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Anemia in Chronic Kidney Disease Patients: An Update

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Abstract

Chronic kidney disease (CKD) is one of the most common disabling diseases globally. The main etiopathology of CKD is attributed to progressive renal fibrosis secondary to recurrent renal insults. Anemia is a known complication in CKD patients, associated with higher hospitalization rates and increased mortality risk. CKD-associated anemia (CKD-AA) is either due to true iron deficiency and/or functional iron deficiency anemia. There is new emerging evidence about the effects of erythropoiesis stimulating agents in the treatment of CKD-AA and their role in reversing and preventing kidney fibrosis in the early stages of CKD. This effect potentially provides new scopes in the prevention and treatment of CKD-AA and in decreasing the progression of CKD and the associated long-term complications. Epidemiology, pathophysiology, and treatments of CKD-AA will be discussed.

Keywords
- EPO-H
- CKD-AA
- hepcidin
- CKD anemia
- iron therapy
- kidney fibrosis

Introduction

Chronic kidney disease (CKD) prevalence has increased in recent decades and has become a global public health challenge, requiring more costs.[1] Recently, it has been reported that >500 million people have CKD with a prevalence of 11%.[2] CKD deterioration is associated with anemia, adversely affecting patients' clinical outcomes.[3] Hence, the early diagnosis of CKD-associated anemia (CKD-AA) slows the progression, thereby reducing associated complications and decreasing morbidity and mortality rates.

It is well recognized that CKD-AA is linked with poor life quality and clinical outcomes. The treatment for CKD-AA requires an appropriate balance between stimulating erythropoiesis and maintaining sufficient iron levels and other elements to achieve optimum hemoglobin (Hb) levels.[4] Furthermore, other causes such as bleeding and bone marrow suppression should also be considered.

Epidemiology

In the late stages of CKD and patients on hemodialysis (HD), anemia is present in ~90% of the patients.[5] Astor et al reported that the rate of anemia increased from 1% in patients who had an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 to 9% when the eGFR was 30 mL/min/1.73 m^2 and to 33 to 67% at eGFR of 15 mL/min/1.73 m^2.[6] Inhome-care patients' study, CKD-AA was diagnosed in 50% of the CKD patients.[7] In diabetic patients with

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CKD, Jones et al[8] reported that the overall CKD-AA prevalence rate in the UK was 22%,[9] whereas it was 15% in the USA.[10] Other countries showed different prevalence; in China, in stage I, it was 46 to 53%,which increased to 70 to 90% in stage V.[11] It has been stated that the prevalence of CKD-AA is higher among CKD patients who have died as a result of CKD-AA cardiac complications.[12]

Pathophysiology

Hepcidin is an essential regulatory protein, controlling intestinal iron absorption and iron distribution throughout the body, and it is the primary regulator of iron metabolism.[13] High-circulating hepcidin reduces iron absorption in response to oral or intravenous (IV) iron. It is formed and secreted mainly by the liver and the β-cells of the pancreas, controlling intestinal iron absorption and managing iron stores in the body.[14] Hypoglycemia stimulates hepcidin formation and is released by pancreatic β-cells.[15] It is believed that iron overload occurs in hepcidin deficiency, increasing β-cell apoptosis.[16] Inflammatory responses happen in the early phase of CKD, manifesting by releasing pro-inflammatory cytokines, acute phase reactants, and hepcidin in CKD patients.[17]

Hepcidin formation and secretion are affected by many factors, including hypoxia, anemia, serum erythropoietin (EPO), transferrin saturation, and liver iron load in CKD patients.[18] Clearance of hepcidin is primarily by the kidneys, and the serum level of prohepcidin, hepcidin, and hepcidin metabolite concentrations are increased in CKD and dialysis patients.[17] It was reported that stimulation of erythropoiesis by EPO hormone (EPO-H) decreases serum hepcidin, enhancing iron absorption, mobilization, and utilization.[19]

Hypoxia is not uncommon in CKD patients. Hypoxia reduces serum hepcidin via hypoxia-inducible factor (HIF).[20] HIF works as a transcriptional activator to sense and adapt the cellular response to oxygen availability. Hypoxia directly affects intestinal iron absorption. Anemic hypoxia stimulates the hypoxia HIF/hypoxia response element (HRE) system. Hydroxylase enzyme activity reduces hypoxic status, leading to HIF-1α building with HIF-1β, presenting the HRE to the target gene promoters. Similarly, the stability of HIF-2α is affected by the partial pressure of oxygen via the altered activity of prolyl hydroxylase. HIF-2α has a role in hypoxic EPO expression signals.[21] HIF system is a negative modulator for hepcidin, stimulates erythropoiesis, and increases iron utilization. Furthermore, hypoxia downregulates hepcidin and induces oxidative stress, diminishing hepcidin expression.[22,23] In the late stages of CKD, Idris et al reported that the most common type of CKD-AA in type 2 diabetes mellitus was normocytic normochromic.[24] The anemia is mainly due to the reduction in EPO-H synthesis by the kidneys and/or poor response to EPO-H.[25] Iron is essential in cell metabolism, and it is necessary for oxygen transportation by Hb.

Causes of Anemia in CKD Patients (►Table 1)

CKD-AA is due to EPO-H deficiency, but iron, vitamin B12, and folic acid deficiency can cause anemia in CKD patients. However, secondary parathyroids' increased activity and uremic bone marrow suppression, including other common associated chronic diseases, are also contributory causes of CKD-AA. Iron deficiency anemia in CKD patients occurs either due to real (absolute or true) and/or functional iron deficiency. Actual iron deficiency anemia is due to the absence of or severe reduction in iron stores in the spleen, liver, and bone marrow. On the contrary, in functional iron deficiency, the iron body storage is either normal or increased, but the iron is not accessible for red blood cell (RBC) production.[12] The main reasons for functional iron deficiency are the increased serum hepcidin in CKD patients and the decreased ability of the body to use the stored iron in reticuloendothelial cells.

Table 1 Causes of chronic kidney disease-associated anemia and the underlying mechanism of the cause

Causes of anemia in CKD	Mechanism
1. Decreased serum EPO	Due to progressive damage of the kidneys
2. Increased serum hepcidin	Due to: a. Progressive GFR reduction that causes low hepcidin clearance b. Increased IL-6 due to an inflammatory response
Increased serum hepcidin causes	a. Macrophage's iron sequestration b. RBC production c. Response to EPO therapy d. Duodenal iron absorption
3. Iron loss	Bleeding mostly due to uremic platelet dysfunction and uremic gastritis
4. Decreased RBC life span	Due to uremic status and inflammatory process
5. RBC production reduction in the associated acute inflammatory process	Due to increased inflammatory cytokines

Abbreviations: CKD, chronic kidney disease; EPO, erythropoietin;GFR, glomerular filtration rate; IL-6, interleukin;RBC,red blood cell.

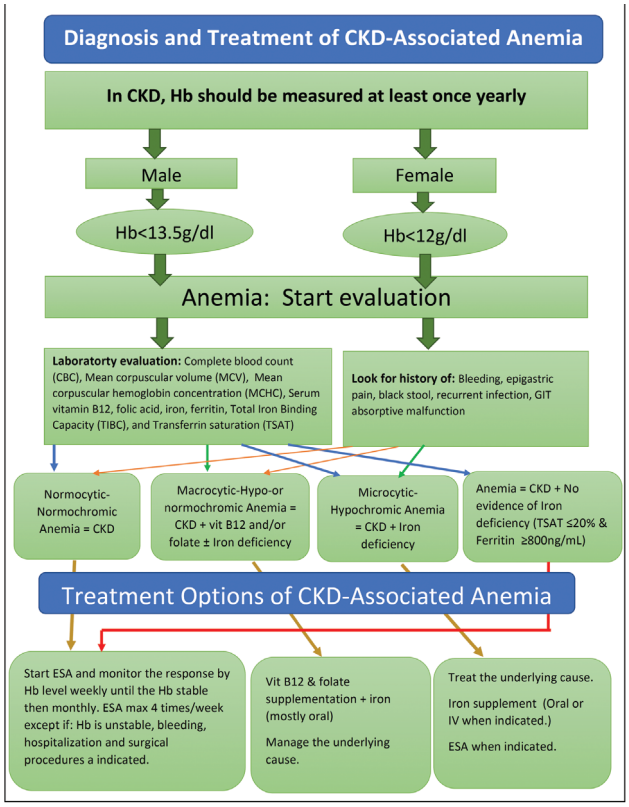

Fig. 1 Chronic kidney disease-associated anemia(CKD-AA) diagnosis and treatment. ESA, erythropoiesis stimulating agent; GIT, gastrointestinal tract; Hb, hemoglobin.

Hemoglobin (Hb) Monitoring and Diagnosis (►Fig. 1)

Kidney Disease Improving Global Outcomes (KDIGO) guidelines noted no indications for regular check-ups for anemia,[5] and Hb level is assessed only when clinically indicated, or at least annually in CKD stage III and twice a year in CKD stages IV to V nondialyzed patients. On the other hand, the KDIGO recommendation is to assess the Hb level only when clinically indicated for anemic CKD patients who are not treated with an erythropoiesis stimulating agent (ESA). At least every 3 months in CKD stages III to V, patients are not started on regular HD. Iron status of the patient should be assessed in CKD patients, while iron deficiency anemia is not uncommon, and diagnosis of iron deficiency anemia is suspected when the transferrin saturation (TSAT) is ≤20% with low serum iron.

The World Health Organization, Kidney Disease Improving Global Outcomes (KDOQI) guidelines, and the European Renal Best Practice (ERBP) group recommendation agreed that anemia in CKD patients means a reduction in Hb to <13 g/dL in men and <12 g/dL in women.[5] Gafter-Gvili et al reported that anemia investigation should be conducted in CKD patients when Hb <13.5 g/dL in adult males <70 years (≤13.2 g/dL in men >70 years) and <12.0 g/dL in adult females.[26] It is recommended that all CKD patients with an eGFR of <60 mL/min/1.73 m^2 must be checked for anemia, and the underlying causes should be explored.[26] (►Fig. 1)

Treatment (►Fig. 1)

Iron Replacement

Iron therapy is initiated with an absolute iron deficiency (TSAT <20% and serum ferritin <100 ng/mL) or if Hb concentration does not increase with ESA treatment. Oral and/or IV iron supplementation can be used. IV iron is recommended when the TSAT and serum ferritin is less than 30% and 500 ng/mL, respectively.[4] It is claimed that IV iron is better tolerated, given in higher doses, and efficiently replaces iron deficiency.[27] Moreover, IV iron attains a continuous persistent Hb response than oral iron supplementation, lowering the need for blood transfusion;[28] however, allergic reactions can occur.

KDIGO, KDOQI, and ERBP urge iron supplementation in CKD-AA. However, the exact points of initiation of iron supplementation based on ferritin and TSAT levels are variable between the guidelines. Most guidelines agree that IV iron supplementation is better in patients on dialysis. On the other hand, IV and oral iron can be given to CKD stages IIIto V patients. A 1 to 3-month trial of oral iron therapy can be used primarily if Hb concentration increases without EPO-H treatment and the anemia symptoms are improving.[26] Although IV iron is accepted by the KDIGO, the KDOQI commentary group reported concerns about IV iron infusion in CKD patients.[28] The ERBP group guidelines recommended oral iron supplementation in nonhemodialyzed CKD patients, particularly in CKD stages II and III patients. However, supplementation shifts to IV iron if the oral iron is intolerable or not enough to achieve the desired response.

National Institute for Health and Care Excellence guideline recommends oral iron supplements for CKD patients who had not received EPO-H. However, IV iron can be used for patients who do not tolerate oral iron or have not reached the therapeutic target during the first 3 months of oral iron supplementation.[29] The safety of IV iron is not different from oral iron therapy. Furthermore, there are no significant differences in side effects and infection rates between these two routes.[29] However, it was noted that the early introduction of IV iron before initiating dialysis was more valuable than oral iron therapy.[30] Although there are conflicting reports about the superiority of one iron supplementation route over the other, the IV iron supplementation seems preferable as it rapidly replaces the iron deficit and is given in intermittent doses. On the other hand, oral iron is taken daily, needs practical intestinal absorption ability, and often causes constipation, leading to the patient's poor compliance.

EPO-H Replacement Indications and Benefits

The kidneys and liver produce EPO-H, which stimulates erythropoiesis by the bone marrow. EPO-H is a glycoprotein hormone that acts via the second messenger pathway, stimulating cell precursor proliferation, differentiation, and maturation.[31] It was noted that the administration of EPO-H in nonsevere CKD-AA patients impairs CKD progression and postpones the early initiation of dialysis.[32] The concept of EPO-H-specific effect on the erythroid progenitor cells encouraged the scientists to study EPO-H receptors in

renal tubular, mesangial, and collecting duct, and other cells in the kidneys.[33] Furthermore, there is evidence that EPO-H has cellular-protective effects in the heart, kidneys, brain, and vascular bed via regulating mitosis, reducing oxidative stress, inhibiting apoptosis, and promoting vascular repair.[34] Furthermore, it has been reported that EPO-H enhances the revival in acute kidney injury (AKI), and it improves proteinuria and blood biomarkers of kidney injury in CKD patients.[35]ESAs have essential protective effects on the kidneys and improve the prognosis in CKD patients.[36] These effects of ESAs were not supported by a study that reported EPO-receptor (EPO-R) protein was almost undetectable in renal cells, and there was no evidence of EPO-R expression and function in the studied group.[36] Furthermore, it was observed that ESAs did not improve renal function in AKI.[37]

In renal hypoxia, the kidney interstitial fibroblasts produce EPO-H, preventing renal interstitial fibrosis.[38] It was reported that EPO administration impairs fibrocyte activity, inhibiting renal interstitial fibrosis.[38] Conversely, it was reported that ESAs reactivate renal EPO-producing cells to produce EPO-H without significant effect on renal fibrosis and/or inflammation.[39] It seems that the EPO-R activators and EPO-H have a tissue-protective effect.[40] There are disagreements about the effects of EPO-H and its analogs to improve renal fibrosis. Hence, new studies are needed to investigate the beneficial effect of ESAs on kidney cell regeneration and the prevention of kidney cell damage. Additionally, it is deemed that EPO has a role in renal fibrosis improvement and prevention, though the mechanism(s) is/are not clear. Therefore, studies are required to elucidate these mechanisms further.

Apoptosis is a spontaneous process that maintains the internal environment stability via mitochondrial-, endoplasmic reticulum-, and death receptor-mediated mechanism,[41] inducing fibrosis and renal tissue damage. It has been claimed that EPO-H has anti-apoptotic effects.[42] Hence, apoptosis inhibition may downregulate renal interstitial fibrosis, improving CKD-AA.

Persistent inflammation is a feature in CKD, causing interstitial fibrosis.[43] EPO-H treatment decreases inflammation due to injuries, toxins, and hypoxia by inhibiting tumor necrosis factor-α, interleukin (IL)-1b, and IL-10 production.[44] EPO-H in the proper doses improves anemia, but higher doses are associated with increased major cardiovascular events in 1-year therapy.[45]

Autophagy is a cell self-degradation by which the damaged organelles and macromolecules are destroyed. Autophagy reduces the number of aged cells and prevents the incidence of tissue fibrosis via different mechanisms.[46] However, extensive autophagy may cause different pathological changes.[47] ESA therapy enhances normal autophagy and prevents renal interstitial fibrosis,[48] decreasing CKD progression and CKD-AA risk. New studies are required to explore this and find new agents impairing the abnormal autophagy process.

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) enzyme inhibitors such as roxadustat, vadadustat, daprodustat, and solid-state are oral agents under testing for CKD-AA treatment.[49] The HIF-PH inhibitors act by stimulating EPO-H production via maintaining HIF complex stability. They have some cardiovascular side effects. These agents are still under trial and are not approved for use yet.

CKD-AA Outcome

The target of CKD-AA treatment is to improve the symptoms of anemia, decrease blood transfusion complications, and prevent cardiovascular complications. Although the epidemiological study reported better outcomes when Hb normalized or was at least near the normal Hb concentration,[50] another study denied full anemia correction.[51] Generally, the strategy of targeting normal Hb concentration is not usually beneficial and may be associated with potential harm to some patients, increasing mortality and/or cardiovascular events. Determining Hb cut-off values in CKD patients needs a longer duration and more extensive studies.

Conclusions

CKD-AA is common in nondialyzed and dialyzed CKD patients. It occurs as early as eGFR drops below 60mL/min/1.73 m^2. CKD-AA might be due to functional and/or absolute iron, EPO-H deficiency, frequent blood extraction, gut blood loss, etc. Most of the published guidelines recommend IV iron, but some guidelines recommend a trial of oral iron, but if the oral supplement does not improve the anemia, IV iron must be used, mainly in CKD stages II and III. The preference for IV iron therapy, especially in absolute iron deficiency anemia, is established in some studies, but its absolute superiority, effectivity, adverse effects, and safety are not superior to oral iron in some reported studies. More studies are required to investigate these issues.

EPO-H, EPO-H analogs, ESAs, and others are used for Hb correction. However, it has been thought that they may prevent kidney fibrosis, but there are conflicting reports about their role as renoprotective and their effect to improve renal interstitial fibrosis. Therefore, new studies are urged to understand the mechanism(s) of these renoprotective and reno-repair effects and how these effects can reduce CKD-AA prevalence and cardiovascular complications.

Authors' Contributions
All named authors contributed to the drafting and finalization of the draft.

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Conflict of Interest
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References

1 Ng JK, Li PK. Chronic kidney disease epidemic: how do we deal with it? Nephrology (Carlton) 2018;23(Suppl 4):116–120
2 Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet 2017;389(10075):1238–1252
3 Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet 2012;379 (9818):815–822
4 Thomas R, Kanso A, Sedor JR. Chronic kidney disease and its complications. Prim Care 2008;35(02):329–344, vii
5 Locatelli F, Bárány P, Covic A, et al;ERA-EDTA ERBP Advisory Board. Kidney Disease Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. Nephrol Dial Transplant 2013;28(06):1346–1359
6 Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Arch Intern Med 2002;162(12):1401–1408
7 McClellan WM, Resnick B, Lei L, et al. Prevalence and severity of chronic kidney disease and anemia in the nursing home population. J Am Med Dir Assoc 2010;11(01):33–41
8 Jones CS, Smith D, Nag S, Bilous TM, Winship S, Wood A, Bilous WR. Prevalence and nature of anaemia in a prospective, population? based sample of people with diabetes: teesside anaemia in diabetes (TAD) study. Diabetic Medicine 2010 Jun;27(06): 655–659
9 Ravindran A, Fervenza FC, Smith RJH, Sethi S. C3 glomerulopathy associated with monoclonal Ig is a distinct subtype. Kidney Int 2018;94(01):178–186
10 Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PLoS One 2014;9(01):e84943
11 Li Y, Shi H, Wang WM, et al. Prevalence, awareness, and treatment of anemia in Chinese patients with nondialysis chronic kidney disease: first multicenter, cross-sectional study. Medicine (Baltimore) 2016;95(24):e3872
12 Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. Am J Hematol 2016;91(01):31–38
13 Kühn LC. Iron regulatory proteins and their role in controlling iron metabolism. Metallomics 2015;7(02):232–243
14 Kulaksiz H, Fein E, Redecker P, Stremmel W, Adler G, Cetin Y. Pancreatic beta-cells express hepcidin, an iron-uptake regulatory peptide. J Endocrinol 2008;197(02):241–249
15 Backe MB, Moen IW, Ellervik C, Hansen JB, Mandrup-Poulsen T. Iron regulation of pancreatic beta-cell functions and oxidative stress. Annu Rev Nutr 2016;36:241–273
16 Zhou Z, Ribas V, Rajbhandari P, et al. Estrogen receptor α protects pancreatic β-cells from apoptosis by preserving mitochondrial function and suppressing endoplasmic reticulum stress. J Biol Chem 2018;293(13):4735–4751
17 Coyne DW. Hepcidin: clinical utility as a diagnostic tool and therapeutic target. Kidney Int 2011;80(03):240–244
18 Santos-Silva A, Ribeiro S, Reis F, Belo L. Hepcidin in chronic kidney disease anemia. Vitam Horm 2019;110:243–264
19 Nemeth E, Ganz T. The role of hepcidin in iron metabolism. Acta Haematol 2009;122(2-3):78–86
20 Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci U S A 1995;92(12):5510–5514
21 Semenza GL. Involvement of oxygen-sensing pathways in physiologic and pathologic erythropoiesis. Blood 2009;114(10): 2015–2019
22 Leung PS, Srai SK, Mascarenhas M, Churchill LJ, Debnam ES. Increased duodenal iron uptake and transfer in a rat model of chronic hypoxia is accompanied by reduced hepcidin expression. Gut 2005;54(10):1391–1395
23 Choi SO, Cho YS, Kim HL, Park JW. ROS mediate the hypoxic repression of the hepcidin gene by inhibiting C/EBPalpha and STAT-3. Biochem Biophys Res Commun 2007;356(01):312–317
24 Idris I, Tohid H, Muhammad NA, et al. Anaemia among primary care patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD): a multicentred cross-sectional study. BMJ Open 2018;8(12):e025125
25 Stevens PE. Anaemia, diabetes and chronic kidney disease: where are we now? J Ren Care 2012;38(Suppl 1):67–77
26 Gafter-Gvili A, Schechter A, Rozen-Zvi B. Iron deficiency anemia in chronic kidney disease. Acta Haematol 2019;142(01):44–50
27 Thorp ML, Johnson ES, Yang X, Petrik AF, Platt R, Smith DH. Effect of anaemia on mortality, cardiovascular hospitalizations and end-stage renal disease among patients with chronic kidney disease. Nephrology (Carlton) 2009;14(02):240–246
28 Kliger AS, Foley RN, Goldfarb DS, et al. KDOQI us commentary on the 2012 KDIGO clinical practice guideline for anemia in CKD. Am J Kidney Dis 2013;62(05):849–859
29 Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. Am J Kidney Dis 2016;68(05):677–690
30 Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc 2015;90(01):12–23
31 Dunlop EA, Percy MJ, Boland MP, Maxwell AP, Lappin TR. Induction of signalling in non-erythroid cells by pharmacological levels of erythropoietin. Neurodegener Dis 2006;3(1-2):94–100
32 Gouva C, Nikolopoulos P, Ioannidis JPA, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. Kidney Int 2004;66(02): 753–760
33 Hu MC, Shi M, Cho HJ, et al. The erythropoietin receptor is a downstream effector of Klotho-induced cytoprotection. Kidney Int 2013;84(03):468–481
34 Palaka E, Grandy S, van Haalen H, McEwan P, Darlington O. The impact of CKD anaemia on patients: incidence, risk factors, and clinical outcomes-a systematic literature review. Int J Nephrol 2020;2020:7692376
35 Zhang Y, Zhu X, Huang X, et al. Advances in understanding the effects of erythropoietin on renal fibrosis. Front Med (Lausanne) 2020;7:47
36 Elliott S, Busse L, Swift S, et al. Lack of expression and function of erythropoietin receptors in the kidney. Nephrol Dial Transplant 2012;27(07):2733–2745
37 Endre ZH, Walker RJ, Pickering JW, et al. Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). Kidney Int 2010;77(11):1020–1030
38 Geng XC, Hu ZP, Lian GY. Erythropoietin ameliorates renal interstitial fibrosis via the inhibition of fibrocyte accumulation. Mol Med Rep 2015;11(05):3860–3865
39 Souma T, Nezu M, Nakano D, et al. Erythropoietin synthesis in renal myofibroblasts is restored by activation of hypoxia signaling. J Am Soc Nephrol 2016;27(02):428–438
40 Fischer C, Deininger N, Wolf G, Loeffler I. CERA attenuates kidney fibrogenesis in the db/db mouse by influencing the renal myofibroblast generation. J Clin Med 2018;7(02):1–14
41 Abate M, Festa A, Falco M, et al. Mitochondria as playmakers of apoptosis, autophagy and senescence. Semin Cell Dev Biol 2020; 98:139–153
42 Lacombe C, Mayeux P. Biology of erythropoietin. Haematologica 1998;83(08):724–732
43 Morgado-Pascual JL, Marchant V, Rodrigues-Diez R, et al. Epigenetic modification mechanisms involved in inflammation and fibrosis in renal pathology. Mediators Inflamm 2018; 2018:2931049

44 Mateus V, Rocha J, Alves P, Mota-Filipe H, Sepodes B, Pinto RM. Anti-inflammatory effect of erythropoietin in the TNBS-induced colitis. Basic Clin Pharmacol Toxicol 2017;120(02):138–145
45 Evans M, Bower H, Cockburn E, Jacobson SH, Barany P, Carrero J-J. Contemporary management of anaemia, erythropoietin resistance and cardiovascular risk in patients with advanced chronic kidney disease: a nationwide analysis. Clin Kidney J 2020;13(05): 821–827
46 Ryter SW, Mizumura K, Choi AM. The impact of autophagy on cell death modalities. Int J Cell Biol 2014;2014:502676
47 Yu Y, Shiou SR, Guo Y, et al. Erythropoietin protects epithelial cells from excessive autophagy and apoptosis in experimental neonatal necrotizing enterocolitis. PLoS One 2013;8(07):e69620
48 Yang C, Xu Z, Zhao Z, et al. A novel proteolysis-resistant cyclic helix B peptide ameliorates kidney ischemia reperfusion injury. Biochim Biophys Acta 2014;1842(11):2306–2317
49 Macdougall IC, Akizawa T, Berns JS, Bernhardt T, Krueger T. Effects of molidustat in the treatment of anemia in CKD. Clin J Am Soc Nephrol 2019;14(01):28–39
50 Regidor DL, Kopple JD, Kovesdy CP, et al. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. J Am Soc Nephrol 2006;17(04):1181–1191
51 Singh AK, Szczech L, Tang KL, et al;CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355(20):2085–2098

