Research Review
EDUCATIONAL SERIES

Anaemia management in patients with diabetes and kidney disease

Introduction

Diabetes, particularly type 2, is now the leading single cause of chronic kidney disease (CKD) and is associated with excessive overall and cardiovascular morbidity and mortality.[1,2]

Anaemia is commonly found in diabetic patients with CKD and represents a significant burden, with observational studies suggesting that low haemoglobin (Hb) levels in such patients may both increase risk for progression of kidney disease and worsen cardiovascular morbidity and mortality.[4-6]

This publication is intended as an educational resource for health professionals. It presents a short background on the prevalence, causes, and clinical consequences of anaemia, discusses the benefits and risks of treatment, and provides insight into anaemia management based on peer-reviewed clinical trial evidence in patients with diabetes and kidney disease who are not on dialysis. It is intended to help readers stay informed of developments and advancing clinical practice in the areas covered.

About Research Review

Research Review is an independent medical publishing organisation producing journals including Diabetes and Obesity Review, Anaesthesia Research Review, and Sexual Health Review. These journals provide summaries of studies from the most respected medical journals in the world together with a local specialist commentary indicating why they matter in New Zealand.

About the Reviewers

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The burden of anaemia in diabetes and chronic kidney disease

Worldwide literature increasingly attests to the significant morbidity, mortality and economic burden of CKD.[7,8] With a growing number of patients expected to be affected in the future, approaches are required to improve anaemia management in CKD without increasing the burden on healthcare professionals.[7] It has been estimated that CKD and its effects may account for about one-third of New Zealand's health costs[9] and numbers of sufferers are predicted to rise dramatically; epidemiological research predicts that up to one in seven New Zealanders may have some degree of renal disease.[9] The current epidemic of type 2 diabetes in New Zealand will have major implications for this country's limited health resources.[10] In 2007, diabetic kidney disease accounted for 46% of new patients commencing dialysis.[11] Further, patients with CKD have a 3- to 5-fold higher risk of cardiovascular events; the death rate is 20-fold higher in those with diabetes and CKD compared to the healthy population.[10] Due to the public health burden and cost it is important to raise awareness of this condition and encourage early detection and treatment.[12-16] Renal replacement therapy (RRT) costs between NZ$25,000 and NZ$70,000 per year, dependent on modality of dialysis.

CKD is defined as kidney damage with structural and/or functional abnormalities or a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, or both, for ≥3 months. In adults, the best equation to use for predicting GFR from serum creatinine is the Modification of Diet in Renal Disease calculator. Although this approach does not correct adequately for age and ethnicity, it remains superior to creatinine alone. CKD is staged as follows:[3]

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage* with normal or increased GFR	>90
2	Kidney damage with mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure	<15 or dialysis

* Defined by the National Kidney Foundation as 'pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies'.

eGFR = estimated Glomerular Filtration Rate.

Definition and prevalence of anaemia in diabetic patients with CKD

Anaemia in CKD is defined as a Hb concentration below certain threshold levels, which vary slightly between the National Kidney Foundation Disease Outcome Quality Initiative (NKF-KDOQI),[3] the World Health Organisation (WHO),[25] and the European Best Practice Guidelines (EBPG) for the Management of Renal Anaemia in Patients with Chronic Renal Failure.[26]

Organisation	Threshold haemoglobin concentrations for the diagnosis of anaemia (g/L)	
	Adult males	Adult females
NKF-KDOQI[11]	135	120
WHO[12]	130	120 (110*)
EBPG[13]	135 (120†)	115

* Pregnant women; † Men >70 years old.

An estimated one in five patients with diabetes and stage 3 CKD have anaemia, with severity worsening in more advanced stages of CKD and in those with proteinuria.[18,27,28] The distribution of Hb in patients with diabetes and CKD is similar to that in those without diabetes, but on average, Hb levels are slightly lower, possibly attributable to reduced erythropoietin levels. It is therefore recommended that clinicians measure serum creatinine, to estimate GFR and quantify albumin excretion rate (albumin:creatinine ratio) and measure haemoglobin in diabetic patients with CKD.

Diabetes, predominantly type 2, is now the leading cause of renal failure requiring RRT in New Zealand. Diabetic nephropathy usually, but not always, manifests as microalbuminuria. Proteinuria progressively increases, often followed by a progressive decline in GFR and eventually end-stage renal failure (ESRF).[29] A variety of interventions have the potential to slow or even halt the progression of diabetic nephropathy, delay the requirement for RRT and thus extend patient survival.

Hypertension, ACE inhibitors and ARBs

Tight blood pressure (BP) control is the mainstay of therapy for all renal disease. Due to direct effects on glomeruli, ACE inhibitors and angiotensin receptor blockers (ARBs) provide renal protection over and above their effect on BP and are thus the antihypertensive agents of choice.[35-39] BP targets are patient-dependent; any reduction in BP is beneficial. A target of 120–130/70–80 mmHg in proteinuric patients is recommended. Proteinuric patients should be on the maximal recommended dose of ACE inhibitors or ARBs if tolerated.

ACE inhibitors and ARBs both slightly reduce haemoglobin concentration, possibly by reducing erythropoietin secretion. The benefits of these agents in the setting of CKD and proteinuria far outweigh the small impact they have on haemoglobin concentration. Dual blockade is controversial and use should be limited to nephrologists or diabetologists.

Salt intake

A high sodium intake results in higher and more difficult to control BP. Reducing salt intake enhances the anti-proteinuric effect of ARBs.[40] Diuretics in combination with an ACE inhibitor or ARB are a mainstay of antihypertensive therapy, as sodium retention is a feature of the condition. Loop diuretics are often needed with established stage 3 or worse CKD.

Spironolactone and aldosterone antagonists (not available in New Zealand) further reduce BP and proteinuria, but have not been shown to influence outcomes; both have high rates of side effects.

Weight reduction

Significant weight loss in obese patients results in a reduction in proteinuria and BP in addition to its other benefits.[41]

Glycaemic control

Tight glycaemic control prevents the development of proteinuria, reduces proteinuria when present and delays progression of renal failure.[30-33] Glycaemic targets are patient-dependent, but a target HbA1c of 7% in type 1 and 7% (not less than 6.5%) in type 2 diabetics seems reasonable.[34] "Tight" control is less advised when ischaemic heart disease is present and hypoglycaemia must be energetically avoided in these patients. Renal failure results in reduced excretion of both sulphonylureas and insulin, and doses may need to be reduced, often substantially. Gliclazide is the preferred sulphonylurea due to its shorter half-life and part hepatic metabolism.

Metformin

Metformin is widely used in the treatment of type 2 diabetes. However, because it is excreted unchanged in the urine, impaired renal function will lead to accumulation and increases the risk of potentially life-threatening lactic acidosis. Recommendations for use in renal impairment vary between international guidelines. New Zealand guidelines advise that metformin is contraindicated in those with renal impairment and those at risk of sudden deterioration of renal function (i.e. serum creatinine ≥0.15 mmol/L, or creatinine clearance <60 mL/sec). This is controversial with less evidence of lactic acidosis than previously thought and many experts continue to use metformin to GFRs of around 35. Any decision to continue metformin at GFR values of <40–45 mL/min should probably be in consultation with diabetologists and nephrologists.

Lipid control

Aggressive lipid lowering is an essential part of the cardiovascular risk management of most patients with diabetes. The effect of lipid lowering on diabetic nephropathy and outcomes is not clear.

Anaemia

Anaemia is a feature of all CKD, most commonly with GFRs of <30 mL/min, but is often present at earlier stages. It is useful to measure Hb early in the course of renal disease to establish a "normal" baseline for that individual. Renal anaemia does occur at higher GFRs and people with diabetes ('diabetics' regarded as insulting) seem to become anaemic at a higher GFR than CKD patients without diabetes. Untreated anaemia is associated with deterioration in cardiac function, decreased cognition and mental acuity, fatigue, and other signs and symptoms. There are also associations with an increased risk of morbidity and mortality, principally due to cardiac disease and stroke. Correction of anaemia with ESAs results in an improvement in QoL, improved cognitive functioning, reduced transfusion requirement and possible prevention of left ventricular hypertrophy.[42-44] From a patient's perspective, correction of anaemia results in better symptom control than any other intervention. It has not, however, been demonstrated to alter mortality, correct left ventricular hypertrophy or to slow progression of CKD.[17-21] All CKD patients should therefore have their haemoglobin checked and erythropoietin considered if they are anaemic. Correction of haemoglobin to 125–130 g/L seems to be associated with an increase in cardiovascular events (CHOIR, CREATE and TREAT) – see page 4. Thus, a target haemoglobin of 110–120 g/L is currently suggested.

Causes of anaemia

Vitamin deficiencies such as folate and B_{12} are relatively uncommon causes of anaemia in diabetic patients with CKD, and clinical practice guidelines do not recommend routine measurement of these serum levels unless the blood indices and film indicate a need.

Iron deficiency

Iron deficiency is a major cause of anaemia in patients with diabetes and CKD, in whom dietary deficiency, low intestinal absorption, and gastrointestinal bleeding may lead to absolute iron deficiency anaemia. As many as 50% of patients with CKD stages 2–5 have absolute or relative (functional) iron deficiency anaemia, according to the U.S. National Health and Nutrition Examination Survey IV.[45] Both absolute and relative iron deficiency are common in CKD. Absolute iron deficiency is defined as a depletion of tissue iron stores (serum ferritin level <100 ng/mL or a transferrin saturation of <20%), while functional iron deficiency anaemia is adequate tissue iron defined as a serum ferritin level ≥100 ng/mL and a reduction in iron saturation. The latter is more common and is strongly associated with upregulation of inflammatory cytokines and impaired tissue responsiveness to erythropoietin (EPO), which can inhibit iron transport from tissue stores to erythroblasts.[46] Increased levels of inflammatory cytokines such as interleukin-6 enhance production and secretion of hepcidin, a hepatic protein that inhibits intestinal iron absorption and impairs iron transport from the reticuloendothelial system to bone marrow. In addition, EPO, which normally enhances iron transport from macrophages to the blood stream, is impaired, thereby exacerbating relative iron deficiency.[47]

Notably, up to 50% of patients with CKD and inflammation develop anaemia of chronic disease, increasingly known as "anaemia of inflammation", which develops under chronic inflammatory disorders such as chronic infections, cancer or autoimmune conditions.[48] While EPO treatment of severe anaemia may improve well-being and decrease the frequency of transfusion in patients with renal failure, some suggest that anaemia of chronic disease is a beneficial adaptive response and could be beneficial to patients with inflammatory disease; pharmacological over-ride of anaemia of chronic disease may then be harmful and even increase mortality.[49]

Erythropoietin deficiency and hypo-responsiveness

Both deficiency and hypo-responsiveness to EPO contribute to anaemia in diabetic patients with CKD.[28,50] It is thought these patients develop erythropoietin deficiency due to reduced renal mass with consequent depletion of the hormone. Hypo-responsiveness is defined clinically as a requirement for high doses of EPO in order to raise the haemoglobin level in the absence of iron deficiency. It is believed to represent impaired anti-apoptotic action of EPO on proerythroblasts. Possible causes of this erythropoietin hyporesponsiveness include systemic inflammation and microvascular damage in the bone marrow.[28,50] However, some studies suggest that other factors (i.e. autonomic failure from the diabetes) may play a role in impaired erythropoietin production or secretion by failing kidneys.[51]

Nephrotic syndrome

Diabetic nephropathy is the most common cause of secondary nephrotic syndrome in New Zealand. This often presents with oedema in the setting of heavy proteinuria and may occur before GFR begins to decline, but may initially be noted only on laboratory results; serum albumin should be checked in all patients with heavy proteinuria. The presence of nephrotic range proteinuria usually heralds a progressive decline in renal function and ESRF. Urinary iron excretion is increased early in the course of diabetic renal disease and is exacerbated by development of nephrotic range proteinuria. Nephrotic syndrome is characterised by significant losses of transferrin and erythropoietin, leading to both iron- and erythropoietin-deficiency anaemia in patients with diabetes.[51]

Consequences of anaemia

Progression of kidney disease

Anaemia is thought to play a role in the progression of kidney disease and contribute to worsening kidney function by aggravating underlying heart failure.[18,52-54] Recent clinical evidence indicates that EPO supplementation may ameliorate renal tubular damage by reducing oxidative stress in patients with anaemia and CKD, independently of Hb level.[55] However, using EPO to correct anaemia has not shown any renal outcome benefit in clinical trials.[22,56]

Cardiovascular disease

In patients with diabetes and CKD, cardiovascular disease is the most common cause of death and anaemia appears to add to the risk of all-cause mortality in these patients. Observational data demonstrate that, compared with the general population, the risk of anaemia is increased 10-fold in patients with CKD, heart failure and diabetes, and is a risk factor amenable to treatment, particularly related to complications such as advancing heart failure.[57,58] Treatment of anaemia in patients with diabetes and CKD has therefore been advocated as a means of reducing excessive cardiovascular morbidity and mortality.

Quality of life

Anaemia in patients with diabetes and CKD is associated with poor QoL. Such patients experience significant physical and mental impairments such as malaise, fatigue, weakness, dyspnoea, impaired cognition, amongst other symptoms. Evidence also indicates that anaemia in diabetes contributes to retinopathy, neuropathy, diabetic foot ulcer, hypertension, progression of kidney disease, and cardiovascular events.[28] In clinical trials, treatment of anaemic diabetic patients with CKD has been shown to improve cognitive function, sexual function, general well-being, exercise capacity, and reduces the need for blood transfusions.[17,19-21,59]

How often should GFR and serum creatinine be checked in patients with diabetes and renal anaemia?

Optimum frequency of blood tests in patients with CKD is dependent predominantly on individual patient characteristics, mainly the stability of renal function. Patients with stage 3 CKD should have their renal function checked every 3 months, and this can coincide with their regular diabetes checks (HbA1c). Patients with diabetes and no known renal disease should have yearly renal function assessment. Patients with later-stage CKD will usually be known to a nephrologist and may or may not require more frequent checks of renal function (national referral guidelines).

How often should their haemoglobin be checked?

Diabaetic CKD patients not on EPO should have their haemoglobin checked when they are having other bloods, but not more often than 3-monthly. The Caring for Australasians with Renal Impairment (CARI) guidelines[60] recommend checking haemoglobin levels every 2 weeks. Individual renal units may have slightly different protocols.

What is the cut-off haemoglobin level to start EPO?

Haemoglobin of ≤100 g/L with normal iron studies and no other cause for anaemia (and see below).

What is the GFR cut-off level for referral to a nephrologist?

As per the national renal referral guidelines, which have been sent to all GPs and are available on the Kidney Health NZ website under Resources, Health Professionals: http://www.kidneys.co.nz/health-professionals .

Indications for referral to a nephrologist:

- All patients with stage 4 or 5 CKD.
- Patients with Stage 3 if they are young, have haematuria, proteinuria or if renal function is not stable or there is no clear cause of CKD.
- Stage 1 and 2 CKD if active urinary sediment.

What can be done for renal anaemia while a patient is waiting for a specialist appointment?

There is regional variation. Most large centres have an anaemia nurse who will co-ordinate EPO therapy. Smaller centres may either see the patient first or apply and ask the patient's GP to commence EPO and then see the patient later in clinic.

Treating patients with renal anaemia

The evidence-based CARI guidelines and diabetes guidelines[61] provide guidance on patient management. The treatment of choice for the anaemia of CKD and ESRF is recombinant EPO (rhEPO), which obviates the need for blood transfusions. The two forms of rhEPO available in New Zealand are rhEPO alfa (Eprex®; Janssen-Cilag) and rhEPO beta (NeoRecormon®; Roche).[62,63] These variations of rhEPO appear to have the same efficacy, although rhEPO beta is associated with a lower reported incidence of serious idiosyncratic adverse events (pure red cell aplasia). Both can be administered subcutaneously or intravenously. PHARMAC fully subsidises both formulations.

The PHARMAC criteria for rhEPO beta allow fully funded drug therapy for patients who:

- have a haemoglobin of ≤100 g/L AND
- have an eGFR of ≤45 ml/min (with diabetes mellitus) OR
- have an eGFR of ≤30 ml/min (without diabetes mellitus) OR
- are on haemodialysis or peritoneal dialysis.

In most patients with CKD, investigations of anaemia yield no other cause apart from reduced GFR.

rhEPO dosage

The starting dose should be 50–120 IU/kg/week, administered subcutaneously (via the anterior abdominal wall) as 2 to 3 divided doses. The Hb concentration should be monitored fortnightly until the target Hb is reached, then monthly thereafter. The initial rate of Hb increase should be 10–20 g/L/month. If there is a change of <10 g/L/month over 2–3 months, the weekly rhEPO dose should be increased by 25%. If the Hb rate of increase is >20 g/L/month, the total weekly dose should be reduced by 25–50%. In the maintenance phase, once the target level is achieved, Hb monitoring should be 2–3-monthly. For any change of Hb by 10 g/L, the rhEPO weekly dose should be increased or decreased by 25%. With education (hospital or community nurses), most patients are able to administer the injection which comes in pre-filled syringes. Caregivers and community nurses can administer the injection in those cases where the patient cannot manage self administration.

Oral iron such as ferrous fumarate should also be started concurrently with rhEPO. The target ferritin level (often high and unreliable in poorly-controlled diabetes) may not be achieved with oral iron as its absorption is poor in those with significant renal dysfunction. In such cases, iron infusion is recommended.

BP should be monitored closely, especially in the initiation phase. Up to a quarter of patients will develop or exacerbate pre-existing hypertension, needing altered treatment.

New Zealand perspective on management

Despite the dramatic increase in the prevalence of type 2 diabetes, the numbers of patients with diabetes requiring dialysis has not increased to the same extent. This represents a real success and has been seen even more dramatically in the USA, although the rate of RRT continues to rise in Australia. There are relatively high rates of ACE inhibitor/ARB use in New Zealand, although perhaps 20% of patients still reach ESRF without prior detection and treatment; Māori and Pacific patients are over-represented among these.

Rigorous annual testing for microalbuminuria and plasma creatinine would detect almost all of these patients. The challenge is in early detection and energetic treatment, especially of BP, and prompt referral to diabetologists (stage 3) or nephrologists (stage 4) of those patients whose renal function continues to deteriorate. Once renal function has declined below an eGFR of approximately 30 without treatment, it is unlikely that subsequent treatment will halt progression of the renal failure before ESRF occurs.

While erythropoietin-stimulating agents (ESAs) are associated with improved quality of life (QoL) in controlled trials of anaemia treatment, ESAs do not improve patient outcomes.[17-21] Indeed, ESA treatment targeting high Hb levels has been linked to worse outcomes such as increased thrombosis and possibly stroke risk.[17,22] In the TREAT study, treatment with the ESA darbepoetin alfa had no effect on reducing mortality, heart failure, heart attacks, or the need for dialysis in diabetic patients with anaemia and CKD.[23] In fact, darbepoetin alfa was associated with a higher risk for stroke and cancer-related mortality. It is important to emphasise that these adverse outcomes are linked to the achievement of higher Hb targets; when rhEPO is administered with a target Hb level of 110–120 g/L (as recommended by current international guidelines) and patients undergo frequent monitoring for Hb levels, then patients will potentially benefit from being treated for their anaemia.

Insight into anaemia management based on clinical trial evidence

CREATE study

Normalization of hemoglobin level in patients with chronic kidney disease and anemia

Authors: Drüeke TB et al.

Summary: The multinational CREATE study involved 603 patients with stage 3 to 4 CKD and mild-to-moderate anaemia (Hb 110–125 g/L), who were randomised to treatment with epoetin beta to a target Hb of either 130–150 g/L (group 1) or 105–115 g/L (group 2). The primary endpoint was a composite of eight cardiovascular events. In a 3-year follow-up, there were no significant differences in cardiovascular event rates or in all-cause mortality between the two treatment groups. A greater number of patients required dialysis in group 1 than in group 2 (127 vs 111), but patients in group 1 achieved significantly better QoL outcomes (particularly with regard to physical function, vitality, and mental health). Overall, there were no significant differences in adverse events between the two groups, but vascular disorders were more prevalent in group 1, mainly because of a greater incidence of hypertension and more headaches.

Comment: See on right.

Reference: N Engl J Med. 2006;355:2071-84.

CHOIR study

Correction of anemia with epoetin alfa in chronic kidney disease

Authors: Singh AK et al.

Summary: In the US-based CHOIR study, 1432 patients with CKD not on dialysis were randomised to receive a dose of epoetin alfa targeted to achieve a Hb level of 135 g/L (high-Hb group; n=715) or 113 g/L (low-Hb group; n=717). The median study duration was 16 months. The primary endpoint was a composite of death, myocardial infarction, hospitalisation for congestive heart failure (other than for RRT), and stroke. Patients in the high-Hb group did not reach the 135 g/L target but achieved a mean Hb level of 126 g/L and did not show any additional QoL benefits over patients in the low-Hb group. A total of 125 primary composite endpoint events occurred in the high-Hb group versus 97 such events in the low-Hb group (HR 1.34; p=0.03). More patients in the high-Hb group had at least one serious adverse event (54.8% vs 48.5% of the low-Hb group).

Comment: See on right.

Reference: N Engl J Med. 2006;355:2085-98.

TREAT study

A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease

Authors: Pfeffer MA et al

Summary: This multinational trial sought to determine whether the use of darbepoetin alfa for the treatment of anaemia would reduce the risk of death, major cardiovascular events, and renal events in patients with CKD, type 2 diabetes, and anemia. The median achieved Hb concentrations were 125 g/L in the 2012 darbepoetin alfa recipients and 106 g/L in the 2026 placebo recipients. No between-group differences were observed in the overall rates of the primary endpoints (of death or a cardiovascular event or of death or ESRD). Fatal or nonfatal stroke occurred in 101 darbepoetin alfa recipients and 53 placebo recipients (HR 1.92; p<0.001). There was only a modest improvement in patient-reported fatigue in the darbepoetin alfa group as compared with the placebo group.

In an accompanying editorial, Dr. Marsden considers that the TREAT findings "*will influence practice guidelines and inform physicians, patients, and policymakers. In many of these stakeholders, the risk of stroke will outweigh the potential benefits of darbepoetin alfa*". (N Engl J Med. 2009;361:2089-90)

Comment: See on right.

Reference: N Engl J Med. 2009;361:2019-32.

Combined commentary:

CREATE was a randomised trial where patients with GFRs of 15–35 mL/min and mild anaemia (Hb 110–125 g/L) were treated to achieve a Hb of 130–150 g/L in the intervention arm and 105–115 g/L in the control arm. EPO was commenced in each arm when the Hb fell below the target range. The primary outcome was time to a composite cardiovascular endpoint. Secondary endpoints included all-cause mortality, cardiac death, heart failure, hospitalisation, cardiovascular intervention markers of left ventricular hypertrophy, time to initiation of renal replacement therapy, markers of nutrition and QoL.

A 19 g/L difference in Hb was achieved and there was no difference in cardiovascular endpoints, time to starting dialysis or left ventricular function indices. There was an improvement in QoL in the intervention arm.

CHOIR was published in the same issue of the New England Journal of Medicine. Over 1400 patients with stage 3 and 4 CKD and HB <110 g/L were randomised to receive EPO with a target Hb of 130–135 g/L vs 105–110 g/L. The primary endpoint was a composite cardiovascular endpoint. The main secondary endpoint was QoL. Almost 40% of the subjects did not complete the trial due to initiation of dialysis (17%) or other reasons (21%).

The study was terminated early because of low plausibility of achieving a benefit in the primary endpoint. For the primary endpoint, there was a higher risk of the combined cardiovascular endpoint in the high Hb arm (17.5% vs 13.5%; p=0.03).

Very recently, TREAT has been published. This study involved over 4000 subjects with type 2 diabetes, CKD (GFR 20–60 mL/min) and anaemia (Hb ≤110 g/L) and randomised them to EPO use with a target Hb of 130 g/L or placebo with rescue therapy if the Hb fell to <90 g/L. Once again, the primary endpoint was a cardiovascular composite endpoint. A difference in Hb of 19 g/L was attained. There was no difference between the groups in the primary endpoint, but there was a doubling of the rate of strokes in the intervention arm (5% vs 2.6%; p<0.001). BP was the same in both groups. There was an improvement in QoL in the intervention arm.

Taking these three trials together, there is a suggestion that using ESAs to achieve a Hb >130 g/L may result in an increased rate of adverse events and current international guidelines reflect this, with a suggested target Hb of 110–120 g/L.

Haemoglobin and haematocrit targets for the anaemia of chronic kidney disease

Authors: Strippoli GF et al

Summary: Data were reviewed from 22 randomised clinical trials and quasi-RCTs (n=3707) comparing different Hb and haematocrit targets in patients with anaemia of CKD. Increasing Hb to higher targets (≥133 g/L) did not reduce the risk of all-cause mortality compared with lower Hb targets (<120 g/L) in dialysis and pre-dialysis patients. In pre-dialysis patients, there was a significantly lower end of treatment creatinine clearance with Hb <120 g/L compared to ≥130 g/L but no significant difference in the risk of ESRF. Lower Hb targets were significantly associated with an increased risk for seizures but a reduced risk of hypertension. There were no significant differences in the risk of vascular access thrombosis.

Comment: It is important to note that this review included clinical studies dating from as early as 1966 and that its conclusions echo those from the CREATE, CHOIR and TREAT trials. Higher Hb targets lowered the risk of seizure, but increased BP. Higher Hb targets did not reduce the risk of death.

Reference: Cochrane Database Syst Rev 2006;4:CD003967.

Impact of epoetin alfa on clinical end points in patients with chronic renal failure: A meta-analysis

Authors: Jones M et al

Summary: When study outcomes were pooled from 16 early controlled trials, rhEPO alfa administration substantially increased Hb levels by 40% to 50%, from a baseline level of <80 g/L to a nonanaemic state (Hb >110 g/L). Substantial improvements (10% to 70%) were observed for all QoL measures. In addition, patients who received rhEPO alfa had substantial reductions in hospitalisation rate, hospital length of stay, transfusion rate, and number of units transfused.

Comment: This is a meta-analysis of studies using rhEPO alfa. The studies included are heterogeneous and are either small randomised trials or uncontrolled trials. Sixteen trials were included, showing consistent improvements in Hb concentration, reduced need for transfusion, reduction in hospitalisation and improved QoL, which was reflected in the meta-analysis.

Reference: Kidney Int. 2004; 65:757-67.

The high prevalence of unrecognized anaemia in patients with diabetes and chronic kidney disease: a population-based study

Authors: New JP et al

Summary: These researchers assessed the prevalence of anaemia, by stage of CKD, in the general diabetic population (n=840) in the north-west of England over a period of 6 weeks in 2007. Hb was measured on all HbA1c samples and the most recent (<4 months) estimated GFR was obtained. Anaemia (at treatment level) was defined as Hb <110 g/L or the use of ESA. Twelve per cent of patients had Hb <110 g/L. The prevalence of anaemia increased progressively with worsening CKD. Those with CKD stage 3 accounted for the largest number of people with anaemia; 18% had Hb <110 g/L. Those with a GFR <60 mL/min/1.73 m^2 and not on ESA or dialysis were four times more likely than patients with better renal function to have Hb <110 g/L. The relation between Hb and GFR became approximately linear below a GFR of 83 mL/min/1.73 m^2, where, for every 1 mL/min/1.73 m^2 fall in GFR, there was a 0.4 g/L fall in Hb level.

Comment: This is a prevalence study from Manchester, UK. All blood sent for glycated haemoglobin also had an additional haemoglobin assay performed. Diabetes, mostly type 2, was confirmed in the study population and renal function was assessed. It demonstrates that there is a strong association between anaemia (Hb <110 g/L) and CKD and that a significant proportion (25%) of diabetic patients with stage 3 CKD are anaemic. Because of study design, other causes of anaemia are not able to be assessed and a small proportion of cases of anaemia will be due to non-renal causes.

Reference: Diabetic Medicine. 2008;25(5):564-9.

'Microalbuminuric anaemia'—The relationship between haemoglobin levels and albuminuria in diabetes

Authors: Adetunji OR et al

Summary: Among 502 patients with diabetes, 118 (23.5%) had anaemia (Hb levels of <130 g/L for men and <120 g/L for women). The prevalence of anaemia increased from 19% in patients with a normal urinary albumin creatinine ratio (ACR of <2.5 mg/mmoL in men and <3.5 mg/mmoL in women) to 29% in those with microalbuminuria and to 41% in macroalbuminuria (ACR >25 mg/mmoL in both sexes). This increase in the prevalence of anaemia in microalbuminuria compared to normoalbuminuria was not explained by declining renal function as there was no significant difference in eGFR between the two groups.

Comment: An interesting but somewhat limited study suggesting that anaemia related to kidney disease may start earlier than hitherto recognised. The use of thresholds such as Hb <130 or <120 g/L may not be appropriate, as there is a wide reference range in normal men and women.

Reference: Diabetes Res Clin Pract. 2009;85(2):179-82.

Anemia in patients with type 1 diabetes

Authors: Thomas MC et al

Summary: An assessment of the prevalence and predictors of anaemia (Hb level <130 g/L in men and <120 g/dl in women) in 312 outpatients with type 1 diabetes revealed that one in seven patients had anaemia (14%). Patients at greatest risk had diabetic kidney disease. More than half (52%) of patients with macroalbuminuria (2 of 3 albumin excretion rate measurements >200 µg/min) had anaemia, compared with 24% of patients with microalbuminuria (2 of 3 albumin excretion rate measurements between 20–200 µg/min) and fewer than 8% of normoalbuminuric patients (2 of 3 albumin excretion rate measurements <20 µg/min). Patients with diabetes and renal impairment were 6 times more likely to have anaemia than those with normal renal function. Patients with anaemia were more likely to have retinopathy and macrovascular complications than those with a normal haemoglobin level, independent of comorbid renal disease.

Comment: This is an audit of patients with type 1 diabetes mellitus attending clinics in 3 Australian hospitals. Haemoglobin was assessed. Fourteen percent of the patients were anaemic. Proteinuria and CKD independently predicted anaemia. The authors note that another small study also demonstrated a similar association of proteinuria and anaemia. In this study, anaemia was associated with low circulating concentrations of erythropoietin. The mechanism for this apparent erythropoietin deficiency in the setting of proteinuria has not been established.[51]

Reference: J Clin Endocrinol Metab. 2004;89(9):4359-63.

Conclusions and recommendations

Anaemia is common in patients with diabetes and seems to occur at milder levels of renal dysfunction than in non-diabetic patients, and also earlier than hitherto recognised. Renal anaemia is primarily a result of reduced erythropoietin production from peritubular endothelial cells in the kidney, secondary to interstitial fibrosis, though failures in iron metabolism and utilisation also play a part. Anaemia is associated with an increase in morbidity, mortality and health care costs; it is under-diagnosed and under-treated, particularly in the early stages of chronic kidney disease.

ESAs treat anaemia with resultant reduced transfusion requirements, reduced need for hospitalisation, improvement in quality of life, improved cognitive function and possible prevention of left ventricular hypertrophy. They do not, however, result in a reduction in cardiovascular mortality nor can they slow the progression of renal failure. Higher haemoglobin targets (>120–130 g/dL) may be associated with an increase in morbidity and mortality.

For rhEPO to be effective, patients require sufficient iron stores and frequently require intravenous iron supplementation.

Due to the potential benefit of treating anaemia, all diabetic patients with significant proteinuria or renal impairment should have regular (yearly) haemoglobin checks. If the patient is anaemic, other reversible causes of anaemia should be considered, especially in type 1 diabetes where vitamin B_{12} deficiency and coeliac disease are more common. As type 2 diabetes now arises in younger age-groups, other frequent causes such as menstrual loss should be considered, and some GI cancers are more common in type 2 diabetes. Aspirin use as vascular preventative therapy may also cause anaemia from GI-related blood loss.

If there is no other cause for anaemia apart from the degree of renal impairment, the haemoglobin is ≤100 g/L and they fulfil GFR requirements, then they are eligible for rhEPO and this should be commenced. Most main centres have renal anaemia nurses who can help co-ordinate this or your local nephrology service can be contacted. Once rhEPO is commenced, regular monitoring of haemoglobin is required to allow dose adjustment with a target haemoglobin of 110–120 g/L.

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