

Anemia in the Elderly Population

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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, underevaluated 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; Hepdinin; Interleukines; Testosterone; Chronic disease

Introduction

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

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 ≥ 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

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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 O_2^- , 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 interleukine: 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 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 μ g/dL in women and 60 μ 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 μ 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.

References

1. 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(10):3841-3846.
2. Denny SD, Kuchibhatla MN, Cohen HJ. Impact of anemia on mortality, cognition, and function in community-dwelling elderly. *Am J Med*. 2006;119(4):327-334.
3. 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(19):2214-2220.
4. 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(11):1811-1816.
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(5):474-479.
6. Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A, Remme W, et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. *Eur Heart J*. 2006;27(12):1440-1446.
7. Izaks GJ, Westendorp RG, Knook DL. The definition of anemia in older persons. *JAMA*. 1999;281(18):1714-1717.
8. Endres HG, Wedding U, Pittrow D, Thiem U, Trampisch HJ, Diehm C. Prevalence of anemia in elderly patients in primary care: impact on 5-year mortality risk and differences between men and women. *Curr Med Res Opin*. 2009;25(5):1143-1158.

9. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med*. 2001;345(17):1230-1236.
10. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, van der Meer P. Anemia and mortality in heart failure patients: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2008;52(10):818-827.
11. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation*. 2003;107(2):223-225.
12. Poludasu S, Marmur JD, Weedon J, Khan W, Cavusoglu E. Effect of hemoglobin level on long-term all-cause mortality after percutaneous coronary intervention in African-Americans. *Am J Cardiol*. 2009;103(8):1078-1082.
13. 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(2):104-110.
14. Penninx BW, Pahor M, Cesari M, Corsi AM, Woodman RC, Bandinelli S, Guralnik JM, et al. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. *J Am Geriatr Soc*. 2004;52(5):719-724.
15. Cesari M, Penninx BW, Lauretani F, Russo CR, Carter C, Bandinelli S, Atkinson H, et al. Hemoglobin levels and skeletal muscle: results from the InCHIANTI study. *J Gerontol A Biol Sci Med Sci*. 2004;59(3):249-254.
16. Bach V, Schruckmayer G, Sam I, Kemmler G, Stauder R. Prevalence and possible causes of anemia in the elderly: a cross-sectional analysis of a large European university hospital cohort. *Clin Interv Aging*. 2014;9:1187-1196.
17. 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(8):2263-2268.
18. Shavelle RM, MacKenzie R, Paculdo DR. Anemia and mortality in older persons: does the type of anemia affect survival? *Int J Hematol*. 2012;95(3):248-256.
19. Tettamanti M, Lucca U, Gandini F, Recchia A, Mosconi P, Apolone G, Nobili A, et al. Prevalence, incidence and types of mild anemia in the elderly: the "Health and Anemia" population-based study. *Haematologica*. 2010;95(11):1849-1856.
20. Price EA, Mehra R, Holmes TH, Schrier SL. Anemia in older persons: etiology and evaluation. *Blood Cells Mol Dis*. 2011;46(2):159-165.
21. Artz AS, Thirman MJ. Unexplained anemia predominates despite an intensive evaluation in a racially diverse cohort of older adults from a referral anemia clinic. *J Gerontol A Biol Sci Med Sci*. 2011;66(8):925-932.
22. Ferrucci L, Semba RD, Guralnik JM, Ershler WB, Bandinelli S, Patel KV, Sun K, et al. Proinflammatory state, hepcidin, and anemia in older persons. *Blood*. 2010;115(18):3810-3816.
23. den Elzen WP, de Craen AJ, Wiegerinck ET, Westendorp RG, Swinkels DW, Gussekloo J. Plasma hepcidin levels and anemia in old age. The Leiden 85-Plus Study. *Haematologica*. 2013;98(3):448-454.
24. WHO. Nutritional Anemia: Report of a WHO Scientific Group. Tech Rep Ser. 1968;405:1-40.
25. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood*. 2006;107(5):1747-1750.
26. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst*. 1999;91(19):1616-1634.
27. Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. *Am J Med*. 2004;116(Suppl 7A):44S-49S.
28. Sears DA. Anemia of chronic disease. *Med Clin North Am*. 1992;76(3):567-579.
29. Salive ME, Cornoni-Huntley J, Guralnik JM, Phillips CL, Wallace RB, Ostfeld AM, Cohen HJ. Anemia and hemoglobin levels in older persons: relationship with age, gender, and health status. *J Am Geriatr Soc*. 1992;40(5):489-496.
30. Robins EB, Blum S. Hematologic reference values for African American children and adolescents. *Am J Hematol*. 2007;82(7):611-614.
31. Woodman R, Ferrucci L, Guralnik J. Anemia in older adults. *Curr Opin Hematol*. 2005;12(2):123-128.
32. Kikuchi M, Inagaki T, Shinagawa N. Five-year survival of older people with anemia: variation with hemoglobin concentration. *J Am Geriatr Soc*. 2001;49(9):1226-1228.
33. Guralnik JM, Ershler WB, Schrier SL, Picozzi VJ. Anemia in the elderly: a public health crisis in hematology. *Hematology Am Soc Hematol Educ Program*. 2005:528-532.
34. Patel KV, Harris TB, Faulhaber M, Angleman SB, Connelly S, Bauer DC, Kuller LH, et al. Racial variation in the relationship of anemia with mortality and mobility disability among older adults. *Blood*. 2007;109(11):4663-4670.
35. Riva E, Tettamanti M, Mosconi P, Apolone G, Gandini F, Nobili A, Tallone MV, et al. Association of mild anemia with hospitalization and mortality in the elderly: the Health and Anemia population-based study. *Haematologica*. 2009;94(1):22-28.
36. Landi F, Russo A, Danese P, Liperoti R, Barillaro C, Bernabei R, Onder G. Anemia status, hemoglobin concentration, and mortality in nursing home older residents. *J Am Med Dir Assoc*. 2007;8(5):322-327.
37. Liu K, Kaffes AJ. Iron deficiency anaemia: a review of diagnosis, investigation and management. *Eur J Gastroenterol Hepatol*. 2012;24(2):109-116.
38. Ershler WB, Sheng S, McKelvey J, Artz AS, Denduluri N, Tecson J, Taub DD, et al. Serum erythropoietin and aging: a longitudinal analysis. *J Am Geriatr Soc*. 2005;53(8):1360-1365.
39. Canestrari F, Buoncristiani U, Galli F, Giorgini A, Albertini MC, Carobi C, Pascucci M, et al. Redox state, antiox-

- idative activity and lipid peroxidation in erythrocytes and plasma of chronic ambulatory peritoneal dialysis patients. *Clin Chim Acta*. 1995;234(1-2):127-136.
40. Beasley JM, Shikany JM, Thomson CA. The role of dietary protein intake in the prevention of sarcopenia of aging. *Nutr Clin Pract*. 2013;28(6):684-690.
 41. Lipschitz DA, Mitchell CO, Thompson C. The anemia of senescence. *Am J Hematol*. 1981;11(1):47-54.
 42. Gale RE, Fielding AK, Harrison CN, Linch DC. Acquired skewing of X-chromosome inactivation patterns in myeloid cells of the elderly suggests stochastic clonal loss with age. *Br J Haematol*. 1997;98(3):512-519.
 43. Marley SB, Lewis JL, Davidson RJ, Roberts IA, Dokal I, Goldman JM, Gordon MY. Evidence for a continuous decline in haemopoietic cell function from birth: application to evaluating bone marrow failure in children. *Br J Haematol*. 1999;106(1):162-166.
 44. Winterbourn CC. Oxidative denaturation in congenital hemolytic anemias: the unstable hemoglobins. *Semin Hematol*. 1990;27(1):41-50.
 45. Johnson RM, Goyette G, Jr., Ravindranath Y, Ho YS. Hemoglobin autooxidation and regulation of endogenous H₂O₂ levels in erythrocytes. *Free Radic Biol Med*. 2005;39(11):1407-1417.
 46. Friedman JS, Rebel VI, Derby R, Bell K, Huang TT, Kuypers FA, Epstein CJ, et al. Absence of mitochondrial superoxide dismutase results in a murine hemolytic anemia responsive to therapy with a catalytic antioxidant. *J Exp Med*. 2001;193(8):925-934.
 47. Costagliola C, Romano L, Sorice P, Di Benedetto A. Anemia and chronic renal failure: the possible role of the oxidative state of glutathione. *Nephron*. 1989;52(1):11-14.
 48. Taccone-Gallucci M, Giardini O, Lubrano R, Bandino D, Mazzarella V, Mannarino O, Meloni C, et al. Red blood cell lipid peroxidation in predialysis chronic renal failure. *Clin Nephrol*. 1987;27(5):238-241.
 49. Sommerburg O, Grune T, Hampl H, Riedel E, van Kuijk FJ, Ehrlich JH, Siems WG. Does long-term treatment of renal anaemia with recombinant erythropoietin influence oxidative stress in haemodialysed patients? *Nephrol Dial Transplant*. 1998;13(10):2583-2587.
 50. Usberti M, Lima G, Arisi M, Bufano G, D'Avanzo L, Gazzotti RM. Effect of exogenous reduced glutathione on the survival of red blood cells in hemodialyzed patients. *J Nephrol*. 1997;10(5):261-265.
 51. Gallucci MT, Lubrano R, Meloni C, Morosetti M, Manca di Villahermosa S, Scoppi P, Palombo G, et al. Red blood cell membrane lipid peroxidation and resistance to erythropoietin therapy in hemodialysis patients. *Clin Nephrol*. 1999;52(4):239-245.
 52. Ludat K, Sommerburg O, Grune T, Siems WG, Riedel E, Hampl H. Oxidation parameters in complete correction of renal anemia. *Clin Nephrol*. 2000;53(1 Suppl):S30-35.
 53. Cruz DN, de Cal M, Ronco C. Oxidative stress and anemia in chronic hemodialysis: the promise of bioreactive membranes. *Contrib Nephrol*. 2008;161(89-98).
 54. Usberti M, Gerardi G, Micheli A, Tira P, Bufano G, Gaggia P, Movilli E, et al. Effects of a vitamin E-bonded membrane and of glutathione on anemia and erythropoietin requirements in hemodialysis patients. *J Nephrol*. 2002;15(5):558-564.
 55. Yarasheski KE, Zachwieja JJ, Bier DM. Acute effects of resistance exercise on muscle protein synthesis rate in young and elderly men and women. *Am J Physiol*. 1993;265(2 Pt 1):E210-214.
 56. Giannoulis MG, Jackson N, Shojaaee-Moradie F, Nair KS, Sonksen PH, Martin FC, Umpleby AM. The effects of growth hormone and/or testosterone on whole body protein kinetics and skeletal muscle gene expression in healthy elderly men: a randomized controlled trial. *J Clin Endocrinol Metab*. 2008;93(8):3066-3074.
 57. Welle S. Cellular and molecular basis of age-related sarcopenia. *Can J Appl Physiol*. 2002;27(1):19-41.
 58. Fujita S, Volpi E. Amino acids and muscle loss with aging. *J Nutr*. 2006;136(1 Suppl):277S-280S.
 59. Fujita S, Dreyer HC, Drummond MJ, Glynn EL, Cadenas JG, Yoshizawa F, Volpi E, et al. Nutrient signalling in the regulation of human muscle protein synthesis. *J Physiol*. 2007;582(Pt 2):813-823.
 60. Chung HY, Cesari M, Anton S, Marzetti E, Giovannini S, Seo AY, Carter C, et al. Molecular inflammation: underpinnings of aging and age-related diseases. *Ageing Res Rev*. 2009;8(1):18-30.
 61. Castaneda C, Gordon PL, Parker RC, Uhlin KL, Roubenoff R, Levey AS. Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. *Am J Kidney Dis*. 2004;43(4):607-616.
 62. Fujita S, Rasmussen BB, Cadenas JG, Grady JJ, Volpi E. Effect of insulin on human skeletal muscle protein synthesis is modulated by insulin-induced changes in muscle blood flow and amino acid availability. *Am J Physiol Endocrinol Metab*. 2006;291(4):E745-754.
 63. Evans WJ. Skeletal muscle loss: cachexia, sarcopenia, and inactivity. *Am J Clin Nutr*. 2010;91(4):1123S-1127S.
 64. Argiles JM, Busquets S, Felipe A, Lopez-Soriano FJ. Muscle wasting in cancer and ageing: cachexia versus sarcopenia. *Adv Gerontol*. 2006;18:39-54.
 65. Hu M, Lin W. Effects of exercise training on red blood cell production: implications for anemia. *Acta Haematol*. 2012;127(3):156-164.
 66. Woods JL, Walker KZ, Iuliano Burns S, Strauss BJ. Malnutrition on the menu: nutritional status of institutionalised elderly Australians in low-level care. *J Nutr Health Aging*. 2009;13(8):693-698.
 67. Roberts SB, Hajduk CL, Howarth NC, Russell R, McCrory MA. Dietary variety predicts low body mass index and inadequate macronutrient and micronutrient intakes in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci*. 2005;60(5):613-621.
 68. Vikstedt T, Suominen MH, Joki A, Muurinen S, Soini H, Pitkala KH. Nutritional status, energy, protein, and micronutrient intake of older service house residents. *J Am Med Dir Assoc*. 2011;12(4):302-307.
 69. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, et al. A proposed nomenclature and diagnostic criteria for protein-energy wast-

- ing in acute and chronic kidney disease. *Kidney Int.* 2008;73(4):391-398.
70. Payne PR. Safe protein-calorie ratios in diets. The relative importance of protein and energy intake as causal factors in malnutrition. *Am J Clin Nutr.* 1975;28(3):281-286.
 71. Jeejeebhoy KN. Nutritional assessment. *Nutrition.* 2000;16(7-8):585-590.
 72. Anthony JC, Yoshizawa F, Anthony TG, Vary TC, Jefferson LS, Kimball SR. Leucine stimulates translation initiation in skeletal muscle of postabsorptive rats via a rapamycin-sensitive pathway. *J Nutr.* 2000;130(10):2413-2419.
 73. Liu Z, Jahn LA, Wei L, Long W, Barrett EJ. Amino acids stimulate translation initiation and protein synthesis through an Akt-independent pathway in human skeletal muscle. *J Clin Endocrinol Metab.* 2002;87(12):5553-5558.
 74. Wolfe RR. Regulation of muscle protein by amino acids. *J Nutr.* 2002;132(10):3219S-3224S.
 75. Nishimura M, Naito S. Tissue-specific mRNA expression profiles of human solute carrier transporter superfamilies. *Drug Metab Pharmacokinet.* 2008;23(1):22-44.
 76. Drummond MJ, Glynn EL, Fry CS, Timmerman KL, Volpi E, Rasmussen BB. An increase in essential amino acid availability upregulates amino acid transporter expression in human skeletal muscle. *Am J Physiol Endocrinol Metab.* 2010;298(5):E1011-1018.
 77. Anderson CF, Wochos DN. The utility of serum albumin values in the nutritional assessment of hospitalized patients. *Mayo Clin Proc.* 1982;57(3):181-184.
 78. Apeltgren KN, Rombeau JL, Twomey PL, Miller RA. Comparison of nutritional indices and outcome in critically ill patients. *Crit Care Med.* 1982;10(5):305-307.
 79. Reinhardt GF, Myscowski JW, Wilkens DB, Dobrin PB, Mangan JE, Jr., Stannard RT. Incidence and mortality of hypoalbuminemic patients in hospitalized veterans. *J Parenter Enteral Nutr.* 1980;4(4):357-359.
 80. Ikizler TA. The use and misuse of serum albumin as a nutritional marker in kidney disease. *Clin J Am Soc Nephrol.* 2012;7(9):1375-1377.
 81. Kalantar-Zadeh K, Cano NJ, Budde K, Chazot C, Kovesdy CP, Mak RH, Mehrotra R, et al. Diets and enteral supplements for improving outcomes in chronic kidney disease. *Nat Rev Nephrol.* 2011;7(7):369-384.
 82. Mehrotra R, Duong U, Jiwakanon S, Kovesdy CP, Moran J, Kopple JD, Kalantar-Zadeh K. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. *Am J Kidney Dis.* 2011;58(3):418-428.
 83. Cheu C, Pearson J, Dahlerus C, Lantz B, Chowdhury T, Sauer PF, Farrell RE, et al. Association between oral nutritional supplementation and clinical outcomes among patients with ESRD. *Clin J Am Soc Nephrol.* 2013;8(1):100-107.
 84. Lacson E, Jr., Wang W, Zebrowski B, Wingard R, Hakim RM. Outcomes associated with intradialytic oral nutritional supplements in patients undergoing maintenance hemodialysis: a quality improvement report. *Am J Kidney Dis.* 2012;60(4):591-600.
 85. Bossola M, Tazza L, Giungi S, Luciani G. Anorexia in hemodialysis patients: an update. *Kidney Int.* 2006;70(3):417-422.
 86. Carrero JJ. Identification of patients with eating disorders: clinical and biochemical signs of appetite loss in dialysis patients. *J Ren Nutr.* 2009;19(1):10-15.
 87. Chung SH, Carrero JJ, Lindholm B. Causes of poor appetite in patients on peritoneal dialysis. *J Ren Nutr.* 2011;21(1):12-15.
 88. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. *Am J Clin Nutr.* 2004;80(2):299-307.
 89. DeBoer MD, Scarlett JM, Levasseur PR, Grant WF, Marks DL. Administration of IL-1beta to the 4th ventricle causes anorexia that is blocked by agouti-related peptide and that coincides with activation of tyrosine-hydroxylase neurons in the nucleus of the solitary tract. *Peptides.* 2009;30(2):210-218.
 90. Raj DS, Adeniyi O, Dominic EA, Boivin MA, McClelland S, Tzamaloukas AH, Morgan N, et al. Amino acid repletion does not decrease muscle protein catabolism during hemodialysis. *Am J Physiol Endocrinol Metab.* 2007;292(6):E1534-1542.
 91. Ikizler TA, Greene JH, Yenicesu M, Schulman G, Wingard RL, Hakim RM. Nitrogen balance in hospitalized chronic hemodialysis patients. *Kidney Int Suppl.* 1996;57:S53-56.
 92. de Mutsert R, Grootendorst DC, Axelsson J, Boeschoten EW, Krediet RT, Dekker FW. Excess mortality due to interaction between protein-energy wasting, inflammation and cardiovascular disease in chronic dialysis patients. *Nephrol Dial Transplant.* 2008;23(9):2957-2964.
 93. Farid K, Zhang Y, Bachelier D, Gilson P, Teixeira A, Safar ME, Blacher J. Cognitive impairment and malnutrition, predictors of all-cause mortality in hospitalized elderly subjects with cardiovascular disease. *Arch Cardiovasc Dis.* 2013;106(4):188-195.
 94. Cook JD. Diagnosis and management of iron-deficiency anaemia. *Best Pract Res Clin Haematol.* 2005;18(2):319-332.
 95. Drewnowski A, Shultz JM. Impact of aging on eating behaviors, food choices, nutrition, and health status. *J Nutr Health Aging.* 2001;5(2):75-79.
 96. Coban E, Timuragaoglu A, Meric M. Iron deficiency anemia in the elderly: prevalence and endoscopic evaluation of the gastrointestinal tract in outpatients. *Acta Haematol.* 2003;110(1):25-28.
 97. Rockey DC, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. *N Engl J Med.* 1993;329(23):1691-1695.
 98. Joosten E, Ghesquiere B, Linthoudt H, Krekelberghs F, Dejaeger E, Boonen S, Flamaing J, et al. Upper and lower gastrointestinal evaluation of elderly inpatients who are iron deficient. *Am J Med.* 1999;107(1):24-29.
 99. Casale G, Bonora C, Migliavacca A, Zurita IE, de Nicola P. Serum ferritin and ageing. *Age Ageing.* 1981;10(2):119-122.

100. Witte DL. Can serum ferritin be effectively interpreted in the presence of the acute-phase response? *Clin Chem.* 1991;37(4):484-485.
101. Rimon E, Levy S, Sapir A, Gelzer G, Peled R, Ergas D, Sthoeger ZM. Diagnosis of iron deficiency anemia in the elderly by transferrin receptor-ferritin index. *Arch Intern Med.* 2002;162(4):445-449.
102. Ferrucci L, Guralnik JM, Bandinelli S, Semba RD, Lauretani F, Corsi A, Ruggiero C, et al. Unexplained anaemia in older persons is characterised by low erythropoietin and low levels of pro-inflammatory markers. *Br J Haematol.* 2007;136(6):849-855.
103. Raynaud-Simon A. Levels of plasma insulin-like growth factor I (IGF I), IGF II, IGF binding proteins, type 1 IGF receptor and growth hormone binding protein in community-dwelling elderly subjects with no malnutrition and no inflammation. *J Nutr Health Aging.* 2003;7(4):267-273.
104. Livingstone C. Insulin-like growth factor-I (IGF-I) and clinical nutrition. *Clin Sci (Lond).* 2013;125(6):265-280.
105. Ferrucci L, Maggio M, Bandinelli S, Basaria S, Lauretani F, Ble A, Valenti G, et al. Low testosterone levels and the risk of anemia in older men and women. *Arch Intern Med.* 2006;166(13):1380-1388.
106. Ferrucci L, Bandinelli S, Benvenuti E, Di Iorio A, Macchi C, Harris TB, Guralnik JM. Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J Am Geriatr Soc.* 2000;48(12):1618-1625.
107. Naets JP, Wittek M. The mechanism of action of androgens on erythropoiesis. *Ann N Y Acad Sci.* 1968;149(1):366-376.
108. Shahani S, Braga-Basaria M, Maggio M, Basaria S. Androgens and erythropoiesis: past and present. *J Endocrinol Invest.* 2009;32(8):704-716.
109. Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. *J Am Geriatr Soc.* 2003;51(1):101-115; discussion 115.
110. Teruel JL, Marcen R, Navarro-Antolin J, Aguilera A, Fernandez-Juarez G, Ortuno J. Androgen versus erythropoietin for the treatment of anemia in hemodialyzed patients: a prospective study. *J Am Soc Nephrol.* 1996;7(1):140-144.
111. Navarro JF, Mora C, Macia M, Garcia J. Randomized prospective comparison between erythropoietin and androgens in CAPD patients. *Kidney Int.* 2002;61(4):1537-1544.
112. Adamu B, Ma'aji SM, Erwin PJ, Tleyjeh IM. Meta-Analysis of Randomized Controlled Trials on Androgens versus Erythropoietin for Anaemia of Chronic Kidney Disease: Implications for Developing Countries. *Int J Nephrol.* 2012;2012:580437.
113. Drinka PJ, Jochen AL, Cuisinier M, Bloom R, Rudman I, Rudman D. Polycythemia as a complication of testosterone replacement therapy in nursing home men with low testosterone levels. *J Am Geriatr Soc.* 1995;43(8):899-901.
114. Paller CJ, Shiels MS, Rohrmann S, Menke A, Rifai N, Nelson WG, Platz EA, et al. Association between sex steroid hormones and hematocrit in a nationally representative sample of men. *J Androl.* 2012;33(6):1332-1341.
115. Lewerin C, Nilsson-Ehle H, Jacobsson S, Johansson H, Sundh V, Karlsson MK, Lorentzon M, et al. Serum estradiol associates with blood hemoglobin in elderly men: the MrOS Sweden study. *J Clin Endocrinol Metab.* 2014;99(7):2549-2556.
116. Moore KL, Boscardin WJ, Steinman MA, Schwartz JB. Age and sex variation in prevalence of chronic medical conditions in older residents of U.S. nursing homes. *J Am Geriatr Soc.* 2012;60(4):756-764.
117. Artz AS, Fergusson D, Drinka PJ, Gerald M, Gravenstein S, Lechich A, Silverstone F, et al. Prevalence of anemia in skilled-nursing home residents. *Arch Gerontol Geriatr.* 2004;39(3):201-206.
118. Robinson B, Artz AS, Culleton B, Critchlow C, Sciarra A, Audhya P. Prevalence of anemia in the nursing home: contribution of chronic kidney disease. *J Am Geriatr Soc.* 2007;55(10):1566-1570.
119. Reardon G, Pandya N, Bailey RA. Falls in nursing home residents receiving pharmacotherapy for anemia. *Clin Interv Aging.* 2012;7:397-407.
120. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med.* 2005;352(10):1011-1023.
121. Bloxham E, Vagadia V, Scott K, Francis G, Saravanan V, Heycock C, Rynne M, et al. Anaemia in rheumatoid arthritis: can we afford to ignore it? *Postgrad Med J.* 2011;87(1031):596-600.
122. Spivak JL. Iron and the anemia of chronic disease. *Oncology (Williston Park).* 2002;16(9 Suppl 10):25-33.
123. Moura E, Noordermeer MA, Verhoeven N, Verheul AF, Marx JJ. Iron release from human monocytes after erythrophagocytosis in vitro: an investigation in normal subjects and hereditary hemochromatosis patients. *Blood.* 1998;92(7):2511-2519.
124. Andrews NC. The iron transporter DMT1. *Int J Biochem Cell Biol.* 1999;31(10):991-994.
125. Ludwiczek S, Aigner E, Theurl I, Weiss G. Cytokine-mediated regulation of iron transport in human monocytic cells. *Blood.* 2003;101(10):4148-4154.
126. Means RT, Jr. Recent developments in the anemia of chronic disease. *Curr Hematol Rep.* 2003;2(2):116-121.
127. Wang CQ, Udupa KB, Lipschitz DA. Interferon-gamma exerts its negative regulatory effect primarily on the earliest stages of murine erythroid progenitor cell development. *J Cell Physiol.* 1995;162(1):134-138.
128. Denz H, Huber P, Landmann R, Orth B, Wachter H, Fuchs D. Association between the activation of macrophages, changes of iron metabolism and the degree of anaemia in patients with malignant disorders. *Eur J Haematol.* 1992;48(5):244-248.
129. Maciejewski JP, Selleri C, Sato T, Cho HJ, Keefer LK, Nathan CF, Young NS. Nitric oxide suppression of human hematopoiesis in vitro. Contribution to inhibitory action of interferon-gamma and tumor necrosis factor-alpha. *J Clin Invest.* 1995;96(2):1085-1092.

130. Dallaglio G, Law E, Means RT, Jr. Hepcidin inhibits in vitro erythroid colony formation at reduced erythropoietin concentrations. *Blood*. 2006;107(7):2702-2704.
131. Sandborn W. Erythropoietin for inflammatory bowel disease anemia. *Gastroenterology*. 1997;112(2):660-661.
132. Cazzola M, Ponchio L, de Benedetti F, Ravelli A, Rosti V, Beguin Y, Invernizzi R, et al. Defective iron supply for erythropoiesis and adequate endogenous erythropoietin production in the anemia associated with systemic-onset juvenile chronic arthritis. *Blood*. 1996;87(11):4824-4830.
133. Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. *J Interferon Cytokine Res*. 1998;18(8):555-559.
134. Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, Ganz T, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science*. 2004;306(5704):2090-2093.
135. Zhao N, Zhang AS, Enns CA. Iron regulation by hepcidin. *J Clin Invest*. 2013;123(6):2337-2343.
136. Ramey G, Deschemin JC, Durel B, Canonne-Hergaux F, Nicolas G, Vaulont S. Hepcidin targets ferroportin for degradation in hepatocytes. *Haematologica*. 2010;95(3):501-504.
137. Rivera S, Liu L, Nemeth E, Gabayan V, Sorensen OE, Ganz T. Hepcidin excess induces the sequestration of iron and exacerbates tumor-associated anemia. *Blood*. 2005;105(4):1797-1802.
138. Semrin G, Fishman DS, Bousvaros A, Zholudev A, Saunders AC, Correia CE, Nemeth E, et al. Impaired intestinal iron absorption in Crohn's disease correlates with disease activity and markers of inflammation. *Inflamm Bowel Dis*. 2006;12(12):1101-1106.
139. Ganz T, Nemeth E. Iron imports. IV. Hepcidin and regulation of body iron metabolism. *Am J Physiol Gastrointest Liver Physiol*. 2006;290(2):G199-203.
140. Nemeth E, Valore EV, Territo M, Schiller G, Lichtenstein A, Ganz T. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. *Blood*. 2003;101(7):2461-2463.
141. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, Ganz T. IL-6 mediates hypoferrremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Invest*. 2004;113(9):1271-1276.
142. Vokurka M, Krijt J, Sulc K, Necas E. Hepcidin mRNA levels in mouse liver respond to inhibition of erythropoiesis. *Physiol Res*. 2006;55(6):667-674.
143. Nicolas G, Chauvet C, Viatte L, Danan JL, Bigard X, Devaux I, Beaumont C, et al. The gene encoding the iron regulatory peptide hepcidin is regulated by anemia, hypoxia, and inflammation. *J Clin Invest*. 2002;110(7):1037-1044.
144. Pak M, Lopez MA, Gabayan V, Ganz T, Rivera S. Suppression of hepcidin during anemia requires erythropoietic activity. *Blood*. 2006;108(12):3730-3735.
145. Gardner FH, Gorshein D. Regulation of erythropoiesis by androgens. *Trans Am Clin Climatol Assoc*. 1973;84:60-70.
146. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, et al. Anemia and blood transfusion in critically ill patients. *JAMA*. 2002;288(12):1499-1507.
147. Blumberg N. Deleterious clinical effects of transfusion immunomodulation: proven beyond a reasonable doubt. *Transfusion*. 2005;45(2 Suppl):33S-39S; discussion 39S-40S.