

Anemia in the Elderly Population

Vittorio Emanuele Bianchi

Abstract

Anemia is a clinical condition whose incidence increases with age. It represents a severe risk factor with adverse outcomes, including hospitalization and mortality. In population-based studies, the incidence of anemia in the elderly was found to be 16.8% in women and 17.5% in men, but 30.7% in men of 85 years and older. The aim of the study was to identify the most important factors responsible for the incidence of anemia in the elderly. Pubmed was used, and we searched for the most important epidemiological and clinical studies conducted over last 10 years on anemia in the elderly population. After a comprehensive and standardized evaluation, only studies that accurately determined the causes of anemia and their proportion in older adults were considered. Anemia has been classified into three major classes: nutrient deficiencies, chronic disease or inflammation, and unexplained anemia. Malnutrition is a frequent, undervalued clinical condition, including iron, folate or B₁₂ deficiencies, and accounts for one-third of all anemia in the elderly. The anemia of chronic disease (ACD) develops specifically in patients suffering from chronic inflammatory diseases, such as auto-immune disorders, cancer or chronic infections, or in patients undergoing dialysis. In ACD, cytokines and macrophages play a fundamental role. Unexplained anemia (UA) is the most relevant group, due to the reduction of hypoxia/erythropoietin-sensing mechanisms, oxidative stress, sarcopenia, and sex hormone reduction accounting for more than one-third of all anemia. The correct diagnosis allows physicians to perform the best therapeutic strategies that include energy, protein diet, and iron supplementation, erythropoietin, androgen administration and blood transfusion.

Keywords: Anemia; Sideremia; Transferrin; Hepcidin; Interleukines; Testosterone; Chronic disease

Introduction

Anemia is an emerging risk factor in the older population as-

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Department of Internal Medicine, Hospital of Cagli, Asur1, Italy.
Email: dott.vbianchi@gmail.com

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sociated with a variety of adverse outcomes, including hospitalization, disability and mortality [1-5]. In Comet investigation it was found that the reduction of hemoglobin (Hb) level is related to future increased morbidity and mortality [6]. Subjects older than 85 years with anemia had a higher 5-year mortality rate than subjects with normal Hb levels [7]. Among individuals (mean age 72.5 years), mild anemia (Hb levels \geq 10 g/dL) was found in 6.1% of women and 8.1% of men, and a greater mortality risk, near doubling the 5-year risk, was found in anemic men but not in women [8]. An increase in mortality has been associated with Hb levels less than 11 g/dL [4]. Anemia induced a higher mortality rate in persons 65 years and older hospitalized for myocardial infarction [9], in systolic and diastolic in chronic heart failure (CHF) [10] and in older CHF patients [11]. Anemia has been shown to be a strong and independent predictor of all-cause, long-term mortality after percutaneous coronary intervention [12]. Anemia is also an independent risk factor for decline in physical performance [13] and has a negative impact on quality of life, physical functioning and reduced muscular strength in older patients [14, 15].

For the clinically relevant importance of anemia on the quality and duration of the life of patients and the sanitary cost of hospitalization of the chronic patients, it is imperative to recognize the basic mechanisms underlining the anemia. These are the expression of a complex variety of interacting factors. Despite management guidelines, anemia remains underrecognized and undertreated.

Literature Search Methods

A search of epidemiological studies in Pubmed was undertaken using the keywords: anemia, elderly, prevalence, causes, myelodysplastic syndromes, limited on the last 10 years. After a standardized evaluation, only studies that accurately determined the causes of anemia and proportion in older adults have been considered in this review. Only eight studies reported on the incidence of anemia in persons 65 years and older. The data are reported in Table 1 [16-23].

Literature Search Results

The data showed that cases of anemia were classified into four

Table 1. Types of Anemia in the Elderly in Patients 65 Years and Older

Study	Subjects	IDA %	B ₁₂ /folate deficiency %	ACD %	UA %	Renal insufficiency %
Bach et al, 2014 [16]	4,177	AID: 14.4; FID: 28.2	B ₁₂ : 2.0; B ₆ : 6.7	62.1		11.3
Guralnik, 2004 [17]	2,096	16.6	B ₁₂ : 5.9; B ₆ : 6.4	19.7	33.6	8.2
Shavelle, 2012 [18]	7,171			26	39	11
Tettamanti, 2010 [19]	8,774	16	10.1	17.4	26.4	15
Price, 2011 [20]	190	12		6	35	4
Artz, 2011 [21]	174	25.3	4.6	9.8	43.7	3.4
Ferrucci, 2010 [22]	582	17.4	10.5	24.4	37.2	10.5
den Elzen, 2013 [23]	490	11.4	5.3	20.2	25.4	7

IDA: iron deficiency anemia; ACD: anemia of chronic disease.

main groups. A high incidence of UA, varying from 25.4% to 43.7% is the most prevalent group. Next is ACD that represents an incidence from 6% to 62.1%. Bach et al [16] found the incidence of 62.1% but the authors do not mention cases of UA and probably included these in ACD group. Iron deficiency anemia (IDA) is in third place with an incidence of 11.4-25.3%. Finally, vitamin B₁₂ and folate have an incidence of 4.6-10.5%. These data evidence the importance of UA and ACD in the incidence of anemia in elderly.

Definition of Anemia

The World Health Organization (WHO) definition of anemia limits was less than 13 g Hb/dL for men and less than 12 g Hb/dL for women [24]. These criteria have been challenged recently, and new lower limits for the normal Hb concentration in old age have been suggested using the proposed cut-offs of Hb concentration of lower than 12.2 g/dL in women and lower than 13.2 g/dL in men [25]. By the classification systems, mild grade anemia was defined as an Hb concentration between

10.0 and 11.9 g/dL in women and between 10.0 and 12.9 g/dL in men [26, 27].

IDA was considered present if the elderly had low serum iron (< 50 µg/dL in women and 60 µg/dL in men), low ferritin (< 15 ng/mL), low transferrin saturation rate (< 16%) or increased total iron binding capacity (> 450 µg/dL).

The proportion within this category with macrocytosis (mean corpuscular volume > 100 dL), leucopenia (white blood cell count < 3,000/dL) or thrombocytopenia (platelet count < 150,000/mm³), represents hematologic features consistent with the diagnosis of myelodysplastic syndrome [28].

Epidemiology

Anemia is a multifactorial condition that increases the comorbidities in older adults. According to Third National Health and Nutrition Examination Survey (NHANES III, a national representative study of non-institutionalized civilian adults) [17], the prevalence of WHO-defined anemia among community-dwelling adults aged 65 years and older was 11.0% for men

Table 2. Distribution of Types of Anemia in Persons Age 65 and Older in US

Anemia	Number in the US	All anemia %
With nutrient deficiency		
Iron only	466,715	16.6
Folate only	181,471	6.4
B ₁₂ only	165,701	5.9
Folate and B ₁₂	56,436	2.0
Iron with folate or B ₁₂ or both	95,221	95.221
Total	965,544	34.3
Without nutrient deficiency		
Renal insufficiency only	229,686	8.2
ACI, no renal insufficiency	554,281	19.7
Renal insufficiency and ACI	120,169	4.3
UA	945,195	33.6
Total	1,849,331	65.7

ACI: anemia of chronic inflammation. Reproduced with permission from Guralnick et al [17].

and 10.2% for women. The prevalence of anemia increased as a function of age both in men and in women, but with advanced age, the prevalence was more dramatic for men. At 75 years old, the incidence of anemia was greater in men than in women. In the oldest population (85 years and older), the incidence of anemia was 29.6-30.7% in men and 16.5-17.7% in women [29]. There are also racial differences in Hb distribution, and some expert groups have recommended race-specific criteria for defining anemia [25, 30]. Tettamanti et al [19] found that 16.8% of women and 17.5% of men are anemic and that this prevalence of anemia in the elderly was similar to that found in other population-based studies [17, 29].

Anemia and Mortality

Many studies showed that anemia was an independent strong predictor of morbidity and mortality in the elderly [31-33], particularly in white men and women, but not in black men and women [34]. In patients with anemia, an increased mortality has been demonstrated in disabled, seriously ill, or hospitalized patients. In a study conducted on 2,905 men and 3,975 women aged 65 - 95 years (mean age 72.5 years), mild anemia (Hb levels ≥ 10 g/dL) was found in 6.1% of women and 8.1% of men. Among those patients, 36.1% of anemic men and 15.0% of anemic women died [8]. Anemia in men was related to a significant mortality risk, but not in women. This study evidenced the impact of sex on the outcomes of older subjects with mild anemia. The lower and higher Hb concentrations and anemia are independently associated with increased mortality, but the risk of mortality was not increased due to beta-thalassemia minor [1-3, 35]. Death rates for those with and without anemia based on the WHO criteria were 38% and 28%, respectively, and high levels of Hb were associated with better survival [36]. The risk of hospitalization in the 3 years following recruitment was higher among the mildly anemic elderly subjects than among non-anemic subjects [35]. Anemia is also a risk factor for functional and cognitive decrease [2].

Causes of Anemia

Guralnick et al [17] presented data from the non-institutionalized United States population assessed in the NHANES III. In the approximately 3 million anemic persons older than 50 years, the incidence rate of anemia increased rapidly, to a rate greater than 20% at age 85 and older; overall, 11.0% of men and 10.2% of women 65 years and older are anemic. Two-thirds of participants with anemia had two or more age-associated diseases. Anemia in older persons is divided in four major types according to cause: 1) nutrient deficiencies in one-third; 2) chronic kidney disease (CKD); 3) chronic disease or inflammation (anemia of chronic inflammation, ACI) or chronic renal disease or both were present in one-third; and 4) UA was present in one-third.

For a long time, IDA has been considered the most common form of anemia worldwide, but the Guralnick study [17] showed the real distribution of types of anemia in persons 65

Table 3. Potential Mechanism of UA in the Elderly.

Sarcopenia
Oxidative stress
Quantitative/qualitative alterations in stem cell physiology
Decrease in sex steroids
Polypharmacy
Blunting of hypoxia/erythropoietin sensing mechanism

years and older. The data are summarized in Table 2. Deficiencies of iron, folate, or B₁₂ account for one-third of all anemia in the elderly (34% of the total with an incidence of iron only of 16%). Within this group, half the anemia is related to iron deficiency. The anemia without nutrient deficiency group was 67% of the total population with a prevalence of ACI (no renal insufficiency) of 19.7%. Approximately one-third of older anemic persons have IDA (19.7%), anemia of chronic renal failure (8.2%), or both (4.3%), and the remaining one-third have UA.

In men and postmenopausal women, the commonest cause of IDA is blood loss from lesions in the gastrointestinal tract [37]. From these data, it is evident that the most prevalent incidences of anemia are the IDA and the UA. These results are consistent with other community-based studies, including the Established Populations for the Epidemiologic Study of the Elderly (EPESE) [5] and a representative Italian population [19]. There was a pronounced increase in the prevalence of anemia with increasing age within the older population; in the age group 85 years and older, one-fifth of women and one-fourth of men were anemic.

UA

Anemia that could not be classified into any of the other categories was considered to be an anemia of unexplained origin. Firstly, Guralnick et al [17] found the highest prevalence of anemia is the UA (33%) in the 65 years and older population. Recently, an intensive hematologic evaluation revealed a wide number of anemia etiologies among older adults and that UA in the elderly is the most common category in white and African Americans [21]. Findings from the Baltimore Longitudinal Study on 150 individuals [38] indicated that erythropoietin (EPO) production increases with age among those who maintain Hb levels at 14 g/dL or higher and remains constant over time, even in patients who develop diabetes or hypertension. This suggests deficiencies may occur, at least in some individuals, in the hypoxia/EPO sensing mechanism with age that require increased EPO production to maintain normal erythrocyte production. The mechanism responsible for the decreased red blood cell (RBC) production is not clear. Various biological dysregulation processes, such as the reduction of progenitor mass, blunted effect of EPO on RBCs precursors, altered Hb-oxygen affinity, decreased intracellular oxygen utilization, or alteration in sex steroid milieu have been suspected [39] (Table 3).

A related concept of anemia is its relationship with sarcopenia in the elderly (i.e., those with significant decreases

in body mass). One hypothesis suggests that the decrease in muscle mass may bring about changes in RBC mass, oxygen utilization and perhaps EPO production. In such patients, their anemia may represent a physiological response to their sarcopenia. The relationship between sarcopenia and anemia could be related to the energy and protein malnutrition [40]. Interestingly, in the protein-energy malnutrition model, anemia is not caused by iron or EPO deficiency, but is a result of ineffective erythropoiesis [18].

Changes in stem cell physiology with age are also potentially related to UA in elderly patients. Bone marrow cellularity from marrow aspirates usually declines with age [41]. In humans, the number of clones contributing to hematopoiesis (e.g., colony-forming units erythroid, CFUE) declines with age [42]. Whether this is due predominantly to an absolute decrease in stem cells (as reflected by decreased bone marrow cellularity with age) and/or altered stem cell functional characteristics remains to be defined [43].

Oxidative Stress and Anemia

Oxidative stress is an important cause of anemia and it could be included in the UA. Oxygen is bound to Hb within erythrocytes that make them highly prone to oxidative damage [44]. For this reason, erythroid cells contain numerous antioxidant enzymes to protect them against oxygen radicals [45], and deficient protection from reactive oxygen species (ROS) results in diseases of RBCs, including anemia loss of manganese superoxide dismutase 2 (SOD2), a critical component of the mitochondrial pathway for detoxification of O₂(-), in erythroid progenitor cells results in enhanced protein oxidative damage, altered membrane deformation and reduced survival of red cells [46]. It has been observed that a decrease in RBC count is accompanied by a deficiency of glutathione (GSH) and other antioxidant enzymes that metabolize lipid peroxidation products [47]. RBC-reduced GSH levels were significantly lower in chronic renal failure patients than in healthy subjects, and this alteration could play a role in the pathogenesis of anemia in uremic patients.

Erythrocyte membrane lipid peroxidation occurs in patients with CKD [48]. The availability of antioxidants, reflected by an increase of superoxide dismutase and GSH peroxidase activity, increases after correction of renal anemia [39]. These data suggest that the anemic state itself contributes to free radical production [49]. Exogenous reduced GSH administration results in improved RBC survival in hemodialysis patients [50]. Lipid peroxidation of the RBC membrane caused by oxidative stress may result in resistance to EPO due to enhanced hemolysis [51]. The correction of renal anemia by EPO therapy reduces oxidative stress. Ludat et al [52] compared the malondialdehyde (MDA), GSH and glutathione disulfide (GSSG) levels in chronic hemodialysis patients and showed that after correction of renal anemia, MDA levels are significantly lower, reflecting decreased free radical generation. The rhEPO therapy has clear, positive effects on free radical metabolism, increasing the whole-blood antioxidant capacity.

Antioxidant treatment significantly reduced the high

basal plasma concentrations of free radicals. Vitamin E (α -tocopherol) has a significant effect on anemia and EPO requirements in hemodialysis patients. In chronic hemodialysis patients, both dietary vitamin E supplementation and the use of vitamin E-coated membranes have been associated with reduced RBC fragility, prolonged RBC lifespan, and improvements in Hb and rHuEpo requirements [53]. Anemia significantly improved with antioxidant treatment due to a significant increase in RBC survival. A close direct linear relationship was detected between plasma levels of vitamin E and Hb.

Adequate control of oxidative stress achieves better control of anemia in HD patients. Since several antioxidant systems are impaired in uremia, the combined use of the CL-E membrane and GSH seems to be the best antioxidant therapy so far, with significant saving of the rhEPO dose [54].

Sarcopenia

The clinical feature of sarcopenia is the loss of muscle protein mass and function that occur during aging. Sarcopenia is associated with physical inactivity [55], endocrine changes [56], neuronal/denervation [57], anorexia or insufficient macronutrient intake, digestion and absorption [58, 59], proinflammatory processes [60], impaired kidney function [61] and reduced muscle blood flow [62]. The clinical consequences of bed rest and reduced nutrition may mimic those of cachexia, including rapid loss of muscle, insulin resistance and weakness. Prophylaxis against bed rest-induced atrophy includes nutrition support with an emphasis on high-quality protein. Nutritional supplementation alone may not prevent muscle loss secondary to cachexia, but in combination with the use of an anabolic agent, it may slow or prevent muscle loss [63].

Muscle wasting during aging and cancer shares many common metabolic pathways and mediators. Due to the size of the population involved, both cancer cachexia and aging sarcopenia may represent targets for future promising clinical investigations [64]. Resistance exercise training may counteract the muscle loss, improving muscle mass and function in elderly [55] and could increase total Hb and red mass cell, enhancing the oxygen-carrying capacity of the patient [65]. Exercise training might be a promising additional safe and economical method to improve anemia. There is a need for further investigation to determine the role for exercise intervention in anemia, particularly among cancer patients.

Nutrient Deficiency-Related Anemia

Approximately one-third of anemia cases in older adults are related to malnutrition and attributed to iron, folate, and/or vitamin B₁₂ deficiencies [17]. Iron deficiency alone accounts for nearly half of the nutrient deficiency-related anemia cases. The malnutrition risk in institutionalized elderly is usually very high. The meals do not supply the estimated average requirements. Energy, protein and micronutrient intake, such as calcium, magnesium, folate, zinc, dietary fibers and vitamin D are deficient [66-68].

The evaluation of nutritional status is an essential component of physiological health and to identify the protein energy wasting [69]. In 1975, Payne [70] explained the relative importance of protein and energy intake as causal factors in malnutrition. A clinical assessment of nutritional status is a complex topic and should be able to evaluate the protein energy wasting and the possible benefit of nutritional intervention [71]. Protein intake is necessary to maintain the plasma level of essential amino acids. Essential amino acids are necessary to stimulate skeletal muscle protein synthesis [72, 73]. Wolfe [74] showed that the increases in amino acid availability are strongly correlated with the change in muscle protein synthesis and in other tissues such as liver, kidney and brain. Amino acid transporters are ubiquitously expressed in the plasma membrane of many cell types, including human skeletal muscle [75]. The expression of amino acid transporters is a unique regulatory mechanism associated with the muscle protein anabolic response following an increase in essential amino acid availability [76].

Serum albumin is the most extensively studied serum protein for assessment of nutritional status in chronic patients particularly in CKDs and hemodialysis patients. Various studies have shown a strong correlation between low levels of serum albumin and the increased risk of morbidity and mortality [77-79]. Serum albumin could be considered not only a nutritional marker but also an overall health status marker [80]. A strong association between protein energy wasting and the risk of hospitalization and death has been observed [81, 82]. Recent epidemiological studies showed a concomitant improvement in survival in hemodialysis patients after nutritional intervention on mortality and a concomitant improvement in survival when the nutritional markers are improved [83, 84].

Decreased dietary nutrient intake in anorexia patients has been reported in 35-50% of chronic patients [85] and in patients with CKD that frequently experience loss of appetite (anorexia), which increases in severity [86]. Anorexia is mediated by various circulating appetite regulators, such as gastric mediators (cholecystokinin, peptide YY, ghrelin), adipokines and cytokines (such as interleukin: IL-6, IL-1 β , TNF- α) [87]. Anorexia is the metabolic response to inflammation [88], and IL-1 and TNF can cause anorexia through their effect of satiety acting on the central nervous system [89]. During the acute or chronic illness conditions, the accelerated degradation of protein is not adequately suppressed, and the increase in protein synthesis is insufficient [90], with a loss in cellular protein stores [91]. An excess of mortality due to the interaction between protein energy wasting, inflammation and cardiovascular disease in dialysis patients has been observed [92]. In elderly inpatients aged above 70 years with cardiovascular diseases, cognitive impairment and malnutrition are associated, and both are predictors of all-cause mortality [93].

Iron Deficiency

IDA is characterized by a low serum iron (< 50 $\mu\text{g/dL}$ in women and 60 $\mu\text{g/dL}$ in men), low Hb level (men < 13 g/dL; women < 12 g/dL), TfS less than 20% and ferritin concentration less than 30 ng/mL, low transferrin saturation rate (< 16%) but no

sign of inflammation [94]. While some cases of iron deficiency result from diet [95], blood loss through gastrointestinal lesions is the primary cause of iron deficiency in older adults [96-98].

Gastrointestinal endoscopy in 100 consecutive patients with IDA showed that 62% had a lesion that could potentiate blood loss and 16% had premalignant polyps or colon cancer [97]. Diagnosing iron deficiency in older adults is difficult because serum ferritin concentration, a key test of iron storage, is known to increase with age and age-associated diseases [99]. A study conducted on hospitalized patients of 80 years and older showed that the routine blood tests of serum iron, ferritin and transferrin saturation had poor screening sensitivity for capturing iron deficient patients [99-101]. Considering that the more sensitive transferrin receptor-ferritin index or ratio has only recently become more widely available, prevalence of IDA based on the routine blood tests among older adults might be underestimated in NHANES III [17], although a recent representative study of older adults used the transferrin receptor-ferritin index and showed that 16.7% of anemia cases were attributed to IDA (similar to the 16.6% estimate from NHANES III) [102]. Anemia associated with folate or vitamin B₁₂ deficiency was defined as concentrations of folate lower than 3.0 ng/mL or vitamin B₁₂ lower than 200 $\mu\text{g/mL}$ and MCV higher than 95 fL. Subjects were classified as having anemia related to chronic renal disease when affected by renal insufficiency.

Nutrition and GH/IGF1

Nutrition significantly affects the level of anabolic hormones, such as testosterone and GH/IGF-1 axis. There is also an evident age-related decline in plasma levels of IGF-I, IGF-II and IGFBP-3 occurring independently from the malnutrition and inflammation processes [103]. IGF-1 is the most important indicator of clinical nutrition [104] and a regulator of tissue protein synthesis, particularly in muscle, bone, brain and kidney. The measurement of IGF-I will become a routine part of nutritional assessment in a number of these contexts.

Sex Hormones and Anemia

Older men and women with low testosterone levels have a higher risk of anemia [105]. The total and bioavailable testosterone level in all InCHIANTI participants, restricted to cases of UAa (i.e., normal serum iron levels and no deficiencies of iron, cyanocobalamin or vitamin B₁₂) or folate, was still statistically significant for both men and women [106]. Androgens (including testosterone and its derivatives nandrolone, oxandrolone, etc.) stimulate the hematopoietic system by various mechanisms. Testosterone exerts its erythropoietic activity by stimulating EPO [107]. These include stimulation of EPO release, increasing bone marrow activity and iron incorporation into the red cells, and anabolism is an additional advantage of androgen therapy [108]. Testosterone administration leads to an increase in Hb by as much as 5-7% [109].

Androgen, compared with EPO, has similar effects on

erythropoiesis [110]. The comparison between androgen and EPO effects have been evaluated in patients who were under continuous ambulatory peritoneal dialysis therapy, and it was found that androgen administration improved the anemia in a similar manner as observed with rhEPO. Navarro et al evaluated the anabolic properties of androgens (nandrolone decanoate, 200 mg/week IM) on the nutritional status in this population as therapy for anemia [111]. Nandrolone improved the anemia in elderly male, continuous ambulatory, peritoneal dialysis patients in a similar manner to that observed with rHuEPO. A systematic review and meta-analysis revealed no difference between nandrolone and EPO for the treatment of anemia of CKD in men over 50 years [112]. The role of androgen therapy in various types of anemia should be readdressed. Polycythemia remains a known side effect of androgen therapy [113]. Finally, both androgen and estrogen have an important role in regulating RBC concentration. High estradiol plasma levels have been associated with high hematocrit [114] and estradiol has been found to be correlated positively and independently to Hb [115].

Prevalence in Nursing Homes

Anemia is even more common in institutional settings and recently, the incidence and complication due to anemia among elderly nursing home residents have been observed to be increasing. In the retrospective, cross-sectional study of the NANHS III in the United States, the incidence of anemia was 17% in men and 20% in women [116]. Artz et al [117] reported that 48% of residents had anemia. Among these patients, 30% had been hospitalized within the past 6 months, whereas 16% of non-anemic patients were hospitalized. Robinson et al [118] found that 60% of older nursing home residents had anemia and that 43% had CKD. Landi et al [36] reported an incidence of anemia in 63% of older residents in a single nursing home and the risk of death, adjusting for age and sex, in the next 2 years was 60% higher in anemic than in non-anemic residents. Half the anemic residents were found to be using anemia therapy (vitamin B₁₂, folic acid or iron). A reduced number of recurrent falls were observed for DARB or EPO users [119]. In conclusion, the incidence of anemia in nursing homes elderly has a relevant incidence and it should be considered for a primary prevention of clinical complications.

ACD

ACD is considered to be the third most frequent group of anemia worldwide, and it develops specifically in patients suffering from chronic inflammatory diseases, such as autoimmune disorders, cancer, chronic infections or in patients undergoing dialysis. The term "anemia of chronic disease" is traditionally used for what is called ACI. The diagnosis of ACD may be complicated in patients with an unknown diagnosis that includes a variety of clinical conditions, such as infections, chronic heart failure, autoimmune conditions, chronic renal failure, malignancies, and often includes any anemia in per-

sons with a high burden of chronic disease without a clearly defined etiology [17]. The ACD was defined as low circulating iron in the presence of increased iron stores (normal or increased ferritin > 100 ng/mL, transferrin saturation > 25% and < 50%) and decreased total iron binding capacity (< 250 µg/dL). ACD is typically normochromic and normocytic, but with the progression of the disease, it may become microcytic. The prevalent causes of anemia to be excluded include: nutritional deficiencies, hemoglobinopathies, hemolysis, hypogonadism, hypothyroidism, myelodysplastic syndrome, drug effects and recurrent flebotomy [120, 121]. The reticulocyte count is low. The presence of inflammation may be inferred by leukocytosis, thrombocytosis or inflammatory markers.

ACD is the interaction between iron, immunity and infection [120, 122]. The dysregulation of iron homeostasis in ACD is characterized by an increased uptake and retention of iron within cells of the reticuloendothelial system. This leads to a diversion of iron from the circulation into storage sites of the reticuloendothelial system, subsequent limitation of the availability of iron for erythroid progenitor cells, and iron-restricted erythropoiesis. In chronic inflammation, the acquisition of iron by macrophages most prominently takes place through erythrophagocytosis [123] and the transmembrane import of ferrous iron by the protein divalent metal transporter 1 (DMT1) [124]. The interleukin interferon- γ (IFN- γ), lipopolysaccharide, and TNF- α upregulate the expression of DMT1, with an increased uptake of iron into activated macrophages. Proinflammatory stimuli also induce the retention of iron in macrophages by downregulating the expression of ferroportin, thus blocking the release of iron from these cells [125].

Role of Cytokines in Anemia

Cytokines play an important role in the formation of chronic anemia. During an infection, autoimmune disease or cancer, the immune cells are activated and produce a great variety of cytokines, some of which exert specific effects on iron homeostasis. In these patients, the proliferation and differentiation of erythroid precursors cell are impaired [126]. This inhibitory effect is due to the effect of IFN- γ , TNF- α , and IL-1 that influence the growth of the erythroid unit and the colony-forming unit. IFN- γ is the most potent inhibitor of erythroid progenitor cells [127]; an inverse correlation with Hb concentration and reticulocyte counts has been observed [128]. Cytokines exert a direct toxic effect on progenitor cells by inducing the formation of free radicals by neighboring macrophage-like cells. IFN- γ and TNF- α , potent inhibitors of hematopoiesis, induce nitric oxide synthase in various cell types, and nitric oxide may be one mediator of cytokine-induced hematopoietic suppression [129]. Furthermore, cytokines (IL-1, IL-6, IL-22, TNF- α or endoplasmic reticulum stress) induce the formation of hepcidin in the liver, the most important regulator of iron homeostasis that decreases the EPO synthesis and impairs its biological activity [130]. In fact, anemia in chronic disease patients' EPO levels has found to be inadequate [131, 132]. Low EPO production is due to the direct inhibition of the EPO promoter gene through cytokine-induced toxic radicals [133].

The reduced biological activity of EPO determines that a much higher amount of EPO is needed to restore the formation of the colony-forming unit in the bone marrow.

Hepcidin

Hepcidin is a peptide hormone secreted by hepatocytes that regulates iron homeostasis, and its fundamental role came from the discovery in 2004 that hepcidin acts by binding to and downregulating the iron transporter ferroportin (FPN1) [134]. FPN1 is the only known transporter for the efflux of iron from cells. Downregulation of FPN1 by hepcidin in splenic or hepatic macrophages decreases the ability of macrophages to export the recycled iron from senescent RBCs that constitute the primary source of iron in the plasma [135]. Decreased hepcidin levels determine a tissue iron overload, whereas hepcidin overproduction leads to hypoferrinemia and anemia of inflammation. Hepcidin affects cellular iron homeostasis upon binding to FPN1, inducing its internalization and degradation, resulting in cellular iron retention and decreased iron export [136]. The regulation of FPN1 by hepcidin may thus complete a homeostatic loop: iron regulates the secretion of hepcidin, which in turn controls the concentration of FPN1 on the cell surface.

In ACD, usually associated with a chronic-immune activation that include CKD, diabetes, severe trauma, rheumatoid arthritis, chronic infections, inflammatory bowel diseases and cancer [137, 138], the patients have low plasma iron and transferrin saturation, despite normal or elevated body iron store [139]. The mechanism underlying this disrupted iron balance involves hepcidin. Both acute and chronic inflammation induces hepcidin expression. IL-6 and lipopolysaccharide induce hepcidin expression in human hepatocytes [140] and are inhibited by TNF- α [141]. Erythropoietic activity suppresses hepcidin expression. Most of the iron for erythropoiesis comes from the catabolism of senescent RBCs by macrophages in the reticuloendothelial system. Hepcidin expression is downregulated by erythropoietic stimuli, such as anemia, hypoxia and synthetic EPO administration [142, 143].

Stimulation of erythropoiesis by EPO, phlebotomy or phenylhydrazine suppresses hepcidin expression [144] while tissue hypoxia directly inhibits hepcidin expression in hepatocytes independently of iron stores in the body [143]. Hypoxia may play a role in iron regulation in patients with anemia accompanied by ineffective erythropoiesis.

Conclusion

Anemia could be considered a syndrome caused by many physiological and pathological factors, and the incidence of anemia on mortality should provide stimulus for future trials on anemia correction in elderly [1]. The correct treatment of anemia starts from an adequate diagnosis and recognizing the underlying conditions. One-third of anemia in the community-dwelling older population is related to nutrient deficiencies, including iron and cobalamin deficiency and readily managed

with safe and inexpensive therapy. It is necessary to understand better the mechanisms and the possible treatment of UA that represents one-third of older anemic patients. Sarcopenia, low testosterone and estrogen levels, and high free radicals levels are also important factors regulating the erythropoiesis processes.

Androgen therapy should be considered an important therapeutic strategy in anemia for the direct stimulation effect on erythropoiesis and on protein synthesis in different tissues. The beneficial effect of androgens on erythropoiesis has been known from a long time [145], as the positive anabolic action in patients in critical conditions. RBC transfusions should be limited only to severe anemic conditions, because transfusion itself has been associated with multiorgan failure and increased mortality in patients who are in critical care [146]. RBC transfusions initiate a systematic inflammatory response, induce nonspecific immunosuppression and probably occlude local microvascular vessels, causing local tissue hypoxemia [147]. Future studies on the kinetic causes of anemia are necessary to improve the EPO sensing and response mechanisms during aging and improve treatment and clinical outcomes.

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