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REVIEW

Anaemia in chronic kidney disease

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Anaemia, occurring in over 50% of patients with stages 3 to 5 chronic kidney disease (CKD), often causes fatigue, shortness of breath, cardiac dysfunction and cognitive impairment. The major causes include disorders of iron metabolism (both iron deficiency and iron blockade) and erythropoietin deficiency. Treatment should be aggressive, and treated to specific targets. Nutritional deficiencies should be treated first, and only once replete, should erythropoiesis-stimulating agents (EPO-stimulating agents [ESAs]) be considered. Careful consideration must be given to the adverse effects of ESAs, and prescribed only after discussion with the patient. Patients with refractory anaemia, rapidly deteriorating glomerular filtration rate (GFR), and who have stage 3–5 CKD should be referred timeously to a nephrologist.

Keywords: anaemia in chronic kidney disease (AiCKD), haemoglobin, iron, erythropoietin, uraemic toxins

Introduction

Anaemia in chronic kidney disease (CKD) is present in over 50% of patients with a glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2 and increases exponentially as the GFR falls.[1] This is compared to an incidence of approximately 1% in patients with a GFR above 60.[2] Anaemia in CKD (AiCKD) is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) group as a haemoglobin concentration less than 13.0 g/dl in adult males and 12.0 g/dl in adult females, and is identical to the definition by the World Health Organization.[3,4] Strict management of anaemia is vital, as both lower and higher haemoglobin concentrations are associated with increased morbidity and mortality: Ma et al. found an increased all-cause mortality with AiCKD, while Palmer et al. found an increased incidence of stroke, hypertension and death at higher haemoglobin levels.[5,6]

AiCKD is often underrecognised as a cause of clinically relevant CKD symptoms, including reduced physical performance, fatigue, shortness of breath, insomnia and cognitive impairment.[7,8] Similarly, anaemia can increase cardiac output, leading to left ventricular hypertrophy, angina and cardiac failure.[7,9] Therefore, understanding and reversing the causes of AiCKD is vital. The pathophysiological causes of AiCKD can be broadly divided into major causes (disorders of iron metabolism [including chronic inflammation and loss of erythropoietin [EPO] production]), and minor causes (hyperparathyroidism, uraemic toxins and drug effects).[7]

Major anaemia factors in chronic kidney disease

The majority of anaemia cases in CKD are due to two major factors: disorders of iron metabolism (both iron deficiency and hepcidin-mediated iron blockade) and a relative EPO deviancy. CKD patients often have increased iron losses, decreased iron absorption and decreased reticuloendothelial iron recycling.[10] Total iron loss in a healthy individual is approximately 0.5 to 2.5 mg daily, while a patient with CKD loses 2.7 to 8.2 mg iron daily, occurring mostly via chronic bleeding (usually gastrointestinal) from uraemic platelet dysfunction, repeated phlebotomies and dialysis-associated losses.[7,10] The maximum daily iron intestinal absorption is estimated at 2–3 mg per day, leading to a net iron loss and thus leading to AiCKD.[7] This also underlies the reason why oral iron supplementation often fails in CKD patients. To compound this, CKD patients have a functional iron deficiency, thought to be mediated by increased hepcidin concentrations.[10,11] Hepcidin, an acute phase reactant, is released by the liver in response to inflammation.[10,11] Additionally, hepcidin is excreted in the urine, and therefore hepcidin levels increase as CKD progresses.[11] Hepcidin, via inhibition of ferroportin, impairs both iron absorption in intestinal enterocytes and iron recycling in macrophages and hepatocytes. This decreased iron availability limits erythropoiesis even in the presence of adequate total body iron stores; the so-called reticuloendothelial iron blockade.[10] These factors can often be ameliorated, to a large degree, by the intravenous administration of iron.

EPO is an oxygen-sensitive glycoprotein secreted predominately by fibroblasts of the renal cortex and outer medulla.[12] Red cell production is exquisitely sensitive to EPO, and red cell production can rapidly be increased by elevated EPO levels.[7,12] As CKD progresses, overall renal mass declines, as does the total number of renal fibroblasts, ultimately leading to a reduction of EPO production, and hence a normochromic normocytic anaemia.[10,13] This can be corrected by administration of recombinant EPO analogues, once other causes of anaemia have been treated.

Minor anaemia factors in chronic kidney disease

Secondary hyperparathyroidism (SHPT) is a common complication of CKD, and often manifests at CKD stage 3 or later.[3,14] Raised parathyroid hormone (PTH) has been associated with anaemia, and hyporesponsiveness to EPO-stimulating agents (ESAs).[14] Additionally, parathyroidectomy has been associated

with improved haemoglobin levels, as well as restoration of responsiveness to ESAs.[15] Lastly, there is some evidence that increased PTH may lead to bone marrow fibrosis.[14,15] While the role of SPTH in AiCKD is established, its effect is modest; hence clinical priority in AiCKD should be targeted at replenishing EPO and iron stores, and thereafter the focus should turn to SHPT treatment.[14]

Uraemic toxins are known to decrease the survival of red blood cells.[3,7] The most important uraemic toxins associated with AiCKD are the polyamines such as spermine, spermidine, putrescine and cadaverine.[7] These polyamines are organic cations that are involved with cell growth and maturation, and in excess, reduce the proliferative activity of erythroid cells in the bone marrow.[7] The removal of such polyamines with dialysis is associated with improvement in anaemia symptoms, and highlights the need for regular adequate dialysis.[7,16]

Multiple drugs have been associated with anaemia, but in CKD, the most common causes are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).[7] Both these drug classes are extensively used in CKD due to their markedly beneficial renal and cardiovascular benefits.[17] However, a minor class side-effect of both drugs, leading to anaemia, is sometimes seen.[18,19] This class effect is caused mainly by direct inhibition of the angiotensin II receptor on erythroid cells and by the accumulation of N-acetyl-seryl-aspartyl-lysyl-proline (usually degraded by angiotensin), a potent natural inhibitor of haematopoietic cell proliferation.[18,20] Additional drugs that can cause anaemia include the antimetabolites azathioprine and mycophenolate (via myelosuppression), and cyclosporin A and mTOR inhibitors (via haemolysis).[7] Therefore, it is always prudent to review drug usage in patients with AiCKD.

Treatment of anaemia in chronic kidney disease patients

Most guidelines, including the KDIGO guidelines, recommend that all patients diagnosed with CKD should be screened for anaemia at initial presentation and when clinically indicated. Additional ongoing AiCKD screening is indicated thereafter, and the recommended frequency increases with increasing CKD severity. A CKD stage-based AiCKD screening regimen, derived from the KDIGO guidelines, is shown in Table I.[3]

Table I: Frequency of testing for AiCKD

	Anaemia absent	Anaemia present
CKD stage 1–2	As clinically indicated	Hb three monthly
CKD stage 3	Hb yearly	Hb three monthly
CKD stage 4–5	Hb six monthly	Hb three monthly
CKD Stage 5 PD	Hb three monthly	Hb three monthly
CKD Stage 5 HD	Hb three monthly	Hb monthly

Tests required if anaemia is present: full blood count, differential count, absolute reticulocyte count, ferritin level, transferrin saturation, vitamin B_{12} and folate levels. CKD – chronic kidney disease, Hb – haemoglobin, PD – peritoneal dialysis, HD – haemodialysis

To investigate the AiCKD, KDIGO recommends the following minimum tests should be done: full blood count, differential count, absolute reticulocyte count, ferritin level, transferrin saturation, vitamin B_{12} and folate levels.[3] Treatment should be initiated based on the laboratory tests, and replacement should follow targets set out in Table II. Iron replacement should ideally be given intravenously in CKD stages 3–5, but a trial of oral iron can be administered for one to three months based on patient preference. Only once all deficiencies are replaced, should ESAs be considered.

Table II: Treatment targets for AiCKD

	Deficiency	Target
Hb	< 12.0 g/dl in females < 13.0 g/dl in males	10–11.5 g/dl (Up to 13.0 g/dl)*
TSAT	< 30%	> 30%
Ferritin	< 500 ng/ml	> 500 ng/ml
Vitamin B_{12}	Below local laboratory reference range	Within local laboratory reference range
Folate	Below local laboratory reference range	Within local laboratory reference range

* Higher Hb targets (up to 13 g/dl) can be targeted in certain patients, based on the patients' clinical symptoms and if the patient accepts the risks. Hb – haemoglobin, g/dl – grams per deciliter, TSAT – transferrin saturation, ng/ml – nanogram per milliliter

Once all deficiencies are corrected, and if AiCKD is still present, the use of ESAs should be considered. Initiation of ESAs should be considered carefully, and the risks of ESA usage (cardiovascular accidents, hypercoagulability and progression of non-benign lesions) versus the benefits (improvement of anaemia symptoms) should be discussed with the patient.[3] If the patient accepts the risk, this should be documented, and ESA use begun. The ideal haemoglobin target in KDIGO should ideally not be above 11.5 g/dl, but this can be individualised in patients willing to accept the risk, to a haemoglobin level of not more than 13.0 g/dl.[3]

Transfusion and use of whole blood products should be used only in emergencies, or after failure of nutritional support and ESA use. This is because the use of blood products is expensive, associated with many adverse reactions, and can potentially allo-immunise the patient against non-ABO blood antigens, increasing the risk of rejection events during future kidney transplant.[21] Therefore, the clinician should attempt to minimise transfusions, maximise nutritional and ESA usage, and be aggressive in investigating anaemias.

Conclusion

Anaemia in CKD is very common, is associated with adverse patient outcomes and can be difficult to treat. Treatment targets are lower than those in the general population (haemoglobin 10–11.5 g/dl), and can be easy to overshoot. Hence, the clinician should be careful in monitoring the AiCKD patient. The first step is to identify and treat nutritional deficiencies to target (iron, vitamin B_{12} and folate). Iron replacement in CKD stages 3–5 should ideally be intravenous. Once all nutritional deficiencies are treated, and if AiCKD is still present, ESAs can be initiated. The clinician should be aware that ESAs are associated with significant adverse effects and should only be initiated after discussing the risks with the patient. Blood transfusion for AiCKD remains an emergency stopgap, is associated with

significant adverse events (short and long term) and should only be used in emergencies. If all of this fails, then referral to a nephrologist should occur for further in-depth anaemia assessment and treatments.

Key learning points

- Anaemia is present in over 50% of CKD stage 3–5 patients
- Iron deficiency is the most common cause of anaemia in CKD
- Iron should ideally be replaced intravenously in CKD stages 3–5
- All nutritional deficiencies (iron, vitamin B_{12} and folate) should be replaced before ESAs are initiated
- Blood transfusions should be reserved for emergencies only
- Nephrology consultation for AiCKD should occur in the following instances:
  - Refractory anaemia causes such as:
    - Secondary hyperparathyroidism
    - Severe uraemia
    - Suspected drug toxicities
  - For patients with CKD stages 3–5
  - For patients with a rapidly deteriorating GFR

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References

1. Alagoz S, Dincer MT, Eren N, et al. Prevalence of anemia in predialysis chronic kidney disease: Is the study center a significant factor? PLoS ONE. 2020;15(4):e0230980. https://doi.org/10.1371/journal.pone.0230980.
2. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia. Arch Intern Med. 2002;162(12):1401-8. https://doi.org/10.1001/archinte.162.12.1401.
3. Summary of recommendation statements. Kidney Int Suppl. 2012;2(4):283-7. https://doi.org/10.1038/kisup.2012.41.
4. World Health Organizaion. Nutritional anaemias: report of a WHO scientific group [meeting held in Geneva from 13 to 17 March 1967]. In: WSGoNAWHO, editor. Switzerland: World Health Organisation; 1968.
5. Ma JZ, Ebben J, Xia H, Collins AJ. Hematocrit level and associated mortality in hemodialysis patients. J Am Soc Nephrol. 1999;10(3):610-9. https://doi.org/10.1681/ASN.V103610.
6. Palmer SC, Navaneethan SD, Craig JC, et al. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. Ann Intern Med. 2010;153(1):23-33. https://doi.org/10.7326/0003-4819-153-1-201007060-00252.
7. Zadrazil J, Horak P. Pathophysiology of anemia in chronic kidney diseases: A review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015;159(2):197-202. https://doi.org/10.5507/bp.2013.093.
8. Johansen KL, Finkelstein FO, Revicki DA, et al. Systematic review and meta-analysis of exercise tolerance and physical functioning in dialysis patients treated with erythropoiesis-stimulating agents. Am J Kidney Dis. 2010;55(3):535-48. https://doi.org/10.1053/j.ajkd.2009.12.018.
9. Patel TV, Singh AK. Anemia in chronic kidney disease: new advances. Heart Fail Clin. 2010;6(3):347-57. https://doi.org/10.1016/j.hfc.2010.02.001.
10. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012;23(10):1631-4. https://doi.org/10.1681/ASN.2011111078.
11. Zaritsky J, Young B, Wang H-J, et al. Hepcidin-A potential novel biomarker for iron status in chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(6):1051-6. https://doi.org/10.2215/CJN.05931108.
12. Eckardt KU. Biology of erythropoietin production. Nephrol Dial Transplant. 1995;10(9):1572-4.
13. Makusidi MA, Chijioke A, Braimoh KT, et al Usefulness of renal length and volume by ultrasound in determining severity of chronic kidney disease. Saudi J Kidney Dis Transpl. 2014;25(5):1117-21. https://doi.org/10.4103/1319-2442.139981.
14. Weir MR. Managing anemia across the stages of kidney disease in those hyporesponsive to erythropoiesis-stimulating agents. Am J Nephrol. 2021;52(6):450-66. https://doi.org/10.1159/000516901.
15. Tanaka M, Komaba H, Fukagawa M. Emerging association between parathyroid hormone and anemia in hemodialysis patients. Ther Apher Dial. 2018;22(3):242-5. https://doi.org/10.1111/1744-9987.12685.
16. Igarashi K, Ueda S, Yoshida K, Kashiwagi K. Polyamines in renal failure. Amino Acids. 2006;31(4):477-83. https://doi.org/10.1007/s00726-006-0264-7.
17. Maione A, Navaneethan SD, Graziano G, et al. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials. Nephrol Dial Transplant. 2011;26(9):2827-47. https://doi.org/10.1093/ndt/gfq792.
18. Cheungpasitporn W, Thongprayoon C, Chiasakul T, Korpaisarn S, Erickson SB. Renin-angiotensin system inhibitors linked to anemia: a systematic review and meta-analysis. QJM. 2015;108(11):879-84. https://doi.org/10.1093/qjmed/hcv049.
19. Gossmann J, Thürmann P, Bachmann T, et al. Mechanism of angiotensin converting enzyme inhibitor-related anemia in renal transplant recipients. Kidney Int. 1996;50(3):973-8. https://doi.org/10.1038/ki.1996.398.
20. Sica DA, Gehr TW. The pharmacokinetics and pharmacodynamics of angiotensin-receptor blockers in end-stage renal disease. J Renin Angiotensin Aldosterone Syst. 2002;3(4):247-54. https://doi.org/10.3317/jraas.2002.046.
21. Bianchi M, Vaglio S, Pupella S, et al. Leucoreduction of blood components: an effective way to increase blood safety? Blood Transfus. 2016;14(2):214-27.