mean SCr 209 – 100 μmol/l)	sc EPO and iv Fe to achieve Hb >12.5 g/dl, follow-up 11.8 – 8.2 months Hb increased to 13.1 – 1.3 g/dl in diabetics, 12.9 – 1.2 g/dl in nondiabetics, SCr remained unchanged NYHA class improved by 34.8% in diabetics, 32.4% in nondiabetics LVEF increased by 7.4% in diabetics, 11.5% in nondiabetics Hospitalisation fell by 96.4% in diabetics, 95.3% in nondiabetics cf pretreatment

CCF = congestive heart failure; cf = compared with; EPO = erythropoietin; Fe = iron; Hb = haemoglobin; iv = intravenous; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; sc = subcutaneous; SCr =serum creatinine.

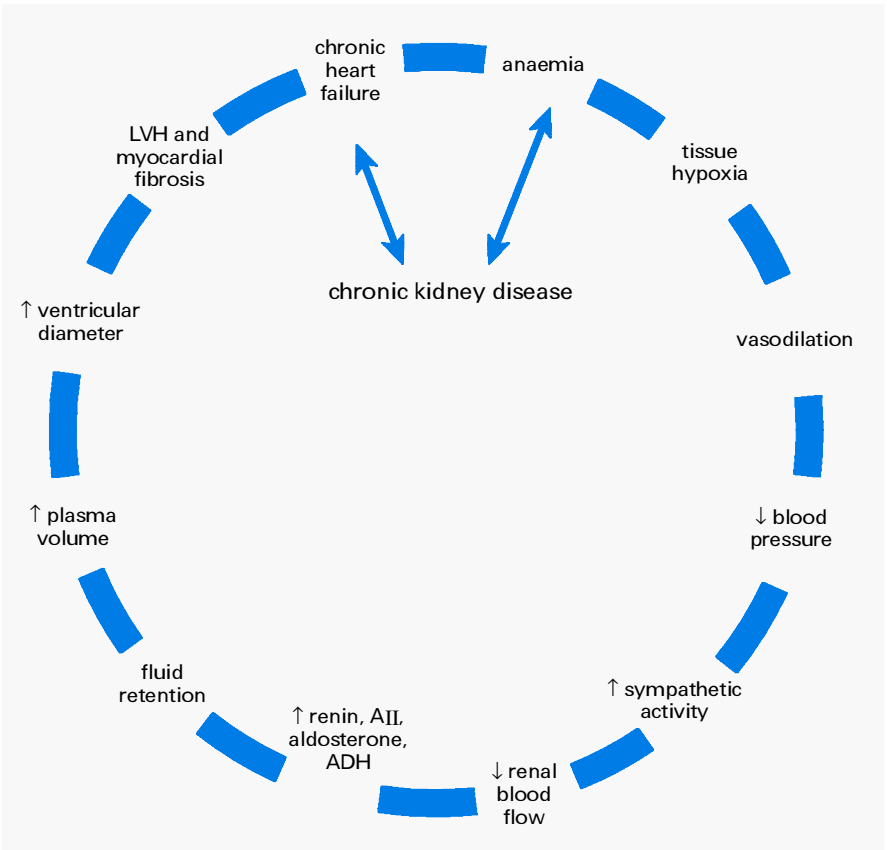

Fig 1. Relationship between anaemia, chronic kidney disease and heart failure (AII = angiotensin II; ADH = antidiuretic hormone; LVH = left ventricular hypertrophy) (adapted from Ref 19).

nary heart disease (CHD). The annual mortality from heart failure ranges from 10–50% (or higher) depending on severity. Standard 11 of the National Service Framework for CHD dictates that treatments most likely to relieve symptoms and reduce the risk of death in patients with heart failure should be offered.[16]

Improvements in cardiac function, shorter hospitalisation and reduction in the rate of progression of renal failure have been reported in uncontrolled and controlled studies of correction of anaemia with iron and EPO in patients with resistant heart failure (Table 5).[17–19] The authors called this close association between anaemia, renal failure and cardiac failure the 'cardio-renal anaemia syndrome', and suggested that aggressive control of anaemia may slow the progression of both CRF and heart failure (Fig 1).

Two studies, CREATE and CHOIR, are currently addressing this in less selected populations of patients with renal impairment (Fig 2). Both have a similar design and seek to establish whether early intervention in terms of anaemia treatment prevents development of LVH,

Key Points

Anaemia associated with pre-endstage renal failure is under-recognised and under-treated

Risk of cardiovascular disease begins early in the evolution of chronic kidney disease and is increased by anaemia

KEY WORDS: anaemia, cardiovascular disease, chronic kidney disease, erythropoietin (EPO) deficiency

reduces cardiovascular mortality and morbidity, delays progression of CRF and reduces stroke- and heart failure-related hospitalisation.

Treatment of anaemia, adverse effects and haemoglobin target levels

Recombinant human EPO is an effective treatment for renal anaemia. A treatment algorithm is shown in Fig 3. The usual starting dose of EPO is 40–60 iu/kg, once a week or in two or three divided doses, or the equivalent dose of darbopoietin (1 µg to 200 iu EPO), once a week or fortnightly. The subcutaneous route is both more efficient and easier to administer in predialysis patients. The rate of increase in Hb should be 0.5–1.0 g/dl per month. EPO therapy requires monitoring (Table 6); adverse effects are few, mainly relating to increase in haematocrit and blood viscosity (Table 7).

Target haemoglobin

What should be the target haemoglobin level? The EBPG and NKF-KDOQI both recommend correction to Hb levels of at least 11 g/dl. Large observational studies in dialysis patients have shown improvements in mortality and hospitalisation rates up to Hb levels of 13g/dl.[13] The largest randomised controlled trial (the US normalisation of haematocrit trial) suggested increased cardiovascular mortality with higher Hb levels in dialysis patients.[20] However, studies in cardiac failure clearly demonstrate better survival with higher Hb levels in nondialysed patients.[14,15] Studies of treatment of anaemia in heart failure aimed for Hb levels of at least 12.5 g/dl, with improvements in mortality, NYHA grade, LV ejection fraction and hospitalisation rates.[18,19] It is likely that the two large trials in predialysis patients, CREATE and CHOIR, will provide the answer and dictate future practice in the correction of predialysis anaemia.

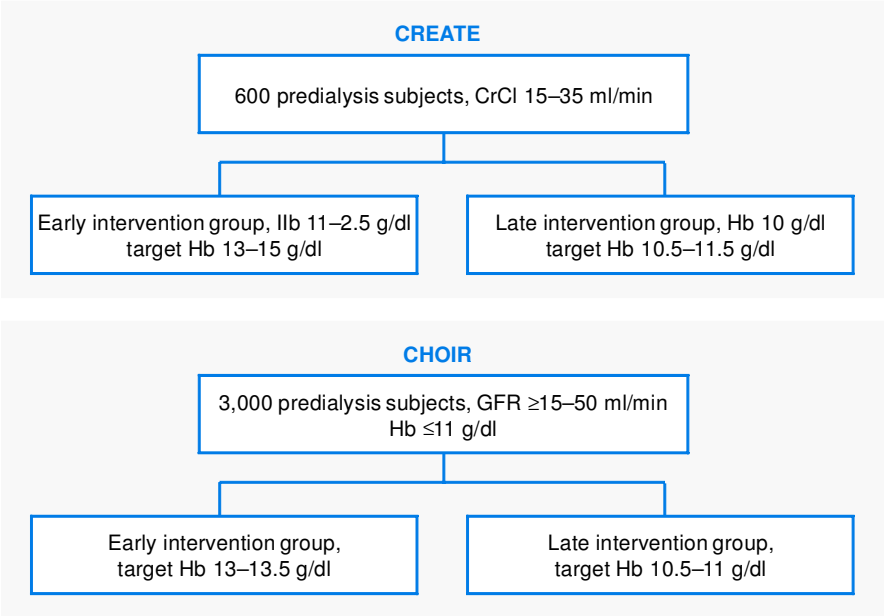

Fig 2. Randomised controlled trials of anaemia treatment in pre-endstage renal failure (see end of text for explanation of studies) (CrCl = creatinine clearance; GFR = glomerular filtration rate; Hb = haemoglobin).

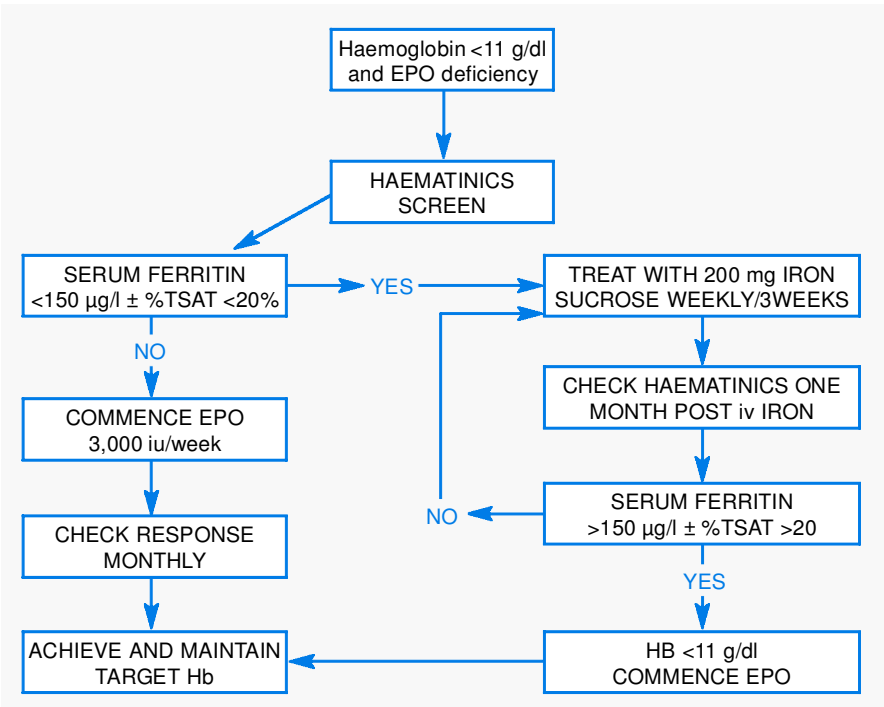

Fig 3. Treatment algorithm for anaemia treatment in pre-endstage renal failure (EPO = erythropoietin; Hb = haemoglobin; iu = international unit; iv = intravenous; TSAT = transferrin saturation).

Table 6. Monitoring of treatment with erythropoietin.

Test	Frequency
Full blood count	Every 2 weeks until target Hb level reached and Hb stabilised. Thereafter, every 1–3 months depending on clinical circumstances
Iron studies (serum ferritin and TSAT/% hypochromic red cells)	Every 4 weeks until Hb stabilised, then 3–monthly
Vitamin B12 and folate	Every 6 months

Hb = haemoglobin; TSAT = transferrin saturation.

Table 7. Adverse effects of erythropoietin therapy.

- Hypertension: occurs in 20–30% patients, easily treatable
- Vascular access thrombosis
- Hyperkalaemia
- Myalgia and flu-like symptoms
- Injection pain and skin irritation around the injection site
- Pure red cell aplasia: very rare, associated with anti-erythropoietin antibodies

Trial acronyms

HDFP	Hypertension Detection and Follow-up Program
HOPE	Heart Outcomes Prevention Evaluation
SOLVD	Studies Of Left Ventricular Dysfunction
CREATE	Cardiovascular Reduction Early Anaemia Treatment with Epoetin Beta
CHOIR	Correction of Haemoglobin and Outcomes in Renal Insufficiency
NHANES	National Health and Nutrition Examination Survey

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