The future of anemia of CKD: where are we going?

The latest on the underlying mechanism

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Anemia is a condition where the number of red blood cells (RBCs) is insufficient to meet the body's physiologic needs. It is diagnosed by measuring blood hemoglobin (Hb) levels. The World Health Organization (WHO) defines anemia for pregnant and non-pregnant women, and for men at <11.00 g/dL, <12.00 g/dL and <13.00 g/dL Hb respectively.[1]

Anemia of chronic kidney disease (CKD) mainly occurs in patients with a glomerular filtration rate >30ml/min/1.73 m^2. Two different pathways can lead to anemia of CKD: [2]Reduced production of erythropoietin (EPO) leading to reduced erythropoiesis; and

(i) Inflammation leading to the release of inflammatory cytokines causing excess production of hepcidin which, in turn, induces degradation of the iron exporter ferroportin and reduced iron availability.

Increased hepcidin restricts iron availability.[2] When hepcidin levels are normal, iron can be mobilized from intracellular ferritin stores through ferroportin channels. In the presence of higher levels of hepcidin, the ferroportin channels are blocked, leading to an accumulation of ferritin inside the cell. In this way, increased hepcidin levels lead to decreased iron absorption in the gut, reduced iron mobilization from intracellular stores,[2,3]and reduced iron in the circulation available for erythropoiesis,[3] resulting in low serum iron, low transferrin saturation and normal-high ferritin.[4]

Two regulatory systems maintain iron homeostasis: systemic regulation through hepcidin and the iron exporter ferroportin, and cellular regulation by iron regulatory proteins.[5]

In CKD, increased hepcidin secretion from the liver causes functional iron deficiency and reduces erythropoiesis, leading to anemia.[3]

Production and secretion of EPO, and the expression of EPO receptors are regulated by tissue oxygen supply via activation of the HIF pathway.[6] The kidneys produce EPO in response to hypoxia which in turn increases the red cell mass, thereby improving tissue oxygenation.[6]

EPO is the critical growth factor that acts on bone marrow erythroid progenitor cells to prevent them undergoing apoptosis.[6] In normal conditions, low concentration of EPO allows only a small percentage of erythroid progenitor cells to survive, while the remaining progenitors undergo apoptosis.[6]In contrast, when the concentration of EPO rises in blood (either endogenously or exogenously), many more erythroid progenitor cells escape from apoptosis and proliferate to mature into erythroblasts and, eventually, RBCs.[6]

The HIF pathway is a direct oxygen sensing system. It plays an important role in cellular response to hypoxia by controlling a broad spectrum of biological processes and is regulated by two major sets of proteins: Hypoxia Inducible Factor (HIF) and Prolyl Hydroxylase Domains (PHD).[2] HIF transcription factors are protein heterodimers composed of an oxygen-sensitive α subunit and a constitutively expressed β subunit.[2] In humans, there are three HIF-α paralogs (HIF-1α, -2α, -3α, although HIF-3α does not have a prominent role in the regulation of cellular hypoxia responses) and two HIF-β paralogs, aryl hydrocarbon receptor nuclear translocator (ARNT) and ARNT2.[7] HIF 1α and -2α facilitate oxygen delivery and cellular adaptation to hypoxia by controlling a broad spectrum of biological processes. Under hypoxia, HIF induces the expression of genes that influence both erythropoiesis and iron metabolism/utilization. Under basal normoxia, HIF-α is downregulated/degraded.[2]

PHD proteins are oxygen-sensitive enzymes that regulate activity and degradation of HIF transcription factors.[8] They are hydroxylase enzymes, which have three isoforms (PHD1, PHD2, PHD3), all of which are involved in the regulation of gene expression and activity of HIF proteins in response tissue hypoxia.[2] Under hypoxia, the rate of PHD-dependent hydroxylation and degradation of HIF-α is reduced.[2]

CKD-induced dysregulation of the HIF pathway leads to impaired cellular responses to hypoxia and reduced EPO production.[9]

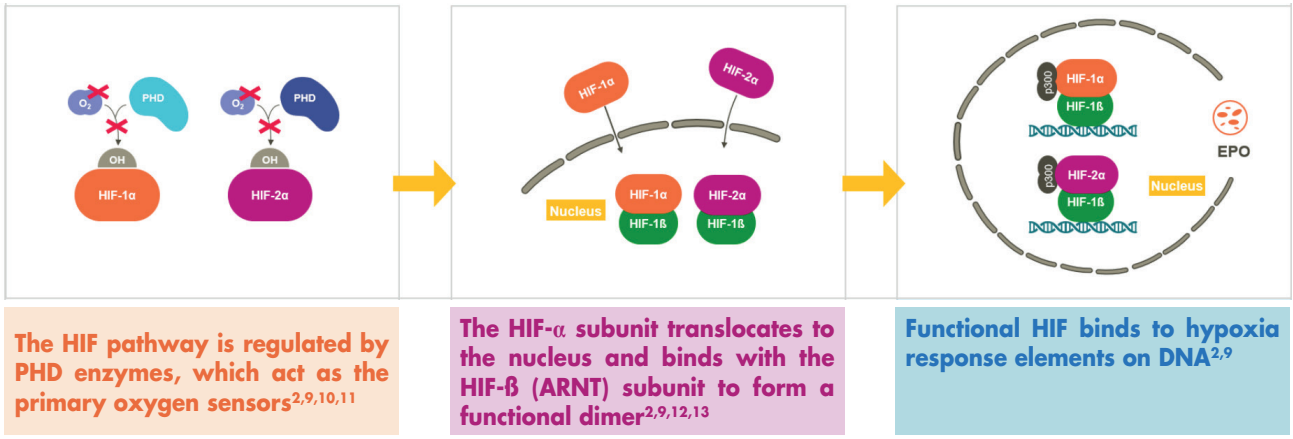

Figure 1. HIF pathway in hypoxia (in animal models). Image independently created by GSK from Ariazi JL, *et al. J Pharmacol Exp Ther* 2017;363(3):336–47 and Koury MJ, *et al. Nat Rev Nephrol* 2015;11:394–410.

In anemia, decreased oxygen transport causes tissue hypoxia, which through activation of the HIF system stimulates the production of EPO.[2] This classic hypoxia response is greatly impaired in patients with kidney failure, as the kidney is the major site of erythropoietin production under physiologic and hypoxic conditions.[2] In CKD, hypoxia-induced signaling is disrupted and anemia develops as CKD progresses.[2]

Current treatment options for anemia in the KDIGO Guidelines are:

- First line: supplemental iron,[14] oral > IV
- Second line: recombinant EPO therapy, in combination with iron supplements[14]
- Blood transfusion is a rescue therapy if other treatments for anemia fail[14]
- Kidney transplant may be curative in patients with ESRD[15]

HIF-PHIs are a novel therapeutic class for the treatment of anemia.[16] They stabilise HIF by suppressing/inhibiting PHD to mimic the physiologic response to hypoxia, stimulating erythropoiesis via endogenous EPO production and modulating iron metabolism in animal models.[16,17] As HIF-PHIs maintain a physiologic elevation of EPO production, the risk of Hb overshoots brought by erythropoiesis stimulating agents (ESAs) may be reduced.[9,18]

The HIF-PHI mechanism of action is depicted in Fig 2.

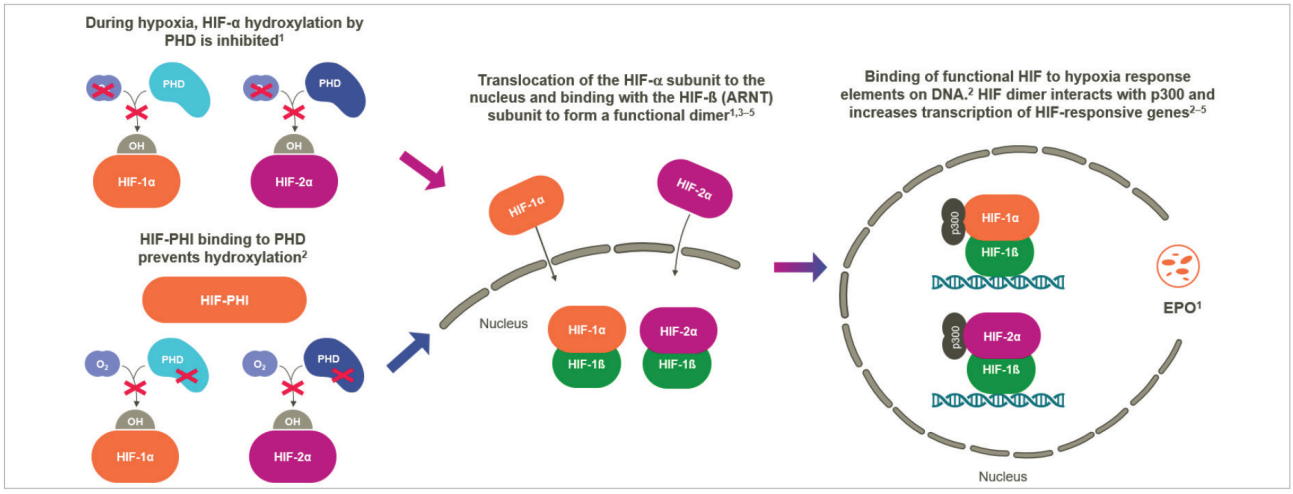

Figure 2. The HIF-PHI mechanism of action. Adapted from 1. Ariazi JL, et al. J Pharmacol Exp Ther 2017;363:336–47; 2. Koury MJ, Haase VH. Nat Rev Nephrol 2015;11:394–410; 3. Haase VH. Kidney Int Suppl 2021;11:8–25; 4. Wang GL, Semenza GL. J Biol Chem 1995;270:1230–7; 5. Ratcliffe PJ. J Clin Invest 2007;117:862–5.

HIF-PHIs have the potential to impact both absolute and functional iron deficiency directly, via the regulation of iron homeostasis proteins (e.g. transferrin, divalent metal-ion transporter 1 [DMT1], ferroportin and duodenal cytochrome B [DcytB]),[19,20] and indirectly, via suppression of hepcidin (through erythroferrone) which may increase iron availability.[19]

When to treat, why, and challenges of management

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Unfortunately, at least in the US, anemia of CKD is underdiagnosed and undertreated, due to both provider- and patient-related factors.

From the patient's perspective, there is often a failure to recognize the symptoms of anemia and to distinguish them from symptoms of CKD and other comorbid conditions.[21] On the provider side, Hb and iron stores are measured less frequently that recommended in the guidelines, particularly in non-dialysis patients. This may be due to payment issues, or time constraints and the difficulty of managing this complex condition.[21-26]

As a result, treatment is often not initiated, even when a patient's Hb is less than 10 g/dL. It may be that it is deprioritized over other topics like hypertension, especially in the non-dialysis population.[24] From the patient's perspective, polypharmacy is often an issue as multiple medications may be needed to control the sequelae of CKD, and the inconvenience of clinic visits and injections also plays a role.[25,26]

All these factors lead to undertreatment of CKD anemia. This is illustrated by the results of a large study from the Humana Research Database among 31,026 patients with non-dialysis CKD and Hb <10 g/dL who all had private health insurance. The study showed that only 39% and 50% of patients at CKD stages 4 and 5 respectively were receiving anemia treatments including oral iron, IV iron, ESA and RBC transfusion.[27] Consequently, approximately 40% of adults starting dialysis in the US have Hb <10 g/dL at the time that they start.[28]

Most of the data on the consequences of this undertreatment come from observational studies. A large systematic literature review and meta-analysis (191 studies; 2002-2018) showed that low Hb (<10 g/dL) is associated with increased all-cause mortality in both dialysis-dependent and non-dialysis-dependent CKD patients. The analysis further showed that both dialysis-dependent and non-dialysis-dependent patients with low Hb had increased cardiovascular mortality and an increased incidence of MACE (CV events including stroke, coronary heart/artery disease, heart failure, myocardial infarction and atrial fibrillation), while non-dialysis-dependent patients with low Hb were more likely to be hospitalized and to experience progression of their CKD.[29]

A more recent analysis from the DOPPS study (n=4,604 from 21 countries; 2009-2015) found that the mortality risk is higher for patients starting hemodialysis (HD) at lower Hb levels. It showed a 2-fold higher mortality for ESA experienced patients who started HD with Hb <8.0 vs ≥11.0 g/dL, despite having a similar comorbidity profile, and that every 1 g/dL Hb increase at Month 1 after starting HD, up to 11 g/dL, was associated with an 11% lower mortality during Months 4-12.[30]

Lower Hb levels are also associated with worse health-related quality of life in patients with CKD. There have been a number of studies using various quality of life instruments including:[31]

- Health status (EQ-5D-3 L): all domains showed significantly greater problems/issues among participants with lower Hb levels ($p < 0.0001$ all domains)
- Health related quality of life (HRQoL): numerically lower mean scores, indicating poorer HRQoL, were reported by patients with lower Hb levels across all CKD stages (with the exception of stage 3a) for KDQOL-36, SF-12 physical component summary, SF-12 mental component summary, symptoms and problems with kidney disease subscale, effects of kidney disease on daily life subscale, and the burden of kidney disease subscale
- Work productivity and activity impairment (WPAI): numerically higher mean percentage absenteeism, presenteeism and overall work impairment were reported by patients with lower Hb levels at CKD Stages 4 and 5 and increasing levels of total activity impairment were observed with lower Hb levels across all CKD stages (with the exception of stage 3a).

Today in the US, ESA treatment is initiated at 9.0 g/dL in dialysis-dependent patients, with the target range between 9.0-11.5 g/dL; in non-dialysis patients it is initiated at 10.0 g/dL with the target range between 10.0-11.5 g/dL.[14] These levels are well below the normal range for the non-CKD population (13-17 g/dL in men and 12-15 g/dL in women)[32] as clinicians aim to balance the increased symptoms and blood transfusions that are seen with low Hb levels against the increased risk of mortality and thrombosis seen with high Hb levels in some studies.

Current treatment options for anemia in the KDIGO Guidelines are:

- First line: supplemental oral or IV iron[14]
- Second line: recombinant EPO therapy, in combination with iron supplements[14]
- Blood transfusion is a rescue therapy if other treatments for anemia including ESAs fail, if the risk of ESAs outweigh the benefits, or when rapid correction of Hb is indicated[14]

A US study into treatment of non-dialysis patients with anemia covered by Medicare (aged 66-85 years), showed that 6.7% of patents were treated with IV or oral iron, 12.7% received ESAs and 22.2% received blood transfusions, despite their position in the guidelines as a rescue therapy.[33]

Iron supplementation is another very important treatment. There is a growing body of evidence to show that iron deficiency itself may be harmful in both heart failure and CKD patients. We also need to ensure that there is sufficient iron available for erythropoiesis. Treating iron deficiency is often enough to raise Hb levels and, especially in earlier stages of CKD, no additional treatment with ESAs may be needed. However, if ESA therapy is needed, adequate iron for erythropoiesis can improve the response to and reduce dose of ESA therapy.[14]

We have shown that the benefits of treatment for anemia of CKD include improvements in quality of life, avoidance of transfusion and how important that is for our patients, and avoidance of absenteeism and, in pediatric patients, this includes improvement in school attendance and performance.[14]

But there are challenges to the standard of care:

- Oral iron frequently causes gastrointestinal side effects – either constipation or nausea – which can lead to poor adherence which limits its use.[34]
- IV iron is associated with some toxic reactions, and there is concern about an increased risk of infection and oxidative stress[35]
- Potential limitations of ESAs include increased cardiovascular morbidity and mortality, worsening hypertension, stroke and thrombotic events and ESA hyporesponsiveness in the dialysis population[35]

But equally important as some of these risks are the difficulties and physical challenges of the burden of administration, additional clinic visits required to give injectable medication, particularly for IV iron. Even if patients are able to have these treatments at home, there is a requirement for cold storage and there are logistical challenges in getting the medication to them at home.[36]

Approximately 20% of patients with anemia of CKD are hyporesponsive to ESA therapy.[37] In general, ESA hyporesponsiveness refers to patients requiring high doses of ESAs (25-100% higher doses than recommended)[38] to increase and/or maintain their Hb levels within the acceptable range.[38] Both ESA hyporesponse and higher ESA doses are associated with poor clinical outcomes, including increased risk of cardiovascular and all-cause mortality.[14,39]

A secondary analysis of the CHOIR trial, among patients with non-dialysis-dependent CKD, looked at the association between achieved Hb and mortality and the dose of ESA required to reach that Hb. There was some association between the level of Hb and mortality, but the higher the ESA dose needed to get there was associated with a higher mortality. Average epoetin-alfa doses >10,095 U/week were associated with increased risks for CV events irrespective of the Hb achieved within the first 4 months of treatment (P=0.0074).[40]

The Nobel prize was awarded in 2019 for the discovery of the HIF pathway and the important role it plays in the physiological response to hypoxia, inducing expression of EPO in the kidney and liver; as well as influencing a wide range of hypoxia-sensitive proteins that regulate lipid metabolism, iron metabolism/utilisation, and angiogenesis.[41]

HIF-PFIs have the potential to increase EPO production, by playing an important role in the expression of EPO in both the kidney and the liver.[2] They are also involved in regulating the iron pathway and increasing iron utilization,[2] as well as downregulating hepcidin, either through erythroferrone, or by erythropoiesis itself.[2]

There have been large, clinical trial programmes for three HIF-PHI agents to date. The comprehensive study programs are in large patient populations and include both dialysis-dependent and non-dialysis-dependent patients with CKD anemia.

Further readings

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