



Review article

Anemia of chronic disease: A unique defect of iron recycling for many different chronic diseases

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ABSTRACT

Anemia of chronic disease (ACD) is frequently observed in patients with chronic diseases as a significant contributor to morbidity and mortality, which can aggravate the severity of symptoms of the underlying inflammatory status. The pathophysiology of ACD is multifactorial, including three mechanisms: shortened erythrocyte survival, impaired proliferation of erythroid progenitor cells, and abnormalities of iron metabolism. These mechanisms are “immune and inflammation”-driven, but several other factors, including chronic blood loss, hemolysis, or vitamin deficiencies, can aggravate anemia. All the abnormalities of iron metabolism observed in ACD can be explained by the effect of hepcidin upregulation. Hepcidin is a small liver peptide, that inhibits the cellular macrophage efflux of iron and intestinal iron absorption, binding to ferroportin and inducing its internalization and degradation. In ACD the synthesis of hepcidin is upregulated by increased inflammatory cytokines, causing the two main principal features: the macrophage iron sequestration and the iron-restricted erythropoiesis. ACD is the most complex anemia to treat. The recommended approach is the treatment of the underlying disease, which can lead to a major improvement or even resolution of ACD. Currently available treatments (transfusion, iron, and erythropoiesis-stimulating agents) can ameliorate anemia, but a considerable percentage of non-responders exist. On this evidence new treatment strategies might arise from the knowledge of the pathophysiology of ACD, in which hepcidin plays the central role. Prospective studies are needed to evaluate the safety and the efficacy of the new emerging treatments, which modulate hepcidin expression through different mechanisms.

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1. Introduction

The terms anemia of chronic disease (ACD) or “anemia of inflammation” are used interchangeably to indicate an acquired condition that is commonly observed in the clinical settings of a wide variety of diseases, including infections, inflammatory conditions and malignancies (Table 1) [1,2].

ACD is the second most prevalent form of anemia after iron deficiency anemia (IDA) [3], and occurs in patients with chronic immune activation [2,4–6], mainly in hospitalized patients [7].

The incidence and prevalence of anemia increase with advancing age: up to 26.1% in men and 20.1% in women aged 85 years and over [8]. In this context low hemoglobin levels can be a marker of an underlying chronic disease even in absence of influence on health. Generally, the causes of anemia in the elderly can be divided into three groups: nutrient-deficiency anemia (34%), ACD (20%), and unexplained anemia (34%) [9,10]. Gastrointestinal blood loss is the primary cause of iron-deficiency anemia in older adults, even if anemia in the elderly is often

not linked to a single cause, but generally related to several factors, including: chronic renal insufficiency, sex hormone deficiency, bone marrow failure and metabolic diseases. The cause of ACD in the elderly has not yet completely clarified and it seems more plausible that the oxidative stress that accompanies the evolution of our life is responsible of ACD [11]. Elderly individuals affected by ACD have a fivefold increase in mortality risk and hospitalization, as confirmed by a large prospective population-based study performed between 2003 and 2007 [12].

ACD is usually a mild-moderate (hemoglobin level 8–9.5 g per deciliter), normochromic, normocytic anemia, characterized by low iron and normal-low transferrin levels with normal or increased ferritin. The reticulocyte count is low as expression of underproduction of red cells, while the hypoferrremia is due to acquisition of iron by the reticular endothelial system (RES). The consequence of decreased levels of serum iron is the reduction of transferrin saturation. If IDA and ACD coexist, transferrin saturation may be even lower. Ferritin levels are normal or increased in patients with ACD, reflecting increased storage and retention of iron within the RES, along with increased ferritin levels due to immune activation.

The anemia can become microcytic and tends to be more severe in presence of concomitant IDA. In this context the levels of the concentration of soluble transferrin receptor, a truncated fragment of the membrane receptor usually increased in iron deficiency, can be helpful [13].

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Table 1

The most common causes of ACD. The prevalence is estimated and shown as range. Modified from Weiss 2005 [1].

Disease	Prevalence (%)
Infections (acute and chronic)	18–95
Cancer (hematologic and solid tumors)	30–77
Autoimmune disorders	8–71
Chronic kidney diseases	23–50
GvHD after solid-organ transplantation	8–70

The correlation between chronic inflammation, anemia and iron was recognized over 50 years ago [14], but only in the last decade the antimicrobial peptide hepcidin has emerged as the key hormone regulatory of the iron homeostasis involved in causing the anemia in chronic diseases [15]. Since the identification of the iron regulatory hormone hepcidin, our understanding of the molecular pathway of iron metabolism has increased dramatically. Genetic defects leading to hepcidin deficiency cause iron overload associated with hereditary hemochromatosis [16]. Conversely, overexpression of hepcidin leads to severe iron deficiency and a fatal anemia in transgenic mice [17]. Substantial progress has been made recently into elucidating the mechanism of action of hepcidin, and the link between hepcidin and inflammation is now evident [15].

The prototypical type of ACD is the anemia observed in patients with rheumatoid arthritis (RA) [1,18]. Generally, the prevalence of anemia in chronic rheumatic diseases is high, and in RA the development of anemia is associated with more advanced stage of the disease [1,19], and is more common in women than in men [20]. ACD can be found also in children affected by the juvenile form of RA, called juvenile idiopathic arthritis, characterized by a systemic disease more than in patients with involvement of only single joints [19,21].

2. Pathophysiology

The pathogenesis of ACD is complex and multifactorial, linked to the underlying chronic disease, but mainly due to alterations in iron balance, derived from the immune activation.

At least three major immune-driven mechanisms contribute to the development of ACD:

1. the reduction in the lifespan of erythrocytes;
2. the impaired proliferation of erythroid progenitor cells;
3. the increased uptake and retention of iron within cells of the reticuloendothelial system (RES) [1,3].

The molecular basis of ACD involves cytokines and acute phase proteins that affect the regulation of iron homeostasis and erythropoiesis, but several other factors, including hemolysis, disease and treatment-associated adverse events or vitamin deficiencies can also influence the development of anemia. In addition, the prevalence of anemia can be influenced by other factors not linked to the underlying disease, such as age or gender; and, in particular, an increased prevalence of multifactorial anemia is found in elderly patients [22,23].

2.1. The reduction in the lifespan of erythrocytes

The mechanism underlying the reduction in the lifespan of erythrocytes is the most difficult aspect in the pathophysiology of ACD to clarify.

In 1966 Cartwright and Wintrobe demonstrated a modest reduction of erythrocyte survival lifespan in ACD [2]. This reduction seems not due to an intrinsic defect of the red cell, as the survival of red cells from patients with ACD is normal when the red cells are infused into normal subjects. The underlying mechanism is not yet fully understood and probably other factors are involved and necessary to explain the degree of anemia. Most recently, it was suggested that elevated concentrations of inflammatory cytokines, such as interleukin-1 (IL-1), produced by activated macrophages as observed in patients affected by RA, could enhance the ability of macrophages to ingest and destroy red cells [24],

particularly through a selective hemolysis of newly formed erythrocytes [25].

2.2. The impaired proliferation of erythroid progenitor cells

In ACD the proliferation and differentiation of erythroid precursors are impaired [6] for two main reasons: the reduced or impaired erythropoietin (EPO) production, and the inhibitory effect on bone marrow by inflammatory cytokines.

EPO is the most important erythropoiesis-inducing hormone. During inflammation EPO expression is decreased or inadequate for the degree of anemia [26,27]. The reduced level of EPO is at least in part due to the cytokine-mediated formation of reactive oxygen species (ROS), which in turn affects the binding affinities of EPO-inducing transcription factors and also damages EPO-producing cells. Studies *in vivo* have demonstrated that the injection of lipopolysaccharide (LPS) into mice results in reduced expression of EPO mRNA in kidneys and decreased levels of circulating EPO [28]. A reduced EPO activity can promote iron retention in the reticular endothelial cells because EPO and stressed erythropoiesis have been identified as important negative regulators of hepcidin production [29,30].

In addition, the overproduction of inflammatory cytokines, such as interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and interferon- γ (IFN- γ) [1] can influence the growth of erythroid burst-forming units and erythroid colony-forming units [6]. Interestingly, IFN- γ seems to be the most potent inhibitor, that can also reduce the responsiveness of erythroid progenitor cells to EPO decreasing EPO-receptors on erythroid progenitor cells [31].

Moreover, cytokines, including IFN- γ and TNF- α , may directly damage the erythroid progenitors by inducing the formation of labile free radicals, such as nitric oxide or superoxide anion [32], decreasing erythrocyte half-life and promoting erythrophagocytosis [33]. Patients with RA have reduced numbers of erythroid burst-forming units and hemoglobin levels, which inversely correlate with the circulating concentration of TNF [18,34]. Anti-TNF administration rescues erythroid-progenitor-cell proliferation and reduces apoptosis of these cells *in vitro* [35] and *in vivo* [34], confirming the correlation between TNF, anemia and defective erythropoiesis in patients with RA. Interestingly, in some patients with systemic lupus erythematosus (SLE), autoantibodies against EPO were detected in association with decreased circulating EPO levels and the development of anemia [36].

In addition, a possible role of hepcidin (see above) as inhibitor of erythroid colony formation *in vitro* has been demonstrated although the mechanisms are still undefined [37].

2.3. The increased uptake and retention of iron within cells of the reticuloendothelial system

The diagnostic feature of ACD is hypoferrremia in the setting of adequate or increased iron stores [2] due to an impaired iron mobilization with an increased uptake and retention of iron within the cells of the RES. This diversion of iron from the circulation into storage sites of the RES leads to a limitation of the availability of iron for the erythroid progenitor cells and, as a consequence, to an iron-restricted erythropoiesis. The main actor involved in this pathophysiological mechanism is hepcidin.

2.3.1. Hepcidin

Hepcidin is a small liver peptide that acts as a systemic iron-regulatory hormone by regulating iron transport from tissue to plasma and it responds to body iron status, hypoxia and inflammation [15]. It was independently isolated from plasma by Krause et al. [38] and from human urine by Park et al. [39]. Since this peptide was mainly produced by hepatocytes and had antimicrobial effects, it was firstly termed liver-expressed antimicrobial peptide-1 (LEAP-1), and later hepcidin.

The structure of hepcidin is highly conserved among mammalian species, suggesting a key role in important biologic mechanisms as part of the innate immune response [40]. The bioactive form of hepcidin is a cationic peptide with 25 amino acid residues and 4 disulfide bridges, derived from the C-terminus of an 84-amino acid prepropeptide, encoded by the HAMP gene on chromosome 19. This peculiar structure resembles that of many antimicrobial peptides, and *in vitro* hepcidin exerts a modest antimicrobial activity. Other two forms of hepcidin are detectable in the urine: hepcidin-22 and hepcidin-20, but the real role of these peptides is ignote.

Hepcidin is considered the key regulator of iron balance, acting as the central regulator of intestinal iron absorption and iron recycling by macrophages. It binds to the sole iron exporter protein, ferroportin, on duodenal enterocytes and macrophages, triggering its internalization and degradation, resulting in the blockage of cellular iron exporter [41]. The decrease in plasma iron concentration and the iron sequestration in macrophages induced by hepcidin leads to iron-restricted erythropoiesis and result in ACD.

The link between hepcidin and the ACD was found by Fleming and Sly, who suggested that hepcidin mediated the changes in iron homeostasis seen in inflammation [42]. They proposed that hepcidin excess would cause reduced intestinal iron absorption, reduced serum iron and increased reticuloendothelial iron. In 2003 Nemeth defined hepcidin as a type II acute-phase protein similar to ferritin [15] and for this reason hepcidin is now considered the key mediator of ACD.

The study of hepcidin regulatory pathway is still incomplete. Hepcidin expression is enhanced by several factors, including iron overload, inflammatory cytokines, such as IL-1 and IL-6, and infectious stimuli such as LPS, while is inhibited by TNF- α , anemia and hypoxia [43–45]. The process of hepcidin suppression that occurs in iron deficiency, hypoxia and erythropoiesis expansion is only partially known [46].

IL-6 plays a central role in the induction of hepcidin synthesis: it binds to its receptor, activating JAK2 signaling and STAT3 phosphorylation [47], and the response is likely to be amplified by the interaction with BMP-HJV-SMAD pathway.

Experiments in humans have demonstrated that the infusion of IL-6 in healthy volunteers rapidly induces hepcidin synthesis, and is quickly followed by hypoferrinemia and a decrease in transferrin saturation [43].

The evidence that hepcidin excess causes iron deficiency anemia in transgenic mice was first shown in 2002, suggesting that hepcidin may be involved in the diversion of iron traffic through decreased duodenal absorption of iron and the blocking of iron release from macrophages as observed in ACD [17]. Hepcidin overexpression has been reported in two acquired conditions: hepatic adenomas and ACD. Rare cases of benign hepcidin-producing hepatic adenomas have been diagnosed in patients treated for inherited glycogen storage disease type 1a caused by glucose-6-phosphatase-deficiency [48]. All the patients developed microcytic anemia, with features of iron deficiency, but normal ferritin values. Anemia completely solved after the surgical removal of the adenoma. More commonly, hepcidin overexpression occurs in ACD, causing the two main principal features of the disease: the macrophage iron sequestration and the iron-restricted erythropoiesis. For this reason, ACD is different from both iron deficiency and overload, and can be classified as a defect of iron recycling or a condition of iron maldistribution.

Recently, ACD due to hyperproduction of hepcidin has been also demonstrated in patients affected by hematological malignancies, such as multiple myeloma [49], Hodgkin's lymphoma [50], and Waldenström macroglobulinemia [51].

3. Diagnosis

The diagnosis of ACD is clinical and laboratory: it is characterized by persistent mild-moderate normocytic, normochromic anemia with hemoglobin values between 9 and 10 g/dL and low reticulocyte index [52], associated to a chronic inflammatory disorder. Over time

the anemia can become more severe, with microcytic and hypochromic red blood cells as expression of a true iron deficiency.

The iron pattern is peculiar in ACD and its evaluation rules out iron deficiency anemia (IDA), although the two conditions may co-exist. A “true” iron deficiency can frequently occur in patients with ACD and must be considered in the diagnosis. In patients with acute or chronic inflammation the diagnosis of iron deficiency can be particularly challenging because most of the biochemical markers for iron metabolism (serum ferritin and transferrin) are affected by acute phase reaction. For these reasons, interest has been generated in the use of erythrocyte and reticulocyte parameters, such as the percentage of hypochromic red cells and the reticulocyte hemoglobin content, available on the modern hematology analyzers based on flow cytometry technology [53].

Chronic gastrointestinal bleeding as a consequence of the underlying disease, such as chronic inflammatory bowel diseases, and treatment modalities including NSAIDs and glucocorticoids, can complicate ACD [1,54]. In some patients, iron deficiency can result from impaired iron absorption due to autoimmune gastritis, celiac disease or *Helicobacter Pylori* infection [55]. Rarely, reduced dietary iron due to extreme dietary restrictions can result in iron deficiency during ACD.

In ACD ferritin values can be normal or increased as expression of both increased storage and retention of iron in the RES, and due to the immune activation [56]. In presence of hemoglobin level lower than 9.0 g/dL and MCV less than 80 fL, iron deficiency has to be ruled out. The diagnosis of iron deficiency is confirmed by serum ferritin level less than 20 ng/mL, even if in presence of inflammation, also ferritin levels between 20 and 50 ng/mL are suggestive of iron deficiency, and levels up to 100 ng/mL cannot exclude an iron deficiency. Serum iron concentration and transferrin saturation are typically reduced in both ACD and IDA, reflecting sequestration of iron in RES and impaired release of iron from stores in ACD and absolute iron deficiency in IDA. The soluble transferrin receptor (sTFR), a truncated fragment of the membrane receptor, has been suggested in differential diagnosis between patients with ACD alone (with normal or high level of ferritin and low level of soluble transferrin receptor) and patients with ACD plus iron deficiency (with low ferritin levels and high levels of soluble transferrin receptor) [57]. Moreover, the sTFR to the log of serum ferritin ratio is useful in the diagnosis of ACD associated to IDA [13]. A low ratio index (<1) indicates ACD, in contrast an index of >2 suggests the combination of ACD with IDA [58] (Fig. 1).

In ACD reticulocyte count is low, according to hypoproliferative anemia, but the use of EPO levels in clinical practice is problematic. First of all, the interpretation of an EPO level should take into account the degree of anemia and mathematical corrections, such as observed/predicted (O/P) ratios must be used [59]. Since EPO levels are inadequate for the degree of anemia in anemic patients with cancer or on renal dialysis, the measurement of EPO levels is not useful in these settings.

All these iron abnormalities are explained by inappropriately high hepcidin expression by IL-6-dependent activation of the STAT3 pathway. According to the hepcidin role in pathophysiology of ACD, its dosage can be a helpful diagnostic tool in the differential diagnosis of ACD and ACD associated to iron deficiency: hepcidin levels are increased in ACD, and normal or reduced in ACD associated to IDA [60] (Table 2). However, the dosage of hepcidin is not routinely employed in clinical practice because of its costs and the need of specialized laboratories. Moreover, despite the importance of hepcidin, the methodologies for measuring hepcidin concentrations have been troublesome. The first methods measured urinary hepcidin by selective extraction of hepcidin from urine by cation-exchange chromatography; more recently mass spectrometric and immunological methods in serum and urine became available [61,62].

Finally, considering the multifactorial pathophysiology of ACD and the hyporigenerative mechanism, vitamin deficiencies should be ruled out. Folic acid and vitamin B12 are essential for normal erythropoiesis and supplementation could be necessary in ACD. In

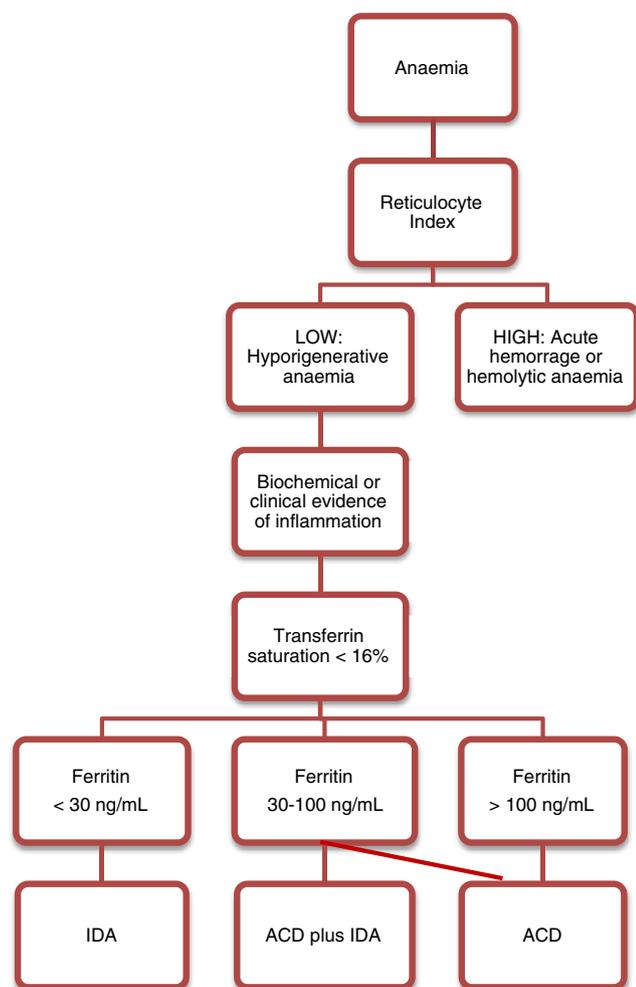


Fig. 1. Flow-chart for the differential diagnosis of ACD, IDA, and ACD plus IDA. Modified from Weiss 2005 [1].

addition, 25-hydroxyvitamin D deficiency can be associated with ACD, especially in elderly patients; vitamin D supplementation can partially improve the degree of anemia [63], as observed in patients with RA [64].

4. Treatment

The recommended approach to ACD is the direct treatment of the underlying disorder when possible. Generally, the reversal of the underlying inflammatory state results in an improvement or even a correction of the anemia. As an example, a significant increase in hemoglobin

Table 2

Laboratory findings in ACD, IDA and combined anemia (ACD plus IDA). ACD, anemia of chronic disease; IDA, iron deficiency anemia; Log, logarithm; sTR, soluble transferrin receptor; IL-1, interleukin-1; TNF- α , tumor necrosis factor- α ; IL-6, interleukin-6; IFN- γ , interferon- γ ; N, normal. Modified from Weiss 2005 [1].

	ACD	IDA	ACD plus IDA
Iron	↓	↓	↓
Transferrin	↓/N	↑	↓
Transferrin saturation	↓	↓	↓
Ferritin	N / ↑	↓	↓ / N
sTR	N	↑	N / ↑
sTR/Log ferritin	↓ (<1)	↑ (>2)	↑ (>2)
Cytokine levels (IL-6, IL-1, TNF- α , IFN- γ)	↑	N	↑
Hepcidin	↑	↓	N/↓

values has been shown in patients with RA treated with anti-TNF antibodies [65] or combined TNF-inhibitors and methotrexate [34]. Unfortunately not all the patients with ACD achieve a full remission of the underlying disease and anemia still persists, reducing quality of life and increasing morbidity and mortality. In these cases a specific treatment of ACD should be indicated.

In case of severe or life-threatening anemia blood transfusion is an efficient therapeutic intervention to rapidly increase the hemoglobin level [66]. In patients with chronic kidney disease (CKD) or cancer, blood transfusion therapy is not recommended because of the risks related to long-term transfusions, such as iron overload and sensitization to HLA antigens in patients undergoing or in list for renal transplantation [67].

When ACD is associated with a true iron deficiency, iron therapy is the first choice treatment. Iron can be administered either orally or intravenously. Many patients do not respond to oral iron administration because of the impaired iron absorption and transfer from enterocytes to circulation, as discussed above; while intravenous iron administration can usually correct the deficit and improve the hemoglobin levels. In particular, in patients with inflammatory bowel disease, the intravenous iron therapy is strongly indicated, and the efficacy is high [68]. On the other side, a high dose of intravenous iron is a potent stimulus for hepcidin production and has been demonstrated to increase hepcidin levels in patients with CKD on hemodialysis within 24 hours of administration [69]. In addition, considering iron blockage into the RES as a potentially effective defense strategy to inhibit the growth of pathogens [70], iron therapy can increase the risk of infection [71,72], and can promote the highly toxic hydroxyl radical formation, strictly related to the increased risk of acute cardiovascular events [73,74]. For all these reasons, iron treatment can be effective in some patients with ACD, but not without the potential risk discussed and the evaluation of the possible complications secondary to iron overload.

Iron replacement should also be considered in patients with ACD who are unresponsive to therapy with erythropoietic stimulating agents because of the functional iron deficiency. It has been shown that correction of functional iron deficiency with intravenous iron supplementation can improve the effect of erythropoietic stimulating agents and reduce their required dosage [75–77].

Erythropoietic stimulating agents include recombinant human erythropoietin and its extended half-life formulations, and have been demonstrated to improve anemia in patients with systemic inflammatory diseases, with a remarkable gain in quality of life and a reduction of the transfusional support. Response to these agents is highly variable, depending on factors like the type of underlying disease and its activity, iron availability and other cofactors that contribute to the anemia development [78]. Some patients with ACD are poorly responsive to erythropoietic stimulating agents, requiring high doses to reach target hemoglobin levels. Recent clinical studies revealed a higher incidence of adverse outcome, such as cardiovascular events, stroke, progression of cancer and death, in patients receiving erythropoietic stimulating agents doses to achieve hemoglobin levels ≥ 13 g/dL, but further studies will be necessary to understand the possible association between erythropoietic stimulating agents and cancer [79,80]. According to these new results, the FDA approved erythropoietic stimulating agents to treat some forms of anemia resulting from chronic kidney disease, chemotherapy and certain other conditions with limited use in cancer and with a downward adjustment of hemoglobin target in CKD patients [81].

New emerging treatments directly address the pathophysiology of the ACD, targeting the hepcidin-ferroportin axis [82].

These therapeutic strategies aim to decrease hepcidin production and to increase ferroportin activity, in order to allow a better bioavailability of dietary and deposit iron for erythropoiesis, avoiding the adverse effects of intravenous iron and erythropoietic stimulating agents administration.

All these treatments are currently under investigation and include direct hepcidin antagonists, such as anti-hepcidin antibodies [83,84], short interference RNA and anti-sense oligonucleotides against hepcidin [85]; hepcidin binding proteins and hepcidin binding spiegelmers [86,87]; hepcidin production inhibitors, that target the positive regulators of hepcidin to reduce its expression including BMP6–HJV–SMAD pathway inhibitors [88,89], IL-6 pathway inhibitors [90–92]; and vitamin D [93]; and ferroportin agonists and stabilizers, useful to correct the functional iron deficit of ACD [94].

5. Conclusion

ACD is a common consequence of chronic diseases, characterized by an impaired mobilization of iron from stores. The development and the persistence of the ACD negatively influence the quality of life of patients, as well as affecting patients' morbidity and mortality, and it must be considered in the treatment of the disease, particularly in elderly patients who have an increased prevalence of multifactorial anemia.

The discovery of hepcidin and its pathway has significantly progressed our understanding of iron metabolism, providing new molecular targets for the development of novel therapeutic approaches for iron disorders. Hepcidin is considered the key hormone of the iron metabolism, regulating the iron recycling and absorption. The development of a reliable laboratory immunoassay could have potential clinical utility in the future in both the diagnosis and the classification of iron disorders, and the monitoring of their treatments.

Since hepcidin overproduction is considered the key pathogenic feature of ACD, synthetic hepcidin antagonists or anti-hepcidin antibodies could be a potential option of treatment of patients with ACD, in whom the underlying condition is not reversible and the degree of severe anemia warrants the need of blood transfusion. This group of patients may gain significant benefit from this new drugs and potential reversal of the iron-restricted erythropoiesis contributing to the anemia.

Learning points

- Anemia of chronic disease is very common in internal medicine words since it is associated with several chronic conditions, which affect the elderly people admitted to IM Units. Quite often is neglected or improperly treated. The understanding of iron metabolism during the last 5–8 years has allowed to better define the pathophysiology of ACD and to better define the therapeutic approach.
- All the abnormalities of iron metabolism observed in ACD can be explained by the effect of hepcidin upregulation.
- Currently available treatments (transfusion, iron, and erythropoiesis-stimulating agents) can ameliorate anemia, but a considerable percentage of non-responders exist. On this evidence new treatment strategies might arise from the knowledge of the pathophysiology of ACD, in which hepcidin plays the central role. Prospective studies are needed to evaluate the safety and the efficacy of the new emerging treatments, which modulate hepcidin expression through different mechanisms.

Conflict of interests

None of the authors has conflict of interest.

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