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Anemia in Frailty

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Synopsis

While anemia is regarded as a relatively common occurrence in older adults, the vigor with which the medical community should intervene to correct this common problem is disputed. Epidemiologic data clearly correlate anemia with functional decline, disability and mortality. Anemia may contribute to functional decline by restricting oxygen delivery to muscle, or to cognitive decline by restricting oxygen delivery to the brain. On the other hand, the erythron may be a separate target of the same biological mediators that influence deterioration of physiologic systems that contribute to weakness, functional and cognitive decline and mortality. Clinical trials aimed to treat anemia in older adults could assess whether physical performance is improved or whether mortality risk declines with improved hemoglobin, but sufficient evidence from such trials is currently lacking. With few guidelines regarding treatment for older adults and significant risk for adverse events associated with transfusion and erythroid stimulating agents (ESA), anemia often goes untreated or ignored in geriatric clinics. This article reviews the problem of anemia in older adults, with a particular emphasis on the frail elderly. We will review the gaps in our evidence base for the treatment of anemia in older adults and assess options for advancing the field.

Keywords

Anemia; frailty; hemoglobin; disability; older adult; inflammation

Prevalence of Anemia in Older Adults

The purpose of this article is to highlight the problem of anemia in a challenging population of patients that are often referred to as the “frail elderly”. This population of older adults often live in the community, as opposed to residential facilities for older adults. Hence, the focus of this article is on data gathered in community-dwelling older adults (Table 1). With the establishment of criteria from the World Health Organization (WHO) [1], anemia is usually defined as hemoglobin less than 13 g/dL for men and less than 12 g/dL for women. These criteria are based on values collected in average individuals with no underlying disease. Using this criteria, a study of the third National Health and Nutrition Examination survey (NHANES 1991–1994) found that 10.2% of community-dwelling adults over 65 years of age were anemic [2]. The incidence of anemia more than doubles to >20% in adults over 85 years of age in the same survey. This is consistent with the general prevalence of anemia reported earlier in the Leiden 85-plus Study [3], the Cardiovascular Health Study

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[4], and the Established Populations for Epidemiologic Studies of the Elderly (EPESE) [5,6]. These studies further showed that a greater percentage of men develop anemia late in life than women [2,3] and that anemia affects non-Hispanic blacks at a rate nearly three times greater than that of non-Hispanic whites [2,4–6].

Outside of using the WHO-defined criteria for anemia, another approach to establish the "ideal" hemoglobin value in a population is to assay a selected population for the variable in question. This approach was used by Milman and colleagues [7] who determined hemoglobin concentration in 358 80-year old Danes. In practice, this selects for a population of older adults that has successfully survived 80 years. They determined the average hemoglobin for 80 year old men to be 14.0 g/dL and for 80 year old women to be 13.1 g/dL - higher than the WHO-defined cut-off. Using the WHO anemia criteria, the prevalence of anemia in this Danish population of adults 80 years of age was similar (17–18%) to that found for NHANES III adults over 85. The authors concluded "optimal" hemoglobin concentrations for older adults may be higher than the WHO cut-off for anemia. This has led to concern that the WHO hemoglobin cut-off is not sufficient when screening vulnerable older adults, which will be discussed in the next section.

Consequences of Anemia in Older Adults and in Frailty

Low hemoglobin, independent of other health conditions puts older adults at risk for several adverse health outcomes associated with poor oxygen delivery including exhaustion, fatigue [8], failing muscle strength [9], and cognitive decline [5,10]. The increased mortality risk for older adults with anemia is well documented [3–6,11,12]. This risk is not accounted for by underlying disease [3,4,6], suggesting anemia, alone, is a risk factor for death in older adults. Several of these studies also provide evidence that older adults who are not anemic by WHO standards, but have low-normal hemoglobin, still have higher mortality risk than non-anemic controls [4,6,11]. Frailty has been associated with being African American [13], and because anemia is more likely to affect non-Hispanic black older adults [2,6], several investigators have looked more closely at anemia as a predictor of mortality for either blacks or whites. A recent follow up study assessed the relationship between hemoglobin concentration and a significant increase in the risk of death in both race groups in NHANES III [14]. The authors concluded that the risk of death for non-Hispanic blacks increases significantly at 0.7g/dL below the WHO-defined hemoglobin limit, while the risk of death for non-Hispanic whites is 0.4 g/dL above the WHO-defined limit. The difference in hemoglobin concentration for the mortality "signal" in these two groups is similar to the overall difference in average hemoglobin between these groups and was not explained by variability in the cause or type of anemia. Similar results were reported for mortality rates of anemic black and white older adults in Chicago [12]. These findings support more specific, stratified criteria for anemia in older adults based on race, in addition to gender and are especially important to consider when designing studies to treat anemia in these groups.

To investigate the impact of anemia on adverse clinical outcomes prior to death, Chaves and colleagues assessed whether WHO anemia criteria also identified women at risk for mobility difficulty [8]. Using self-reported mobility difficulty scores and a performance-based summary score obtained from the Women's Health and Aging Study, the authors showed that mobility scores improved for women as hemoglobin concentrations rose from 12 to 14 g/dL. They concluded that 12 or even 13 g/dL hemoglobin might not be sufficient for identifying women at risk for disability. Similarly, the prevalence of frailty in the Cardiovascular Health Study significantly increased as hemoglobin declined, even though hemoglobin concentration remained above the WHO cut-off for anemia [4].

Strong relationships exist between anemia and the expected physiologic effects of reduced hemoglobin concentration such as reduced physical performance, fatigue, and declining muscle strength in the elderly [15]. Low-normal hemoglobin above the WHO cut-off was associated with decreased hand grip strength, fatigue, and decreased quality of life in older community-dwelling adults in the United States [16]. Anemic older adults were found to have lower muscle strength [9,17] and lower muscle density [17] than non-anemic controls in the InCHIANTI study. Even measurable declines in executive function [10] and cognitive impairment [18] are associated with anemia in older women.

Given that anemia affects between 10 and 20% of older adults and given that anemia is closely associated with impaired cognition, fatigue, disability, and mortality, the identification of effective strategies for the treatment of anemia in older adults seems to be an area worthy of intense biomedical investigation. However, the vast majority of the data is epidemiologic in nature and does not prove a causal role for anemia with respect to these poor health outcomes. Randomized, controlled clinical trials to improve hemoglobin concentration might provide evidence for a causal role and may positively impact physical performance and quality of life for older adults. Unfortunately, such studies have been severely hindered because the underlying cause of anemia in older adults varies widely and, most often, cannot be easily treated.

Pathogenesis of Anemia in Older Adults

Approximately one-third of the anemia diagnosed in the NHANES study [2] could be attributed to nutrient deficiencies (iron, vitamin B12, and folate), another third attributed to chronic inflammation (renal disease = 12%, chronic inflammation = 24%), and the final third had no explained etiology. The results were consistent with an earlier study of adults admitted to an acute geriatric ward that identified anemia of chronic inflammation in 35% of patients [19] and with findings from the InCHIANTI study [20]. Because diagnostic and treatment algorithms for nutrient deficiencies are commonly utilized in clinical practice settings (Table 2), most of this article will focus on the pathogenesis of anemias that are more likely to impact frail, older adults, namely anemia related to inflammation and anemia of unclear etiology.

Frail older adults have poorer health status than robust older adults, more chronic diseases and more comorbid conditions [13]. Active, low-grade inflammation is, therefore, a common finding in the frail elderly [21]. Activation of Nuclear Factor kappa B (NFkB) is the hallmark of chronic inflammation, making NFkB and its transcriptional target genes (see Figure 1) prime candidates for interventions against frailty and pathophysiologic outcomes related to frailty, like anemia. NFkB drives transcription of multiple inflammatory biomediators such as IL-6 and chemokines that promote the clearance of infection and the healing of wounds [22,23]. Increasingly, genes and proteins recognized for their ability to promote longevity have been shown to dampen NFkB activity, drawing a molecular link between aging biology and chronic inflammation.

The mammalian longevity gene, SIRT1, deacetylates NFkB and prevents transcription of its target genes [24]. SIRT6 has also been shown to inhibit NFkB -mediated gene expression [25]. FOXO3A is implicated in the regulation of NFkB inhibitors [26], while estrogen [27] and testosterone [28] have also been shown to inhibit NFkB activity. Global expression of NFkB gene targets were recently shown to increase with chronological age in both humans and mice [29]. Increased free radicals, which accumulate with age, also activate NFkB and inflammation [30]. These data suggest chronic inflammation driven by NFkB may promote specific poor health outcomes in frail older adults. In the next sections, we will investigate potential mechanisms by which inflammation might promote anemia in the frail elderly.

IL-6 and anemia

Given their chronic pro-inflammatory state, we would expect much of the anemia in the frail elderly to be consistent with anemia of inflammation or chronic disease (AICD). AICD is most often described as a normocytic, normochromic anemia, but in severe cases, AICD can become microcytic and hypochromic [31]. AICD is characterized by some combination of iron restriction, insufficient marrow response to the anemia, and decreased erythrocyte survival [31]. Significantly elevated serum CRP and IL-6 in frail patients clearly demonstrate a low-grade, chronic pro-inflammatory phenotype. The serum concentrations of these inflammatory markers are many orders of magnitude lower than concentrations achieved during acute infection, yet the physiology of frail older adults suggest even low concentrations impact on key biological systems [32], including the erythron. Understanding how specific cytokines regulate erythrocyte production and turnover will uncover new pathways that may serve as targets for novel anemia treatment strategies in the frail elderly. Progress in this field has been limited by a poor understanding of the key inflammatory mediators that drive anemia in general.

Recently, compelling evidence has emerged supporting the relationship between anemia and IL-6, which has been dubbed “the cytokine for gerontologists” [33]. IL-6 correlates best with anemia in a number of disease states. In the elderly, frail older adults in particular, anemia is most closely associated with increased IL-6 [34–36]. Nikolaisen and colleagues measured IL-1β, IL-2, IL-6, IL-8, and TNFα in rheumatoid arthritis patients with and without anemia and found that IL-6 levels were highest in the anemic group. Importantly, IL-6 was the only cytokine of those tested that negatively correlated with hemoglobin concentration [37]. IL-6 was also found to be significantly elevated in anemic patients over non-anemic patients with systemic lupus erythematosus [38]. The same study found a negative correlation between hemoglobin and IL-6. Although no causality can be proven from these population studies, they provide important evidence that the mechanisms underlying AICD and anemia associated with frailty may be conserved.

IL-6 has been shown to specifically down regulate beta globin mRNA in BFU-E cultures [39], which would be expected to decrease hemoglobin production. The observation that erythrocyte numbers increase while platelet numbers decrease after prolonged hypoxia, has led many investigators to hypothesize that stem cell competition, or limited proliferative capacity of MEP, may explain these phenomena [40–42]. Because erythrocyte numbers decrease while platelet numbers increase in the context of inflammation, inflammatory cytokines may similarly encourage cell fate. IL-6 induces thrombocytosis in primates while simultaneously reducing red blood cell number [43–45]. However, IL-6 seems to stimulate increased platelet production from conserved numbers of megakaryocytes [46]. IL-6 may, therefore, have independent effects on later stage erythroid and platelet precursors. Interactions between IL-6, erythrocytes, and platelet numbers become important as we consider interventions for improving anemia and the factors that might promote adverse events, such as thromboembolism, in response to interventional therapy.

In addition to the potential for direct effects of IL-6 on erythroid precursors, IL-6 orchestrates the type II acute phase response which restricts iron availability by inducing the expression of factors including serum Ceruloplasmin (Cp) [47] and Hepcidin antimicrobial peptide (Hepc) [48]. As Both Cp and Hepc regulate iron delivery to the erythron, they strongly impact hemoglobin production and the final stages of erythroid development.

Peripheral white cells and anemia in frail older adults

NFkB also promotes transcription of chemokines such as IL-8 and Monocyte Chemoattractant Protein 1 (MCP1), which facilitate homing of neutrophils and monocytes to

sites of tissue injury or infection. Recently, elevated circulating neutrophil and monocytes counts have been associated with frailty, independent of IL-6 [49]. Whether the appearance of such inflammatory cells in frail older adults is indicative of peripheral tissue injury resulting from underlying disease or the consequence of dysregulated chemokine expression, courtesy of NFkB, remains to be seen. In either case, we would expect oxidative stress levels to be higher in individuals with higher numbers of circulating inflammatory cells. Anemia has been linked to increased oxidative stress in a number of experimental and disease states [50–53]. Because the primary role of an erythrocyte is to carry oxygen, many enzymes which scavenge reactive oxygen species are expressed in terminally differentiated erythrocytes [52]. When these enzymes are overwhelmed in their capacity to scavenge reactive oxygen species, erythrocyte life span is reduced and eventually anemia can result [51,52].

A striking example of the important relationship between antioxidant capacity and anemia has come from WHAS I and II and NHANES III. In both cohorts [54,55], anemia was strongly associated with low serum selenium. Further, individuals with anemia due to nutritional causes, inflammation, or unexplained etiologies were more likely to have low selenium. Selenium is a critical co-factor for antioxidant enzymes such as glutathione peroxidase [56], which is highly expressed in erythrocytes [52]. Thus, selenium deficiency in older adults is likely to promote anemia related to multiple causes.

Anemia of unexplained etiology

The NHANES III study which investigated anemia in older adults determined 1/3 of anemia in older adults could not be explained using the diagnostic tests and criteria available [2]. Any subject with anemia and normal nutrients (serum iron, folate and vitamin B12) would fall into this category. Studies in other, community-based populations have also identified a significant proportion of patients whose anemia cannot be clearly diagnosed with available diagnostic criteria [57,58]. Generally speaking, such unexplained anemia tends to be mild and normocytic with normal iron parameters [59]. Though the anemia is “unexplained” or “unclear”, many known biological processes which occur with age may contribute, individually or in combination, to this anemia [59,60]. Such biological processes might include erythropoietin insufficiency [20,61]; androgen insufficiency [27,28]; alterations in erythroid progenitors, hematopoietic stem cells, and their bone marrow niche [62–64]; hypoxia sensing [65,66]; inflammation [36] or developing myelodysplastic syndrome [67].

Unfortunately, we have scant knowledge regarding these possible causes in large numbers of healthy or frail human subjects because they require advanced technology for analysis or because they are difficult to assess in the bone marrow of frail elderly. Sufficient levels of Erythropoietin (Epo) are critical for maintenance of red blood cell number. Epo is primarily produced by the kidney, so in the context of mild renal disease, low Epo levels may be suspected [58]. Many older adults with unexplained anemia and no evidence of inflammation have low Epo levels [20], thus routine analysis of serum Epo concentration in anemic older adults may be useful. Additionally, inflammation can suppress erythropoietic drive [68]. As such, inflammatory markers such as C-reactive protein (CRP), specific pro-inflammatory cytokines, and Hepc should be investigated. Myelodysplastic syndrome is a bone marrow failure syndrome that is common in older adults. Often, pancytopenia, including anemia, is an initial feature that may be followed by transformation to leukemia [69]. Bone marrow biopsy to assess dysplastic changes in multiple hematopoetic cell lines is essential for a definitive diagnosis of myelodysplastic syndrome. Because frail older adults often have multiple chronic diseases and a “poor aging” phenotype, it would not be surprising to find mutifactorial causes for their anemia. Continued collaboration between

large epidemiologic studies and molecular hematologists will remain a requirement for successful analyses and for advancing our knowledge regarding anemia in the frail elderly.

Interventions for consideration

An extensive evidence base concerning the problem of anemia in the elderly has developed in the last decade. However, the majority of the evidence is epidemiologic in nature and does not support causal relationships between anemia and poor health outcomes. This section addresses the areas of research that would extend our clinical and basic biology evidence base toward appropriate diagnostic tools and feasible interventions or preventative measures against anemia in frail older adults. The diagnostics or pharmacologic agents outlined below lack sufficient evidence to be appropriately indicated for treatment of anemia in the frail elderly or accepted as part of standard clinical practice. As such, anemia is most often treated in the elderly when hemoglobin falls sufficiently low enough to require transfusion.

Frail older adults share a pro-inflammatory phenotype without regard to underlying disease status. Much of the anemia observed in this population is likely to be the result of chronic inflammation, but standard clinical practice does not utilize the most sensitive assays (e.g. IL-6 ELISA) that would diagnose chronic inflammation. In principal, anemia associated with chronic inflammation is treated when the underlying disease is successfully treated. However, for frail older adults, the underlying disease, often cannot be resolved. Because anemia is strongly associated with impaired cognition, fatigue, disability, and mortality in older adults, independent of disease state, the medical community must consider the safety and efficacy of anemia treatment for the frail elderly in the absence of a direct diagnosis of disease. As such, we will have to increase the rigor with which we assess anemia in the elderly and test new strategies for their ability to successfully predict patients that will benefit from treatment.

For older adults without the diagnosis of a chronic inflammatory disease or infection and no evidence of nutrient deficiencies, erythropoietin stimulating agents (ESAs) may seem like a plausible option for anemia treatment. Many anemic older adults have lower Epo concentrations that non-anemic controls [70]. However, Epo levels tend to increase with age even while hemoglobin levels decrease [71], suggesting the problem is not production of Epo, but an effective response to it. The serious nature of off-target effects of recombinant human Epo [72–74], including myocardial infarction and stroke, usually preclude the use of this potential intervention in the frail elderly. One randomized, placebo-controlled clinical trial has demonstrated that ESAs can be used safely and effectively in older adults [61]. However, without specific guidelines for their use in the frail elderly and without strong evidence for improved quality of life with treatment, ESAs will remain an unpalatable choice for most geriatric patients.

Inhibition of hemoglobin production by IL-6 is likely to be a key step in the pathophysiology of anemia in frail older adults which could be targeted by novel treatments. Importantly, hemoglobin synthesis occurs after Epo is required. Treatment options that target hemoglobin production independent of Epo are especially relevant considering the serious adverse events associated with ESA use. Modulators of the IL-6 signalling pathway, such as tocilizumab, are available. However, this class of drugs has mild to moderate complications including infusion reactions, liver dysfunction and infections [75]. Another drawback to interventions that specifically target IL-6 is that IL-6 is only one part of a widespread inflammatory response in most frail patients. Identification of an intervention that targets inflammation more broadly may be more beneficial to this population.

Agents that target NFkB would certainly provide broad spectrum inhibition of inflammatory mediators. Aspirin and salicylates prevent activation of NFkB [76], making them potentially very useful. However, the use of aspirin and non-steroidal anti-inflammatory drugs is associated with gastrointestinal bleeding [77]. Nonacetylated salicylates, like salsalate, inhibit NFkB activity and have a smaller risk of bleeding [78,79]. Epidemiologic studies investigating the relationship between the use of nonacetylated salicylates and outcomes like anemia and frailty and randomized controlled trials would be useful to assess the feasibility of this drug class to improve anemia and quality of life for frail older adults.

Summary

The last decade has produced an overwhelming amount of epidemiologic evidence which indicates anemic older adults are at risk for impaired cognition, fatigue, disability, and death. However, sufficient evidence from randomized controlled trials that supports a causative role for anemia associated with functional decline and death does not exist. Justified subject and Institutional Review Board resistance to clinical trials and poorly defined pathogenesis of anemia in the elderly pose significant barriers to the development of informative randomized controlled trials. Studies in the frail elderly should focus on the role of the inflammatory process in the pathogenesis of anemia. Outcomes and endpoints in clinical trials should focus on specific indicators of physical function such as grip strength, walking speed or “timed up and go” rather than on hemoglobin concentration alone. Investing material resources and expertise in the development of new strategies and practices for the diagnosis, treatment and prevention of anemia in the elderly will surely result in improved quality of care and improved quality of life for one of the most vulnerable groups of our society.

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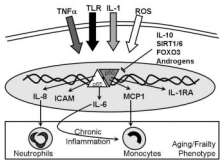

Figure 1. Overview of NFkB and Chronic Inflammation

Type I acute phase cytokines, tumor necrosis factor α (TNFα), interleukin-1 (IL-1); signaling through the toll like receptors (TLR); and reactive oxygen species (ROS) all induce translocation of NFkB (p65/p50) to the nucleus where it induces transcription of the chemokines IL-8 and Monocyte Chemoattractant Protein 1 (MCP1) as well as the proinflammatory cytokine IL-6. Increased circulating neutrophils, increased circulating monocytes and increased IL-6 are all markers of aging and a central piece of the frailty phenotype (Courtesy of Cindy N. Roy, PhD, Baltimore, MD)

Table 1

Population-Based Study Groups Important to Anemia of Aging

Study	Abbreviation	Location	Participants	Ages	Reference(s)
Baltimore Longitudinal Study on Aging	BLSA	Baltimore, MD	1400	20 years +	[71]
Cardiovascular Health Study	CHS	United States	5888	65 years +	[4]
Chicago Health Aging Project	CHAP	Chicago, IL	1806	65 years +	[12]
Established Populations for Epidemiologic Studies of the Elderly	EPESE	United States	3607	71 years +	[5,6]
Invecchiare in Chianti	InCHIANTI	Chianti, Italy	1156	65 years +	[9,17,20,70,80]
Leiden 85-plus Study	Leiden	Leiden, the Netherlands	1258	85 years +	[3]
Milman Study	N/A	Denmark	359	80 years	[7]
Third National Health and Nutrition Examination Survey	NHANES III	United States	4199	65 years +	[2]
Women's Health and Aging Study	WHAS	Baltimore, MD	1002	65 years +	[8,10,11,18]

Table 2

Clinical Diagnostic Tests Important to the Diagnosis of Anemia in Older Adults

Test	Pathogenic	Discriminates	References
Mean Cell Volume (MCV)	> 100 fL < 80 fL	Iron vs. B_{12}/folate deficiency Iron deficiency vs. AICD	[31]
Mean Cell Hemoglobin (MCH)	< 27 pg or > 31 pg	Iron deficiency vs. AICD	
Vitamin B_{12} (B_{12})	< 200 pg/mL	Macrocytic anemia	[2]
Folate	RBC: <102.6 ng/mL Serum: < 2.6 ng/mL	Macrocytic anemia	[2]
Serum Iron (Fe)	< 60 mcg/dL	Iron deficiency/AICD vs. Unexplained anemia	[59]
Transferrin Saturation (TS)	< 15%	Iron deficiency/AICD vs. Unexplained anemia	[68,81]
Serum Ferritin (sFt)	< 12 ng/mL	Iron deficiency vs. AICD	[2,82]
Soluble Transferrin Receptor/log (serum Ferritin) [sTfR/log sFt]	> 1.5 > 0.8	Iron deficiency vs. AICD AICD with iron deficiency anemia	[81]
Estimated Creatinine Clearance (eCC)	< 30 mL/min	AICD vs. anemia of chronic kidney disease	[83]
C reactive Protein (CRP)	> 10 mg/dL	Iron deficiency vs. AICD	