

Prognostic implications of anemia in older adults

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Anemia is a common condition among community-dwelling older adults, with prevalence estimates ranging from 9-18% in men and 8-13% in women.¹ In those aged 85 years and older – a rapidly growing segment of the world's population – the prevalence of anemia exceeds 20%.² Importantly, however, less than 1% of community-dwelling older adults have a hemoglobin concentration below 10 g/dL and, therefore, the majority of cases of anemia are mild.² In contrast, anemia is more severe in institutionalized settings, such as nursing homes, in which the prevalence of anemia ranges from 48-63% in older residents.¹ Nonetheless, numerous studies over the past decade have shown that anemia is an independent predictor of a variety of adverse outcomes in both community-dwelling and institutionalized older adults. While evidence continues to accrue suggesting that anemia initiates or exacerbates functional decline, it remains unresolved whether anemia is a marker or a cause of poor prognosis in older adults.

Mortality and hospitalization

Mortality risk is significantly higher in older anemic adults than in the non-anemic elderly. This association was observed in several major cohort studies and remains significant even after excluding older adults with comorbid conditions (e.g., cardiovascular disease, cancer, kidney disease).³⁻⁵ Low-normal hemoglobin concentrations have also been shown to be associated with increased mortality,⁵⁻⁸ although this finding is not consistent across studies and depends on the definition of low-normal and the comparison group as well as race/ethnicity and comorbidity.^{4,9,10} It has been suggested that anemia might be masked in some older adults taking diuretics, which can decrease plasma volume, potentially explaining the low-normal hemoglobin concentration to mortality association.¹¹ Alternatively, it is probable that some older adults with low-normal hemoglobin concentrations are more likely to eventually go on to become anemic, potentially increasing their risk of adverse events. Indeed, a recent study of heart failure patients showed that those who had persistent anemia or developed new onset anemia over a 6-month period were more likely to die than patients who remained non-anemic.¹² Importantly, patients whose anemia resolved within 6 months did not have increased mortality, but it was unclear what role treatment played in the resolution of anemia.¹²

In this issue of the journal, Riva and colleagues reported the risk of hospitalization and death by anemia status in Italian adults aged 65-84 living in Biella, Piedmont.¹³ These investigators were particularly interested in the effects of mild anemia, defined as a hemoglobin concentration between 10.0 and 11.9 g/dL in women and 10.0 and 12.9 g/dL in men. Consistent with other population-based studies, less than 1% (31/4,501) of the study participants had a hemoglobin concentration below 10 g/dL. After adjusting for potential confounding factors, over the 3-3.5 year follow-up period there was a 32% increased risk of

hospitalization and a nearly two-fold increased mortality risk in older adults with mild anemia compared with the risks in those who were non-anemic. The effect of anemia on hospitalization risk is particularly important as only two other studies have previously reported this association in community-dwelling older adults.^{5,7} Given that the 3-year incidence of hospitalization in the Biella study population was 29% overall (1,296/4,470), the magnitude of this association is not trivial. The increased risk of death and hospitalization associated with anemia might result from hemodynamic stresses related to increased cardiac output, which if sustained leads to left ventricular enlargement and increased risk of cardiovascular events. However, while cardiovascular disease was the most common discharge diagnosis in the study by Riva *et al.*, it did not seem to differ significantly by anemia status (5.9% in non-anemic subjects and 7.4% in anemic individuals).

Physical function

In addition to the independent effects on hospitalization and mortality, anemia has also been shown to increase the risk of functional decline in older adults. For example, in community-dwelling women aged 70-80 years, Chaves *et al.* showed that anemia was associated with increased probability of self-reported mobility limitations (difficulty with walking one-quarter of a mile or climbing 10 stairs).¹⁴ Similarly, Penninx *et al.* prospectively showed that anemia was associated with decreased performance in objectively measured balance, ability to rise from a chair, and walking speed over a 4-year time period in community-dwelling adults aged 71 years and older.¹⁵ Furthermore, muscle strength as well as muscle mass and density measured by quantitative computed tomography were significantly lower in anemic than in non-anemic community-dwelling older adults.^{16,17} However, the mechanisms that account for these associations have not been elucidated.

Considering that fatigue is often a chief complaint among anemic patients, it is conceivable that older adults with anemia decrease their physical activity and lose muscle strength and mass through disuse. Also, a decreased hemoglobin concentration can reduce oxygenation of muscle, particularly in those older adults with a greater burden of vascular disease that can impair perfusion of tissues. In fact, in community-dwelling older women with cardiovascular disease, lower hemoglobin concentration was more strongly associated with increased risk of frailty (a geriatric syndrome characterized by unintentional weight-loss, exhaustion, weakness, slowness, and inactivity) than in those without cardiovascular disease.¹⁸ Another real possibility is that the association of anemia with physical function outcomes in older adults might reflect increased inflammation or decreased testosterone levels, factors that can adversely affect erythropoiesis and muscle mass.

Randomized, controlled trials of erythropoiesis-stimulating agents in older adults would help sort out whether

anemia causes decreased physical function. One recent trial evaluated the effect of epoetin- α treatment on hemoglobin concentration, fatigue, quality of life, and physical performance in 58 older adults with chronic anemia using a randomized, placebo-controlled, cross-over design over a 32-week period.¹⁹ Subjects were 65 years and older with a hemoglobin concentration of 11.5 g/dL or less for 3 or more months. Patients were not included in the trial if their glomerular filtration rate was below 30 mL/min/1.73 m² or if they were deficient in iron, vitamin B12, or folate. The trial was able to demonstrate the safety of epoetin- α therapy as well as its efficacy in achieving hemoglobin targets, reducing fatigue, and improving health-related quality of life, but the trial showed no improvement in objective physical performance as assessed by the Timed Up and Go test. It might be that the Timed Up and Go test does not have enough of an endurance component to detect change. Other physical performance outcome measures, such as the 400-meter walk test or the 6-minute walk test, might be more responsive to correction of anemia.

Cognitive function

Few studies have examined the association of anemia with cognitive function in older adults.²⁰ It is plausible that decreased cerebral oxygenation could lead to decrements in cognitive function. Interestingly, Inzitari and colleagues investigated whether anemia predicted 5-year progression of white matter hyperintensities (WMH) assessed by magnetic resonance imaging of the brain in 1,846 community-dwelling older adults.²¹ WMH result from small-vessel disease and are associated with decreased cognitive and physical function as well as mortality. While anemia was not associated with increased WMH grade over the 5-year follow-up period, there was a significant interaction between anemia and hypertension. In those with hypertension, anemia significantly increased the risk of worsening WMH grade by 80%; whereas there was no association in normotensive participants. The authors speculated that hypertension-induced structural changes to the vasculature of white matter could make these patients more susceptible to decreased oxygen-carrying capacity of the blood.²¹ Replication of these findings is needed as well as better characterization of the relationship of anemia with cognitive function.

In summary, anemia is highly prevalent in geriatric practice. Many longitudinal studies have demonstrated that anemia is associated with adverse health and functional outcomes in older persons. Whether treatment of anemia with erythropoiesis-stimulating agents or other interventions obviates adverse health risks is unknown. Further research is needed to define the mechanisms through which anemia relates to functional decline in older adults, which will help to guide the design and development of intervention trials. Additionally, the role of anemia as a comorbid condition merits attention as it might aggravate the functional consequences of diabetes, hypertension, renal disease, and other age-associated conditions. Therefore, both observational studies and randomized trials are needed to improve our understanding of anemia in the older population.

References

1. Patel KV. Epidemiology of anemia in older adults. *Semin Hematol* 2008;45:210-7.
2. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood* 2004;104:2263-8.
3. Izaks GJ, Westendorp RG, Knook DL. The definition of anemia in older persons. *JAMA* 1999;281:1714-7.
4. Patel KV, Harris TB, Faulhaber M, Angleman SB, Connelly S, Bauer DC, et al. Racial variation in the relationship of anemia with mortality and mobility disability among older adults. *Blood* 2007;109:4663-70.
5. Penninx BW, Pahor M, Woodman RC, Guralnik JM. Anemia in old age is associated with increased mortality and hospitalization. *J Gerontol A Biol Sci Med Sci* 2006;61:474-9.
6. Chaves PH, Xue QL, Guralnik JM, Ferrucci L, Volpato S, Fried LP. What constitutes normal hemoglobin concentration in community-dwelling disabled older women? *J Am Geriatr Soc* 2004;52:1811-6.
7. Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. *Blood* 2006;107:3841-6.
8. Zakai NA, Katz R, Hirsch C, Shlipak MG, Chaves PH, Newman AB, Cushman M. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: the Cardiovascular Health Study. *Arch Intern Med* 2005;165:2214-20.
9. Denny SD, Kuchibhatla MN, Cohen HJ. Impact of anemia on mortality, cognition, and function in community-dwelling elderly. *Am J Med* 2006;119:327-34.
10. Dong X, Mendes de Leon C, Artz A, Tang Y, Shah R, Evans D. A population-based study of hemoglobin, race, and mortality in elderly persons. *J Gerontol A Biol Sci Med Sci* 2008;63:873-8.
11. Price EA, Schrier SL. Anemia in the elderly: introduction. *Semin Hematol* 2008;45:207-9.
12. Tang WH, Tong W, Jain A, Francis GS, Harris CM, Young JB. Evaluation and long-term prognosis of new-onset, transient, and persistent anemia in ambulatory patients with chronic heart failure. *J Am Coll Cardiol* 2008;51:569-76.
13. Riva E, Tettamanti M, Mosconi P, Apolone G, Gandini F, Nobili A, et al. Association of mild anemia with hospitalization and mortality in the elderly: the Health and Anemia population-based study. *Haematologica* 2009;94:22-8.
14. Chaves PH, Ashar B, Guralnik JM, Fried LP. Looking at the relationship between hemoglobin concentration and prevalent mobility difficulty in older women. Should the criteria currently used to define anemia in older people be reevaluated? *J Am Geriatr Soc* 2002;50:1257-64.
15. Penninx BW, Guralnik JM, Onder G, Ferrucci L, Wallace RB, Pahor M. Anemia and decline in physical performance among older persons. *Am J Med* 2003;115:104-10.
16. Cesari M, Penninx BW, Lauretani F, Russo CR, Carter C, Bandinelli S, et al. Hemoglobin levels and skeletal muscle: results from the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2004;59:249-54.
17. Penninx BW, Pahor M, Cesari M, Corsi AM, Woodman RC, Bandinelli S, et al. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. *J Am Geriatr Soc* 2004;52:719-24.
18. Chaves PH, Semba RD, Leng SX, Woodman RC, Ferrucci L, Guralnik JM, Fried LP. Impact of anemia and cardiovascular disease on frailty status of community-dwelling older women: the Women's Health and Aging Studies I and II. *J Gerontol A Biol Sci Med Sci* 2005;60:729-35.
19. Agnihotri P, Telfer M, Butt Z, Jella A, Cella D, Kozma CM, et al. Chronic anemia and fatigue in elderly patients: results of a randomized, double-blind, placebo-controlled, crossover exploratory study with epoetin alfa. *J Am Geriatr Soc* 2007;55:1557-65.
20. Chaves PH. Functional outcomes of anemia in older adults. *Semin Hematol* 2008;45:255-60.
21. Inzitari M, Studenski S, Rosano C, Zakai NA, Longstreth WT Jr, Cushman M, Newman AB. Anemia is associated with progression of white matter disease in older adults with high blood pressure: the Cardiovascular Health Study. *J Am Geriatr Soc* 2008;56:1867-72.