La anemia ferropénica en pacientes ancianos en la era de la hepcidina

New insights into iron deficiency anemia in the elderly after hepcidin discovery.

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Abstract

Anemia is highly prevalent in the elderly, particularly in patients with multimorbidity, where entails relevant consequences in terms of either survival or quality of life. Iron deficiency anemia (IDA) alone represents at least 25% of cases, and iron deficiency (ID) often contributes to the remaining cases. ID in the elderly is generally multifactorial, being associated with several concurring causes. These typically include malnutrition, malabsorption, chronic occult bleeding, or iatrogenic conditions like frequent use of non-steroidal anti-inflammatory drugs (NSAIDs). The diagnosis of ID in the elderly with multimorbidity is challenging, particularly when it has to be dissected from other coexisting causes of anemia, like anemia of chronic inflammation (ACD). ID treatment with different iron formulas is also problematic in the elderly, because of general slowness in responding to oral iron, while some patients remain refractory and require cumbersome intravenous administration. Since 2001, the discovery of hepcidin as the key-regulatory hormone of iron metabolism has revolutionized our approach to the disorders of iron metabolism. Here, ID in the elderly is revisited in light of the massive new knowledge on iron regulation. The possible role of hepcidin as an aid for diagnosis and treatment of such common clinical condition will be also discussed.

General considerations on anemia in the elderly.
Anemia represents an important health problem in the elderly. Its prevalence has been estimated up to 25%, depending on the different decades and setting considered, e.g. general versus community-dwelling populations[1]. According to the third US National Health and Nutrition Examination Survey (NHANES III), 10.2% of females and 11% of males over 65 years of age from the general population are anemic[2]. When analyses were restricted to subjects with more than 85 years, anemia was present in 26.1% and 20.1% of males and females, respectively[2].

Most studies used a definition of anemia based on the classic World Health Organization (WHO) criteria, which consider hemoglobin levels less than 13 g/dL in males and less than 12 g/dL in females, respectively[3]. However, such criteria are no more generally accepted, particularly in the elderly, since they were originally extrapolated from population studies not including subjects with more than 65 years[4-5]. On the other hand, it has recently become clear that healthy elderly subjects tend to have lower hemoglobin levels than younger adults, with gradual disappearing of gender differences in the extreme decades[1]. As a consequence, new criteria for definition of anemia in the elderly have been proposed, considering hemoglobin levels less than 12 g/dL as a common threshold in both sexes[6-7].

Although anemia in the elderly is generally relatively mild[2], it deserves particular attention, since in the recent years a number of investigations have clearly demonstrated that it is independently associated with severe adverse outcomes, including even an increased risk of death[8-14]. Of note, the overall quality of life is clearly compromised in the anemic and "frail" elderly, since symptoms like fatigue, decreased muscle strength (with ensuing risk of falls), and cognitive dysfunction have been associated also with marginally decreased hemoglobin levels[15-16].

Regarding etiology, nearly one-third of anemias in elderly are ascribed to a chronic disease (e.g. inflammatory or renal diseases), and another third is related to nutrient deficiencies (e.g. folate, vitamin B12, and iron). Within this group, iron deficiency (ID) is the most important nutritional deficiency, accounting for more than one-half of cases, either alone or in combination with other nutrient deficiencies. The remaining third of all cases of anemia in the elderly still does not have clear etiology, so it is commonly designated as "unexplained"[2]. On the other hand, it has to be taken into account that anemia in the elderly is rarely due to a single cause, but, rather, up to half of patients have multiple causes[17]. This phenomenon parallels the fact that the elderly patient is typically affected by several different diseases (multimorbidity), which in turn often requires polypharmacy. As a result, distinguishing the etiology of anemia is often challenging at the individual level[7].

Iron deficiency in the elderly

ID is by far the most common and widespread nutritional disorder worldwide (http://www.who.int/nutrition/topics/ida/en/), affecting approximately one billion people, particularly children and young women from low-incoming nations. Nevertheless, in industrialized countries the elderly population represents an additional category at risk of developing ID syndromes[18-20], a term that, in turn, encompasses different conditions[21]. The most obvious is "absolute" ID, defined by the lack of storage iron[22-23]. At variance with children and fertile females, in whom ID is generally due to increased iron demand (because of growth and menses, respectively), in the elderly ID is often associated with the triad malnutrition/malabsorption/pathological blood losses.

"Functional" or "relative" ID is instead defined by the presence of iron-restricted erythropoiesis notwithstanding normal (or even increased) body iron stores. This is generally related to impaired iron distribution (i.e. "macrophage block" during inflammatory diseases), but can also occur when iron demand exceeds iron supply (i.e. during treatment with erythropoiesis stimulating agents) [21, 24-25]. Whatever the mechanism, either absolute or functional ID lead to iron-restricted erythropoiesis, and finally to anemia. Two ID stages are traditionally distinguished, based on the fact that anemia is known to be the final event of a spectrum of disabling conditions: a) initial, "simple" ID without anemia, biochemically characterized by reduced transferrin saturation and ferritin levels; and b) advanced, when overt microcytic, hypochromic iron-deficiency anemia (IDA) is detectable.

The above-mentioned "bad triad" of malnutrition/malabsorption/pathological blood losses typical of the ID elderly patient recognizes multiple gastrointestinal (GI) etiologies, which frequently occur in combination in a given individual. Chronic blood losses, at either upper or lower GI level, can be associated with a number of conditions including esophagitis, gastritis, peptic ulcer, colon cancer or pre-malignant polyps, inflammatory bowel disease, or angiodysplasia[15]. Most of these conditions have

an increased prevalence in the elderly, particularly as regards to malignancies[26] and angiodysplasia[27]. Their risk of bleeding in the elderly is clearly favored by common concomitant drug therapies, e.g. antithrombotic drugs for cardiovascular diseases (especially for atrial fibrillation) and NSAIDs for osteoarthritis.

Iron malabsorption is also relatively common in the elderly, and can determine a condition known as "acquired IRIDA" (iron refractory iron deficiency anemia), characterized by refractoriness to oral iron treatment[19], which should be suspected whenever IDA occur without evidence of gastrointestinal blood loss. Possible causes include atrophic gastritis, Helicobacter pylori (HP) infection[28], and celiac disease (CD). Indeed, while CD is generally believed a disease of childhood and young adults, recent studies have reported that near thirty percent of newly diagnosed patients have more than 65 years[29-31]. In the elderly, CD frequently presents with anemia[32], rather than with the classical triad of diarrhea, weight loss and abdominal pain[33], so that the correct diagnosis can be challenging. Since gastric acid is known to be essential for optimal iron absorption[34], long-term use of proton pump inhibitors (PPI) could also theoretically contribute to iron malabsorption in the elderly, but this remains controversial[35].

Finally, malnutrition is also a frequent contributing factor to ID in elderly, but rarely sufficient to cause IDA by alone. Anyway, a detailed evaluation of nutritional status is mandatory in any elderly with anemia.

Measurement of Hepcidin, the key regulator of iron homeostasis.

In 2001, the hepatic hormone hepcidin has been discovered, and soon after recognized as the key regulator of iron metabolism[36]. It acts by binding to its cell membrane receptor, ferroportin, which is highly expressed by duodenal enterocytes, macrophages, and hepatocytes, which exports iron into the bloodstream[37]. Hepcidin binding to ferroportin determines degradation of the cell membrane iron exporter, ultimately leading to hypoferremia because of reduced intestinal absorption and iron recycling from macrophages[36]. A detailed description of the complex molecular regulation of hepcidin synthesis is beyond the scope of this paper, and can be found elsewhere[34, 38]. Hepcidin is typically suppressed in ID, to allow maximal iron absorption form the gut[39]. By contrast, hepcidin production is strongly induced by inflammatory cytokines such interleukin-6 (IL-6), determining hypoferremia and iron-restricted erythropoiesis which play a central role in the pathogenesis of ACD[40-43].

The active form of hepcidin, able to bind and inactivate ferroportin, is a 25-amino acid peptide deriving from an 84-mer precursor. Others truncated isoforms, e.g. hepcidin-20 and hepcidin-22, can be found in biological fluids[44], but their biological meaning is unknown[45]. Hepcidin can be measured by two main methodologies, immunological (ELISA based on anti-hepcidin antibodies), and mass spectrometry (MS)[44, 46]. The latter has the advantage of distinguishing the active 25-mer peptide from the above-mentioned isoforms, which often cross-react with currently available antibodies[44, 46]. While a "gold standard" assay for routine clinical practice at reasonable costs is still lacking, serum hepcidin measurement represents a promising tool in the diagnosis and management of ID/IDA. Of note, correct interpretation needs a proper definition of age- and sex-specific reference ranges[47-48].

Soon after its discovery, increased serum hepcidin due to subclinical inflammation was postulated as a possible mechanism contributing to the "unexplained" anemia of elderly[49-50].

While some studies tend to support this hypothesis (51), the two largest population studies, the Nijmegen Biomedical Study (NBS)[47], and the Val Borbera Study (VBS)[48], failed to detect a relevant increase of hepcidin levels in the extreme decades. Thus, at present, a major role of hepcidin in the "unexplained" anemia of the elderly appears unlikely. This complex condition is currently believed the result of several concurrent age-related changes, including stem cell aging, subclinical impairment of renal function, androgen insufficiency, and others still unknown[2, 52].

Diagnosis of in the elderly

While guidelines exist for IDA diagnosis in the general population[22, 53], a consensus on the optimal approach in the elderly is lacking. The general principles of searching and treating the underlying cause(s) are valid also in the elderly, but this is not always possible[7]. Indeed, the diagnostic approach should theoretically include relatively invasive procedures, i.e. endoscopy when GI bleeding is suspected or demonstrated by positive noninvasive fecal tests. Old age does not represent by itself a contraindication to an extensive workup, but a particular skill is required in any given "frail" patient to properly evaluate the risk-benefit ratio and prognostic implications. In our experience, a

frequent and challenging condition in the elderly is represented by GI angiodysplasia[54]. Indeed, in patients with angiodysplasia bleeding is typically discontinuous (with ensuing possibility of false-negative fecal tests), and difficult to be visualized when lesions are localized into the small bowel, unless performing video capsule endoscopy (VCE)[27]. Of note, angiodysplasias in the elderly are frequently associated with aortic stenosis[55], a condition known as Heyde's syndrome, and characterized by acquired von Willebrand disease[56-57]. This in turn induces a vicious circle aggravating bleeding from angiodysplasia, and, consequently, IDA.

The diagnosis of IDA in the elderly is also challenging because of the highly prevalent comorbidities that hamper interpretation of traditional laboratory biomarkers. For example, reduction of erythrocyte mean corpuscular volume (MCV) can be blunted by concomitant nutritional deficiencies of folic acid and/or vitamin B12. Similarly, serum ferritin and transferrin saturation have low sensitivity in the elderly[23]. Indeed, true ID can occur at ferritin values higher than the classical threshold of 12-15 µg/L for younger adults[58-60]. This has been attributed to the fact that ferritin tends to increase with aging[61], and can be influenced by common comorbidities in the elderly, including inflammations, infections, malignancies. For these reasons, an higher ferritin cut-off (<50 µg/L) has been proposed for predicting ID in the elderly[62]. An indirect confirmation of the validity of such assumption comes by studies showing amelioration of anemia after iron supplementation in elderly patients with "normal" iron indices[14].

As mentioned above, hepcidin has been suggested as a promising tool for diagnosis and treatment of iron-related disorders[25, 46]. In ID serum and urinary hepcidin levels are typically low to undetectable[39, 44, 63], even prior the clinical manifestation of anemia[39, 64]. On the contrary, hepcidin is high in ACD[65]. A special problem is represented by distinguishing the presence of true ID in the context of concomitant ACD. This could occur, for example, in a malnourished elderly patient affected by inflammatory bowel disease. Since preclinical studies have shown that concomitant ID blunts hepcidin response to pro-inflammatory cytokines[66-67], IDA or mixed IDA/ACD could be theoretically differentiated by "pure" ACD through demonstration of low or high hepcidin levels, respectively. Pilot studies in patients with rheumatoid arthritis[68] or inflammatory bowel disease[69] are consistent with this hypothesis, but larger data are required for confirmation.

Treatment of IDA in elderly

No specific guidelines currently exist for treatment of anemia in the elderly. Evaluation of iron status should represent the first step[70], and, if IDA is ascertained or deemed likely, a therapeutic trial with oral iron should be pursued. This should be continued for at least 3 months, since the goal is not simply the correction of anemia, but also the replenishment of iron stores[71]. Such long time may be even longer in the elderly, because of slow bone marrow response, and can result in poor compliance, particularly when multimorbidity requires daily assumption of numerous pills. Moreover, concomitant malabsorption is not rare in the elderly, resulting in high rate of treatment failure and the need of intravenous (IV) iron therapy[72-74]. Currently available IV iron formulations are generally effective and well tolerated, with an overall low incidence of serious adverse effects[75-77]. The total iron dose to be infused is 1,000 to 1,500 mg, which requires multiple hospital accesses when traditional formulation with a maximal dose per infusion between 125 mg and 200 mg are used (e.g. iron gluconate or iron sucrose). This can be problematic in the frail elderly with limited autonomy, often hampering treatment feasibility. The recent advent of new IV iron formulations allowing infusion of the total dose with just one or two hospital accesses promises significant amelioration of this scenario[77]. Such formulations include low molecular weight iron dextran[78], ferumoxytol[77], iron isomaltoside[79], and ferric carboxymaltose[80-81]. However, clinical trials specifically devoted to IDA in the elderly are needed to confirm such promises.

As hepcidin inhibits duodenal iron absorption, measuring its levels may theoretically help to select a personalized approach for iron administration. A recent retrospective study by Bregman and co-workers showed that hepcidin levels below a given cut-off (20 ng/ml) effectively discriminated IDA patients who actually responded to oral iron[82]. If such data will be confirmed by further studies, hepcidin measurement could be used to select patients candidates to first-line IV therapy (e.g. those with hepcidin levels above a critical cut-off), avoiding time wasting with poorly tolerated and likely ineffective oral formulations, particularly in the geriatric setting.

Conclusions

Hepcidin discovery has revolutionized our approach to the disorders of iron metabolism, including IDA. Measuring circulating levels of this key-regulatory

hormone may assist clinicians in either diagnosis or treatment of IDA in the elderly. In such patients, the use of new and easy-to-use IV formulations promises to increase substantially success rate.

Declaración de conflictos de interés:
Los autores declaran no poseer conflictos de interés

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