Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018

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Anemia is a frequent complication during the later stages of chronic kidney disease. When present, it may cause symptoms such as fatigue and shortness of breath. The pathogenesis of anemia in chronic kidney disease is complex, but a central feature is a relative deficit of erythropoietin. New information has elucidated the critical role of the hypoxia-sensing system in mediating erythropoietin synthesis and release. Iron deficiency is a second important factor in the anemia of chronic kidney disease. New insights into the dynamics of iron metabolism have clarified the role of chronic inflammation and hepcidin as key mediators of impaired iron utilization. In this article, we review the epidemiology, pathobiology, clinical evaluation, and treatment of anemia in chronic kidney disease.

Complete author and article information provided before references.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Case: *A 54-year-old man with diabetes mellitus, hypertension, and coronary artery disease is being treated for chronic kidney disease (CKD). His estimated glomerular filtration rate has declined over the past 2 years from 40 to 14 mL/min/1.73 m^2. The patient reports increased fatigue and asks about the causes of his anemia. Red blood cell indexes are normal, and iron test results and serum folate and vitamin B_{12} concentrations are found to be normal.*

Question 1: What is the most likely cause or causes of the patient's anemia?

a) Diabetes mellitus
b) Relative erythropoietin deficiency
c) Iron deficiency
d) Multiple myeloma

For answer, see Appendix.

Introduction

Kidney failure produces numerous changes that destabilize homeostasis. An important example is diminished erythropoiesis, with anemia being a common complication of kidney disease. The anemia that accompanies kidney failure was recognized by Sir Robert Christison in 1839, who observed that "by far the most remarkable character of the blood in the advanced stage of the Bright's disease is a gradual and rapid reduction of its colouring" and "no other natural disease came as close to hemorrhage for impoverishing the red particles of the blood." Similarly, Richard Bright had noticed that patients with kidney disease had paleness of the skin: "after a time, the healthy colour of the countenance fades."*

*Christison R. On Granular Degeneration of the Kidnies and Its connexions With Dropsy Inflammations and Other Diseases. Black, Edinburgh: 1839, pp. 63-74.

Anemia remains an important complication experienced by patients with kidney disease, although one that is treatable. The prevalence of anemia depends on its definition, but generally increases in frequency and severity in the more advanced stages of CKD. Studying adult patients at Boston health clinics, Hsu et al published in 2001 the fact that mean hematocrit (Hct) values decreased with creatinine clearance < 60 mL/min in men and <40 mL/min in women. More severe anemia (Hct < 33%) was common among patients with estimated glomerular filtration rates < 30 mL/min/1.73 m^2 in women and <20 mL/min/1.73 m^2 in men. Hsu et al published a separate study the next year that used the third National Health and Nutrition Examination Survey (NHANES III [1988-1994]). Among 15,971 adults, anemia as defined by hemoglobin (Hb) concentration < 12 g/dL in men and <11 g/dL in women was more common with creatinine clearances < 70 mL/min and <50 mL/min in men and women, respectively. A more significant mean decrease in Hb concentration of 1.0 g/dL was found for patients with creatinine clearances < 30 mL/min.

Among patients with diabetes mellitus and CKD, anemia tends to be more severe and to develop at an earlier point in CKD. El-Achkar et al studied 5,380 individuals who were surveyed as part of the National Kidney Foundation's Kidney Early Evaluation Program (KEEP), a community-based screening program for patients at higher risk for kidney disease. Using a definition of anemia as Hb concentration < 12 g/dL in men and in women older than 50 years and <11 g/dL in women 50 years and younger, the prevalence was greater among patients with CKD with diabetes (Fig 1). In patients with stage 3 CKD, 22.2% of patients with diabetes were anemic, increasing to 52.4% in

stage 4 CKD. The difference in prevalence between those with and without diabetes was greatest in stage 3 CKD, for which the rate of anemia was 3 times as high among the former. Erythropoietin deficiency is the most common cause of anemia in CKD, and the deficiency may be more severe in patients with diabetes. In a study of 694 anemic patients, Symeonidis et al observed that serum erythropoietin concentrations, in relation to anemia severity, were lower in patients with diabetes.

Additional Readings

- El-Achkar TM, Ohmit SE, McCullough PA, et al. Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: the Kidney Early Evaluation Program. *Kidney Int.* 2005;67:1483-1488.
- Hsu C, Bates D, Kuperman G, Curhan G. Relationship between hematocrit and renal function in men and women. *Kidney Int.* 2001;59:725-731.
- Hsu C, McCulloch C, Curhan G. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: results from the Third National Health and Nutrition Examination Survey. *J Am Soc Nephrol.* 2002;13:504-510. ★ ESSENTIAL READING
- Symeonidis A, Kouraklis-Symeonidis A, Psiroyiannis A, et al. Inappropriately low erythropoietin response for the degree of anemia in patients with noninsulin-dependent diabetes mellitus. *Ann Hematol.* 2006;85(2):79-85.

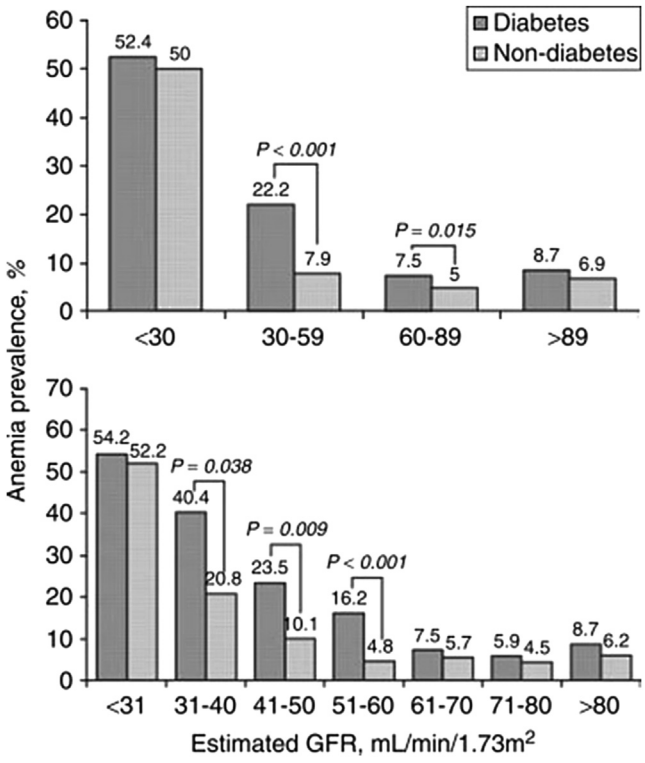

Figure 1. Prevalence of anemia (hemoglobin < 12 g/dL in men and <11 g/dL in women) in patients with or without diabetes. Abbreviation: GFR, glomerular filtration rate. Reproduced from El-Achkar et al (*Kidney Int.* 2015;67:1483-1488) with permission of the copyright holder (International Society of Nephrology).

Question 2: Which factor is most responsible for sensing cellular hypoxia?

a) Erythropoietin
b) Hepcidin
c) Hypoxia-inducible factor (HIF)-prolyl hydroxylase
d) Fibroblast growth factor 23
e) Ferroportin

For answer, see Appendix.

Physiology/Pathophysiology

Background

The erythropoietic system maintains homeostasis in the red blood cell supply to achieve adequate tissue oxygen delivery. Balance is achieved by replacing erythrocytes lost due to senescence and bleeding (if the blood loss is not severe). In addition, it has long been known that hypoxia stimulates new erythrocyte production. Hypoxia could be due to pulmonary disease, reduced tissue perfusion, or living at high altitude. The expectation that a circulating factor governed the erythropoietic response was followed by the discovery of erythropoietin and the cloning of its gene in 1985. Soon thereafter, the mechanism by which cells sensed hypoxia and the central role of the transcriptional factor, hypoxia inducible factor 1 (HIF-1), was identified.

Tissue oxygen availability is sensed continually at the cellular level. If hypoxia is detected, a multifaceted response is triggered. An important component of the response is increased production of the glycoprotein hormone erythropoietin. This 30.4-kDa molecule is the key stimulus for erythrocyte production in mammals. It acts as a true hormone in that it is produced in the kidneys and circulates and acts at tissue receptors throughout the body, most importantly in bone marrow. Erythropoietin binds to its marrow cell-surface receptors to stimulate erythropoiesis.

Hypoxia Sensing: The HIF System

The body's sensing of tissue hypoxia, and thereby recognition of anemia, occurs by the HIF system (Fig 2). Central to this function are 2 proteins, HIF-α and HIF-β. HIF-α is continually produced, but when sufficient oxygen is present, it is rapidly "marked" (hydroxylated) for degradation by enzymes, the HIF-prolyl hydroxylases. The prolyl hydroxylases work as oxygen sensors because they require oxygen as a co-substrate. After hydroxylation, HIF-α is recognized by the von Hippel-Lindau protein, polyubiquitinated, and destroyed. HIF-β is constitutively expressed, but is not sensitive to hypoxic degradation. When tissue hypoxia occurs, HIF-α accumulates, translocates to the nucleus, forms a heterodimer with HIF-β, and binds to hypoxia response elements of a large number of oxygen-sensitive genes. One of these is the erythropoietin gene, leading to increased erythropoietin production. Numerous other genes, including those coding for enzymes