Guest Editorial

Closing in on a Killer: Anemia in Elderly People

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ANEMIA as defined by World Health Organization criteria (i.e., <12 g/dL in women; <13 g/dL in men) is noted in 10%–11% of community-dwelling people aged 65 years or older (1). Iron-, B12-, and/or folate deficiency accounts for approximately 34% of cases, chronic disease (renal disease, chronic inflammatory disease, or both) accounts for approximately 32%, and the rest are unexplained. Among nursing home residents, the prevalence of anemia is 48% and the cause is unexplained in 45% of those individuals (2).

Regardless of the mechanism, anemia is a poor prognostic factor for an enormous range of health outcomes. Patients with cardiovascular disease, renal disease, and cancer all have poorer quality of life and survival if they are anemic (3–5). Perioperative mortality is also adversely affected by anemia (6). In nursing home residents, 5-year survival is related to hemoglobin level as well as age; for the group aged 80–89 years, 5-year survival was 62% in the absence of anemia and 41% in its presence (7). Anemia is also associated with increased mortality in community-dwelling older women with moderate-to-severe disability (8).

In this issue of the Journal, data are presented for the first time linking alterations in hemoglobin levels even within the low normal range to an increased risk of frailty in community-dwelling older women who were participants in the Women’s Health and Aging Studies (9). The relative risk of developing frailty was 7.1 for women with hemoglobin levels of 10 g/dL, 4.3 for women with hemoglobin levels of 10.5 g/dL, and 1.9 for women with hemoglobin levels of 11.5 g/dL compared with those with hemoglobin levels of 13.5 g/dL, the level at which frailty risk was lowest. The risk was increased 50% at hemoglobin levels of 12 g/dL. The presence of cardiovascular disease further augmented the risk.

From one perspective, this important finding is a direct extension of prior work that has shown a relationship between anemia and most of the components of the frailty syndrome including reduced muscle strength and density (10), impaired mobility (11), disability, and poor physical performance (12). However, the novel promise of the work is that anemia may be a component of the pathophysiology of frailty and, if it is, correction of anemia may prevent or delay the onset of frailty.

Although it is possible that heterogeneous mechanisms contribute to the unexplained anemia in elderly people, recent and ongoing studies suggest that a final common pathway involves erythropoietin production and responsiveness. We evaluated hemoglobin and erythropoietin levels longitudinally in participants of the Baltimore Longitudinal Study of Aging and found that, in participants who maintain normal hemoglobin levels over time, serum erythropoietin levels increase with age (13). The rising erythropoietin levels imply stress on the erythron. Is red cell life span shorter in older people with increased erythropoietin levels compensating for the increased red cell turnover? No definitive data are available, but it appears that reticulocyte counts are not increased in the setting of normal hemoglobin levels and elevated erythropoietin levels (unpublished observations).

Red cell life-span studies in older people need to be performed. Are the erythroid progenitors less responsive to erythropoietin as we age, requiring higher concentrations of erythropoietin to generate the number of cells needed to maintain normal levels? No data have been published that address this question. Is the elevated erythropoietin level with normal hemoglobin a reflection of poorer oxygen delivery to the tissues a relative tissue hypoxia? The hemoglobin/oxygen dissociation curve has not been measured in red blood cells from older people. It is conceivable that 2,3-bisphosphoglycerate levels are lower in the red cells of older people or that the hemoglobin molecule is more susceptible to auto-oxidation, which inhibits its ability to deliver oxygen to the tissues. This question has not been addressed experimentally. The underlying physiology that leads to increased erythropoietin levels is unclear. However, in individuals who go on to develop frank anemia that is otherwise unexplained, they often have reduced serum erythropoietin levels even in the absence of detectable renal disease (13). Thus, at least some, and perhaps most of, the unexplained anemia in elderly people is related to inadequate erythropoietin production.

The test of a causal linkage between anemia and frailty is not completely straightforward for a variety of reasons. First, frailty incidence is approximately 14% in the group older than 65 years. Studies aimed at showing a significant drop in incidence will need to enroll many participants. Furthermore, anemia has heterogeneous causes, and a single type of intervention will not be appropriate to all cases. In about one third of patients, repletion of a deficient nutritional component (and reversal of structural causes of blood loss) will be therapeutic. However, for the two thirds of patients with anemia of chronic disease and erythropoietin deficiency (this excludes the very small group with primary marrow disease such as myelodysplasia), the potential interventions each have associated problems. Transfusion has a low, but
not insignificant, infectious disease risk and can be immunosuppressive. Erythropoietin seems highly likely to be able to increase hemoglobin levels appreciably in both the anemia of chronic disease and low erythropoietin states based on the existing limited evidence [e.g., (14)]; however, its chronic use can lead to neutralizing autoantibodies and the development of pure red cell aplasia (15), a complication to which older people may be particularly prone in light of an increased risk of autoimmunity. Furthermore, overshoot of the hemoglobin level can cause or exacerbate hypertension and promote thrombosis. In addition, what level of hemoglobin would trigger an intervention? All evidence to date suggests that even low normal levels of hemoglobin are associated with increased risk.

While these are difficult questions, the goal is clear. Elevating hemoglobin levels improves the outcome for perioperative patients (16), and improves at least quality of life in patients with renal failure (17) or cancer (18). It is not clear that erythropoietin improves survival in the setting of renal failure and cancer. It is time to elucidate the mechanism(s) of unexplained anemia in elderly persons and find out whether elevating hemoglobin levels in older people prevents the loss of strength, mobility, and functioning that leads ultimately to frailty and death.

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References