AKDHC

Arizona Kidney Disease & Hypertension Center

Anemia and Chronic Kidney Disease

We present this article to demonstrate the strong relationship between anemia and chronic kidney disease (CKD). Statistical estimates place the number of patients with CKD and anemia at 1.5 million in the United States of America. Recently, anemia has been linked to cardiovascular disease, which is a major cause of mortality in CKD. When anemia is corrected in hemodialysis patients, overall health and quality of life improve. In spite of this, early nephrology consultation to correct anemia may be required to reduce the high mortality rates.

Below we present some case histories, the etiology, and recommended treatment of anemia; demonstrate both the relationship with kidney disease that our medical practice specializes in, and, cardiovascular disease (CVD). It is also emphasized, how important it is to assess kidney function by calculating the glomerular filtration rate (GFR).

CASE PRESENTATION

Case 1

Female, age 82, with past medical history significant for type 2 diabetes, hypertension and hyperlipidemia. She presents to the Emergency Room, with severe weakness and fatigue. She had not seen a doctor for the last 7 years. Her physical examination was significant for blood pressure (BP): 140/85, Pulse 70 per minute, Weight 90 lbs., otherwise unrevealing. Laboratory investigations showed: blood sugar: 180 mg/dl, blood urea nitrogen (BUN): 30 mg/dl, serum Creatinine (SCr): 1.9 mg/dl. Urinalysis showed 3+ protein, no red blood cells. Hemoglobin (Hgb) 7.9 gr/dl. Stat Hematology Consult was obtained.

Case 2

Male, age 42, with past medical history significant for type 2 diabetes, hypertension and hyperlipidemia for the last five years, presents to the Emergency Room with severe weakness and fatigue. He admits non compliance with his regimen and no medical follow up for two years. Physical examination is significant for BP: 160/90, Pulse 85/min., Weight 220 lbs, Extremities with two plus pitting edema, otherwise unremarkable. Laboratory data showed a blood sugar: 250 mg/dl, BUN: 60 mg/dl, SCr: 4.2 mg/dl, Hgb: 7 gr/dl. Stat Nephrology Consult was obtained.

These two cases that presented with severe anemia have been chosen to emphasize that SCr has limited value in assessing the accurate level of kidney function. In the first case, the patient was referred to a hematologist, based on severe anemia. Because of a SCr mildly elevated, kidney disease is not evident. The second patient was referred to a nephrologist because of an obviously elevated SCr.

Surprisingly, when GFR calculations are performed, the first patient showed a lower level of kidney function. In case 1 the GFR was 17 ml/min indicating CKD stage 4, and in case 2 the GFR was 31 ml/min which places him in the category of CKD stage 3. His kidney function is better, even with a higher SCr. Anemia is most likely secondary to renal disease in both patients.

Glomerular filtration rate (GFR) estimation is the most appropriate method to establish kidney function. (See our first Newsletter). The numbers were developed using the Cockcroft-Gault formula.

The association between anemia and CKD was

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first noted by Richard Bright back in 1836. However, it was not until 1953, when an erythropoietic factor was identified in the serum of anemic rabbits. Later on, Goldwasser demonstrated that the kidney was the site that regulated the production of this factor. In 1985, erythropoietin was isolated. This advancement started a new era of treatment for anemia, establishing the basis for cloning and drug development.

Anemia develops as CKD progresses, due to the decreased erythropoietin synthesis associated with loss of kidney mass. Recent observations have shown that anemia can be observed as early as CKD stage 2, at a GFR level of 70 ml/min, especially in patients with diabetic nephropathy. Hematocrit (Hct) generally declines around 3% for every 10 ml/min/1.73 m2 of reduction in GFR. Hsu et al have estimated that 800,000 patients with CKD have anemia, defined as Hgb less than 11 g/dl. Likewise, from extrapolated data on the distribution of Hct levels among patients with various degrees of CKD from a Health Maintenance Organization, there are as many as 1.5 million individuals with CKD and anemia in the USA.

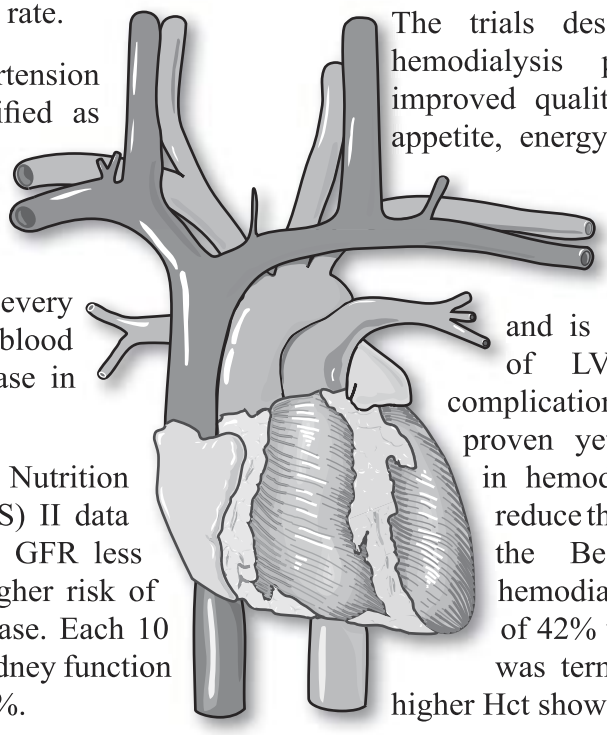
HEART DISEASE

The anemia of early stages of CKD contributes to the development of cardiovascular disease (CVD), an independent determinant of mortality among patients with end stage renal disease (ESRD).

CVD is common (46%) before dialysis, and worsens after the initiation of dialysis (up to 80%). Several lines of evidence have shown that 50% of deaths in dialysis patients are caused by CVD, the most common of which is heart failure. Furthermore, the probability of developing Chronic Heart Failure (CHF) after starting dialysis is 80% within the first year, and the presence of CHF and Left Ventricular Hypertrophy (LVH) signal a higher mortality rate.

In CKD patients, systolic hypertension and anemia have been identified as independent-risk factors for left ventricular wall growth. For each 0.5 g/dl decline in Hgb there is a 32% increase in risk for LVH, whereas for every 15 mmHg increase in systolic blood pressure there is a 36% increase in risk for LVH.

The National Health and Nutrition Examination Survey (NHANES) II data demonstrated that people with GFR less than 70 ml/min exhibited a higher risk of death from cardiovascular disease. Each 10 ml/min/1.73 m2 of decline in kidney function increased the risk of CVD by 5%.



Furthermore, Levin et al have shown that the presence of low Hgb and CVD independently predicts shortened time to renal failure. This can happen, by at least two mechanisms:

1) Renal tissue hypoxia, and/or

2) Cardiac failure. Even if renal blood flow is normal, relative tissue hypoxia could worsen renal structure and function, up-regulating metalloproteinases and nitric oxide synthetases associated with interstitial fibrosis. This will lead to decrease in GFR and worsening anemia.

The trials designed to correct anemia in hemodialysis patients, have demonstrated improved quality of life, overall well being, appetite, energy level, work capacity, aerobic capacity, cognitive function, sexual function, and immunity. A higher Hgb level will improve hemostatic defects of uremia, and is a key factor in the regression of LVH, reducing cardiovascular complications. However, it has not been proven yet, that improving Hgb levels in hemodialysis patients contributes to reduce the overall mortality. Additionally, the Besarab study, which treated hemodialysis patients to a normal Hct of 42% versus maintaining Hct of 30%, was terminated early, since those with higher Hct showed higher mortality.

On the other hand, there are several small observational studies in pre-dialysis patients that have demonstrated reduction in cardiovascular morbidity and mortality when anemia is treated. One by Hayashi, involved nine CKD patients, and showed regression of pre-existing LVH with normalization of Hgb.

The data demonstrates that the correction of Hgb in patients on hemodialysis, with established complications, might be too late to change end-results. Therefore, all efforts are being targeted to intervene in regards to anemia management prior to dialysis. It has been hypothesized that the exposure to the uremic milieu, which includes middle molecules, acidosis, abnormalities of mineral metabolism, and high levels of known growth factors, leads to irreversible myocardial changes in structure and function. Thus, maintaining adequate Hgb levels before the initiation of renal replacement therapy could be a key factor in the reduction of mortality and cardiovascular complications in patients with kidney disease.

Treatment

How should we treat anemia associated with kidney disease? In 1997, the National Kidney Foundation, published recommendations that were updated in the year 2000. They are available on the Internet for health care professionals at: (www.kidney.org/professionals). They are as follows:

1) Establish the level of kidney function, most frequently using the Modification of Diet in Renal Disease (MDRD), and/or the Cockcroft –Gault equations, as it was reviewed in a former newsletter. (see www.AKDHC.com)

2) If GFR less than 60 ml/min, initiate anemia work up.

3) Anemia is considered when Hct level is less than 33% in pre-menopausal women and pre-pubertal patients, or if Hct is less than 36% in post menopausal females and adult males. The classical features of anemia of renal disease are normocytic, normochromic, non regenerative.

4) Check indices such as complete blood count, reticulocyte count, iron studies, vitamin B12 level, folic acid level and occult blood in stool, especially in elderly patients that may have nutritional deficiencies.

5) Once secondary causes have been discarded, then the patient can be treated with Erythropoietin.

Erythropoietin is synthesized predominantly in the liver in utero. However at birth, a transition, triggered by hypoxia occurs, and the kidney takes over. Although some controversy still exists, the interstitial fibroblasts within the deep cortex are thought to be the major site of production.

Since 1985, when it was cloned and produced by genetic engineering, it has been approved for clinical use in CKD and ESRD patients. It is considered the most significant advance in the treatment of hemodialysis patients in the last 40 years.

The primary mechanism of action of r-HuEPO is stimulation of erythropoiesis by binding to specific receptors on erythroid precursors that have already differentiated from pluripotential stem cells. It may also act as a permissive survival factor, preventing apoptosis, thus allowing red blood cell precursors to reach a stage at which they will inevitably mature into red blood cells.

Dose and Route of Administration

The appropriate dose of r-HuEPO is based on the severity of the anemia. Starting doses range between 50-150 U/Kg/week. Subcutaneous administration once a week, or every two weeks is the most practical way to treat patients with CKD. It also allows for lower doses, to maintain target Hgb levels (11-12 g/dl), and may have better effect on erythropoiesis. Hct/Hgb levels should be monitored every two to four weeks at the beginning of therapy, or after a significant adjustment in the dose. Patients should achieve target levels within a period of four to twelve weeks. Erythropoietin levels are not helpful to monitor the response to therapy.

The long half life of r-HuEPO and the long half life of red blood cells mean that changes in steady state hemoglobin concentration take weeks to develop. Therefore, in patients who exceed the target or rapidly respond, should not have the medication held, but adjusted appropriately. Likewise, adjust the dose and/or frequency incrementally for slow responders.

Darbepoetin Alfa (Aranesp ®)

A genetically engineered analogue of r-HuEPO, has been recently released to the market. The erythropoietic mechanism is identical to r-HuEPO. However, it has an increased amount of sialic acid-containing carbohydrate, which provides a longer half life and greater in-vivo biological activity. A single IV injection lasts approximately 25.3 hours compared with 8.5 hours with r-HuEPO. The dose is 0.45 ug/Kg/week, subcutaneously. Depending on the response, it can be dosed every two to four weeks.

Potential Side Effects

Both r-HuEPO and Darbepoetin alfa have potential side effects as follows:

1) Uncontrolled hypertension, the most common side effect, is seen in about 25 to 30% of patients with CKD or ESRD. The mechanisms are not clearly understood, however, it is not a reason to discontinue the medication. Interestingly, HTN is not seen in patients treated with r-HuEPO without renal disease.

2) Pure Red Cell Aplasia is an adverse consequence of certain therapies. Since 1999, r-HuEPO has been associated with this entity. The majority of the cases have been described in patients treated with Eprex ® brand of r-HuEPO alfa outside the USA. Research is being performed to understand the process; however some speculation exists that changes in the albumin content of the molecule, made by the pharmaceutical company, may have played a role in the development of antibodies.

3) Minor side effects, reported in 3-11% of patients, include body aches, headache, nausea, fever, lethargy, and anxiety.

r-HuEPO Resistance

96% of patients will respond to r-HuEPO or Aranesp if the appropriate dose is administered. However if patients do not achieve the target Hgb/Hct within 4 to 6 months, this can be interpreted as resistance. The most common cause of an incomplete response is iron deficiency. After the evaluation of iron stores, measuring levels of Reticulocyte Hemoglobin, Iron level, Transferrin Saturation and Ferritin levels, the levels can be replaced.

There are new safe formulations (Iron sucrose, and Sodium ferric gluconate complex) for the IV administration of iron that do not need test dose, and the side effects are similar to placebo.

Once the above steps are completed, the following conditions need to be evaluated:

1) Infection/inflammation

2) Chronic blood loss

3) Osteitis fibrosa

4) Aluminum toxicity

5) Hemoglobinopathies

6) Folate or vitamin B12 deficiency

7) Multiple myeloma

8) Malnutrition

9) Hemolysis, and

10) Use of angiotension converting enzyme inhibitors or Angiotensin receptor antagonists.

Anemia in the Critically Ill Patient

Anemia of critical illness is a multi-factorial condition caused by phlebotomy, ongoing blood loss, and inadequate production of red blood cells, maybe

partly explained by the effect of inflammatory cytokines on erythropoietin.

Although red blood cell transfusion is the treatment of choice for immediate therapy, the use of erythropoietin has significantly reduced the overall blood use in critical care. Additional studies are ongoing to further demonstrate this benefit. Current recommended dose is 40,000 U of r-HuEPO subcutaneously once a week, after the third day in the intensive care unit.

SUMMARY AND CONCLUSIONS

The ten steps below briefly outline pertinent factors in anemia and CKD:

1) Anemia is a significant co-morbid condition in CKD patients. It represents a major contributor to CVD disease, and is deleterious to the quality of life.

2) The use of r-HuEPO to a target Hg between 11 - 12 g/dl decreases LVH and cardiovascular complications. It also improves quality of life, cognitive function, functional capacity, appetite, and sexual function. Studies are ongoing to assess the impact on mortality in the pre-dialysis stages.

3) Treatment with r-HuEPO should be initiated when GFR is less than 60 ml/min.

4) The best methods to assess kidney function are the MDRD and the Cockcroft-Gault formulas.

5) Anemia is defined as Hct less than 33% in pre-menopausal women, and less than 36% in post-menopausal women and adult males.

6) Refer to a nephrologist to initiate therapy, before cardiovascular complications develop.

7) The guidelines for evaluation and treatment of anemia are posted on DOQI guidelines website. www.kidney.org/professionals

8) Treatment with r-HuEPO is initiated at a dose of 50-150 U/Kg/week, subcutaneously. Hypertension - a major side effect is not a reason to discontinue therapy.

9) Darbepoetin Alfa, a variant of r-HuEPO that contains more carbohydrates is available, with the advantage of a longer half-life and better in-vivo biological activity, promising for reduced-dosage and cost.

10) The use of r-HuEPO in critical care may help decrease the use of blood transfusions and their risks, however further studies are needed to prove this benefit.